SHORT COMMUNICATION

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Standard-dose osimertinib for refractory leptomeningeal metastases in T790M-positive *EGFR*-mutant non-small cell lung cancer

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Background: Osimertinib demonstrated promising efficacy for refractory leptomeningeal metastases (LM) in preclinical data and a clinical study at 160 mg, but there is limited data for the standard 80 mg dose.

Methods: T790M-positive patients with suspected LM after classical epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI) failure were enroled.

Results: We investigated 13 patients (5 definitive and 8 possible LM cases). In two of the five definitive cases with T790M in and outside the central nervous system (CNS), osimertinib was effective for both lesions, with cerebrospinal fluid (CSF) clearance of cancer cells and sensitive/T790M mutations. In three definitive cases with extra-CNS T790M without CSF T790M, cancer cells and sensitive mutations in the CSF persisted after osimertinib initiation. The median progression-free survival of all 13 patients was 7.2 months. Osimertinib was generally well-tolerated despite poor performance status, but interstitial lung disease (grade 2) was confirmed in one patient. Based on 25 samples from 13 patients, the osimertinib CSF penetration rate was 2.5 ± 0.3%.

Conclusions: Osimertinib 80 mg is a useful therapeutic option for refractory LM after classical EGFR-TKI failure. It appears more effective in CSF T790M-positive cases.

Epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs) show impressive effectiveness for patients with non-small cell lung cancer (NSCLC) harbouring *EGFR*-sensitive mutations (Lynch *et al*, 2004; Paez *et al*, 2004). Despite an initial dramatic response, most cancer cells that respond to these TKIs acquire resistance. Several mechanisms have been identified and the 'gatekeeper' *EGFR* mutation, a threonine-to-methionine substitution at amino acid position 790 in exon 20 (T790M), is the most common and accounts for more than half of acquired resistance cases (Yu *et al*, 2013). To overcome T790M-mediated resistance, third-generation EGFR-TKIs have been developed. Among them, osimertinib has demonstrated remarkable efficacy for patients with T790M resistant to classical EGFR-TKIs (Jänne *et al*, 2015; Mok *et al*, 2017).

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Central nervous system (CNS) metastases, especially leptomeningeal metastases (LM), are associated with poor prognosis in NSCLC (Hata *et al*, 2015). Although radiation therapies such as stereotactic radiosurgery or whole-brain radiotherapy (WBRT) are indicated for solitary or multiple brain metastases, they are not associated with prognosis in patients with LM (Morris *et al*, 2012). Epidermal growth factor receptor-TKIs are initially sensitive to CNS metastases in early clinical course (Park *et al*, 2012), whereas there are few therapeutic options for refractory LM after failure of classical EGFR-TKIs. High-dose EGFR-TKIs were investigated for such cases, but their effects were only moderate (Hata *et al*, 2011; Grommes *et al*, 2011). Notably, osimertinib has promising efficacy for refractory LM in preclinical data and a clinical study at 160 mg (Nanjo *et al*, 2016 and Yang *et al*, 2017), but there are limited clinical data at the 80 mg globally approved standard dosage.

Table 1. Patient characteristics

Characteristic	Number (%)
Age	
Median (range)	67 (54–79)
Sex	
Male	5 (38%)
Female	8 (62%)
Smoking history	
Never	7 (54%)
Former/current	6/0 (46%)
Histology	
Adenocarcinoma	13 (100%)
Primary *EGFR*-sensitive mutations	
Del-19	10 (77%)
L858R	3 (23%)
Prior regimens	
Median (range)	4 (3–8)
Number of prior EGFR-TKIs	
Median (range)	2 (1–3)
Prior whole-brain radiotherapy	
Irradiated	3 (23%)
None	10 (77%)
Anti-brain edema therapy	
Steroids/glycerol	7 (54%)
None	6 (46%)

Abbreviations: EGFR = epidermal growth factor receptor; TKI = tyrosine kinase inhibitor.

MATERIALS AND METHODS

Patients. This was a prospective pilot study to evaluate the efficacy and safety of clinical standard-dose osimertinib (80 mg) for refractory LM in T790M-positive *EGFR*-mutant NSCLC patients after failure of standard-dose EGFR-TKIs. The cerebrospinal fluid (CSF) penetration rate of osimertinib and CSF-*EGFR* mutational status were also investigated. T790M-positive patients with suspected LM after classical EGFR-TKI failure were enroled. We defined: (1) definitive cases as having confirmed cancer cells and *EGFR* mutations in CSF, and (2) possible cases as continuously unconfirmed cancer cells and mutations in CSF, but suspected LM by radiographical and/or neurological findings. Informed consent was obtained by all enroled patients. The study was approved by the institutional review board and complied with the Declaration of Helsinki.

Evaluation of efficacy and safety. Two to 4 weeks after initiation of 80 mg osimertinib, brain magnetic resonance imaging (MRI) and lumbar puncture were routinely performed, following that, chest/abdominal computed tomography, brain MRI, and lumbar puncture were performed every 1–3 months. The progression-free survival (PFS) of osimertinib therapy was estimated based on a systemic (intra-/extra-CNS disease mixed) evaluation. Radiographical, cytological, neurological, and *EGFR* mutational findings were regularly evaluated. Neurological changes were evaluated by the following factors: disorientation (date and time, location, and name), headache, diplopia, blindness, paraesthesia, gait disturbance, and grip strength. We also performed the finger-nose test, eye movement test, meningeal sign test, Barre test, and sense of touch test. Extra-CNS response was evaluated according to the Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1. As CNS radiographic changes are difficult to assess by the RECIST, they were evaluated as improved, stable, and progressed based on findings of dura mater thickening, exuding contrast agent, ventricular distention, and/or, concomitant substantial brain metastases with confirmation by at least two doctors. Adverse

Table 2. CSF mutational and therapeutic results

Patient	CSF-sensitive mutation	CSF T790M	PS	Neurological Findings → Change	CNS radiographic change	Extra-CNS rebiopsy site/ T790M status	Extra-CNS response
1	L858R	+	3 → 1	Abnormal → Improved	Improved	Bone/ +	PR
2	Del-19	+	3 → 1	Abnormal → Improved	Improved	Lung/ +	NE
3	Del-19	–	3 → 3	Abnormal → Stable	Stable	Liver/ +	PR
4	Del-19	–	2 → 2	Abnormal → Stable	Stable	Lymph node/ +	NE
5	L858R	–	3 → 4	Abnormal → Worsened	Progressed	Lung/ +	SD
6	–	–	1 → 1	Normal → Stable	Improved	Pleura/ +	PR
7	–	–	2 → 1	Normal → Stable	Stable	Pleura/ +	SD
8	–	–	1 → 1	Normal → Stable	Improved	Lung/ +	PR
9	–	–	1 → 1	Normal → Stable	Improved	Lung/ +	PR
10	–	–	1 → 1	Abnormal → Improved	Improved	Lung/ +	PR
11	–	–	3 → 1	Abnormal → Improved	Improved	Liver/ +	SD
12	–	–	1 → 1	Normal → Stable	Improved	Pleura/ +	PR
13	–	–	1 → 1	Normal → Stable	NE	Lung/ +	PR

Abbreviations: CNS = central nervous system; CSF = cerebrospinal fluid; NE = not evaluable; PR = partial response; PS = performance status; Pt = patient; SD = stable disease.

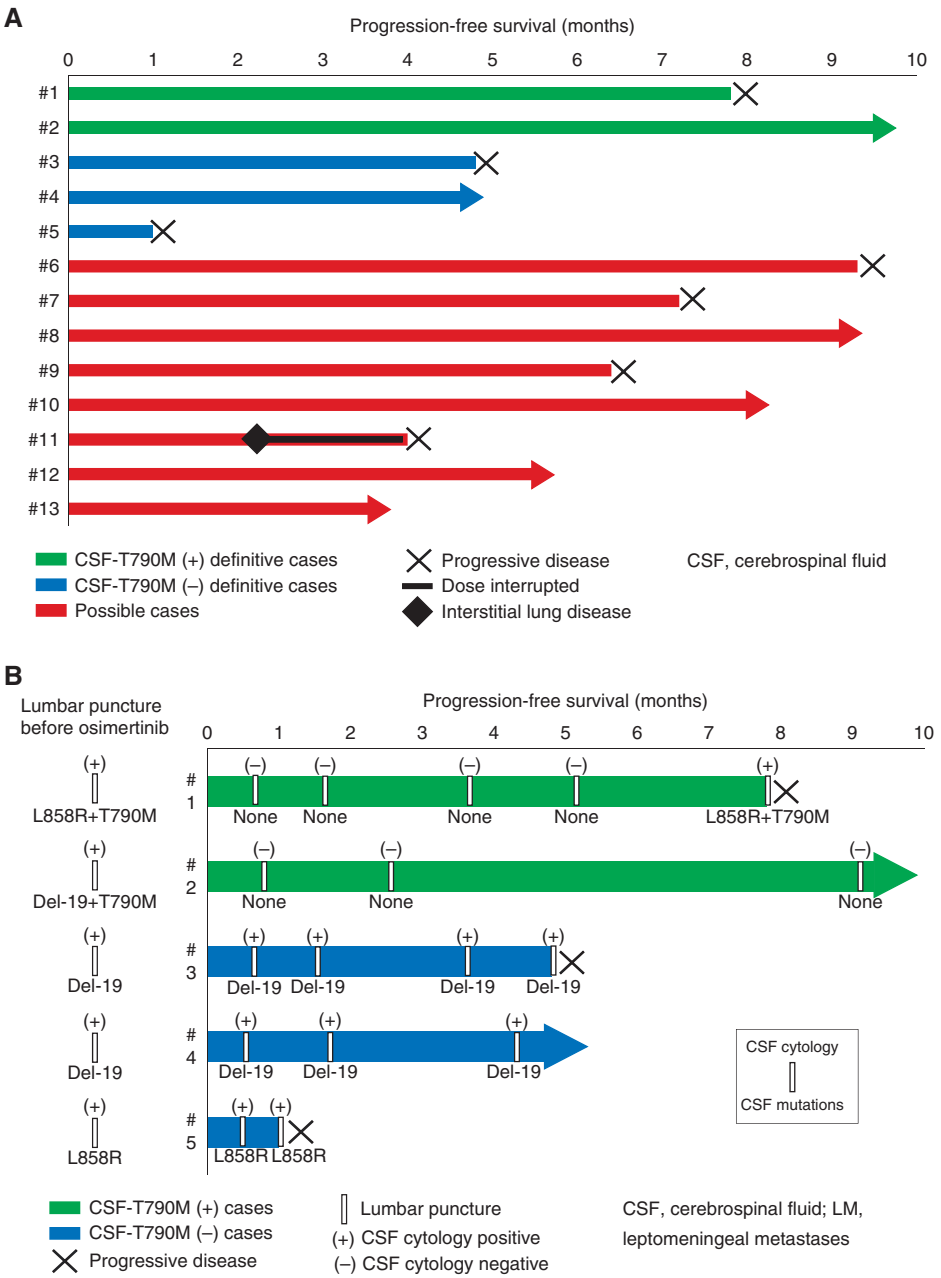

Figure 1. **Treatment and CSF results.** (**A**) Treatment timelines. (**B**) Cerebrospinal fluid (CSF) cytology/mutation status in definitive LM cases.

events (AEs) were evaluated based on the National Cancer Institute-Common Toxicity Criteria, version 4.0.

Epidermal growth factor receptor mutational analyses and quantitative analyses of osimertinib. We isolated DNA from each tumour specimen by sampling extra-CNS lesions and CSF. *EGFR*-sensitive and T790M mutations were analysed using highly sensitive assays: the peptide nucleic acid-locked nucleic acid PCR clamp method or the mutation-biased PCR quenching probe method (Nagai *et al*, 2005; Nakamura *et al*, 2011).

All CSF samples were collected after 6 ± 2 h from osimertinib administration and plasma samples were simultaneously collected. Cerebrospinal fluid and plasma concentrations of osimertinib were measured using liquid chromatography–tandem mass spectrometry (LC–MS/MS). The CSF penetration rate of osimertinib was estimated based on CSF/plasma concentrations.

RESULTS

Patients. We enroled a total of 13 patients (5 definitive and 8 possible cases) following osimertinib approval in April 2016. Patient characteristics are shown in Table 1. The median age was 67 (range 54–79). All tumour histology was adenocarcinoma. The types of *EGFR*-sensitive mutation were as follows: 10 (77%) deletional mutations in exon 19 (Del-19) and 3 (23%) L858R point mutations in exon 21. The median numbers of prior regimens and EGFR-TKIs (gefitinib, erlotinib, and/or afatinib) were four (range 3–8) and two (range 1–3), respectively. Prior WBRT was performed in three (23%) patients. Seven (54%) patients underwent anti-brain edema therapy (steroids/glycerol). No patients received intrathecal chemotherapy, high-dose EGFR-TKIs, or third-generation EGFR-TKIs before enrolment.

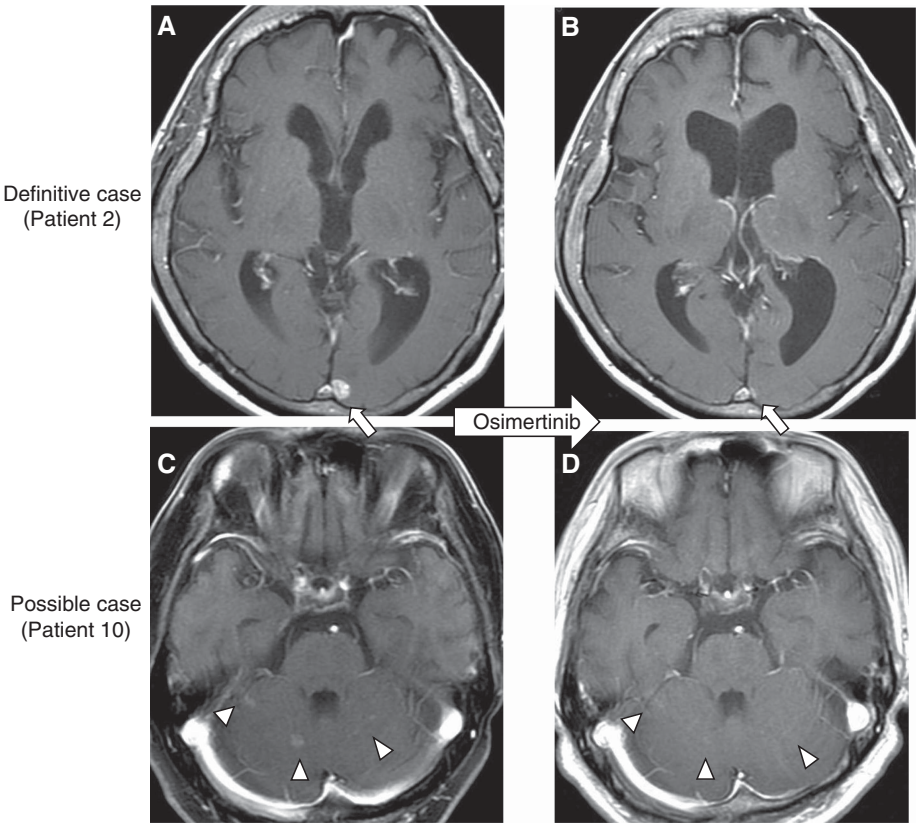

Figure 2. Representative magnetic resonance images before and after osimertinib (patients 2 and 10) Patient 2 (definitive case): (**A**) before osimertinib and (**B**) 2 months after osimertinib initiation. Patient 10 (possible case): (**C**) before osimertinib and (**D**) 2 months after osimertinib initiation.

Mutation and therapeutic results. Table 2 shows the mutation and therapeutic results. T790M was confirmed by extra-CNS rebiopsy in all 13 cases. In all five definitive cases, malignant cells and sensitive *EGFR* mutations were detected in CSF, and T790M was confirmed in two of these five patients. Osimertinib was markedly effective in both confirmed T790M CNS and extra-CNS cases (patients 1 and 2). Radiographical improvement, improved performance status (PS), and better neurological findings were also observed. In three definitive cases with T790M outside the CNS but not the CSF (patients 3–5), disease control of both areas were achieved in two cases (patients 3 and 4), whereas osimertinib was ineffective in CNS, despite being effective for lung lesions in another case (patient 5). In all eight possible cases (patient 6–13), disease control was achieved both in and outside the CNS. Central nervous system and extra-CNS improvements were observed in six (75%) and five (63%) patients, respectively. Abnormal neurological findings improved in two of two patients (10 and 11). Performance status ameliorated in the two of two patients with poor PS (7 and 11).

Figure 1A depicts treatment times. The median PFS of all 13 patients was 7.2 (95% confidence interval: 4.0, undeterminable) months. Progression was confirmed in seven cases and six patients are currently being treated. The PFS was longer in CSF-T790M (+) cases (9.6+ and 7.8 months) than in CSF-T790M (−) cases (4.8, 4.7+, and 1.0 months). Median overall survival was not reached. Regarding post-osimertinib therapy, best supportive care only was chosen in 1 (8%) case. Osimertinib was continued beyond progression in four (31%) cases. Cytotoxic chemotherapy was administered in two (15%) cases. Whole-brain radiotherapy was performed in three (23%) cases where CNS lesions progressed.

Figure 1B shows CSF cytology/mutation status in definitive cases. Cerebrospinal fluid clearance of cancer cells and sensitive/T790M mutations were confirmed after osimertinib initiation in CSF-T790M (+) cases. In patient 1 (PFS: 7.8 months), cancer cells and L858R + T790M were detected again by lumbar puncture at the time of progression. In patient 2 (PFS: 9.6+ months), cancer cells and Del-19 + T790M were not detected by lumbar puncture 9 months after osimertinib initiation. In CSF-T790M (−) cases, cancer cells and sensitive mutations in CSF remained positive continuously after osimertinib therapy.

Figure 2 shows representative MRIs before and after osimertinib (patients 2 and 10).

Safety. Ten (77%) patients had rash ⩽grade 2. Paronychia ⩽grade 2 was observed in six (46%) patients. No ⩾grade 3 AEs, diarrhoea, or liver dysfunction were observed. Interstitial lung disease (ILD, grade 2) was confirmed in one patient and occurred 2 months after osimertinib initiation. The patient initially complained of dyspnea on effort and productive cough. Clinical and radiographic findings were improved following corticosteroid therapy. There were no dose reductions and o1 dose interruptions due to ILD.

Cerebrospinal fluid penetration rate. Based on 25 samples from 13 patients, CSF and plasma concentrations of osimertinib (mean ± s.d.) were 14.4 ± 2.8 nM and 555.3 ± 51.5 nM, respectively. The corresponding medians were 8.1 (range, 1.6–56.6) nM and 483.3 (95.4–1267.0) nM. The CSF penetration rate of osimertinib was estimated at 2.5 ± 0.3% (mean ± s.d.) and the median was 2.0 (range 0.5–6.9).

DISCUSSION

Our study suggested the efficacy and safety of standard-dose osimertinib (80 mg) for refractory LM in T790M-positive *EGFR*-mutant NSCLC patients. It was especially effective in two CSF T790M-positive definitive cases, and CSF clearance of cancer cells and sensitive/T790M mutations was confirmed during response

continuation. Conversely, CSF cancer cells and sensitive mutations remained continuously positive after osimertinib initiation in three CSF T790M-negative definitive cases. Yang *et al* (2017) showed the efficacy of high-dose (160 mg) osimertinib for refractory LM in CSF T790M-positive patients (). Notably, CSF clearance was only confirmed in two CSF T790M-positive patients of their study. These results suggest superior efficacy of osimertinib in CSF T790M-positive patients.

One ILD (grade 2) was observed, but osimertinib was generally safe despite poor PS populations with LM. Although afatinib and high-dose erlotinib are potentially effective for refractory LM, their toxicities might be unsuitable for poor PS with LM (Hata *et al*, 2011; Grommes *et al*, 2011; Hoffknecht *et al*, 2015). In two of three CSF T790M-negative definitive cases, osimertinib could control disease for ~5 months and was well-tolerated without CSF clearance. Thus, osimertinib may be a suitable option for poor PS patients with LM.

Our study results estimated an osimertinib CSF penetration rate of 2.5 ± 0.3%. Poor EGFR-TKI penetration is a main cause of 'pharmacokinetic failure' in the CNS. Cerebrospinal fluid penetration rates of classical EGFR-TKIs were reported at 0.7–2.8% (Pareek *et al*, 2016). Among them, erlotinib is effective for refractory LM (Grommes *et al*, 2011; Hata *et al*, 2011). The CSF penetration rate of osimertinib in our study was comparable to that of erlotinib. From a pharmacokinetic perspective, osimertinib may be a reasonable option for LM.

Our study has several limitations. First, it was small sample size. However, it is extremely difficult to conduct a large study of refractory LM patients. In fact, only a few case reports have been published (Takeda *et al*, 2017). Second, we cannot directly compare 160 mg clinical trial data with our 80 mg results. A previous osimertinib 160 mg trial estimated a higher CSF penetration rate (16%) (Yang *et al*, 2017) than our results, and it may be better to deliver the higher dosage to the CNS. However, osimertinib 160 mg is not available in clinical practice, and their penetration rate was based on a different definition. Although previous studies used the same method (LC–MS/MS) and showed similar CSF and plasma concentrations of osimertinib (Planchard *et al*, 2016; Yang *et al*, 2017), their study assumed 5.3% as the ratio of plasma free osimertinib, and adopted plasma free osimertinib as the denominator. We decided to include all plasma osimertinib since no accurate measurement of plasma free osimertinib was available. This dose was effective and safe; 10 of 23 patients showed radiological improvement and all AEs were grade ½, except one case of grade 3 diarrhoea and nausea in their study, which is comparable to our findings.

In conclusion, osimertinib at 80 mg has a similar or higher CSF penetration rate compared with classical EGFR-TKIs and is a notable therapeutic option for refractory LM after classical EGFR-TKI failure in T790M-positive *EGFR*-mutant NSCLC patients. It appears more effective in CSF T790M-positive cases. Further studies are warranted to evaluate clinical efficacy of standard-dose osimertinib for refractory LM.

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CONFLICT OF INTEREST

AH received lecture fees from Chugai, Astra Zeneca, Boeringer Ingelheim, and Eli Lilly. NK received grants from Astra Zeneca, Eisai, Ono, Kyowa Kirin, Shionogi, Daiichi-Sankyo, Taiho, Chugai, Eli Lilly, Boeringer Ingelheim, and Merck Serono, and payment for lectures from Dainippon Sumitomo, Chugai, Boeringer Ingelheim, Astra Zeneca, Eli Lilly, Taiho, Janssen, Novartis, Pfizer, Ono, and Daiichi-Sankyo. All other authors declare no conflict of interest.

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