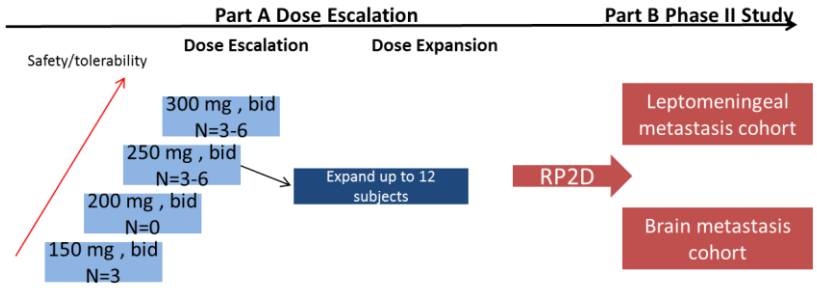
PROTOCOL SYNOPSIS

Title of Study	A Phase I/II, Open-label, Multi-center Study to Evaluate Safety, Tolerability, Pharmacokinetics and Anti-tumor Activity of AZD3759 in Chinese Patients with Advanced Epidermal Growth Factor Receptor Mutation Positive (EGFRm+) Non-small Cell Lung Cancer (NSCLC) with Central Nervous System (CNS) Metastases
Phase of Clinical Trial	Phase I/II
Indications	Advanced epidermal growth factor receptor mutation positive (EGFRm+) non-small cell lung cancer (NSCLC) with central nervous system (CNS) metastases
Study Objectives	**Primary Objective** Dose escalation study in Part A: to evaluate safety and tolerability of AZD3759 in treatment of Chinese patients with EGFRm+ NSCLC. Phase II study in Part B: To evaluate anti-tumor activity of AZD3759 in treatment of Chinese patients with EGFRm+ NSCLC with CNS metastases. **Secondary Objectives:** Dose escalation study in Part A: • To evaluate plasma pharmacokinetics (PK) of AZD3759 and AZ'1168 (the N-desmethyl metabolite) after a single-dose and multi-dose administration. • To preliminarily evaluate anti-tumor activity. • To explore recommended phase II dose (RP2D) Phase II study in Part B: • To confirm safety and tolerability of AZD3759 in treatment of Chinese patients with EGFRm+ NSCLC with CNS metastases.
Study Design	This is a multi-center, open-label, dose escalation and phase II study, consisting of dose escalation study in Part A and phase II study in Part B.



Dose escalation study includes dose escalation and dose expansion. Four planned dose groups are 150, 200, 250 and 300 mg twice daily. Patients will receive a single dose followed by 48 hours washout and then commence multiple twice daily dosing at C1D1 for 21 days. A cycle is defined as 21 days of continuous dosing. It is planned to perform single-center dose escalation study. The investigator and the Sponsor will make the decision on dose escalation and interruption by evaluating safety and tolerability which occurs from the first dose to last dose of Cycle 1. The investigator will decide to expand the dose group to 12 subjects if there is at least 1 out of the first 3 subjects in each dose group has trough plasma concentration exceeding IC50 (7 nM) or stable disease (tumor reduction) or has symptom improvement and safety in LM patients in dose escalation. It is planned to perform multi-center dose expansion study, and decision on early termination of expansion will be made based on safety data as appropriate.

According to the up-to-date results of BLOOM study, the dose can be directly escalated to 250mg without testing the 200mg dose during the dose escalation phase. The principle investigator could decide whether or not to expand a dose group with the consent of the sponsor during the dose expansion phase.

Analysis of prior BLOOM data demonstrates that 300 mg BID is not usually tolerated as well after 3 to 6 weeks by patients, however, the 300 mg BID cohort for BM and LM patients clearly demonstrated the efficacy was superior to 200 mg BID.

Since the data are clear regarding potential clinical efficacy using 300 mg BID in LM and BM patients from the BLOOM study and there is no DLT at the 250 mg BID dose level in this current Phase I/II study, and the Sponsor have made this amendment to allow dose escalation to 300 mg BID and assessing safety and

	tolerability of AZD3759 in treatment of Chinese patients. A Data Monitoring Committee (DMC) will be established for this trial. The DMC will review trial data from Part A, consider overall risks and benefits of trial participants and provide recommendation for the Sponsor concerning whether to conduct phase II study in Part B at RP2D to continue the trial according to the protocol. In phase II study in Part B, it is planned to extend cohorts of patients with leptomeningeal metastasis (LM) and brain metastasis (BM) separately to further evaluate anti-tumor activity, safety and tolerability of AZD3759.
Study Endpoints	Dose escalation study in Part A **Primary endpoints:** • Safety and tolerability **Secondary endpoints:** • Pharmacokinetics analysis • To evaluate extracranial lesion and intracranial disease efficacy separately according to modified RECIST 1.1, including objective response rate (ORR), disease control rate (DCR), duration of response (DOR) and change from baseline in tumor size, PFS (progression free survival). • LM patients: investigator assessed response rate, control rate, response duration • CSF negative conversion rate and control rate of neurological function in LM patients • Patient reported outcomes (PROs) **Exploratory endpoints:** • CSF drug exposure in LM patients Phase II study in Part B **Primary endpoint:** • BM cohort: (overall) ORR • LM cohort: intracranial lesion control rate, intracranial lesion response rate **Secondary endpoint:** • BM cohort: to evaluate ORR, DCR, DOR, PFS and change from baseline in tumor size for extracranial lesion and intracranial lesion due to brain metastasis separately

	• BM cohort: overall DCR, DOR, PFS, OS, safety and PROs • LM cohort: to evaluate response duration and PFS for intracranial lesions due to LM, and ORR, DCR, DOR, PFS and change from baseline in tumor size for extracranial lesions • LM cohort: overall OS, PFS, safety and PROs • LM cohort: CSF negative conversion rate and control rate of neurological function
Sample Size	The sample size for Part A of the study is not formally determined. According to tolerability and safety evaluation of the study drug, 3-6 patients will be included in each dose group in dose escalation phase, which may be expanded up to 12 subjects based on investigators' discretion, with a maximum of 21 subjects included in Part A. In phase II study in Part B, sample size of LM and BM cohorts will be adjusted appropriately based on study data and study endpoints.
Study Treatment	Study drug: AZD3759 Strength: 50mg/tablet, 100mg/tablet Dosage and administration: twice daily administration under fasting state. Each patient should take the drug at fixed time points during study treatment as far as possible. Dosing interval is 12 hours. Patients will take no food for 2h and no water for 1h after dosing. If the patient misses a dose and time window is within 2 hours, the dose can be made up. If it is 2 hours beyond scheduled dosing time, the dose should not be made up and the patient should be instructed to take the next dose at the next scheduled time. A treatment cycle consists of consecutive 21 days of dosing. Patients in Part A will take intensive pharmacokinetic blood sampling, who will take the study drug with 200 mL warm water under fasting state (defined as fasting for at least 2 hours before administration) in the morning of C0D1 and C1D21, respectively, and they will take no food for 2h and no water for 1h after dosing. The 2nd dose of C1D21 will be taken at 12h after administration in the morning. Light diet will be supplied during PK intensive

	sampling days.
Main inclusion/exclusion criteria	**Inclusion criteria:** Patients must meet all of the following criteria to participate in the study: 1. Subjects must provide written informed consent before any study related procedure. 2. Male or female Chinese patients ≥18 years old. 3. Histologically or cytologically confirmed non-small cell lung cancer with activating mutation in EGFR gene (including Exon19Del and/or L858R). A validated and robust test method reviewed and approved by the regulatory authority should be used to determine EGFR mutation status in tissue or plasma locally. 4. Patients with advanced non-small cell lung cancer (stage IV) with documented BM and/or LM. Part A dose escalation can include EGFR TKI-naïve NSCLC patients with measurable lung lesion and no BM. Patients with BM and/or LM in each dose group shall account for at least one-third. 5. According to Eastern Cooperative Oncology Group (ECOG) Scale, performance status is grade 0 to 1, without worsening in the past 2 weeks, and life expectancy of at least 3 months. If ECOG performance status is grade 2 due to LM disease, the patient can also be enrolled. 6. Non-surgical sterilized women of child-bearing potential and male subjects shall agree to take medically acceptable contraception measures during dosing of investigational drug and 3 months after completion of study treatment. Non-surgical sterilized women of child-bearing potential must have negative blood pregnancy test at screening. 7. Asymptomatic **BM patients** who have not received prior treatment with any EGFR TKI or symptomatic BM patients who are not warranted temporally for definitive local treatment (surgery or radiotherapy). For patients with prior local treatment for BM lesion (surgery or radiotherapy), intracranial lesion progression is required. 8. **BM patients** must have at least one measurable intracranial lesion; in case of prior radiotherapy for BM lesion, progression is required and must meet measurable lesion

	criteria again. Measurable extracranial disease is not required. 9. **LM patients** must be confirmed by the presence of malignant cells by cerebrospinal fluid (CSF) cytology. Diagnosis of LM disease by MRI alone does not meet inclusion criteria. Patients with both BM and LM are considered as LM. 10. **LM patients** must have at least one leptomeningeal lesion which shows visible abnormality by MRI. Measurable extracranial disease is not required. **Exclusion criteria:** Patients meeting any of the following criteria cannot participate in the study: 1. Have taken any other investigational drug in a clinical trial within 30 days prior to initial dose. 2. Prior treatment with any EGFR TKI within 8 days or 5 half-lives of the drug (see table 19 Washout of EGFR TKIs) prior to initial dose of study drug. If the washout period for the EGFR TKI cannot be reached due to schedule or pharmacokinetic properties, an alternative washout period can be proposed based on recovery period of known adverse drug reactions, which must be agreed to in advance by the Investigator and the Sponsor. 3. T790M mutation positive patients. 4. Have received previous treatment regimen including any cytotoxic chemotherapy or other anti-cancer drugs (other than EGFR TKIs) for treatment of advanced non-small cell lung cancer within 14 days prior to initial dose of study drug. 5. Patients with medically uncontrollable seizures and/or untreated (eg., requiring mannitol and/or placement a VP shunt) intracranial hypertension are excluded. 6. Have undergone major surgical procedure (excluding placement of vascular indwelling needle) or serious trauma within 4 weeks prior to initial dose of study drug, or major surgical procedure is expected during the study. 7. Patients who have received radiotherapy for a large area within 4 weeks, or local palliative radiotherapy for a small area within 1 week prior to initial dose of study drug (for

	subjects requiring radiotherapy for more than 30% bone marrow, the radiotherapy must be completed before 4 weeks prior to initial dose). 8. BM and LM patients who have received whole-brain radiotherapy. 9. Patients with a history of allergy to AZD3759 and its structural analogues (Gefitinib) or pharmaceutical excipients (whether active or not). 10. Subjects who are receiving (or cannot discontinue at least 1 week prior to initial dose of study drug) any drug or traditional Chinese medicine known to inhibit or induce CYP3A4 or CYP3A5 activity. 11. Subjects who have received AZD3759 treatment previously. 12. Unresolved adverse events of greater than CTCAE grade 1 caused by previous treatment at study initiation, not including hair loss or fatigue. 13. Any of the following criteria for cardiac disorders: - QTc interval >470 ms. - Any clinically significant arrhythmia, resting ECG conduction and morphological abnormalities, e.g. complete left bundle branch block, third degree heart block and second-degree or higher heart block, history of Torsades des Points, ventricular tachycardia, or Wolff-Parkinson-White syndrome. - Any factor that may increase risk of QTc prolongation and arrhythmia, e.g. heart failure, hypokalemia, congenital long QT syndrome, drugs being received known to prolong QT interval, family history of long QT syndrome or unexplained sudden death of a first degree relative at the age under 40 years. 14. Any of the following laboratory results indicate insufficient bone marrow reserve or organ dysfunction: - Absolute neutrophil count (ANC) <1.5 × 10^9/L - Platelet count <100 × 10^9/L - Hemoglobin < 90 g/L - ALT or AST > 2.5 × ULN without confirmed liver metastasis - ALT or AST > 5 × ULN with concurrent liver metastasis - Total bilirubin > 1.5 × ULN without confirmed liver

	metastasis, or total bilirubin > 3 × ULN with liver metastasis or Gilbert syndrome - Creatinine clearance < 50 mL/min (measured or estimated using Cockcroft and Gault formula) and creatinine > 1.5 × ULN. Creatinine clearance will be confirmed only when creatinine is > 1.5 × ULN. - In case of bone metastasis and the investigator considers liver function is sufficient, subjects will not be excluded from the study because of isolated increased alkaline phosphatase. - Subjects who have received hematopoietic growth factor treatment or blood transfusion within 4 weeks prior to initial dose of study drug. 15. History of interstitial lung disease, drug-induced interstitial lung disease or radiation pneumonitis requiring steroids, or any evidence of clinically active interstitial lung disease. 16. Severe or uncontrolled systemic diseases as judged by the investigator, including uncontrolled hypertension, active bleeding or active hepatitis B, hepatitis C and human immunodeficiency virus (HIV) infection. 17. Known intracranial hemorrhage not related to tumor or recent history of stroke within the past 6 months. 18. Subjects with nausea and vomiting that is uncontrolled by supportive treatment, chronic gastrointestinal disease, inability to swallow prescription drug or prior gastric surgery that would prevent or interfere with sufficient absorption of AZD3759. 19. Serious medical or psychiatric disorders that prevent subjects from following or tolerating study treatment. 20. Central nervous system complications requiring emergency neurosurgical intervention (e.g. resection or shunt). 21. LM patients: unable to undergo CSF collection through repeated lumbar puncture or Ommaya reservoir placement. 22. Subjects who may have poor compliance with study procedures, study restrictions and requirements as judged by the investigator. 23. Any staff involved in study planning and conduct (applicable to the Sponsor's staff or staff working at study site).

Treatment Duration and End of Study	End of study is defined as the last visit of the last subject. All subjects benefiting from AZD3759 treatment as assessed by the investigator and not meeting any of discontinuation criteria may continue treatment. Two data cut-off points will be set for data analysis, defined as 6 weeks after initiation of study drug for the last subject in single-center dose escalation portion of dose escalation study in Part A and after the last visit of the last subject in dose expansion study in Part A, on which basis the clinical study report will be prepared.
Safety Assessment	Any adverse event (AE), vital signs, and ECG will be observed and recorded, and physical examination and laboratory safety tests will be performed and the results will be recorded during the study. CTCAE 4.03 will be used for grading of AEs.
Tumor Response Assessment	RECIST 1.1 will be used to assess extracranial lesion and intracranial lesion separately. Radiographic assessment performed within 28 days prior to initiation of treatment can be used as baseline assessment, including brain, thorax, abdomen and pelvic CT/MRI；subsequent radiographic assessments will be performed every 6 weeks ± 1 week (relative to Cycle 1 Day 1) by CT/MRI scan of brain, thorax, abdomen and pelvis (only brain, thorax and epigastrium will be scanned in follow up visits if no lesions found in abdomen and pelvis at baseline), until objective disease progression or death (non-cancer-progression-related death) or initiation of another anti-tumor treatment, regardless of withdrawal from AZD3759 treatment. Moreover, other areas should be examined according to the patient's signs and symptoms. Appropriate radiological examination should also be performed for any other sites with suspected new lesion. If unscheduled assessment reveals no progression, follow-up assessment in subsequent visits should be performed as originally scheduled if possible. For LM patients, treatment response of LM disease will be evaluated by neurological function, imaging and CNS symptoms as well as CSF cytology response.
Pharmacokinetic Evaluation	Pharmacokinetic evaluation will be performed in Part A. Pharmacokinetic blood sampling is required for subjects for determination of plasma concentrations of AZD3759 and AZ'1168 (the N-desmethyl metabolite). For patients participating

	in plasma PK evaluation in single-center dose escalation, 0.5 ml CSF sample shall be collected pre-dose on Day 1 Cycle 2 (C2D1) for assessment of drug exposure.
Patient Reported Outcomes	QLQ C-30 and QLQ BN-20 developed by the European Organization for Research and Treatment of Cancer (EORTC) will be used to assess patients' health related quality of life and symptoms and improvement of central nervous system symptoms.
Statistical Analysis	For dose escalation phase in Part A, safety data will be summarized based on doses, and efficacy data will be summarized based on type of metastasis and dose. For the Phase II study in Part B, data will be summarized based on type of metastasis and dose.

Study Flowchart

Table 1 Flow chart of dose escalation in Part A

	Screening period	Single dose / Cycle 0			Cycle 1				Cycle 2	Cycle 3 and thereafter	End of treatment/withdrawal	28-day follow-up	Disease progression
Follow-up visit	1	1.1	1.2	1.3	2	3	4	5	6	7 and thereafter			
Day	-28~0	C0D1	C0D2	C0D3	C1D1	C1D8	C1D15	C1D21	C2D1	D1			
Visit window (day)	NA	0	0	0	0	0	0	0	0	±3	±3	±3	
Informed Consent Form	X												
Demographic data[1]	X												
Tumor history / other medical history[2]	X												
Inclusion / exclusion criteria	X												
Screen for infectious diseases[3]	X												
ECOG [4]	X	X			X				X	X	X		
EGFR testing[5]	X												
Physical examination[6]	X	X			X	X	X	X		X	X		
Vital signs[7]	X	X	X		X	X	X	X	X	X	X		
Height[8]	X												
Body weight[8]	X	X			X				X	X	X		
Clinical laboratory tests (hematology, blood biochemistry and urinalysis)[9]	X				X	X	X	X		X	X		

ECG[10]	X	X	X		X	X	X	X		X	X		
Pregnancy test (only for women of childbearing age)[11]	X										X		
Nervous system examination[12]	X	X							X	X (D1 of each cycle until PD)			
Ophthalmology examination[13]	X										X		
CSF collection for cytological test and biochemical test (only for LM patients)[14]	X								X	X			
CSF collection for assessment of drug exposure[15]									X				
Imaging evaluation[16]	X								X	X (relative to C1D1, every 6 weeks up to PD)			
QLQ C-30[17]	X								X	X (relative to C1D1, every 6 weeks up to end of treatment)			
QLQ BN-20[17]	X								X	X (relative to C1D1, every 6 weeks up to PD)			
Administration of AZD3759[18]		X			←	—	—	—	→				
Subject's diary card[18]					←	—	—	—	→				
PK sampling[19]		X	X	X	X	X	X	X	X				
Concomitant medications[20]	←	—	—	—	—	—	—	—	—	—	—	—	→
Adverse events[21]	←	—	—	—	—	—	—	—	—	—	—	—	→

1. Demographics, including gender, date of birth, nationality, smoking history, height and body weight.
2. Tumor history and other medical history will be recorded separately. Other medical history includes all active diseases, and any diseases diagnosed in the past 10 years that the investigator considers clinically significant. Tumor history includes all previous tumors other than that evaluated in this study, even the diagnosis was made more than 10 years prior to screening visit.

3. Screen for infectious diseases include HIV antibody, two pairs of semi-hepatitis B (quantification of HBV-DNA may be performed if required) and HCV antibody (HCV RNA is required if HCV antibody is positive).
4. ECOG score will be obtained at screening period, on C0D1, C1D1 and Day 1 of every cycle until end of treatment/withdrawal.
5. At screening period, EGFR mutation in blood or tumor tissue should be determined in a qualified laboratory, and T790M mutation status will also be determined.
6. Physical examination includes: general appearance, skin, head and neck (including ears, eyes, nose and throat), respiratory, cardiovascular, abdomen, lymph nodes, thyroid gland and musculoskeletal system (including spine and limbs). Physical examination will be performed at Screening period, and on C0D1, C1D1, C1D8, C1D15, C1D21 and on Day 1 of cycle 3 and each cycle afterwards until the end of treatment.
7. Vital signs include blood pressure, pulse and body temperature, and will be monitored at screening period, pre-dose and 2h, 6h and 24h post-dose at C0D1, pre-dose at C1D1, C1D8 and C1D15, pre-dose and 2h and 6h post-dose at C1D21, pre-dose at C2D1 and pre-dose on day 1 of Cycle 3 and each cycle starts afterwards. Moreover, additional vital signs may be determined as needed in case of any cardiac adverse event, and vital signs should be performed at withdrawal of study treatment. A time window of 30 minutes is permitted for vital signs.
8. Height will be measured only at screening period. Body weight will be measured at screening period, on Day 1 of every cycle and at withdrawal of study treatment.
9. Blood and urine samples for clinical laboratory tests will be collected from subjects at screening period, pre-dose on C1D1, C1D8, C1D15, C1D21 and pre dose on Day 1 of cycle 3 and each cycle afterwards and at withdrawal of study treatment. The clinical laboratory tests of screening should be performed within 7 days prior to the initiation of treatment.
10. ECG should be obtained in supine position after adequate rest. A time window of 1 hour is permitted. At screening period, pre-dose and 2h, 6h and 24h post-dose on C0D1, pre-dose on C1D1, C1D8 and C1D15, pre-dose and 2h and 6h post-dose on C1D21, and on Day 1 during follow-up of each cycle from cycle 3. Moreover, additional ECG may be obtained as needed in case of any cardiac adverse event. If QTcF $\geqslant$ CTC AE 3, repeat ECG measurements for consecutive 3 times immediately and take the average. ECG should be obtained at withdrawal of study treatment.
11. For non-surgical sterilized women of child-bearing potential, blood sample for pregnancy test shall be collected at screening and withdrawal of study treatment. Menopause is defined as permanent cession of menorrhea. Women are considered post-menopausal if they (usually older than 45 years) have had 12 months of natural (spontaneous) amenorrhea.
12. Neurological examination will be performed at screening period and on C0D1 and Day 1 of every cycle from Cycle 2until disease progression or death (death not due to disease progression) or initiation of another anti-tumor treatment. For patients who discontinue the study treatment due to reasons other than disease progression, neurological examination after treatment discontinuation should be performed at follow-up tumor radiographic assessment. Neurological examination should be recorded on a separate "Neurological Function Examination" Case Report Form.
13. Ophthalmological examination should be performed at screening period and withdrawal of study treatment, or in case of any visual symptom (including blurred vision).

14. For LM patients with implanted Ommaya reservoir, CSF samples will be collected at screening and every 6 weeks ± 1 week (relative to C1D1) until disease progression or death (death not due to disease progression) or initiation of another anti-tumor treatment. For LM patients without implanted Ommaya reservoir, CSF samples will be collected at least at screening and Week 12. For LM patients in single-center dose escalation in Part A who participate in plasma PK assessment, 0.5 mL CSF will be collected for assessment of drug exposure pre-dose on Day 1 Cycle 2 (C2D1) in addition to CSF collection for cytological test and biochemical test.10 ml CSF shall be collected each time. CSF responders should be confirmed through repeated test at least 4 weeks after initial negative conversion.
15. For subjects who participate in Part A plasma PK assessment, 0.5 mL CSF will be collected for assessment of drug exposure pre-dose on C2D1.
16. Radiographic assessment performed within 28 days before initiation of study treatment can be used as the baseline assessment, radiographic assessment will be performed on C2D1, and subsequent radiographic assessments will be performed every 6 weeks ± 1 week (relative to C1D1) until disease progression or death (death not due to disease progression) or initiation of another anti-tumor treatment, regardless of withdrawal from AZD3759 treatment. For patients who withdraws from the study due to reasons other than disease progression, if time to the last scheduled assessment from withdrawal from the study is more than 4 weeks, additional radiographic assessment should be performed at study withdrawal.
17. Questionnaire will be completed at screening period, on C2D1 and every 6 weeks ± 1 week (relative to C1D1) thereafter. QLQ C-30 has to be collected until the withdrawal of study treatment, and QLQ BN-20 has to be collected until disease progression or death (death not due to disease progression) or initiation of another anti-tumor treatment. For patients who withdraws from the study due to reasons other than disease progression, if time to the last scheduled assessment from withdrawal from the study is more than 4 weeks, QLQ BN-20 questionnaire should be completed at study withdrawal. Patients must complete the questionnaire before visit study procedures and communication with the doctor about disease condition. Patients will have to complete the questionnaire independently.
18. The first dose should be taken at C0D1 and then commence twice daily dosing at C1D1 in fasting state. Each patient should take the drug at fixed time points during study treatment as far as possible. Dosing interval is 12 hours. Patients should not eat in 2 h post-dose nor drink in 1h post-dose. Administration in the hospital will be supervised by a doctor or nurse, and administered dose and time will be recorded on eCRF. For self-administration at home, time of administration and administered dose every day should be recorded on subject's diary card.
19. Venous blood samples (3 mL each time) for PK evaluation will be collected at pre-dose and 0.5h, 1h, 1.5h, 2h, 3h, 4h, 6h, 8h, 10h, 12h, 24h (C0D2) and 48h (C0D3) after the first dose (C0D1). Blood samples for PK evaluation will be collected during multiple dosing at pre-dose of C1D15, C1D21 and C2D1 and 0.5h, 1h, 1.5h, 2h, 3h, 4h, 6h, 8h, 10h, 12h post dose on C1D21.
20. Concomitant medications and treatments received within 28 days prior to screening and during study treatment will be recorded through completion of 28-day follow-up after the end of study treatment.
21. Adverse events will be recorded from signing informed consent form through 28-day follow-up after the end of study treatment, and will be followed up till adverse event is resolved or stable.

Table 2 Flow chart of dose expansion in Part A

	Screening period	Single dose / Cycle 0			Cycle 1				Cycle 2	Cycle 3 and thereafter	End of treatment/withdrawal	28-day follow-up	Disease progression
Follow-up visit	1	1.1	1.2	1.3	2	3	4	5	6	7 and thereafter			
Day	-28~0	C0D1	C0D2	C0D3	C1D1	C1D8	C1D15	C1D21	C2D1	D1			
Visit window (days)	NA	0	0	0	0	0	0	0	0	±3	±3	±3	
Informed Consent Form	X												
Demographic data[1]	X												
Tumor history/other medical history[2]	X												
Inclusion/exclusion criteria	X												
Screen for infectious diseases[3]	X												
ECOG[4]	X	X			X				X	X	X		
EGFR testing[5]	X												
Physical examination[6]	X	X			X	X	X	X		X	X		
Vital signs[7]	X	X	X		X	X	X	X	X	X	X		
Height[8]	X												
Body weight[8]	X	X			X				X	X	X		
Clinical laboratory tests (hematology, blood biochemistry and urinalysis)[9]	X				X	X	X	X		X	X		
ECG[10]	X	X	X		X	X	X	X		X	X		
Pregnancy test (only for women of childbearing age)[11]	X										X		

Nervous system examination[12]	X	X							X	X (D1 of each cycle until PD)			
Ophthalmology examination[13]	X										X		
CSF collection for cytological test and biochemical test (only for LM patients)[14]	X									X			
Imaging evaluation [15]	X									X (relative to C1D1, every 6 weeks up to PD)			
QLQ C-30[16]	X								X	X (relative to C1D1, every 6 weeks up to end of treatment)			
QLQ BN-20[16]	X								X	X (relative to C1D1, every 6 weeks up to PD)			
Administration of AZD3759 [17]		X			⟷								
Subject's diary card [17]					⟷								
PK sampling[18]		X	X	X	X	X	X	X	X				
Concomitant medications [19]	⟷												
Adverse events[20]	⟷												

1. Demographics, including gender, date of birth, nationality, smoking history, height and body weight.
2. Tumor history and other medical history will be recorded separately. Other medical history includes all active diseases, and any diseases diagnosed in the past 10 years that the investigator considers clinically significant. Tumor history includes all previous tumors other than that evaluated in this study, even the diagnosis was made more than 10 years prior to screening visit.
3. Screen for infectious diseases include HIV antibody, two pairs of semi-hepatitis B (quantification of HBV-DNA may be performed if required) and HCV antibody (HCV RNA is required if HCV antibody is positive).
4. ECOG score will be obtained at Screening period, on C0D1, C1D1 and Day 1 of every cycle until end of treatment/withdrawal.
5. At screening period, EGFR mutation in blood or tumor tissue should be determined in a qualified laboratory, and T790M mutation status will also be determined.

6. Physical examination includes: general appearance, skin, head and neck (including ears, eyes, nose and throat), respiratory, cardiovascular, abdomen, lymph nodes, thyroid gland and musculoskeletal system (including spine and limbs). Physical examination will be performed at screening period, and on C0D1, C1D1, C1D8, C1D15, C1D21 and on Day 1 of cycle 3 and each cycle afterwards until the end of treatment.
7. Vital signs include blood pressure, pulse and body temperature, and will be monitored at screening period, pre-dose and 2h, 6h, and 24h post-dose at C0D1, pre-dose at C1D1, C1D8 and C1D15, pre-dose and 2h and 6h post-dose at C1D21, and pre-dose on Day 1 of every cycle from Cycle 2. Moreover, additional vital signs may be determined as needed in case of any cardiac adverse event, and vital signs should be performed at withdrawal of study treatment. A time window of 30 minutes is permitted for vital signs.
8. Height will be measured only at screening period. Body weight will be measured at screening period, on Day 1 of every cycle and at withdrawal of study treatment.
9. Blood and urine samples for clinical laboratory tests will be collected from subjects at screening period, pre-dose on C1D1, C1D8, C1D15, C1D21 and pre dose on Day 1 of cycle 3 and each cycle afterwards and at withdrawal of study treatment. The clinical laboratory tests of screening should be performed within 7 days prior to the initiation of treatment.
10. ECG should be obtained in supine position after adequate rest. A time window of 1 hour is permitted. At screening period, pre-dose and 2h, 6h and 24h post-dose on C0D1, pre-dose on C1D1, C1D8 and C1D15, pre-dose and 2h and 6h post-dose on C1D21, and on Day 1 during follow-up of each cycle from cycle 3. Moreover, additional ECG may be obtained as needed in case of any cardiac adverse event. If QTcF $\geqslant$ CTC AE 3, repeat ECG measurements for consecutive 3 times immediately and take the average. ECG should be obtained at withdrawal of study treatment.
11. For non-surgical sterilized women of child-bearing potential, blood sample for pregnancy test should be collected at screening and withdrawal of study treatment. Menopause is defined as permanent cession of menorrhea. Women are considered post-menopausal if they (usually older than 45 years) have had 12 months of natural (spontaneous) amenorrhea.
12. Neurological examination will be performed at screening period and on C0D1 and Day 1 of every cycle from Cycle 2 until disease progression or death (death not due to disease progression) or initiation of another anti-tumor treatment. For patients who discontinue the study treatment due to reasons other than disease progression, neurological examination after treatment discontinuation should be performed at follow-up tumor radiographic assessment. Neurological examination should be recorded on a separate "Neurological Function Examination" Case Report Form.
13. Ophthalmological examination should be performed at screening period and withdrawal of study treatment, or in case of any visual symptom (including blurred vision).
14. For LM patients with implanted Ommaya reservoir, CSF samples will be collected at screening and every 6 weeks ± 1 week (relative to C1D1) until disease progression or death (death not due to disease progression) or initiation of another anti-tumor treatment. For LM patients without implanted Ommaya reservoir, CSF samples will be collected at least at screening and Week 12. 10 ml CSF shall be collected each time.. CSF responders should be confirmed through repeated test at least 4 weeks after initial negative conversion.

15. Radiographic assessment performed within 28 days before initiation of study treatment can be used as the baseline assessment, and subsequent radiographic assessments will be performed every 6 weeks ± 1 week (relative to C1D1) until disease progression or death (death not due to disease progression) or initiation of another anti-tumor treatment, regardless of withdrawal from AZD3759 treatment. For patients who withdraws from the study due to reasons other than disease progression, if time to the last assessment from the withdrawal from study is more than 4 weeks, additional radiographic assessment should be performed at study withdrawal.
16. Questionnaire will be completed at screening period, on C2D1 and every 6 weeks ± 1 week (relative to C1D1) thereafter. QLQ C-30 has to be collected until the withdrawal of study treatment, and QLQ BN-20 has to be collected until disease progression or death (death not due to disease progression) or initiation of another anti-tumor treatment. For patients who withdraws from the study due to reasons other than disease progression, if time to the last assessment from the withdrawal from study is more than 4 weeks, QLQ BN-20 questionnaire should be completed at study withdrawal. Patients must complete the questionnaire before visit study procedures and communication with the doctor about disease condition. Patients will have to complete the questionnaire independently.
17. The first dose should be taken at C0D1 and then commence twice daily dosing at C1D1 in fasting state. Each patient should take the drug at fixed time points during study treatment as far as possible. Dosing interval is 12 hours. Patients should not eat in 2 h post-dose nor drink in 1h post-dose. Administration in the hospital will be supervised by a doctor or nurse, and administered dose and time will be recorded on eCRF. For self-administration at home, time of administration and administered dose every day should be recorded on subject's diary card.
18. Venous blood samples (3 mL each time) for PK evaluation will be collected at pre-dose and 0.5h, 1h, 1.5h, 2h, 3h, 4h, 6h, 8h, 10h, 12h, 24h (C0D2) and 48h (C0D3) after the first dose (C0D1). Blood samples for PK evaluation will be collected during multiple dosing at pre-dose of C1D15, C1D21 and C2D1 and 0.5h, 1h, 1.5h, 2h, 3h, 4h, 6h, 8h, 10h, 12h post dose on C1D21.
19. Concomitant medications and treatments received within 28 days prior to screening and during study treatment will be recorded through 28-day follow-up after the end of study treatment.
20. Adverse events will be recorded from signing informed consent form through 28-day follow-up after the end of study treatment, and will be followed up till adverse event is resolved or stable.

Table 3 Flow chart of Phase II study in Part B

	Screening period	Cycle 1	Cycle 2 and thereafter	End of treatment/withdrawal	28-day follow-up	Disease progression	Survival follow-up
Follow-up visit	1	2	3 and thereafter				
Day	-28~0	C1D1	D1				
Visit window (days)	NA	0	±3	±3	±3		±7
Informed Consent Form	X						
Demographic data[1]	X						
Tumor history/other medical history[2]	X						
Inclusion/exclusion criteria	X						
Screen for infectious diseases[3]	X						
ECOG score[4]	X	X	X	X			
EGFR testing[5]	X						
Physical examination[6]	X	X	X	X			
Vital signs[7]	X	X	X	X			
Height[8]	X						
Body weight[8]	X		X	X			
Clinical laboratory tests (hematology, blood biochemistry and urinalysis)[9]	X	X	X	X			
ECG[10]	X	X	X	X			
Pregnancy test (only for women of childbearing age)[11]	X			X			
Nervous system examination[12]	X	X	X	X (D1 of each cycle until progression)			
Ophthalmology examination[13]	X			X			

CSF collection for cytological test and biochemical test (only for patients with metastases to meninges)[14]	X		X				
Oncologic imaging evaluation[15]	X		X(relative to C1D1, every 6 weeks up to progression)				
QLQ C-30[16]	X		X(relative to C1D1, every 6 weeks)	X			
QLQ BN-20[16]	X		X(relative to C1D1, every 6 weeks up to progression)				
Administration of AZD3759[17]		←	→				
Subject's diary card[17]		←	→				
Concomitant medications[18]	←	→					
Adverse events[19]	←	→					
Survival follow-up[20]							X (every 6 weeks)

1. Demographics, including gender, date of birth, nationality, smoking history, height and body weight.
2. Tumor history and other medical history will be recorded separately. Other medical history includes all active diseases, and any diseases diagnosed in the past 10 years that the investigator considers clinically significant. Tumor history includes all previous tumors other than that evaluated in this study, even the diagnosis was made more than 10 years prior to screening visit.
3. Screen for infectious diseases include HIV antibody, two pairs of semi-hepatitis B (quantification of HBV-DNA may be performed if required) and HCV antibody (HCV RNA is required if HCV antibody is positive).
4. ECOG score will be obtained at Screening period, on C1D1 and Day 1 of every cycle until end of treatment/withdrawal.
5. At screening period, EGFR mutation in blood or tumor tissue should be determined in a qualified laboratory, and T790M mutation status will also be determined.
6. Physical examination includes: general appearance, skin, head and neck (including ears, eyes, nose and throat), respiratory, cardiovascular, abdomen, lymph nodes, thyroid gland and musculoskeletal system (including spine and limbs). Physical examination will be performed at screening period, and on C1D1 and Day 1 of every cycle until end of treatment.

7. Vital signs include blood pressure, pulse and body temperature, and will be monitored at screening period, pre-dose on C1D1, and pre-dose on Day 1 of every cycle from Cycle 2. Moreover, additional vital signs may be performed as needed in case of any cardiac adverse event, and vital signs should be performed at withdrawal of study treatment.
8. Height will be measured only at screening period. Body weight will be measured at screening period, on Day 1 of every cycle and at withdrawal of study treatment.
9. Blood and urine samples for clinical laboratory tests will be collected from subjects at screening period, pre-dose on C1D1 and Day 1 of every cycle from Cycle 2, and at withdrawal of study treatment.
10. ECG should be obtained in supine position after adequate rest. At screening period, pre-dose and post-dose on C1D1, and post-dose on Day 1 of every cycle from Cycle 2 for the day of dosing. Moreover, additional ECG may be obtained as needed in case of any cardiac adverse event. If QTcF ≥CTC AE 3, repeat ECG measurements for consecutive 3 times immediately and take the average. ECG should be obtained at withdrawal of study treatment.
11. For non-surgical sterilized women of child-bearing potential, blood sample for pregnancy test should be collected at screening and withdrawal of study treatment. Menopause is defined as permanent cession of menorrhea. Women are considered post-menopausal if they (usually older than 45 years) have had 12 months of natural (spontaneous) amenorrhea.
12. Neurological examination will be performed at screening period and on Day 1 of every cycle until disease progression or death (death not due to disease progression) or initiation of another anti-tumor treatment. For patients who discontinue the study treatment due to reasons other than disease progression, neurological examination after treatment discontinuation should be performed at follow-up tumor radiographic assessment. Neurological examination should be recorded on a separate "Neurological Function Examination" Case Report Form.
13. Ophthalmological examination should be performed at screening period and withdrawal of study treatment, or in case of any visual symptom (including blurred vision).
14. For LM patients with implanted Ommaya reservoir, CSF samples will be collected at screening and every 6 weeks ± 1 week (relative to C1D1) until disease progression. For LM patients without implanted Ommaya reservoir, CSF samples will be collected at least at screening and Week 12. 10 ml CSF shall be collected each time. CSF responders should be confirmed through repeated test at least 4 weeks after initial negative conversion.
15. Radiographic assessment performed within 28 days before initiation of study treatment can be used as the baseline assessment, and subsequent radiographic assessments will be performed every 6 weeks ± 1 week (relative to C1D1) until disease progression or death (death not due to disease progression) or initiation of another anti-tumor treatment, regardless of withdrawal from AZD3759 treatment. For patients who withdraws from the study due to reasons other than disease progression, if time to the last assessment from the withdrawal from study is more than 4 weeks, additional radiographic assessment should be performed at study withdrawal.
16. Questionnaire will be completed at screening period and every 6 weeks ± 1 week (relative to C1D1). QLQ C-30 has to be collected until the withdrawal of study treatment, and QLQ BN-20 has to be collected until disease progression or death (death not due to disease progression) or

initiation of another anti-tumor treatment. For patients who withdraws from the study due to reasons other than disease progression, if time to the last scheduled assessment from withdrawal from the study is more than 4 weeks, QLQ BN-20 questionnaire should be completed at study withdrawal. Patients must complete the questionnaire before visit study procedures and communication with the doctor about disease condition. Patients will have to complete the questionnaire independently.

17. Administration will be twice daily in fasting state. Each patient should take the drug at fixed time points during study treatment as far as possible. Dosing interval is 12 hours. Patients should not eat in 2 h post-dose nor drink in 1h post-dose. Administration in the hospital will be supervised by a doctor or nurse, and administered dose and time will be recorded on eCRF. For self-administration at home, time of administration and administered dose every day should be recorded on subject's diary card.
18. Concomitant medications and treatments received within 28 days prior to screening and during study treatment will be recorded through 28-day follow-up after the end of study treatment.
19. Adverse events will be recorded from signing informed consent form through 28-day follow-up after the end of study treatment, and will be followed up till adverse event is resolved or stable.
20. Once 28-day follow-up visit is completed, all patients in Phase II study period will be contacted by phone every 6 weeks for overall survival follow-up, until patient's death or loss to follow-up or withdrawal of informed consent. During this period, any other treatment for non-small cell lung cancer should be collected via eCRF.