Editorial

Central nervous system activity of first-line osimertinib in epidermal growth factor receptor-mutant advanced non-small cell lung cancer

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Although the majority of patients with epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI)-sensitizing mutations experience good initial response to first-generation (erlotinib, gefitinib) and second-generation (afatinib, dacomitinib) EGFR-TKIs, they invariably suffer disease progression either due to a pharmacodynamic resistance to the EGFR-TKI or a pharmacokinetic failure resulting in central nervous system (CNS) progression (1-3). Despite the efficacy and superiority of first- and second-generation EGFR-TKIs in the treatment of extracranial *EGFR*-mutant non-small cell lung cancer (NSCLC) compared to conventional chemotherapy, treating and preventing the development of CNS metastases is a challenge because of the limited ability of first-generation and second-generation EGFR-TKIs to cross the blood-brain barrier (BBB) as shown by preclinical and clinical studies leading to the emergence of the CNS as a sanctuary site for metastasis (4-7). Accordingly, the CNS is not an uncommon site of disease progression following initial response to targeted therapy with EGFR-TKIs (2,3). The high incidence of brain metastases (BMs) in patients with *EGFR*-mutated disease is not only reflective of the pharmacokinetic failure of EGFR-TKIs to penetrate the brain but also the increased likelihood of developing BMs with their long survival on EGFR-TKI therapy (8-10). In fact, up to two-fifths of *EGFR*-mutant NSCLC patients develop CNS metastases over the course of their treatment with EGFR-TKIs (11).

EGFR-TKIs are a substrate of BCRP1 and P-glycoproteins which are drug efflux transporters at the BBB thought to be responsible for the reduced brain penetration of erlotinib and gefitinib (12). Osimertinib, an oral third-generation EGFR-TKI, selectively and potently inhibits both EGFR-TKI-sensitizing and *T790M* (substitution of threonine with methionine at codon 790)-resistance mutations by irreversible covalent binding to the *C797* residue while sparing wild-type *EGFR* (13). Osimertinib has improved BBB penetration and its activity against BMs in patients with disease progression on first- and second-generation EGFR-TKIs has been demonstrated by recent clinical trials (14,15). Osimertinib is approved for second-line treatment of *EGFR*-mutant NSCLC following treatment failure with earlier generation EGFR-TKIs due to acquired *T790M* mutation (16) following the positive results of phase I/II AURA and phase II AURA2 studies, as well as the confirmatory phase III AURA3 study in which 419 patients were randomly assigned in a ratio of 2:1 to receive osimertinib 80 mg once daily or platinum (cisplatin or carboplatin)/pemetrexed chemotherapy up to six cycles with optional pemetrexed maintenance (17). Superior median progression-free survival (PFS) (10.1 *vs.* 4.4 months) and objective response rate (ORR) (71% *vs.* 31%) were observed with osimertinib treatment compared to chemotherapy. Osimertinib has been shown by preclinical studies to be highly distributed in the nonhuman primate brain, with higher cerebrospinal fluid (CSF)/brain-to-blood ratio in

mouse models than gefitinib, erlotinib or afatinib (4,18).

The Phase I BLOOM study reported antitumor activity of osimertinib in the brain and also demonstrated improved BBB penetration by osimertinib with CSF concentration supporting activity in patients with leptomeningeal metastases (LMs) (19). The AURA studies have demonstrated CNS activity of osimertinib in pre-specified subgroup analyses of patients with *EGFR* T790M-positive NSCLC who had progressed while on previous EGFR-TKI treatment (14,15). In a pooled analysis of two AURA phase II single-arm studies (AURA extension and AURA2), an intracranial ORR in 50 patients with one or more measurable CNS lesions on baseline brain scan was 54% (27 of 50), with a 12% complete response and a 92% disease control rate in the CNS (14). The pooled analysis of these two phase II AURA studies showed the median CNS duration of response (at 22% maturity) was not reached (range, 1–15 months); and 75% of patients were estimated to remain in response at 9 months. Median CNS PFS was not reached with a median CNS PFS follow-up of 11 months (14). In the phase III AURA3 study, the CNS ORR to osimertinib was 70% (21 of 30 patients with measurable CNS disease) (15). In patients with measurable and/or non-measurable CNS lesions, the median CNS duration of response was 8.9 months in patients treated with osimertinib and 5.7 months in those treated with platinum/pemetrexed. The median CNS PFS was 11.7 months with osimertinib and 5.6 months with platinum/pemetrexed [hazard ratio (HR), 0.32; 95% CI, 0.15 to 0.69; P=0.004] (15). CNS response in the patients analysed in these AURA studies was not affected by prior radiotherapy to the brain.

The FLAURA phase III, randomized, double-blind study compared osimertinib (80 mg once daily) head-to-head with standard of care (SOC) first-generation EGFR-TKIs (gefitinib 250 mg once daily or erlotinib 150 mg once daily) as first-line therapy in patients with advanced NSCLC harboring exon 19 deletion or exon 21 L858R *EGFR* mutations (20). The median PFS was nearly doubled with osimertinib compared to SOC EGFR-TKIs (18.9 *vs.* 10.2 months; HR, 0.46; 95% CI, 0.37 to 0.57; P<0.001) at a median follow-up of 15 months. The study allowed enrolment of patients with asymptomatic or neurologically stable CNS metastases after completion of definitive and corticosteroid treatment who accounted for 21% of the total study population of 556. Systemic responses and investigator-assessed CNS progression event frequency in the overall FLAURA study population with and without known or treated CNS metastases at study entry have already been reported (20). Briefly, osimertinib treatment benefitted patients with baseline CNS metastases and those without baseline CNS metastases to a similar degree in terms of PFS (HR =0.47 and HR =0.46, respectively). Treatment with osimertinib significantly reduced the incidence of events signifying CNS progression [6% (17 of 279)] compared to SOC EGFR-TKIs [15% (42 of 277)] regardless of the presence or absence of known or treated CNS metastases at study enrolment. The protective effect of osimertinib against CNS metastasis is suggested by the reduced frequency of CNS progression in patients without known or treated CNS metastases at study entry treated with osimertinib compared to patients treated with SOC EGFR-TKIs [3% (7 of 226) versus 7% (15 of 214)]. Preliminary overall survival (OS) data showed a strong trend toward improved OS favoring osimertinib with the risk of death reduced by 37% (HR 0.63; 95% CI, 0.45 to 0.88; P=0.007) which did not reach statistical significance because the maturity of the survival data was only 25% at the time of interim OS analysis (20). Despite crossover, the percentage of patients who were alive at 12 months and at 18 months was higher in the osimertinib arm than in the SOC EGFR-TKI arm (89% *vs.* 82% and 83% *vs.* 71%, respectively) (20). With the significantly improved PFS, ORR and CNS efficacy, and more tolerable toxicity profile compared to erlotinib or gefitinib according to the FLAURA study findings, osimertinib has also received approval for the first-line treatment of *EGFR*-mutant NSCLC (18).

With the results of the FLAURA study we are faced with the dilemma of whether osimertinib should be used upfront for all patients with deletion 19 or L858R *EGFR*-mutant NSCLC or should it only be introduced as second-line treatment for those with disease progression due to acquired *T790M* mutation. Median PFS with first-line osimertinib in the FLAURA study is 18.9 months (21) while median PFS with second-line osimertinib in patients who had failed prior EGFR-TKI treatment due to acquired *T790M* resistance mutation is 10.1 months according to the AURA3 study (19). Although osimertinib has demonstrated superiority over first-generation EGFR-TKIs from the perspectives of PFS and side-effect profile, OS data from the FLAURA study are currently not mature. Final OS data from the AURA3 study which are pending may also provide guidance on the optimal treatment sequence to achieve the longest OS in patients with *EGFR*-mutant NSCLC.

In an article entitled "*CNS response to osimertinib versus SOC epidermal growth factor receptor tyrosine kinase inhibitors*

in patients with untreated EGFR-mutated advanced Non-Small Cell lung cancer" published in the *Journal of Clinical Oncology* in August 2018 (22), Reungwetwattana and colleagues reported the results of a preplanned, exploratory analysis of the CNS efficacy of osimertinib compared to SOC EGFR-TKIs in a subset of treatment naïve *EGFR*-mutated advanced NSCLC patients from the FLAURA trial with CNS metastases on baseline brain imaging [magnetic resonance imaging (MRI) and/or computed tomography (CT)]. Of note, brain imaging by MRI and/or CT in the FLAURA trial was mandatory only in patients with known or suspected to have CNS metastases, or performed according to local practice in those without known or suspected CNS metastases.

The primary endpoint of PFS and the secondary endpoint of OS in the overall FLAURA population and CNS PFS endpoint in the patients with measurable and/or non-measurable CNS lesions were tested in sequence (22). Testing for statistical significance of CNS PFS was only performed if there was statistical significance of OS analysis at the time of PFS analysis (i.e., interim OS analysis) or at final OS analysis. If the OS analysis did not reach statistical significance at the interim analysis, the P value for the statistical significance testing of CNS PFS would be considered nominally significant.

Of 556 patients randomly assigned to study treatment in the FLAURA study, 200 patients had baseline brain scans—128 of whom had measurable and/or non-measurable CNS lesions and were included in the CNS full-analysis set of patients (cFAS) (osimertinib, n=61; SOC first-generation EGFR-TKIs, n=67). Of these 128 patients, 41 had at least one measurable CNS lesion and were evaluable for CNS response (cEFR) (osimertinib, n=22; SOC EGFR-TKIs, n=19). Fifteen patients (25%) in the osimertinib arm and 16 patients (24%) in the SOC EGFR-TKI arm had received cranial irradiation in the last 6 months prior to study entry.

Median CNS PFS in patients with measurable and/or non-measurable CNS metastases at study entry (cFAS) was not reached with osimertinib and 13.9 months with SOC first-generation EGFR-TKIs. The difference was of nominal statistical significance (HR, 0.48; 95% CI, 0.26 to 0.86; P=0.014) (22). In other words, first-line osimertinib in *EGFR*-mutant NSCLC patients with CNS metastases reduced the risk of CNS progression by 52% compared to SOC EGFR-TKIs. These results were in keeping with the PFS analysis of the overall FLAURA population (20). CNS progression occurred in 12 (20%) of 61 patients in the osimertinib arm compared to 26 (39%) of 67 patients in the SOC EGFR-TKI arm. Progression in the CNS due to new lesions was less frequent with osimertinib [12% (7 of 61) compared to SOC EGFR-TKIs [30% (20 of 67)]. In the absence of a non-CNS progression or death from any cause, the probability of CNS progression was lower with osimertinib both at 6 months (estimated to be 5% *vs.* 18% with SOC EGFR-TKIs) and at 12 months (estimated to be 8% *vs.* 24% with SOC EGFR-TKIs) (22). However, a limitation of this analysis is that brain imaging by MRI and/or CT before starting first-line therapy was only compulsory in patients with known or suspected CNS metastases, or as part of local practice in those who did not have known or suspected CNS metastases. Some patients with asymptomatic CNS metastases could have been missed.

In patients with at least one measurable CNS lesion, the CNS ORR was 91% [20 of 22 patients with 5 (23%) experiencing complete response] when treated with osimertinib and 68% (13 of 19 patients with none having complete response) when treated with SOC first-generation EGFR-TKIs (P=0.066). In patients with measurable and/or non-measurable CNS lesions, the CNS ORR was and 66% when treated with osimertinib and 43% when treated with SOC first-generation EGFR-TKIs (P=0.011) (22). The CNS DCR in in patients with at least one measurable CNS lesion was 95% with osimertinib compared to 89% with SOC EGFR-TKIs (P=0.462). Of five patients in the osimertinib arm with radiologic evidence suggestive of LMs at baseline, four had a complete radiographic response while of two patients in the SOC arm with suspected LMs, one patient had stable disease and the other did not have CNS follow-up.

In conclusion, data from this analysis (22) show that osimertinib has better CNS efficacy and suggest a greater reduction in the risk of CNS progression with osimertinib compared with first-generation EGFR-TKIs in treatment naive *EGFR*-mutant advanced NSCLC patients.

The National Comprehensive Cancer Network (NCCN) guidelines recommend osimertinib for the treatment of *EGFR*-mutant NSCLC patients with CNS metastases, including LMs (16). The activity of osimertinib patients with LMs was commendable although the number of patients with suspected LMs in the analysis by Reungwetwattana *et al.* was small (22). In the phase I BLOOM study, 21 patients with *EGFR*-mutant advanced NSCLC who had disease progression on previous EGFR-TKI treatment and had CSF cytology proven LM were

treated with osimertinib at 160 mg a day (19). Five patients had neurologic improvement. MRI showed radiologic improvement in seven patients (33%) and stable disease in nine patients (43%).

Compared to extracranial progression, CNS progression has a considerable impact on the patient's quality of life (23). As a CNS active EGFR-TKI, osimertinib offers clinical benefit both in preventing or delaying the onset of CNS metastases, and in leading to intracranial response of preexisting CNS lesions. This is one of the arguments in favor of starting osimertinib upfront rather than initiating treatment with first- or second-generation EGFR-TKIs.

A retrospective multicenter study of 351 patients with *EGFR*-mutant NSCLC and BM compared treatment with stereotactic radiosurgery (SRS) followed by erlotinib, whole brain radiotherapy (WBRT) followed by erlotinib, or erlotinib followed by radiotherapy (SRS or WBRT) upon intracranial progression (21). Patients treated by upfront SRS had longer OS (46 months) than those treated by upfront WBRT followed by erlotinib (30 months), or upfront erlotinib (25 months). Patients treated with SRS upfront were more likely to have BMs larger than 1 cm and were more likely to be symptomatic from their BMs compared to those treated with erlotinib upfront.

As a CNS-active TKI with compelling data on CNS disease prevention, CNS response and durability of CNS disease control, osimertinib is the EGFR-TKI of choice in patients with newly diagnosed NSCLC harboring *EGFR* exon 19 deletion or L858R point mutations, with or without BM. Until we have data from prospective studies comparing optimal, CNS-active EGFR-TKI therapy versus radiotherapy, the data from the retrospective analysis on upfront SRS followed by EGFR-TKI (although the EGFR-TKI used in that analysis was erlotinib which is less CNS-active compared to osimertinib) (21) need to be considered when individualizing treatment options for *EGFR*-mutant NSCLC patients with CNS metastases. BMs that are large, symptomatic or immediately life-threatening need local treatment with radiotherapy or surgical resection followed by a CNS-active EGFR TKI such as osimertinib. Patients with oligometastatic CNS metastases which are symptomatic may benefit from upfront SRS. Patients with solitary or multiple, small, asymptomatic BM may be treated with upfront osimertinib and the need for radiation therapy be omitted or deferred until CNS imaging or symptom progression (24). WBRT is an option reserved for BM refractory to SRS and EGFR-TKI therapy, thus delaying the neurocognitive side effects of WBRT in view of the extended survival of these EGFR-TKI-treated patients (25).

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Footnote

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References

1. Cortot AB, Jänne PA. Molecular mechanisms of resistance in epidermal growth factor receptor-mutant lung adenocarcinomas. Eur Respir Rev 2014;23:356-66.
2. Park SJ, Kim HT, Lee DH, et al. Efficacy of epidermal growth factor receptor tyrosine kinase inhibitors for brain metastasis in non-small cell lung cancer patients harboring either exon 19 or 21 mutation. Lung Cancer 2012;77:556-60.
3. Lee YJ, Choi HJ, Kim SK, et al. Frequent central nervous system failure after clinical benefit with epidermal growth factor receptor tyrosine kinase inhibitors in Korean patients with non-small-cell lung cancer. Cancer 2010;116:1336-43.
4. Ballard P, Yates JW, Yang Z, 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;22:5130-40.
5. Togashi Y, Masago K, Masuda S, et al. Cerebrospinal fluid concentration of gefitinib and erlotinib in patients with non-small cell lung cancer. Cancer Chemother Pharmacol 2012;70:399-405.
6. Hoffknecht P, Tufman A, Wehler T, 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 2015;10:156-63.
7. Batra U, Lokeshwar N, Gupta S, et al. Role of epidermal growth factor receptor tyrosine kinase inhibitors in the management of central nervous system metastases in epidermal growth factor receptor mutation positive

non-small cell lung cancer patients. Indian J Cancer 2017;54:S37-44.
8. Shin DY, Na II, Kim CH, et al. EGFR mutation and brain metastasis in pulmonary adenocarcinomas. J Thorac Oncol 2014;9:195-9.
9. Ge M, Zhuang Y, Zhou X, et al. High probability and frequency of EGFR mutations in in non-small cell lung cancer with brain metastases. J Neurooncol 2017;135:413-8.
10. Heon S, Yeap BY, Britt GJ, et al. Development of central nervous system metastases in patients with advanced non-small cell lung cancer and somatic EGFR mutations treated with gefitinib or erlotinib. Clin Cancer Res 2010;16:5873-82.
11. Rangachari D, Yamaguchi N, VanderLaan PA, et al. Brain metastases in patients with EGFR-mutated or ALK-rearranged Non-Small Cell lung cancers. Lung Cancer 2015;88:108-11.
12. de Vries NA, Buckle T, Zhao J, et al. Restricted brain penetration of the tyrosine kinase inhibitor erlotinib due to the drug transporters P-gp and BCRP. Invest New Drugs 2012;30:443-9.
13. Cross DA, Ashton SE, Ghiorghiu S, et al. AZD9291, an irreversible EGFR-TKI, overcomes T790M-mediated resistance to EGFR inhibitors in lung cancer. Cancer Discov 2014;4:1046-61.
14. Goss G, Tsai CM, Shepherd FA, et al. CNS response to osimertinib in patients with T790M-positive advanced NSCLC: Pooled data from two phase II trials. Ann Oncol 2018;29:687-93.
15. Wu YL, Ahn MJ, Garassino MC, et al. CNS efficacy of osimertinib in patients with T790M-positive advanced Non-Small Cell lung cancer: Data from a randomized phase III trial (AURA3). J Clin Oncol 2018;36:2702-9.
16. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology, Non-Small Cell Lung Cancer (version 2.2019). Available online: https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf
17. Mok TS, Wu YL, Ahn MJ, et al. Osimertinib or platinum-pemetrexed in EGFR T790M-positive lung cancer. N Engl J Med 2017;376:629-40.
18. Colclough N, Ballard PG, Barton P, et al. 64 - Preclinical comparison of the blood brain barrier (BBB) permeability of osimertinib (AZD9291) with other irreversible next generation EGFR-TKIs. Eur J Cancer 2016;69:S28.
19. Yang JC, Cho BC, Kim DW, 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. J Clin Oncol 2017;35:2020.
20. Soria JC, Ohe Y, Vansteenkiste J, et al. Osimertinib in untreated EGFR-mutated advanced non-small-cell lung cancer. N Engl J Med 2018;378:113-25.
21. Magnuson WJ, Lester-Coll NH, Wu AJ, et al. Management of brain metastaseses in tyrosine Kinase inhibitor-naïve epidermal growth factor receptor-mutant Non-Small Cell lung cancer: a retrospective multi-institutional analysis. J Clin Oncol 2017;35:1070-7.
22. Reungwetwattana T, Nakagawa K, Cho BC, et al. CNS response to osimertinib versus SOC epidermal growth factor receptor tyrosine kinase inhibitors in patients with untreated EGFR-mutated advanced Non-Small Cell lung cancer. J Clin Oncol 2018. [Epub ahead of print].
23. Peters S, Bexelius C, Munk V, et al. The impact of brain metastasis on quality of life, resource utilization and survival in patientswith Non-Small Cell lung cancer. Cancer Treat Rev 2016;45:139-62.
24. Bansal P, Rusthoven C, Boumber Y, et al. The role of local ablative therapy in oligometastatic Non-Small Cell lung cancer: hype or hope. Future Oncol 2016;12:2713-27.
25. Monaco EA III, Faraji AH, Berkowitz O, et al. Leukoencephalopathy after whole-brain radiation therapy plus radiosurgery versus radiosurgery alone for metastatic lung cancer. Cancer 2013;119:226-32.

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