

PROTOCOL SYNOPSIS

Protocol Number	AZD3759-003
Title of Study	A Randomized, Open-Label, Controlled, Multi-Center Phase II/III Study to Assess the Efficacy and Safety of AZD3759 vs. Standard of Care Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor (Erlotinib or Gefitinib) as First Line Treatment in Patients with Epidermal Growth Factor Receptor Mutation Positive Advanced Non-Small Cell Lung Cancer with Central Nervous System Metastasis
Phase of Clinical Trial	Phase II/III
Indications	To be administered as first line treatment of Epidermal Growth Factor Receptor (EGFR) mutation positive Advanced Non-Small Cell Lung Cancer (NSCLC) patients with Central Nervous System (CNS) metastasis
Study Objectives	<p>Primary Objective:</p> <p>The primary objective of this study is to determine if administration of single agent AZD3759 compared to Standard of Care (SoC) EGFR-TKI as first-line therapy results in a significant increase in Progression Free Survival (PFS) in the study patient population by Blinded Independent Central Radiological(BICR) review.</p> <p>Secondary Objectives:</p> <p>Key secondary objective for this study is to determine if AZD3759 vs. SoC EGFR TKI administration demonstrates additional benefit in terms of safety, Objective Response Rate (ORR), Disease Control Rate (DCR), Duration of Response (DoR), and overall PFS using modified RECIST 1.1 criteria by investigator assessment. Additional secondary objectives include assessment of Health Related Quality of Life (HRQoL), neurological function, and Overall Survival (OS).</p> <p>Exploratory Objectives:</p> <p>Key exploratory objectives will involve key genetic and proteomic markers.</p>
Study Design	<p>This is a Phase II/III randomized, open-label, multicenter study to compare the efficacy and safety of first line single-agent AZD3759 vs. Erlotinib or Gefitinib treatment in patients with advanced NSCLC with CNS metastases.</p> <p>Eligible patients with documented EGFR mutation+ (L858R and/or Exon 19Del) TKI-naïve advanced NSCLC and documented intracranial disease will be enrolled. Eligible patients will receive AZD3759 twice daily dosing until disease progression provided that they are continuing to derive clinical benefit based on the investigator's judgement, or until they experience unacceptable drug related toxicity.</p> <p>Approximately 300 patients (150 patients in each cohort) will be randomized in a 1:1 ratio (AZD3759: SoC EGFR-TKI) in this study. The stratification factors of randomization will be (i) sex (male vs. female); (ii) smoking status (never vs. current/former); and (iii) ECOG performance status (PS = 0 vs. PS =1).</p> <p>Sites in China will be required to only use Gefitinib as the sole study treatment comparator as control; sites in other countries will select either Gefitinib or Erlotinib as the control study treatment comparators. Each site will have to use one SoC EGFR TKI either Gefitinib or Erlotinib as the sole comparator for the duration of the trial. The selected SoC EGFR-TKI will be used in accordance with the marketing authorization for the specific country or area.</p> <p>This study consists of three phases: (i) screening and randomization; (ii) treatment;</p>

	<p>and (iii) follow up. During the screening, each potential subject will provide informed consent prior to starting any study specific procedures. The randomization of subjects to study groups (Arm A, AZD3759; Arm B, Erlotinib or Gefitinib) will be performed centrally by an Interactive Web-Response System (IWRS) using a randomization scheme that will be reviewed and approved by an independent statistician. During the treatment period, randomized subjects will be provided the treatment and assessment according to the protocol. Follow up includes Investigational Product (IP) discontinuation visit, 28 days follow up, progression follow up and survival follow up.</p> <p>Patient randomized into AZD3759 group will receive a 300 mg twice daily dose. Patient randomized into Erlotinib group will receive a dose of 150 mg once daily, or patients randomized into Gefitinib group will receive a 250 mg once daily dose.</p> <p>Patients will continue their randomized treatment until disease progression or treatment discontinuation or study withdrawal. All patients who continue to experience documented clinical benefit to treatment by radiographic and clinical assessment will continue to receive their assigned treatment indefinitely until relapse or progression. In the event patients experience documented disease progression, the treating physician may continue assigned treatment in accordance with their clinical judgement. There is no maximum duration of treatment for this study. All radiographic tumor assessments will be carried out in accordance with mRECIST 1.1 criteria and are to be performed every 6 weeks (± 7 days) relative to first dose of study drug, and will be repeated until objective disease relapse or progression or as per standard practice post progression.</p> <p>Patients will be followed for survival every 6 weeks following objective disease progression.</p>
<p>Treatment Duration and End of Study</p>	<p>A cycle of treatment is defined as 21 days of treatment with AZD3759 or SoC EGFR-TKI Erlotinib or Gefitinib. Treatment with AZD3759 (300 mg twice daily), or SoC EGFR-TKI Erlotinib (150 mg once daily) or Gefitinib (250 mg once daily) will commence following randomization.</p> <p>Patients may continue to receive AZD3759 or a SoC EGFR-TKI Erlotinib or Gefitinib as long as they are continuing to show clinical benefit, as judged by the Investigator, and in the absence of discontinuation criteria.</p> <p>Patients must be followed until evidence of modified RECIST 1.1 defined progression (regardless of reason for treatment discontinuation). It is important that subjects are assessed according to the intended scanning schedule to prevent the bias in analysis that can occur if one treatment group is assessed more or less often than the other.</p> <p>Estimated Study period: Q2 2018 - Q2 2021</p> <p>Collection of data will cease at the time of database lock for final OS analysis.</p>
<p>Study Centers</p>	<p>Approximately 40 sites in Asia Pacific region will participate in this trial.</p>
	<p>Primary endpoint</p> <p>To assess if first line treatment with AZD3759 results in significant overall PFS efficacy compared to Gefitinib or Erlotinib as determined by Blinded Independent Central Radiological (BICR) review using modified RECIST 1.1.</p> <p>Secondary endpoints:</p> <ol style="list-style-type: none"> Investigator assessment of PFS using modified RECIST 1.1

<p>Study Endpoints</p>	<ol style="list-style-type: none"> 2. Assess and compare intracranial PFS (iPFS) and extracranial (ePFS) by investigator assessment vs. BICR assessment using modified RECIST 1.1 between the study cohorts. 3. To assess ORR, DCR and DoR between study cohorts for: <ol style="list-style-type: none"> (i) Intracranial lesions; (ii) Extracranial lesions; and (iii) Overall ORR, DCR and DoR between the study cohorts using modified RECIST 1.1 and modified RANO criteria (for intracranial disease) per Investigator’s assessment. 4. Overall Survival (OS) 5. Change from baseline in European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30, QLQ-BN20) 6. Neurological function improvement rate by Mini-Mental Status Examination (MMSE) and modified RANO criteria; 7. Safety parameters: Adverse Events (AEs), Serious Adverse Events (SAEs), laboratory abnormalities, ECG changes, and vital signs etc. <p>Exploratory endpoints</p> <ol style="list-style-type: none"> 1. Assess key genetic and proteomic markers to include, but not limited to, EGFR mutations (eg., T790M) pre- vs. following progression, human epidermal growth factor receptor2 (HER2), and proto-oncogene encoding Hepatocyte Growth Factor Receptor (cMET) expression and/or amplification 2. Correlation of polymorphisms with variation in safety or response observed in patients treated with AZD3759 or comparator 3. Change in number of CNS lesions in patients that may relate to outcome of study treatment
<p>Study Treatment</p>	<p>Study drug: AZD3759</p> <p>Strength: 50 mg or 100 mg tablets</p> <p>AZD3759 300 mg orally twice daily (dosing interval is 12 hours +/- 4 hours) before or after meals</p> <p>One treatment cycle = 21 consecutive days of dosing</p> <p>Control drug: either Erlotinib or Gefitinib as designated per site</p> <p>Strength: Erlotinib 150 mg or Gefitinib 250 mg tablets</p> <p>Erlotinib (150 mg P.O.) or Gefitinib (250 mg P.O.) will be administered once daily. A treatment cycle consists of consecutive 21 days of dosing</p> <p>Subjects may continue treatment until disease progression per investigator’s judgement, or until they experience unmanageable drug related toxicity, as long as they are continuing to derive clinical benefit</p>
	<p>Inclusion criteria</p> <p>For inclusion in the study, patients must meet ALL of the following criteria.</p>

**Eligibility
Criteria**

1. Properly completed patient informed consent
2. Male or female aged at least 18 years
3. Histologically or cytologically confirmed diagnosis of NSCLC with activating EGFR mutations including L858R and/or Exon19Del. EGFR mutation status will be determined by local or central laboratory testing on tumour tissue or plasma utilizing a validated methodology which has been approved by the regulatory authority.
4. No prior treatment with chemotherapy, EGFR-TKIs, or biological therapies that are considered first line treatment for advanced NSCLC.
5. All patients must have a documented diagnosis of advanced (Stage IV) NSCLC with Magnetic Resonance Imaging (MRI) documented CNS metastases that include brain metastases (BM). BM + patients with co-existent leptomeningeal involvement are eligible for the study.
6. Eligible patients are not candidates for definitive surgical resection or radiation of all lesions in the opinion of the treating physician.
7. All patients must be stable without any systemic (oral or parenteral) corticosteroid or anticonvulsant therapy for at least 2 weeks prior to study treatment. Inhaled non-absorbable and topical corticosteroid use are permitted as indicated.
8. Patients may have prior placement of a properly functioning CNS shunt or Ommaya reservoir.
9. Eastern Cooperative Oncology Group (ECOG) performance status 0 to 1 with no deterioration over the previous 2 weeks.
10. Women of child-bearing potential and male subjects shall agree to take medically acceptable contraception measures while on study treatment and for 3 months following completion of study treatment. All women of child-bearing potential must have a negative blood pregnancy test at screening.
11. 1) For Patients with measurable CNS lesions must have AT LEAST ONE site of CNS lesion, which was not previously irradiated, that can be accurately measured at baseline as ≥ 10 mm in the longest diameter by MRI and which is suitable for accurate repeated measurements. Measurable extracranial disease is not required.
2) For Patients with non-measurable CNS lesions must have AT LEAST ONE extracranial lesion, which has not been previously irradiated, within the screening period that can be accurately measured at baseline as ≥ 10 mm in the longest diameter (except lymph nodes which must have short axis ≥ 15 mm) by CT/MRI and are suitable for accurate repeated measurement.

Exclusion criteria

Patients must not enter the study if ANY of the following exclusion criteria is present:

1. Prior treatment with an EGFR-TKI.
2. Positive for T790M mutation documented by central or local laboratory using an approved or validated methodology of testing.
3. Patients receiving any investigational drug, biological, immunological

- therapy within the previous 21 days for their malignancy.
4. Any major surgical procedure (excluding the need for placement of vascular access or a CNS shunt), or significant traumatic injury within 4 weeks of the first dose of study treatment, or have an anticipated need for major surgery during the study.
 5. Documented presence of leptomeningeal (LM) disease only by absence of documented BM by MRI and/or positive CSF cytology for malignant cells.
 6. Prior radiation therapy for CNS metastases that involves measurable or non-measurable sites of disease to assess efficacy
 7. Patients receiving radiation to more than 30% of the bone marrow must be completed 2 weeks before the first dose of study treatment.
 8. Patients currently receiving (or unable to stop use at least 1 week prior to receiving the first dose of study drugs) medications or herbal supplements that are known to be potent inhibitors or inducers of CYP3A4/5 (Appendix G).
 9. Prior gastric resection or surgical procedure that would interfere with absorption of study medications.
 10. History of concurrent and/or other active malignancy requiring treatment within 5 years of study treatment, excluding prior treated squamous cell or basal carcinomas or carcinoma in situ.
 11. History of any type of documented interstitial lung disease or radiation pneumonitis.
 12. Presence of any severe or uncontrolled systemic disease or condition, including: (i) uncontrolled hypertension or diabetes; (ii) serious cardiac, pulmonary or renal conditions; (iii) active bleeding diatheses; (iv) any active type of bacterial, viral, fungal or other infection that would pose a significant risk to the patient in the opinion of the investigator; or (v) active Hepatitis B or positive HCV antibodies or positive HIV test result.
 13. Women who are pregnant or lactating. Women of child-bearing potential (WOCBP), and fertile men with a WOCBP-partner not using adequate birth control.
 14. Patients with unstable and/or symptomatic metastases: any CNS or distant metastases that are unstable are symptomatic and not controlled by prior surgery, radiotherapy or corticosteroids to control symptoms for a period of within 3 weeks of initiation study treatment.
 15. Any unresolved toxicities from prior therapy, greater than Common Terminology Criteria for Adverse Events (CTCAE) grade 1 at the time of starting study treatment, with exception of alopecia. Patients are having undergone any major surgical procedure within 4 weeks prior to first study drug administration.
 16. Patients with a significant cardiovascular disease or condition, including any of the following:
 - a. Congestive heart failure (CHF) currently requiring therapy and patients with New York Heart Associate Class III/IV CHF (see Appendix M)
 - b. Need for antiarrhythmic medical therapy for a ventricular

- arrhythmia or patients with uncontrolled or unstable cardiac arrhythmias
- c. Severe conduction disturbance (e.g., second- or third-degree AV block)
 - d. Angina pectoris requiring therapy
 - e. QTc interval > 450 msec (males) or > 470 msec (females)
 - f. History of congenital long QT syndrome, congenital short QT syndrome, Torsades de Pointes, or Wolff Parkinson White syndrome
 - g. LVEF < 50% as determined by echocardiography or MUGA scan
 - h. Myocardial infarction diagnosed within the last 6 months.
17. Inadequate bone marrow reserve or organ function as demonstrated by any of the following laboratory values:
- a. Absolute neutrophil count < $1.5 \times 10^9/L$
 - b. Platelet count < $100 \times 10^9/L$ (Transfusion-dependent patients are excluded)
 - c. Haemoglobin < 90 g/L
 - d. Alanine aminotransferase > 2.5 times the upper limit of normal (ULN) if no demonstrable liver metastases or > 5 times ULN in the presence of liver metastases
 - e. Aspartate aminotransferase > 2.5 times ULN if no demonstrable liver metastases or > 5 times ULN in the presence of liver metastases
 - f. Total bilirubin > 1.5 times ULN. Total bilirubin > 3 times the ULN in patients with documented Gilbert's Syndrome (unconjugated hyperbilirubinemia) or in the presence of liver metastases
 - g. Creatinine > 1.5 times ULN concurrent with creatinine clearance < 50 mL/min (measured or calculated by Cockcroft and Gault equation). Confirmation of creatinine clearance is only required when creatinine is > 1.5 times ULN;
 - h. If bone metastases are present and liver function is otherwise considered adequate by the investigator, then isolated elevated alkaline phosphatase (ALP) will not exclude the patient;
18. History of hypersensitivity to active or inactive excipients of study drugs or drugs with a similar chemical structure or class to study drugs.
19. Judgment by the investigator that the patient should not participate in the study if the patient is unlikely to comply with all study procedures and treatment.
20. History of recent stroke (< 6 months), or prior CNS injury that has persistent neurologic deficits that would confound neurologic assessments.
21. Significant medical or psychiatric illness that would interfere with compliance and ability to tolerate treatment as outlined in the protocol.

In addition, the following are considered criteria for exclusion from the exploratory genetic research:

- 22. Previous allogeneic bone marrow transplant.
- 23. Non-leukocyte depleted whole blood transfusion within 120 days of the

	date of the genetic sample collection.												
Sample Size	<p>Assuming a median PFS for the AZD3759 arm is 13.9 months (Company data-Bloom study) and 9.6 months (J.-C. Soria et al. 2017) for the Gefitinib/Erlotinib arm, the total study duration is 36 months with enrollment period of 15 months, and the dropout rate per year is 5%.</p> <p>Using a two-sided alpha level of 0.05, a total of 300 subjects with 230 PFS events is required to achieve 80% power.</p>												
Statistical Analysis	<p>Approximately 300 patients (150 patients in each cohort) will be randomized in a 1:1 ratio (AZD3759: SoC EGFR-TKI) in this study. The primary endpoint of the study is overall PFS. The final analysis of PFS will be performed at approximately 36 months based on 15 months enrollment and 21 months of treatment and follow up and will be conducted when at least 230 PFS events are observed. The sample size is based on 9.6 months median PFS in the control group and 13.9 median PFS in the AZD3759 treatment group using a 5% 12-month dropout rate, two-sided alpha of 0.05 and 80% power.</p> <p>An interim efficacy analysis of PFS will be performed by an Independent Data Monitoring committee (IDMC) after approximately 156 documented PFS events have been observed by BICR, where 0.0144 of the alpha will be spent at the time of the interim PFS analysis with the remainder (final adjusted alpha =0.0452) at the final PFS analysis.</p> <p>According to the interim analysis results of hazard ratio (HR), the sample size can be adjusted to preserve the power and the significance level. The decision to perform or not perform any sample size adjustment will be made based on the observed hazard ratio determined at interim analysis in accordance with the possible pre-specified interim hazard ratio outcomes as described below:</p> <table border="1" data-bbox="386 1060 1349 1270"> <thead> <tr> <th>HR</th> <th>Sample Size Adjustment</th> <th>Event</th> </tr> </thead> <tbody> <tr> <td>HR<=0.7</td> <td>No adjustment</td> <td>230</td> </tr> <tr> <td>0.7<HR<=0.72</td> <td>374</td> <td>292</td> </tr> <tr> <td>0.72<HR<=0.75</td> <td>482</td> <td>381</td> </tr> </tbody> </table> <p>Progression free survival (PFS) will be analyzed using a log rank test stratified by: (i) sex (male vs. female); (ii) smoking status (never vs. current/former); and (iii) ECOG performance status (PS = 0 vs. PS =1). The primary endpoint analysis will be based on blinded independent central review (BICR) using mRECIST 1.1 criteria applied to the primary PFS endpoint.</p> <p>A separate sensitivity analysis and correlation of the BICR and investigator determined PFS will be performed based on data assessed by investigator assessment of PFS for the study population.</p> <p>An Independent Data Monitoring Committee (IDMC) will be convened, and will meet initially when approximately 50 patients have been enrolled and followed up for 3 months (estimated to be 6 months from first patient randomized). Thereafter, the IDMC will conduct further reviews of safety data when all patients have been randomized (estimated to be 12 months from first patient randomized). Further meetings for review of safety data may be convened at the discretion of IDMC. The IDMC will review safety assessments and make recommendations to continue, amend, or stop the study based on safety findings. Serious adverse events, adverse events, and other safety data will be reviewed, and individual and aggregated safety data will be evaluated by the IDMC. Furthermore, the IDMC will conduct the planned interim efficacy analysis (see Section 7.5.1. Analysis of the primary variable) to be performed when at least 156 PFS events are observed by BICR. Safety will also be</p>	HR	Sample Size Adjustment	Event	HR<=0.7	No adjustment	230	0.7<HR<=0.72	374	292	0.72<HR<=0.75	482	381
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	reviewed at this time. Full details of the IDMC procedures and processes can be found in the IDMC Charter.
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Study Flow Chart

Phase II/III portion	Screening	C1D1	C2D1 onwards	IP Discontinuation /withdrawal of study treatment	28-dayfollow-up	Progression follow -up	Survival follow-up
Visit	0	1	2 onwards				
Day	D-28 to -1	Day 1	D22 (+/- 3 days)				Every 6 weeks (+/- 7 days)
Informed consent	X						
Demography & Baseline Characteristics ¹	X						
Medical/surgical history ²	X						
Inclusion/exclusion criteria	X	X					
Screen for infectious diseases ³	X						
Physical examination ⁴	X	X	X	X			
ECOG Score	X	X	X	X		X at start of subsequent treatment	
EGFR testing ⁵	X					X (Optional)	
Neurological examination ⁶	X	X	X (D1 of each cycle until progression)				
Ophthalmologic assessment ⁷	X			X			
Vital Signs ⁸	X	X	X	X			
Height	X						
Weight	X	X	X	X			
Clinical chemistry (hematology, blood biochemistry and urinalysis)	X	X	X	X			
ECG ⁹	X	X	X	X			
Echocardiogram/MUGA Scan ⁹	X						
Pregnancy test (female of child-bearing potential only) ¹⁰	X	X		X			
QLQ C-30 ¹¹	X		X (Every 6 weeks (relative to C1D1) until progression				X after progression, optional, maximum twice with 6 weeks interval
QLQ BN-20 ¹¹	X		X (Every 6 weeks (relative to C1D1) until progression				X after progression, optional, maximum twice with 6 weeks interval
MMSE ¹²	X		X (Every 6 weeks (relative to C1D1) until progression				X after progression, optional, maximum twice with 6 weeks interval
Modified RANO assessment (for Intracranial disease)	X		X (Every 6 weeks (relative to C1D1) until progression				X after progression, optional, maximum twice with 6 weeks interval
Blood-borne biomarker samples (plasma) ¹³ (Optional)	X		X on week 3, 6, 18 (relative to C1D1), and every 12 weeks until progression.				

Phase II portion	Screening	C1D1	C2D1 onwards	IP Discontinuation /withdrawal of study treatment	28-dayfollow-up	Progression follow -up	Survival follow-up
Visit	0	1	2 onwards				
Day	D-28 to -1	Day 1 (0 days)	D22(+/- 3 days)				Every 6 weeks (+/- 7 days)
Dispense study drug		X	X				
Dose with study drug		< -----Daily dosing ----->					
CT/MRI imaging (modified RECIST 1.1) ¹⁴	X		X (Every 6 weeks (relative to C1D1) until progression/ Per standard practice post-progression <----->				
Concomitant Medication	<----->					X done if prior to 28-day follow-up	
Adverse events	<----->					X done if prior to 28-day follow-up	
Anti-cancer and surgery treatment						X	X
Subsequent response/progression data ¹⁵						X (freq as per SOC)	X (freq as per SOC)
Survival follow- up ¹⁶							X

C1D1=Cycle 1 Day 1

1. Demographics, including sex, date of birth, race, smoking history, height and body weight.
2. Medical/surgical 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 tumours other than that evaluated in this study, even the diagnosis was made more than 10 years prior to screening visit. Smoking history includes never, light (<100 cigarettes/lifetime), active smokers, and former smokers (quit date). History of number packs/day ,number of smoking years and quitting time for former and active smokers.
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. 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), and documented neurological examination.
5. During screening, the presence of EGFR activating mutations in blood or tumour tissue should be determined in a qualified laboratory, and T790M mutation status will also be determined. KRAS and C-MET mutation will not be tested during the screening, If there are available KRAS and C-MET

mutation results before screening, KRAS and C-MET mutation positive patients should be excluded. If progression, retesting of EGFR status will include T790M, KRAS and C-MET as optional.

6. 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 off study for any reason. 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 tumour radiographic assessment. Neurological examination should be recorded on a separate "Neurological Function Examination" Case Report Form.
7. Ophthalmological examination should be performed at screening period and withdrawal of study treatment, or in case of any visual symptom (including blurred vision).
8. Vital signs include blood pressure, pulse and body temperature. 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.
9. ECG should always be obtained in supine position after adequate rest. Moreover, additional ECG may be obtained as needed in case of any cardiac adverse event. If corrected QT interval prolonged \geq CTC AE 3, repeat ECG measurements for consecutive 3 times immediately and average the result. An Echocardiogram or MUGA scan to assess LVEF will be conducted at screening (prior to first dose of study treatment) and whenever necessary as clinically indicated throughout the study. The modality of the cardiac function assessments must be consistent within a patient i.e. if echocardiogram is used for the screening assessment then echocardiogram should also be used for subsequent scans if required.
10. For non-surgical sterilized women of child-bearing potential, blood sample for pregnancy test should be collected at screening, before the first dose and withdrawal of study treatment. Menopause is defined as permanent cessation of menorrhoea. Women are considered post-menopausal if they (usually older than 45 years) have had 12 months of natural (spontaneous) amenorrhoea.
11. Questionnaire will be completed at screening period and every 6 weeks \pm 1 week (relative to C1D1). 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. After progression, questionnaire is optional, maximum twice with 6 weeks interval.
12. MMSE will be accessed at screening period and every 6 weeks \pm 1 week (relative to C1D1). After progression, MMSE is optional, maximum twice with 6 weeks interval.
13. Blood-borne biomarker samples (plasma) will be collected at screening period and on week 3, 6, 18 (relative to C1D1), and every 12 weeks until progression is the subject consents.
14. 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 \pm 1 week (relative to C1D1) until disease progression or death (death not due to disease progression) or initiation of another anti-tumour treatment, regardless of withdrawal from study 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
15. Investigator assessment of response to be collected

16. Once 28-day follow-up visit is completed, all patients 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.