Osimertinib versus afatinib in patients with T790M-positive, non-small-cell lung cancer and multiple central nervous system metastases after failure of initial EGFR-TKI treatment

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Abstract

Background The purpose of this study was to compare the efficacy of osimertinib (OSI) versus afatinib (AFA) in patients with T790M-positive, non-small-cell lung cancer (NSCLC) and multiple central nervous system (CNS) metastases after failure of initial epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) treatment. Methods The cohort consisting of 124 patients (OSI: n=60, median age=64.24 years [range, 51.91 to 76.57]; AFA: n=64, median age=64.13 years [range, 50.41 to 77.85]) with T790M-positive NSCLC and multiple CNS metastases after failure of initial EGFR-TKI treatment were consecutively identified at the Cancer Medical Center, Sun Yat-Sen University between March 2017 and July 2017; patients underwent either oral OSI (80 mg/day) or oral AFA (40 mg/day) until the occurrence of disease progression, intolerable adverse events (AEs), or death. The co-primary endpoints were overall survival (OS) and progression-free survival (PFS). Results After a median follow-up of 24 months (range, 6 to 26), a significant improvement in OS was observed in the OSI group compared with the AFA group (hazard ratio [HR] 0.30, 95% confidence interval [CI] 0.23 - 0.41; p = 0.009; median, 13.0 versus 9.2 months). The median duration of PFS was significantly longer with OSI than with AFA (HR 0.25, 95% CI 0.11 - 0.34; p = 0.001; median, 5.4 versus 4.3 months). The proportion of grade 3 or higher AEs was lower with OSI (22.4%) than with AFA (39.4%). Conclusion In patients with T790M-positive NSCLC and multiple CNS metastases after failure of initial EGFR-TKI treatment, OSI was associated with significantly improved survival benefit compared with AFA, and OSI exhibited a controllable tolerability profile.

Background

Patients with activated epidermal growth factor receptor (EGFR) mutation–positive, advanced non–small-cell lung cancer (NSCLC) are at increased risk for developing acquired resistance from the p.Thr790Met point (T790M) mutation in EGFR; this often occurs 9–13 months after first- and second-generation EGFR tyrosine kinase inhibitors (TKIs) treatment initiation and has an incidence of greater than 50%[1-4]. Central nervous system (CNS) metastases due to disease progression are frequent in these patients with advanced NSCLC harbouring EGFR-TKI–sensitizing mutations[4, 5]. Poor binding of previous EGFR-TKIs to the ATP-binding pocket of EGFR is triggered by the T790M variant, potentially resulting in disease progression[6, 7].

Osimertinib (OSI; TAGRISSO, AstraZeneca), an oral, 3rd-generation, irreversible EGFR-TKI that selectively inhibits both EGFR-TKI-sensitizing and EGFR T790M resistance mutations, has been approved by the Food and Drug Administration (FDA) on November 13, 2015 to treat patients with acquired EGFR T790M resistance or progression on or after EGFR-TKI therapy, and it may resolve the impasse[8, 9]. Data from previous trials indicated that OSI efficacy in the EGFR-mutated NSCLC cohort with T790M mutation was superior to that of first- or second-generation EGFR-TKIs, with a similar safety profile and lower rates of serious adverse events (AEs)[8]. In a phase I/II clinical trial (AURA Study Phase II Extension Component, NCT01802632)[2] involving 198 evaluable patients with EGFR-TKI–pretreated EGFR- and T790M-positive NSCLC, showed that OSI leads to a promising median progression-free survival (PFS)(12.3 months, 95% CI, 9.5 to 13.8), and median durable response (15.2 months, 95% CI, 11.3 to not calculable). These

findings were verified by 2 subsequent Phase II studies involving OSI (80 mg/d) in 411 individuals with T790M-positive NSCLC, in which the median PFS was 11.0 months[5].

Afatinib (AFA), an irreversible ErbB family blocker, inhibits tyrosine kinase activity of EGFR and pertinent ErbB family dimers[10, 11]. Single-agent AFA has shown remarkable survival benefits compared with platinum-based chemotherapy in earlier treatment-naïve EGFR-mutated NSCLC[12-15]. It has also exhibited modest clinical activity in those cases who acquired resistance to first- and second-generation EGFR-TKIs and progressed on these drugs following initial benefit[16-18]. After the approval of OSI for T790M-positive NSCLC, the standard of care should be OSI rather than AFA. However, in China, the reasons why AFA is used for so many patients are that compared with OSI, AFA with lower cost is easier to obtain for patients.

Nevertheless, whether OSI has superior survival benefits and higher activity against T790M-positive NSCLC and multiple CNS metastases after failure of initial EGFR-TKI treatment compared with AFA remains unknown[16-19]. Furthermore, prior contradictory data could be clarified, indicating heterogeneous data resulting from the subjects harbouring indeterminate EGFR-mutated subtypes, small sample sizes, confounding terminology, non-targeted therapy, wide confidence intervals (CI), or dubious statistical power[1, 6]. We therefore conducted a retrospective review of patients with T790M-positive NSCLC and multiple CNS metastases after failure of initial EGFR-TKI treatment to compare the efficacy of OSI versus AFA therapy. To our knowledge, this is the first analysis that retrospectively compared OSI against AFA for the management for T790M-positive NSCLC and multiple CNS metastases after failure of initial EGFR-TKI treatment in an Asian population.

Methods

Study design and patients

Clinical data of individuals with T790M-positive NSCLC and multiple CNS metastases after failure of initial EGFR-TKI treatment from a registry database were identified at the Cancer Medical Centre, Sun Yat-Sen University (CMC; Guangzhou, China) between March 2017 and July 2017. Information regarding OSI or AFA delivery, tumour EGFR mutation status, and survival were retrieved from medical records. Tumours were assessed every 6 weeks thereafter by CT, X-rays, bone scans, and MRI as indicated. AEs were evaluated in accordance with the US National Cancer Institute's Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE)[20]. The co-primary endpoints were overall survival (OS) and PFS. Inclusion criteria were defined as: patients aged ≥50 years with a histologically and/or cytologically confirmed NSCLC harbouring a sensitizing EGFR T790M mutation after failure of initial EGFR-TKI treatment; available NSCLC specimens before initial EGFR-TKI treatment; multiple CNS metastases (≥ 3 metastatic lesions) confirmed by imaging evidence (e.g., computed tomography [CT], magnetic resonance imaging [MRI]); patients receiving either oral 80 mg/d OSI or oral 40 mg/d AFA until disease progression, intolerable AEs, or death after failure of initial EGFR-TKI treatment[2, 10]; adequate organ function[13]; Eastern Cooperative Oncology Group (ECOG) status of 0-1.

The main exclusion criteria were: previous chemotherapy, radiotherapy, chemoradiotherapy, or surgery for NSCLC and/or CNS metastases; symptomatic CNS metastases at the initial administration of OSI or AFA; severe digestive diseases affecting drug absorption (e.g., perforation and/or fistula formation); insufficient imaging data; discontinuation or interruption of OSI or AFA; intolerable AEs: (e.g., uncontrolled diabetes or hypertension) that have a significant impact on the co-primary endpoints; severe infection (e.g., HIV infection).

We included a total of 172 patients with T790M-positive NSCLC and multiple CNS metastases after failure of initial EGFR-TKI treatment from the retrospective cohort between March 2017 and July 2017. Forty-eight (27.9%) individuals were excluded on account of the inclusion and exclusion criteria, leaving 124 eligible cases for final analysis, as summarized in Figure 1 (OSI: n=60, median age=64.24 years [range, 51.91 to 76.57]; AFA: n=64, median age=64.13 years [range, 50.41 to 77.85]). No significant differences were detected in the demographic data between groups, as presented in Table 1.

Statistical analysis

NSCLC stage was determined according to the Lung Cancer Stage Classification System. Tumour mutation status was tested on plasma or tissue specimens at the State Key Laboratory, Sun Yat-Sen University, as reported[1, 5]. PFS was calculated from the initiation of drug treatment until the date of disease progression according to RECIST 1.1 or death from any cause, whichever occurred first. OS was calculated from the initiation of drug treatment until the date of death. Comparisons of continuous variables between groups were evaluated using Student's t-test or ANOVAs. The Fisher exact test or Pearson χ^2 were used for binary categorical variables. Time-to-symptom progression in the subgroup with baseline multiple CNS metastases, median PFS, and median OS were estimated using the Kaplan–Meier methodology. Between-group comparisons for survival probabilities were assessed using the log-rank test. Survival differences were estimated using the Cox proportional hazard regression model in which partial baseline data (e.g., age, smoking status) were adjusted. Missing data were not included in the study, which is consistent with previous descriptions[21]. The hazard ratio (HR) and corresponding 95% CIs were estimated using Cox proportional hazards models. HRs for PFS and OS were also estimated using a multivariate Cox regression model with adjustment for potential confounding factors. A two-sided *p* value of <0.05 was considered statistically significant. Data were analysed using SPSS, version 24.0 (IBM Corp., Armonk, NY).

Results

Survival analysis

The median duration of follow-up was 24 months (range, 6 to 26). At the final follow-up, the median duration of OS was 13.0 months (range, 3.4 to 15.8) in the OSI group and 9.2 months (range, 3.2 to 11.1) in the AFA group. The main cause of death in patients tends to coma induced by CNS metastases. The median duration of OS was significantly longer with OSI than with AFA (HR 0.30; 95% CI 0.23 - 0.41; *p* =

0.009; Figure 2). The median duration of PFS was 5.4 months (range, 2.4 to 9.2) in the OSI group and 4.3 months (range, 2.2 to 7.9) in the AFA group. The median duration of PFS was significantly longer among patients undergoing OSI than among those treated with AFA (HR 0.25; 95% CI 0.11 - 0.34; p = 0.001; Figure 3).

Adverse events

Safety was assessed for each patient treated with OSI or AFA. AEs occurred in 48 of 60 patients (80.0%) in the OSI group and in 59 of 64 (92.2%) in the AFA group. Drug-related AEs are summarized in Table 2. The proportion of grade 3 or higher AEs was lower with OSI (22.4%) than with AFA (39.4%). Most AEs were mild-to-moderate in severity and reversible. In our study, there was not significant difference in the hematological toxicity between groups, although it is one of the major side effects of EGFR-TKI.

The OSI-related AEs that were most commonly reported included diarrhoea (24 patients [28.2%]; 8 [9.4%] were deemed as ≥ grade 3), rash (in 22 [25.9%]; 5 [5.9%] were ≥ grade 3), dry skin (in 18 [21.2%]; 6 [7.1%] were deemed as ≥ grade 3), and paronychia (in 11 [12.9%]; no one was deemed as ≥ grade 3). Most rashes were regarded as grade 1 or 2 (17 [20.0%] vs. 11 [10.1%] in the OSI and AFA groups, respectively; p = 0.05). The most common AFA-related AEs were diarrhoea (47 patients [43.1%]; 25 [22.9%] were deemed as ≥ grade 3), alopecia (in 15 [13.8%]; 6 [5.5%] were ≥ grade 3), asthenia (in 6 [5.5%]; no one was deemed as ≥ grade 3), decreased appetite (in 5 [4.6%]; no one was deemed as ≥ grade 3) and rash (in 18 [16.5%]; 7 [6.4%] were deemed as ≥ grade 3). OSI was associated with a lower rate of AEs leading to dose reductions than was AFA (in 6 [7%] and 16 [10%], respectively, p = 0.02).

Discussion

Findings from our retrospective analysis comparing the efficacy of OSI versus AFA in patients with T790M-positive NSCLC and multiple CNS metastases after failure of initial EGFR-TKI treatment, showed that despite the short follow-up time, our finding confirmed similar results from prior reports[1, 22]with the same treatment regimen associated; we observed improved outcomes for patients with T790M-positive NSCLC and multiple CNS metastases, including similar survival benefit from OSI for such cohort. However, the shorter survival was detected in our study compared some previous studies[2, 6, 8]. The underlying background and reason of the shorter survival could be the fact that patients with T790M-positive NSCLC and multiple CNS metastases tend to have a worse prognosis than those who have no such metastases.

Previous reports of OSI or AFA in T790M-positive NSCLC have encountered unexpected obstacles, including non-uniform definitions of variables, undefined CNS metastases, and incoherent treatment regimens, which may lead to survival variability among patient reports[1, 2, 23-25]. Although the limited sample size makes it difficult to reach convincing conclusions in the current analysis, the survival advantage of OSI is more significant compared with that of AFA, but further validation of our findings is required. The key limiting factor for such cohort is to grasp the timing of multiple CNS metastases. For PFS, a well-defined finding favouring the OSI regimen was described[2, 25], although PFS was not the

primary endpoint. The reason why PFS but not OS was affected could be associated with small cohort of research subjects with NSCLC progression who failed to undertake EGFR-TKI treatment.

A population-based study involving 15 medical institutes that cover a population of three million people indicated the disadvantages of pre-treatment before AFA in patients with NSCLC harboring an acquired EGFR T790M mutation[18]. However, the evidence-based trials regarding the optimal regimen in the management of cases with T790M-positive NSCLC and multiple CNS metastases remain controversial[23, 26]. Within this context, evidence has indicated that neither the first-generation nor second-generation EGFR-TKIs distinctly improve the OS among those cases with T790M-positive NSCLC[23, 27]. Nonetheless, whether there were multiple CNS metastases in the studied cohorts and whether CNS metastases offset some of the EGFR-TKI efficacy remain ambiguous[27, 28], which could obscure the facts. There is a significant difference in the composition ratio of patients with multiple CNS metastases in each group, possibly resulting from variability in the response to the EGFR-TKI in diverse reports[19, 29]. In the present study, the survival benefits of OSI over AFA were consistent with prospective randomized trials[22, 25, 30, 31]in which the composition ratio of multiple CNS metastases was assessed in subgroup analyses. Consequently, the between-group differences in survival benefits might be attributed to drug mechanistic differences[22, 32]. Additionally, analogous studies, which compared OSI with AFA in individuals with T790M-positive NSCLC following chemotherapy, also demonstrated similar findings[15, 33, 34].

However, consensus is lacking as to what is the optimal treatment regimen for such cohorts[5, 32, 35]. At present, patients with progressing NSCLC who received first- or second-generation EGFR-TKIs are best treated with OSI alone or in combination with chemotherapy, if possible[2, 5, 7]. Although OSI is not part of the current standard of care in China, it was approved by the FDA for the management of the T790M-positive NSCLC patients[22, 36]. Previous studies of cases with T790M-positive NSCLC have confirmed that the irreversible inhibitor OSI offers more survival benefits compared with other reversible EGFR-TKIs[4, 7]. Of note, those studies in which some subjects failed to be included based on the T790M mutation appear to have unclear data or to have restricted subjects according to the researcher's preference. Additionally, OSI has been less frequently used because the empirical use of drugs is common in clinical practice despite the lack of reliable supportive evidence in the first few years[2, 22, 27].

Although our analysis contributes to gaining a better understanding of the survival benefits of the continued OSI treatment in the setting of T790M-positive NSCLC and multiple CNS metastases after failure of initial EGFR-TKI treatment, there are certain limitations to discuss. First, the level of evidence in the current study is limited due to the weaknesses inherent in a retrospective analysis including treatments, follow-up, and missing data. A number of cases were excluded at the final follow-up owing to imperfect follow-up data, which may introduce bias. Although the capacity to draw reliable conclusions may be reduced due to the biases that may have contributed to differences in outcomes, it is almost impossible for these issues to play a crucial role due to the baseline data and the contemporaneous methods following widespread standards. However, prospective studies are required to verify the survival

benefit of OSI over AFA. Second, the current outcomes were limited by our follow-up protocol (i.e. frequency, length). Third, possible heterogeneity seems hard to avoid, even though considerable variables have been adjusted.

Conclusions

Our study demonstrated that a noteworthy survival superiority of OSI over AFA was observed in patients with T790M-positive NSCLC and multiple CNS metastases after failure of initial EGFR-TKI treatment. The survival benefits with OSI might reflect its broader mechanism of action compared with AFA. We believe that OSI could be a more effective therapeutic option than AFA in the current setting. Although our analysis was powered to assess end-points, given the high mortality associated with T790M-positive NSCLC, if OSI or AFA were to be re-evaluated in a comparable setting, extended follow-up time is needed to determine whether our findings are confirmed over an extended follow-up period.

Abbreviations

OSI: osimertinib; **AFA**: afatinib; **NSCLC**: non-small-cell lung cancer; **EGFR-TKI**: epidermal growth factor receptor tyrosine kinase inhibitor; **AEs**: adverse events; **OS**: overall survival; **PFS**: progression-free survival; **SD**: standard deviation; **CI**: confidence interval; **IQR**: interquartile range; **HR**: hazard ratio; **T790M**: p.Thr790Met; **CT**: computed tomography; **MRI**: magnetic resonance imaging; **ECOG**: Eastern Cooperative Oncology Group; **VCI**: vascular cognitive impairment; **RECIST**: Response Evaluation Criteria in Solid Tumours.

Declarations

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Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author upon reasonable request.

Authors' contributions

YJ: Planning and study design, study execution, and writing-initial draft. **XH**: Statistical analysis/interpretation, and writing-final revision. **JL**, **LX**, and **DL**: Planning and study design. **NS**: Data collection and study execution. **NS**, **MZ** and **GH**: Writing-initial draft, and writing-final revision. All authors were involved in the manuscript preparation and approved the submitted version.

Ethics approval and consent to participate

This retrospective study was approved by the Institutional Review Board and Ethics Review Board of The First Affiliated Hospital, Sun Yat-sen University (No. 2014594). Patients' informed consent was waived by the Ethics Review Boards.

Consent for publication

Not applicable.

Competing interests

The authors declare that there is no conflict of interest.

Tables

Table 1. Baseline characteristics of patient groups

Variable	OSI (n=60)	AFA (n=64)	*p* - value
Age (years)	64.24±12.33	64.13±13.72	0.72[a]
Sex (male/female)	25/35	28/36	0.82[b]
BMI (kg/m^2)	23.74±2.31	24.15±2.46	0.26[a]
Smoking status			0.81[c]
Never a smoker	11	13	
Former smokers	32	30	
Current smokers	17	21	
Time from diagnosis of NSCLC (months)			0.78[c]
< 6	15	17	
6–12	35	33	
>12	10	14	
Largest size of brain metastasis			0.31[c]
≤10 mm	22	18	
>10 mm	38	46	
Number of brain metastases			0.47[c]
≤3	32	30	
>3	28	34	
ECOG performance status			0.97[c]
0	9	12	
1	27	25	
2	24	27	

[a]Analysed using independent-samples t-test. [b]Analysed using Chi-squared test. [c]Analysed using the Mann-Whitney test. BMI: body mass index; OSI: osimertinib; AFA: afatinib; NSCLC: non–small-cell lung cancer; ECOG: Eastern Cooperative Oncology Group.

Table 2. Drug-related adverse events

Variable	OSI (n = 85 AEs involving 48 patients)		AFA (n = 109 AEs involving 59 patients)		*p* - value[a]	
	All grades (%)	≥Grade 3 (%)	All grades (%)	≥Grade 3 (%)	All grades (%)	≥Grade 3 (%)
Diarrhoea	24 (28.2)	8 (9.4)	47 (43.1)	25 (22.9)	0.03*	0.13
Rash	22 (25.9)	5 (5.9)	18 (16.5)	7 (6.4)	0.11	0.88
Dry skin	18 (21.2)	6 (7.1)	12 (11.0)	5 (4.6)	0.52	0.46
Paronychia	11 (12.9)	0 (0.0)	6 (5.5)	0(0.0)	0.07	NA
Alopecia	3 (3.5)	0 (0.0)	15 (13.8)	6 (5.5)	0.02*	0.03*
Asthenia	2 (2.4)	0 (0.0)	6 (5.5)	0 (0.0)	0.27	NA
Decreased appetite	5 (5.8)	0 (0.0)	5 (4.6)	0 (0.0)	0.69	NA

**Statistically significant. [a]Analysed using Chi-squared test. AEs: adverse events; OSI: osimertinib; AFA: afatinib; NA: not applicable.*

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Figures

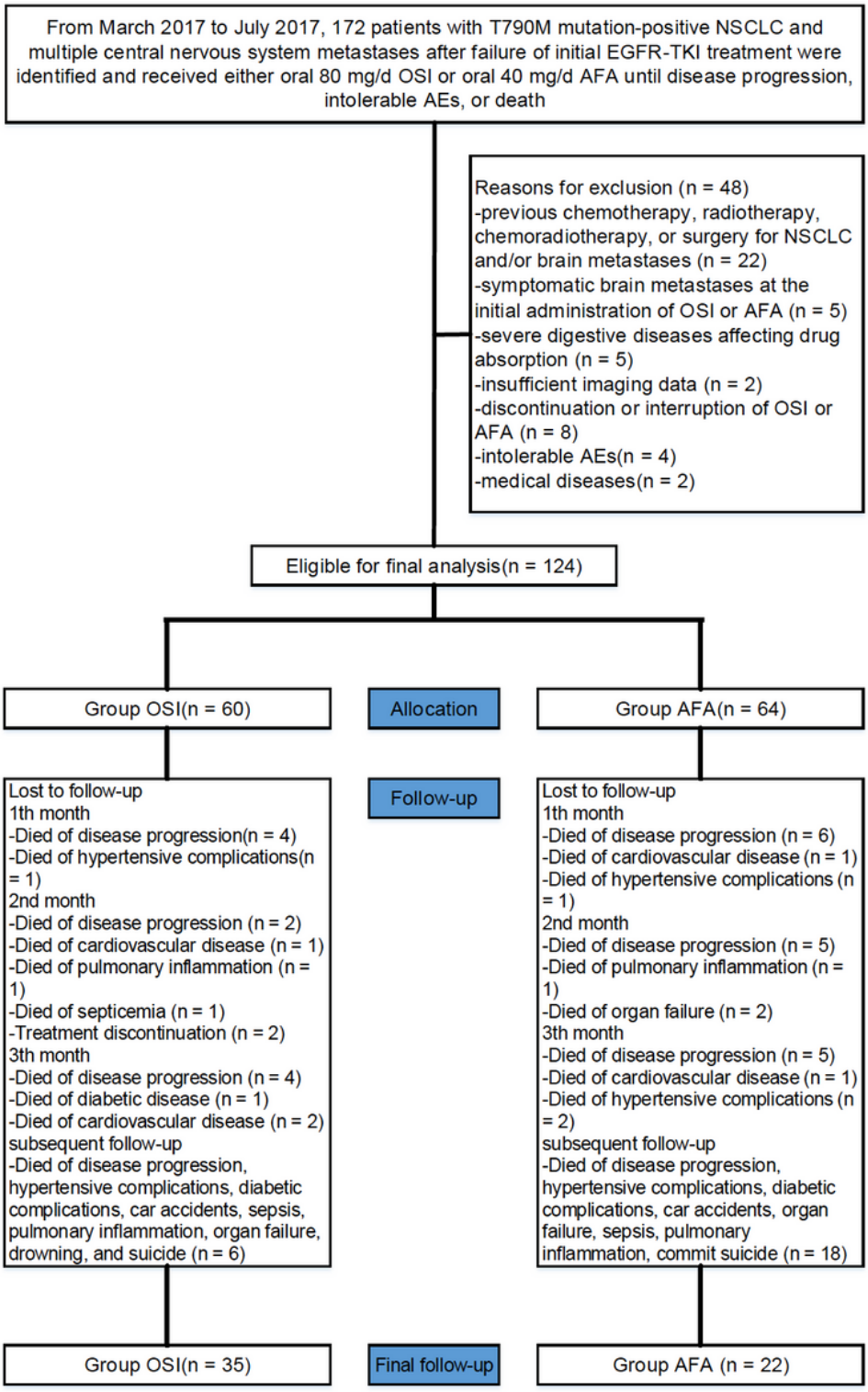


Figure 1

Flow diagram illustrating the methods used to identify studies to retrospectively compare the efficacy of osimertinib (OSI) versus afatinib (AFA) in patients with T790M-positive, non-small-cell lung cancer (NSCLC) and multiple central nervous system (CNS) metastases after failure of initial epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) treatment.

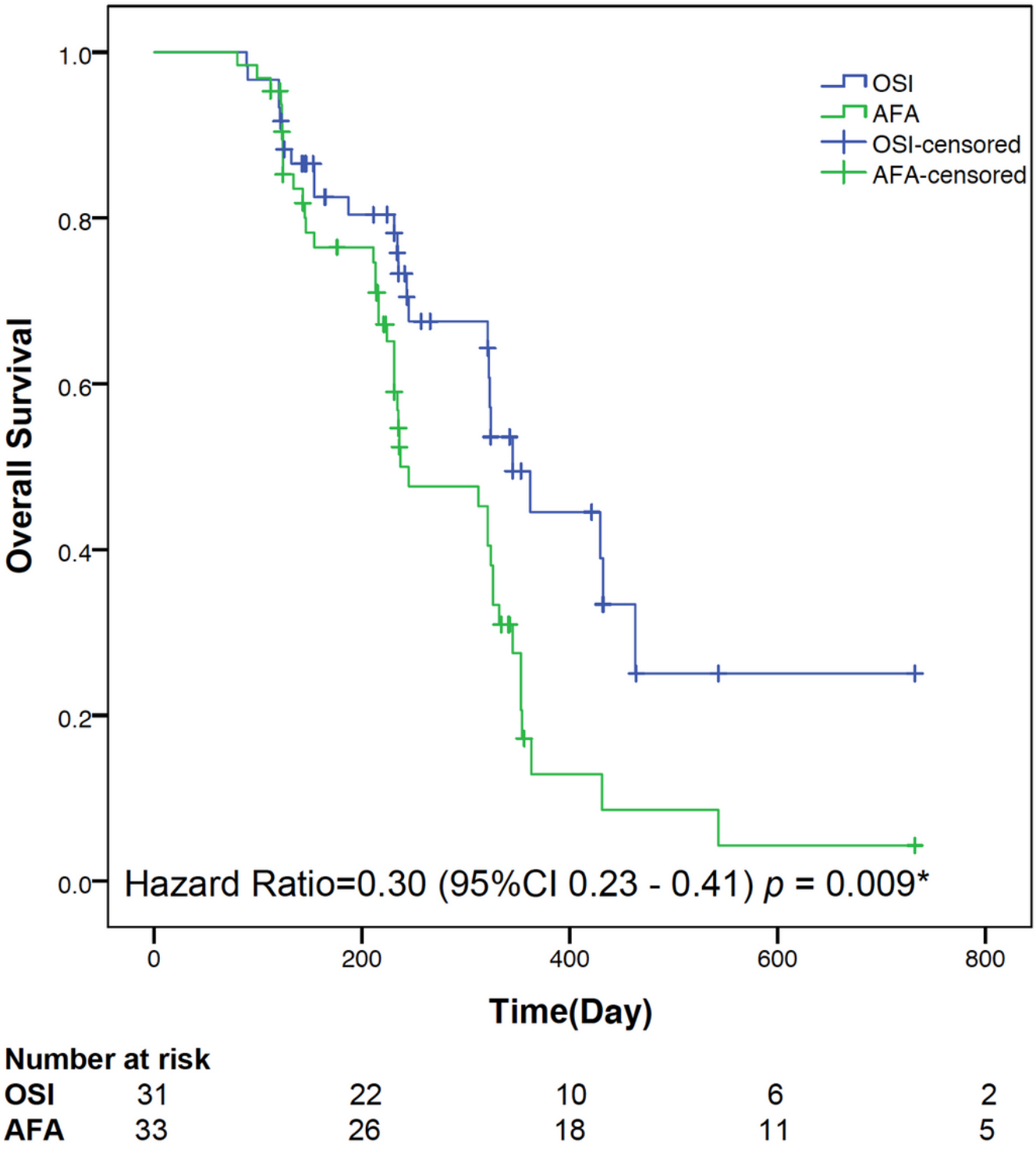
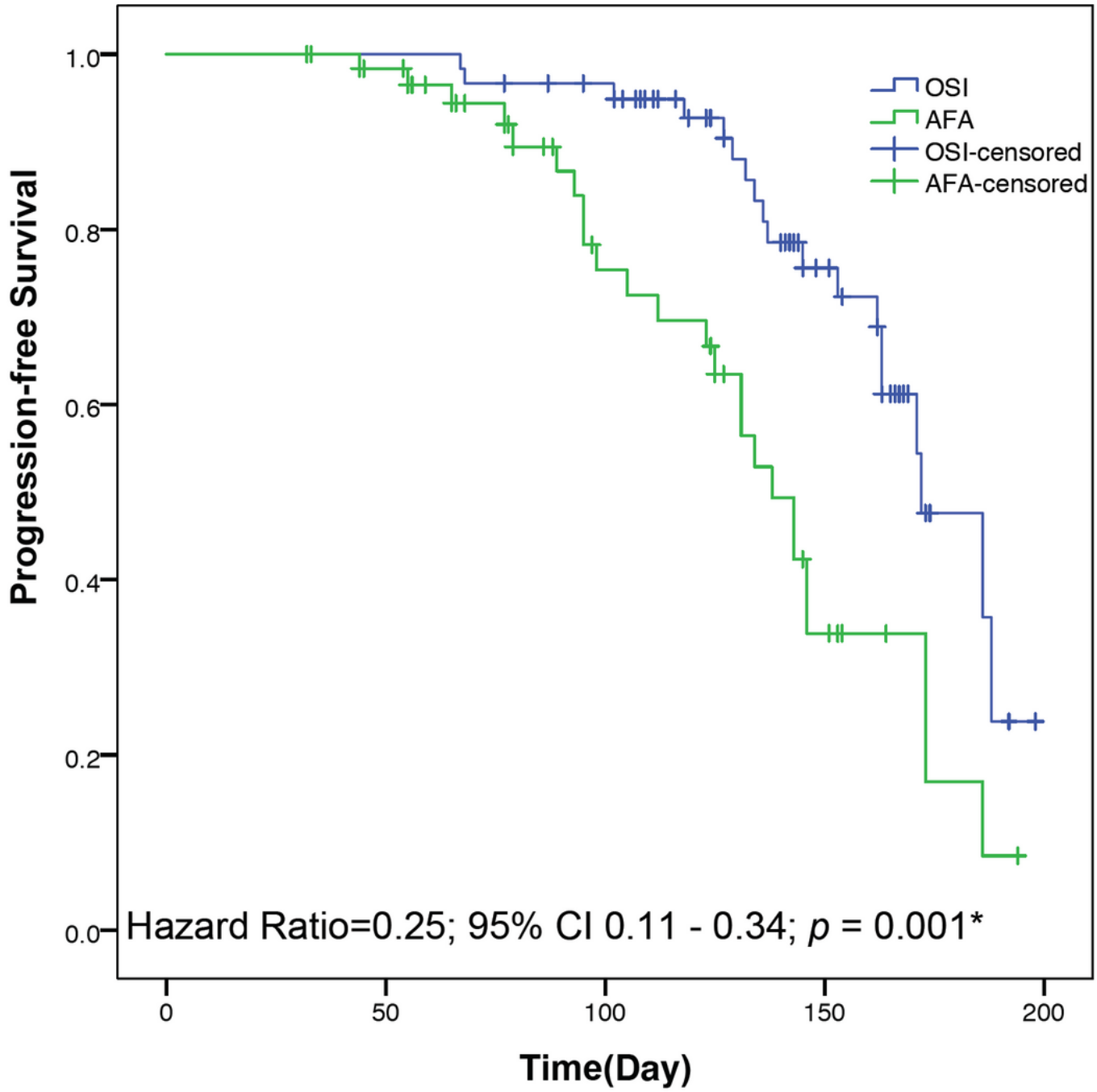


Figure 2

Kaplan–Meier curves for OS The median OS was 13.0 months (range, 3.4 to 12.8) for OSI and 9.2 months (range, 3.2 to 10.0) for AFA. A significant difference was observed in the median OS between groups. *HR was calculated using the Cox proportional hazards model, with age, sex and time span of smoking history as covariates and OSI/AFA therapy as the time-dependent factor. With respect to OS, the results were analysed using the log-rank test (p = 0.009).



Number at risk					
OSI	21	17	8	4	1
AFA	27	21	12	7	3

Figure 3

Kaplan–Meier curves for PFS The median PFS was 5.4 months (range, 2.4 to 6.2) for OSI and 4.3 months (range, 2.2 to 4.9) for AFA. A significant difference was detected in the median PFS between groups. *HR was calculated using the Cox proportional hazards model, with age, sex and time span of smoking history as covariates and OSI/AFA therapy as the time-dependent factor. With respect to PFS, the results were analysed using the log-rank test (p = 0.001).