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

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Summary

Background CNS metastases—including brain and leptomeningeal metastases—from epidermal growth factor receptor (EGFR)-mutant non-small-cell lung cancer (NSCLC) are associated with poor prognosis. AZD3759 is a novel EGFR tyrosine kinase inhibitor with high capability to penetrate the blood–brain barrier. We aimed to assess the safety, tolerability, pharmacokinetics, and efficacy of AZD3759 in patients with EGFR-mutant NSCLC with brain and leptomeningeal metastases.

Methods This open-label, multicentre, phase 1 study was undertaken at 11 centres and hospitals in Australia, South Korea, Taiwan, and the USA. Eligible patients included those with histologically confirmed, advanced-stage, EGFR-mutant NSCLC. The study was done in two parts, with dose-escalation and dose-expansion phases. In the dose-escalation phase, patients who had progressed after treatment with an EGFR tyrosine kinase inhibitor received AZD3759 at 50 mg, 100 mg, 200 mg, 300 mg, or 500 mg twice a day. In the dose-expansion phase, AZD3759 at 200 mg or 300 mg twice a day was administered to patients with either brain or leptomeningeal metastases who had never received an EGFR tyrosine kinase inhibitor and patients with leptomeningeal metastases who had been pretreated with an EGFR tyrosine kinase inhibitor. The primary objective was safety and tolerability, with severity of adverse events assessed with the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 4.03. This trial is registered with ClinicalTrials.gov, number NCT02228369.

Findings Between Nov 18, 2014, and Sept 7, 2016, 67 patients with NSCLC were enrolled into the study, 29 to the dose-escalation phase and 38 to the dose-expansion phase. At data cutoff (Dec 12, 2016), three (10%) patients in the dose-escalation phase and 20 (53%) in the dose-expansion phase were still receiving treatment. Dose-limiting toxic effects occurred in two (67%) of three patients who received 500 mg twice a day in the dose-escalation phase (grade 3 acne [n=1] and intolerable grade 2 mucosal inflammation [n=1]); hence, doses of 200 mg and 300 mg twice a day were selected for further assessment in the dose-expansion phase. Drug-related skin and gastrointestinal disorders of any grade occurred in 35 (92%) and 29 (76%) patients in the dose-expansion phase, respectively, and led to treatment discontinuation in one (4%) patient treated with 200 mg twice a day (grade 3 increase of alanine aminotransferase and aspartate aminotransferase) and two (13%) patients given 300 mg twice a day (grade 3 diarrhoea [n=1] and grade 3 skin rash [n=1]). Grade 3 skin and gastrointestinal disorders occurred in four (17%) and two (9%) patients, respectively, at a dose of 200 mg twice a day, and in six (40%) and four (27%) patients, respectively, at a dose of 300 mg twice a day. No grade 4 disorders arose. Other grade 3 disorders included hepatobiliary and renal disorders (three [13%] at 200 mg twice a day), asthenia (one [7%] at 300 mg twice a day), infections and infestations (one [7%] at 300 mg twice a day), and metabolism and nutrition disorders (one [4%] at 200 mg twice a day and one [7%] at 300 mg twice a day).

Interpretation AZD3759 at a dose of 200 mg twice daily showed a tolerable safety profile in patients with NSCLC and CNS metastases who had either never received a tyrosine kinase inhibitor or who had been pretreated with a tyrosine kinase inhibitor. The good penetration of the blood–brain barrier by AZD3759, and its promising clinical activity, support further assessment of this compound in studies.

Funding AstraZeneca.

Lancet Respir Med 2017

Published Online
October 19, 2017
http://dx.doi.org/10.1016/S2213-2600(17)30378-8

See Online/Comment/
http://dx.doi.org/10.1016/S2213-2600(17)30395-8

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Introduction

CNS metastases (eg, brain and leptomeningeal metastases) in non-small-cell lung cancer (NSCLC) are associated with poor prognosis and low quality of life. More than 50% of patients with NSCLC and epidermal growth factor receptor (EGFR)-activating mutations develop CNS metastases during their lifespan.[1–3] Median overall survival is about 16 months for patients with brain metastases[4] and 4·5–11 months for those with leptomeningeal metastases.[5,6]

Radiotherapy is the standard treatment for brain metastases. The benefit of radiotherapy for patients' survival is limited, and this treatment is associated with

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Research in context

Evidence before this study

We searched PubMed for reports published between Jan 1, 2009, and July 20, 2017, with the terms "EGFR", "tyrosine kinase inhibitor", "lung cancer", "CNS metastases", "brain metastasis", "BM", "leptomeningeal metastasis", or "LM". We did not restrict our search by language. In some reports, approved epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors had limited effects on leptomeningeal metastases and variable clinical activity on brain metastases. Increasing approved doses of EGFR tyrosine kinase inhibitors by up to ten times showed modest palliative effect on CNS metastases (eg, brain and leptomeningeal metastases), but patients could not tolerate such high doses. These findings suggest that it would be valuable to have a drug with better penetration of the blood–brain barrier, which can achieve efficacious concentrations in the CNS at clinically tolerable doses. These clinical data formed the basis of the design of AZD3759—an EGFR tyrosine kinase inhibitor that can penetrate the blood–brain barrier. This drug is anticipated to achieve efficacious concentrations in the CNS for treatment of brain and leptomeningeal metastases.

Added value of this study

This phase 1 study assessed the safety, tolerability, pharmacokinetics (in both plasma and cerebrospinal fluid [CSF]) and antitumour activity of AZD3759 in patients with EGFR-mutant non-small-cell lung cancer (NSCLC) who had either never received an EGFR tyrosine kinase inhibitor or who had been pretreated with an EGFR tyrosine kinase inhibitor. AZD3759 at a dose of 200 mg twice daily was well tolerated and achieved efficacious drug concentrations in plasma and CSF. To our knowledge, AZD3759 is the first EGFR tyrosine kinase inhibitor proven to achieve equivalent drug concentrations in plasma and CSF in patients. Moreover, AZD3759 was associated with promising, durable, clinical activity, attributable to effective penetration of the blood–brain barrier.

Implications of all the available evidence

In patients with NSCLC and CNS metastases who had never received an EGFR tyrosine kinase inhibitor, intracranial objective responses achieved with AZD3759 were augmented compared with other EGFR tyrosine kinase inhibitors. Furthermore, extracranial objective responses were comparable between AZD3759 and other similar drugs, suggesting the potential for AZD3759 to be first-line treatment for this group of patients as monotherapy. However, in patients with NSCLC and CNS metastases who progressed after treatment with an EGFR tyrosine kinase inhibitor, AZD3759 showed encouraging intracranial antitumour activity but diminished activity in extracranial tumours, suggesting the potential for AZD3759 to treat this group of patients in combination with other agents. The results of this phase 1 study warrant further clinical development of AZD3759.

toxic effects and long-term sequelae.[7,8] In phase 2 studies with small sample sizes, clinical activity of approved EGFR tyrosine kinase inhibitors (eg, gefitinib and erlotinib) was reported in patients with brain metastases.[9–11] In a pooled meta-analysis of these EGFR tyrosine kinase inhibitors, an objective response was achieved by about 52% of patients.[4] EGFR tyrosine kinase inhibitors approved or under clinical development show variable penetration across the blood–brain barrier, with $K_{puu,CSF}$ values (ie, ratio of cerebrospinal fluid [CSF] concentration to free plasma concentration) ranging from 0·066 to 0·29.[12]

No treatment has been approved for lung cancer with leptomeningeal metastases. Current EGFR tyrosine kinase inhibitors cannot treat leptomeningeal metastases effectively at the approved doses. Increases of up to ten times the approved dose of gefitinib or erlotinib reach the predicted efficacious concentration in CSF transiently and show modest palliative effect, but patients could not tolerate long-term treatment with such high doses because of serious adverse effects.[13,14] Furthermore, the response duration was very short.[15] Doubling the approved dose of osimertinib ($K_{puu,CSF}$ 0·29)[12] derived encouraging clinical activity in leptomeningeal metastases.[16] This evidence suggests that a drug with full penetration of the blood–brain barrier ($K_{puu,CSF}$ close to 1) could potentially achieve a better clinical outcome for patients with CNS metastases.

AZD3759 is an oral EGFR tyrosine kinase inhibitor with effective penetration of the blood–brain barrier designed to treat EGFR-mutant NSCLC with CNS metastases.[17,18] Here, we report the results of a phase 1, open-label, multicentre study (BLOOM) to assess the safety, tolerability, pharmacokinetics, and preliminary antitumour efficacy of AZD3759 in patients with EGFR-mutant, advanced-stage NSCLC. The BLOOM study also contained an independent non-randomised cohort to assess osimertinib 160 mg once a day in patients with leptomeningeal metastases pretreated with an EGFR tyrosine kinase inhibitor. The study is ongoing for this cohort and findings will be reported separately.

Methods

Study design and patients

BLOOM was an open-label, phase 1, multicentre study undertaken at 11 centres and hospitals in Australia, South Korea, Taiwan, and the USA. The study consisted of two parts: a dose-escalation phase and a dose-expansion phase. For the dose-escalation phase, we enrolled patients with NSCLC who had progressed after treatment with EGFR tyrosine kinase inhibitors and chemotherapy and who had brain or leptomeningeal metastases. For the dose-expansion phase, we enrolled patients with NSCLC who had never been treated with an EGFR tyrosine kinase inhibitor and who had brain or leptomeningeal

metastases, and patients with NSCLC pretreated with a tyrosine kinase inhibitor who had leptomeningeal metastases. We did not plan to enrol patients with NSCLC pretreated with a tyrosine kinase inhibitor who had brain metastases. A full list of inclusion and exclusion criteria is provided in the study protocol (appendix).

Key inclusion criteria were: age 18 years or older and histologically or cytologically confirmed NSCLC with activating mutations in EGFR (Leu858Arg or exon19del), which we assessed retrospectively. Furthermore, the cohort with brain metastases had to have at least one measurable lesion (≥1 cm) in the brain parenchyma, and the cohort with leptomeningeal metastases had to have positive CSF cytology and at least one site with an observable leptomeningeal lesion; patients without brain or leptomeningeal metastases had to have at least one measurable extracranial lesion. Moreover, an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 was required for the patients in the cohort with brain metastases, but an ECOG performance status of 0–2 was allowed for those with leptomeningeal metastases. All patients needed adequate haematological, hepatic, and renal function (defined in the study protocol [appendix]), and life expectancy of at least 3 months. Furthermore, for the dose-expansion phase cohorts, all patients who had brain metastases had to have never been treated with an EGFR tyrosine kinase inhibitor. Patients with leptomeningeal metastases could have been treated with or without an EGFR tyrosine kinase inhibitor. Patients pretreated with an EGFR tyrosine kinase inhibitor who had leptomeningeal metastases had to have stable extracranial disease at the time of enrolment.

Key exclusion criteria were: unresolved toxic effects from previous treatment (ie, worse than grade 1, according to the National Cancer Institute's Common Terminology Criteria for Adverse Events [CTCAE] version 4.03); a medical history of interstitial lung disease, drug-induced interstitial lung disease, radiation pneumonitis that needed steroid treatment, or any evidence of clinically active interstitial lung disease; and CNS complications that needed urgent neurosurgical intervention.

All patients provided written informed consent before enrolment into this study. The study protocol (appendix) was approved by the institutional review board or ethics committee at every centre participating in this study before site activation. The study was undertaken in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines, as defined by the International Conference on Harmonization. A Safety Review Committee—of which the core members comprised study clinicians employed by the funder and investigators from every site—was formed for study monitoring, safety management, and decision making.

Procedures

During the dose-escalation phase of the study, we administered AZD3759 orally twice a day in five dose cohorts: 50 mg, 100 mg, 200 mg, 300 mg, and 500 mg. We defined the starting dose as 50 mg twice a day based on findings from preclinical toxicity studies. We enrolled a minimum of three evaluable patients into each dose cohort for safety assessment before escalating to the next dose level, with up to seven patients in each dose cohort. We continued treatment until disease progression, unacceptable toxic effects, or consent withdrawal. Patients could continue treatment beyond progression, as assessed by modified Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 (appendix), as long as the investigator considered that patients were still deriving clinical benefit and tolerating

See Online for appendix

	Total (n=29)	No brain or leptomeningeal metastases (n=3)	Brain metastases (n=21)	Leptomeningeal metastases (n=5)
Age (years)	59 (41–80)	57 (52–67)	59 (43–80)	56 (41–62)
Sex				
Men	7 (24%)	0 (0%)	6 (29%)	1 (20%)
Women	22 (76%)	3 (100%)	15 (71%)	4 (80%)
Tumour histology				
Adenocarcinoma	28 (97%)	3 (100%)	20 (95%)	5 (100%)
Other	1 (3%)	0 (0%)	1 (5%)	0 (0%)
Disease type				
Measurable brain lesion	22 (76%)	0 (0%)	21 (100%)	1 (20%)
Measurable extracranial lesion	25 (86%)	3 (100%)	19 (90%)	3 (60%)
ECOG status				
0	8 (28%)	0 (0%)	8 (38%)	0
1	20 (69%)	3 (100%)	13 (62%)	4 (80%)
2	1 (3%)	0 (0%)	0 (0%)	1 (20%)
EGFR mutation in primary tumour				
Leu858Arg	17 (59%)	2 (67%)	11 (52%)	4 (80%)
Exon19del	12 (41%)	1 (33%)	10 (48%)	1 (20%)
Dose cohort				
50 mg	5 (17%)	1 (33%)	3 (14%)	1 (20%)
100 mg	7 (24%)	1 (33%)	5 (24%)	1 (20%)
200 mg	7 (24%)	1 (33%)	4 (19%)	2 (40%)
300 mg	7 (24%)	0	6 (29%)	1 (20%)
500 mg	3 (10%)	0	3 (14%)	0
History of whole-brain radiotherapy				
Yes	10 (34%)	0	7 (33%)	3 (60%)
No	19 (66%)	3 (100%)	14 (67%)	2 (40%)
History of EGFR tyrosine kinase inhibitor treatment				
Yes	29 (100%)	3 (100%)	21 (100%)	5 (100%)
No	0	0	0	0
History of chemotherapy				
Yes	29 (100%)	3 (100%)	21 (100%)	5 (100%)
No	0	0	0	0
Neurological examination at baseline				
Normal	19 (66%)	3 (100%)	14 (67%)	2 (40%)
Abnormal	10 (34%)	0	7 (33%)	3 (60%)

Data are median (range) or number of patients (%). ECOG=Eastern Cooperative Oncology Group. EGFR=epidermal growth factor receptor.

Table 1: **Baseline characteristics of patients in the dose-escalation phase**

	Total (n=38)	Brain metastases		Leptomeningeal metastases	
		200 mg (n=14)	300 mg (n=2)	200 mg (n=9)	300 mg (n=13)
Age (years)	57 (36–74)	58 (36–74)	56 (53–58)	52 (39–60)	60 (44–69)
Men	14 (37%)	7 (50%)	0 (0%)	4 (44%)	3 (23%)
Women	24 (63%)	7 (50%)	2 (100%)	5 (56%)	10 (77%)
Tumour histology					
Adenocarcinoma	38 (100%)	14 (100%)	2 (100%)	9 (100%)	13 (100%)
Disease type					
Measurable brain lesion	23 (61%)	14 (100%)	1 (50%)	3 (33%)	5 (38%)
Measurable extracranial lesion	31 (82%)	11 (79%)	0 (0%)	9 (100%)	11 (85%)
ECOG status					
0	5 (13%)	4 (29%)	0 (0%)	1 (11%)	0 (0%)
1	26 (68%)	8 (57%)	2 (100%)	7 (78%)	9 (69%)
2	7 (18%)	2 (14%)	0 (0%)	1 (11%)	4 (31%)
EGFR mutation in primary tumour					
Leu858Arg	16 (42%)	7 (50%)	1 (50%)	3 (33%)	5 (38%)
Exon19del	20 (53%)	7 (50%)	1 (50%)	6 (67%)	6 (46%)
Leu858Arg and Thr790Met	1 (3%)	0 (0%)	0 (0%)	0 (0%)	1 (8%)
Exon19del and Thr790Met	1 (3%)	0 (0%)	0 (0%)	0 (0%)	1 (8%)
History of whole-brain radiotherapy					
Yes	8 (21%)	0 (0%)	0 (0%)	4 (44%)	4 (31%)
No	30 (79%)	14 (100%)	2 (100%)	5 (56%)	9 (69%)
History of EGFR tyrosine kinase inhibitor treatment					
Yes	18 (47%)	0 (0%)	0 (0%)	8 (89%)	10 (77%)
No	20 (53%)	14 (100%)	2 (100%)	1 (11%)	3 (23%)
History of chemotherapy					
Yes	17 (45%)	2 (14%)	1 (50%)	6 (67%)	8 (62%)
No	21 (55%)	12 (86%)	1 (50%)	3 (33%)	5 (38%)
Lines of previous treatment					
0	16 (42%)	12 (86%)	1 (50%)	1 (11%)	2 (15%)
1	6 (16%)	1 (7%)	1 (50%)	0	4 (31%)
2	5 (13%)	1 (7%)	0 (0%)	3 (33%)	1 (8%)
≥3	11 (29%)	0 (0%)	0 (0%)	5 (56%)	6 (46%)
Neurological examination at baseline					
Normal	28 (74%)	12 (86%)	2 (100%)	6 (67%)	8 (62%)
Abnormal	10 (26%)	2 (14%)	0 (0%)	3 (33%)	5 (38%)

Data are median (range) or number of patients (%). ECOG=Eastern Cooperative Oncology Group. EGFR=epidermal growth factor receptor.

Table 2: **Baseline characteristics of patients in the dose-expansion phase**

the treatment. We allowed dose interruption and reduction in the circumstances described in the study protocol (appendix). We stopped dose escalation when two or more patients in a dose cohort had dose-limiting toxic effects. The investigators assessed safety at every scheduled visit (timing of visits described in the study protocol [appendix]). Categories of adverse events were based on terms from the Medical Dictionary for Regulatory Activities, version 18.1. We graded the severity of adverse events using CTCAE version 4.03, and investigators judged whether adverse events were caused by AZD3759. We assessed CNS and extracranial activity separately. For extracranial lesions, we used RECIST version 1.1, whereas for CNS tumours, we used modified RECIST version 1.1 (appendix). We selected a maximum of five measurable CNS lesions (longest diameter ≥1 cm) as target lesions on the basis of their size, and we regarded the remainder of the CNS lesions as non-target lesions. We required both target and non-target lesions to be repeatedly measurable. Investigators assessed CNS and extracranial tumour response with brain MRI and CT with contrast, respectively, every 6 weeks until disease progression.

During the dose-expansion phase, we assessed AZD3759 at two defined doses, 200 mg and 300 mg twice a day. We enrolled patients to the 300 mg cohort first; however, after recruitment of 15 patients we noted that most needed dose interruption or reduction, at

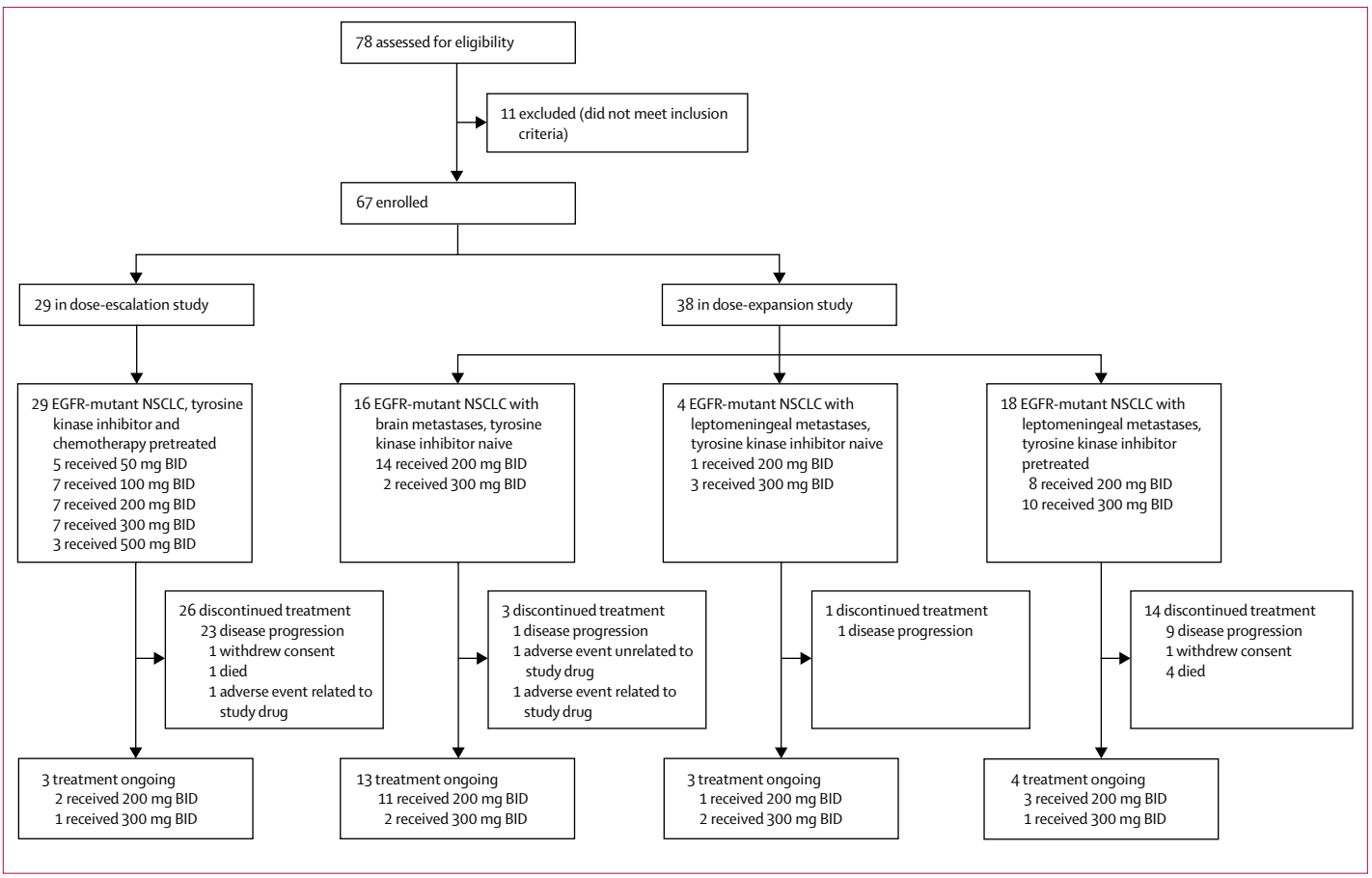

Figure 1: **Trial profile**
BID=twice a day. EGFR=epidermal growth factor receptor. NSCLC=non-small-cell lung cancer.

which point we began enrolling patients to the 200 mg cohort. We planned to recruit a total of 12 patients with leptomeningeal metastases and 15 patients with brain metastases, with the goal to identify safety and efficacy signals for future development. We did safety monitoring and assessment of clinical response in the same way as in the dose-escalation phase. Furthermore, we followed up patients for survival every 6 weeks after discontinuation of study treatment until death.

Before the first dosing of AZD3759, we obtained plasma samples from patients with brain and leptomeningeal metastases, and CSF samples from patients with leptomeningeal metastases, for assessment of EGFR mutations. This testing was done retrospectively at local laboratories using droplet digital PCR (ddPCR).[19] We also obtained samples of plasma and CSF at C_{trough} timepoint after 1 week of repeated dosing of AZD3759 from patients with brain or leptomeningeal metastases to establish the concentrations of AZD3759 and its *N*-demethylated metabolite (AZ'1168). We analysed samples using a validated bioanalytical method (appendix). In patients with leptomeningeal metastases, we gathered CSF tumour cells before the first dose of AZD3759 and at C_{trough} timepoint after 1 week of repeated dosing to assess EGFR expression by immunohistochemistry.[18] In the dose-expansion phase, we obtained CSF samples from patients with leptomeningeal metastases at baseline, 7 days after repeated dosing, and every 6 weeks during follow-up to assess changes in EGFR mutant DNA copies by ddPCR.[19]

Outcomes

The primary objective was to assess the safety and tolerability profile of AZD3759 and define the maximum tolerated dose. Secondary objectives included the pharmacokinetics of AZD3759 and its *N*-demethylated metabolite (AZ'1168) and antitumour efficacy. Other secondary endpoints will be reported separately. A full list of endpoints is provided in the study protocol (appendix).

Statistical analysis

We used a Bayesian adaptive design to define dose escalation and maximum tolerated dose.[20] The maximum tolerated dose was defined as the highest dose at which the predicted probability of a dose-limiting toxic effect

was less than 25%. We planned to do data analyses when the last dosed patient completed 12 weeks of treatment. All patients who received at least one dose of AZD3759 were included in the safety and efficacy analyses. We analysed the correlation between free plasma and CSF concentrations using Pearson's coefficient method.

This trial is registered with ClinicalTrials.gov, number NCT02228369.

Role of the funding source

The funder contributed to study design, data analysis, data interpretation, and drafting of the report. M-JA, SR, PO, BH, ZY, and JC-HY had access to raw data. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication.

Results

Between Nov 18, 2014, and Sept 7, 2016, AZD3759 was administered to 67 patients with EGFR-mutant NSCLC. 29 patients were enrolled to dose-escalation cohorts (table 1) and 38 patients were enrolled to dose-expansion cohorts (table 2). At data cutoff (Dec 12, 2016), enrolment of all planned cohorts had been completed. In the dose-escalation phase of the study, five dose cohorts were studied (50 mg, 100 mg, 200 mg, 300 mg, and 500 mg twice a day), with between three and seven patients in each cohort (figure 1). Based on safety, tolerability, and efficacy signals in dose-escalation cohorts, two doses (200 mg and 300 mg twice a day) were selected for further assessment in patients with brain metastases (n=16) or leptomeningeal metastases (n=4) who had never been treated with an EGFR tyrosine kinase inhibitor and patients with leptomeningeal metastases who had been pretreated with a tyrosine kinase inhibitor (n=18). At data cutoff, three patients in the dose-escalation phase and 20 patients in the dose-expansion phase were still receiving AZD3759 (figure 1). 46 (69%) of 67 patients in the study were women. Adenocarcinoma was the major tumour type in 66 (99%) of 67 patients. 34 (51%) patients had a Leu858Arg mutation and 33 (49%) had an exon19del mutation in primary tumours (archived tumour tissue obtained before any treatment with an EGFR tyrosine kinase).

	Total (n=29)	50 mg (n=5)		100 mg (n=7)		200 mg (n=7)		300 mg (n=7)		500 mg (n=3)	
		Grade 1 and 2	Grade ≥3	Grade 1 and 2	Grade ≥3	Grade 1 and 2	Grade ≥3	Grade 1 and 2	Grade ≥3	Grade 1 and 2	Grade ≥3
Skin and subcutaneous tissue disorders	21 (72%)	2 (40%)	0 (0%)	2 (29%)	0 (0%)	6 (86%)	1 (14%)	5 (71%)	2 (29%)	2 (67%)	1 (33%)
Rash	18 (62%)	1 (20%)	0 (0%)	2 (29%)	0 (0%)	7 (100%)	0 (0%)	5 (71%)	2 (29%)	1 (33%)	0 (0%)
Pruritus	13 (45%)	1 (20%)	0 (0%)	1 (14%)	0 (0%)	4 (57%)	1 (14%)	3 (43%)	1 (14%)	2 (67%)	0 (0%)
Dry skin	5 (17%)	0 (0%)	0 (0%)	1 (14%)	0 (0%)	3 (43%)	0 (0%)	1 (14%)	0 (0%)	0 (0%)	0 (0%)
Eczema	3 (10%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (14%)	0 (0%)	1 (14%)	0 (0%)	1 (33%)	0 (0%)
Nail disorder	3 (10%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	3 (43%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Acne	10 (34%)	0 (0%)	0 (0%)	2 (29%)	0 (0%)	2 (29%)	0 (0%)	3 (43%)	0 (0%)	2 (67%)	1 (33%)
Gastrointestinal disorders	16 (55%)	0 (0%)	0 (0%)	1 (14%)	0 (0%)	4 (57%)	1 (14%)	7 (100%)	0 (0%)	3 (100%)	0 (0%)
Diarrhoea	14 (48%)	0 (0%)	0 (0%)	1 (14%)	0 (0%)	3 (43%)	1 (14%)	6 (86%)	0 (0%)	3 (100%)	0 (0%)
Stomatitis	7 (24%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (29%)	0 (0%)	3 (43%)	0 (0%)	2 (67%)	0 (0%)
Vomiting	2 (7%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (67%)	0 (0%)
General disorders	7 (24%)	0 (0%)	0 (0%)	1 (14%)	0 (0%)	3 (43%)	0 (0%)	2 (29%)	0 (0%)	1 (33%)	0 (0%)
Mucosal inflammation	5 (17%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	3 (43%)	0 (0%)	1 (14%)	0 (0%)	1 (33%)	0 (0%)
Xerosis	4 (14%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (29%)	0 (0%)	1 (14%)	0 (0%)	1 (33%)	0 (0%)
Infections and infestations	8 (28%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	3 (43%)	1 (14%)	2 (29%)	0 (0%)	2 (67%)	0 (0%)
Folliculitis or furuncle	3 (10%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (14%)	1 (14%)	0 (0%)	1 (33%)	0 (0%)
Paronychia	5 (17%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	3 (43%)	0 (0%)	1 (14%)	0 (0%)	1 (33%)	0 (0%)
Hepatobiliary disorders	3 (10%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (14%)	0 (0%)	1 (14%)	0 (0%)	0 (0%)	1 (33%)
Increased ALT	3 (10%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (14%)	0 (0%)	1 (14%)	0 (0%)	0 (0%)	1 (33%)
Increased AST	3 (10%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (14%)	0 (0%)	1 (14%)	0 (0%)	0 (0%)	1 (33%)
Metabolism and nutrition disorders	5 (17%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (14%)	0 (0%)	3 (43%)	0 (0%)	1 (33%)	0 (0%)
Decreased appetite	4 (14%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (14%)	0 (0%)	2 (29%)	0 (0%)	1 (33%)	0 (0%)

For patients with more than one adverse event in the same category, we only recorded the most severe adverse event. ALT=alanine aminotransferase. AST=aspartate aminotransferase. CTCAE=National Cancer Institute's Common Terminology Criteria for Adverse Events.

Table 3: **Commonly reported drug-related adverse events and grading by CTCAE version 4.03 in the dose-escalation phase**

In the dose-escalation phase, no dose-limiting toxic effects were noted in the 50 mg, 100 mg, 200 mg, and 300 mg cohorts. Drug-related skin and gastrointestinal disorders, mainly grade 1 or 2, occurred in 21 (72%) and 16 (55%) of 29 patients, respectively, across the different doses (table 3). Two patients had dose-limiting toxic effects at a dose of 500 mg twice a day—one grade 3 acne and one intolerable grade 2 mucosal inflammation. A dose-dependent increase in grade 3 skin disorders was noted. Other commonly reported adverse events are listed in table 3. Based on safety and tolerability data in the dose-escalation phase, 300 mg twice a day was defined as the maximum tolerated dose, and dose-expansion cohorts were recruited at this dose level. Because tolerability was diminished when patients were treated for a period longer than 3 months, the 200 mg dose level was also selected for expansion. At these two doses, the frequency and severity of adverse events were comparable with those recorded in the dose-escalation phase, except the frequency of hepatobiliary disorders was higher (table 4). No drug-related CNS toxic effects were noted in either dose-escalation or dose-expansion phases. More than 40% of patients dosed with 200 mg or higher needed dose interruption or dose reduction because of drug-related adverse events (table 5). Three patients in the dose-expansion phase discontinued treatment because of drug-related adverse events, one who received 200 mg twice a day and two who received 300 mg twice a day.

Plasma and CSF samples were obtained from all 38 patients in the dose-expansion phase at C_{trough} timepoint after 1 week of repeated dosing of AZD3759. Of these, 35 patients with paired CSF and plasma concentrations (22 in the 200 mg cohort, 14 with brain metastases and eight with leptomeningeal metastases; 13 in the 300 mg cohort, two with brain metastases and 11 with leptomeningeal metastases) were included in the analysis of $K_{puu,CSF}$ values (figure 2). A significant correlation was noted between free plasma and CSF concentrations for both AZD3759 and AZ'1168 (both $p<0·0001$). At the 200 mg dose, AZD3759 and AZ'1168 mean C_{trough} CSF concentrations were 31·5 nmol/L (range 6·52–61·3) and 44·2 nmol/L (11·6–75·6), respectively. A roughly two-fold increase of drug concentrations was noted at a dose of 300 mg (AZD3759, 66·9 nmol/L [range 27·8–123]; AZ'1168, 93·6 nmol/L [31·1–183]). Corresponding free plasma concentrations of AZD3759 were approximately at the same range as that in CSF and yielded $K_{puu,CSF}$ values of 1·18 and 1·0 for 200 mg and 300 mg doses, respectively (overall $K_{puu,CSF}$ 1·11 [range 0·29–1·96]). By contrast, the $K_{puu,CSF}$ values of AZ'1168 were around 0·4 across these two doses (overall $K_{puu,CSF}$ 0·44 [0·19–1·42]). Concentrations of AZD3759 and AZ'1168 in plasma and CSF were above or at the range of EGFR inhibition determined preclinically (concentrations needed to achieve 50% inhibition of EGFR phosphorylation in EGFR-mutant tumour cells [IC_{50}], 7·4 nmol/L and 5·3 nmol/L for AZD3759 and AZ'1168, respectively; figure 2).

In the dose-expansion phase, ten of 22 patients with leptomeningeal metastases (four who received the 200 mg

	Total (n=38)	200 mg (n=23)		300 mg (n=15)	
		Grade 1 and 2	Grade ≥3	Grade 1 and 2	Grade ≥3
Skin and subcutaneous tissue disorders	35 (92%)	17 (74%)	4 (17%)	8 (53%)	6 (40%)
Rash	20 (53%)	10 (43%)	2 (9%)	4 (27%)	4 (27%)
Pruritus	11 (29%)	5 (22%)	0 (0%)	5 (33%)	1 (7%)
Dry skin	9 (24%)	1 (4%)	0 (0%)	7 (47%)	1 (7%)
Eczema	1 (3%)	0 (0%)	0 (0%)	1 (7%)	0 (0%)
Acne	23 (61%)	12 (52%)	2 (9%)	7 (47%)	2 (13%)
Nail disorder	6 (16%)	3 (13%)	0 (0%)	3 (20%)	0 (0%)
Gastrointestinal disorders	29 (76%)	13 (57%)	2 (9%)	10 (67%)	4 (27%)
Diarrhoea	24 (63%)	10 (43%)	2 (9%)	8 (53%)	4 (27%)
Stomatitis	5 (13%)	4 (17%)	0 (0%)	1 (7%)	0 (0%)
Vomiting	10 (26%)	3 (13%)	0 (0%)	7 (47%)	0 (0%)
General disorders	10 (26%)	3 (13%)	0 (0%)	6 (40%)	1 (7%)
Mucosal inflammation	7 (18%)	2 (9%)	0 (0%)	5 (33%)	0 (0%)
Asthenia	2 (5%)	0 (0%)	0 (0%)	1 (7%)	1 (7%)
Infections and infestations	14 (37%)	11 (48%)	0 (0%)	2 (13%)	1 (7%)
Paronychia	13 (34%)	10 (43%)	0 (0%)	2 (13%)	1 (7%)
Pustular rash	1 (3%)	1 (4%)	0 (0%)	0 (0%)	0 (0%)
Hepatobiliary and renal disorders	12 (32%)	5 (22%)	3 (13%)	4 (27%)	0 (0%)
Increased ALT	10 (26%)	5 (22%)	2 (9%)	3 (20%)	0 (0%)
Increased AST	10 (26%)	5 (22%)	2 (9%)	3 (20%)	0 (0%)
Increased total bilirubin	4 (11%)	1 (4%)	1 (4%)	2 (13%)	0 (0%)
Increased creatinine	2 (5%)	1 (4%)	1 (4%)	0 (0%)	0 (0%)
Metabolism and nutrition disorders	11 (29%)	3 (13%)	1 (4%)	6 (40%)	1 (7%)
Decreased appetite	11 (29%)	3 (13%)	1 (4%)	6 (40%)	1 (7%)

ALT=alanine aminotransferase. AST=aspartate aminotransferase. CTCAE=National Cancer Institute's Common Terminology Criteria for Adverse Events.

Table 4: **Commonly reported drug-related adverse events and grading by CTCAE version 4.03 in the dose-expansion phase**

	Dose interruption	Dose reduction	Dose discontinuation
Dose-escalation phase			
Total (n=29)	13 (45%)	9 (31%)	0 (0%)
50 mg (n=5)	0 (0%)	0 (0%)	0 (0%)
100 mg (n=7)	2 (29%)	0 (0%)	0 (0%)
200 mg (n=7)	5 (71%)	3 (43%)	0 (0%)
300 mg (n=7)	3 (43%)	3 (43%)	0 (0%)
500 mg (n=3)	3 (100%)	3 (100%)	0 (0%)
Dose-expansion phase			
Total (n=38)	28 (74%)	22 (58%)	3 (8%)
200 mg (n=23)	15 (65%)	12 (52%)	1 (4%)
300 mg (n=15)	13 (87%)	10 (67%)	2 (13%)

Data are number of patients (%).

Table 5: **Dose interruptions and dose reductions due to adverse events and dose discontinuations due to drug-related adverse events**

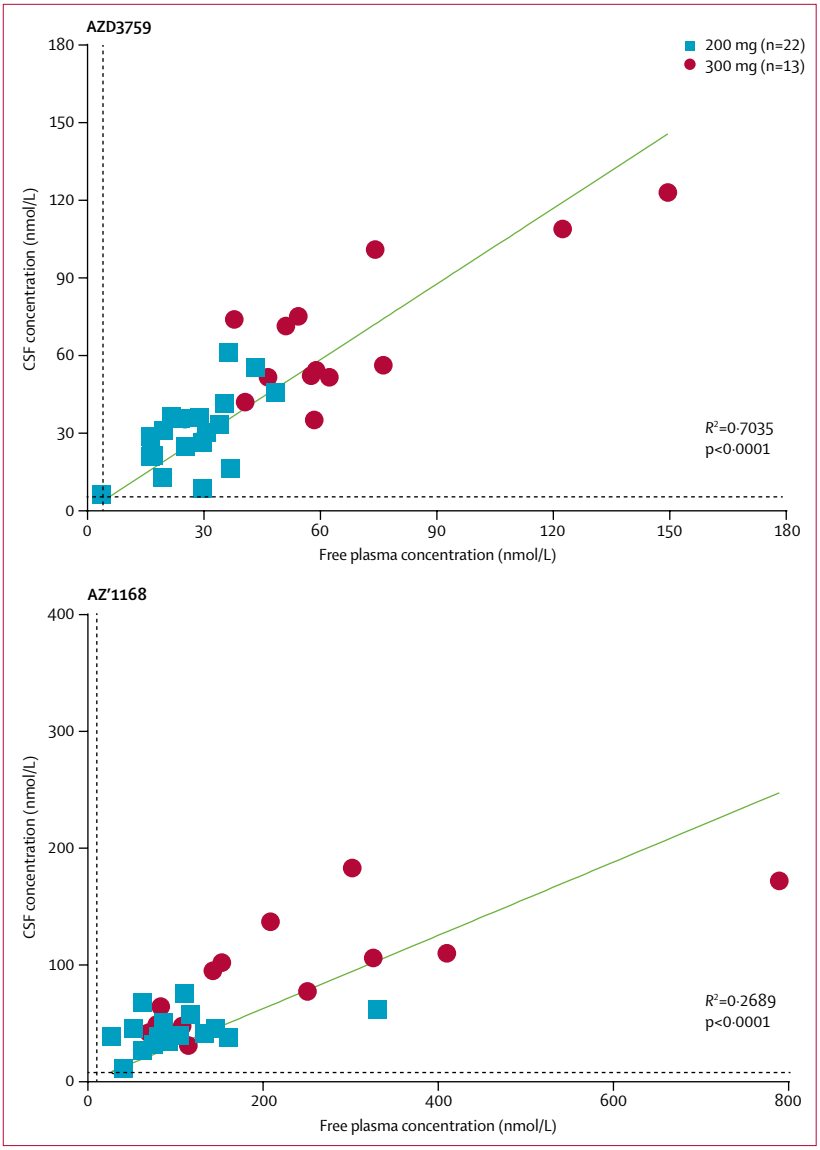

Figure 2: **Concentrations of AZD3759 and its *N*-demethylated metabolite (AZ'1168) in plasma and CSF**
Dotted lines represent the IC_{50} of AZD3759 or AZ'1168 in EGFR-mutant tumour cells. Green line shows the correlation between free plasma and CSF concentrations. EGFR=epidermal growth factor receptor. IC_{50}=concentrations of AZD3759 or AZ'1168 needed to achieve 50% inhibition of EGFR phosphorylation in EGFR-mutant tumour cells.

dose and six who received 300 mg) had assessable CSF samples gathered at baseline and at least two follow-up visits for detection of EGFR-mutant DNA copies. A transient increase of EGFR-mutant DNA copy number was noted after 7 days repeated dosing of AZD3759 in eight of ten patients; subsequently, in nine of ten patients, the EGFR-mutant DNA copy number dropped below the baseline level during follow-up visits (appendix). In addition to quantification of EGFR-mutant DNA copies, CSF samples were also gathered from 11 patients with leptomeningeal metastases (five who received the 200 mg dose and six who received 300 mg) before and 7 days after repeated dosing of AZD3759 to ascertain the change in EGFR phosphorylation in tumour cells using the immunohistochemistry assay. Six of 11 patients had decreased phosphorylation of EGFR in CSF tumour cells, with complete inhibition of expression of phosphorylated EGFR in four patients (appendix).

Antitumour efficacy was analysed by grouping patients into CNS, extracranial, and overall assessable sets. In the dose-escalation phase, only CNS activity of AZD3759 was assessed, because all patients had progressed on previous EGFR tyrosine kinase inhibitor treatment and AZD3759 was not anticipated to be active against extracranial disease in this group of patients. Of 21 patients with assessable CNS target lesions, 11 (52%) had tumour shrinkage (figure 3A), with three (14%) confirmed and three (14%) unconfirmed partial responses. Two patients treated with twice-daily doses of 200 mg or higher had disease control for longer than 11 months (appendix). Of 22 patients with evaluable extracranial target lesions, eight (36%) had tumour shrinkage (figure 3B) but no confirmed objective response (appendix). Five patients had the Thr790Met mutation in plasma before first dosing of AZD3759.

In the dose-expansion phase, of 18 patients who had never been treated with an EGFR tyrosine kinase inhibitor with assessable CNS target lesions, 15 (83%) had a confirmed objective response (14 partial responses and one complete response; figure 3C) and 16 (89%) had confirmed disease control (table 6; appendix). Of 18 patients who had never been treated with an EGFR tyrosine kinase inhibitor with assessable extracranial lesions (14 with target lesions [figure 3D] and four with non-target lesions), 13 (72%) had a confirmed tumour response (11 partial responses in target lesions and two complete responses in non-target lesions) and 17 (94%) showed confirmed disease control (table 6; appendix). Overall, after combining CNS and extracranial responses, 13 (65%) of 20 patients had achieved an objective response and 18 (90%) of 20 had achieved disease control (table 6). By data cutoff, treatment was ongoing for 16 patients and 15 were still responding.

In the cohort of 18 patients with leptomeningeal metastases pretreated with an EGFR tyrosine kinase inhibitor, four had assessable CNS target lesions (figure 3E), of whom one had a confirmed partial response (appendix). Similar to findings from the dose-escalation phase, no confirmed objective response was noted in 17 patients with assessable extracranial target lesions in this cohort (figure 3F; appendix). A separate assessment of leptomeningeal lesions by MRI showed that five (28%) patients had a confirmed response and 14 (78%) achieved disease control (table 7). Four of 18 (22%) patients were continuing treatment at data cutoff.

Discussion

The development of EGFR tyrosine kinase inhibitors, such as gefitinib, erlotinib, or afatinib, has substantially improved clinical outcomes in patients with EGFR-mutant NSCLC, including increased proportions achieving a

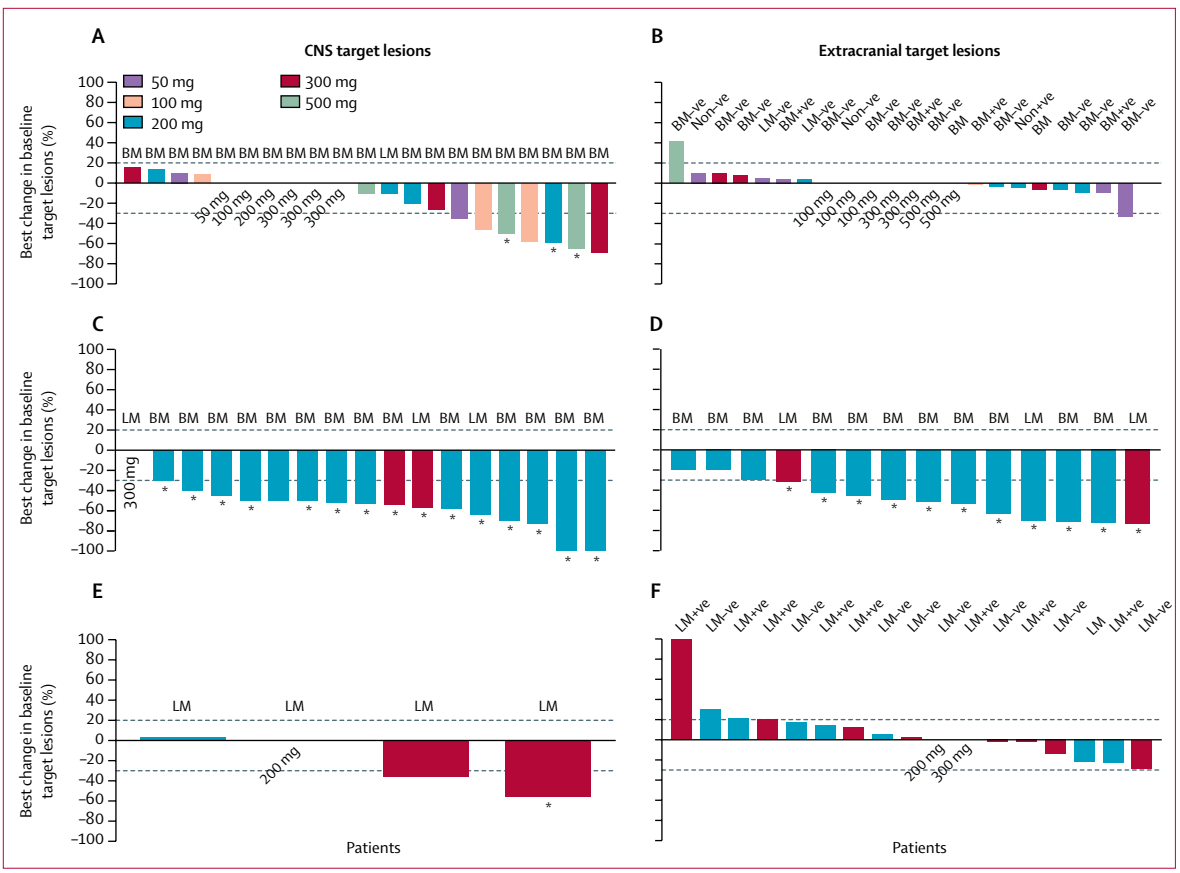

Figure 3: **Clinical activity of AZD3759 in patients with post-baseline target lesion assessments**
Best change in (A) CNS target lesions and (B) extracranial target lesions in patients who progressed on previous EGFR tyrosine kinase inhibitor treatment in dose-escalation cohorts. Best change in (C) CNS target lesions and (D) extracranial target lesions in patients who had never received an EGFR tyrosine kinase inhibitor with BM or LM in dose-expansion cohorts. Plot in (C) shows data for 17 patients because one participant withdrew from the study without any post-treatment assessment. Best change in (E) CNS target lesions and (F) extracranial target lesions in patients with LM pretreated with an EGFR tyrosine kinase inhibitor. The dashed line at 20% represents the boundary for determination of progressive disease, and the dashed line at –30% represents the boundary for determination of partial response, based on the definition by modified Response Evaluation Criteria in Solid Tumors. BM=brain metastases. EGFR=epidermal growth factor receptor. LM=leptomeningeal metastases. Non=neither measurable BM nor LM. –ve=no Thr790Met mutation in plasma. +ve=Thr790Met mutation present in plasma. *Confirmed response.

response and prolonged progression-free survival. However, more than 50% of patients develop CNS metastases during their disease course. Particularly for patients with leptomeningeal metastases, no standard treatment exists. Novel agents that can achieve high concentrations in the brain or CSF to control CNS metastases and treat leptomeningeal disease are, therefore, an area of need for these patient groups.

In this study, AZD3759 achieved a $K_{puu,CSF}$ value of 1·11, and its metabolite achieved a value of 0·44, consistent with our preclinical prediction for blood–brain barrier penetration.[21] C_{trough} free plasma and CSF concentrations of AZD3759 and AZ'1168 were above the IC_{50} for phosphorylated EGFR in EGFR-mutant cells at both 200 mg and 300 mg doses, suggesting that either dose was sufficient for continuous target coverage. Moreover, the target engagement was further confirmed by inhibition of EGFR phosphorylation detected in CSF tumour cells in more than 50% of patients with leptomeningeal metastases.

AZD3759 showed promising clinical activity in patients with CNS metastases. The CNS tumour response recorded in patients pretreated with an EGFR tyrosine kinase inhibitor suggests that AZD3759 could potentially treat relapsed CNS metastases. However, because of the drug's weak activity against individuals with the Thr790Met mutation, and with only stable disease as the best effect in extracranial lesions, combination of AZD3759 with other agents might be needed to achieve better overall disease control. AZD3759 as a monotherapy might be of value for patients pretreated with an EGFR tyrosine kinase inhibitor with only disease progression in the CNS. We noted that two patients with leptomeningeal metastases (without extracranial lesions) remained progression free for more than 15 months, with improvement of neurological symptoms and brain imaging, and these individuals remain on AZD3759 treatment to date.

It is noteworthy that in patients who had never received an EGFR tyrosine kinase inhibitor, a high proportion achieved a response with AZD3759 in both CNS lesions

	Total	Brain metastases		Leptomeningeal metastases	
		200 mg	300 mg	200 mg	300 mg
Overall tumour response*					
Confirmed objective response†	13/20 (65%)	9/14 (64%)	1/2 (50%)	1/1 (100%)	2/3 (67%)
Confirmed disease control‡	18/20 (90%)	13/14 (93%)	2/2 (100%)	1/1 (100%)	2/3 (67%)
Best response§					
CR	0/20 (0%)	0/14 (0%)	0/2 (0%)	0/1 (0%)	0/3 (0%)
PR	13/20 (65%)	9/14 (64%)	1/2 (50%)	1/1 (100%)	2/3 (67%)
SD	5/20 (25%)	4/14 (29%)	1/2 (50%)	0/1 (0%)	0/3 (0%)
PD	1/20 (5%)	0/14 (0%)	0/2 (0%)	0/1 (0%)	1/3 (33%)
Unable to determine¶	1/20 (5%)	1/14 (7%)	0/2 (0%)	0/1 (0%)	0/3 (0%)
CNS activity‖					
Confirmed objective response†	15/18 (83%)	12/14 (86%)	1/1 (100%)	1/1 (100%)	1/2 (50%)
Confirmed disease control‡	16/18 (89%)	13/14 (93%)	1/1 (100%)	1/1 (100%)	1/2 (50%)
Best response§					
CR	1/18 (6%)	1/14 (7%)	0/1 (0%)	0/1 (0%)	0/2 (0%)
PR	14/18 (78%)	11/14 (79%)	1/1 (100%)	1/1 (100%)	1/2 (50%)
SD	1/18 (6%)	1/14 (7%)	0/1 (0%)	0/1 (0%)	0/2 (0%)
PD	1/18 (6%)	0/14 (0%)	0/1 (0%)	0/1 (0%)	1/2 (50%)**
Unable to determine¶	1/18 (6%)	1/14 (7%)	0/2 (0%)	0/2 (0%)	0/2 (0%)
Extracranial activity††					
Confirmed objective response†	13/18 (72%)	9/12 (75%)	1/2 (50%)	1/1 (100%)	2/3 (67%)
Confirmed disease control‡	17/18 (94%)	12/12 (100%)	2/2 (100%)	1/1 (100%)	2/3 (67%)
Best response§					
CR	2/18 (11%)	1/12 (8%)	1/2 (50%)	0/1 (0%)	0/3 (0%)
PR	11/18 (61%)	8/12 (67%)	0/2 (0%)	1/1 (100%)	2/3 (67%)
SD	4/18 (22%)	3/12 (25%)	1/2 (50%)	0/1 (0%)	0/3 (0%)
PD	0/18 (0%)	0/12 (0%)	0/2 (0%)	0/1 (0%)	0/3 (0%)
Unable to determine¶	1/18 (6%)	0/12 (0%)	0/2 (0%)	0/1 (0%)	1/3 (33%)

Data are number of patients/total number of patients (%). All assessments were based on investigators' evaluation. Only assessable patients are included in this table. For overall response, all 20 patients were included; two patients did not have CNS target lesions and were excluded from CNS activity evaluation; two patients had neither extracranial target lesions nor non-target lesions and were excluded from the extracranial activity evaluation. CR=complete response. EGFR=epidermal growth factor receptor. PD=progressive disease. PR=partial response. SD=stable disease. *All patients dosed with AZD3759 were included. †Includes patients with either confirmed CR or PR by two consecutive assessments with ≥8-week interval. ‡Includes patients with either confirmed CR, PR with ≥8-week interval, or SD with ≥12-week interval by two consecutive assessments. §Tumour assessment up to initial disease progression, or consent withdrawal, whichever occurred first. ¶Patients withdrew consent before initial modified Response Evaluation Criteria in Solid Tumors assessment or death. ||Dosed patients with measurable CNS target lesions at baseline were included. **This patient had de novo Thr790Met mutation in tumour tissue. ††Dosed patients with extracranial disease (target or non-target lesions) at baseline were included.

Table 6: **Antitumour activity of AZD3759 in patients who had never received an EGFR tyrosine kinase inhibitor**

	Total (n=18)	200 mg (n=8)	300mg (n=10)
Confirmed response*	5 (28%)	1 (13%)	4 (40%)
Confirmed disease control†	14 (78%)	6 (75%)	8 (80%)
Best response			
CR	1 (6%)	0 (0%)	1 (10%)
Responding‡	4 (22%)	1 (13%)	3 (30%)
SD	9 (50%)	5 (63%)	4 (40%)
PD	2 (11%)	1 (13%)	1 (10%)
Unable to determine§	2 (11%)	1 (13%)	1 (10%)

Data are number of patients (%). All assessments were based on investigators' evaluation. Dosed patients with assessable leptomeningeal metastases by brain and spinal MRI were included. CR=complete response. EGFR=epidermal growth factor receptor. PD=progressive disease. SD=stable disease. *Includes patients either with confirmed CR or responding by two consecutive assessments with ≥8-week interval. †Includes patients either with confirmed CR, responding with ≥8-week interval, or with SD with ≥12-week interval by two consecutive assessments. ‡Improvement of leptomeningeal lesions. §Patients withdrew consent before initial modified Response Evaluation Criteria in Solid Tumors assessment or death.

Table 7: **Antitumour activity of AZD3759 in patients with leptomeningeal metastases pretreated with an EGFR tyrosine kinase inhibitor**

(83%) and extracranial disease (72%), supporting the potential use of this drug as monotherapy in the first-line setting for EGFR-mutant NSCLC. Further follow-up for progression-free and overall survival is warranted. Encouragingly, three of four patients with leptomeningeal metastases who had never received an EGFR tyrosine kinase inhibitor achieved a response, suggesting potential application for AZD3759 in this devastating disease. Compared with previous data for other EGFR tyrosine kinase inhibtors,[4] objective responses and disease control in the CNS were achieved by a higher proportion of patients in our study, which warrants future studies comparing agents. Importantly, the CNS activity of AZD3759 could potentially improve neurological function or prevent deterioration of neurological function in patients with CNS metastases, which is important to maintain quality of life for this group of patients.

The most commonly recorded adverse events with AZD3759 were skin and gastrointestinal disorders, which were comparable with those reported for other approved EGFR tyrosine kinase inhibitors.[22,23] Most skin and gastrointestinal disorders were grade 1 and 2, but severity of these adverse events increased as the dose rose from 200 mg to 300 mg to 500 mg. Skin and gastrointestinal disorders were reversible with dose interruptions for roughly 7 days to 2 weeks. In the dose-escalation cohorts, although 300 mg was defined as the maximum tolerated dose, this dose was not well tolerated when treatment duration exceeded 3 months. Hence, we evaluated both 200 mg and 300 mg in the expansion cohorts and established 200 mg as the recommended phase 2 dose. It is noteworthy that no drug-related CNS toxic effects have been recorded so far.

We incorporated exploratory biomarker analysis into this study, at both DNA and protein levels, to provide direct evidence of antitumour activity of AZD3759 in the CSF. EGFR mutation status in paired plasma and CSF samples from patients with leptomeningeal metastases before first dosing of AZD3759 showed that, among patients who progressed after previous EGFR tyrosine kinase inhibitor treatment, nine of 18 (50%) had the Thr790Met mutation in plasma (appendix). This finding was consistent with previous reports[24] and could potentially account for the scant extracranial tumour response with AZD3759

treatment. By contrast, the Leu858Arg or exon19del mutation was the major mutation type in CSF samples, similar to findings of previous reports,[25,26] which might account for the leptomeningeal response noted in this group of patients. A transient increase of EGFR-mutant copies in CSF 7 days after AZD3759 treatment suggested massive DNA release because of tumour cell death, and the decrease of EGFR-mutant copies during later follow-up visits supported the antiproliferation mechanism of this compound. The target engagement of AZD3759 was further validated by inhibition of phosphorylation of EGFR in CSF tumour cells.

Findings of two phase 3 studies with larger sample sizes showed encouraging clinical activity of osimertinib and icotinib in brain metastases, with objective responses achieved by 71% and 67% of patients, respectively.[27,28] These two EGFR tyrosine kinase inhibitors could partly cross the blood–brain barrier.[12,29] With these encouraging clinical results, the sequence to use each EGFR tyrosine kinase inhibitor, including AZD3759, should be studied in the future.

Because of the limited follow-up time, data for progression-free survival and duration of response are not mature for calculation. However, with the noted clinical response and proportion of patients receiving ongoing treatment, we are confident that AZD3759 might have a specific role for treatment of patients with an EGFR mutation and CNS metastases.

In conclusion, AZD3759 is tolerable up to 300 mg twice a day, with promising clinical activity in EGFR-mutant NSCLC with CNS metastases. The recommended phase 2 dose was defined as 200 mg twice a day, at which level both AZD3759 and AZ'1168 reached efficacious concentrations for target inhibition. The promising clinical activity seen in patients both pretreated and never treated with an EGFR tyrosine kinase inhibitor warrants future development of AZD3759.

Contributors

M-JA and JC-HY are lead study investigators and contributed to study design and implementation, data interpretation, and writing of the report. D-WK, BCC, S-WK, JSL, J-SA, TMK, C-CL, HRK, TJ, SK, JWG, W-CS, and RN are study investigators and contributed to study implementation, revision of the report, and final approval. SR contributed to analysis of pharmacokinetics and writing of the report. BH contributed to study implementation, revision of the report, and final approval. PO contributed to statistical analysis and writing of the report. ZY contributed to study design and implementation, data interpretation, and writing of the report.

Declaration of interests

M-JA and JC-HY have been consultants for AstraZeneca during the conduct of this study and outside of the submitted work. BCC has been a consultant for AstraZeneca outside of the submitted work. M-JA, JC-HY, and BCC have received honoraria and research funding from AstraZeneca outside of the submitted work. TJ, SK, and JWG have received honoraria from AstraZeneca outside of the submitted work; JWG has also received research funding from AstraZeneca outside of the submitted work. RN has been a consultant for AstraZeneca outside of the submitted work; and has received research funding from AstraZeneca outside of the submitted work. SR, BH, PO, and ZY are employees of AstraZeneca. D-WK, S-WK, J-SA, JSL, TMK C-CL, HRK, and W-CS declare no competing interests.

Acknowledgments

This study was funded by AstraZeneca. We thank the patients, their families, and the investigators and study teams for making this trial possible.

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