Clinical Study Report Synopsis	
Drug Substance	Oleclumab (MEDI9447)
Study Code	D6070C00001
Edition Number	1
Date	07 March 2022
EudraCT Number	Not applicable
NCT Number	NCT02503774

A Phase I Multicenter, Open-label, Dose-escalation and Dose-expansion Study to Evaluate the Safety, Tolerability, Pharmacokinetics, Immunogenicity, and Antitumor Activity of MEDI9447 Alone and in Combination with MEDI4736 in Adult Participants with Select Advanced Solid Tumors

Study dates: First participant enrolled: 24 July 2015
Last participant last visit: 22 January 2021
The analyses presented in this report are based on a clinical data lock date of 24 May 2021

Phase of development: Clinical pharmacology (I)

International Co-ordinating Investigator: PPD
300 George Street
New Haven, Connecticut 06520

Sponsor's Responsible Medical Officer: PPD
AstraZeneca
35 Gatehouse Drive, Waltham, MA, 02451

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

Study Centres

This was a multicentre study conducted at 30 sites in 3 countries (United States, Australia, and South Korea).

Publications

Bendell JC, LoRusso P, Overman MJ, Noonan AM, Dong-Wan K, Strickler J, et al. Safety and efficacy of the anti-CD73 monoclonal antibody (mAb) oleclumab ± durvalumab in patients (pts) with advanced colorectal cancer (CRC), pancreatic ductal adenocarcinoma (PDAC), or EGFR-mutant non-small cell lung cancer (EGFRm NSCLC). J Clin Oncol. 2021; 39 (15): abstr 9047.

Overman MJ, LoRusso P, Strickler J, Patel SP, Clarke SJ, et al. Safety, efficacy and pharmacodynamics (PD) of MEDI9447 (oleclumab) alone or in combination with durvalumab in advanced colorectal cancer (CRC) or pancreatic cancer (panc). J Clin Oncol. 2018; 36 (15): abstr.

Objectives and Criteria for Evaluation

Table 1 Objectives and Endpoints

Objectives	Endpoints
Primary	
• To assess the safety and tolerability, describe any DLT, and determine the MTD or the highest protocol-defined dose (in the absence of exceeding the MTD) for oleclumab when administered as a single agent and in combination with durvalumab in participants with selected advanced solid tumors	• Presence of AEs, SAEs, DLTs, and changes from baseline in laboratory parameters, vital signs, and ECG results
Secondary	
• To describe the preliminary antitumor activity of oleclumab when administered as a single agent and in combination with durvalumab in participants with selected advanced solid tumors using RECIST version 1.1	• OR, DC, DoR, PFS, and OS. RECIST version 1.1 was used for assessment of tumor response.
• To determine the PK of oleclumab administered as a single agent and the PK of both oleclumab and durvalumab when administered in combination	• Individual participant oleclumab concentrations in serum at different time points after oleclumab administration • Durvalumab concentrations in serum at different time points after durvalumab administration (oleclumab/durvalumab combination arm) • PK parameters that may be modelled on these data included, but were not limited to C_{max}, AUC, clearance, and $t_{1/2}$
• To determine the immunogenicity of oleclumab administered as a single agent and the immunogenicity of both oleclumab and durvalumab when administered in combination	• Number and percentage of participants who developed detectable ADAs
• To evaluate candidate pharmacodynamic biomarkers of oleclumab activity in tumor biopsy specimens when oleclumab was administered as a single agent and in combination with durvalumab	• Assessment of target expression (eg, CD73, PD-L1) in tumor biopsy specimens

ADA = anti-drug antibody; AE = adverse event; AUC = area under the concentration-time curve; C_{max} = maximum observed concentration; DC = disease control; DLT = dose-limiting toxicity; DoR = duration of response; MTD = maximum tolerated dose; OR = overall response; OS = overall survival; PD-L1 = programmed death ligand 1; PFS = progression-free survival; PK = pharmacokinetics; RECIST = Response Evaluation Criteria in Solid Tumours; SAE = serious adverse event; $t_{1/2}$ = terminal half-life.

Study Design

This was a first time in human (FTIH) Phase I, multicentre, open-label, dose-escalation, and dose-expansion study of oleclumab administered as a single agent or in combination with durvalumab to evaluate the safety, tolerability, pharmacokinetics (PK), immunogenicity, pharmacodynamics, and preliminary antitumor activity in adult participants with selected advanced solid tumors.

The dose-escalation phase of the study consisted of 2 arms: (i) ascending dose levels of oleclumab monotherapy and (ii) ascending dose levels of oleclumab in combination with a single dose level of durvalumab, both administered in participants with advanced colorectal cancer (CRC), or pancreatic adenocarcinoma.

The intention was to initiate the dose-expansion of oleclumab/durvalumab combination therapy once the maximum tolerated dose (MTD) or maximum administered dose was established in the combination therapy arm of the dose-escalation phase. The combination therapy dose-expansion phase included the following 3 tumor-specific cohorts: a) participants with previously treated MSS-CRC, b) participants with previously treated pancreatic adenocarcinoma, and c) participants with previously treated EGFRm NSCLC.

All participants were evaluated regularly for antitumor activity and their clinical status classified according to RECIST version 1.1 guidelines and followed for survival until the end of study (approximately 3 years after the final participant was entered into the study), or when the sponsor stopped the study, whichever occurred earlier.

Target Population and Sample Size

Approximately 348 participants were planned, with the possibility of enrolling more participants if necessary based on emerging PK, pharmacodynamic, safety, and response data generated from the study or other ongoing immunotherapy studies.

Based on 4 dose-level cohorts in each arm, the total number of participants planned for enrolment in the dose-escalation phase was 30 to 48 DLT-evaluable participants (15 to 24 participants per treatment arm) with the possibility of expanding to a total of 18 participants per dose-level cohort with mandatory paired pre-treatment and on-treatment biopsies. Participants were ≥ 18 years of age, with histologically- or cytologically-confirmed advanced CRC or pancreatic adenocarcinoma, that was refractory to standard therapy or for which no standard therapy exists.

The combination therapy dose-expansion phase included the following 3 tumor-specific cohorts: a) participants with previously treated MSS-CRC, b) participants with previously treated pancreatic adenocarcinoma, and c) participants with previously treated EGFRm NSCLC. Participants were ≥ 18 years of age, with histologically-or cytologically-confirmed advanced, CRC, pancreatic adenocarcinoma, or EGFRm NSCLC. Participants with CRC or pancreatic adenocarcinoma had received and progressed, were refractory, or were intolerant to standard therapy, and prior to the first interim analysis for each of these cohorts, participants had positive CD73 expression by immunohistochemistry (IHC) on at least 10% of tumor cells. Participants with EGFRm NSCLC had received an approved epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) and then radiologically progressed or were intolerant.

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

Oleclumab (MEDI9447) was administered via intravenous (IV) infusion over approximately 1 hour (+15 minutes) at doses of 5, 10, 20, or 40 mg/kg Q2W.

Durvalumab (MEDI4736) was administered via IV infusion (no less than 15 minutes after the end of oleclumab infusion) over approximately 1 hour (+15 minutes) at doses of 10 mg/kg Q2W.

Batch numbers for oleclumab were CCI, CCI, CCI, and CCI.
Batch numbers for durvalumab were CCI, CCI, and CCI.

Duration of Treatment

All treatment was administered beginning on Day 1 until confirmed radiological progressive disease (PD), unless there was unacceptable toxicity, withdrawal of consent, or another treatment discontinuation criterion was met.

Statistical Methods

The data analyses were conducted using the SAS® System (SAS Institute Inc., Cary, NC) Version 9.1.3 or above.

Analyses of Primary Variables

- The number and percentage of participants with a DLT during the dose-escalation phase were presented.
- Tolerability and safety was assessed by summarizing AEs and SAEs occurring after the first dose of investigational product, laboratory assessments during the study, ECG results, ECOG performance status, and vital signs. The safety evaluation was based on the As-treated Population.

Analyses of Secondary Variables

- The efficacy analyses were based on the As-treated Population. Sensitivity analysis of OR (by ORR) and DC (by DCR) was performed based on the Response-evaluable Population.
- Individual serum concentrations of oleclumab and durvalumab were reported in listings and summarized in tables by cohort and visit using descriptive statistics.
- For participants who were ADA positive for oleclumab or durvalumab at any visit on the study, their ADA titre results were summarized in a listing for every visit.
- Assessment of immune subtypes such as T cells and myeloid cells by flow cytometry were tabulated by dose cohort within each treatment arm for change in absolute level of cell subsets. Tumour biopsies, by dose cohort, were assessed by IHC for markers of

TIL remodelling that may have included, but was not limited to, CD8, CD73, PD-1, PD-L1, FoxP3, and CD11b.

Study Population

The study was conducted at 30 sites across 3 countries (United States, Australia, and South Korea). The first participant was enrolled on 24 July 2015, the last participant completed the last visit on 22 January 2021, and the database was locked on 24 May 2021.

Of the 286 participants screened, 192 participants were enrolled and were treated with at least 1 dose of study treatment in the dose-escalation phase for oleclumab monotherapy (42 participants), dose-escalation phase for oleclumab and durvalumab combination therapy (24 participants), or dose-expansion phase for oleclumab and durvalumab combination therapy (126 participants).

Participant demographics and baseline characteristics were generally similar and well balanced across all treatment groups. By the end of the study, all participants had discontinued study treatment and had discontinued from the study. The primary reason for discontinuation of study treatment was disease progression, and the primary reason for study discontinuation was death.

Two/42 (4.8%) participants discontinued treatment due to AEs in the oleclumab monotherapy dose escalation phase; 2/24 (8.3%) participants discontinued treatment due to AEs in the oleclumab and durvalumab combination therapy dose-escalation phase, and 5/126 (4.0%) participants discontinued treatment due to AEs in the oleclumab and durvalumab combination therapy dose-expansion phase.

Summary of Efficacy Results

The majority of the participants across all groups had a best overall response of progressive disease. In the oleclumab and durvalumab combination therapy dose-expansion phase, 2/126 (1.6%) participants had a best overall response of complete response: 1/42 (2.4%) participant in the CRC cohort and 1/42 (2.4%) participant in the pancreatic adenocarcinoma cohort. Five/126 (4.0%) participants had a partial response, 4 of which were in the NSCLC cohort; and 26/126 (20.6%) participants had stable disease. The median time for progression-free-survival was 1.8 months in every group. No participant in the dose-escalation phase of the study had a response to study treatment. In the durvalumab combination therapy dose-expansion phase, the overall median duration of response was 36.2 months (range of 5.6 to 37.0 months).

Summary of Pharmacokinetic Results

Over the dose levels of 5 mg/kg to 40 mg/kg after the first IV infusion dose of oleclumab, the geometric mean PK exposures [C_{max} and $AUC_{(0-14)}$] of oleclumab appeared to increase in a

near dose proportional manner for dose-escalation phase in both oleclumab monotherapy and combination therapy with durvalumab. The geometric mean C_{trough} appeared to increase in a near dose proportional manner over the dose levels of 10 mg/kg to 40 mg/kg. Similar oleclumab PK parameters were observed when administered as both monotherapy and in combination with durvalumab, which could indicate durvalumab does not affect the PK of oleclumab.

Summary of Pharmacodynamic Results

Treatment with oleclumab and/or durvalumab had CD73 and CD8 expression consistent with mechanism of action.

Summary of Pharmacokinetic/Pharmacodynamic Relationships

Not applicable.

Summary of Pharmacogenetic Results

Not applicable.

Summary of Immunogenicity Results

One/126 participant in the dose-expansion phase had an ADA-positive, post-baseline result for oleclumab, and 2/126 participants in the dose-expansion phase had an ADA positive post-baseline result for durvalumab; none of these participants had persistent positive results. As the number of participants who had an oleclumab or durvalumab ADA-positive result at baseline were small, no meaningful analysis to determine the effect of this on immunogenicity or PK was possible. No other participant had an ADA-positive post-baseline result for oleclumab or durvalumab.

Summary of Safety Results

There were no DLTs in this study, and the MTD was not reached. Therefore, the highest dose of oleclumab used in the dose-expansion phase (oleclumab 40 mg/kg) was chosen as the recommended Phase II dose (RP2D) based on the prediction that this dose would lead to > 90% receptor occupancy of CD73 activity.

The majority of participants in the study experienced at least 1 treatment-emergent adverse event (TEAE) (95.2%, 100%, and 95.2% of participants in the oleclumab monotherapy dose-escalation phase, the oleclumab and durvalumab combination therapy dose-escalation phase, and the oleclumab and durvalumab combination therapy dose-expansion phase, respectively) and approximately half of all participants in each phase of the study experienced at least 1 treatment-related adverse event. In the monotherapy dose-escalation cohort, the most commonly reported treatment-related TEAEs were fatigue (16.7%), anaemia (9.5%), and nausea (9.5%). In the combination therapy dose-escalation cohort, the most commonly reported treatment-related TEAEs included fatigue (25.0%), nausea, vomiting, and aspartate

aminotransferase increased (12.5% each). In the dose combination dose-expansion phase, the most commonly reported treatment-related TEAEs included fatigue (15.1%), diarrhoea (8.7%), and rash (7.1%).

One participant (4.2%) in the combination therapy cohort of the dose-escalation phase experienced at least 1 serious treatment-related event, and 10 (7.9%) participants in the dose combination therapy of the dose-expansion phase experienced at least 1 serious treatment-related event. No serious treatment-related events were reported in the monotherapy cohort of the dose-escalation phase of the study.

Of the participants that died in the study, the most common cause of death was the disease under study treatment (69.0%, 75.0%, and 65.1% of participants in the oleclumab monotherapy dose-escalation phase, the oleclumab and durvalumab combination therapy dose-escalation phase, and the oleclumab and durvalumab combination therapy dose-expansion phase, respectively). No deaths in the dose-escalation phase of the study were considered to be related to study treatment. One participant in the CRC oleclumab 40 mg/kg and durvalumab 10 mg/kg cohort of the dose-expansion phase died due to an event of systemic inflammatory response syndrome, which was considered by the investigator to be related to study treatment.

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

Conclusions

- The safety profile of oleclumab alone and in combination with durvalumab was manageable and generally consistent with the underlying disease of the study population and known toxicity of the anti-PD-L1/PD-1 and anti-CD73 drug classes. A MTD was not identified. In the absence of the MTD, (oleclumab 40 mg/kg Q2W + durvalumab 10 mg/kg Q2W) was selected as the RP2D dose level for the dose-expansion phase based on the prediction that the oleclumab 40 mg/kg dose would lead to > 90% receptor occupancy of CD73 activity.
- The combination of oleclumab with durvalumab demonstrated potential clinical activity: 2 patients had complete response and five participants had partial response. Across both phases of the study, the majority of participants had a best overall response of progressive disease, with small numerical differences between the cohorts.
- Olelcumab shows linear PK at doses above or equal to 10 mg/kg Q2W, evidenced by dose proportionality of C_{trough}. Co-administration with durvalumab did not affect PK of oleclumab.
- One/126 participant in the dose-expansion phase had an ADA-positive, post-baseline result for oleclumab, which was not a persistent positive result. As the number of participants who had an oleclumab or durvalumab ADA-positive result at baseline were

small, no meaningful analysis to determine the effect of this on immunogenicity or PK was possible. No other participant had an oleclumab ADA positive result post baseline.

- Treatment with oleclumab and/or durvalumab had changes in CD73 and CD8 expression consistent with mechanism of action.