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First-Line Treatment in EGFR Mutant Non-Small Cell Lung Cancer: Is There a Best Option?

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First generation or second generation EGFR tyrosine kinase inhibitors are currently the standard of care for the first-line management of non-small cell lung cancer (NSCLC) patients with activating mutations within the kinase domain of the epidermal growth factor receptor gene (1, 2). Resistance to targeted therapy can develop after 9–11 months (3–8). Third generation inhibitors were developed to target the EGFR T790M clone, which is the most common dominant second site resistance mutation after first or second generation inhibitors. Osimertinib received full FDA approval for the second-line treatment of advanced NSCLC based on a phase III study comparing the compound to chemotherapy. Recent data demonstrates an important impact for osimertinib in the front-line space based on results comparing the compound to first-generation erlotinib or gefitinib therapy.

Keywords: lung cancer, epidermal growth factor receptor, targeted therapy, osimertinib, afatinib, gefitinib, erlotinib

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THE STORY SO FAR

First and second generation EGFR tyrosine kinase inhibitors (EGFR TKIs) improve progression-free survival (PFS) from 5 to 11 months compared to chemotherapy in the front line (6, 9–11). Second generation inhibitors were created as an attempt to target the second site T790M mutation by irreversibly binding to the EGFR tyrosine kinase domain. Afatinib was developed as an irreversible EGFR/HER2 inhibitor designed to covalently bind to Cys 773 on the *EGFR* tyrosine kinase domain, and had improved inhibition of EGFR T790M in preclinical models (12, 13). However, in the LUX-LUNG 1 clinical trial, the response to afatinib after progression on erlotinib or gefitinib and chemotherapy was only 7% suggesting that use after progression on a first-generation TKI may be less efficacious than second-line chemotherapy alone. In the front line LUX-Lung 3 and LUX-Lung 6 trials, afatinib did not significantly improve overall survival (OS) versus chemotherapy (5, 14). Although a pre-specified subanalysis of each trial suggested a statistically significant improvement in OS in patients with the exon 19 del *EGFR* mutation (15), the LUX-LUNG 7 trial failed to identify a statistically significant superior OS with afatinib compared to gefitinib. Updated analysis of co-primary end points in LUX-LUNG 7 showed a superior time-to-treatment failure, PFS, overall response rate (ORR) for afatinib

Abbreviations: Mo, months; NA, not available; OS, overall survival; PFS, progression-free survival; ORR, overall response rate; Soc, standard of care; NSCLC, non-small cell lung cancer; HR, hazard ratio; cfDNA, cell-free DNA; ctDNA, circulating tumor DNA.

albeit with more diarrhea and rash toxicity compared to gefitinib which had higher transaminase elevation (16).

Osimertinib was developed to target the T790M clone and has irreversible binding affinity to the cysteine-797 residue at the ATP binding site of EGFR (17). Pre-clinically, the drug also inhibits cellular growth in EGFR exon 19del, L858R, and EGFRm(+)/T790M(+) mutant cell lines (18). The phase I AURA trial had an objective response rate in T790M positive NSCLC patients of 61%, and a median duration of PFS of 9.6 months (19). Two subsequent phase II trials confirmed these results in more than 400 patients with a PFS of approximately 11 months (20), and the FDA approved osimertinib under the breakthrough therapy designation.

The AURA3 phase III trial showed a greater than 70% ORR and 10.1 month PFS (HR 0.30 systemically and HR of 0.32 in the CNS) (21). The FDA granted fast-track approval based on these initial trial data in November 2015 and full approval in March 2017 for patients with metastatic *EGFR* T790M mutant positive NSCLC after progression on first or second generation anti-EGFR TKIs.

FLAURA (NCT02296125) is a phase III head-to-head trial that directly compared first-line osimertinib (80 mg daily) with standard first-line therapy with gefitinib or erlotinib in a total of 556 patients. The magnitude of improvement in the interim analysis was important (HR 0.46), with a superior PFS (18.9 versus 10.2 months) compared to standard of care (SOC) erlotinib and gefitinib (18.9 versus 10.2 months, 9 month PFS). A similar HR of 0.47 was seen in the CNS metastasis cohort and suggests encouraging CNS activity (22).

PREVIOUS HEAD TO HEAD TRIALS OF EGFR TKIs

Several previous studies have compared EGFR inhibitors head-to-head, but have failed to drive a new SOC in this setting. Both the CTONG 0901 (3) trial which compared erlotinib with gefitinib in a Chinese patient population and the multi-national LUX-LUNG 7 which compared afatinib to gefitinib did not identify a clearly superior drug in terms of PFS, OS, or toxicity. In LUX-LUNG 7, the median OS with afatinib was 27.9 months compared to 24.5 months in patients who received gefitinib (HR 0.85; $P = 0.19$) with a higher ORR of 70% with afatinib versus 56% with geftinib (16, 23, 24). The higher RR in LUX-LUNG 7 with afatinib was met with more frequent treatment-related grade ≥3 AEs and included diarrhea (13.1 versus 1.3%), rash (9.4 versus 3.1%), and fatigue (5.6 versus 0%) (16). Dacomitinib, another irreversible pan-Her tyrosine kinase inhibitor, was compared head-to-head to gefitinib in the ARCHER 1050 trial with a greater median PFS (14.7 versus 9.2 months; HR 0.59, $p < 0.0001$). However, there were increased grade 3 toxicities with 66% of patients requiring dose reduction (25). In ARCHER 1050, there was a significant increase in dermatitis acneiform (13.7%), diarrhea (8.4%), increased ALT (8.5%), paronychia (7.5%) and stomatitis (3.5%) in the dacomitinib arm (26). A different third-generation inhibitor, ASP8273, was compared to erlotinib/gefitinib in the first-line SOLAR study, and the trial was discontinued based on results from an interim data analysis in the investigational arm (27).

CLINICAL OUTCOMES WITH OSIMERTINIB

Clinical efficacy with osimertinib has been documented in the first-line and second-line space. The treatment naïve cohort of the AURA I trial (NCT01802632) demonstrated a 19.3 month PFS for osimertinib and suggested a future role for the compound in treatment naïve patients with EGFR mutant lung cancer (28). Pre-clinical evidence suggests that T790M outgrowth may occur early or late, and that the suppression of resistance clones earlier in therapy may translate into improved PFS and time to treatment failure on the compound (18, 29, 30).

The interim data cutoff of June 2017 of the phase III FLAURA trial (NCT02296125) comparing first-line osimertinib with erlotinib/gefitinib demonstrated an improved PFS over SOC options in patients with and without CNS metastases. A response rate of 80% was noted with 3% of patients (7/279) achieving a complete response. The median PFS was longer with osimertinib than with SOC options (18.9 versus 10.2 months, HR 0.46, $p < 0.001$). The ORR was similar in the two groups (80% with osimertinib and 76% in the SOC group). The duration of response was 17.2 months with osimertinib versus 8.5 months with standard EGFR TKIs (22). OS data is currently awaiting full maturity.

CNS CONTROL

Brain recurrence is a major site of progression on EGFR TKIs given the challenging pharmacokinetics, drug efflux transporter mechanisms, and molecular weight (31). Afatinib and gefitinib have a CNS PFS of 7.2–7.4 months (19, 30). The promising early CNS data with osimertinib showed higher tissue concentration, higher blood brain barrier (BBB) penetration, and lower influence of efflux transporters when compared to gefitinib and afatinib (32). Evidence from the BLOOM study (NCT02228369) showed higher BBB penetration with CSF concentration supporting activity in patients with leptomeningeal disease (33). Second-line therapy in the AURA3 study showed a CNS ORR of 70% (21/30) with osimertinib and 31% with chemotherapy (34) with a median CNS PFS of 11.7 versus 5.6 months (HR 0.32; $p = 0.004$). The hazard ratio for systemic disease control and CNS control was similar in the FLAURA study supporting the preclinical data of high penetration across the BBB (35). The CNS ORR was 66 versus 43% in favor of osimertinib ($n = 128$, $p = 0.01$) with a shorter time to response of 6.2 versus 11.9 months. For the 22 evaluable patients receiving osimertinib, five complete responses were noted compared with none in the SOC arm (36).

TOXICITY OF OSIMERTINIB

Although there was no specific statistical comparison of safety data in grades 1 and 2 reported, osimertinib had lower rates of all grade and grade 3–4 adverse events compared to first generation EGFR TKIs (34 versus 45%) despite a longer median duration of exposure with osimertinib. A separation of the distribution of grade 1 and 2 toxicities would help to put into context the AE profile of gefitinib and erlotinib versus osimertinib. Osimertinib has

less than 1% risk of grade 3 skin rash, paronychia, and stomatitis (17). Dose reductions in FLAURA were 5.4% and discontinuations were 13% which was favorable compared to other EGFR TKIs (22). LUX-LUNG 7 had 13% skin rash, 9% diarrhea, 2–4% paronychia and stomatitis with an overall dose reduction rate of 42.6% with afatinib (24). Importantly, while rare, an awareness of QTc prolongation and cardiomyopathy (with echocardiogram surveillance for patients with cardiac risk factors), keratitis, and interstitial lung disease are important considerations for patients on osimertinib therapy.

CLINICAL PRACTICE RECOMMENDATIONS

FLAURA has achieved an impressive triad of doubling of PFS, improved RR, and lower toxicity, and this serves as a compelling reason to consider osimertinib first-line therapy. This consideration also helps to address the nuanced issue of penetration of T790M testing in the real world setting which is disappointingly low at 16.8% overall. In certain regions testing at initial diagnosis for EGFR mutation remains quite low and may occur at a rate of 22.6% for stage IV adenocarcinoma patients (37). When an EGFR mutation is detected, some reports have documented that only 48.3% of stage IV patients will receive an EGFR TKI (37). The drop off in testing for mechanisms of resistance will be important in treatment selection for considering front-line use of osimertinib in EGFR mutated NSCLC patients.

Another concern that affects treatment selection decisions is the fact that almost 18% of the gefitinib and 36% afatinib patients did not receive further lines of treatment in the LUX-LUNG 7 trial (16). In the AURA 3 clinical trial, only 24% in the osimertinib group and 71% in the platinum-pemetrexed group received subsequent systemic treatment (21). Only 67% of advanced NSCLC patients overall receive a second-line therapy demonstrating the importance of patient drop off in clinical practice (16, 24).

LIMITATIONS OF FLAURA

A balanced analysis of FLAURA does present some additional considerations. The patients in the SOC arm mainly received gefitinib, while erlotinib has been more prevalently utilized in the United States (38). It is not clear is how osimertinib would have compared to second generation irreversible inhibitors, and afatinib and dacomitinib have a non-significant numerical advantage in PFS compared to first generation TKIs erlotinib and gefitinib (39, 40).

Further investigation across large cohorts is needed to determine if the mechanisms of resistance to first-line osimertinib are unique. Based on second-line data, early progression on osimertinib may be more often associated with the development of alternate resistance mechanisms, such as MET upregulation, MEK activation, and small cell transformation among others. Patients with longer duration of response may stay addicted to EGFR with additional second site mutations noted, including C797S and others (41–43). The incidence of C797S resistance after first-line osimertinib is unknown at this time, and it remains to be determined if second-line first-generation inhibitors will be an adequate strategy against the C797S acquired resistance mutation. Evaluation of samples from the treatment naïve AURA patients and at progression revealed JAK2, PI3K, Her2 exon 20 insertions, and NOTCH mutations as acquired bypass mechanisms. Combined RB1 loss and p53 aberrations were identified in 3/19 patients by ctDNA (44). The possibility that this may select a pre-existing small cell clone is not yet known, and *EGFR* mutant SCLC transformed tumors frequently have p53, RB1, and PI3K aberrations (45–47). An MRI brain was not mandated at baseline in the FLAURA trial confounding the detection of asymptomatic cranial metastases on study (22). The optimal timing of osimertinib therapy will be further explored in the Phase II APPLE trial through the EORTC, in which first line osimertinib will be compared with osimertinib after gefitinib based on ctDNA progression.

ROLE OF MOLECULAR TESTING IN PATIENT SELECTION

The limited dataset in the AURA 1 trial showed no cases of acquired T790M after progression on osimertinib in the first-line space (35). Currently, there is FDA approval for plasma Cobas testing for EGFR mutations when tissue is not available. Because of the rates of small cell lung cancer identified and a false negative rate in plasma, tissue testing will remain an important source for testing. Patients who had EGFR mutations identified by plasma ctDNA (359 patients) had a similar PFS to the full tissue positive set (15.2 months versus 9.7 months with SOC) (48).

The timing for surveillance of resistance clones may provide important information about disease biology (49). In the first assessment at 6 weeks, FLAURA showed an early separation of the PFS Kaplan–Meier curves which may indicate a lower frequency of early resistance to osimertinib (22). Monitoring for resistance mutations through plasma ctDNA will likely be a strategy forward for identifying resistance pathways.

OVERCOMING C797S

Strategies to overcome resistance with C797 mutation are evolving. Chemotherapy is a standard option for those who progress on first-line osimertinib. In pre-clinical models, EGFR C797 mutations may respond to cetuximab and brigatinib, however, this remains to be tested in human clinical trials (50). When EGFR T790M and C797S are in the *cis* conformation (on the same allele), there are no active EGFR TKIs or combinations which have shown clinical responses in this setting to date (51, 52). Through plasma surveillance, it has been seen that C797S may exist in *trans* conformation (on different alleles) in approximately 8% of cases (52). There are reports of clinical efficacy with therapy combining first and third generation TKIs when T790M and C797S mutations are in the *trans* conformation. Wang et al. reported a short response with osimertinib and erlotinib targeting concomitant *EGFR* T790M and C797S in *trans*, and this was followed by a change in clonal dynamics in C797S from *trans* to *cis* (53). In another report in which T790M and C797S mutations were in *trans*, a ctDNA assay showed a rapid decline in the C797S

mutation within 2 weeks of starting a gefitinib and osimertinib combination (54). These reports suggest the importance of making available the reporting of *cis* versus *trans* conformation for C797S after osimertinib therapy on sequencing reports to potentially guide therapies.

CONCLUSION

Mounting clinical data supports that osimertinib will likely be a pivotal first-line treatment for EGFR mutant metastatic NSCLC. The FDA recently awarded breakthrough therapy designation to osimertinib in the first-line treatment of metastatic EGFR mutated NSCLC. The improvement in PFS, ORR, CNS efficacy, and toxicity demonstrate its important capacity as an important front-line option and have led the NCCN to recommend the compound in the first-line treatment of EGFR mutant patients. An important goal for EGFR mutant patients is to ensure early access to effective agents recognizing that not all patients will receive second-line therapy. Osimertinib is an attractive choice for CNS disease with early data on the prevention of CNS metastasis. The toxicity profile of the compound appears to be superior to other compounds in this space. Ongoing work to identify the mechanisms of secondary resistance to osimertinib can lead to rationale combinations of targeted therapy. The TATTON Phase Ib study evaluates combinations of osimertinib at increasing doses in combination with selumetinib (MEK inhibitor), AZD6094 (MET inhibitor) in T790M mutation-positive patients who have progressed *EGFR* tyrosine kinase inhibitor therapy harboring the T790M mutation. It is not entirely known if the mechanisms of resistance after second-line osimertinib will faithfully resemble all the mechanisms of resistance to first-line osimertinib, and this is an active area of ongoing research (NCT03122717).

AUTHOR CONTRIBUTIONS

Both authors were involved in the conception, design, and writing of the manuscript.

REFERENCES

1. Hanna N, Johnson D, Temin S, Baker S Jr, Brahmer J, Ellis PM, et al. Systemic therapy for stage IV non-small-cell lung cancer: American society of clinical oncology clinical practice guideline update. *J Clin Oncol* (2017) 35(30):3484–515. doi:10.1200/JCO.2017.74.6065
2. Novello S, Barlesi F, Califano R, Cufer T, Ekman S, Giaj Levra M, et al. Metastatic non-small-cell lung cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol* (2016) 27:v1–27. doi:10.1093/annonc/mdw326
3. Yang JJ, Zhou Q, Yan HH, Zhang XC, Chen HJ, Tu HY, et al. A phase III randomised controlled trial of erlotinib vs gefitinib in advanced non-small cell lung cancer with EGFR mutations. *Br J Cancer* (2017) 116:568–74. doi:10.1038/bjc.2016.456
4. Killock D. Lung cancer: a new generation of EGFR inhibition. *Nat Rev Clin Oncol* (2015) 12:373. doi:10.1038/nrclinonc.2015.80
5. Sequist LV, Yang JC, Yamamoto N, O'Byrne K, Hirsh V, Mok T, et al. Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. *J Clin Oncol* (2013) 31:3327–34. doi:10.1200/JCO.2012.44.2806
6. Rosell R, Carcereny E, Gervais R, Vergnenegre A, Massuti B, Felip E, 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* (2012) 13:239–46. doi:10.1016/S1470-2045(11)70393-X
7. Zhou C, Wu YL, Chen G, Feng J, Liu XQ, Wang C, 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* (2015) 26:1877–83. doi:10.1093/annonc/mdv276
8. Maemondo M, Inoue A, Kobayashi K, Sugawara S, Oizumi S, Isobe H, et al. Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. *N Engl J Med* (2010) 362:2380–8. doi:10.1056/NEJMoa0909530
9. Mok TS, Wu YL, Thongprasert S, Yang CH, Chu DT, Saijo N, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. *N Engl J Med* (2009) 361:947–57. doi:10.1056/NEJMoa0810699
10. Yang JC, Sequist LV, Zhou C, Schuler M, Geater SL, Mok T, et al. Effect of dose adjustment on the safety and efficacy of afatinib for EGFR mutation-positive lung adenocarcinoma: post hoc analyses of the randomized LUX-Lung 3 and 6 trials. *Ann Oncol* (2016) 27:2103–10. doi:10.1093/annonc/mdw322
11. Wu YL, Zhou C, Liam CK, Wu G, Liu X, Zhong Z, 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* (2015) 26:1883–9. doi:10.1093/annonc/mdv270
12. Solca F, Dahl G, Zoephel A, Bader G, Sanderson M, Klein C, et al. Target binding properties and cellular activity of afatinib (BIBW 2992), an irreversible ErbB family blocker. *J Pharmacol Exp Ther* (2012) 343:342–50. doi:10.1124/jpet.112.197756
13. Li D, Ambrogio L, Shimamura T, Kubo S, Takahashi M, Chirieac LR, et al. BIBW2992, an irreversible EGFR/HER2 inhibitor highly effective in preclinical lung cancer models. *Oncogene* (2008) 27:4702–11. doi:10.1038/onc.2008.109
14. Wu YL, Zhou C, Hu CP, Feng J, Lu S, Huang Y, 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* (2014) 15:213–22. doi:10.1016/S1470-2045(13)70604-1
15. Yang JC, Wu YL, Schuler M, Sebastian M, Popat S, Yamamoto N, 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* (2015) 16:141–51. doi:10.1016/S1470-2045(14)71173-8
16. Paz-Ares L, Tan EH, O'Byrne K, Zhang L, Hirsh V, Boyer M, 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* (2017) 28:270–7. doi:10.1093/annonc/mdw611
17. Yang JC-H, Ahn M-J, Kim D-W, Ramalingam SS, Sequist LV, Su WC, et al. Osimertinib in pretreated T790M-positive advanced non-small-cell lung cancer: AURA study phase II extension component. *J Clin Oncol* (2017) 35:1288–96. doi:10.1200/JCO.2016.70.3223
18. Cross DA, Ashton SE, Ghiorghiu S, Eberlein C, Nebhan CA, Spitzler PJ, et al. AZD9291, an irreversible EGFR TKI, overcomes T790M-mediated resistance to EGFR inhibitors in lung cancer. *Cancer Discov* (2014) 4:1046–61. doi:10.1158/2159-8290.CD-14-0337
19. Jänne PA, Yang JC, Kim DW, Planchard D, Ohe Y, Ramalingam SS, et al. AZD9291 in EGFR inhibitor-resistant non-small-cell lung cancer. *N Engl J Med* (2015) 372:1689–99. doi:10.1056/NEJMoa1411817
20. Yang J, Ramalingam SS, Jänne PA, Cantarini M, Mitsudomi T. LBA2_PR: osimertinib (AZD9291) in pre-treated pts with T790M-positive advanced NSCLC: updated phase 1 (P1) and pooled phase 2 (P2) results. *J Thorac Oncol* (2016) 11:S152–3. doi:10.1016/S1556-0864(16)30325-2
21. Mok TS, Wu Y-L, Ahn M-J, Garassino MC, Kim HR, Ramalingam SS, et al. Osimertinib or platinum-pemetrexed in EGFR T790M-positive lung cancer. *N Engl J Med* (2017) 376:629–40. doi:10.1056/NEJMoa1612674
22. Soria JC, Ohe Y, Vansteenkiste J, Reungwetwattana T, Chewaskulyong B, Lee KH, et al. Osimertinib in untreated EGFR-mutated advanced non-small-cell lung cancer. *N Engl J Med* (2018) 378:113–25. doi:10.1056/NEJMoa1713137
23. Paz-Ares L. Afatinib (A) vs gefitinib (G) in patients (pts) with EGFR mutation-positive (EGFRm+) non-small-cell lung cancer (NSCLC): overall

survival (OS) data from the phase IIb trial LUX-Lung 7 (LL7). *Presented at the European Society for Medical Oncology (ESMO) 2016 Congress*. Copenhagen, Denmark (2016). Abstract #LBA43.
24. Park K, Tan EH, O'Byrne K, Zhang L, Boyer M, Mok T, 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* (2016) 17:577–89. doi:10.1016/S1470-2045(16)30033-X
25. Wu YL, Cheng Y, Zhou X, Lee KH, Nakagawa K, Niho S, 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* (2017) 18:1454–66. doi:10.1016/S1470-2045(17)30608-3
26. Mok T, Cheng Y, Zhou X, Lee KH, Nakagawa K, Niho S. Dacomitinib versus gefitinib for the first-line treatment of advanced EGFR mutation positive non-small cell lung cancer (ARCHER 1050): a randomized, open-label phase III trial. *2017 ASCO Annual Meeting Abstracts. Presented at the ASCO 2017*. Chicago, IL, USA (2017).
27. Kelly R, Horn L, Chih-Hsin Yang J, et al. P2.06-021 efficacy and safety of ASP8273 versus erlotinib or gefitinib as first-line treatment in subjects with EGFRMut+ NSCLC. *J Thorac Oncol* (2017) 12:S1083–4. doi:10.1016/j.jtho.2016.11.1514
28. Ramalingam SS, Yang JC, Lee CK, Kurata T, Kim DW, John T, et al. LBA1_PR: osimertinib as first-line treatment for EGFR mutation-positive advanced NSCLC: updated efficacy and safety results from two phase I expansion cohorts. *J Thorac Oncol* (2016) 11(4 Suppl):S152. doi:10.1016/S1556-0864(16)30324-0
29. Hata AN, Niederst MJ, Archibald HL, Gomez-Caraballo M, Siddiqui FM, Mulvey HE, et al. Tumor cells can follow distinct evolutionary paths to become resistant to epidermal growth factor receptor inhibition. *Nat Med* (2016) 22:262–9. doi:10.1038/nm.4040
30. Rosell R, Molina MA, Costa C, Simonetti S, Gimenez-Capitan A, Bertran-Alamillo J, et al. Pretreatment EGFR T790M mutation and BRCA1 mRNA expression in erlotinib-treated advanced non-small-cell lung cancer patients with EGFR mutations. *Clin Cancer Res* (2011) 17:1160–8. doi:10.1158/1078-0432.CCR-10-2158
31. Baik CS, Chamberlain MC, Chow LQ. Targeted therapy for brain metastases in EGFR-mutated and ALK-rearranged non-small-cell lung cancer. *J Thorac Oncol* (2015) 10:1268–78. doi:10.1097/JTO.0000000000000615
32. Ballard P, Yates JW, Yang Z, Kim DW, Yang JC, Cantarini M, et al. Preclinical comparison of osimertinib with other EGFR-TKIs in EGFR-mutant NSCLC brain metastases models, and early evidence of clinical brain metastases activity. *Clin Cancer Res* (2016) 22(20):5130–40. doi:10.1158/1078-0432.CCR-16-0399
33. Yang JC-H, Cho BC, Kim D-W, Kim S-W, Lee J-S, Su W-C, et al. Osimertinib for patients (pts) with leptomeningeal metastases (LM) from EGFR-mutant non-small cell lung cancer (NSCLC): updated results from the BLOOM study. *2017 ASCO Annual Meeting Abstracts. Presented at the ASCO 2017*. Chicago, IL, USA (2017).
34. Mok T, Ahn M-J, Han J-Y, Kang JH, Katakami N, Kim H, et al. CNS response to osimertinib in patients (pts) with T790M-positive advanced NSCLC: data from a randomized phase III trial (AURA3). *2017 ASCO Annual Meeting Abstracts. Presented at the ASCO 2017*. (2017).
35. Ramalingam SS, Yang JC-H, Lee CK, Kurata T, Kim D-W, John T. Osimertinib as first-line treatment of EGFR mutation-positive advanced non-small-cell lung cancer. *J Clin Oncol* (2017) 36(9):841–9. doi:10.1200/JCO.2017.74.7576
36. Vansteenkiste J, Reungwetwattana T, Nakagawa K, Cho BC, Cobo Dols MA, Cho EK, et al. LBA5CNS response to osimertinib vs standard of care (SoC) EGFR-TKI as first-line therapy in patients (pts) with EGFR-TKI sensitising mutation (EGFRm)-positive advanced non-small cell lung cancer (NSCLC): data from the FLAURA study. *Ann Oncol* (2017) 28:.007–.729. doi:10.1093/annonc/mdx729.007
37. Enewold L, Thomas A. Real-world patterns of EGFR testing and treatment with erlotinib for non-small cell lung cancer in the United States. *PLoS One* (2016) 11:e0156728. doi:10.1371/journal.pone.0156728
38. Soo RA, Loh M, Mok TS, Ou SH, Cho BC, Yeo WL, et al. Ethnic differences in survival outcome in patients with advanced stage non-small cell lung cancer: results of a meta-analysis of randomized controlled trials. *J Thorac Oncol* (2011) 6:1030–8. doi:10.1097/JTO.0b013e3182199c03
39. Krawczyk P, Kowalski DM, Ramlau R, Kalinka-Warzocha E, Winiarczyk K, Stencel K, et al. Comparison of the effectiveness of erlotinib, gefitinib, and afatinib for treatment of non-small cell lung cancer in patients with common and rare EGFR gene mutations. *Oncol Lett* (2017) 13:4433–44. doi:10.3892/ol.2017.5980
40. Lim SH, Lee JY, Sun JM, Ahn JS, Park K, Ahn MJ. Comparison of clinical outcomes following gefitinib and erlotinib treatment in non-small-cell lung cancer patients harboring an epidermal growth factor receptor mutation in either exon 19 or 21. *J Thorac Oncol* (2014) 9:506–11. doi:10.1097/JTO.0000000000000095
41. Oxnard GR, Arcila ME, Sima CS, Riely GJ, Chmielecki J, Kris MG, et al. 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* (2011) 17:1616–22. doi:10.1158/1078-0432.CCR-10-2692
42. Oxnard GR, Janjigian YY, Arcila ME, Sima CS, Kass SL, Riely GJ, et al. Maintained sensitivity to EGFR tyrosine kinase inhibitors in EGFR-mutant lung cancer recurring after adjuvant erlotinib or gefitinib. *Clin Cancer Res* (2011) 17:6322–8. doi:10.1158/1078-0432.CCR-11-1080
43. Oxnard GR, Thress KS, Alden RS, Lawrance R, Paweletz CP, Cantarini M, et al. 135O_PR: plasma genotyping for predicting benefit from osimertinib in patients (pts) with advanced NSCLC. *J Thorac Oncol* (2016) 11:S154. doi:10.1016/S1556-0864(16)30328-8
44. Ramalingam SS, Blackhall F, Krzakowski M, Barrios CH, Park K, Bover I, et al. Randomized phase II study of dacomitinib (PF-00299804), an irreversible pan-human epidermal growth factor receptor inhibitor, versus erlotinib in patients with advanced non-small-cell lung cancer. *J Clin Oncol* (2012) 30:3337–44. doi:10.1200/JCO.2011.40.9433
45. Marcoux N, Piotrowska Z, Farago AF, Hata AN, Mooradian MJ, Drapkin BJ, et al. 1531PDClinical outcomes for EGFR-mutant adenocarcinomas (AC) that transform to small cell lung cancer (SCLC). *Ann Oncol* (2017) 28:005–386. doi:10.1093/annonc/mdx386.005
46. Popat S, Wotherspoon A, Nutting CM, Gonzalez D, Nicholson AG, O'Brien M, et al. Transformation to "high grade" neuroendocrine carcinoma as an acquired drug resistance mechanism in EGFR-mutant lung adenocarcinoma. *Lung Cancer* (2013) 80:1–4. doi:10.1016/j.lungcan.2012.12.019
47. Suda K, Murakami I, Sakai K, Mizuuchi H, Shimizu S, Sato K, et al. Small cell lung cancer transformation and T790M mutation: complimentary roles in acquired resistance to kinase inhibitors in lung cancer. *Sci Rep* (2015) 5:14447. doi:10.1038/srep14447
48. Gray J, Okamoto I, Sriuranpong V, Vansteenkiste J, Imamura F, Lee JS, et al. OA 05.02 osimertinib vs SoC EGFR-TKI as first-line treatment in patients with EGFRm advanced NSCLC (FLAURA): plasma ctDNA analysis. *J Thorac Oncol* (2017) 12:S1754–5. doi:10.1016/j.jtho.2017.09.348
49. Oxnard GR, Paweletz CP, Sholl LM. Genomic analysis of plasma cell-free DNA in patients with cancer. *JAMA Oncol* (2017) 3:740–1. doi:10.1001/jamaoncol.2016.2835
50. Uchibori K, Inase N, Araki M, Kamada M, Sato S, Okuno Y, et al. Brigatinib combined with anti-EGFR antibody overcomes osimertinib resistance in EGFR-mutated non-small-cell lung cancer. *Nat Commun* (2017) 8:14768. doi:10.1038/ncomms14768
51. Oxnard GR, Paweletz CP, Kuang Y, Mach SL, O'Connell A, Messineo MM, et al. Noninvasive detection of response and resistance in EGFR-mutant lung cancer using quantitative next-generation genotyping of cell-free plasma DNA. *Clin Cancer Res* (2014) 20:1698–705. doi:10.1158/1078-0432.CCR-13-2482
52. Niederst MJ, Hu H, Mulvey HE, Lockerman EL, Garcia AR, Piotrowska Z, et al. The allelic context of the C797S mutation acquired upon treatment with third-generation EGFR inhibitors impacts sensitivity to subsequent treatment strategies. *Clin Cancer Res* (2015) 21:3924–33. doi:10.1158/1078-0432.CCR-15-0560
53. Wang Z, Yang JJ, Huang J, Ye JY, Zhang XC, Tu HY, et al. Lung adenocarcinoma harboring EGFR T790M and in trans C797S responds to combination therapy of first- and third-generation EGFR TKIs and shifts allelic configuration at resistance. *J Thorac Oncol* (2017) 12:1723–7. doi:10.1016/j.jtho.2017.06.017
54. Arulananda S, Do H, Musafer A, Mitchell P, Dobrovic A, John T. Combination osimertinib and gefitinib in C797S and T790M EGFR-mutated non-small cell lung cancer. *J Thorac Oncol* (2017) 12:1728–32. doi:10.1016/j.jtho.2017.08.006

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