Abbreviated Clinical Study Report Synopsis	
Drug Substance	Oleclumab (MEDI9447)
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A Multiarm, Open-label, Multicenter, Phase Ib/II Study to Evaluate Novel Combination Therapies in Subjects with Previously Treated Advanced EGFRm NSCLC

Study dates: First subject enrolled: 08 May 2018
Last subject last visit: 24 May 2021
The analyses presented in this report are based on a clinical data lock date of 09 July 2021

Phase of development: Clinical pharmacology (I)
Therapeutic exploratory (II)

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This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents.

This submission /document contains trade secrets and confidential commercial information, disclosure of which is prohibited without providing advance notice to AstraZeneca and opportunity to object.

Study Centre(s)

This was a multicenter study conducted at 11 study centres within the Republic of Korea, Taiwan, and the United States.

Publications

Kim D-W, Kim S-W, Camidge DR, Rizvi NA, Marrone KA, Le X et al. Abstract CT163: CD73 inhibitor oleclumab plus osimertinib for advanced EGFRm NSCLC: First report of a Phase 1b/2 study. Cancer Research. 2021;81(13 Supplement):CT163.

Objectives and Criteria for Evaluation

Table S1 Objectives and Endpoints

Objectives	Endpoints
Primary	
Part 1 - Safety To investigate the safety and tolerability of novel combination therapies administered in subjects with advanced EGFRm NSCLC and confirm the combination dose(s) for further clinical evaluation	• Incidence of AEs and SAEs • DLTs • Clinically meaningful changes from baseline in laboratory parameters, vital signs, and ECG results
Part 2 - Efficacy To investigate the antitumor activity of novel combination therapies administered in subjects with advanced EGFRm NSCLC by evaluation of tumor response based on RECIST version 1.1	• OR, according to RECIST version 1.1
Part 2 - Safety To investigate the safety and tolerability of novel combination therapies administered in subjects with advanced EGFRm NSCLC	• Incidence of AEs and SAEs • Clinically meaningful changes from baseline in laboratory parameters, vital signs, and ECG results
Secondary	
Part 1 and 2 - Efficacy To obtain a preliminary assessment of the antitumor activity of novel combination therapies administered in subjects with advanced EGFRm NSCLC by evaluation of tumor response based on RECIST version 1.1	• DoR, DC, PFS, and OS. RECIST version 1.1 will be used for assessment of tumor response.
To evaluate the antitumor activity of novel combination therapies administered in subjects with advanced EGFRm NSCLC based upon T790M testing at baseline confirmed by a central lab	• OR and DC by T790M status at baseline (determined by a central lab) in archival and/or fresh tumor biopsies
Part 1 and 2 - Pharmacokinetic To determine the PK profile of individual analytes of novel combination therapies (oleclumab, osimertinib, and AZD4635) administered in subjects with advanced EGFRm NSCLC	• Summary PK for all therapies and/or their metabolites
Part 1 and 2 - Immunogenicity To determine the immunogenicity of oleclumab administered in subjects with advanced EGFRm NSCLC	• Development of detectable ADAs

NOTE: Results from exploratory objectives are not reported in this abbreviated CSR.

AE = adverse event; ADA = antidrug antibody(ies); DC = disease control; DLT = dose-limiting toxicity; DoR = duration of response; ECG = electrocardiogram; EGFRm = epidermal growth factor receptor mutant; NSCLC = non-small cell lung cancer; OR = objective response; OS = overall survival; PFS = progression free survival; PK = pharmacokinetic(s); RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event.

Study Design

This was a multiarm, open-label, multicenter, phase Ib/II study to evaluate novel combination therapies in patients with previously treated advanced epidermal growth factor receptor mutant (EGFRm) non-small cell lung cancer (NSCLC).

Patients were treated in Arm A (oleclumab [a human monoclonal antibody that binds to cluster of differentiation 73] in combination with osimertinib [a third generation EGFR tyrosine kinase inhibitor; TKI] combination therapy) or Arm B (oleclumab in combination with AZD4635 [a small molecule inhibitor of adenosine 2a receptor signaling] combination therapy). The allocation of patients to treatment arms was dependent upon the patient's EGFR mutation status and prior therapies.

Target Subject Population and Sample Size

The target population were male or female patients ≥ 18 years of age with histologically or cytologically-confirmed locally advanced/metastatic advanced NSCLC with EGFR mutation known to be associated with EGFR TKI sensitivity (including G719X, exon 19 deletion, L858R, L861Q). All patients had received and then progressed on at least one approved first or second generation EGFR TKI (eg, erlotinib or gefitinib [first generation] or afatinib [second generation]). For Arm A, patients had received 1 prior line of therapy with an EGFR TKI in the locally advanced/metastatic setting. For Arm B, patients had received at least 2, but not more than 4, prior lines of therapy (including investigational therapy) in the locally advanced/metastatic setting.

It was planned for a total enrollment of up to approximately 98 patients at approximately 15 sites globally - approximately 46 patients in treatment Arm A, and up to approximately 52 patients in treatment Arm B.

CCI [redacted]

Investigational Product and Comparator(s): Dosage, Mode of Administration and Batch Numbers

Oleclumab (MEDI9447) was administered via intravenous infusion at doses of 1500 mg, or 3000 mg, osimertinib was administered orally as a tablet at a dose of 80 mg, and AZD4635 was administered orally as a nanosuspension at doses of 50 mg, or 75 mg.

The drug product batch numbers for oleclumab were: CCI, CCI, and CCI; for osimertinib: CCI, CCI, CCI, CCI; and for AZD4635: CCI and CCI.

Duration of Treatment

All patients remained on their respective treatments until documentation of disease progression, intolerable toxicity, or another protocol-defined reason for patient withdrawal developed. The assigned investigational product could be continued in the setting of progressive disease (PD) as long as the patient did not meet any of the investigational product discontinuation criteria and the treatment criteria in the setting of PD were met.

Statistical Methods

All analyses were performed with Statistical Analysis System® (SAS®, SAS Institute Inc, Cary, North Carolina, United States) Version 9.3 or above.

Efficacy

The efficacy analyses of antitumor activity were based on the As-treated Population. The rates of objective response and disease control based on Response Evaluation Criteria in Solid Tumors version 1.1 were summarized with 95% confidence interval based on the exact binomial distribution. Time to-event endpoints (duration of response, progression-free survival, and overall survival) were analyzed using the Kaplan-Meier method. Patient's tumor samples (archival and/or from fresh biopsies) were analyzed for T790M mutation that could predict increased frequency of response or longer disease stabilization.

Interim Analysis

Bayesian predictive probabilities were used for continuous interim monitoring by estimating the probability of observing a targeted treatment effect or futility of the treatment if the trial were to continue to its predefined maximum sample size.

Pharmacokinetics

Individual concentrations were tabulated by dose cohort along with descriptive statistics. Non-compartmental pharmacokinetics (PK) data analysis was performed from each dose cohort with scheduled PK sample collection where data allowed. Relevant descriptive statistics of non-compartmental PK parameters was provided for individual compounds.

Immunogenicity

For each arm, the immunogenic potential of oleclumab was assessed by summarizing the number and percentage of patients who developed detectable anti-drug antibodies.

Safety

Safety data, including dose-limiting toxicities (DLTs), adverse events (AEs), serious adverse events (SAEs), laboratory evaluations, vital signs, cardiac left ventricular function (Arm A only), and electrocardiogram (ECG) results were summarized based on the As-treated Population, defined as all patients who received any investigational product, analyzed according to treatment received. Summary statistics were provided for AEs, SAEs, AE grade (severity) and relationship to investigational product(s), clinical laboratory parameters, vital signs, cardiac left ventricular function (Arm A only), and ECG. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03.

Study Population

A total of 43 patients were enrolled in the study in 11 centres in the United States, South Korea, and Taiwan: 26 in the Arm A (oleclumab + osimertinib) dose-escalation/dose-expansion (oleclumab 1500 mg + osimertinib 80 mg [N=5]; oleclumab 3000 mg + osimertinib 80 mg [N=21]) and 17 in the Arm B (oleclumab + AZD4635) dose-escalation (oleclumab 1500 mg + AZD4635 75 mg [N=6]; oleclumab 1500 mg + AZD4635 50 mg [N=6]; oleclumab 3000 mg + AZD4635 50 mg [N=5]).

At database lock, all patients had discontinued from the study. Six patients were still receiving treatment in a continued treatment period.

Summary of Efficacy Results

The primary endpoint of the Part 2 dose expansion phase of the study was OR according to RECIST version 1.1. In the Arm A dose expansion phase, a total of 4/21 (19%; 95% confidence interval: 5.4, 41.9) patients receiving the RP2D of oleclumab 3000 mg + osimertinib 80 mg had a BOR of confirmed PR. Per the inclusion criteria for Arm A, patients were to be T790M negative by local laboratory on tumor biopsy, and plasma if tested, however, 3 of the 21 patients (including 2 of the 4 patients with a response) were confirmed to be T790M positive by plasma testing in the central laboratory.

The OR in Part 2 of Arm A in this study for patients who were T790M negative at baseline in plasma (a secondary endpoint) was 2/17 patients (11.8%; 95% CI, 1.5 – 36.4).

Arm B did not proceed to the dose expansion phase.

Summary of Pharmacokinetic Results

Serum oleclumab concentrations were generally similar within each dose level and across Arm A and Arm B. Moderate accumulation of oleclumab was observed following multiple doses with accumulation ratios based on end of infusion concentrations (Rac CEOI) ranging from 1.15 to 2.55.

In Arm A, following single and multiple oral administration of osimertinib 80 mg in combination with oleclumab 1500 mg or 3000 mg, plasma osimertinib or AZ5104 (a metabolite of osimertinib) concentrations were similar across oleclumab dose level.

In Arm B, maximum plasma concentrations (C_{max}) of AZD4635 and metabolites were reached rapidly with median time to maximum plasma concentration (t_{max}) values ranging from 0.917 to 2.13 hours across all treatments and analytes. Exposure to AZD4635 and metabolites was similar across treatment groups and within AZD4635 dose level. Although multiple dose pharmacokinetic data were limited, there was no apparent accumulation of AZD4635 or metabolites based on Rac C_{max} (accumulation ratio based on maximum concentration) and Rac AUC (accumulation ratio based on area under the curve) values spanning unity.

Summary of Safety Results

The safety profile of oleclumab in combination with osimertinib or AZD4635 in this study was consistent with the established safety profile for the oleclumab, osimertinib, and AZD4635 components.

All patients in Arm A, and 16/17 patients (94.1%) in Arm B had at least 1 treatment-emergent adverse event (TEAE); around half of patients in each Arm (50.0% and 52.9% in Arms A and B, respectively) experienced at least one Grade 3 or 4 TEAE.

In Arm A, the most frequently reported TEAEs (≥ 10% of total patients) were paronychia (9 patients [34.6%]), rash (7 patients [26.9%]), stomatitis (6 patients [23.1%]), diarrhoea, and dyspnoea (5 patients [19.2%] each), decreased appetite, fatigue, and nausea (4 patients [15.4%] each), aspartate aminotransferase increased, constipation, headache, haemoptysis, pneumonia, and upper respiratory tract infection (3 patients [11.5%] each). In Arm B, the most frequently reported TEAEs were nausea (9 patients [52.9%]), vomiting (7 patients [41.2%]), fatigue, and headache (5 patients [29.4%] each), constipation, cough, dizziness, and dyspnoea (4 patients [23.5%] each), and anaemia, diarrhoea, non-cardiac chest pain, infusion related reaction, dehydration, hypocalcaemia, back pain, hypoaesthesia, hypoxia, and pulmonary embolism (2 patients [11.8%] each).

Treatment-related TEAEs were reported in 21 [80.8%] patients in Arm A, and 11 [64.7%] patients in Arm B. Oleclumab-related TEAEs were reported in 16 (61.5%) and 7 (41.2%) of patients in Arm A and B, respectively. One patient in each Arm experienced treatment-related AEs leading to treatment discontinuation.

Nine patients (34.6%) in Arm A and 6 patients (35.3%) in Arm B had at least 1 AESI for oleclumab. Treatment-related oleclumab AESIs were urticaria, infusion-related reaction, and angina pectoris in Arm A, and infusion-related reaction, and pulmonary embolism in Arm B. Three patients (14.3%) in the Arm A osimertinib 3000 mg + osimertinib 80 mg dose cohort had at least 1 AESI for osimertinib. Treatment-related osimertinib AESIs were ejection

fraction decreased and pneumonitis. One patient in each Arm had an AESI for oleclumab that led to systemic steroids (brain oedema, and localised oedema in Arms A and B, respectively), and 1 patient in Arm A had an AESI for osimertinib that led to systemic steroids (pneumonitis). No patients had AESIs for oleclumab or osimertinib that led to other immunosuppressive medications. No AESIs were defined for AZD4635.

Serious adverse events were reported in 9/26 (34.6%) and 8/17 (47.1%) patients in Arms A and B, respectively.

One patient (16.7%) in the Arm B oleclumab 1500 mg + AZD4635 75 mg dose cohort had a Grade 1 DLT of vomiting, determined as related to AZD4635, and a Grade 3 DLT of pulmonary embolism, determined as related to oleclumab and AZD4635.

Generally, changes in laboratory parameters were not clinically significant. No clinically meaningful trends in vital signs, or ECG findings were observed, and there were no physical findings or observations related to safety.

Conclusion(s)

- Overall, the safety profile of oleclumab in combination with osimertinib or AZD4635 was consistent with the known safety profiles of the oleclumab, osimertinib, and AZD4635 components in this study. The safety profile would not preclude further development of these combinations.
- In the Arm A dose expansion phase, 4/21 (19%) of patients receiving the RP2D of oleclumab 3000 mg + osimertinib 80 mg had a BOR of confirmed PR. Two of the 4 patients were T790M positive. Arm B was not expanded at the RP2D dose of oleclumab 3000 mg + AZD4635 50 mg. Due to lack of response to treatment and a change in the formulation of AZD4635 it was decided to terminate this Arm.
- Serum oleclumab CEOI and C_{trough} (trough concentration immediately prior to dosing) were generally similar within each dose level and across Arm A and Arm B. In Arm A, osimertinib and metabolite PK were similar when administered with two different doses of oleclumab. In Arm B, AZD4635 and metabolite PK were similar within each dose level when administered with two different doses of oleclumab.