Clinical Study Report	
Drug Substance	Osimertinib
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The Efficacy and Safety of Osimertinib with Platinum plus Pemetrexed Chemotherapy, as First-line Treatment in Recurrent or Locally Advanced or Metastatic Non-small Cell Lung Cancer (NSCLC) Patients with Uncommon Epidermal Growth Factor Receptor Mutations (EGFRm): A phase2, Open Label, Single Arm, Multicenter, Exploratory Study

Study dates:	First subject enrolled: 19 January 2022 Last subject last visit: 9 March 2023 The analyses presented in this report are based on a clinical data lock date of 23 March 2023
Phase of development:	Therapeutic exploratory (II)
International Co-ordinating Investigator:	[redacted] [redacted], Chengdu, China
Sponsor's Responsible Medical Officer:	[redacted] [redacted] Shanghai, [redacted] China

This study was performed in compliance with International Council for Harmonisation (ICH) Good Clinical Practice, including the archiving of essential documents.

2. SYNOPSIS

Study centre(s)

This study was initiated at 11 sites, and a total of 4 subjects were enrolled at 4 sites in China.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Objectives and Endpoints

Objectives	Endpoints
Primary	
To describe the efficacy signals of Osimertinib with platinum plus pemetrexed as first-line treatment	• ORR (objective response rate) defined as the proportion of participants who achieved a complete response (CR) or partial response (PR) as their best overall response based on Response Evaluation Criteria in Solid Tumours (RECIST) 1.1 as assessed by the investigator;
Secondary	
To further describe the efficacy signals of Osimertinib with platinum plus pemetrexed as first-line treatment	• PFS (progression free survival) defined as time from first dose of study intervention until progression (PD) per RECIST 1.1 as assessed by the investigator or death due to any cause prior to PDOS (overall survival) defined as the time from first dose of study intervention until the date of death due to any cause; • DoR (duration of response), defined as time from first occurrence of a response to a documented PD per RECIST 1.1 as assessed by the investigator or death of any cause; • Depth of response, defined as maximum response of target lesions per RECIST 1.1 as assessed by the investigator; • DCR (disease control rate) defined as the percentage of participants who achieved CR, PR or stable disease (SD) based on RECIST 1.1 as assessed by the investigator; • Time to treatment failure (TTF), defined as the time from first dose of study intervention to earlier of the date of last study intervention administration or death due to any cause; • Time to first subsequent treatment (TFST), defined as the time from first dose of study intervention to the earlier of the date of anti-cancer therapy start date following study intervention discontinuation or death due to any cause;
To describe the safety and tolerability of Osimertinib with platinum plus pemetrexed as first-line treatment	• All adverse events (AEs) graded by CTCAE v5 • Incidence of ≥grade 3 AE/Serious AE (SAE); • Incidence of all ADR; • Discontinuation rate due to AEs; • Clinical chemistry, hematology and urinalysis; • Vital signs (pulse and blood pressure); physical examination; weight; LVEF; ECG parameters; • ECOG/WHO Performance Status.

Note: The exploratory objectives and endpoints are not included in the clinical study report (CSR) synopsis, but can be found in the CSR.

Study design

This was a phase II, open-label, single-arm, multicenter, exploratory study to assess the efficacy and safety of Osimertinib plus standard chemotherapy in locally advanced or metastatic or recurrent non-small cell lung cancer (NSCLC) participants with uncommon EGFRm (single or multiple mutations of G719X/L861Q/S768I/de novo T790M without other EGFR mutations including ex19del and L858R).

Target population and sample size

Male or female patients at least 18 years of age with locally advanced or metastatic NSCLC, about to start first-line treatment composed of platinum plus pemetrexed chemotherapy, harbouring uncommon EGFRm of G719X/L861Q/S768I/de novo T790M and without other EGFR mutations including ex19del/L858R were included.

Approximately 35 participants were planned to be enrolled in this study. A total of 4 participants were enrolled in the study.

Investigational product and comparator(s): dosage, mode of administration and batch numbers

Osimertinib [redacted]) was supplied as tablets for [redacted].

Duration of treatment

Participants successfully enrolled into the study received [redacted] osimertinib [redacted] plus standard chemotherapy composed of cisplatin or carboplatin and pemetrexed [redacted] followed by osimertinib [redacted] pemetrexed maintenance [redacted] until RECIST 1.1-defined radiological progression as judged by the investigator.

Statistical methods

All statistical analyses were completed using SAS version 9.4 or later.

Sample size:

Approximately 40 participants were screened to enrol 35 participants into the study. With the assumption of expected ORR as 60%, the sample size of 35 participants provided the 95% confidence interval estimation as [42.2%, 78.2%], assuming a potential dropout rate for loss to follow-up as 10%.

Efficacy analyses:

The efficacy analyses were based on the Full Analysis Set (FAS), which included all participants who had taken at least one dose of study intervention.

Primary endpoints

ORR (per RECIST 1.1 using Investigator assessments) was defined as the proportion of participants who achieved a complete or partial response as their best overall response based on RECIST 1.1 as assessed by the investigator, where the response must be confirmed by a later scan conducted at least 4 weeks after the initial response was observed. Data obtained up until progression, or the last evaluable assessment in the absence of progression, were included in the assessment of ORR. Participants who discontinued treatment without progression, or who received a subsequent therapy and then responded were not included as responders in the ORR calculation, where the denominator was always the total number of participants in FAS.

ORR were presented as s percentage, with the corresponding 95% confidence interval using the Clopper-Pearson (exact) method.

In each subgroup, the analysis was carried out using the same type of methodology and the same analysis set as described above. Results of the subgroup analyses were presented using descriptive summaries and the ORR and its corresponding 95% CI of all subgroups were also presented in a forest plot.

Secondary endpoints

PFS was defined as the time from first dose of study intervention until progression per RECIST 1.1 as assessed by the investigator or death due to any cause prior to PD. The analysis of secondary endpoint, PFS, (based on Investigator assessment) occurred when approximately 21 progression events were observed in the 35 participants (approximately 60% PFS maturity). Kaplan-Meier method was used to estimate the median PFS and its 95% confidence interval.

OS was defined as the time from the first dose of treatment to the date of death, regardless of the actual cause of the subject's death. The analysis of OS occurred when approximately 21 death events were observed in the 35 participants (approximately 60% maturity). Results were analysed with the same method as PFS.

DoR was defined as the time from the date of first documented response until the date of documented progression or death in the absence of disease progression. The analysis of DoR was based on the responding subjects. Analysis method of DoR was the same as PFS.

DCR was defined as the percentage of subjects who had a best overall response of CR or PR or SD by RECIST 1.1 as assessed by the investigator. DCR was summarized

and presented as percentage, with 95% confidence interval estimated using Clopper-Pearson exact method.

Depth of response (ie, tumour shrinkage / change in tumour size) by Investigator was defined as the relative change in the sum of the longest diameters of RECIST target lesions at the nadir in the absence of NLs or progression of NTLs when compared to baseline. The best absolute change in target lesion tumour size from baseline, and best percentage change in target lesion tumour size from baseline were summarized using descriptive statistics. The best change in tumour size included all assessments prior to progression or start of subsequent anti-cancer therapy.

TTF or death was defined as the time from first dose of study intervention (osimertinib) to earlier of the date of last study intervention administration or death due to any cause. Any participant not known to have permanently discontinued study intervention and not known to have died at the time of the analysis was censored at the last known time on which the participant was known to be alive. Kaplan-Meier method was used to estimate the median TTF and its 95% confidence interval.

TFST or death was defined as the time from first dose of study intervention to the earlier of the date of anti-cancer therapy (except cisplatin or carboplatin or pemetrexed) start date following study intervention discontinuation or death due to any cause. Any participant not known to have had a subsequent therapy or not known to have died at the time of the analysis was censored at the last known time to have not received subsequent therapy. Kaplan-Meier method was used to estimate the median TFST and its 95% confidence interval.

Safety analyses:

Safety and tolerability were assessed in terms of AEs, deaths, laboratory data, vital signs (pulse and BP), ECG, LVEF, and ECOG performance score (PS). These were collected for all enrolled participants and were summarized per descriptive analysis.

Adverse events (AEs) (coded both in terms of Medical Dictionary for Regulatory Activities [MedDRA] preferred terms and CTCAE grade) were listed individually by participant. Any AE occurring before treatment with Investigational product (IP) was included in the data listings but was not included in the summary tables of AEs. Any AE occurring within 28 days of discontinuation of study intervention and prior to start of a new anti-cancer treatment was included in the AE summaries. Any events in this period that occurred after a participant received further therapy for cancer (following discontinuation of study intervention) were flagged in the data listings.

The AE/SAE incidence rate, ≥grade 3 AE/SAE incidence rate (AE/SAE graded by CTCAE v5), related AE incidence rate, and discontinuation rate due to AE were summarized by MedDRA system organ class and preferred term.

The clinical chemistry, hematology, urinalysis results, vital signs (pulse and blood pressure); physical examination; weight; LVEF; ECG parameters and ECOG PS were summarized by visit if applicable. The abnormalities with above measurement were summarized by visit as well.

Study population

Summary of efficacy results

Not applicable.

Summary of safety results

Not applicable.

Conclusion

As the delay in study enrolment, the Sponsor decided to terminate the study on 29 December 2022 and all subjects were followed up to 9 March 2023. By data cut-off date of 23 March 2023, all 4 subjects discontinued treatment due to study terminated by Sponsor, subject lost to follow-up, subject decision and disease progression respectively.