Statistical Analysis Plan	
Drug Substance	DZD9008
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A Phase I/II, Open-Label, Multicenter Study to Assess the Safety, Tolerability, Pharmacokinetics and Anti-tumor Efficacy of DZD9008 in Patients with Advanced Non-Small Cell Lung Cancer (NSCLC) with EGFR or HER2 mutation (Part B only)

Sponsor: Dizal (Jiangsu) Pharmaceutical Co., Ltd

APPROVALS

The undersigned agree that all required reviews of this document are completed and approve this Statistical Analysis Plan as final. Changes after approval should be documented appropriately following the standard operating procedure applicable.

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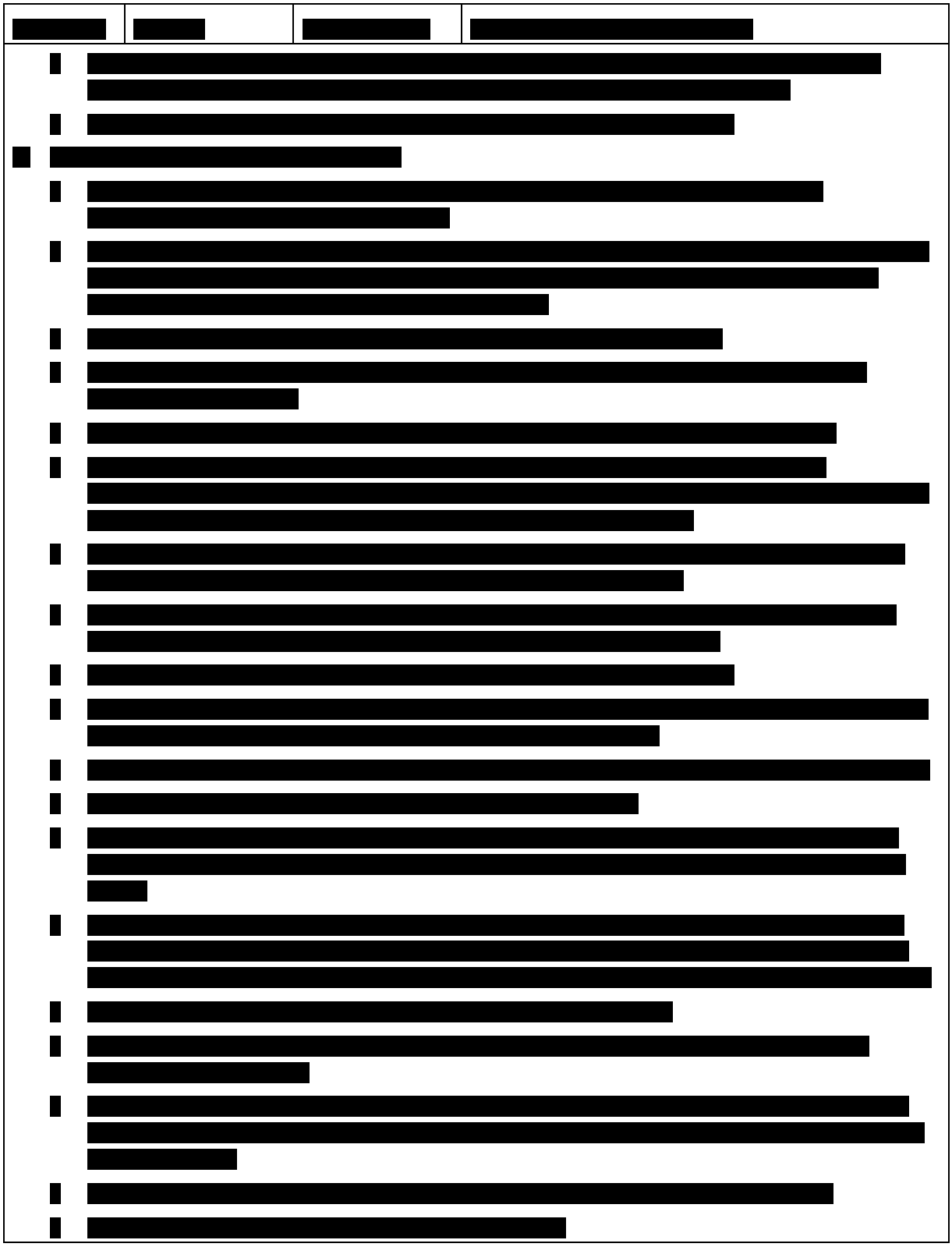

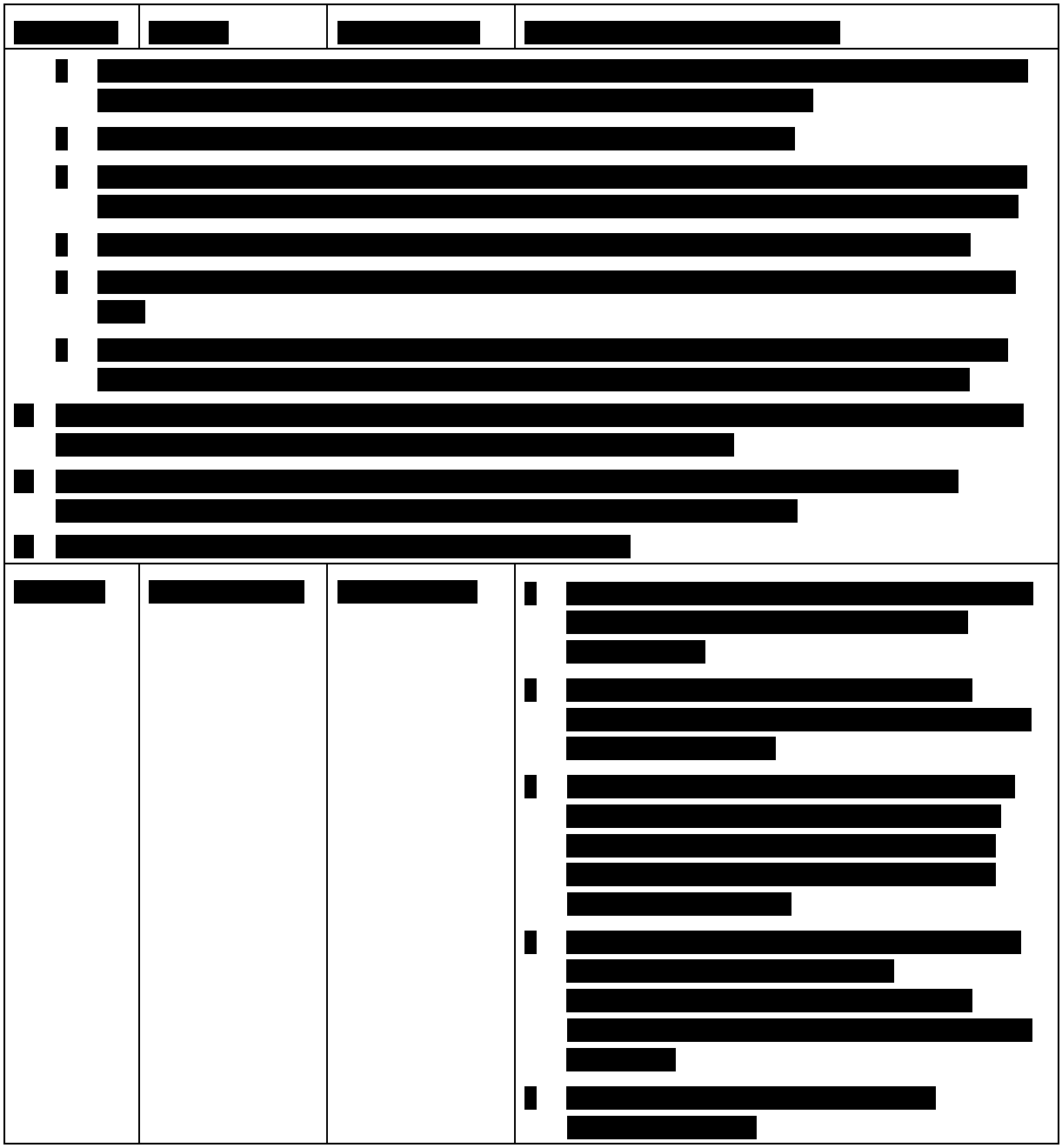

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LIST OF ABBREVIATIONS

Abbreviation	Full Term
ADI	Actual Dose Intensity
AE	Adverse event
ALT	Alanine aminotransferase
APTT	Activated Partial Thromboplastin Time
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
$AUC_{(0-24)}$	Area under the plasma concentration-time curve from time zero to 24 hours [amount·time/volume]
$AUC_{(0-t)}$	Area under the plasma concentration-time curve from time zero to t [amount·time/volume]
AUC_{ss}	Area under the plasma concentration-time curve during any dosing interval at steady state [amount· time/volume]
BLQ	Below the Limit of Quantification
BMI	Body Mass Index
BOR	Best Overall Response
CD_x	Companion Diagnostic
CI	Confidence Interval
CL_{ss}/F	Total body clearance of drug from plasma after an oral dose at steady state
C_{max}	Maximum plasma concentration
CR	Complete Response
CRF	Case Report Form
CSP	Clinical Study Protocol
CSR	Clinical Study Report
$C_{ss,max}$	Maximum plasma concentration at steady state
$C_{ss,min}$	Minimum plasma concentration at steady state
ctDNA	Circulating Tumor Deoxyribonucleic Acid
CV	Coefficient of Variation
DCR	Disease Control Rate
DLCO	Diffusing Capacity of Lung for Carbon Monoxide
DoR	Duration of Response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EG	Enterprise Guide
EGFR	Epidermal Growth Factor Receptor
Exon20ins	Exon20 insertion
FAS	Full Analysis Set
FEV1	Forced Expiratory Volume in 1 second
HER2	Human Epidermal growth factor Receptor 2
IEC	Independent Ethics Committee
INR	International Normalized Ratio
IRB	Institutional Review Boards
IRC	Independent Review Committee
LLN	Lower Limit of Normal
LVEF	Left Ventricular Ejection Fraction
LLOQ	Lower Limit of Quantification
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
MUGA	Multi Gated Acquisition scan

Abbreviation	Full Term
NC	Not Calculable
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NE	Not Evaluable
NQ	Not Quantifiable
NSCLC	Non-Small Cell Lung Cancer
NTL	Non-Target Lesion
ORR	Objective Response Rate
OS	Overall Survival
pEGFR	EGFR phosphorylation
PFS	Progression Free Survival
PK	Pharmacokinetics
PKS	Pharmacokinetics Set
PD	Progressive Disease
ppFEV1	percent predicted Forced Expiratory Volume in 1 Second
PR	Partial Response
PRO	Patient-Reported Outcome
PT	Preferred Term
PoM	Proof-of-Mechanism
QTcB	Bazett Corrected QT Interval
QTcF	Fridericia Corrected QT Interval
RAC	Extent of accumulation on multiple dosing
RDI	Relative Dose Intensity
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	Recommend Phase 2 Dose
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SD	Standard Deviation
SD	Stable Disease
SOC	System Organ Class
SOP	Standard Operation Procedures
SS	Safety Set
TEAE	Treatment-Emergent Adverse Event
TL	Target Lesion
TLG	Table, Listing and Graph
t_{max}	Time to maximum plasma concentration
$t_{ss\ max}$	Time to maximum plasma concentration at steady state
ULN	Upper Limit of Normal

1. INTRODUCTION

This Statistical Analysis Plan (SAP) describes the analyses for Part B of study DZ2019E0001, which is a phase 2 pivotal study. The statistical analyses required for part A of DZ2019E0001 were documented in a separate analysis plan.

The SAP contains a more technical and detailed elaboration of the analysis described in the Clinical Study Protocol (CSP). It also includes detailed procedures for executing the statistical analysis required.

The SAP was written based on the following documents:

Document	Version #	Date
Protocol	12.0	July 24, 2023
CRF	8.0	February 28, 2023
Memo for dropping dose	NA	July 27, 2023

2. OVERVIEW AND INVESTIGATIONAL PLAN

2.1 Study Objectives and Endpoints/Estimand

The objectives of part B of study DZ2019E0001 are listed as below.

2.1.1 Primary Objective and Estimand

Objectives	Endpoint/Estimand Description
To evaluate anti-tumor activity of DZD9008 in advanced NSCLC patients with EGFR Exon20ins at defined dose(s) by assessment of Objective Response Rate (ORR)	**Endpoint:** Objective Response Rate (ORR) according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 evaluated by an Independent Review Committee (IRC), where confirmation of response is required. **Estimand Description:** **Treatment:** DZD9008 200 mg or 300 mg QD. **Population:** Full Analysis Set (FAS) will be used for analysis, including all the NSCLC patients with documented EGFR Exon20ins mutations in tumor tissue, who were previously treated with platinum-based chemotherapy, received at least one dose of DZD9008, have at least one measurable lesion at baseline as identified by IRC. **Variable：** Binary variable indicating whether patient is a responder who achieved confirmed complete response (CR) or partial response (PR) prior to progressive disease (PD), as evaluated by IRC according to RECIST 1.1;

Objectives	Endpoint/Estimand Description
	Intercurrent Event with Strategy: • PD evaluated by IRC While on treatment strategy: the intercurrent event is already captured in the variable definition • Treatment Discontinuation due to reason other than PD evaluated by IRC Treatment policy strategy: Intercurrent event is ignored, tumor response data irrespective of treatment discontinuation are considered in analysis. • New Anticancer Therapy While on treatment strategy: Only the tumor response data prior to start of the new anticancer therapy are of interest. **Population-level Summary:** Confirmed ORR, which is defined as the proportion of responders.

2.1.2 Secondary Objectives and Endpoints

Objectives	Endpoint/Variable
To assess anti-tumor efficacy of DZD9008 using additional endpoints	DoR, Progression Free Survival (PFS), DCR and BOR and % of Change in Size of tumor lesion according to RECIST 1.1 using assessments performed by an IRC ORR, DoR, PFS, DCR, and BOR and % of Change in Size of tumor lesion using investigators assessments according to RECIST 1.1 Description of OS
To determine the safety and tolerability of DZD9008	AEs/SAEs Laboratory data Vital signs Physical examination ECG Echocardiogram/MUGA Pulmonary function test
To characterize the PK of DZD9008	Plasma DZD9008 and metabolite concentration and derived PK parameters if deemed appropriately

2.1.3 Exploratory Objectives and Endpoints

The analysis of exploratory endpoints below will also be included in this SAP.

- To explore the impact of DZD9008 treatment and disease state on health state utility by using EQ-5D-5L health state utility index based on patient reported data.
- To assess AEs of DZD9008 by using subjects reported specific CTCAE symptoms (PRO-CTCAE) and FACIT GP5 questionnaire.
- To investigate the effect of DZD9008 on proof-of-mechanism (PoM) biomarkers in tumor biopsy, e.g., EGFR phosphorylation (pEGFR)

The EQ-5D-5L, PRO-CTCAE and FACIT GP5 are collectively called patient-reported outcome (PRO) data.

2.2 Overall Study Design

DZ2019E0001 is a phase I/II, open-label, multicenter study of DZD9008 administered orally in patients with advanced stage NSCLC with EGFR or HER2 mutation. There are two parts in this study: Part A and Part B (dose extension).

Cohorts for dose escalation, dose expansion and food effect will be included in part A of the study.

Part B is a phase 2, open-label, randomized pivotal study with 2 dose arms to evaluate the anti-tumor efficacy of DZD9008 in previously treated NSCLC patients with EGFR Exon20ins mutation. Simon two-stage design [1] will be used within each dose arm respectively. When both dose arms pass stage 1, the response rate of two arms will be compared using stage 1 data to identify the more effective arm .

It's anticipated to enrol approximately 103 NSCLC patients with EGFR Exon20ins into each arm. Each patient who signed informed consent form will undergo screening during the 28 days prior to first dosing to confirm eligibility. Patient passed screening will be randomized at ratio of 1:1 to receive DZD9008 300 mg or 200 mg once daily with food until disease progression. RECIST 1.1 assessments are scheduled from Cycle 3 Day 1 (± 7 days) and then every 6 weeks (± 7 days). Patients who discontinue DZD9008 for reasons other than progression will continue RECIST 1.1 assessments as scheduled until objective disease progression. A discontinuation visit may be performed after drug discontinuation to collect the data required, and a safety follow up will be conducted 28 days following the discontinuation of DZD9008. Following disease progression, the patient, patient's family, or the patient's current physician must be contacted every 6 weeks for survival information up to the time of the final OS analysis. The detailed schedule of events for part B of study can be found in Appendix A.

[redacted]

[redacted]

The earliest data cut-off for the primary analysis of ORR may take place 3 months after the last patient enrolled, to allow all patients to complete two follow-up RECIST assessments. At this time, DoR and safety/tolerability will also be summarized. The Clinical Study Report (CSR) of primary analysis may include, but not limited to, ORR, DoR, safety and tolerability data.

The full CSR of Part B will report the analysis of all primary and secondary endpoints (including updated ORR and DoR, DCR, tumor shrinkage, PFS and OS). The data cut-off for this analysis will take place approximately 8 months after the last patient is enrolled to ensure that the last responder could be followed up for at least 6 months after initial documented response. All patients will continue to be followed up for an updated analysis based on cut-off that will occur between 12 - 24 months after the last patient is enrolled. All endpoints will be updated and summarized in an addendum to the CSR.

2.3 Randomization

Eligible patients will be stratified by the brain metastasis at baseline (Yes, No) and number of regimens of prior anti-cancer systemic therapy (<3, 3) and randomized to the DZD9008 200 mg QD or 300 mg QD at the ratio of 1:1.

[redacted]

2.4 Determination of Sample Size

In Part B, patients will be randomized into one of the two dose arms. Each dose arm uses a Simon two-stage design.

Bonferroni method is employed to control the family-wise type I error. The analysis in two arms will be performed independently, at one-sided significance level of 0.0125.

The primary endpoint will be ORR by IRC. Under a Simon two-stage design, a sample size of 103 within each arm is required to test a null hypothesis of ORR [redacted] at one-sided significance level of 0.0125, with expected ORR of 0.3 and [redacted]. The null hypothesis refers to real world data of 2nd line chemotherapy for NSCLC patients with EGFR Exon20ins [2-3].

In the first stage, [redacted] patients will be enrolled in each arm. If the number of responses is less than or equal to [redacted] out of [redacted] patients in the first stage then the arm will be stopped. If the arm proceeds to the second stage, additional [redacted] patients will be enrolled to reach a total of 103 patients. If [redacted] or more responses are observed, then the null hypothesis is rejected in this arm.

[redacted]

3. ANALYSIS SET

The analysis of data will be based on different subsets according to the purpose of the analysis, which are also called analysis sets. The definitions of the analysis sets applicable for part B of study are provided in this section.

3.1 All Patients

All patients screened (who signed informed consent form) will be included in this analysis set. It's mainly used for the individual data listing, and also the overall summary of screen failures.

3.2 All Randomized Patients

All patients randomized will be included in this analysis set.

Note: This analysis set will not be used for analysis directly considering that randomization is not applicable for all patients enrolled in part B. But the data for the randomized patients in safety analysis set and full analysis set will be presented following the principle in Section 5.1.

3.3 Safety Analysis Set (SS)

All patients who received at least 1 dose of DZD9008 will be included in the Safety Analysis Set.

SS is the primary analysis set for safety data. And the safety analysis will be performed according to the actual treatment received by each patient, including the erroneously treated patients (e.g., those assigned to receive dose A who actually received dose B, those who failed to meet the selection criteria). If there is dose modification (such as dose reduction or shift from 200 mg to 300 mg), the initial actual dose taken by the patient during the treatment period will be regarded as actual treatment for analysis.

3.4 Full Analysis Set (FAS)

The Full Analysis Set (FAS) will consist of all NSCLC patients with documented EGFR Exon20ins mutations in tumor tissue, who were previously treated with platinum-based chemotherapy, received at least 1 dose of DZD9008 and have measurable disease at baseline as identified by IRC. The mutation in tumor tissue (resection, biopsy, pleural effusion pellet processed in formalin-fixed paraffin-embedded block, etc.) will be determined based on the clinical trial assay. The patients wrongly reported as EGFR Exon20ins mutations by local lab will be excluded from FAS, such as the complex mutation [redacted]

FAS is the primary set for efficacy analysis. Patients will be analyzed according to their initially assigned dose level in FAS.

To support the development and approval of companion diagnosis devices, two additional analysis sets were defined in CSP as subset of FAS:

- Centrally Confirmed EGFR Exon20ins by Tumor Tissue Analysis Set

  All patients in FAS with EGFR Exon20ins mutation confirmed in tumor tissue by central laboratory.

- Centrally Confirmed EGFR Exon20ins by Plasma ctDNA Analysis Set

  All patients in FAS with EGFR Exon20ins mutation confirmed in plasma ctDNA by central laboratory.

3.5 Pharmacokinetics Set (PKS)

All dosed patients who has at least one measurable plasma concentration of DZD9008 post dose with no protocol deviations or AE thought to impact the analysis of the PK data.

The statistical analysis of PK data will be performed based on the PKS.

3.6 Paired Biopsy Set (PoM cohort)

All dosed patients with a pre-study tumor biopsy and one tumor biopsy on study treatment will be included in the paired biopsy set.

4. ENDPOINTS DEFINITION AND DERIVATION

4.1 Extent of Exposure

Extent of exposure to DZD9008 will be checked for all treated patients based on the variables below:

- Treatment duration (months): calculated as (last dose date of DZD9008 during treatment period – first dose date of DZD9008 during treatment period + 1)/30.4375;

  If the treatment is ongoing (any status other than permanently discontinued) for the patient at the cut-off for analysis, the last dose date can be imputed as the cut-off date. If the first/last dose date is missing/partial after imputation for cut-off, the treatment duration cannot be calculated and will be reported as missing.

- Cumulative dose (mg): the sum of actual doses administered during treatment period;

- Actual Dose Intensity (ADI) (mg/day): calculated as cumulative dose (mg)/total planned days of exposure (day), where total planned days of exposure in part B of study is equal to the treatment duration in days;

- Relative Dose Intensity (RDI) (%): Actual dose intensity /planned dose intensity*100%, where planned dose intensity is defined as the daily dose assigned at the beginning of study.

Patients with at least one dose reduction and patients with at least one dose interruption during the whole exposure period before 'Drug Permanently Discontinued' was recorded will be identified for analysis purpose.

4.2 Efficacy Endpoints

The tumor assessment will be performed by the IRC and investigators independently in this study, following RECIST version 1.1. The efficacy endpoints related to RECIST assessment will be derived based on the evaluation by IRC and investigators respectively, following the rules in subsections below. More details for IRC assessment are documented in the independent review charter.

4.2.1 Primary Efficacy Endpoint

The primary efficacy endpoint is ORR according to RECIST 1.1 assessed by IRC, where confirmation of response is required.

ORR is defined as the percentage of patients who have best overall response (BOR) of Complete Response (CR) or Partial Response (PR) prior to any evidence of progression (as evaluated by IRC based on RECIST 1.1). Any CR or PR which occur after a further anticancer therapy is received will not be included in numerator of the ORR calculation, where further anticancer therapy (also called as new anticancer therapy) includes the systematic anticancer therapy or definitive radiothrapy received for the study indication after first dose of DZD9008.

In part B of study, RECIST assessments will be performed by IRC and investigator independently, from Cycle 3 Day 1 (± 7 days) and then every 6 weeks (± 7 days). A visit overall response of CR is defined when all Target Lesion (TL) and Non-Target Lesion (NTL) lesions present at baseline have disappeared (with the exception of lymph nodes which must have short axis < 10 mm to be considered non-pathological) and no new lesions have developed since baseline. A visit response of PR is defined when the sum of diameters of the TLs has decreased by 30% or more compared to baseline (with no evidence of progression) and the NTLs are at least stable with no evidence of new lesions. More details regarding RECIST assessment can be found in the appendix F of CSP.

BOR is defined as the best response recorded from first dose of DZD9008 until RECIST progression is documented for each patient. BOR represents the best response that a patient has had prior to any subsequent cancer therapy received, irrespective of whether or not patients discontinued treatment of DZD9008. There are 5 potential categories for BOR (from best to worst): CR, PR, Stable Disease (SD), Progressive Disease (PD) and Not Evaluable (NE). When SD is believed to be the best response, at least 35 days from first dose (6 weeks minus 7-day visit window) is required.

When confirmation of CR/PR is required, BOR of CR or PR will only be claimed if a response of CR/PR is recorded by two visits with time interval of at least 4 weeks (28 days). For confirmed CR, one intervening response of NE are possible and are acceptable, but PD is not; For confirmed PR, one intervening response of NE or SD are possible and are acceptable, but PD is not. More examples for BOR derivation with confirmation required are provided in Table 1. Note the BOR variable provided by IRC will not be used for statistical analysis directly, as new anticancer therapy was not considered in the derivation rule by IRC.

BOR where confirmation of response is required or not will be derived and reported respectively. Eventually ORR will be calculated based on the BOR derived for each patient, as defined above.

Table 1 Derivation of BOR where confirmation is required

Assessment x	Assessment x+1	Assessment x+2	BOR
Death			NE (for death before the first RECIST assessment)
CR	CR	CR/PD/NE	CR
CR	NE	CR	CR
PR	CR	CR	CR
PR	CR	PD/NE	PR
PR	PR	Any	PR
PR	SD/NE	PR	PR
CR	PR		Not allowed. Reappearance is progression
CR	PD/NE		SD*
PR	SD/PD/NE		SD*
SD/NE	CR	PD/NE	SD*
SD/NE	PR	SD/PD/NE	SD*
SD	PD		SD*
PD			PD
NE			NE
NE	PD		PD
NE	NE		NE

* SD is believed to be the best overall response only if the minimum time requirement (5 weeks from baseline) for SD is met.

4.2.2 Secondary Efficacy Endpoint

4.2.2.1 Duration of Response (DoR) by IRC

DoR will be derived from those patients who had a BOR of confirmed CR or PR only.

DoR by IRC is defined as the time from the date of first documented response, which is subsequently confirmed, until the date of documented progression or death (by any cause in the absence of progression). Documented response and progression are both identified based on the IRC evaluation. If a patient has not progressed or died at the cut-off for analysis, his/her duration of response will be consored at the last evaluable RECIST assessment.

The end of response should coincide with the date of progression or death from any cause used for the PFS endpoint (including primary analysis and sensitivity analysis, see more details in Section 4.2.2.2).

The algorithm for DoR is provided below:

DoR (months) = (date of event/censoring – date of first response+1)/30.4375.

The rules for determination of response or progression date are described in Section 7.3.

4.2.2.2 Progression-Free Survival (PFS) by IRC

PFS by IRC is defined as the time from first dose of DZD9008 until the date of objective disease progression as defined by RECIST 1.1 based on IRC evaluation or death (by any cause in the absence of progression), regardless of whether the subject discontinues the study treatments or receives another anti-cancer therapy prior to progression.

Symptomatic deterioration will not be regarded as a progression event in this study.

For PFS primary analysis, PFS will be derived following the rules below: Patients who have not progressed or died at the cut-off for analysis will be censored at the time of the latest date of assessment from their last evaluable RECIST assessment. If the patient progresses or dies after two or more consecutively missed RECIST assessments visits, the patient will be censored at the latest evaluable RECIST assessment before the missed visit. If the patient has no evaluable visits post-baseline or does not have baseline data they will be censored on the first dose date unless they die within two RECIST assessment visits after baseline. If a patient discontinues treatment prior to progression and/or receives a new anticancer therapy prior to progression then these patients will continue to be followed until evidence of objective disease progression as defined by RECIST 1.1 and their PFS time will be derived as defined above.

Sensitivity analysis will be performed to handle the missing data with alternative methods. e.g.: If the patient progresses or dies after two or more consecutively missed RECIST assessments visits, the patient will be considered as event on the date of first radiological progression or death. More censoring rules for PFS are presented in Table 2.

The PFS will be calculated as:

PFS (months) = (date of event/censoring –first dose date of DZD9008+1)/30.4375.

Table 2 Censoring Rules for PFS Analyses

No.	Scenarios	PFS Primary Analysis	Sensitivity Analysis
1.1	No baseline or any post-baseline tumor assessments and without death during study	Censored/ Date of first dose	Same as primary analysis
1.2	No baseline or any post-baseline tumor assessments, but died after two tumor assessment visits (13 weeks) from date of the first dose.	Censored/ Date of first dose	Event/Date of Death
2	Progression documented between scheduled visits	Event/ Date of first radiological PD	Same as primary analysis
3	No progression at the time of data cut-off/discontinuation from the study	Censored/ Date of last visit with evaluable* radiological tumor assessment prior to data cut-off or discontinuation from the study.	Same as primary analysis
4	Treatment discontinuation for reason other than radiological PD	Data after discontinuation of treatment will be included when determining the time to progression	Same as primary analysis
5	New anticancer treatment started	Data after new anticancer treatment will be included when determining the time to progression	Same as primary analysis
6	Death between scheduled tumor assessment visits	Event/ Date of death	Same as primary analysis
7	Death or progression after two or more missed tumor assessment visit**	Censored/Date of last evaluable* radiological tumor assessment with documented non-progression	Event/Date of first radiological progression or death
8	No baseline or any post-baseline tumor assessments and died within two tumor assessment visits (13 weeks) from date of first dose	Event/Date of death	Same as primary analysis

*Evaluable tumor assessment is a radiologic assessment of CR, PR, SD, non-CR/non-PD or PD.
**Interval between the death/progression and the last evaluable tumor assessment before missed visits is longer than 14 weeks (98 days).

4.2.2.3 Disease Control Rate (DCR) by IRC

DCR by IRC is defined as the proportion of patients with a BOR of CR, PR or SD, based on the IRC evaluation. Details about BOR derivation (where confirmation of response is required or not) can be found in Section 4.2.1.

4.2.2.4 Percentage Change in Tumor Size by IRC

Tumor size by IRC is defined as the sum of the longest diameters (or short diameter for lymph nodes) of the target lesions identified by IRC according to RECIST 1.1. Percentage change in tumor size will be calculated for patients with measurable disease at baseline as below:

Percentage change from baseline (%)= tumor size at post-baseline visit – tumor size at baseline)/tumor size at baseline*100%.

Best change from baseline in percentage will also be identified based on the smallest tumor size post baseline. Only changes up to progression and before the start of new anticancer therapy will be considered for best change.

If best percentage change cannot be calculated due to missing data in tumor size, a value of 20% increase will be imputed as the best percentage change from baseline in the following situations (otherwise best percentage change will be left as missing):

- If a patient has died;
- If a patient has objective PD documented;
- If a patient discontinued treatment due to PD.

4.2.2.5 Endpoints by Investigators

In addition to the primary and secondary efficacy endpoints described above, the same set of endpoints (ORR, DoR, PFS, DCR and tumor size change) assessed by investigators will also be regarded as secondary endpoints.

The similar definition and derivations described above are also applicable for the endpoints assessed by investigators. The derivation will be made based on the visit overall response assessed by investigator.

4.2.2.6 Overall Survival (OS)

Following disease progression, the patient, patient's family, or the patient's current physician must be contacted every 3 months for survival information up to the time of the final OS analysis.

Overall survival is defined as the interval between the date of first dose and the date of patient death due to any cause. Patients who have not died at the cut-off for analysis will be censored at the time they were last known to be alive.

OS will be calculated as:

OS (months) = (date of event/censoring –first dose date of DZD9008+1)/30.4375.

4.2.3 Exploratory Efficacy Endpoint

In addition to the primary and secondary efficacy endpoint defined in CSP, time to response (TTR) will be derived for patients who achieved confirmed CR or PR in order to describe the onset of drug action.

TTR is defined as the time (days) from the first dose date of DZD9008 to the first documented response, which is subsequently confirmed. In addition, the visit at which the patient achieved the first response will also be identified.

4.3 Safety

4.3.1 Adverse Events (AE)

All AEs recorded on the CRF will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary Version 25.0 (or a later version if updated during the study). Assessment of AE grade will be based on the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE, version 5.0).

The treatment-emergent AEs (TEAEs) are defined as the events meeting any of the criteria below: any event starting or worsening (in severity or seriousness) on or after the date of first dose of treatment (DZD9008) and up to 28 days after date of last dose of treatment; any events considered as related or with unknown/missing relationship to treatment.

If an event cannot be classified as TEAE or not after applying imputation rules for missing/incomplete dates (see Section 7.2), it will be considered as TEAE in analysis.

A treatment-related AE is an AE considered as ‘related’ or with unknown/missing relationship to treatment.

4.3.2 Laboratory Data

Data for the serum chemistry, hematology, coagulation and urinalysis analytes will be collected as scheduled in the protocol, through local laboratory.

Serum Chemistry	**Hematology**	**Coagulation**	**Urinalysis**
Serum (S)/Plasma (P)- Albumin S/P-Alkaline phosphatase S/P-ALT S/P-AST S/P-Bicarbonate S/P-Urea nitrogen S/P-Calcium S/P-Creatinine S/P-Glucose	Blood (B)-Hemoglobin B-Hematocrit B-Platelet count B-Reticulocyte B-Red blood cell count B-White blood cell count B-Absolute leukocyte differential cell count: • Basophils • Eosinophils	APTT INR	U-Glucose U-Protein U-Blood

Serum Chemistry	Hematology	Coagulation	Urinalysis
S/P-Potassium	• Lymphocytes		
S/P-Magnesium	• Monocytes		
S/P-Sodium	• Neutrophils		
S/P-Total bilirubin			
S/P-Total serum protein			
S/P-Lipase			
S/P-Amylase			
S/P-Creatine phosphokinase			

Additional urine/serum samples will be collected from all females of childbearing potential at screening before first dose, and at treatment discontinuation for a pregnancy test.

All laboratory data will be converted to International System of Units (SI) for analysis purpose. All values will be checked against the reference range (if available) and values out of reference range will be flagged as high or low (or abnormal for urinalysis data).

For analysis purposes, values preceded by a '<' or a '>' sign (i.e. those below or above the limits of quantification) will be multiplied by 0.5 and 1.5, respectively.

The CTCAE grade will be assigned for the laboratory tests applicable, following the criteria in NCI-CTCAE version 5.0. Data not meeting the existing criteria will be assigned as grade 0. The detailed criteria are shown in Appendix B.

To examine the abnormality in liver function tests (including potential Hy's law cases), patients meeting the criteria in Appendix C from first dose of DZD90008 until 28 days post last dose will be identified for further analysis.

4.3.3 Electrocardiograms (ECG)

Twelve-lead triplicate ECG will be performed following the schedule in CSP. The following quantitative ECG measurements will be taken:

- Heart rate (bpm);
- PR interval (msec);
- RR interval (msec);
- QRS interval (msec);
- QT interval (msec);
- Fridericia Corrected QT Interval (QTcF);
- Bazett Corrected QT Interval (QTcB).

An overall Investigator assessment of ECG will be provided (categories “normal”, “abnormal, not clinically significant” and “abnormal, clinically significant”).

If multiple measurements exist at the same visit/schedule timepoint, average of the quantitative measurement will be used for analysis, and the mode value will be used for category data. In cases of ties, the best interpretation will be used for baseline whereas the worst interpretation will be used for post-baseline measurements.

4.3.4 Vital Signs

The following vital signs will be collected following the schedule in protocol.

- systolic and diastolic blood pressure (mmHg);
- pulse rate (bpm);

In addition to the vital signs, body weight will also be collected and height will be collected at screening.

4.3.5 Physical Examination

A physical examination will be performed and include an assessment of the followings: general appearance, skin, head and neck (including ears, eyes, nose and throat), respiratory, cardiovascular, abdomen, lymph nodes, thyroid, musculo-skeletal (including spine and extremities) and neurological systems. New or aggravated findings when compared to baseline should be recorded as adverse events, so detailed physical examination results will not be collected.

Performance status will be assessed as scheduled in CSP according to ECOG criteria (score 0 to 4).

4.3.6 Other Safety endpoints

Echocardiogram/MUGA, Pulmonary Function Test, Ophthalmologic Assessment, and etc will also be performed.

4.4 Pharmacokinetics

4.4.1 Drug Concentration

Venous blood samples will be collected following the schedule in CSP, for quantification of DZD9008 and metabolite (DZ0753). Patients in part B of study will be invited for intense PK sampling (approximately 10-30% of patients) and the remaining for sparse PK to characterize DZD9008 and metabolite pharmacokinetics. The timepoints are specified in CSP.

Concentrations of DZD9008 and metabolite measured on Cycle 1 Day 1 (prior to dosing on Cycle 1 Day 2) will be regarded as single dose component, and concentations measured on Cycle 3 Day 1 (prior to dosing on Cycle 3 Day 2) will be regarded as steady state after multiple dose. All pre-dose concentrations measured after Cycle 1 Day 1 will be considered as trough concentrations.

4.4.2 Pharmacokinetic Parameters

The following PK parameters will be determined where possible from the plasma concentrations of DZD9008 and metabolite (DZ0753), using no-compartmental methods performed using Phoenix WinNonlin (Certara USA, Inc., Version 8.1 or higher):

Table 3 Single Dose Component for Intense PK (Cycle 1 Day 1 in Part B)

Parameters	Definition
$AUC_{(0-t)}$	area under the plasma concentration-time curve from time zero to the time of last measurable concentration
$AUC_{(0-24)}$	area under the plasma concentration-time curve from time zero to 24 hours
C_{max}	maximum plasma concentration
t_{max}	time to C_{max}
Metabolite/Parent Ratio for AUC	ratio of AUC between metabolite and DZD9008 after first dose
Metabolite/Parent ratio for C_{max}	ratio of C_{max} between metabolite and DZD9008 after first dose

Table 4 Multiple Dose for Intense PK (Cycle 3 Day 1 in Part B)

Parameters	Definition
AUC_{ss}	area under the plasma concentration-time curve from time zero to the end of the dosing interval (dosing interval = 24 hours)
$C_{ss,max}$	maximum plasma concentration at steady state
$C_{ss,min}$	minimum plasma concentration at steady state
$t_{ss,max}$	time to $C_{ss,max}$
CL_{ss}/F	apparent plasma clearance at steady state, calculated by dose/AUC_{ss}
RAC_{AUC}	extent of accumulation on multiple dosing based on multiple dose AUC_{ss}/single dose $AUC_{(0-24)}$
RAC_{Cmax}	accumulation in C_{max} on multiple dosing based on multiple dose $C_{ss,max}$/single dose C_{max}
Metabolite/Parent ratio for AUC_{ss}	ratio of AUC_{ss} between metabolite and DZD9008 after multiple dose
Metabolite/Parent ratio for $C_{ss,max}$	ratio of $C_{ss,max}$ between metabolite and DZD9008 after multiple dose

Additional PK parameters may be determined where appropriate.

The PK analysis will, where possible, be carried out using actual postdose times recorded in the raw data. If actual times are missing, nominal times may be used.

Concentrations are used as supplied by the analytical laboratory for PK analysis. The units of concentration and resulting PK parameters, with amount or concentration in the unit, will be presented as they are received from the analytical laboratory.

C_{max}, $C_{ss,max}$ $C_{ss,min}$, t_{max} and $t_{ss,max}$ will be obtained directly from the plasma concentration-time profiles.

For multiple peaks, the highest postdose concentration will be reported as C_{max} and $C_{ss,max}$. In the case that multiple peaks are of equal magnitude, the earliest t_{max} and $t_{ss,max}$ will be reported.

AUC values ($AUC_{(0-t)}$, $AUC_{(0-24)}$, AUC_{ss}) will be calculated using the linear trapezoidal rule for increasing concentrations and the logarithmic rule for decreasing concentrations (linear up/log down rule).

Non-compartmental PK parameters will not be derived for the patients with sparse PK sampling. The PK data from these patients will be used in population PK analyses reported outside the CSR.

4.4.2.1 Criteria for Handling Concentrations Below the Limit of Quantification in Pharmacokinetic Analysis

For PK parameter calculation purpose, concentration below the limit of quantification (BLQ) will be handled following the rules below.

- BLQ value prior to administration of the first dose and up to the first measurable concentration will be set as zero.
- Any embedded BLQ value (between 2 quantifiable concentrations), late quantifiable concentration values (following 2 BLQ values in the apparent terminal phase of the profile) and BLQ values following the last quantifiable concentration in a profile will be set to missing for the purposes of PK analysis unless there is a scientific rationale not to do so which will be documented in the PK Analysis Notes/handover document.
- For single dose part of the study, if a predose concentration is missing for a patient, this will be set to zero by default.

4.4.2.2 Calculation of Area Under the Concentration-time Curve

- The minimum requirement for the calculation of AUC values will be the inclusion of at least 3 consecutive plasma concentrations above the lower limit of quantification (LLOQ), with at least one of these concentrations following C_{max}/$C_{ss,max}$.

- For any partial AUC determination (i.e. AUC over a dosing interval), nominal time will generally be used for the end of the interval. Actual times for partial AUC intervals may be used at the discretion of the pharmacokineticist.

4.4.2.3 Anomalous Values

- If a value is considered to be anomalous due to being inconsistent with the expected PK profile, it may be appropriate to exclude this point from the PK analysis. However, the exclusion of data must have strong justification and will be documented in the raw data and the CSR.
- Quantifiable predose concentrations following the first administration of DZD9008 will be considered anomalous and set to missing for PK analysis.
- Embedded BLQ values may be considered anomalous depending on the route of administration and the characteristics of the drug.

4.5 Exploratory Endpoints

4.5.1 EQ-5D-5L

The EQ-5D-5L index comprises 5 dimensions of health (mobility, self-care, usual activities, pain/discomfort and anxiety/depression). For each dimension, respondent select which statement best describes their health on that day from a possible 5 options of increasing levels of severity (no problems, slight problems, moderate problems, severe problems and unable problems). A unique EQ-5D health state is referred to by a 5-digit code allowing for a total of 3125 health states. For example, state 11111 indicates no problems on any of the 5 dimensions. These data will be converted into a weighted health state index by applying scores from the EQ5D value sets elicited from general population samples. The base case will be the United State valuation set, with other country value sets applied when needed.

In addition to the descriptive system, respondents also assess their health on the day of assessment on a visual analogue scale, ranging from 0 (worst imaginable health) to 100 (best imaginable health).

4.5.2 PRO-CTCAE

To date, The PRO-CTCAE Item Library includes 124 items representing 78 symptomatic toxicities drawn from the CTCAE. PRO-CTCAE items evaluate the symptom attributes of frequency, severity, interference, amount, presence/absence. Each symptomatic AE is assessed by 1-3 attributes.

Patients will be asked to complete those items which are considered relevant to TEAEs observed in this study, i.e. Rash, skin dryness, acne, itching, nail loss, nail ridging, decrease appetite, nausea, vomiting, diarrhea and etc. More details can be found in the protocol.

4.5.3 FACIT GP5

A single PRO questionnaire that can inform the overall tolerability of a dose from Functional Assessment of Cancer Therapy- item GP5 (FACIT- item GP5) will be collected.

4.5.4 PoM Biomarker

The pharmacodynamic effect of DZD9008 on PoM biomarkers in tumor tissue from paired biopsies will be evaluated. The biomarker study will include, but not limit to pEGFR. Percent change from baseline in pEGFR will be derived for analysis purpose.

5. STATISTICAL METHODS

5.1 General Principles

All data processing, summarization and analyses will be performed using SAS® 9.4 (or higher) in Dizal Data Warehouse.

The data in part B of study will be analysed and reported by treatment group (dose), unless otherwise specified. [redacted]

Unless otherwise specified, the typical descriptive statistics for continuous variables will include number of patients (n), mean, standard deviation (SD), median, minimum (min), and maximum (max) values. Categorical variables will be summarized by presenting the number and percentage of patients in each category.

[redacted]

[redacted]			

[redacted]

5.2 Patient Disposition and Analysis Sets

Patient disposition will be summarized by treatment group and overall in SS and will include the number and percentage of patients:

- Treated;
- Treatment status (ongoing, discontinued);
- Study Status (Remained on study, completed, or discontinued);

In addition, for the patients who discontinued the treatment or who discontinued from the study, a breakdown of the primary reasons for discontinuation will be presented.

The number and percentage of patients included in each analysis set (SS, FAS, PKS) will also be reported in SS.

The number of patients screened but not treated as well as a summary of the reasons for screen failure will be produced, based on all patients.

The patient disposition data for patients who discontinued from treatment or study will be listed in the individual data listing. The treated patients excluded from any analysis set will also be listed, with the reason for exclusion.

5.3 Protocol Deviation

All important protocol deviations will summarized by treatment group and overall in SS, number and percentage of patients with each category of deviations will be reported. If applicable, the protocol deviations related to coronavirus disease 2019 (COVID-19) will be reported separately. All important protocol deviations will be presented in the individual data listing.

5.4 Demographic and other Baseline Characteristics

Unless otherwise specified, the demographic and other baseline characteristics in this section will be analyzed and reported in SS. If 10% or higher difference in number of patients is observed between analysis sets, the tables will be repeated in FAS, as applicable.

5.4.1 Demographic and other Data at Baseline

Demographic and baseline characteristics will be listed and summarized by treatment group and overall in analysis set(s) applicable. Standard descriptive statistics will be presented for the continuous variables below:

- age (years);
- weight (kg) at baseline;
- height (cm) at baseline;
- baseline body mass index (BMI) in kg/m^2, calculated as ($weight/height^2$) where weight is in kg and height is in m;

The number and percentages of patients will be presented for the categorical variables below:

- age group (<65 years, ≥65 yeas);
- sex;
- race;

- ethnicity;
- nicotine use (current, former, never)
- ECOG performance at baseline (0, 1)

No formal tests of statistical significance will be performed on the demographic and baseline data.

5.4.2 Medical History

Medical history will be coded using the MedDRA version 25.0 (or a later version if updated during the study).

All medical history will be summarized by treatment group and overall in analysis set(s) applicable. Number and percentage of patients with any medical history will be reported, together with the number of patients with at least one medical history within each MedDRA system organ class (SOC) and preferred term (PT).

All the medical history reported will be listed in the individual data listing.

5.4.3 Prior and Concomitant Medication

Prior and concomitant medications received by patients will be coded using the WHODrug Dictionary version Mar2022 (or a later version if updated during the study), Anatomical Therapeutic Chemical (ATC) Classification codes.

Prior medications and concomitant medications are defined as follows:

Prior medications are those taken prior to the first dose date of investigational product.

Concomitant medications are those administrated during the period from the first dose date of investigational product, till 28 days after the last dose date. i.e., the medications with a start date on or after the first dose date of the investigational product and no later than 28 days after the last dose date; or those with a start date before the first dose date of the investigational product and a stop date on or after the first dose date of the investigational product or ongoing at the end of study.

If a medication cannot be classified as prior or concomitant after applying imputation rules for missing/incomplete dates (see Section 7.2), it will be classified as both prior and concomitant.

Prior medications and concomitant medications will be summarized separately by treatment group and overall in the analysis set(s) applicable. The number and percentage of patients using any medication will be displayed together with the number and percentage of patients using at least one medication within each therapeutic class (ATC-Level 2) and preferred name.

Prior medications and concomitant medications will be listed together in the individual data listing, with the flags for prior or concomitant medication.

5.4.4 Tumor Characteristics

Variables below regarding tumor (NSCLC) characteristics will be summarized by treatment and overall in analysis set(s) applicable.

- time since initial diagnosis of primary tumor to baseline (months), calculated as the (first dose date of DZD9008- initial diagnosis date of primary tumor+1)/30.4375.

  If the diagnosis date is missing/partial, the time will be missing.

- histology type

- extent of disease upon entry to study (metastatic, locally advanced)

  Patients with both metastatic and locally advanced site will be reported as metastatic.

- Number of organs/sites with tumor upon entry to study

- brain metastasis at baseline (Yes, No)

  The brain metastasis will be derived based on extent of disease data upon entry to study.

- mutation subtype

The NSCLC history data will also be listed in the individual data listing, including the extent of disease upon entry to study with the associated sites.

5.4.5 Prior Anti-Cancer Therapy

Variables below regarding prior anti-cancer therapy will be summarized by treatment and overall in analysis set(s) applicable.

- Any prior anti-cancer radiotherapy?

- Any prior anti-cancer systemic therapy?

- Number of regimens (as categorical variable) for prior anti-cancer systemic therapy

- Number of regimens subgroup (<3, 3)

- Categories of prior anti-cancer systemic therapy

Number and percentage of patients with each category of prior anti-cancer systemic therapy will be reported respectively. If patient had multiple medication categories, the same patient will be counted once under each category.

- Failure reason for the last line of prior platinum-based chemotherapy

The prior anti-cancer systemic therapy will be coded using the WHODrug Dictionary version Mar2022 (or a later version if updated during the study). The number and percentage of patients using at least one medication within each therapeutic class (ATC-Level 2) and preferred name will be reported in the analysis sets applicable.

The detailed data for prior anti-cancer therapy and the subsequent anti-cancer therapy will be listed in the individual data listings.

5.5 Extent of Exposure

The extent of exposure data will be listed and summarized by treatment group in the safety set. If 10% or higher difference in number of patients is observed between analysis sets, the tables can be repeated in other analysis sets (e.g., FAS).

The descriptive statistics will be provided for treatment duration, the number and percentage of patients with treatment duration in the following categories will also be reported:

- <3 months;
- 3-<6 months;
- 6-<9 months;
- 9-<12 months;
- ≥ 12 months.

The cumulative dose, ADI and RDI during treatment period will be summarized descriptively in the safety analysis set. A categorical summary of RDI (<80%, 80-100%, >100%) will also be performed.

Number and percentage of patients with at least one dose reduction or treatment interruption will be reported, respectively.

5.6 Efficacy

Unless otherwise specified, the primary analysis population for efficacy in part B will be FAS.

To support the approval of companion diagnosis device, efficacy data analysis will be performed in centrally confirmed EGFR Exon20ins by tumor tissue analysis set. More details will be described in separate SAPs.

Similaly, centrally confirmed EGFR Exon20ins by plasma ctDNA analysis set will also be utilized to support the companion diagnosis by ctDNA.

5.6.1 Primary Efficacy Analysis

The primary endpoint for Part B of study is ORR according to RECIST 1.1 by IRC, where confirmation of response is required. The definition and derivation of ORR can be found in Section 4.2.1.

Analysis of ORR will be performed by treatment group in FAS, using the methods below. [redacted]

- [redacted]300 mg[redacted]

  P value for the test against the null hypothesis of ORR[redacted] will reported based on the Simon's two-stage method. ORR and two-sided 97.5% CI will be calculated based on Jung's method [4] to adjust the bias caused by optional sampling in the Simon's two-stage design. Jung's method will provide the uniformly minimum variance unbiased estimator of ORR and CI based on binomial distribution.

- [redacted]200 mg[redacted]

  [redacted]P value in this cohort will be calculated based on binomial exact test and the 97.5% CI of ORR will be calculated using the exact (Clopper - Pearson) method. These statistics will be considered as descriptive.

The number (%) of patients with best overall response will also be provided in the following categories: CR, PR, SD, PD and NE.

5.6.2 Secondary Efficacy Analysis

Efficacy endpoints related to RECIST tumor assessment will be analyzed and reported based on the evaluation by IRC and investigators respectively, using the same statistical analysis method. So the analysis methods for DoR, PFS, DCR and percentage change in tumor size are described below regardless of assessment by IRC or investigaors.

5.6.2.1 DoR

The definition and derivation of DoR can be found in Section 4.2.2.1.

DoR will be analyzed and reported by treatment group in a subset of FAS, including patients with an objective response (BOR is confirmed CR or PR).

Number of patients achieving a confirmed objective response and the number (%) of responding patients with event or censored, and the number (%) of responding patients with a duration of response > 3, > 6, > 9 and > 12 months will be presented. Or if data are appropriate, the durable response rate at some milestones (like 3, 6, 9 and 12 months) and the

quartiles (25%, 50%, 75%) of DoR will be provided with 95% CIs based on the Kaplan-Meier method, along with a Kaplan Meier plot.

To demonstrate tumor response episodes over the treatment period, swimmer plot of tumor response overtime will be provided based on patients in FAS. A bar showing the length of treatment duration will be presented for each patient in the plot. Indicators for visit overall responses over time will be added into the bar, so start and end of each response episode can be identified through this plot. [redacted]

5.6.2.2 PFS

The definition and derivation of PFS can be found in Section 4.2.2.2.

PFS will be analyzed in FAS. The number (%) of patients with event or censored before data cut-off will be reported. Breakdown of events (PD or death) and censors will also be summarized.

The progression-free survival rates (at 3, 6, 9 and 12 months and etc) and quartiles of PFS will be estimated for each treatment group based on Kaplan-Meier method. PFS data will also be displayed graphically using a Kaplan-Meier plot.

5.6.2.3 DCR

Similar to ORR, DCR will be calculated and reported in FAS.

DCR will be reported along with two-sided 97.5% CI based on Exact (Clopper-Pearson) method, by treatment group.

5.6.2.4 Percentage Change in Tumor size

Only tumor size data up to progression and before the start of further anticancer therapy will be included in the analysis.

The absolute values and percentage change from baseline in tumor size will be summarized using descriptive statistics by RECIST visit and treatment group in FAS. The best change from baseline will also be summarized.

Waterfall plots will be displayed by treatment group showing best tumor change from baseline (%) in the vertical axis and each individual patient in the horizontal axis. Positive values indicate tumor growth; on the contrary, negative values indicate tumor reduction. Each patient's percentage change in tumor size will be presented by a separate bar, with the bars ordered from the largest increase to the largest decrease. Reference line at the -30% and 20% change in tumor size levels will be added to the plots, which corresponds to the definition of PR and PD respectively.

To show tumor size change over time, spider plot will also be displayed showing percentage tumor change from baseline (%) for each individual patient in the vertical axis and time from baseline tumor assessment in the horizontal axis.

5.6.2.5 ORR by Investigators

ORR assessed by investigators will be analyzed in FAS using the same analysis method described in Section 5.6.1. But the p value and confidence interval reported will only be considered as descriptive.

5.6.2.6 OS

The definition and derivation of OS can be found in Section 4.2.2.6.

Overall survival will be analyzed in FAS. The number (%) of patients with event (death) or censored before data cut-off will be summarized. Breakdown of censors (alive at the end of study, lost to follow-up and etc) may also be summarized.

The overall survival rates (at 3, 6, 9 and 12 months and etc) and quartiles of OS will be estimated for each treatment group based on Kaplan-Meier method. OS data will also be displayed graphically using a Kaplan-Meier plot.

5.6.3 Subgroup Analysis

In addition to the analysis above, confirmed ORR assessed by IRC in part B will be analyzed by subgroup variables below.

- Number of regimens (<3, 3)
- Prior onco-immunotherapy (with, without)
- Prior amivantamab treatment (with, without)
- Brain metastasis at baseline (Yes, No)
- Mutation subtype group (e.g.: A767_V769dup, S768_D770dup and other)
- Race (Asian, White, Other)

  Patients with race information missing (not reported) will also be included in the subgroup of 'other'.
- Region (Asia, Non-Asia)
- Age group (<65 years, ≥65 yeas)
- Sex (Female, Male)
- Smoking history (Never, Ever)
- Failure reason for the last line of prior platinum-based chemotherapy (Progression, Toxicity or other)

ORR will be reported along with 95% exact CI based on Clopper Pearson method within each level of the subgroup variables respectively. ORR and it's 95% CI within each level of the subgroup variables will also be presented in forest plot. [redacted]

If the number of patients is small (less than 10) in a specific level of the subgroup variables, appropriate combination of the levels will be considered for subgroup analysis (in this case subgroup analysis will not be performed for the two-level subgroup variable).

[redacted]

5.6.4 Exploratory Analysis

To show the consistency between the RECIST assessments performed by the IRC and investigators, concordance table will be provided based on the binary variable of objective response (achieving confirmed response or not) derived from IRC or the investigators data.

TTR will be summarized by treatment group in a subset of FAS, including FAS patients who achieved confirmed CR or PR. TTR in days will be summarized as continuous variable in this subset, and the visit of first response will also be summarized as category variable.

The subsequent anti-cancer therapy post the objective disease progression (evaluated by investigators) will also be summarized for better understanding of the patient journey and long-term data.

5.6.5 Multiplicity Adjustment

Considering there are two dose arms in the pivotal study and the primary endpoint will be analyzed within each arm independently, Bonferroni method will be employed to control the family-wise type I error (at one-sided 0.025). That is, the statistical test for primary efficacy endpoint will be performed at one sided significance level of 0.0125, within each dose arm.

5.7 Safety

5.7.1 Adverse Event

Summary tables of AEs by treatment group and overall will be produced in the safety set. Only the TEAEs will be included in the summaries.

An overview table will be created to present the number and percentage of patients with at least one of the following TEAEs, where patients with more than one TEAE in a particular category will be counted only once in that category.

- any TEAE;
- drug-related TEAE;
- TEAE grade 3 or higher;
- drug-related TEAE grade 3 or higher;

- Treatment-emergent SAE;
- drug-related SAE;
- TEAE leading to drug interruption;
- drug-related TEAE leading to drug interruption;
- TEAE leading to dose reduction;
- drug-related TEAE leading to dose reduction;
- TEAE leading to drug discontinuation;
- drug-related TEAE leading to drug discontinuation;
- TEAE with fatal outcome;
- drug-related TEAE with fatal outcome;

The number and percentage of patients reporting each TEAE will be summarized by MedDRA System Organ Class (SOC) and/or Preferred Term (PT). The following summaries will be produced:

- TEAEs, by SOC and PT;
- drug-related TEAEs, by SOC and PT;
- TEAEs of Grade 3 or higher, by SOC and PT;
- drug-related TEAEs of Grade 3 or higher, by SOC and PT;
- TEAEs, by SOC, PT and maximum CTCAE grade;
- drug-related TEAEs, by SOC, PT and maximum CTCAE grade;
- Treatment-emergent SAEs, by SOC and PT;
- drug-related treatment-emergent SAEs, by SOC and PT;
- TEAEs leading to drug interruption, by SOC and PT;
- drug-related TEAEs leading to drug interruption, by SOC and PT;
- TEAEs leading to dose reduction, by SOC and PT;

- drug-related TEAEs leading to dose reduction, by SOC and PT;
- TEAEs leading to drug discontinuation, by SOC and PT;
- drug-related TEAEs leading to drug discontinuation, by SOC and PT;
- TEAEs with fatal outcome, by SOC and PT;
- drug-related TEAEs with fatal outcome, by SOC and PT;

Additional tables for common TEAEs may be provided to facilitate the CSR development.

In the above summaries, patients with more than one AE within a particular SOC are counted only once for that SOC. Similarly, patients with more than one AE within a particular PT are counted only once for that PT.

For summaries by maximum severity, patients with multiple AEs within a particular SOC or PT will be counted under the category of their most severe AE within that SOC or PT. If CTCAE grade is missing for a TEAE, it will be counted as missing category in the summary tables by maximum grade.

In all summary tables, the events will be sorted by descending frequency in the overall group, at SOC and/or PT level respectively.

No statistical comparisons of AEs between treatment groups will be performed.

All individual AE data collected will be listed together, and treatment-emergence status will be flagged in the listing. Any adverse events that occur after a patient has received further therapy for cancer will be flagged in the data listings. In addition, listings of serious AEs (SAEs), AEs leading to drug discontinuation, AEs with fatal outcome and all deaths will be produced. If data are appropriate, the number of deaths and primary reason will be summarized by period (from the first dose to 28 days after the last dose; post 28 days after last dose) in the safety analysis set.

5.7.2 Laboratory Data

The laboratory tests as specified in Section 4.3.2 will be summarized by treatment group and overall in the safety set.

For the laboratory test with applicable CTCAE grade criteria, shift tables will be provided to show the shift from baseline CTCAE grade (0 to 4) to the worst grade post-baseline. For the tests (like ALT, AST, ALP, and total bilirubin) where CTCAE grade is not applicable for the baseline value, summary of worst grade post-baseline by baseline status (normal/abnormal) will be provided instead of shift table. In addition, summary tables will be provided to present the maximum grade increase from baseline for each abnormality applicable.

To present the status change in clinical significance from baseline to the worst case (abnormal clinically significant > abnormal not clinically significant > normal) post-baseline, shift tables will be provided for the laboratory tests not covered by CTCAE.

In the shift tables, only the patients with non-missing data at both baseline and the corresponding post-baseline visit(s) will be included.

Number and percentage of patients meeting the criteria in Appendix C during the analysis period (from the first dose date of DZD9008 until 28 days after the last dose) will be reported. Shift table will also be provided to tabulate the AST or ALT elevation status at baseline against the worst case during the analysis period.

Graphic displays may be provided for some laboratory tests of interest (such as tests related to common AEs) to show the trend of change relative to the baseline.

All abnormal laboratory data observed in the study will be included in the individual data listing.

5.7.3 Vital Signs

Vital signs data together with the changes from baseline will be summarized by visit and Final Visit using standard descriptive statistics in the safety set. The body weight and BMI will also be summarized similarly.

All the measurements and change from baseline will be listed in the individual data listing.

5.7.4 Electrocardiograms

The central ECG data will be summarized by treatment group and overall in the safety set, while the local ECG data will be presented in the individual data listing only.

The ECG measurements and changes from baseline will be summarized by visit (and timepoint when applicable) and Final Visit using standard descriptive statistics.

The number and percentage of patients with abnormal ECG measurement meeting each criterion below will be reported respectively, based on the worst (highest) case post-baseline.

- absolute prolongation in QTcF interval (msec):
  - > 450
  - > 480
  - > 500
- Change from baseline in QTcF interval (msec):
  - increases from baseline >30
  - increases from baseline >60

- QTcF > 500 msec and increases from baseline > 60 msec

For the overall ECG interpretation, shifts from baseline to the worst case (abnormal clinically significant > abnormal not clinically significant > normal) post-baseline will be presented in the shift table.

In the shift tables, only the patients with non-missing data at both baseline and the corresponding post-baseline visit will be included.

All the ECG measurements (both central and local) and change from baseline will be listed in the individual data listing, together with the Overall ECG Interpretation.

5.7.5 ECOG

The ECOG performance status will be summarized as category variable by visit and Final Visit in the safety set and also listed in the individual data listing.

5.7.6 Other

The echocardiogram/MUGA, pulmonary function test and ophthalmologic assessment will be listed in the individual data listing.

Parameters below will be summarized with descriptive statistics by visit and treatment group in the safety set.

- Left Ventricular Ejection Fraction (LVEF, %)
- Diffusing capacity of lung for carbon monoxide (DLCO, mL/min/mmHg)
- Forced expiratory volume in one second (FEV1, L)

Number and proportion of subjects meeting each criterion below will be reported by treatment group, based on the worst (lowest) LVEF value post-baseline.

- decrease from baseline ≥ 10- <20% and absolute LVEF< 50%
- decrease from baseline ≥ 10- <20% and absolute LVEF ≥ 50%
- decrease from baseline ≥ 20- <30% and absolute LVEF < 50%
- decrease from baseline ≥ 20- <30% and absolute LVEF ≥ 50%
- decrease from baseline ≥ 30% and absolute LVEF < 50%
- decrease from baseline ≥ 30% and absolute LVEF ≥ 50%

5.8 Pharmacokinetics

The drug concentration and PK Parameters will be analyzed and reported in PKS, as described in subsections below.

Cases listed below will be potentially excluded from statistical analysis and clinical pharmacologist will review and confirm before the final decision for a formal analysis.

[redacted]

5.8.1 Summary of Drug Concentration

Drug concentration data will be analyzed and reported in PKS.

Concentrations of DZD9008 in plasma following single dose and multiple dose (steady state) will be summarized separately by nominal timepoint within each treatment group for subjects with intense PK in PKS. The concentration collected at the overlapped timepoints between intense and sparse PK will be summarized by nominal timepoint and treatment group in PKS. Extra measurements (such as unscheduled or repeat assessments) will not be included in the summary tables, but will be included in individual data listings.

The following summary statistics will be provided for concentration in the summary tables:

- Number of observations
- Number of observations below Lower Limit of Quantification (LLOQ)
- Arithmetic mean calculated using untransformed data
- Standard Deviation (SD) calculated using untransformed data
- The geometric mean (calculated as exp[μ], where μ is the mean of the data on a logarithmic scale)
- Geometric coefficient of variation (CV, calculated as $100\sqrt{[\exp(s2)-1]}$, where s is the standard deviation of the data on a log scale)
- Geometric mean ± SD (calculated as exp[μ±s])

- Median
- Minimum
- Maximum

The drug concentration will also be displayed graphically, including the intense PK samples and the trough (pre-dose) concentration from all patients. Plasma concentration will be plotted (on the linear and log-scale) versus time for each individual patient. The geometric mean will also be plotted versus the nominal timepoint, grouped by treatment. And the error bar for geometric mean ± SD will be added if appropriate.

All drug concentration data collected will be presented in the individual data listing, including the data excluded from analysis and the extra measurements (such as unscheduled or repeat assessments).

Concentration of metabolite (DZ0753) will also be analyzed and reported using the same method.

5.8.1.1 Reporting Concentration below LLOQ

Individual concentrations below the LLOQ of the assay will be reported as NQ (not quantifiable) with the LLOQ defined in the Tables, Listings and Graphs (TLGs). For descriptive statistics:

1. If, at a given time point, 50% or less of the plasma concentrations are not quantifiable (NQ), the geometric mean, geometric CV, geometric SD, arithmetic mean, SD and median will be calculated by substituting the LLOQ for values which are NQ.

2. If more than 50%, but not all, of the concentrations are NQ, the geometric mean, geometric CV, geometric SD, arithmetic mean and SD will be reported as not calculable (NC). The max value will be reported from the individual data, and the min and median will be set as NQ.

3. If all the concentrations are NQ, the median, geometric mean and arithmetic mean will be reported as NQ, and the geometric CV, geometric SD and SD will be reported as NC.

The number of values below LLOQ are reported for each time point along with the total number of collected values. Given that criterion 1 above is met, three observations >LLOQ are required as a minimum for a plasma concentration to be summarised. If only one or two values above LLOQ are available, data are presented as a minimum and maximum with the other summary statistics as NC.

The concentration below LLOQ before the first dose will be reported as zero in the summary table. Although zero is also considered as below LLOQ (reflected in n below LLOQ), the statistics will be calculated based on zero value(s) rather than the rules above.

5.8.2 Summary of Pharmacokinetic Parameters

The derived PK parameters for DZD9008 following single dose and multiple dose (steady state) will be summarized separately by treatment group in PKS.

The parameters required in the summary tables required for each parameter can be found in Table 3 and Table 4. Statistics for each PK parameters will be presented following the Dizal SOP.

Box plots will also be provided for the PK parameters to show the quartiles of the data as well as the outliers.

The PK parameters will be presented in the individual data listing. Data excluded from analysis will also be presented and identified in the listing.

The PK parameters for metabolite (DZ0753) will also be analyzed and reported using the same method.

5.9 Exploratory Endpoints

5.9.1 EQ-5D-5L

The EQ-5D-5L data will be summarized by visit and Final Visit for each treatment group in SS.

The number and percentage of patients with different levels for each item in EQ-5D-5L will be reported. The weighted health state index and VAS score will also be summarized as continuous variable, together with change from baseline.

5.9.2 PRO-CTCAE

PRO-CTCAE data will be summarized with descriptive statistics in SS.

For each selected item from the library, proportion of PRO-CTCAE scores for each item attribute (frequency, severity, interference, amount, presence) will be summarized by visit and Final Visit. Proportions will be calculated based on the number of patients with available data at each visit. Butterfly chart will also be prepared for each item attribute to show the proportion change over time.

In addition, descriptive analysis will be performed for each item attribute to show the percentage of patients with symptom at baseline (PRO-CTCAE score > 0), percentage of patients that show any worsening during the analysis period (change from baseline in PRO-CTCAE score > 0), and percentage of patients that show a worsening to score of 3 or 4 (PRO-CTCAE score ≥ 3 and change from baseline > 0). Proportions will be calculated based on the number of patients with both baseline and post-baseline data available for each item attribute as the denominator.

5.9.3 FACIT GP5

The number and percentage of patients with different responses to FACIT GP5 will be reported by visit and Final Visit for each treatment group in the safety analysis set. Butterfly chart will also be prepared to show the proportion change over time.

In addition, descriptive analysis will be performed to show the percentage of patients bothered by side effect at baseline (FACIT GP5 score > 0), percentage of patients that show any worsening during the analysis period (change from baseline in FACIT GP5 score > 0), and percentage of patients that show a worsening to score of 3 or 4 (FACIT GP5 score ≥ 3 and change from baseline > 0). Proportions will be calculated based on the number of patients with both baseline and post-baseline data available as the denominator.

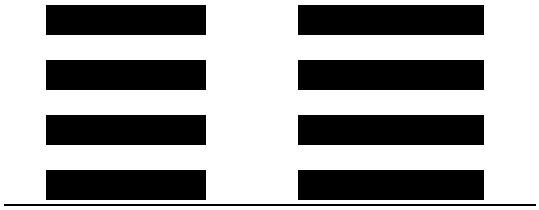
5.9.4 PoM Biomarker

If data are available, pEGFR expression level in tumor tissue at baseline and post baseline (cycle 2), as well as percent change from baseline will be summarized by treatment group in the paired biopsy set. Percent change from baseline for each individual will be graphically displayed together with mean (or median) by treatment group.

6. INTERIM ANALYSES

To check futility and also inform the dose selection, one interim analysis will be performed when [redacted] patients completed at least 2 RECIST assessments in each arm.

If the number of responses is less than or equal to [redacted] out of [redacted] patients in the first stage, then the arm will be stopped. A dose arm passing the first stage is considered as a “competitive” arm. When both dose arms become competitive, the response rate of two arms will be compared using stage 1 data to identify the more effective arm. $Pr(P_A \geq P_B|$ observation), defined as probability of true ORR in arm A higher or equal to arm B given the observation at stage 1 assuming a beta (1,1) prior distribution for both cohorts, is used to determine the winner arm. [redacted]



7. DATA HANDLING RULES

7.1 Time points and Visit Windows

Day 1 is defined as the day of first dose of investigational product. Relative days on or after Day 1 are calculated as (assessment date – Day 1 date) + 1. Relative days prior to Day 1 are calculated as (assessment date – Day 1 date). The day prior to Day 1 is Day -1.

The baseline value was defined as the most recent non-missing value before the first dose of investigational product. The data measured on Day 1 will be considered as candidate of baseline, unless there is information indicating that the data are measured after the dosing.

All post-baseline data (except for the PRO data) will be analyzed using nominal study visits as defined in the Study Schedule and CRF, when required. No visit windows will be applied for summary and analysis and only data from scheduled visits will be included in the by-visit summary. For safety data collected by visit, a Final Visit will be defined at which the last valid measurement post-baseline will be reported.

For the summary of safety data based on the worst case post-baseline, both scheduled visits and unscheduled visits within the analysis period (from the first dose to 28 days after the last dose) can be included.

Table 7 Definition of Analysis Visit Window

Data Domain	**Analysis Visit**	**Target Day of Visit (T)** [a]	Acceptable Visit Window **(Day Range)**
PRO-CTCAE/ FACIT	Baseline	1	≤ 1
	Cycle 1 Day 8	8	2 to 11
	Cycle x Day y [b]	21 × (x - 1) + y	T ± 3
	Cycle 7 Day 1	127	T - 3 to T + 10 (Day 124 to 137)
	Cycle x Day 1	21 × (x - 1) + 1	T ± 10
EQ-5D-5L	Baseline	1	≤ 1
	Cycle 3 Day 1	43	2 to 63
	Cycle x Day 1 [c]	21 × (x - 1) + 1	T - 21 to T + 20

Data Domain	Analysis Visit	Target Day of Visit (T) [a]	Acceptable Visit Window (Day Range)
RECIST assessments from IRC	Tumor assessment visit name in CRF	Tumor assessment date collected in CRF	T ± 14 [d]

[a] Relative to the date of first dose of DZD9008 (Day 1).
[b] Weekly schedule from Cycle 1 Day 15 to Cycle 6 Day 15.
[c] Every 6 weeks (2 cycles) relative to the first dose, x is odd number.
[d] If there is not date-matched tumor assessment visit in CRF, the IRC visit will be mapped by increasing the number in sequence.

For the PRO data, visit information was not collected for all patients in CRF directly, so the analysis visit windows will be used for the by-visit analyses (Table 7).

RECIST visit from IRC will also be mapped to the corresponding tumor assessment visit collected in CRF, based on the actual tumor assessment date. If there is not date-matched tumor assessment visit in CRF (e.g., additional IRC visits after the patient is evaluated as PD by investigator), the IRC visit will be mapped by increasing the visit number in sequence.

Multiple measurements within the same window will be dealt with as follows:

- If there are multiple measurements within a single analysis visit window, the measurement closest to the target day of the visit window will be used in the analysis. If there is a tie, the later one will be used.

7.2 Handling of Missing Dates

To facilitate classification of AEs (TEAE or not) and medications (such as prior or concomitant medication, start date of subsequent anti-cancer therapy), the partial/missing dates will be imputed following the rules below, unless otherwise specified.

End date will be imputed first and start date will be imputed based on the imputed end date. If year of the date is missing, the date will be considered as totally missing and imputed accordingly.

Dates	Imputation Rule
Last dose date	• If the last dose date in Discontinuation of Investigational Product form is partially missing, it will be imputed as the earlier one of: the last date in that year/month; death date (if applicable). Note: The imputed last dose date will be used for safety data derivation (such as TEAE identification and period classification for other safety data) only, but not for the variables in Section 4.1 Extent of Exposure.

Dates	Imputation Rule
AE end Date	• If end date is totally missing, then end date will be imputed as the earlier one of following dates: date of the last visit/contact (up to safety follow up) for the patient and death date (if applicable). • If only day of end date is missing, end date will be imputed as the earlier one of following dates: the last day of that month, date of the last visit/contact (up to safety follow up) for the patient and death date (if applicable). • If only month (or month and day) of end date is missing, end date will be imputed as the earlier one of following dates: the last day (Dec31) in that year, date of the last visit/contact (up to safety follow up) for the patient and death date (if applicable). • If the end date imputed is earlier than the start date collected (if available), then the end date will be set as equal to the start date.
AE start date	• If start date is totally missing and end date is also missing, no imputation will be performed. • If start date is totally missing and end date is not missing, start date will be imputed as the earlier one of following dates: end date of AE and date of the first dose of study medication. • If only day of start date is missing, and start date is in the same month same year of first study medication, start date will be imputed as earlier one of following non-missing dates: end date of AE and date of the first dose of study medication. • If only day of start date is missing, and start date is not in the same month same year of first study medication, start date will be imputed as the first day in that month. • If only month (or month and day) of start date is missing, and start date is in the same year of first study medication, start date will be imputed as earlier one of following non-missing dates: end date of AE and date of first dose of study medication. • If only month (or month and day) of start date is missing, and start date is not in the same year of first study medication, start date will be imputed as the first day (Jan01) in that year.
AE becoming serious date	Two step imputation • The date will be imputed following the rules for AE start date. • Becoming serious date will be imputed as the later one of AE start date and the imputed date from first step,

Dates	Imputation Rule
AE grade change date	Two step imputation • The grade change date will be imputed following the rules for AE start date. • Grade change date will be imputed as the later one of AE start date, the previous AE change date under the same event and the imputed date from first step.
medication/therapy end date	• If ongoing is checked, no imputation will be performed. • If ongoing is not checked and end date is totally missing, then end date will be imputed as the earlier one of following dates: date of the last visit/contact (up to safety follow up for general concomitant medication) and death date (if applicable). • If only day of end date is missing, end date will be imputed as the earlier one of following dates: the last day of that month, date of the last visit/contact (up to safety follow up for general concomitant medication) and death date (if applicable). • If only month (or month and day) of end date is missing, end date will be imputed as the earlier one of following dates: the last day (Dec31) in that year, date of the last visit/contact (up to safety follow up for general concomitant medication) and death date (if applicable).
medication/therapy start date	• If start date is totally missing, no imputation will be performed. • If only day of start date is missing, start date will be imputed as the first day in that month. • If only month (or month and day) of start date is missing, start date will be imputed as the first day (Jan01) in that year.

7.3 Tumor Assessment Date

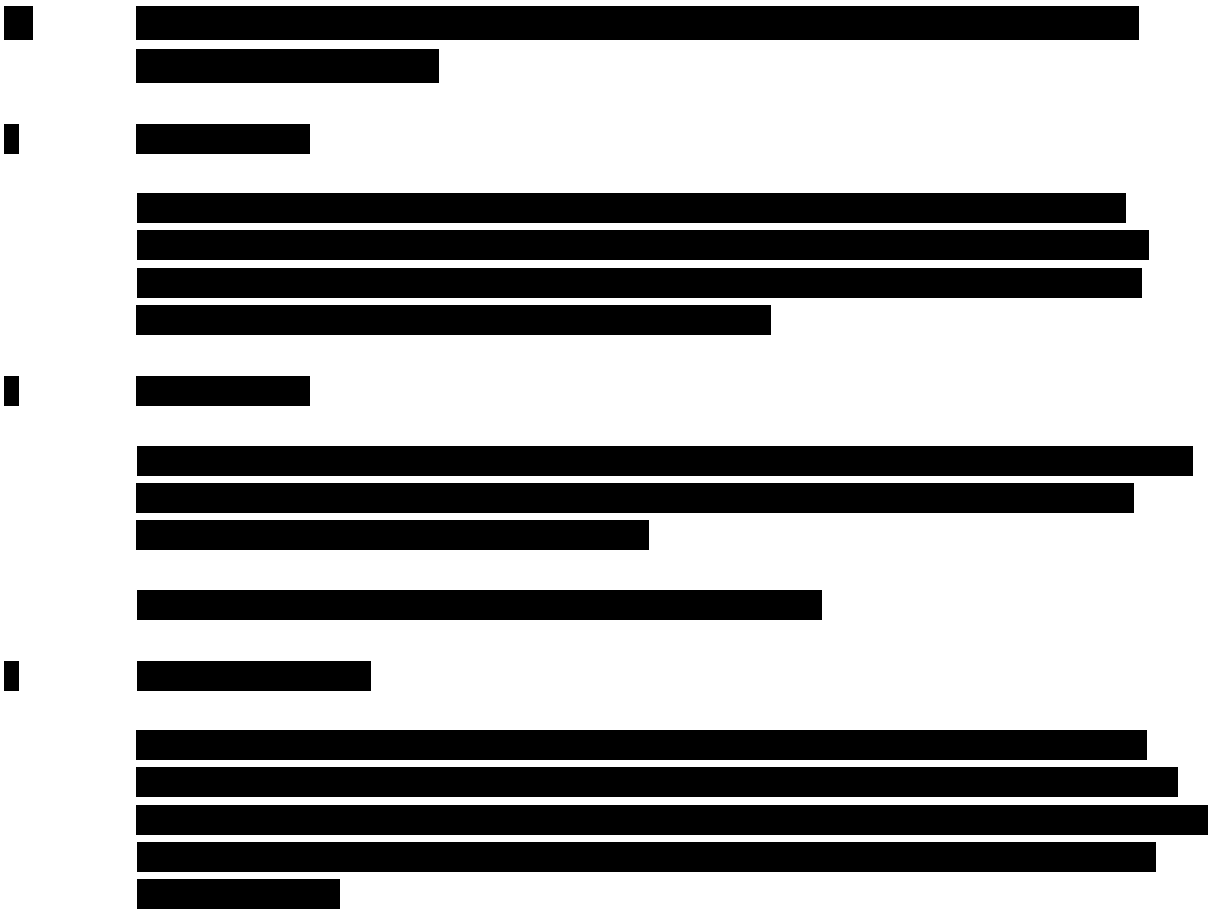
The tumor assessment date in this section refer to image scan date rather than visit dates or image reading date.

The following rules will be applied:

- To calculate the date of progression, use the earliest of the dates of the assessment(s) within the corresponding RECIST visit;
- For patients censored for progression, use the latest date of the assessment from their last evaluable RECIST assessments;
- For determination of SD, use the earliest of the dates contributing towards a particular overall visit assessment;

- For the initial overall visit assessment which shows a response of CR/PR, use the latest of the dates contributing towards a particular overall visit assessment;
- For confirmation of CR/PR, use the earliest of the dates contributing towards the particular overall visit assessment of the subsequent CR/PR.

For the tumor assessment data evaluated by the investigators and collected in CRF, only the latest scan/clinical examination date of the TLs and NTLs will be recorded at each visit; for any new lesions detected, the earliest date will be recorded. The tumor assessment date by investigator will be derived based on the data available in CRF, following the rules above.



9. REFERENCE

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10. APPENDIX

Appendix A Schedule of Event for part B of Study

Assessment	Screen	Cycle 1 (21 days)			Cycle 2 (21 days) onwards	Discontinuation	28-day follow up	Details in section of CSP
Day	-28 to -1	1[h]	8[a]	15[a]	1[b]			
Informed consent	X							4.1.1
Demography & baseline characteristics	X							6.3.1
Medical/surgical history	X							6.3.1
Inclusion/exclusion criteria	X							4.1
Physical examination	X	X			X	X		6.3.2
ECOG performance status	X	X			X	X		6.3.2
Brain MRI or contrast enhanced CT	X							4.1
Pregnancy test (premenopausal females only)	X[c]					X		6.3.4
Ophthalmology assessment[i]	X					X		6.3.5.4
Archival tumor tissue or fresh biopsy (mutation confirmation and/or companion diagnostics development)[m]	X							6.6.1

Assessment	Screen	Cycle 1 (21 days)			Cycle 2 (21 days) onwards	Discontinuation	28-day follow up	Details in section of CSP
Day	-28 to -1	1 [h]	8[a]	15[a]	1[b]			
Vital signs	X	X	X	X	X	X		6.3.3
Height	X							6.3.3
Weight	X	X			X	X		6.3.3
ECG	X	X[##]	X	X	X[##]	X		6.3.5
Clinical chemistry/ Hematology/Urinalysis	X	X	X	X	X	X		6.3.4
HBV/HCV/HIV/COVID-19[d]	X							4.2
APTT/INR	X	X	X	X	X	X		6.3.4
Echocardiogram/MUGA[e]	X	←----------On Cycle 3 Day 1, then every 6 weeks ----------→						6.3.5.2
Lung function test (LFT)[e]	X	←---------- On Cycle 3 Day 1, then every 6 weeks ----------→						6.3.5.3
EQ-5D-5L		X	◄---- Every 6 weeks relative to first dose ----►			X		6.9.1
PRO-CTCAE and FACIT GP5 questions		X	X	X	Weekly until the end of cycle 6, then on day 1 of each cycle ◄----►	X		6.9.2 & 6.9.3

Assessment	Screen	Cycle 1 (21 days)			Cycle 2 (21 days) onwards	Discontinuation	28-day follow up	Details in section of CSP
Day	**-28 to -1**	**1 [h]**	**8[a]**	**15[a]**	**1[b]**			
PK blood samples [l]		X	X	X	X			6.5.1.3
Paired tumor biopsy (Subject joins PoM study only)	X				X (C2D1)			6.6.2.2
Plasma sample for the development of liquid biopsy companion diagnostic	X							6.6.1
Blood sample for ctDNA & exploratory Biomarkers (optional)		X	X	X	X (C2D1-C6D1 and continuous every odd cycle D1 until disease progression)			6.6.2.3
Blood sample for pharmacogenetics (optional)		X[j]						6.6.3
RECIST assessments [f]	X	←----------On Cycle 3 Day 1, then every 6 weeks ----------→						6.8.1
Dose with DZD9008		←----------X (daily dosing) ----------→						5.1.4
Concomitant medication	←---------- X ----------→							4.3.1
Adverse events [g]	←---------- X ----------→							6.4
Survival status [k]	←---------- X ----------→							6.3.6.3

##: multiple time points for ECG.

*: Day 1 of Cycle 2, 3, 4

a. ±1 -day visit window is allowed for C1D8 & D15.

b. All study visits from Cycle 2 Day 1 onwards may be performed within a visit window of ± 2 days. Survival follow up may be performed within a visit window of ± 7 days.

c. Pregnancy test needs to be within 7 days of the first dosing. For Italy only: additional tests at pre-dose on Day 1 of Cycle 2 and each subsequent cycle, as clinically indicated, and during the safety follow-up period (2 weeks ± 3 days after the last dosing).

d. HBV/HCV/HIV/COVID-19 test can be done based on local practice.

e. Echo/MUGA and LFT needs to be done within 14 days of the first dosing.

f. It is suggested that site to conduct the first tumor assessment no earlier than C3D1 (±7days). CT is preferred for extracranial tumor. Same scan modality is required to use for tumor scan and RECIST assessment from baseline till follow up for one patient. Please refer to Appendix F of CSP about the details of RECIST assessment.

g. AE will be collected from the first dosing of DZD9008 and SAE is required to be collected from inform consent

h. For C1D1, -1 day window is allowed for laboratory safety testing and physical examination

i. Eye examination includes: Visual acuity, Pupils, Intraocular pressure, External examination, Slit-lamp examination, and Fundoscopic examination (pupil dilate is not required) and others if clinically indicated.

j. If for any reason the sample is not drawn prior to first dose (pre-dose at C1D1) it may be taken at any visit until the last study visit.

k. Survival status including anti-cancer therapy will be collected every 6 weeks following disease progression or withdrawal from treatment.

l. Multiple time point for PK sampling on C1D1 and C3D1. Hospitalization can be allowed for out of business time PK collection. If there is a dose interruption, dose reduction, or an early termination due to an AE, or there is an SAE, the investigator may choose to collect an unplanned blood sample (if possible) within the 24 hour after the last dose.

m. Adequate amounts of archived tumor tissue or fresh biopsy (if archived tissue is not available) will be collected for Sponsor designated central laboratory confirmation of EGFR Exon20ins mutations. If a pre-study written documentation of EGFR Exon20ins in tumor tissue is available from Sponsor designated central laboratory using the designated assay, no additional tumor sample needs to be submitted. Requirements of tumor tissue sample collection can be referred to the Laboratory Manual.

Appendix B CTCAE Grades Based on Version 5.0 - Adult

Parameter	Direction of Abnormality	Associated CTCAE Term	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Hemoglobin	Increased	Hemoglobin increased	<=ULN	Increase >0 - 20 g/L	Increase >20 - 40 g/L	Increase >40 g/L	-	-
Hemoglobin	Decreased	Anemia	>=LLN	<LLN - 100 g/L	<100 - 80g/L	<80 g/L; transfusion indicated	Life-threatening consequences; urgent intervention indicated	Death
Platelet count	Decreased	Platelet count decreased	>=LLN	<LLN - 75.0 x 10^9 /L	<75.0 - 50.0 x 10^9 /L	<50.0 - 25.0 x 10^9 /L	<25.0 x 10^9 /L	-
White blood cell	Increased	Leukocytosis	<=100 x 10^9/L	-	-	>100 x 10^9/L	Clinical manifestations of leucostasis; urgent intervention indicated	Death
White blood cell	Decreased	White blood cell decreased	>=LLN	<LLN - 3.0 x 10^9 /L	<3.0 - 2.0 x 10^9 /L	<2.0 - 1.0 x 10^9 /L	<1.0 x 10^9 /L	-
Absolute neutrophil count	Decreased	neutrophil count decreased	>=LLN	<LLN - 1.5 x 10^9 /L	<1.5 - 1.0 x 10^9 /L	<1.0 - 0.5 x 10^9 /L	<0.5 x 10^9 /L	-
Absolute lymphocyte count	Increased	lymphocyte count increased	<=4 x 10^9 /L	-	>4 - 20 x 10^9 /L	>20 x 10^9 /L	-	-

Parameter	Direction of Abnormality	Associated CTCAE Term	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Absolute lymphocyte count	Decreased	lymphocyte count decreased	>=LLN	<LLN - 0.8 x 10^9/L	<0.8 - 0.5 x 10^9 /L	<0.5 - 0.2 x 10^9 /L	<0.2 x 10^9 /L	-
Sodium	Increased	Hypernatremia	<=ULN	>ULN - 150 mmol/L	>150 - 155 mmol/L; intervention initiated	>155 - 160 mmol/L; hospitalization indicated	>160 mmol/L; life-threatening consequences	Death
Sodium	Decreased	Hyponatremia	>=LLN	<LLN - 130 mmol/L	<130-125 mmol/L and asymptomatic	<130-125 mmol/L symptomatic; <125-120 mmol/L regardless of symptoms	<120 mmol/L; life-threatening consequences	Death
Potassium	Increased	Hyperkalemia	<=ULN	>ULN - 5.5 mmol/L	>5.5 - 6.0 mmol/L; intervention initiated	>6.0 - 7.0 mmol/L; hospitalization indicated	>7.0 mmol/L life-threatening consequences	Death
Potassium	Decreased	Hypokalemia	>=LLN	<LLN - 3.0 mmol/L;	Symptomatic with <LLN - 3.0 mmol/L; intervention indicated	<3.0 - 2.5 mmol/L; hospitalization indicated	<2.5 mmol/L; life-threatening consequences	Death

Parameter	Direction of Abnormality	Associated CTCAE Term	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Magnesium	Increased	Hypermagnesemia	<=ULN	>ULN - 3.0 mg/dL; >ULN - 1.23 mmol/L	-	>3.0 - 8.0 mg/dL; >1.23 - 3.30 mmol/L	>8.0 mg/dL; >3.30 mmol/L; life-threatening consequences	Death
Magnesium	Decreased	Hypomagnesemia	>=LLN	<LLN - 1.2 mg/dL; <LLN - 0.5 mmol/L	<1.2 - 0.9 mg/dL; <0.5 - 0.4 mmol/L	<0.9 - 0.7 mg/dL; <0.4 - 0.3 mmol/L	<0.7 mg/dL; <0.3 mmol/L; life-threatening consequences	Death
Aspartate aminotransferase (AST)	Increased	Aspartate aminotransferase increased	<=ULN if baseline was normal; <1.5 x baseline if baseline was abnormal	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal	-
Alanine aminotransferase (ALT)	Increased	Alanine aminotransferase increased	<=ULN if baseline was normal; <1.5 x baseline if baseline	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if	>20.0 x ULN if baseline was normal; >20.0 x baseline if	-

Parameter	Direction of Abnormality	Associated CTCAE Term	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
			was abnormal	baseline was abnormal	baseline was abnormal	baseline was abnormal	baseline was abnormal	
Alkaline phosphatase (ALP)	Increased	Alkaline phosphatase increased	<=ULN if baseline was normal; <2.0 x baseline if baseline was abnormal	>ULN - 2.5 x ULN if baseline was normal; 2.0 - 2.5 x baseline if baseline was abnormal	>2.5 - 5.0 x ULN if baseline was normal; >2.5 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal	-
Creatinine		Creatinine increased	<=ULN and <=1.5 x baseline;	>ULN - 1.5 x ULN	>1.5 - 3.0 x baseline; >1.5 - 3.0 x ULN	>3.0 x baseline >3.0 - 6.0 x ULN;	>6.0 x ULN	-
creatine phosphokinase (CPK)	Increased	CPK increased	<=ULN	>ULN - 2.5 x ULN	>2.5 x ULN - 5 x ULN	>5 x ULN - 10 x ULN	>10 x ULN	-
Albumin	Decreased	Hypoalbuminemia	>=LLN	<LLN - 30 g/L	<30 - 20 g/L	<20 g/L	Life-threatening consequences; urgent intervention indicated	Death
Total bilirubin	Increased	Blood bilirubin increased	<=ULN if baseline was normal;	>ULN - 1.5 x ULN if baseline was normal;	>1.5 - 3.0 x ULN if baseline was normal;	>3.0 - 10.0 x ULN if baseline was normal;	>10.0 x ULN if baseline was normal;	-

Parameter	Direction of Abnormality	Associated CTCAE Term	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
			<=baseline if baseline was abnormal	> 1.0 - 1.5 x baseline if baseline was abnormal	>1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 10.0 x baseline if baseline was abnormal	>10.0 x baseline if baseline was abnormal	
Blood glucose	Decreased	Hypoglycemia	>=LLN	<LLN - 55 mg/dL; <LLN - 3.0 mmol/L	<55 - 40 mg/dL; <3.0 - 2.2 mmol/L	<40 - 30 mg/dL; <2.2 - 1.7 mmol/L	<30 mg/dL; <1.7 mmol/L; life-threatening consequences; seizures	Death
Lipase	Increased	Lipase increased	<=ULN	>ULN- 1.5 × ULN;	>1.5 - 2.0 × ULN; >2.0 - 5.0 x ULN and asymptomatic	>2.0 - 5.0 × ULN with signs or symptoms; >5.0 x ULN and asymptomatic	>5.0 × ULN and with signs or symptoms	-
Amylase	Increased	Serum amylase increased	<=ULN	>ULN- 1.5 × ULN	>1.5 - 2.0 × ULN; >2.0 - 5.0 x ULN and asymptomatic	>2.0 - 5.0 × ULN with signs or symptoms; >5.0 x ULN and asymptomatic	>5.0 × ULN and with signs or symptoms	-
Activated partial thromboplastin time (APTT)	Increased	Activated partial thromboplastin time prolonged	<=ULN	>ULN- 1.5 × ULN	>1.5 - 2.5 × ULN	>2.5 × ULN	-	-

Parameter	Direction of Abnormality	Associated CTCAE Term	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
INR	Increased	INR increased	<=1.2	>1.2-1.5; >1 - 1.5 x baseline if on anticoagulation; monitoring only indicated	>1.5-2.5; >1.5 - 2.5 x baseline if on anticoagulation; dose adjustment indicated	>2.5; >2.5 x baseline if on anticoagulation; bleeding	-	-
Urinary protein	Increased	Proteinuria	Non-positive proteinuria; urinary protein<ULN	1+ proteinuria; urinary protein ≥ULN - <1.0 g/24 hrs	2+ and 3+ proteinuria; urinary protein 1.0 - <3.5 g/24 hrs;	4+ proteinuria; Urinary protein >=3.5 g/24 hrs;	-	-

The CTCAE grade will be assigned by programming based on the measurement results, so the criteria highlighted in grey will be ignored.

Appendix C Abnormality in Liver Function Tests

Analyte	Criteria
ALT	≥ 3 × ULN
	≥ 5 × ULN
	≥ 10 × ULN
	≥ 20 × ULN
AST	≥ 3 × ULN
	≥ 5 × ULN
	≥ 10 × ULN
	≥ 20 × ULN
ALT or AST	≥ 3 × ULN
	≥ 5 × ULN
	≥ 10 × ULN
	≥ 20 × ULN
Total bilirubin	≥ 2 × ULN
Alkaline Phosphatase	≥ 1.5 × ULN
ALT, AST, and total bilirubin	(ALT or AST ≥ 3 × ULN) and total bilirubin ≥ 1.5 × ULN, performed at the same visit
	(ALT or AST ≥ 3 × ULN) and total bilirubin ≥ 2 × ULN, performed at the same visit
ALT, AST, total bilirubin and ALP	(ALT or AST ≥ 3 × ULN) and total bilirubin ≥ 2 × ULN and ALP < 2 × ULN, performed at the same visit