ORIGINAL ARTICLE

A Phase II Study of Osimertinib for Radiotherapy-Naive Central Nervous System Metastasis From NSCLC: Results for the T790M Cohort of the OCEAN Study (LOGIK1603/WJOG9116L)

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ABSTRACT

Objectives: Osimertinib has been reported to be effective against central nervous system (CNS) metastasis from activating *EGFR* mutation-positive NSCLC. Nevertheless, the true antitumor effects of osimertinib alone for CNS metastasis are unclear because the aforementioned studies included previously irradiated cases, in which tumor shrinkage can occur later owing to the effects of radiotherapy (RT). This study aimed to evaluate the efficacy of osimertinib against RT-naive CNS metastasis from sensitizing *EGFR* mutation-positive NSCLC.

Methods: The OCEAN study was a two-cohort trial, involving 66 patients (T790M cohort [n = 40] and first-line cohort [n = 26]) with RT-naive CNS metastasis from sensitizing *EGFR* mutation-positive NSCLC. The patients were treated once daily with 80 mg osimertinib. The primary end point was brain metastasis response rate (BMRR) according to the PAREXEL criteria. In this report, we present the results for the T790M cohort with analysis of drug concentrations and plasma circulating tumor DNA.

Results: The median age of the patients was 69 years, and 30% of them were males. Eight patients (20%) were symptomatic, and most had multiple CNS metastases (78%). Among the eligible 39 patients, the BMRR (PAREXEL criteria), median brain metastasis-related progression-free survival (PFS), median overall survival, overall response rate, and median PFS were 66.7% (90% confidence interval: 54.3%–79.1%), 25.2 months, 19.8 months, 40.5%, and 7.1 months, respectively. The BMRR according to the Response Evaluation Criteria in Solid Tumors criteria was 70.0% (n = 20). The brain metastasis-related PFS of patients with *EGFR* exon 19 deletion was significantly longer than that of exon 21 L858R (median = 31.8 versus 8.3 mo; log-rank p = 0.032). The treatment-related pneumonitis was observed in four patients (10%). On or after day 22, the median trough blood and cerebrospinal fluid concentrations of osimertinib were 568 nM and 4.10 nM, respectively, and those of its metabolite AZ5104 were 68.0 nM and 0.260 nM, respectively. The median blood to cerebrospinal fluid penetration rates of osimertinib and AZ5104 were 0.79% and 0.53%, respectively. The blood trough concentration at day 22 was not correlated with the efficacy of osimertinib against CNS metastasis. Plasma T790M and C797S mutations were detected in 83% and 3% of the patients before treatment, 11% and 3% of the patients on day 22, and 39% and 22% of the patients at the detection of progressive disease, respectively.

Conclusions: This study evaluated the efficacy of osimertinib against RT-naive CNS metastasis from T790M-positive NSCLC. The primary end point was met, and

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the results revealed the efficacy of osimertinib in patients with CNS metastasis harboring *EGFR* T790M mutations especially for *EGFR*-sensitizing mutation of exon 19 deletion.

Keywords: Osimertinib; Radiation-naive; CNS metastasis; T790M; NSCLC

Introduction

Patients with NSCLC whose tumors harbor activating *EGFR* mutations exhibit a higher incidence of central nervous system (CNS) metastasis than those whose tumors are free from such mutations.[1–3] Although radiotherapy (RT), such as whole-brain RT (WBRT) and stereotactic RT (SRT), is the standard treatment for CNS metastasis, it can delay the start of systemic chemotherapy, and WBRT carries a risk of cognitive dysfunction.[4,5]

Osimertinib is an irreversible EGFR tyrosine kinase inhibitor (TKI), which selectively inhibits both the T790M mutation, which is a major cause of acquired resistance to EGFR TKIs, and EGFR TKI-sensitizing mutations.[6] In patients with NSCLC harboring the *EGFR* T790M mutation who were treated with EGFR TKIs, osimertinib resulted in significantly longer progression-free survival (PFS) than platinum plus pemetrexed (AURA3 trial; median PFS = 10.1 mo versus 4.4 mo, $p < 0.001$).[7] In previously untreated patients with NSCLC harboring EGFR TKI-sensitizing mutations, osimertinib achieved significantly longer PFS than gefitinib or erlotinib (FLAURA trial; median PFS = 18.9 mo versus 10.2 mo, $p < 0.001$).[8]

Osimertinib is also expected to be effective in patients with CNS metastasis because it displayed greater penetration into the brain than rociletinib, gefitinib, or afatinib in a preclinical model.[9] In a study in which pooled data from two phase 2 trials of osimertinib as a treatment for *EGFR* T790M mutation-positive NSCLC (AURA extension and AURA2) were analyzed, the frequency of confirmed CNS responses to osimertinib was found to be 54% in 50 patients with measurable CNS metastasis, including 19 patients with brain metastasis who had already been treated with RT within the past 6 months.[10] Nevertheless, in a subgroup analysis of the AURA3 trial, the CNS response rate of osimertinib among patients who had been treated with RT within the 6 months before randomization was 70%.[11] In these two subgroup analyses, the true antitumor effects of osimertinib alone were unclear because the studies included previously irradiated cases, in which tumor shrinkage can occur later owing to the effects of RT. A previous multi-institutional retrospective analysis found that patients with brain metastasis who underwent stereotactic radiosurgery (SRS) before EGFR TKI therapy exhibited better overall survival (OS) than their counterparts who received EGFR TKIs before SRS.[12] Nevertheless, these patients were mainly treated with the first-generation EGFR TKI erlotinib between 2008 and 2014, and hence, the efficacy of osimertinib against CNS metastasis in patients who have not received RT remains unclear.

Therefore, we conducted a trial evaluating the efficacy of osimertinib against RT-naive CNS metastasis in patients with sensitizing *EGFR* mutation-positive NSCLC.[13] The OCEAN study has already registered T790M and first-line cohorts. In this article, we evaluate the efficacy of osimertinib for treating CNS metastasis in patients with T790M *EGFR* mutation-positive NSCLC (the T790M cohort) who had previously been treated with EGFR TKIs. The first-line cohort is still immature with registration completed in July 2020. In addition, we evaluated the blood and cerebrospinal fluid (CSF) concentrations of osimertinib.

Materials and Methods

The study protocol was reviewed and approved by the protocol committee of the Lung Oncology Group in Kyushu and the West Japan Oncology Group; it was also approved by the central review board of the Clinical Research Network Fukuoka. Written informed consent was obtained from all study participants. This study was funded by AstraZeneca. The funder provided the necessary financial resources to cover the personal costs needed to allow the OCEAN study to proceed. This study is registered at the University Hospital Medical Information Network in Japan and the Japan Registry of Clinical Trials under registration numbers UMIN000024218 and jRCTs071180017, respectively. The OCEAN study was a two-cohort trial, involving 66 patients (T790M cohort: 40, first-line cohort: 26) with RT-naive CNS metastasis from sensitizing EGFR mutation-positive NSCLC. In this article, the results for the T790M cohort are presented.

Study Design and Patients

The OCEAN study was a multicenter, single-arm, phase 2 study. The overall objective was to evaluate the efficacy of osimertinib against untreated CNS metastasis. The eligibility criteria for the study were as follows: a histologically or cytologically confirmed diagnosis of NSCLC; confirmed *EGFR* mutations (exon 19 deletion [19-del] or an exon 21 L858R point mutation [21-L858R]); radiological disease progression, including CNS and non-CNS progression occurring after treatment with a first- or second-generation EGFR TKI (the CNS

lesions include any of the following: [1] newly diagnosed, [2] previously known and responded to previous lines of therapy and now had CNS progression, [3] previously known that were stable on previous therapy); detection of the *EGFR* T790M mutation in a tumor or plasma sample after disease progression was confirmed after previous treatment; possessing a metastatic brain lesion with a long axis of greater than or equal to 5 mm irrespective of the extracranial metastases with magnetic resonance imaging (MRI) less than or equal to 3 mm slice; not having received previous RT for the brain metastasis; being aged at least 20 years at the time informed consent was provided; having an Eastern Cooperative Oncology Group performance status of 0 to 2, adequate bone marrow function (a neutrophil count of $\geq$1500/μL, a hemoglobin level of $\geq$8.0 g/dL, and a platelet count of $\geq 10.0 \times 10^4/\mu$L), alanine aminotransferase and aspartate transaminase (AST) levels of less than or equal to 100 IU/liter, a serum bilirubin level of less than or equal to 1.5 mg/dL, a serum creatinine level of less than or equal to 1.5 mg/dL, a saturation of peripheral oxygen value of greater than or equal to 90%, a mean corrected QT interval (QTc) of less than or equal to 471 msec, and a life expectancy from the date of the start of the osimertinib treatment of more than 12 weeks; and providing written informed consent. The exclusion criteria were as follows: symptomatic brain metastases that required RT or surgical resection by physician; severe complications, such as a myocardial infarction within the past 3 months, uncontrollable angina pectoris, or heart failure; presence of active double cancer; having previously been treated with anti–programmed cell death protein-1, anti-programmed cell death ligand-1, anti-CD137, or CTLA-4 antibodies; being pregnant or possibly being pregnant; lactating; interstitial lung disease, drug-induced interstitial lung disease, or radiation pneumonitis that required treatment; symptomatic emergent superior vena cava syndrome; psychiatric disorders that would preclude participation in the study; and a history of hypersensitivity to osimertinib.

The patients orally received osimertinib at a dose of 80 mg once daily until progression, death, or when they withdrew their consent to participate in the study. Treatment was postponed if the following occurs: greater than or equal to grade 4 hematological toxicities; greater than or equal to grade 3 increases in the blood levels of bilirubin, AST, or alanine aminotransferase; greater than or equal to grade 3 nonhematologic toxicities, including skin toxicities, mucositis, and diarrhea; or a prolonged QTc interval of greater than or equal to 500 msec. Treatment was discontinued if interstitial lung disease or pneumonitis occurred.

Assessment

Before the patients were registered in this trial, contrast-enhanced computed tomography of the chest and abdomen and contrast-enhanced MRI of the brain with a slice thickness of less than 3 mm were performed. Computed tomography and MRI were performed every 6 weeks in the first year after the date of registration and every 3 months thereafter. The primary end points of the OCEAN study at the start of study enrollment were brain metastasis response rate (BMRR) according to the PAREXEL criteria,[14] in which the target brain metastasis had a long axis of more than or equal to 5 mm. A maximum of five brain lesions were chosen, and the sum of their diameters was calculated. Nontarget lesions included all measurable lesions that were not chosen as target lesions and lesions with a long axis of less than 5 mm. The secondary end points were PFS, the overall response rate (ORR), the BMRR according to the Response Evaluation Criteria in Solid Tumors (RECIST) criteria, brain metastasis-related PFS, and OS. Systemic PFS was based on RECIST criteria and defined as the time from the date of registration to that of death or disease progression, whichever occurred first. Brain metastasis-related PFS was based on PAREXEL criteria and defined as the time from the date of registration to that of death or brain metastasis progression, whichever occurred first. Extracranial disease progression is managed as censoring case for brain metastasis-related PFS. OS was defined as the time from the date of registration to that of death.

To investigate the relationship between the blood concentration of osimertinib and the treatment effect, we evaluated the blood concentration of osimertinib on day 22, which was considered to represent the steady state.[15] We also determined the blood and CSF concentrations of osimertinib and its metabolite AZ5104 to analyze its penetration into the CSF on or after day 22. Blood specimens were collected once at 22 days after the administration of osimertinib. CSF was collected on a voluntary basis. The blood and CSF concentrations were evaluated using HB-13-050 and HB-13-081 (high-performance liquid chromatography-mass spectroscopy and mass spectroscopy). To determine whether the EGFR C797S mutation was present before progression, we also evaluated tumor-derived circulating tumor DNA (ctDNA) by the BEAMing assay from plasma samples for EGFR mutations, including the T790M and C797S point mutations. Plasma samples for the *EGFR* mutation analysis were collected three times, as follows: before treatment, 22 days after the administration of osimertinib, and on the date of the diagnosis of progressive disease (PD). All adverse events were recorded and graded according to the Common Terminology Criteria for Adverse Events, version 4.0.

Statistical Analysis

The primary end point of this study was the BMRR according to the PAREXEL criteria in the full analysis set. To estimate the BMRR, we referred to the results of the AURA trial, in which the ORR was 61% (95% confidence interval [CI]: 52%–70%).[16] Therefore, we decided that osimertinib would be considered effective if it exhibited similar efficacy to that found in the AURA trial. On the basis of the lower limit of the 95% CI of the ORR in the AURA trial, we set a BMRR threshold value of 50%. We also set an expected value of 70% based on the upper limit of the 95% CI of the ORR in the AURA trial. On the basis of a one-sided α value of 0.05 and a power value of 0.9, the required sample size for the OCEAN study was initially calculated to be 60, considering the possibility of patient withdrawal. Nevertheless, we amended our statistical hypothesis from a power of 0.9 to a power of 0.8 because of the slow accrual rate and the fact that osimertinib had started to be used in first-line treatment. Thus, the required sample size was changed to 37 (40, considering the possibility of dropouts). We use 90% CI for the primary end point.

Results

A total of 40 patients from 23 institutions were enrolled in this trial between December 27, 2016, and July 4, 2019. The data cutoff date was July 10, 2020. A consort diagram is illustrated in Figure 1. One patient was later found to be ineligible because of previously receiving RT for brain disease and was only included in the safety analysis. The remaining 39 subjects were included in the evaluation of treatment efficacy, including the treatment response and survival. In the response analyses based on the RECIST criteria 1.1, 2 and 19 patients were excluded because they had systemic and brain metastases, respectively, which measured less than 1 cm, and the remaining 37 and 20 patients, respectively, were included. The baseline characteristics of the 40 patients are found in Table 1. Patients between the ages of 41 and 84 years were enrolled, and their median age was 69 years. All patients had adenocarcinoma. The sizes of the baseline CNS target lesions ranged from 5 to 27 mm, and the median lesion size was 8.4 mm. Regarding previous treatments, all patients had been treated with EGFR TKIs once or more (gefitinib: 25, erlotinib: 17, afatinib: eight), and 15 patients had also been treated with cytotoxic agents or bevacizumab. Regarding the number of lines of previous treatment, 25 patients (63%) had one previous line, eight (20%) had two previous lines, four (10%) had three previous lines, two (5%) had four previous lines, and one (3%) had five previous lines.

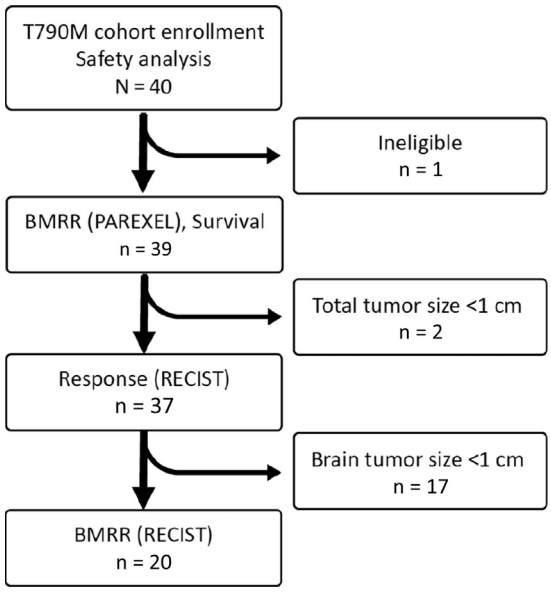

Figure 1. CONSORT diagram. One patient was excluded from the efficacy analysis for previously receiving radiotherapy. BMRR, brain metastasis response rate; RECIST, Response Evaluation Criteria in Solid Tumors.

Table 1. Patients' Baseline Characteristics (N = 40)

Characteristic	No.	%
Age, years		
Median	69	
Range	41–84	
Sex		
Male	12	30
Female	28	70
ECOG performance status		
0–1	36	90
2	4	10
c-Stage		
IV	29	73
Postoperative	11	28
Histological type		
Adenocarcinoma	40	100
Smoking history		
current or former	13	33
Never	27	68
EGFR mutation type		
exon 19 del	25	63
L858R	15	38
CNS lesion		
Single	10	25
Multiple	30	75
Symptomatic CNS metastasis		
Present	8	20
Absent	32	80
Baseline CNS target lesion size (mm)		
Median	8.4	
Range	5–27	

CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group.

Treatment Administration

The trial treatments were completed in 36 patients and were still ongoing in four patients. The median duration of treatment was 179 (range: 4 to >1185) days. Dose reduction to 40 mg osimertinib was used in three cases (8%) for a median period of 46 (range: 5–78) days. The reasons for dose reduction were QTc interval prolongation to more than 500 msec, itching, and the decision of the attending physician. The durations of treatment with 80 and 40 mg osimertinib are found in Figure 2. Treatment was discontinued in 36 patients and continued in four patients. The reasons for treatment discontinuation were tumor progression (n = 26, 67%), adverse events (n = 6, 15%), death (n = 1, 3%), and other considerations of the attending physician (n = 2, 5%).

Efficacy

Brain Metastasis. The BMRR of the 39 patients according to the PAREXEL criteria and that of 20 patients according to the RECIST criteria are found in Figure 3*A*. According to the PAREXEL criteria, the BMRR (90% CI) was 66.7% (54.3%–79.1%), and the best overall responses were as follows: complete response (CR) equal to four, partial response (PR) equal to 22, stable disease equal to eight, PD equal to three, and not evaluable (NE) equal to two. According to the RECIST criteria, the BMRR (95% CI) was 70.0% (49.9%–90.1%), and the best overall responses were as follows: CR equal to one, PR equal to 13, stable disease equal to two, PD equal to two, and NE equal to three. The brain metastasis-related PFS of 39 patients is found in Figure 3*B*. The median brain metastasis-related PFS times (95% CI) and 1-year and 2-year survival rates were 25.2 (7.0–34.5) months, 61.9%, and 52.0%, respectively. The BMRRs of the patients with 19-del and 21-L858R according to the PAREXEL criteria were 66.7% (n = 24; three CR, 13 PR, six stable disease, one PD, one NE) and 66.7% (n = 15; one CR, nine PR, two stable disease, two PD, one NE) and those according to the RECIST criteria were 71.4% (n = 14; one CR, nine PR, two stable disease, two NE) and 66.7% (n = 6; four PR, one PD, one NE), respectively. The brain metastasis-related PFS of 39 patients according to the PAREXEL criteria separated by 19-del and 21-L858R is found in Figure 3*C*. The median brain metastasis-related PFS of 19-del and 21-L858R was 31.8 and 8.3 months, respectively, and brain metastasis-related PFS of 19-del was significantly longer than that of 21-L858R (log-rank $p = 0.032$).

Systemic

The results regarding systemic efficacy are found in Figure 4. Two of the 39 patients in whom efficacy was evaluated were excluded because of a total tumor size of less than 1 cm, and the responses of the remaining 37 patients were evaluated using the RECIST criteria. Among these 37 patients, the overall tumor response rate (95% CI) was 40.5% (24.7%–57.9%), and the best overall responses were as follows: CR equal to zero, PR equal to 15, stable disease equal to 12, PD equal to nine, and NE equal to one. The PFS of the 39 patients is found in Figure 4*A*. The median PFS time (95% CI) and 1-year and 2-year survival rates were 7.1 (3.4–13.6) months, 40.4%, and 22.0%, respectively. The OS of the 39 patients is found in Figure 4*B*. The median OS

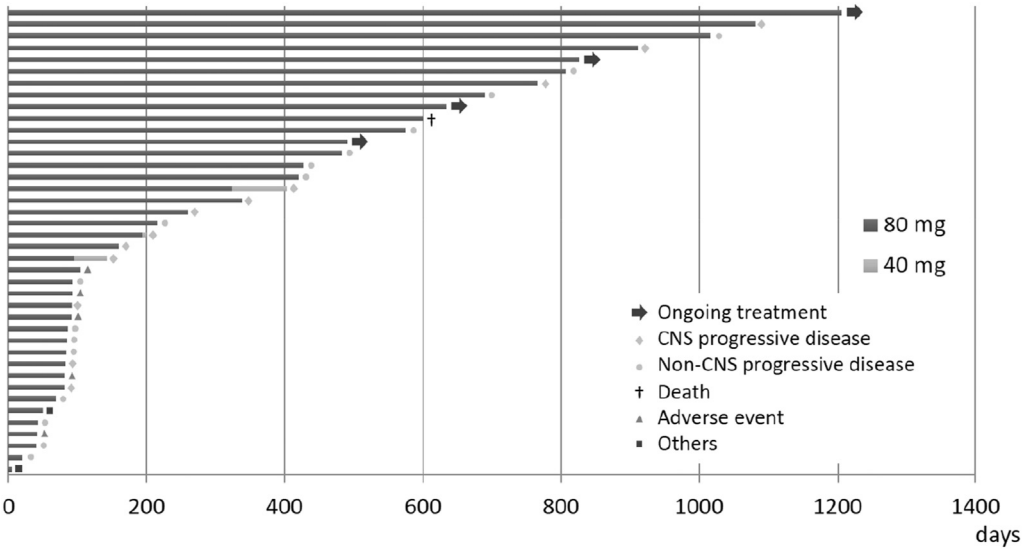

Figure 2. A swimmer plot of osimertinib treatment (N = 40). Dose reduction to 40 mg occurred in three patients. The dark and light gray lines represent the initial dose (80 mg) and reduced dose (40 mg), respectively. CNS, central nervous system.

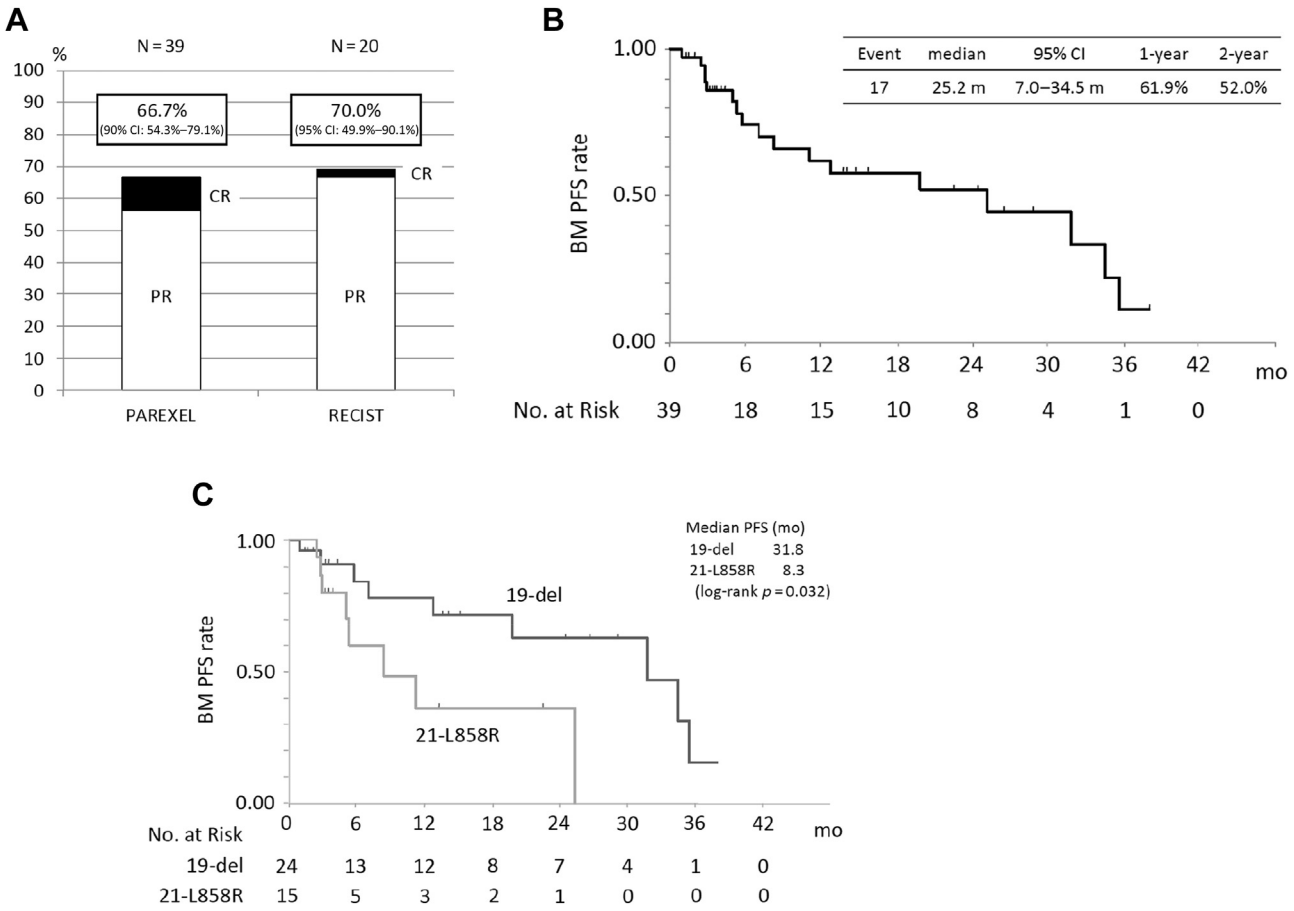

Figure 3. BM results (n = 39). (*A*) BMRR, (*B*) PFS curve, and (*C*) PFS separated by EGFR mutations. 19-del, exon 19-deletion; 21-L858R, exon 21 L858R point mutation; BM, brain metastasis; BMRR, brain metastasis response rate; CI, confidence interval; CR, complete response; PFS, progression-free survival; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors.

time (95% CI) and 1-year and 2-year survival rates were 19.8 (10.9–34.5) months, 64.1%, and 42.0%, respectively.

Adverse Events

The toxicities experienced by the patients, including the grade 3 or 4 hematologic and nonhematologic toxicities, are listed in Table 2. Grade 3 or 4 leukopenia and neutropenia were observed in four patients (10%). Anemia of any grade, leukopenia, neutropenia, an acneiform rash, and increased AST levels were observed in more than or equal to 30% of patients. Grade 2 and 3 pneumonitis was observed in three patients (8%) and one patient (3%), respectively. There were no treatment-related deaths.

Drug Concentrations

Of the 39 patients in which efficacy was evaluated, blood drug concentrations were analyzed in 37 patients and CSF drug concentrations were analyzed in seven patients. The day 22 trough concentrations of osimertinib and its metabolite AZ5104 are found in Figure 5*A*. The median blood and CSF concentrations of osimertinib and AZ5104 were 568 (range: 276–1270) nM and 4.10 (range: 2.45–8.38) nM for osimertinib and 68.0 (range: 24.9–210) nM and 0.260 (range: 0.194–0.380) nM for AZ5104, respectively. The BMRR according to the PAREXEL criteria and day 22 blood trough concentrations of osimertinib and AZ5104 are found in Figure 5*B*. The median osimertinib concentrations of the CR plus PR and stable disease plus PD groups were 553 (range: 276–1190) nM and 774 (range: 339–1270) nM, respectively, whereas the median AZ5104 concentrations of the CR plus PR and stable disease plus PD groups were 58.7 (range: 24.9–160) nM and 89.5 (range: 44.1–210) nM, respectively. The blood concentrations of osimertinib and AZ5104 were not correlated with the BMRR and brain metastasis-related PFS. The brain metastasis-related PFS of high (≥568 nM) or low (<568 nM) osimertinib blood concentrations is found in Figure 5*C*. The brain metastasis-related PFS of high (≥68 nM) or low (<68

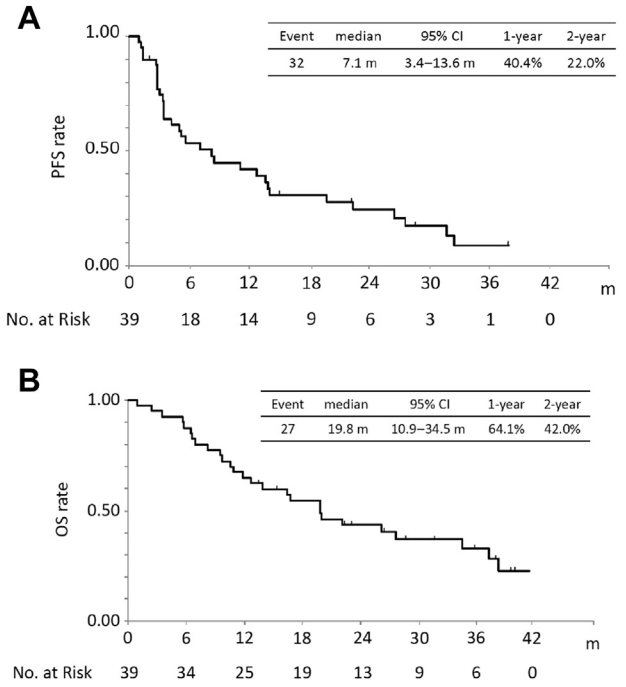

Figure 4. Results regarding systemic efficacy. (*A*) PFS (n = 39) and (*B*) OS curves (n = 39). CI, confidence interval; OS, overall survival; PFS, progression-free survival.

nM) AZ5104 blood concentrations is found in Figure 5*D*. The CSF penetration rates of osimertinib and AZ5104 are illustrated in Figure 5*E*. The median CSF penetration rates of osimertinib and AZ5104 were 0.79% (range: 0.43%–1.32%) and 0.53% (range: 0.31%–0.64%), respectively.

Plasma ctDNA Analysis

The *EGFR* mutations detected in the plasma samples are illustrated in Figure 6. The T790M mutation was detected in 33 of 40 (82.5%), 4 of 38 (10.5%), and 12 of 27 patients (44.4%) before treatment, on day 22, and when PD developed, respectively (Fig. 6*A*). C797S mutations were detected in 1 of 40 (2.5%), 1 of 38 (2.6%), and 5 of 27 patients (22.2%) before treatment, on day 22, and when PD developed, respectively (Fig. 6*B*). In one patient, the C797S mutation was detected at all three time points, whereas in the remaining four patients, it was only detected when PD developed. There were two types of C797S mutations in exon 20, T->A mutations and G->C mutations. The former type was detected in four cases, including the case in which the C797S mutation was detected before treatment, and the latter type was detected in one case after PD developed. The patient in whom C797S and T790M mutations were detected before treatment developed systemic PD after 43 days of osimertinib treatment. The C797S mutation was also detected on day 22 and when PD developed, but the T790M mutation was only detected on day 22 and was no longer detected when the patient developed PD. T790M mutations were also detected in the remaining 4 patients in whom C797S mutations were detected when PD developed.

Table 2. Toxicities (N = 40)

	Any Grade		Grade 3+4	
	No.	%	No.	%
Anemia	29	72.5	1	2.5
Leukopenia	24	60.0	4	10.0
Neutropenia	18	45.0	4	10.0
Thrombocytopenia	8	20.0	1	2.5
AST increased	12	30.0	0	0
ALT increased	10	25.0	0	0
T-Bil increased	3	7.5	0	0
Pruritus	9	22.5	0	0
Rash acneiform	14	35.0	0	0
Dry skin	9	22.5	0	0
Diarrhea	10	25.0	0	0
Mucositis	7	17.5	0	0
Pneumonitis	4	10.0	1	2.5

There were no treatment-related deaths.
ALT, alanine transaminase; AST, aspartate transaminase.

Discussion

The OCEAN study was the first prospective study to evaluate the efficacy of osimertinib against RT-naive CNS metastasis from T790M-positive NSCLC. The BMRR according to the PAREXEL criteria was 66.7% (26 of 39; 95% CI: 54.3%–79.1%). This study met the primary end point and revealed the efficacy of osimertinib in patients with CNS metastasis harboring *EGFR* T790M mutations. Median brain metastasis-related PFS was a promising 25.2 months and better than OS owing to the effect of osimertinib and partly the increase in censored cases who developed extracranial progression. Or the CNS lesions may have underexposure tumor to previous EGFR TKIs compared with extracranial and resulted in a higher response and a longer brain metastasis-related PFS than systemic PFS. In an analysis separated by *EGFR*-sensitizing mutations of 19-del or 21-L858R, the brain metastasis-related PFS according to the PAREXEL criteria of 19-del was longer than that of 21-L858R. This may be helpful on treatment choice of EGFR TKIs or may just be predicting the prognosis. High blood concentrations of osimertinib do not improve BMRR.

Osimertinib is a potent irreversible EGFR TKI, which selectively targets both *EGFR*-sensitizing and *EGFR* T790M resistance mutations, and hence, is expected to be effective in patients with CNS metastasis. In a study of pooled data from two phase 2 trials of osimertinib as a treatment for *EGFR* T790M mutation-positive NSCLC (AURA extension and AURA2), the CNS response was

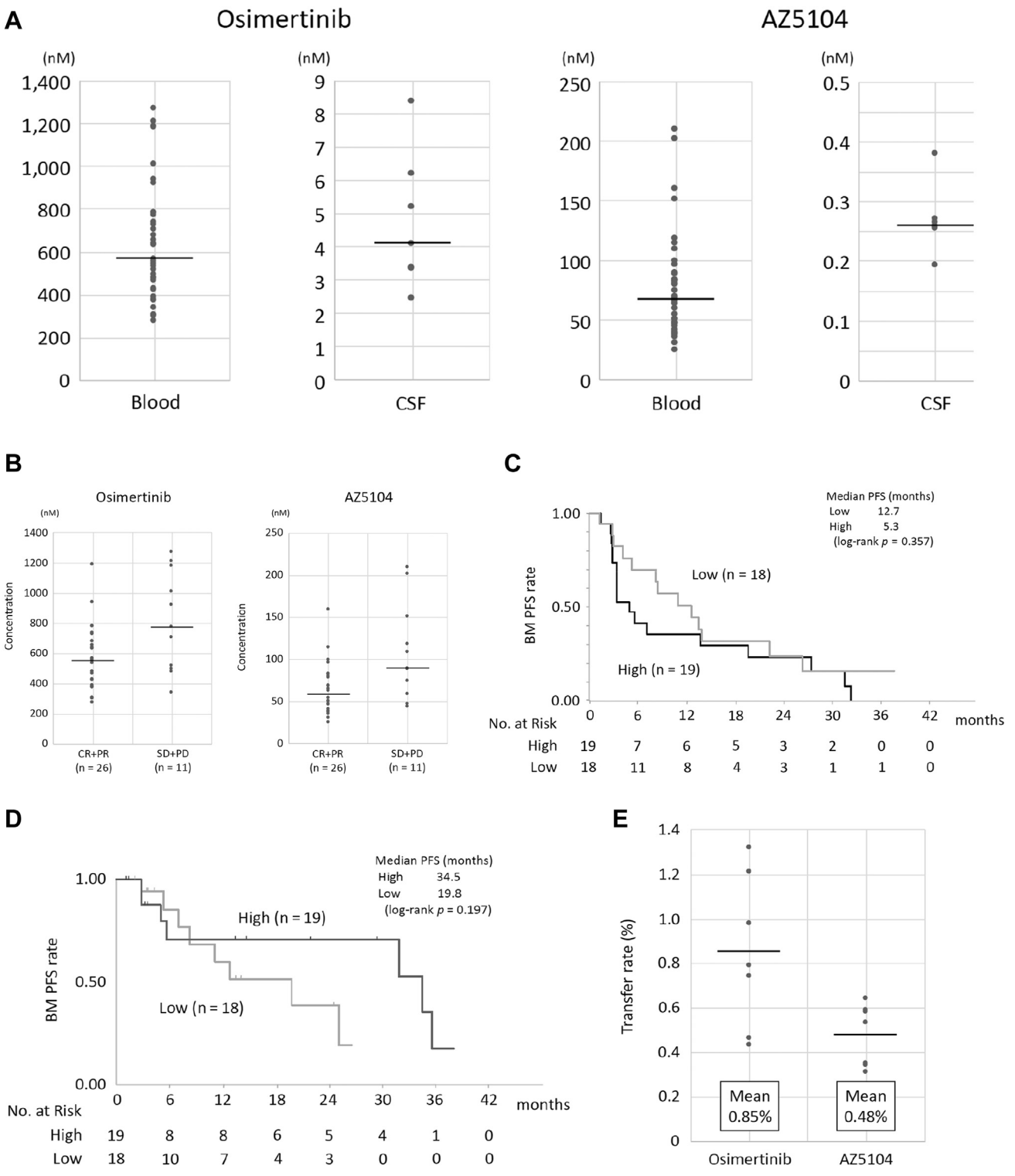

Figure 5. Drug concentrations of osimertinib and its metabolite AZ5104. The bar represents the median. (*A*) Blood and CSF trough concentrations of osimertinib and AZ5104 on day 22; (*B*) BM response rate according to the PAREXEL criteria and trough concentrations of osimertinib and AZ5104 on day 22; (*C*) BM-related PFS separated by osimertinib blood concentrations (high $\geq$568 nM); (*D*) BM-related PFS separated by AZ5104 blood concentrations (high $\geq$68 nM); (*E*) CSF penetration rates (n = 7). BM, brain metastasis; CR, complete response; CSF, cerebrospinal fluid; PFS, progression-free survival; PR, partial response.

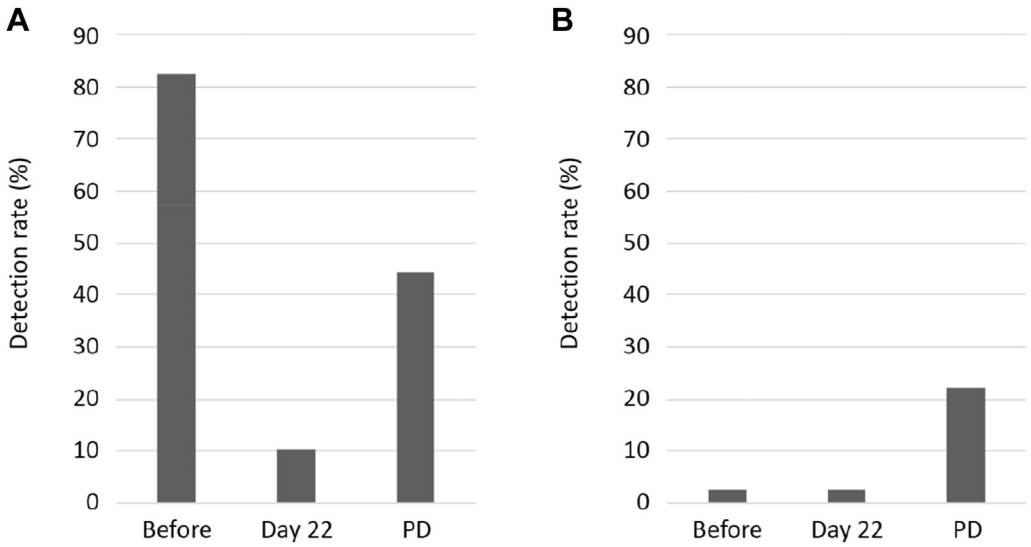

Figure 6. *EGFR* mutations detected in plasma. (*A*) T790M and (*B*) C797S (N = 40). PD, progressive disease.

reported to be 54% (27 of 50).[10] In another subgroup analysis of a phase 3 study comparing osimertinib with platinum-pemetrexed in patients with *EGFR* T790M-positive NSCLC whose disease progressed despite treatment with a first- or second-generation EGFR TKI (AURA3), osimertinib had a CNS response rate of 70% (21 of 30).[11] This study is valuable because it evaluated the true antitumor effects of osimertinib alone for previously untreated CNS metastasis, whereas the abovementioned studies were subgroup analyses and included patients who had previously been treated with RT. In addition, the BMRR achieved in this study was comparable with those found in the previous studies. Magnuson et al.[12] performed a retrospective analysis of 351 patients with EGFR-positive NSCLC who developed brain metastases, in which they compared RT with EGFR TKI for the management of brain metastases. In the multivariate analysis, upfront SRS or WBRT was found to be associated with better OS than upfront EGFR TKI treatment. The median OS for the upfront SRS, WBRT, and EGFR TKI groups was 46, 30, and 25 months, respectively. Although this study excluded patients with T790M mutations, it serves as a reference for the treatment of brain metastasis in patients with EGFR-positive NSCLC. As these patients were mainly treated with the first-generation EGFR TKI erlotinib between 2008 and 2014, the study was not a prospective trial, and considering the high BMRR of osimertinib, it is unclear whether osimertinib or RT should be administered first. Depending on the environment of the patient, RT may not be immediately available and systemic treatment may be urgently required; therefore, the use of upfront EGFR TKI treatment cannot be ruled out. In addition, many clinicians may have already treated first with EGFR TKIs and then use SRS when disease progression occurs for CNS metastasis from NSCLC with sensitizing EGFR mutations. The first-line cohort of the OCEAN study will provide that evidence in the near future. The systemic PFS in this study was a modest 7.1 months. It may suggest reduced systemic benefit to osimertinib for these patient populations with poor prognosis.

Regarding drug concentrations, some previous studies have reported that elevated blood concentrations of EGFR TKIs are correlated with efficacy or toxicity.[17–19] In this study, the blood concentrations of osimertinib and AZ5104 were not correlated with the BMRR. It is known that AZ5104 has a stronger inhibitory effect than osimertinib against EGFR-sensitizing mutations, T790M mutations, and wild-type EGFR, and its human blood concentration is approximately 10% of that of osimertinib.[20] This suggests that even if the current dose of osimertinib (80 mg) were increased, and the blood and CSF concentrations of osimertinib were increased, it would not lead to better outcomes, including regarding the BMRR. Once the concentration of osimertinib or AZ5104 reaches the concentration required to exert the antitumor effect, it is not easy to increase the antitumor effect any more, and the antitumor effect may be determined by the affinity between the drug and the tumor. Park et al.[21] conducted a phase 2 study of 160 mg of osimertinib (BLOOM; NCT02228369) for patients with NSCLC with CNS metastasis harboring *EGFR* T790M mutations. In their brain metastasis cohort, the intracranial ORR was 55.0% (22 of 40), which was not high compared with our BMRR of 66.7%; therefore, even if the dose of osimertinib were set at 80 mg, a sufficient outcome could be expected. It was valuable that the drug concentration of CSF could be measured in this study because there have been few studies on this issue and it

allowed the CSF transfer rate of osimertinib to be determined. Jenkins et al.[22] reported a case in which the plasma and CSF concentrations of osimertinib were analyzed, and the CSF transfer rate was 1.47%, which is higher than the median CSF transfer rate of 0.79% (range: 0.43%–1.32%) in this study. In addition, in the extension cohort and AURA1 of the AURA study, the concentration of osimertinib in blood and CSF was measured each in one patient, and the CSF penetration rates were 0.2% and 1%.[23] According to the studies of EGFR TKIs, the CSF penetration rates of gefitinib were 1.13% to 1.30%[24,25] and that of erlotinib was 2.77%, both of which are higher than the osimertinib penetration rate of this study. These clinical results are different from the preclinical data.[9]

Regarding plasma ctDNA analysis, in the AURA study, plasma ctDNA was analyzed using the cobas plasma test to detect the *EGFR* T790M mutation, and the *EGFR* T790M mutation was detected in 61% of patients with T790M mutation-positive tumor tissue.[22] In this study, *EGFR* T790M mutations were detected in 82.5% of plasma samples before treatment. The detection rates of both AURA and current studies seem to be high, and it is generally known that the detection rate of ctDNA is high in patients with extrathoracic lesions.[26] In addition, the method used in this study is easier than that performing a bronchoscopy or collecting a tissue sample. The C797S mutation was first discovered as a cause of acquired resistance to osimertinib and has since been found to be involved in resistance to all third-generation EGFR TKIs.[27,28] In this study, the C797S mutation was detected before treatment in one patient, in whom osimertinib was not effective, which supports the idea that C797S mutation contributes to osimertinib resistance. The C797S mutation was detected in five other patients who developed PD, and the T790M mutation was also detected in these patients. When PD developed, the T790M mutation was detected again in more than 40% of patients, suggesting T790M mutation is also involved in the acquisition resistance to osimertinib.

The OCEAN study had several limitations. First, it was a single-arm phase 2 study, not comparing the effects of RT plus osimertinib to osimertinib alone to the brain lesions. Instead of being unable to do comparative trial, we excluded all previous cases of radiation to the brain to eliminate the effects of radiation as much as possible and to evaluate the true effect of osimertinib. Second, whether brain metastases had the EGFR T790M mutation was unclear because the presence or absence of the EGFR T790M mutation was evaluated using extracranial tissue or plasma samples. Nevertheless, in clinical practice, CSF sampling is only performed in patients with suspected meningeal carcinomatosis before osimertinib treatment; therefore, requiring CSF sampling before enrollment would be difficult. We consider that the OCEAN study is valuable because its design is suitable for clinical practice.

In conclusion, the OCEAN study was the first to evaluate the efficacy of osimertinib against RT-naive CNS metastasis from T790M-positive NSCLC. The primary end point was met, and the results revealed the efficacy of osimertinib in patients with CNS metastasis harboring *EGFR* T790M mutations especially for *EGFR*-sensitizing mutation of 19-del.

CRediT Authorship Contribution Statement

Hiroyuki Yamaguchi: Management of the trial, Data collection, Draft preparation.

Kazushige Wakuda: Management of the trial, Data collection.

Minoru Fukuda, Hirotsugu Kenmotsu: Study design, Management of the trial, Reviewed the manuscript.

Hiroshi Mukae, Kentaro Ito, Kenji Chibana, Kohji Inoue, Satoru Miura, Kentaro Tanaka, Noriyuki Ebi, Takayuki Suetsugu, Taishi Harada, Keisuke Kirita, Toshihide Yokoyama, Yuki Nakatani: Data collection, Reviewed the manuscript.

Kenichi Yoshimura: Statistic analysis, Reviewed the manuscript.

Kazuhiko Nakagawa, Nobuyuki Yamamoto, Kenji Sugio: Supervision, Reviewed the manuscript.

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