Osimertinib in Patients With Epidermal Growth Factor Receptor Mutation–Positive Non–Small-Cell Lung Cancer and Leptomeningeal Metastases: The BLOOM Study

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PURPOSE In this phase I study (BLOOM), osimertinib, a third-generation epidermal growth factor (EGFR) tyrosine kinase inhibitor (TKI), was evaluated in patients with leptomeningeal metastases (LMs) from EGFR-mutated (EGFRm) advanced non–small-cell lung cancer (NSCLC) whose disease had progressed on previous EGFR-TKI therapy.

PATIENTS AND METHODS Patients with cytologically confirmed LM received osimertinib 160 mg once daily. Objectives were to assess confirmed objective response rate (ORR), duration of response (DoR), progression-free survival (PFS), overall survival (OS), pharmacokinetics (PK), and safety. Additional efficacy evaluations included changes from baseline in CSF cytology and neurologic examination. Measurable lesions were assessed by investigator according to RECIST version 1.1. LMs were assessed by neuroradiologic blinded central independent review (BICR) according to Response Assessment in Neuro-Oncology (RANO) LM radiologic criteria and by investigator.

RESULTS Forty-one patients were enrolled. LM ORR and DoR by neuroradiologic BICR were 62% (95% CI, 45% to 78%) and 15.2 months (95% CI, 7.5 to 17.5 months), respectively. Overall, ORR by investigator was 41% (95% CI, 26% to 58%), and median DoR was 8.3 months (95% CI, 5.6 to 16.5 months). Median investigator-assessed PFS was 8.6 months (95% CI, 5.4 to 13.7 months) with 78% maturity; median OS was 11.0 months (95% CI, 8.0 to 18.0 months) with 68% maturity. CSF tumor cell clearance was confirmed in 11 (28%; 95% CI, 15% to 44%) of 40 patients. Neurologic function was improved in 12 (57%) of 21 patients with an abnormal assessment at baseline. The adverse event and PK profiles were consistent with previous reports for osimertinib.

CONCLUSION Osimertinib showed meaningful therapeutic efficacy in the CNS and a manageable safety profile at 160 mg once daily in patients with EGFRm NSCLC and LM.

J Clin Oncol 38:538-547. © 2019 by American Society of Clinical Oncology

INTRODUCTION Leptomeningeal metastases (LMs), the spread of tumor cells into the leptomeninges and CSF, occurs in approximately 3%-4% of patients with advanced non–small-cell lung cancer (NSCLC).1,2 The incidence of LM rises to approximately 9% in epidermal growth factor receptor-mutated (EGFRm) NSCLC.2,3 Survival for patients with NSCLC and LM is dismal, with a median overall survival (OS) of 3-10 months from diagnosis.2,4,5

Several therapeutic options, including whole-brain radiotherapy (WBRT) and intrathecal chemotherapy, have been applied to manage LM. However, WBRT has limited antitumor activity,6-8 and intrathecal chemotherapy is associated with significant toxicity and complications.9 More recently, EGFR tyrosine kinase inhibitors (TKIs) have shown potential as a treatment option for patients with EGFRm NSCLC and LM; however, results are difficult to interpret because most studies to date have been retrospective,1,2,4,10 and limited data exist from prospective studies.11 In 2017, the Response Assessment in Neuro-Oncology LM (RANO-LM) working group developed a proposal for evaluating responses in patients with LM.12 However, the RANO-LM criteria have not yet been validated, and standardization currently is lacking with respect to LM response criteria (clinical, neuroimaging, and CSF analysis).12,13
Osimertinib, a third-generation, irreversible, EGFR-TKI, is an approved treatment option (80 mg once daily) for patients with EGFRm advanced NSCLC and for patients with T790M-positive NSCLC after disease progression on EGFR-TKIs.\textsuperscript{14,15} Although osimertinib is a substrate for the permeability glycoprotein and breast cancer resistance protein efflux transporters, in vitro data have shown that unlike other EGFR-TKIs, the permeability of osimertinib is sufficient to overcome this efflux.\textsuperscript{16} Preclinical evidence in nonhuman primates shows that osimertinib has greater penetration of the blood-brain barrier and higher brain exposure compared with other EGFR-TKIs.\textsuperscript{16,17} In a positron emission tomography (PET) study of healthy human volunteers, a single microdose of \textsuperscript{11C}osimertinib demonstrated rapid and widespread distribution in the brain.\textsuperscript{18} From this phase I study, we report the antitumor efficacy, pharmacokinetics (PK), and safety of osimertinib 160 mg once daily in patients with EGFRm NSCLC and LM whose disease had progressed on previous EGFR-TKI therapy. The higher 160 mg dose was chosen for this study because limited data with regard to exposure versus response were available at the time of study initiation, treatment of patients with LM has been challenging with other EGFR-TKIs, and early preclinical data\textsuperscript{16,18} suggest that a higher exposure of osimertinib may increase CNS tumor shrinkage.

**PATIENTS AND METHODS**

**Study Design and Patients**

The BLOOM study (ClinicalTrials.gov identifier: NCT02228369) was a 2-part, phase I, open-label, multicenter study in patients with EGFRm NSCLC. Part A, which comprised a dose-escalation and dose-expansion phase, investigated the primary study outcome: the safety and tolerability of AZD3759 in patients with EGFRm NSCLC, the results of which have been published.\textsuperscript{20} Part B, reported here, assessed osimertinib 160 mg once daily (without a dose-escalation phase) in patients with EGFRm NSCLC and LM whose disease had progressed on EGFR-TKI therapy. Objectives included antitumor efficacy, OS, neurologic status, the PK of osimertinib and its metabolites in blood and CSF, EGFRm copy number in CSF, and safety.

Patients were enrolled sequentially into 2 cohorts: unselected and T790M positive (see the Data Supplement, online only, for details). Key inclusion criteria were \( \geq 18 \) years of age with a histologically or cytologically confirmed diagnosis of NSCLC and exon 19 deletions or L858R mutations, confirmed LM diagnosis by positive CSF cytology (up to 28 days before first dosing), \( \geq 1 \) LM site that could be assessed repeatedly by magnetic resonance imaging (MRI), progression on EGFR-TKI therapy, and WHO/Eastern Cooperative Oncology Group (ECOG) performance status of 0-2. For additional inclusion and exclusion criteria and ethical conduct of the study, see the Data Supplement.

**Treatment and Assessments**

Osimertinib 160 mg was administered orally once daily to all patients until disease progression or unmanageable drug-related toxicity. Patients were permitted to continue study treatment beyond disease progression, as defined by RECIST version 1.1 (RECIST 1.1), as long as they were considered by the investigator to be deriving clinical benefit and tolerating treatment.

Before the first dosing of osimertinib, plasma and CSF samples were obtained from patients for assessment of EGFR mutations. EGFR mutation status was determined retrospectively at central and local laboratories using droplet digital polymerase chain reaction.\textsuperscript{21} Radiologic assessments were performed at baseline and every 6 weeks \( \pm 1 \) week until progression or patient withdrawal. Required scans included computed tomography or MRI of the chest and abdomen and MRI of the brain and spine. Non-CNS lesions and measurable CNS lesions were assessed by investigator according to modified RECIST 1.1. Investigators assessed LM response using their institutional standard (most often RECIST 1.1); however, a quantitative measurement of LM cannot be accurately performed using RECIST. Therefore, LMs were also assessed by neuroradiologic blinded central independent review (BICR), either in parallel or retrospectively with other reviews, according to RANO-LM working group criteria (see Data Supplement).\textsuperscript{12} For CSF response assessment (100% CSF clearance of tumor cells), CSF was taken at baseline, day 22, and every 6 weeks \( \pm 1 \) week until progression; responses were confirmed at least 4 weeks after initial CSF clearance. Patients underwent a detailed neurologic examination by investigator to document neurologic status at baseline and every 21 days until discontinuation (Data Supplement). Safety was assessed by investigator throughout the study. Adverse events (AEs) were classified according to the Medical Dictionary for Regulatory Activities version 20.0 and graded using Common Terminology Criteria for Adverse Events (CTCAE), version 4.0. For patients who discontinued treatment for reasons other than disease progression, RECIST 1.1 assessments and/or CSF cytology assessments were performed by investigator every 6 weeks until disease progression. Survival was evaluated every 6 weeks after discontinuation of study treatment. Details of PK sample collection and analysis are provided in the Data Supplement.

**Statistical Procedure**

A sample size of up to approximately 40 patients was determined to provide an 80% chance of observing at least 1 incidence of a safety signal that occurs in 4% of patients in the target population. In addition, on the basis of 20 efficacy responses out of 40, the 2-sided 80% CI for the true objective response rate (ORR) would be 39% to 61%. Details of end point definitions and analysis sets are provided in the Data Supplement.

Journal of Clinical Oncology 539
Estimated time-to-event end points (progression-free survival [PFS], duration of response [DoR], and OS) and associated 95% CIs were calculated using the Kaplan-Meier method. ORR 95% CIs were calculated using the Clopper-Pearson method. Data obtained up until progression, or last evaluation in the absence of progression, were included in the ORR assessment. No formal statistical analyses were conducted on the safety and PK data; these were summarized using appropriate descriptive statistics.

RESULTS

Patients

Between April 2015 and October 2017, 41 patients were enrolled sequentially and treated with osimertinib 160 mg once daily (Fig 1). Patients were enrolled at 5 sites in South Korea and 1 site in Taiwan. All patients were Asian; most were female (71%) with a WHO/ECOG performance status of 2 (51%; Table 1; for EGFR mutations status, see Data Supplement). Patient demographics and characteristics by cohort (unselected cohort, n = 21; T790M-positive cohort, n = 20) are shown in the Data Supplement. Twenty-nine patients (71%) had coexisting brain metastases, and 20 (49%) had prior radiotherapy to the brain, with 15 (37%) having received WBRT. Duration and timing of prior radiotherapy for individual patients are listed in the Data Supplement. At data cutoff (October 15, 2017), 7 patients

| TABLE 1. Patient Demographic and Baseline Characteristics |
|---------------------------------------------------------|
| Characteristic                                          | Patients, No. (%) |
| No. of patients                                        | 41              |
| Median age, years (range)                              | 59 (44-75)      |
| Sex                                                     |                 |
| Male                                                    | 12 (29)         |
| Female                                                  | 29 (71)         |
| Race                                                    |                 |
| Asian                                                   | 41 (100)        |
| Country                                                 |                 |
| South Korea                                            | 40 (98)         |
| Taiwan                                                  | 1 (2)           |
| Median BMI, kg/m² (range)                              | 23 (15-28)      |
| Smoking status                                          |                 |
| Never                                                   | 30 (73)         |
| Current                                                 | 1 (2)           |
| Former                                                  | 10 (24)         |
| Prior brain radiotherapy                                |                 |
| Whole brain                                             | 15 (37)         |
| Other                                                   | 5 (12)          |
| Prior intrathecal chemotherapy                          | 18 (44)         |
| Prior EGFR-TKI therapy                                  |                 |
| Gefitinib                                               | 31 (76)         |
| Erlotinib                                               | 7 (17)          |
| Afatinib                                                | 2 (5)           |
| Dacomitinib                                             | 1 (2)           |
| Prior cytotoxic chemotherapy*                           | 35 (85)         |
| First line                                              | 20 (49)         |
| Second line                                             | 22 (54)         |
| Not applicable                                          | 16 (39)         |
| WHO/ECOG performance status                            |                 |
| 0                                                       | 1 (2)           |
| 1                                                       | 19 (46)         |
| 2                                                       | 21 (51)         |
| Histology type                                          |                 |
| Adenocarcinoma                                          | 41 (100)        |
| Overall disease classification                          |                 |
| Metastatic disease at any site                          | 25 (61)         |
| Metastatic† and locally advanced disease                | 16 (39)         |
| Coexisting measurable CNS lesions†                      | 29 (71)         |
| Coexisting non-CNS lesions††                            | 38 (93)         |

Abbreviations: BMI, body mass index; ECOG, Eastern Cooperative Oncology Group; EGFR-TKI, epidermal growth factor receptor tyrosine kinase inhibitor.

*Patients with multiple administrations of a single treatment within a modality can have >1 treatment status.
†Patient has any metastatic site of disease.
‡Coexisting brain and leptomeningeal metastases.
were still receiving osimertinib (Fig 1). Median total treatment duration was 8.6 months (range, 0.1-29.7 months; Data Supplement).

**Efficacy**

**Tumor response.** Confirmed LM ORR (excluding 4 patients without available BICR data) was observed in 23 (62%) of 37 by BICR (95% CI, 45% to 78%) and in 11 (27%) of 41 by investigator (95% CI, 14% to 43%). Twelve patients had LM complete response (CR), and 11 had LM partial response (PR) by BICR; 1 patient had LM CR, and 10 had PR by investigator. There was a higher proportion of stable disease by investigator (61%) than by BICR (32%). Median LM DoR was 15.2 months by BICR (95% CI, 7.5 to 17.5 months) and 18.9 months by investigator (95% CI, 7.6 months to not calculable). Details of LM ORR in patients with and without prior brain radiotherapy are provided in the Data Supplement. The confirmed CNS ORR was 58% (7 of 12; 95% CI, 28% to 85%). The confirmed overall ORR was 41% (17 of 41; 95% CI, 26% to 58%; Table 2). The LM and overall disease control rates were 78% and 73%, respectively. For efficacy end points by cohort, see the Data Supplement. CNS tumor shrinkage was observed in 8 (73%) of 11 evaluable patients with measurable CNS lesions and postbaseline RECIST target lesion assessment scans, with a mean reduction of 39% (Data Supplement).

**Neurologic function.** Baseline neurologic assessments were normal in 20 patients (49%), mildly abnormal in 14 (34%), moderately abnormal in 6 (15%), and severely abnormal in 1 (2%). Improved neurologic function was observed in 12 (57%) of the 21 patients who had an abnormal assessment at baseline (Fig 2). Twenty-two patients (54%) did not progress or worsen during treatment. Only 2 patients (5%) experienced regression of their neurologic functions. After treatment, information for 5 patients (12%) was missing (Data Supplement). Results of neurologic assessment by cohort are shown in the Data Supplement.

**PFS and OS.** At data cutoff, 32 (78%) of 41 patients had progressed or died (Data Supplement). Median investigator-assessed PFS was 8.6 months (95% CI, 5.4 to 13.7 months; Fig 3A). At 12 months, 42% (95% CI, 27% to 57%) of patients were progression free. Of the 23 LM responders by BICR, site of first progression was most commonly non-CNS (n = 5; 22%), followed by CNS (n = 2; 9%) and LM progression (n = 2; 9%). A similar trend was observed in 26 (84%) of 31 evaluable patients, with a mean reduction of 36% (Data Supplement). Confirmed CSF clearance was observed in 11 (28%) of 40 evaluable patients (95% CI, 15% to 44%) during treatment.

**TABLE 2. Response to Treatment**

| Measure | LM by BICR | LM by Investigator | CNS by Investigator | Non-CNS by Investigator | Overall by Investigator |
|---------|------------|-------------------|--------------------|------------------------|------------------------|
| No. of patients | 37 | 41 | 12 | 38 | 41 |
| Best objective response | | | | | |
| Complete response<sup>a</sup> | 12 (32) | 1 (2) | 0 (0) | 0 (0) | 0 (0) |
| Partial response<sup>a</sup> | 11 (30) | 10 (24) | 7 (58) | 17 (45) | 17 (42) |
| Stable disease ≥ 6 weeks | 12 (32) | 25 (61) | 3 (25) | 14 (37) | 17 (42) |
| Progression | 1 (3) | 3 (7) | 1 (8) | 6 (16) | 6 (15) |
| Not evaluable | 1 (3) | 2 (5) | 1 (8) | 1 (3) | 1 (2) |
| ORR,<sup>bc</sup> % (95% CI) | 62 (45 to 78) | 27 (14 to 43) | 58 (28 to 85) | 45 (29 to 62) | 41 (26 to 58) |
| DCR at 12 weeks, No. (%; 95% CI) | 35 (95; 82 to 99) | 32 (78; 62 to 89) | 10 (83; 52 to 98) | 27 (71; 54 to 85) | 30 (73; 57 to 86) |
| Median DoR,<sup>bc</sup> months (95% CI) | 15.2 (7.5 to 17.5) | 18.9 (7.6 to NC) | 11.0 (3.8 to NC) | 8.3 (5.6 to NC) | 8.3 (5.6 to 16.5) |

Abbreviations: BICR, blinded independent central review; DCR, disease control rate; DoR, duration of response; LM, leptomeningeal metastasis; NC, not calculable; ORR, objective response rate.

<sup>a</sup>Evaluable for LM response analysis set.

<sup>b</sup>Evaluable for measurable CNS response analysis set.

<sup>c</sup>Evaluable for non-CNS response analysis set.

<sup>d</sup>Overall response is derived by combining the CNS and non-CNS lesion time point responses.

<sup>e</sup>Evaluable for response analysis set.

<sup>f</sup>Response required confirmation after 4 weeks. For LM, response was defined as at least 1 confirmed complete or partial response before any evidence of progression (as defined by RECIST version 1.1 or modified RECIST).

<sup>g</sup>ORR was defined as the percentage of patients who had at least 1 confirmed complete or partial response before any evidence of progression (as defined by RECIST version 1.1 or modified RECIST).

<sup>h</sup>DoR was defined as the time from the first documented response (complete or partial response) that was subsequently confirmed, until documented progression, or death in the absence of disease progression.
observed in LM nonresponders, with 6 patients (43%) experiencing progression in non-CNS regions, 3 (21%) in the CNS, and 3 (21%) LM (Data Supplement). Fifteen LM responders (65%) and 6 LM nonresponders (43%) did not experience progression. With a median follow-up of 9.9 months, 28 patients (68%) died. Median OS was 11.0 months (95% CI, 8.0 to 18.0 months; Fig 3B), and the 12-month survival rate was 48% (95% CI, 32% to 63%).

Longer exposure and OS were observed in patients who responded according to the RANO-LM criteria compared with nonresponders, particularly in the unselected cohort (Data Supplement). PFS and OS by cohort are shown in the Data Supplement.

**PK**

The PK analysis set included 35 patients who had reportable concentrations on day 22 (see Data Supplement for PK parameters). Plasma concentrations of osimertinib and its active metabolites (AZ5104 and AZ7550) reached steady state by day 15 and had a relatively flat PK profile with limited fluctuation in the peak-to-trough steady-state drug concentration in plasma ratio, which suggests that steady-state concentrations were maintained across the dosing interval (Data Supplement). This is similar to previous reports of the PK of osimertinib 80 mg.22 AZ5104 and AZ7550 were observed at steady state at approximately 10% of the exposure of osimertinib in plasma and approximately 9% (AZ5104) and 7% (AZ7550) of osimertinib exposure in CSF. The CSF-to-free plasma ratio for osimertinib was approximately 16%.

**Safety**

The safety data in this study indicate that osimertinib 160 mg was generally well tolerated, with a tolerability profile consistent with the known profile of osimertinib and the characteristics of the disease under investigation.23-25 All patients had at least 1 AE, 27 patients (66%) had an AE grade $\geq 3$, and 10 (24%) had AEs possibly causally related to osimertinib as judged by the investigator. AEs that led to discontinuation were reported in 9 patients (22%; Data Supplement), and 5 patients (12%) had AEs that led to dose reduction. Serious AEs were reported in 21 patients (51%; Data Supplement). The most commonly reported AEs are listed in Table 3. There was 1 event of pneumonitis (grade 4) that was possibly causally related to osimertinib according to the investigator. Seven AEs (17%) were fatal, none of which were considered by the investigator to be causally related to the study drug. No AEs of QT interval prolongation, cardiomyopathy, or decreased ejection fraction were reported during the study, and the observed QT interval prolongation effects were as expected for treatment with osimertinib and for this patient.
population. No patients experienced elevated alanine aminotransferase, aspartate aminotransferase, or bilirubin, and no potential Hy's law cases were reported.

**DISCUSSION**

In the BLOOM study, osimertinib demonstrated a clinically meaningful benefit across all efficacy endpoints tested in patients with EGFRm NSCLC and cytologically confirmed LM who had progressed on EGFR-TKIs. To our knowledge, this is the largest prospective study to test the effects of an EGFR-TKI in patients with EGFRm NSCLC and LM.

Osimertinib showed clinically meaningful LM ORR by both investigator and BICR assessment; however, LM ORR was lower by investigator (27%) than by BICR (62%). Fewer patients had CRs by investigator than by BICR (2% vs 32%), and more patients had stable disease by investigator than by BICR (61% vs 32%). These discrepancies may be due to different specialists with different levels of expertise who assessed scans using different radiologic criteria (Data Supplement). The data showed no positive effect of prior brain radiotherapy on LM response to osimertinib. LM ORR was 55% in patients who received prior brain radiotherapy compared with 57% in patients who did not receive prior brain radiotherapy.

Confirmed CSF response was observed in 28% of patients during treatment; however, our definition of CSF response (complete CSF clearance of tumor cells, in line with previous definitions) was stringent and did not capture patients who

| Adverse Event                        | Any Grade | Grade 1 | Grade 2 | Grade ≥ 3 |
|--------------------------------------|-----------|---------|---------|-----------|
| Any                                  | 41 (100)  | 4 (10)  | 10 (24) | 27 (66)   |
| Rash and acne*                       | 24 (59)   | 16 (39) | 7 (17)  | 1 (2)     |
| Diarrhea                             | 23 (56)   | 14 (34) | 7 (17)  | 2 (5)     |
| Nausea                               | 15 (37)   | 14 (34) | 0 (0)   | 1 (2)     |
| Dry skin*                            | 13 (32)   | 11 (27) | 2 (5)   | 0 (0)     |
| Paronychia*                          | 12 (29)   | 8 (20)  | 4 (10)  | 0 (0)     |
| Decreased appetite                   | 10 (24)   | 5 (12)  | 4 (10)  | 1 (2)     |
| Dizziness                            | 10 (24)   | 9 (22)  | 1 (2)   | 0 (0)     |
| Headache                             | 10 (24)   | 8 (20)  | 2 (5)   | 0 (0)     |
| Vomiting                             | 9 (22)    | 5 (12)  | 4 (10)  | 0 (0)     |
| Anemia                               | 8 (20)    | 2 (5)   | 4 (10)  | 2 (5)     |
| Pruritus                             | 8 (20)    | 8 (20)  | 0 (0)   | 0 (0)     |
| Constipation                         | 7 (14)    | 5 (12)  | 2 (5)   | 0 (0)     |
| Alanine aminotransferase increased   | 6 (15)    | 5 (12)  | 1 (2)   | 0 (0)     |
| Asthenia                             | 6 (15)    | 2 (5)   | 4 (10)  | 0 (0)     |
| Fatigue                              | 6 (15)    | 4 (10)  | 1 (2)   | 1 (2)     |
| Nail disorder                        | 6 (15)    | 5 (12)  | 1 (2)   | 0 (0)     |
| Aspartate aminotransferase increased | 5 (12)    | 5 (12)  | 0 (0)   | 0 (0)     |
| Hypokalemia                          | 5 (12)    | 2 (5)   | 2 (5)   | 1 (2)     |
| Stomatitis                           | 5 (12)    | 4 (10)  | 0 (0)   | 1 (2)     |
| Cough                                | 4 (10)    | 3 (7)   | 1 (2)   | 0 (0)     |
| Deafness                             | 4 (10)    | 3 (7)   | 1 (2)   | 0 (0)     |
| Insomnia                             | 4 (10)    | 3 (7)   | 1 (2)   | 0 (0)     |
| Pneumonia                            | 4 (10)    | 0 (0)   | 2 (5)   | 2 (5)     |
| Pneumonia aspiration                 | 4 (10)    | 0 (0)   | 0 (0)   | 4 (10)    |
| Pyrexia                              | 4 (10)    | 2 (5)   | 2 (5)   | 0 (0)     |

**NOTE.** Adverse events reported in ≥ 10% of patients overall treated with osimertinib (safety analysis set). Each patient has only been represented with the maximum reported CTCAE (version 4.0) grade for each preferred term. Patients with adverse events were sorted by most common adverse event of any grade and then alphabetically. Includes adverse events with an onset date on or after the date of first dose and up to and including 28 days after the date of last dose of study medication.

*This category represents a grouped term for the event. If a patient had multiple preferred term–level events within a specific grouped term adverse event, then the maximum grade across those events was counted.
may have had a PR. Because 100% CSF clearance is seldom achieved; recent studies have defined partial CSF response as a ≥ 50% reduction in CSF tumor cells.5

The clinical benefit of osimertinib was also shown by improvements in neurologic performance. Given that most neurologic deficits caused by LMs are considered irreversible,12 the improvement in neurologic status with osimertinib (57%) is encouraging. Of note, 49% of patients had a normal neurologic examination status at baseline, despite cytologically positive LM. While abnormal neurologic symptoms are usually one of the first indicators of leptomeningeal involvement,9 neurologic symptoms related to LM, such as headache or vomiting, were not recorded in this study. Given the lack of standardized radiologic and neurologic response assessment criteria for the evaluation of LM, further prospective studies using standardized criteria, such as those proposed by the RANO-LM working group, are needed. In this study, patients with a response (as assessed by the RANO-LM criteria) had improved OS compared with nonresponders, which supports the validity of using these criteria in this study.

After the initiation of the BLOOM study, encouraging clinical activity with osimertinib 80 mg once daily in the CNS has been reported, including in patients with radiologically-detected LMs.23,26-30 In a retrospective analysis of 22 EGFR-TKI–pretreated patients with T790M mutation–positive advanced NSCLC and radiologically-detected LMs treated with osimertinib 80 mg once daily across the AURA program (AURA, AURA2, AURA17, and AURA3; ClinicalTrials.gov identifiers: NCT01802632, NCT02094261, NCT02442349, and NCT02151981, respectively), a 55% LM ORR according to RANO-LM radiologic criteria, a median LM PFS of 11.1 months, and a median OS of 18.8 months were reported.31 In the phase III FLAURA (ClinicalTrials.gov identifier: NCT02296125) study of EGFR-TKI–naïve patients with EGFRm advanced NSCLC (exon 19 deletion/LS858R), 4 of 5 patients with radiologically-detected LM treated with osimertinib 80 mg once daily had a complete radiologic LM response.52 Moreover, a prospective pilot study (n = 13)53 and small retrospective study (n = 20)54 have reported efficacy with osimertinib 80 mg in patients with pretreated EGFRm NSCLC and LM, which suggests that the 80-mg dose may have similar efficacy to the 160-mg dose. Of note, the AURA phase I study compared varying doses (20-240 mg) of osimertinib and showed no increase in efficacy at 160 mg compared with 80 mg, with a higher frequency of AEs at higher doses and no maximum tolerated dose (up to 240 mg).55,56 Additional prospective studies to evaluate osimertinib 80 mg in the treatment of LM are warranted.

Most studies of EGFR-TKIs for patients with EGFRm NSCLC and LM have been retrospective,1,2,4,10 with limited data from prospective studies.11 In a phase II prospective study that tested the effects of erlotinib to treat patients with NSCLC and LM (n = 17), ORR was 35%, and median time to LM progression and OS were 2.7 and 4.0 months, respectively.37 A prospective study of afatinib (n = 11) reported an ORR of 27%, and median PFS and OS were 2.0 and 3.8 months, respectively.38 High-dose or pulsatile dosing has been reported as an attempt to increase EGFR-TKI concentrations in the CNS. In a phase I prospective study, median neurologic PFS and OS with high-dose gefitinib (750-1,000 mg) were reported as 2.3 and 3.5 months, respectively (n = 7).39 Several case studies have reported successful treatment of LM with high-dose pulsatile administration of erlotinib;40 however, a retrospective study of patients with LM refractory to standard-dose EGFR-TKIs found no difference in median OS between patients treated with high-dose erlotinib (n = 12) and those treated with standard-dose EGFR-TKIs (n = 23; 6.2 vs 5.9 months, respectively); median time to CNS progression was 2.3 months.41 Given the very limited PFS and OS data in patients with LM treated with EGFR-TKIs, the median PFS and OS results (8.6 and 11.0 months, respectively) observed in this study are promising. These data, however, should be interpreted with caution because of study limitations, including the small number of patients enrolled, of whom 40 were from South Korea, and the heterogeneity of prior anticancer treatments, including intrathecal and systemic chemotherapy and radiotherapy to the brain. However, these are all prior anticancer therapies that are expected in this patient setting, and exclusion of patients who received such therapies would greatly affect patient recruitment in any LM study.

Analysis of response by cohort showed that patients in the unselected cohort had higher response rates and numerically longer DoR, PFS, and OS than patients in the T790M-positive cohort. Patients in the unselected cohort, unlike those in the T790M-positive cohort, were required to have stable non-CNS disease, which is likely to have contributed to this observation. In addition, more patients in the unselected cohort received prior WBRT, a recommended therapeutic approach for patients with LM with good risk status, and had a WHO/ECOG performance status of 0-1 compared with patients in the T790M-positive cohort, which suggests that these patients may have had a better good-risk status or prognosis. Because not all patients in the unselected cohort had confirmed T790M, the high response rate in this cohort suggests CNS progression as a frequent failure site for EGFR-TKIs and osimertinib activity in the CNS regardless of T790M mutation status.

The flat PK profile of osimertinib 160 mg was in line with previous osimertinib PK studies.22,36 Furthermore, the CSF concentration of osimertinib and its metabolites indicated good penetration into the CNS, consistent with results from a PET study in healthy volunteers that showed that [11C]osimertinib distributed rapidly to all regions of the brain.18

As expected and consistent with safety findings from the 160-mg dose group in the AURA phase I study,36 the
incidence and severity of AEs were higher than reported for the 80-mg dose. However, no new safety concerns were identified, and overall, safety findings with the 160-mg dose were consistent with the known profile of osimertinib and the characteristics of the disease under study. Treatment discontinuation was reported in 9 patients (22%), with dose reductions reported in 5 patients (12%) and interruptions reported in 24 (59%). In patients who received 160 mg osimertinib who required a dose reduction, the dose was reduced to 80 mg, which is the currently approved osimertinib dose. However, in consideration of the severity of LM and that 51% of patients had a WHO/ECOG performance status of 2, these incidences would be considered acceptable. The actual median treatment exposure (8.1 months; range, 0.1-29.6 months), which excluded treatment interruptions, was similar to the intended treatment exposure, with a mean relative dose intensity of 94% (standard deviation, 11%), which indicates that toxicity was manageable through dose interruptions without a need for treatment discontinuation. Furthermore, previous studies of exposure-response to osimertinib have shown that while exposure affects the safety profile, it has a minimal impact on efficacy.\textsuperscript{30} Indeed, as noted previously here, the ORR and OS outcomes in BLOOM are encouraging compared with historical published data.

In conclusion, osimertinib 160 mg once daily showed meaningful therapeutic efficacy in terms of radiologic response, neurologic improvement, CSF clearance, and a manageable safety profile in patients with LM from EGFRm advanced NSCLC whose disease had progressed on EGFR-TKI therapy. Given the lack of standardized treatment as well as the current treatment limitations and/or invasive nature of the available experimental therapies, osimertinib has the potential to become a treatment option for patients with EGFRm NSCLC and LM previously treated with an EGFR-TKI. Given the success of the FLAURA phase III study with first-line osimertinib, it is likely that osimertinib may also play an important role in the treatment of EGFR-TKI–naïve patients with EGFRm NSCLC and LM. Additional studies are required to confirm these findings using the 80-mg dose.

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**SUPPORT**

Supported by AstraZeneca (Cambridge, United Kingdom), the manufacturer of osimertinib. Writing assistance was funded by AstraZeneca in accordance with Good Publications Practice guidelines.

**CLINICAL TRIAL INFORMATION**

NCT02228369.

**AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT**

Disclosures provided by the authors and data availability statement (if applicable) are available with this article at DOI https://doi.org/10.1200/JCO.19.00457.

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**ACKNOWLEDGMENT**

We thank the patients and their families as well as the investigators and staff at all study sites. We acknowledge Ellen Maxwell, PhD, of iMed Comms, Macclesfield, United Kingdom, an Ashfield Company, part of UDG Healthcare, for medical writing assistance under the direction of the authors. We also acknowledge Haiyi Jiang, MD (AstraZeneca, Gaithersburg, MD), and Zhenfan Yang, MD, PhD (Dizal Pharmaceutical, Shanghai, Peoples Republic of China), for their contributions to the development of the protocol.

Data underlying the findings described in this article may be obtained in accordance with AstraZeneca’s data sharing policy described at https://astrazenecagrouptrials.pharmcm.com/ST/Submission/Disclosure.
REFERENCES

1. Liao BC, Lee JH, Lin CC, et al: Epidermal growth factor receptor tyrosine kinase inhibitors for non-small-cell lung cancer patients with leptomeningeal carcinomatosis. J Thorac Oncol 10:1754-1761, 2015

2. Li YS, Jiang BY, Yang JJ, et al: Leptomeningeal metastases in patients with NSCLC with EGFR mutations. J Thorac Oncol 11:1962-1969, 2016

3. Kuiper JL, Hendriks LE, van der Welken AJ, et al: Treatment and survival of patients with EGFR-mutated non-small cell lung cancer and leptomeningeal metastasis: A retrospective cohort analysis. Lung Cancer 89:255-261, 2015

4. Umemura S, Tsubouchi K, Yoshioka H, et al: Clinical outcome in patients with leptomeningeal metastasis from non-small cell lung cancer: Okayama Lung Cancer Study Group. Lung Cancer 77:134-139, 2012

5. Xu Y, Hu M, Zhang M, et al: Prospective study revealed prognostic significance of responses in leptomeningeal carcinomatosis and clinical value of cerebrospinal fluid-based liquid biopsy. Lung Cancer 125:142-149, 2018

6. Cheng H, Perez-Soler R: Leptomeningeal metastases in non-small-cell lung cancer. Lancet Oncol 19:e43-e55, 2018

7. Morris PG, Reiner AS, Sznemberg OR, et al: Leptomeningeal metastasis from non-small cell lung cancer: Survival and the impact of whole brain radiotherapy. J Thorac Oncol 7:382-385, 2012

8. Sun CS, Cho BC, Soo RA: Treatment options for EGFR mutant NSCLC with CNS involvement—can patients BLOOM with the use of next generation EGFR TKIs? Lung Cancer 108:29-37, 2017

9. Chamberlain MC: Leptomeningeal metastasis. Curr Opin Oncol 22:627-635, 2010

10. Du C, Hong R, Shi Y, et al: Leptomeningeal metastasis from solid tumors: A single center experience in Chinese patients. J Neurooncol 115:285-291, 2013

11. Yufu X, Binbin S, Wenyu C, et al: The role of EGFR-TKI for leptomeningeal metastases from non-small cell lung cancer. Springerplus 5:1244, 2016

12. Chamberlain M, Junck L, Brandsma D, et al: Leptomeningeal metastases: A RANO proposal for response criteria. Neuro-oncol 19:484-492, 2017

13. Remo J, Le Ruhn E, Besse B: Leptomeningeal carcinomatosis in non-small cell lung cancer patients: A continuing challenge in the personalized treatment era. Cancer Treat Rev 53:128-137, 2017

14. TAGRISSO [package insert]. Wilmington, DE, AstraZeneca, 2018. Available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/208065s008lbl.pdf

15. European Medicines Agency: Summary of product characteristics: TAGRISSO, 2018. https://www.ema.europa.eu/en/documents/product-information/tagrisso-epar-product-information_en.pdf

16. 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 22:5130-5140, 2016

17. Colclough N, Ballard PG, Barton P, et al: Preclinical comparison of the blood brain barrier (BBB) permeability of osimertinib (AZD9291) with other irreversible next generation EGFR TKIs. Eur J Cancer 69:528, 2016

18. Vishwanath K, Varonne A, Varnas K, et al: Osimertinib displays high brain exposure in healthy subjects with intact blood-brain barrier: A microdose positron emission tomography (PET) study with 11C-labelled osimertinib. Cancer Res 78, 2018 (suppl; abstr CT013)

19. Kim DW, Yang CH, Cross D, et al: Preclinical evidence and clinical cases of AZD9291 activity in EGFR-mutant non-small cell lung cancer (NSCLC) brain metastases. Ann Oncol 25, 2014 (suppl; abstr 456P)

20. Ahn MJ, Kim DW, Cho BC, et al: Activity and safety of AZD3759 in EGFR-mutant non-small cell lung cancer with CNS metastases (BLOOM): A phase 1, open-label, dose-escalation and dose-expansion study. Lancet Respir Med 5:891-902, 2017

21. Zhu G, Ye X, Dong Z, et al: Highly sensitive droplet digital PCR method for detection of EGFR-activating mutations in plasma cell-free DNA from patients with advanced non-small cell lung cancer. J Mol Diagn 17:265-272, 2015

22. Planchard D, Brown KH, Kim DW, et al: Osimertinib western and Asian clinical pharmacokinetics in patients and healthy volunteers: Implications for formulation, dose, and dosing frequency in pivotal clinical studies. Cancer Chemother Pharmacol 77:767-776, 2016

23. 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 29:697-699, 2018

24. Mok TS, Wu Y-l, Ahn M-J, et al: Osimertinib or platinum-pemetrexed in EGFR T790M-positive lung cancer. N Engl J Med 376:629-640, 2017

25. Soria JC, Ohe Y, Vansteenkiste J, et al: Osimertinib in untreated EGFR-mutated advanced non-small-cell lung cancer. N Engl J Med 378:113-125, 2018

26. Chan OS, Leung WK, Yeung RM: Sustained response to standard dose osimertinib in a patient with plasma T790M-positive leptomeningeal metastases from lung adenocarcinoma. Asia Pac J Clin Oncol 13:428-430, 2017

27. Pareek V, Welch M, Ravera E, et al: Marked differences in CNS activity among EGFR inhibitors: Case report and mini-review. J Thorac Oncol 11:e00241, 2017

28. Uemura T, Oguri T, Okayama M, et al: Dramatic intracranial response to osimertinib in a poor performance status patient with lung adenocarcinoma harboring the epidermal growth factor receptor T790M mutation: A case report. Mol Clin Oncol 6:525-528, 2017

29. Amin HB, Ohake T, Ono H, et al: The role of osimertinib in the treatment of EGFR-mutated advanced non-small cell lung cancer: A phase II clinical study. Br J Cancer 118:32-37, 2018

30. Saboundji K, Auliac JB, Perol M, et al: Efficacy of osimertinib treatment in patients with leptomeningeal carcinomatosis from lung adenocarcinoma pretreated with EGFR-tyrosine kinase inhibitors. Target Oncol 13:501-507, 2018

31. Dearden S, Brown H, Jenkins S, et al: EGFR T790M mutation testing within the osimertinib AURA phase I study. Lung Cancer 109:9-13, 2017

32. Jaeger PA, Yang JC, Kim DW, et al: AZD9291 in EGFR inhibitor-resistant non-small-cell lung cancer. N Engl J Med 372:1689-1699, 2015

33. Ota K, Shiraiishi Y, Harada T, et al: Phase II study of erlotinib in advanced non-small cell lung cancer patients with leptomeningeal metastasis (LOGIK101). J Thorac Oncol 12:5271-5272, 2017

34. Tamaiya A, Tamaiya M, Nishihara T, et al: Cerebrospinal fluid penetration rate and efficacy of afatinib in patients with EGFR Mutation-positive non-small cell lung cancer with leptomeningeal carcinomatosis: A multicenter prospective study. Anticancer Res 37:4177-4182, 2017

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39. Jackman DM, Cioffredi LA, Jacobs L, et al: A phase I trial of high dose gefitinib for patients with leptomeningeal metastases from non-small cell lung cancer. Oncotarget 6:4527-4536, 2015

40. How J, Mann J, Laczniak AN, et al: Pulsatile erlotinib in EGFR-positive non-small-cell lung cancer patients with leptomeningeal and brain metastases: Review of the literature. Clin Lung Cancer 18:354-363, 2017

41. Kawamura T, Hata A, Takeshita J, et al: High-dose erlotinib for refractory leptomeningeal metastases after failure of standard-dose EGFR-TKIs. Cancer Chemother Pharmacol 75:1261-1266, 2015
AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Osimertinib in Patients With Epidermal Growth Factor Receptor Mutation–Positive Non–Small-Cell Lung Cancer and Leptomeningeal Metastases: The BLOOM Study

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO’s conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/journal/jco/site/ifc.

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No other potential conflicts of interest were reported.