Statistical Analysis Plan

A phase I/II, open-label, multicenter study to evaluate the safety, tolerance, pharmacokinetics and antineoplastic activity of AZD3759 in Chinese patients with epidermal growth factor receptor mutation-positive (EGFRm+) advanced non-small cell lung cancer accompanied by central nervous system metastasis

Protocol No.: AZD3759-001

Version: 1.0
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Tibet Pharma Technology Co., Ltd. 
AZD3759-001 
Version 1.0
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<th>Description</th>
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</tr>
<tr>
<td>15.7</td>
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<td>16.5</td>
<td>Ophthalmic/Physical examinations</td>
</tr>
</tbody>
</table>
1. **Abbreviations**

The following abbreviations and special terms are used in the statistical analysis plan (SAP) of this study.

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AE</td>
<td>Adverse event</td>
</tr>
<tr>
<td>BM</td>
<td>Brain metastasis</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>CNS</td>
<td>Central nervous system</td>
</tr>
<tr>
<td>CR</td>
<td>Complete response</td>
</tr>
<tr>
<td>CRF</td>
<td>Case report form</td>
</tr>
<tr>
<td>CSF</td>
<td>Cerebrospinal fluid</td>
</tr>
<tr>
<td>DCR</td>
<td>Disease control rate</td>
</tr>
<tr>
<td>DLT</td>
<td>Dose-limiting toxicity</td>
</tr>
<tr>
<td>DMC</td>
<td>Date management committee</td>
</tr>
<tr>
<td>ECG</td>
<td>Electrocardiogram</td>
</tr>
<tr>
<td>ECOG</td>
<td>Eastern Cooperative Oncology Group</td>
</tr>
<tr>
<td>eCRF</td>
<td>Electronic case report form</td>
</tr>
<tr>
<td>EGFR</td>
<td>Epidermal growth factor receptor</td>
</tr>
<tr>
<td>EGFRm+</td>
<td>Epidermal growth factor receptor mutation-positive</td>
</tr>
<tr>
<td>HR</td>
<td>Heart rate</td>
</tr>
<tr>
<td>LM</td>
<td>Meningeal metastasis</td>
</tr>
<tr>
<td>MedDRA</td>
<td>Medical Dictionary for Drug Regulatory Activities</td>
</tr>
<tr>
<td>NSCLC</td>
<td>Non-small cell lung cancer</td>
</tr>
<tr>
<td>ORR</td>
<td>Objective response rate</td>
</tr>
<tr>
<td>OS</td>
<td>Overall survival</td>
</tr>
<tr>
<td>PD</td>
<td>Pharmacodynamics</td>
</tr>
<tr>
<td>PFS</td>
<td>Progression-free survival</td>
</tr>
<tr>
<td>PK</td>
<td>Pharmacokinetics</td>
</tr>
<tr>
<td>PR</td>
<td>Partial response</td>
</tr>
<tr>
<td>PR</td>
<td>Heart rate-correlated PR interval</td>
</tr>
<tr>
<td>PRO</td>
<td>Patient-reported outcome</td>
</tr>
<tr>
<td>QRS</td>
<td>Cardiac impulse period QRS wave group</td>
</tr>
<tr>
<td>QTc</td>
<td>Heart rate-correlated QT interval</td>
</tr>
<tr>
<td>QTcF</td>
<td>Heart rate-correlated QT interval by Fridericia equation</td>
</tr>
<tr>
<td>RECIST</td>
<td>Response Evaluation Criteria In Solid Tumors</td>
</tr>
<tr>
<td>RP2D</td>
<td>Recommended Phase II Dose.</td>
</tr>
<tr>
<td>RR</td>
<td>Human RR interval of Cardiac impulse period</td>
</tr>
<tr>
<td>-------------</td>
<td>-------------------------------------------</td>
</tr>
<tr>
<td>SAS</td>
<td>Statistical analysis software</td>
</tr>
<tr>
<td>SD</td>
<td>Stable disease</td>
</tr>
<tr>
<td>SOC</td>
<td>System Organ Classification</td>
</tr>
<tr>
<td>tmax</td>
<td>The time at which the maximal plasma concentration is first observed</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
</tbody>
</table>
## Version Revision

<table>
<thead>
<tr>
<th>SAP Version</th>
<th>Date of Revision</th>
<th>Author</th>
<th>Amendments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
3. Introduction

The SAP is written according to the final version of study protocol (4 Jun 2017) and the final version of case report form (14 Sep 2019). The plan describes specific statistical analysis methods and strategies. The SAP needs to be finalized and approved before clinical database shuts down. Any amendments have to be discussed and recorded in the clinical study report after database locking.

Pharmacokinetics (PK) is not included in this SAP. The PK analysis will be described in individual clinical PK.

4. Study Objectives and Endpoints

4.1 Study objectives

4.1.1 Primary objectives

Part A-Dose escalation: To assess the safety and toleration of AZD3759 in Chinese EGFRm+ NSCLC patients

Part B-Phase II study: To assess the antineoplastic activity of AZD3759 in Chinese EGFRm+ NSCLC patients with CNS metastasis

4.1.2 Secondary objectives

Part A-Dose escalation: To assess the safety and toleration of AZD3759 in Chinese EGFRm+ NSCLC patients

- To assess the pharmacokinetics (PK) of AZD3759 and N-demethylated derivatives in plasma following single dosing and multiple dosing
- To evaluate preliminary antineoplastic activity.
- To determine recommended Phase II dose (RP2D).

Part B-Phase II study:

- To verify the safety and tolerance of AZD3759 in Chinese EGFRm+ NSCLC patients with NS metastasis

4.2 Study endpoints

4.2.1 Part A - Dose escalation

Primary endpoints:

- Safety and tolerance

Secondary endpoints:

- Pharmacokinetics
- To evaluate extracranial disease and intracranial disease with brain metastasis based on improved RECIST 1.1 standard, respectively, the changes of ORR, DCR, DOR, PFS and tumor size in relative to baseline
- Leptomeningeal metastasis (LM) patients: response rate, disease control rate, duration of response of LM based on investigator’s assessment
- LM patients: CSF negative conversion rate and nervous system function control rate
- PROs

**Explorative endpoints:**
- Drug exposure in CSF of LM patients

**4.2.2 B Part - Phase II stage**

**Primary endpoints:**
- BM cohort: (overall) ORR
- LM cohort: (intracerebral) ORR

**Secondary endpoints:**
- BM cohort: To evaluate ORR, DCR, DOR, PFS and tumor size of extracranial disease and intracranial disease with brain metastasis in relative to baseline
- BM cohort: overall DCR, DOR, PFS, OS, safety and PROs
- LM cohort: To evaluate DCR, DOR, PFS of intracranial disease and ORR, DCR, DOR, PFS and tumor size of extracranial disease in relative to baseline
- LM cohort: overall OS, PFS, safety and PROs

**5. Study Design**

This study is a multicenter, open-label, dose escalation and Phase II trial, including Part A dose escalation stage and Part B Phase II stage.

**Part A Dose escalation**

<table>
<thead>
<tr>
<th>Dose escalation</th>
<th>Dose expansion</th>
</tr>
</thead>
<tbody>
<tr>
<td>250 mg, bid N=3-6</td>
<td>Expand to ~ 12 subjects</td>
</tr>
<tr>
<td>250 mg, bid N=3-6</td>
<td>Expand to ~ 12 subjects</td>
</tr>
<tr>
<td>250 mg, bid N=3-6</td>
<td>Expand to ~ 12 subjects</td>
</tr>
</tbody>
</table>

**Part B Phase II study**

<table>
<thead>
<tr>
<th>Dose escalation</th>
<th>Dose expansion</th>
</tr>
</thead>
<tbody>
<tr>
<td>250 mg, bid N=3-6</td>
<td>LM cohort</td>
</tr>
<tr>
<td>250 mg, bid N=3-6</td>
<td>RP2D</td>
</tr>
<tr>
<td>250 mg, bid N=3-6</td>
<td>BM cohort</td>
</tr>
</tbody>
</table>
Dose escalation stage includes dose escalation and dose expansion. Three dose groups are planned including 150, 200, and 250 mg b.i.d. Dose escalation of single site is scheduled, and the investigator will make a decision of dose escalation or discontinuation through evaluating the safety and tolerance in cycle 1 of dose escalation. The investigator will decide whether or not to expand the dose group to 12 cases by at least one of the first 3 subjects of each dose group whose plasma peak concentration exceeds IC50 (7 nM) or the improvement and safety of SD or LM patients who have tumor regression. Dose expansion will be conducted at multiple sites, and the investigator will make a decision of early termination of expansion based on safety data.

This study will establish data management committee (DMC) who reviews the data of Part A, considers overall risk and benefit of study participants, and suggest to the sponsor whether or not continue the study and select RP2D for Part B Phase II study according to the protocol. Part B Phase II study will expand the cohorts among patients with leptomeningeal metastases (LM) and brain metastases (BM) to further evaluate the antineoplastic, safety and tolerance of AZD3759.

6. Study Hypothesis
   No statistical inference is conducted in this study.

7. Sample Size Calculation
   Part A of the study has no formally definite sample size. Based on the tolerance and safety assessment of the study drug, 3-6 patients will be enrolled in each dose group during dose escalation in the dose escalation state, and it is possible to expand to 12 patients. Part A will enroll a maximum of 30 patients.

   During Part B-Phase II study stage, the sample size of LM and BM cohorts will be adjusted as appropriate based on the data and endpoints of study.

8. Intermediate Analysis
   An intermediate analysis will be performed in 6 weeks after the last patient begins study treatment during dose escalation of single site in Part A-Dose escalation stage.

9. Final Analysis
   For Part A, a final analysis will be performed after the last subject takes the final visit during dose escalation of Part A.

10. Date Analysis Sets
    - Analysis set: refers to the subjects who sign informed consent form.
    - Successful screening analysis set: refers to the subjects who succeed in screening.
• Safety analysis set: refers to the subjects who received at least one treatment.
• Pharmacokinetic analysis set: refers to all treated subjects who have at least one quantifiable AZD3759 plasma concentration without significant adverse event or protocol deviation that may influence pharmacokinetics.
• Evaluable response analysis set: refers to the treated subjects who have tumor baseline values.
• Evaluable CNS response analysis set: refers to the treated subjects who have baseline assessment on CNS diseases.
• Evaluable CNS target lesion response analysis set: refers to the treated subjects who have baseline assessment on CNS target lesions.
• Evaluable extracranial disease response analysis set: refers to the treated subjects who have extracranial disease baseline values.
• Evaluable extracranial disease target lesion response analysis set: refers to the treated subjects who have extracranial disease target lesion baseline values.
• Evaluable LM response analysis sets: the subjects who meet any of the following subsets will be included in this set:
  1. Evaluable LM response analysis set-RECISIT: refers to the treated subjects who have LM tumor baseline values.
  2. Evaluable LM response analysis set-CSF: refers to the treated LM subjects whose tumor cells are present in CSF at baseline.
  3. Evaluable LM response analysis set-nervous system: refers to the treated subjects who have baseline nervous system scores.
Safety analysis is based on safety analysis sets.

11. General Principles of Statistical Analysis

SAP must be finalized before the database is locked. The tables, lists and figures for statistical analysis are produced by using SAS 9.2 or higher version.

At dose escalation stage, safety data will be summarized by dose stage and efficacy data will be summarized by metastasis type and dose. At dose expansion stage, the data will be summarized by metastasis type and dose. At Phase II study stage, the data will be summarized by metastasis type and dose.

Age: The age is calculated by (the date of signing informed consent form – the date of birth +1)/365.25 and rounded up to the nearest integer. If only the year of birth is recorded, the age is calculated by subtracting the year of birth from the year of signing informed consent form.
If only the date of birth is missed, the last date of the birth month is filled to calculate the age accordingly.
**Date of death:** In case of missed month, 31 Jul is filled. If the date is missed, the 15th day of the month will be filled. If the date is entirely missed, the last visiting time will be filled. For other efficacy endpoints and safety endpoints, no processing is conducted for the missed values.

**BMI:** BMI is calculated by the height and weight at screening. The calculation formula is the body weight at screening (kg)/(the body height at screening (cm)/100)**2).

**Continuous variables:** SAP will describe the number, mean, standard deviation, median, the first and third quartiles (if necessary), minimum and maximum of the subjects without missing values. The number of decimal places for minimum and maximum will remain consistent with the raw data recorded in the database. The mean and median will keep one more decimal than the raw data recorded in the database. The standard deviation will keep two more decimals than the raw data recorded in the database but not more than four decimals at most. The covariance will keep two decimals. The number of decimal places for confidence interval will keep one more decimal than the raw data recorded in the database. P value will keep three decimals. The geometric mean and its confidence interval will keep one more decimal than the raw data recorded in the database.

**Categorical variables:** Categorical variables will be shown in the format of frequency table. The percentage and its confidence interval will keep one decimal unless otherwise specified.

**Baseline data:** For safety analysis, baseline data refers to the last visit before the first dose (excluding the first dose). For efficacy analysis, the tumor assessment during screening will be regarded as baseline data.

**Unscheduled visits:** In addition to the maximal, minimal and worst case analyses of observed values, the data of unscheduled visits will be only included in corresponding tables rather than the descriptive statistical analysis.

### 12. Subject Characteristics and Protocol Deviation

#### 12.1 Subject distribution

Based on the datasets, the subject distribution is summarized as below:

- All subjects signing informed consent form
- Subjects who fail in screening
- Subjects who succeed in screening
- Subjects who succeed in screening but have no dose allocation
- Subjects who succeed in screening and receive at least one treatment
- Subjects who withdraw from the treatment
- Subjects who withdraw from the study

For withdrawal from the study, the subjects who withdraw from the study will be summarized by the reason in a tabular form. The reasons for screening failure will be summarized tabularly. The subjects who experience DLT at dose escalation stage will be also summarized tabularly.
12.2 Protocol deviation

Generally, the following events will be considered as significant protocol violation. Significant protocol violation at subject level needs to be determined by the investigator and the sponsor at data audit meeting.

- Violating inclusion/exclusion criteria
- Not following randomization protocol
- Receiving study drug by mistake
- Medication compliance <80% or >120%
- Receiving medical or non-medical therapy that are prohibited by the study protocol

Significant protocol violations will be described and summarized by the classification according to the safety set with a detailed tabulation.

12.3 Demographic data and baseline characteristics

Demographic data and baseline characteristics will be analyzed by safety analysis set. For the subject demographic data, baseline characteristics will be summarized and tabulated. The tables and lists will include the following subject demographic data:

- Age: describe statistics (number, mean, standard deviation, median, minimum and maximum of the subjects without missing);
- Gender: male, female;
- Race: Han, other;
- EGFR tumor mutation site: Exon 19Del, L858R, other;

The tables and lists will include the following subject baseline characteristics:

- Body height: describe statistics (number, mean, standard deviation, median, minimum and maximum of the subjects without missing);
- Body weight: describe statistics (number, mean, standard deviation, median, minimum and maximum of the subjects without missing);
- BMI: describe statistics (number, mean, standard deviation, median, minimum and maximum of the subjects without missing);
- T90M test: negative, positive, undetected;
- Smoking: non-smoking, current smoking, previous smoking;

12.4 Baseline disease characteristics

Baseline disease characteristics will be analyzed by safety analysis set. The baseline disease characteristics of the subjects will be summarized and tabulated.
The tables and lists will include the following baseline disease characteristics:

- Duration of initial diagnostics: describe statistics (number, mean, standard deviation, median, minimum and maximum of the subjects without missing);
- Tumor histopathology classification: large-cell lung carcinoma, adenocarcinoma, squamous cell carcinoma, small cell carcinoma, adenosquamous carcinoma, other;
- Tumor TNM stage: T stage, N stage, M stage;
- Tumor metastasis: yes, no;
- Tumor metastasis location: meninges (CSF: Yes, No), brain, bone marrow, liver, adrenal gland, unknown, other;
- TKI immunotherapy: yes, no;
- ECOG score: 0, 1, 2, 3, 4, undetected;
- CSF cytological and biomedical test of cancerous cells: negative, positive, undetected;

12.5 Prior medical history

Prior medical history will be analyzed by the safety analysis set.

The prior medical history of the subjects will be summarized and tabulated by preferred terms.

12.6 Prior treatment history

Prior treatment history will be analyzed by the safety analysis set.

The prior treatment history of the subjects will be summarized by therapeutic type, therapeutics and the type of therapeutics. Prior radiotherapy history will be summarized by targeting area. For prior medical treatment history, prior radiotherapy history will be tabulated. The prior surgery history of the subjects will be tabulated as well.

13. Concomitant Medication and Diagnostics

Concomitant medication and diagnostics will be analyzed by safety analysis set.

World Health Organization (WHO)’s Dictionary for Concomitant medicine will be used to classify and summarize. Concomitant medication and diagnostics of the subjects will be tabulated.

14. Treatment Compliance and Dose Exposure

Treatment compliance and dose exposure will be analyzed by safety analysis set.

14.1 Treatment compliance

The compliance of therapeutics is based on safety analysis set.

Drug compliance = actual dose/scheduled dose *100, as shown below:
Actual dose = the sum of actual doses at each period;

Scheduled dose = scheduled dose level at each period * the number of days at each period;

SAP will describe and summarize the treatment compliance of subjects at each visit and overall condition, and calculate the number and proportion of subjects at different level of compliance (<80%, 80% - 120%, >120%).

14.2 Dose exposure

- Duration of treatment (day):
  \[= \text{the data of last dose} - \text{the data of first dose} +1;\]

- Cumulative dose (mg):
  \[= \text{the sum of doses during all treatment cycles}';\]

- Actual dose (mg/cycle):
  \[= \text{cumulative dose (mg)}/(\text{duration of treatment (cycle)} \times 21);\]

- Relative dose (%):
  \[= (\text{actual dose (mg/cycle)}/\text{scheduled dose (mg/cycle)}) \times 100;\]

  * Scheduled dose is produced by Drug Dispense of CRF;

SAP will describe the duration of treatment, cumulative dose, actual dose, relative dose, the number of days of all treatment cycles and the maximal treatment cycle. The details in medication will be tabulated.

The type of dose adjustment and the reason for adjustment will be summarized and tabulated. Additionally, SAP will describe the number and proportion of patients who experienced at least one treatment suspension/treatment delay and at least once dose reduction at any time of study cycle 1 or after cycle 1.

Overdose and the adverse events resulting from overdose will be summarized and tabulated.

15. Efficacy Analysis

15.1 Efficacy analysis endpoints

Secondary efficacy endpoints of Part A and the corresponding analysis sets are shown in Table 1.

<table>
<thead>
<tr>
<th>Extracranial disease response</th>
<th>Brain metastasis and intracranial disease response</th>
<th>Meningeal metastasis lesion response</th>
<th>PROs</th>
</tr>
</thead>
</table>

Table 1: Secondary efficacy endpoints of Part A
### Analysis sets

<table>
<thead>
<tr>
<th>Grouping</th>
<th>Calculation of best overall response is based on</th>
<th>Efficacy endpoints</th>
<th>Safety analysis set</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose group</td>
<td>1. Objective evaluation (radiological assessment)</td>
<td>1. ORR</td>
<td>Dose group (only for brain metastasis subgroup)</td>
</tr>
<tr>
<td>Dose group (only for meningeal metastasis subgroup)</td>
<td>2. Investigator’s assessment</td>
<td>2. DCR</td>
<td>Dose group (only for meningeal metastasis subgroup)</td>
</tr>
<tr>
<td></td>
<td>1. Objective evaluation (radiological assessment)</td>
<td>3. DOR</td>
<td>Dose group (only for meningeal metastasis subgroup)</td>
</tr>
<tr>
<td></td>
<td>2. Investigator’s assessment</td>
<td>4. Changes in tumor size in relative to baseline</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5. PFS</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1. ORR</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. DCR</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>3. DOR</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>4. Changes in tumor size in relative to baseline</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>5. PFS</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1. ORR</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. DCR</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>3. DOR</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>4. Nervous system function control rate</td>
<td>Changes in relative to baseline</td>
</tr>
</tbody>
</table>

### Explorative endpoints of Part A and the corresponding analysis sets are shown in Table 2.

<table>
<thead>
<tr>
<th>Table 2: Explorative endpoints of Part A</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Analysis sets</strong></td>
</tr>
<tr>
<td>Evaluable meningeal metastasis response analysis set</td>
</tr>
<tr>
<td>Dose group</td>
</tr>
</tbody>
</table>

Primary endpoints of Part B and the corresponding analysis sets are shown in Table 3.
Table 3: Primary endpoints of Part B

<table>
<thead>
<tr>
<th>Analysis sets</th>
<th>BM</th>
<th>LM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grouping</td>
<td>Dose group</td>
<td>Dose group</td>
</tr>
<tr>
<td>Calculation of best overall response is based on</td>
<td>1. Objective evaluation (radiological assessment) 2. Investigator’s assessment</td>
<td>1. Objective evaluation (radiological assessment) 2. Investigator’s assessment</td>
</tr>
<tr>
<td>Efficacy parameters</td>
<td>ORR</td>
<td>ORR</td>
</tr>
</tbody>
</table>

Secondary endpoints of Part B and the corresponding analysis sets are shown in Table 3.

Table 4: Secondary endpoints of Part B

<table>
<thead>
<tr>
<th>Analysis sets</th>
<th>BM</th>
<th>LM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grouping</td>
<td>Dose group</td>
<td>Dose group</td>
</tr>
<tr>
<td>Calculation of best overall response is based on</td>
<td>1. Objective evaluation (radiological assessment) 2. Investigator’s assessment</td>
<td>1. Objective evaluation (radiological assessment) 2. Investigator’s assessment</td>
</tr>
<tr>
<td>Efficacy parameters</td>
<td>1. ORR (extracranial, brain metastasis and intracranial, overall) 2. DCR (extracranial, brain metastasis and intracranial, overall) 3. DOR (extracranial, brain metastasis and intracranial, overall) 4. PFS (extracranial, brain metastasis and intracranial, overall) 5. Change in tumor size in relative to baseline (extracranial, brain metastasis and intracranial) OS (overall) PROs (changes in relative to baseline)</td>
<td>1. ORR (extracranial) 2. DCR (extracranial, brain metastasis and intracranial) 3. DOR (extracranial, brain metastasis and intracranial) 4. PFS (extracranial, brain metastasis and intracranial, overall) 5. Change in tumor size in relative to baseline (extracranial) OS (overall) PROs (changes in relative to baseline) CSF negative conversion rate and CNS function improvement rate (meningeal metastasis)</td>
</tr>
</tbody>
</table>
15.2 Tumor response (ORR, DCR)

SAP will report overall efficacy of all patients. Moreover, SAP will report the remission in central nervous system and the investigator’s assessment on leptomeningeal disorder.

Best overall response is defined as the optimal response of overall response between the first dose and when the subject received antineoplastic therapy or have progressed disease (PD) as determined by the order of complete response (CR), partial response (PR), stable disease (SD), progressed disease (PD) and not evaluable (NE), and it needs to be followed up and verified in 4 weeks. For stable disease (SD), the observation period is not less than 6 week.

Objective response rate is defined as the proportion of patients in whom complete response (CR) or partial response (PR) is observed. Disease control rate (DCR) is defined as the proportion of patients in whom the best overall response is determined as complete response (CR), partial response (PR) or stable disease (SD).

SAP will summarize objective response rate and disease control rate. For expanded cohorts, SAP will describe objective response rate and 95% confidence interval (Clopper Pearson).

15.3 Duration of response (DOR)

DOR refers to the minimum from the time when complete response (CR) or partial response (PR) is first observed to the time of progressed disease (PD) or death for the subjects whose best overall response is complete response (CR) or partial response (PR) (being response for LM patients). Or else, DOR will be the time of last tumor assessment.

SAP will summarize DOR and describe the percentage of patients whose DOR is >3, >6, >9 and >12 months. In case of sufficient responders, SAP will present Kaplan Meier plot, the median of DOR (calculated based on Kaplan-Meier) and 95% confidence interval of median time.
15.4 Tumor size change

Percentage of baseline change = (Σ observed value after baseline - Σ observed value at baseline) * 100 / Σ observed value at baseline

Σ = the sum of longest diameter of target lesions as determined by RECIST 1.1. Best tumor change (maximal tumor regression) or the minimal tumor increment based on baseline will be involved in all assessments before disease progression or the beginning of following antineoplastic therapy. The missing target lesion data at visit will be classified by appropriate rule. The changes in tumor size of extracranial disease and intracranial disease will be reported respectively. The overall changes of tumor size will not be included.

By using descriptive statistics, SAP will summarize the absolute value of target lesion and the percentage of change in relative to baseline as well as the changes at each time point. SAP will also summarize the best change. Tumor size will be presented by waterfall plot.

15.5 Progression-free survival (PFS)

PFS analysis population is evaluable responsible population.

PFS refers to the duration from the first study treatment to disease progression or death (not disease progression-induced death) or the beginning of the other antineoplastic therapy regardless of whether or not the subject withdraws form AZD3759 treatment.

During data analysis, the patients who have no disease progression or death will be evaluated by the nearest time of their last evaluable RECIST. If the patient experiences disease progression or death after losing two or more visits, the last evaluable time will be considered. If the patient has no evaluable follow-up or no baseline data, PFS is defined as 0 day, except the patient is died between the baseline to two follow-ups.

If the patient discontinues the treatment and/or receive further therapy before disease progression, they will continue follow-up until the sign of disease progression or reaching PFS as mentioned above.

PFS time is always calculated by the date of scan/evaluation rather than the date of follow-up. Special visits due to improved RECIST assessment may be conducted at different time and follow the rules below:

- The earliest data of observing disease progression is defined as the date of progression.
- When deleting missing data, the time of last follow-up is considered.

15.6 CSF response rate

CSF response rate refers to the percentage of LM patients who have at least one CSF response (100% of tumor cells in CSF is cleaned up) before the sign of disease progression. CSF response must be verified in 4 weeks after the first CSF response.
Analysis population of CSF response refers to the (LM) population of evaluable CSF response. SAP will summarize CSF response rate and its 95% exact confidence interval (Clopper Pearson).

15.7 CSF biochemistry

Analysis population of CSF biochemistry refers to the (LM) population of evaluable CSF response.

CSF glucose and protein changes of LM patients (and the change percentage) will use repeated measurement model by using the study day as the fixed effect, the subject as the random effect and the baseline glucose/protein as covariate. SAP will report the change percentage and its 90% confidence interval.

15.8 Nervous system function control rate

Nervous system evaluation: Disease progression refers to deterioration of ≥2 points in special type, or maximal 3 points or 2 points (in only 3-grade type) in any type.

Nervous system function control rate is defined as the ratio of 100% - disease progression. For details, see protocol 13.2 Table 14 Rating of nervous system function test.

SAP will summarize nervous system function control rate and its 95% exact confidence interval (Clopper Pearson).

15.9 Patient reported outcomes (PROs)

Patient reported analysis population is safety set.

Descriptive statistics will be used to describe the baseline data, visit data, baseline change and effect size of EORTC QLQ C-30 (Aaronson NK et al 1993) and QLQ BN-20 (Taphoorn MJ et al 2010) as well as tabulated. Effect size = baseline change / standard deviation of baseline data.

15.10 Overall survival (OS)

Overall survival analysis population is safety set.

OS will be evaluated at the end of study. The subjects will be classified to survival or death at any reason. OS refers to the time from the first treatment to the death at any reason.

At the end of study, the survival of BM and LM patients will be summarized (death, survival, or lost of follow-up). Moreover, SAP will summarize the number and percentage of patients who be deleted and missed before the deadline of data.

SAP will report medium and quartile survival computed from Kaplan-Meier method by treatment group. Additionally, SAP will tabulate and report the OS rate and its 95% confidence interval (CI) estimate at Month 6 and 12 of Kaplan-Meier survival curve. Meanwhile, OS will be plotted by dose group.
16. Safety Analyses

16.1 Adverse events

Adverse events that occurred from the beginning of treatment to the last dose will be recorded and evaluated. Adverse events will be classified by CTCAE classification criteria version 4.03 and encoded by MedDRA version 19.1.

Adverse events that occurred during prior disease will be summarized by CTCAE classification, system organ classification (SOC) and preferred term (PT), respectively.

**Treatment emergent adverse event (TEAE):** refers to the adverse event occurred or turned serious after the patient receives the treatment. If the onset of adverse event is unknown, it will be also considered as TEAE. All adverse events that occurred in 28-day follow-up period after treatment discontinuation will be included in the analysis.

If the onset or end of adverse event is partially missed, or the toxicity level is missed, the event will be treated as follows:

- **The onset of adverse event:**
  - Day missed: replaced by the first day of the month.
  - Month missed: replaced by January (1 Jan).
  - Year missed: no processing.

- **The end of adverse event:**
  - Day missed: replaced by the last day of the month.
  - Month missed: replaced by December (31 Dec).
  - Year missed: no processing.

Toxicity level: If the toxicity level before the first dose is missed, it is regarded as Level 1; if the toxicity level on the day of treatment or after the day is missed, it is regarded as Level 4.

The following adverse events will be included in frequency statistics by treatment group and the subclass related to study drug.

- Treatment emergent adverse events
- Treatment emergent adverse events of CTCAE grade ≥3
- Adverse event that results in drug dose adjustment
- Non-serious adverse event that results in discontinuation/withdrawal from the treatment
- Non-serious adverse event that results in discontinuation/withdrawal from the study
- Non-serious adverse event that results in drug dose adjustment
- Serious adverse event
- Serious adverse event that results in discontinuation/withdrawal from the treatment
- Serious adverse event that results in discontinuation/withdrawal from the study
- Serious adverse event that results in drug dose adjustment
• Adverse event that results in death
• Adverse event that results in death during 28-day follow-up period after discontinuation

The following adverse events will be summarized by system organ classification (SOC) and preferred term (PT), respectively; meanwhile, they will be summarized in the subclass related to the study drug.

• Treatment emergent adverse event
• Adverse event that results in drug dose adjustment
• Serious adverse event
• Serious adverse event that results in drug dose adjustment
• Serious adverse event that results in discontinuation/withdrawal from the treatment
• Serious adverse event that results in discontinuation/withdrawal from the study

The adverse events will be shown by the descending order of frequency of SOC. In each SOC, they will be shown by the descending order of frequency of PT.

The following adverse events will be summarized by SOT and PT as well as the severity (1, 2, 3, 4, 5, ≥3), respectively; meanwhile, they will be summarized in the subclass related to the study drug.

• Treatment emergent adverse event
• Adverse event that results in drug dose adjustment
• Serious adverse event
• Serious adverse event that results in drug dose adjustment

The adverse events will be shown by the descending order of frequency of SOC. In each SOC, they will be shown by the descending order of frequency of PT.

The following adverse events will be summarized by CTCAE and the severity (1, 2, 3, 4, 5, ≥3), respectively; meanwhile, they will be summarized in the subclass related to the study drug.

• Treatment emergent adverse event
• Serious adverse event

The adverse events will be shown by the descending order of frequency of CTCAE.

Any adverse event that occurred before the first treatment of investigational product will be included in data table, however, such adverse events will be not be included in adverse event summary table.

For individual subject, the adverse event, serious adverse event, adverse event that results in discontinuation/withdrawal from the treatment, adverse event that results in discontinuation/withdrawal from the study, and adverse event that results in drug adjustment will be recorded in the tabular format. The related date of adverse event in the table will be raw data without processing for missing data. Additionally, the adverse event that occurred during 28-day follow-up period after treatment discontinuation will be tabulated.
The death events occurred during treatment and the death events occurred during 30-day follow-up period after treatment discontinuation will be summarized and tabulated by the reason.

16.2 Clinical laboratory tests

Observed values can be classified by NCI CTCAE 4.03 and converted to a 2-D table according to CTCAE and severity (1, 2, 3, 4, 5, \( \geq 3 \)). A comparison between the maximal severity of CTCAE of baseline and treatment period will be performed.

SAP will perform descriptive statistical analyses on quantitative or qualitative clinical tests by visiting point.

Abnormal laboratory values will be tabulated.

Subjects who meet Hy’s law will be tabulated.

16.3 Vital signs

Vital signs (blood pressure, pulse, body temperature, height, weight) will be described and tabulated by visiting point.

16.4 Electrocardiography

QTcF will be calculated by Fridericia equation.

\[
\text{QTcF} = \frac{Q}{3} \sqrt{R/C}
\]

Creatinine clearance will be estimated by using Cockcroft-Gault equation as shown below:

Male: \([(140 - \text{age}) \times \text{body weight (kg)} \times 1.23] / \text{creatinine (\(\mu\)mol/L)}\)

Female: \([(140 - \text{age}) \times \text{body weight (kg)} \times 1.04] / \text{creatinine (\(\mu\)mol/L)}\)

For HR, RR, PR, QRS, QT and QTcF, the observed values, post-treatment observed values and the changes of post-treatment observed values in relative to baseline will be summarized and tabulated.

16.5 Ophthalmic/Physical examinations

Descriptive statistics and tabulation will be performed by visiting points.