Clinical Study Report Synopsis	
Drug Substance	Oleclumab (MEDI9447)
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A Phase Ib/II Study to Evaluate the Safety, Pharmacokinetics, and Clinical Activity of Oleclumab (MEDI9447) with or without Durvalumab in Combination with Chemotherapy in Subjects with Metastatic Pancreatic Ductal Adenocarcinoma

Study dates:
First subject enrolled: 21 June 2018
Data cut-off for the final analysis: 22 July 2022
The analyses presented in this report are based on a clinical data lock date of 11 November 2022

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

Signatory Investigator:
PPD
Sarah Cannon Research Institute, 250 25th Ave N Ste 307, Nashville, TN 37203, USA

Sponsor's Responsible Medical Officer:
PPD
PPD, Early Oncology Global Development
AstraZeneca
35 Gatehouse Drive, Waltham, MA 02451, USA

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

Study Centers

The study was conducted by 29 investigators at 29 sites in 4 countries.

Publications

Coveler AL, Reilley M, Zalpski M, Macarulla T, Fountzilas C, Castanon Alvarez, et al. Safety and clinical activity of oleclumab (O) ± durvalumab (D) + chemotherapy (CT) in patients (pts) with metastatic pancreatic ductal adenocarcinoma (mPDAC): a phase 1b/2 randomized study [abstract 4136]. American Society of Clinical Oncology (ASCO) annual meeting; 2023 Jun 02-06; Chicago (IL), USA [accepted ahead of presentation].

Objectives and Endpoints

Table S1 Objectives and Endpoints

Objective	Endpoint
Primary	
Part 1 - Safety • To assess the safety and tolerability of oleclumab plus durvalumab in combination with chemotherapy administered in subjects with metastatic PDAC	• DLTs • Incidence of AEs and SAEs • Clinically meaningful changes from baseline in laboratory parameters, vital signs, and ECG results
Part 2 - Efficacy • To evaluate the preliminary antitumor activity of oleclumab with or without durvalumab in combination with gemcitabine and nab-paclitaxel compared to gemcitabine and nab-paclitaxel administered in subjects with 1L metastatic PDAC	• OR according to RECIST v1.1
Part 2 – Efficacy [a] • To evaluate the preliminary antitumor activity of oleclumab with or without durvalumab in combination with mFOLFOX compared to mFOLFOX administered in subjects with 2L metastatic PDAC	• OR according to RECIST v1.1
Secondary	
Part 2 - Safety • To assess the safety and tolerability of oleclumab with or without durvalumab in combination with chemotherapy administered in subjects with metastatic PDAC	• Incidence of AEs and SAEs • Clinically meaningful changes from baseline in clinical laboratory parameters, vital signs, and ECG results
Part 1 - Efficacy • To evaluate the preliminary antitumor activity of oleclumab plus durvalumab in combination with gemcitabine and nab-paclitaxel administered in subjects with 1L metastatic PDAC	• OR and DC according to RECIST v1.1

Table S1 Objectives and Endpoints

Objective	Endpoint
Part 1 - Efficacy • To evaluate the preliminary antitumor activity of oleclumab plus durvalumab in combination with mFOLFOX administered in subjects with 2L metastatic PDAC	• OR and DC according to RECIST v1.1
Part 2 - Efficacy • To evaluate the preliminary antitumor activity of oleclumab with or without durvalumab in combination with gemcitabine and nab-paclitaxel compared to gemcitabine and nab-paclitaxel administered in subjects with 1L metastatic PDAC	• OS • PFS, DoR, and DC according to RECIST v1.1
Part 2 – Efficacy [a] • To evaluate the preliminary antitumor activity of oleclumab with or without durvalumab in combination with mFOLFOX compared to mFOLFOX administered in subjects with 2L metastatic PDAC	• OS • PFS, DoR, and DC according to RECIST v1.1
Part 2 - Efficacy • To evaluate the preliminary antitumor activity of oleclumab with or without durvalumab in combination with chemotherapy compared to chemotherapy alone in the population defined by CD73 expression	• OS • OR and PFS according to RECIST v1.1 by CD73 expression at baseline
Parts 1 and 2 - Immunogenicity • To assess the immunogenicity of oleclumab and durvalumab in combination with chemotherapy administered in subjects with metastatic PDAC	• Development of detectable ADAs following oleclumab and durvalumab
Parts 1 and 2 - Pharmacokinetics • To determine the PK profile of oleclumab and durvalumab in combination with chemotherapy administered in subjects with metastatic PDAC	• Summary PK for oleclumab, durvalumab, and selected chemotherapies and/or their metabolites

[a] Results for this endpoint are not reported in this CSR as enrollment for Cohort B Part 2 was not opened.

Not all planned exploratory endpoints are reported in this CSR. For the exploratory objectives and endpoints, see Section 2.1.2 of the CSP in Appendix 16.1.1.

1L = first line; 2L = second line; ADA = anti-drug antibody; AE = adverse event; CD73 = cluster of differentiation 73; CSR = clinical study report; DC = disease control; DLT = dose-limiting toxicity; DoR = duration of response; ECG = electrocardiogram; mFOLFOX = modified regimen of leucovorin, 5-fluorouracil, and oxaliplatin; OR = objective response; OS = overall survival; PDAC = pancreatic ductal adenocarcinoma; PFS = progression-free survival; PK = pharmacokinetic(s); RECIST v1.1 = Response Evaluation Criteria in Solid Tumors version 1.1; SAE = serious adverse event;.

Study Design

This was a Phase Ib/II, multicenter, open-label, dose-escalation and dose-expansion study to assess the safety, preliminary antitumor activity, immunogenicity, and pharmacokinetics (PK) of oleclumab with or without durvalumab in combination with chemotherapy administered in subjects with metastatic pancreatic ductal adenocarcinoma (PDAC). Subjects with previously untreated metastatic PDAC (first line [1L] metastatic PDAC) were enrolled in Cohort A. Subjects with metastatic PDAC previously treated with gemcitabine-based chemotherapy (without exposure to 5-fluorouracil [5-FU], capecitabine, or oxaliplatin; second line [2L] metastatic PDAC) were enrolled in Cohort B. The study consisted of 2 parts, dose escalation (Part 1) and dose expansion (Part 2). All subjects in both cohorts were treated until disease progression, intolerable toxicity, withdrawal of subject consent, or another discontinuation criterion was met.

Planned enrollment for subjects in each cohort in Part 1 was to one of 3 dose levels for oleclumab; however, only 2 of the dose levels were enrolled in each cohort. The following treatment regimens were used:

- Dose 1: Oleclumab 1500 mg intravenously (IV) every 2 weeks (Q2W) × 4 then every 4 weeks (Q4W) and durvalumab 1500 mg IV Q4W (with gemcitabine 1000 mg/m^2 IV + nab-paclitaxel 125 mg/m^2 IV on Days 1, 8, and 15 and then repeated on a Q4W schedule in Cohort A, with modified regimen of leucovorin 400 mg/m^2 IV, 5-FU 400 mg/m^2 IV bolus, and oxaliplatin 85 mg/m^2 IV [mFOLFOX] on Days 1 and 15 and then repeated on a Q4W schedule in Cohort B)
- Dose 2: Oleclumab 3000 mg IV Q2W × 4 then Q4W and durvalumab 1500 mg IV Q4W (with gemcitabine 1000 mg/m^2 IV + nab-paclitaxel 125 mg/m^2 IV on Days 1, 8, and 15 and then repeated on a Q4W schedule in Cohort A, with mFOLFOX at same doses as Dose 1 group, on Days 1 and 15 and then repeated on a Q4W schedule in Cohort B)

During Part 2 (dose expansion), the recommended Phase II dose of oleclumab identified in Part 1 for each regimen was evaluated with or without durvalumab in combination with chemotherapy. Subjects enrolled in Part 2 were stratified according to tumoral expression of cluster of differentiation 73 (CD73) by immunohistochemistry and randomized to a treatment arm.

Subjects in Cohort A (1L metastatic PDAC) were randomized 1:1:1 to one of 3 treatment arms: gemcitabine and nab-paclitaxel (Arm A1); oleclumab + gemcitabine and nab-paclitaxel (Arm A2); or oleclumab + durvalumab + gemcitabine and nab-paclitaxel (Arm A3). Subjects in Cohort B (2L metastatic PDAC) were planned to be randomized 1:1:1 to one of 3 treatment arms: mFOLFOX (Arm B1); oleclumab + mFOLFOX (Arm B2); or oleclumab + durvalumab + mFOLFOX (Arm B3); however, AstraZeneca decided not to open enrollment to Cohort B in Part 2. There was no crossover between treatment arms.

Target Population and Sample Size

The target population were male or female subjects ≥ 18 years of age diagnosed with histologically or cytologically confirmed metastatic PDAC. Subjects in Cohort A had received no previous anticancer therapy for metastatic disease, and subjects in Cohort B had previously been treated with a gemcitabine-based therapy.

It was planned for up to approximately 339 subjects to be enrolled in this study; in Part 1, up to 24 subjects were planned to be enrolled (dose escalation; approximately 9 to 12 subjects in each of Cohort A and Cohort B), and in Part 2 (dose expansion), up to approximately 315 subjects were planned to be enrolled as follows:

- Up to approximately 210 subjects in Cohort A (approximately 70 subjects per treatment arm)
- Up to approximately 105 subjects in Cohort B (approximately 35 subjects per treatment arm)

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

Oleclumab (MEDI9447; investigational medicinal product [IMP] lot numbers CCI , CCI , CCI , CCI , CCI) was administered via IV infusion at doses of 1500 mg or 3000 mg, and durvalumab (IMP lot numbers CCI , CCI , CCI , CCI , CCI) was administered IV at a dose of 1500 mg. All chemotherapy drugs were administered IV; gemcitabine was administered at a dose of 1000 mg/m^2, nab-paclitaxel was administered at a dose of 125 mg/m^2, oxaliplatin was administered at a dose of 85 mg/m^2, leucovorin was administered at a dose of 400 mg/m^2, 5-FU was administered via IV bolus at 400 mg/m^2, followed by 2400 mg/m^2 administered via continuous IV infusion over 46 to 48 hours.

Duration of Treatment

The duration of treatment was to be until disease progression per Response Evaluated Criteria in Solid Tumors version 1.1 (RECIST v1.1), withdrawal, or until continued treatment was unfeasible. Any study subject still receiving investigational product (IP) at the time of data cut-off was able to continue receiving IP within the current study through a continued treatment period after data cut-off for analysis of final study data as long as, in the Investigator's opinion, the study subject was deriving clinical benefit and had not fulfilled any treatment discontinuation criteria. Subjects were able to continue receiving IP after progressive disease (PD) as long as, in the Investigator's opinion, the study subject was still deriving clinical benefit and there was no significant, unacceptable, or irreversible toxicity related to continuing treatment.

Statistical Methods

Efficacy

The efficacy analyses of antitumor activity were based on the intent-to-treat (ITT) population (defined as all subjects who were randomized and receive any amount of IP, analyzed according to randomized treatment assignment) in Part 2 (dose expansion) and on the as-treated population in Part 1 (dose escalation). The rates of objective response (OR) and disease control (DC) based on RECIST v1.1 were summarized with 95% confidence intervals (CIs) based on the exact binomial distribution. The objective response rate (ORR) was estimated by the proportion of OR, and its 80% and 95% CIs were estimated using the exact binomial distribution. Comparison of treatment arms for ORR was obtained from Cochran-Mantel-Haenszel test stratified by CD73 level.

Time-to-event endpoints (duration of response [DoR], progression-free survival [PFS], and overall survival [OS]) were analyzed using the Kaplan-Meier method. Comparison of treatment arms for PFS and OS were obtained from the log-rank test and the hazard ratio (HR) and 95% CI was estimated by a Cox regression model; both of which were stratified by CD73 level.

Analysis of OR, PFS, and OS by CD73 levels at baseline was also performed via Fisher's exact test (for OR analysis) and Cox proportional hazards model (for PFS and OS).

Some analyses of antitumor activity were conducted in the as-treated population (defined as all subjects who receive any investigational product analyzed according to treatment received) for the dose-escalation phase.

Safety

The safety analyses were performed on the as-treated population. Summaries were provided for adverse events (AEs), serious adverse events (SAEs), AE grade (severity), and relationship to IPs, clinical laboratory parameters, vital signs, electrocardiogram results, and Eastern Cooperative Oncology Group (ECOG) performance status. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03 (NCI CTCAE v4.03). Laboratory abnormalities were graded according to the NCI CTCAE v4.03, if applicable.

Pharmacokinetics

The PK analyses were performed on the PK-evaluable populations for oleclumab, durvalumab, gemcitabine, and nab-paclitaxel (defined as all subjects who received at least one dose of treatment with at least one reportable PK concentration). Serum concentrations of oleclumab and durvalumab, and plasma concentrations of gemcitabine and nab-paclitaxel for each scheduled time-point were summarized for each visit/time point and dose level or treatment arm.

Non-compartmental PK data analysis were planned to be performed from each dose cohort if data allowed, but as sparse PK samples were collected, no non-compartmental PK parameters were calculated.

Immunogenicity

The immunogenicity analyses were performed on the antidrug antibody (ADA)-evaluable populations for oleclumab and durvalumab (defined as all subjects in the safety analysis set who had a non-missing baseline ADA result and at least one non-missing post-baseline ADA result). There were ADA-evaluable populations for both oleclumab and durvalumab. Descriptive statistics were provided for ADA-positive results at baseline or post baseline visits, the incidence of ADA, and subject ADA status.

Interim Analysis

An interim analysis was performed when approximately 30 subjects in each treatment arm of Cohort A Part 2 had been dosed and reached the data cut-off criteria (ie, subjects who had a baseline disease assessment, had been dosed at least 16 weeks prior to the time of the data cut-off, and had at least one post-baseline disease assessment and/or discontinued treatment due to death or disease progression). Randomization was allowed to be paused during the interim analysis before the decision was made. If the futility criteria were met for an experimental arm, further enrollment to that arm was be stopped.

Study Population

The first subject was enrolled onto the study on 21 June 2018 and the data cut-off date for the final analysis was on 22 July 2022. The results presented in this synopsis are based on a clinical data lock date of 11 November 2022.

Cohort A Part 1

In Cohort A Part 1, a total of 14 subjects received treatment: 7 subjects in the Dose 1 group (oleclumab 1500 mg) and 7 subjects in the Dose 2 group (oleclumab 3000 mg). All subjects discontinued chemotherapy and immunotherapy, and at the end of the study all subjects had died.

The enrolled subjects generally reflected the 1L metastatic PDAC population and were considered appropriate to achieve the study objectives.

There were no concerns with regard to study conduct or potential effect upon the overall interpretation of the study data based on the frequency and type of important protocol deviations.

Cohort A Part 2

In Cohort A Part 2, a total of 188 subjects were randomized: 75 subjects to Arm A1, 38 subjects to Arm A2, and 75 subjects to Arm A3. Of these, 62 subjects received treatment in

Arm A1, all 38 subjects received treatment in Arm A2, and 70 subjects received treatment in Arm A3. At the time of final data cut-off, most subjects had discontinued chemotherapy and immunotherapy, with the exception of 2 subjects ongoing chemotherapy in Arm A1, 1 subject ongoing chemotherapy and 2 subjects ongoing immunotherapy in Arm A2, and 6 subjects ongoing each of chemotherapy and immunotherapy in Arm A3.

In the CD73 low subgroup, there were 16 subjects in Arm A1, 11 subjects in Arm A2, and 19 subjects in Arm A3 randomized and treated. In the CD73 high subgroup, there were 46 subjects in Arm A1, 27 subjects in Arm A2, and 51 subjects in Arm A3 randomized and treated.

The enrolled subjects generally reflected the 1L metastatic PDAC population and were considered appropriate to achieve the study objectives.

There were no concerns with regard to study conduct or potential effect upon the overall interpretation of the study data based on the frequency and type of important protocol deviations.

The randomized treatment arms were generally well balanced with respect to demographic and prior therapy characteristics, but there were some differences at baseline in disease characteristics which were not considered to have an effect on interpretation of treatment prognosis (time from initial diagnosis, T4 tumor stage, N0 and N1 node stage, and carbohydrate antigen 19-9 [CA19-9] value). Generally, concomitant medication use appeared fairly balanced across the 3 treatment arms, as was the proportion of subjects having any regimen of subsequent anticancer treatment.

Cohort B Part 1

In Cohort B Part 1, a total of 11 subjects received treatment: 3 subjects in the Dose 1 group (oleclumab 1500 mg) and 8 subjects in the Dose 2 group (oleclumab 3000 mg). All subjects discontinued chemotherapy and immunotherapy, and at the end of the study all subjects had died.

The enrolled subjects generally reflected the 2L metastatic PDAC population and were considered appropriate to achieve the study objectives.

There were no concerns with regard to study conduct or potential effect upon the overall interpretation of the study data based on the frequency and type of important protocol deviations.

Summary of Efficacy Results

Cohort A Part 1

One (14.3%) subject in the Dose 2 group had a confirmed OR. Three (42.9%) subjects had DC in the Dose 1 group and 5 (71.4%) subjects had DC in the Dose 2 group.

Cohort A Part 2

In the ITT population, 18 (29.0%) subjects in Arm A1, 8 (21.1%) subjects in Arm A2, and 23 (32.9%) subjects in Arm A3 had an OR. The OR rate difference between Arm A3 and Arm A1 was 3.8% and this was not statistically significant (95% CI: [-13.2%, 20.7%]; p = 0.6503). The one-sided 90% CI was -7.4% and one sided p = 0.3252. There was a lower proportion of subjects with confirmed OR in Arm A2 compared with Arm A1.

The lack of effect on OR between the treatment arms was consistent in the CD73 high population with 16 (31.4%) subjects having a confirmed OR in Arm A3, and 11 (23.9%) subjects having a confirmed OR in Arm A1 (rate difference 7.5%; 95% CI: [-12.6%, 27.0%]).

The proportion of subjects with DC was 41 (66.1%) subjects in Arm A1, 28 (73.7%) subjects in Arm A2, and 53 (75.7%) subjects in Arm A3. The rate difference between Arm A3 and Arm A1 was 9.6% (95% CI: -7.5%, 26.3%). This was not considered a meaningful difference.

There were 132 deaths from 170 subjects. The median OS for Arm A3 (12.9 months) was longer than that for Arm A1 (10.8 months), and the Kaplan-Meier curve showed better OS for Arm A3, but the difference in OS between the 2 treatment arms was not statistically significant (HR = 0.750; 95% CI: [0.498, 1.131]). The median OS for Arm A2 (8.9 months) was shorter than that for Arm A1 and although the Kaplan-Meier curve for Arm A2 looked slightly worse than that for Arm A1 this difference was not perceived as being meaningful. In the CD73 high population, the median OS for Arm A3 (12.1 months) was longer than that for Arm A1 (9.9 months) and there was a statistically significant effect in favor of Arm A3 compared with that in Arm A1 in OS (HR = 0.605, 95% CI: [0.377, 0.968]); indicating a 39% reduction in risk of death in Arm A3 compared with that in Arm A1 over the study period. The median OS for Arm A2 was shorter than that for Arm A1.

There were 126 PFS events from 170 subjects. In the ITT population, the median PFS for Arm A3 (7.5 months) was longer than that for Arm A1 (6.7 months), and the Kaplan-Meier curve showed better PFS for Arm A3, but the difference in PFS between the 2 treatment arms was not statistically significant (HR = 0.719; 95% CI: [0.468, 1.105]). The median PFS for Arm A2 (5.6 months) was shorter than that for Arm A1 and although the Kaplan-Meier curve for Arm A2 looked slightly worse than that for Arm A1, this difference was not perceived as being meaningful. Although the median PFS was similar for subjects with high CD73 levels between Arm A3 (5.5 months) and Arm A1 (5.6 months), the analysis showed a statistically

significant improvement in PFS HR (0.598; 95% CI: [0.366, 0.973]; p = 0.0385), indicating a 40% reduction in progression or death in Arm A3 compared with Arm A1 over the study period.

Both the OS and PFS results in the subjects with high CD73 levels should be interpreted with caution due to the wide CIs, which reflect the small number of subjects and the fact that the study was not powered for these analyses. It was found that there was a difference between Arm A3 and Arm A1 for subjects who contributed to the first interim analysis, but no difference between the treatment arms from the subjects enrolled after the first interim analysis. This can be attributed to the fact that the subjects in Arm A1 in with high CD73 levels who contributed to the first interim analysis had poorer results than expected.

The median DoR was longer for Arm A3 (9.5 months) and Arm A2 (12.9 months) than that for Arm A1 (7.2 months). The CD73 status did not appear to have a predictive value for response to chemotherapy in this subject population.

Cohort B Part 1

One (12.5%) subject in the Dose 2 group had a confirmed OR. Two (66.7%) subjects had DC in the Dose 1 group and 5 (62.5%) subjects had DC in the Dose 2 group.

Summary of Pharmacokinetic and Immunogenicity Results

Cohort A Part 1

In the Dose 1 group, oleclumab serum concentration geometric mean (geomean) (geometric coefficient of variation [geoCV%]) was 128.8.6 (10.00) µg/mL on Cycle 3 Day 1 pre-dose. Summary statistics were not calculated at Cycle 1 Day 1 pre-dose and Cycle 5 Day 1 pre-dose due to low numbers of available PK samples. In the Dose 2 group, oleclumab serum concentration geomean (geoCV%) was 211.5 (73.40) µg/mL at Cycle 3 Day 1 pre-dose and 73.19 (130.2) µg/mL at Cycle 5 Day 1 pre-dose. Summary statistics were not calculated at Cycle 1 Day 1 pre-dose due to low numbers of available PK samples.

In the Dose 1 group, durvalumab serum concentration geomean (geoCV%) was 35.97 (51.44) µg/mL at Cycle 2 Day 1 pre-dose. Summary statistics were not calculated at Cycle 1 Day 1 pre-dose and Cycle 5 Day 1 pre-dose due to low numbers of available PK samples. In the Dose 2 group, durvalumab serum concentration geomean (geoCV%) was 14.39 (5129) µg/mL at Cycle 2 Day 1 pre-dose and 74.52 (28.32) µg/mL at Cycle 5 Day 1 pre-dose. Summary statistics were not calculated at Cycle 1 Day 1 pre-dose due to low numbers of available PK samples.

Out of the 13 subjects who were ADA evaluable for oleclumab, one subject was ADA positive at post baseline only in the Dose 1 group. One out of the 13 subjects who were ADA evaluable for durvalumab developed positive ADA at post baseline only in the Dose 1 group.

Cohort A Part 2

In Arm A2, oleclumab serum concentration geomean (geoCV%) was 164.8 (324.1) µg/mL at Cycle 3 Day 1 pre-dose and 85.99 (192.0) µg/mL at Cycle 5 Day 1 pre-dose. In Arm A3, oleclumab serum concentration geomean (geoCV%) was 226.8 (70.41) µg/mL at Cycle 3 Day 1 pre-dose and 116.4 (54.00) µg/mL at Cycle 5 Day 1 pre-dose. There were no marked differences in oleclumab serum concentrations between Arm A2 and Arm A3, indicating that combination with durvalumab did not affect the PK of oleclumab.

In Arm A3, durvalumab serum concentration geomean (geoCV%) was 86.20 (97.95) µg/mL at Cycle 2 Day 1 pre-dose and 137.9 (48.85) µg/mL at Cycle 5 Day 1 pre-dose.

One out of 31 oleclumab ADA-evaluable subjects in Arm A2 developed positive ADA at post baseline only. Two out of 60 durvalumab ADA-evaluable subjects in Arm A3 developed a positive ADA result to durvalumab and both were positive at baseline only.

Cohort B Part 1

In the Dose 1 group, oleclumab serum concentration geomean (geoCV%) was 134.3 (141.5) µg/mL at Cycle 3 Day 1 pre-dose. Summary statistics were not calculated at Cycle 1 Day 1 pre-dose and Cycle 5 Day 1 pre-dose due to low numbers of available PK samples. In the Dose 2 group, oleclumab serum concentration geomean (geoCV%) was 368.9 (2.461) µg/mL at Cycle 3 Day 1 pre-dose and 235.7 (27.68) µg/mL at Cycle 5 Day 1 pre-dose. Summary statistics were not calculated at Cycle 1 Day 1 pre-dose due to low numbers of available PK samples.

In the Dose 1 group, durvalumab serum concentration geomean (geoCV%) was 50.52 (57.30) µg/mL at Cycle 2 Day 1 pre-dose. Summary statistics were not calculated at Cycle 1 Day 1 pre-dose due to low numbers of available PK samples, and summary statistics were not applicable at Cycle 5 Day 1 due to no subjects in the PK evaluable durvalumab population. In the Dose 2 group, durvalumab serum concentration geomean (geoCV%) was 0.0777 (75.01) µg/mL at Cycle 1 Day 1 pre-dose, 59.97 (176.7) µg/mL at Cycle 2 Day 1 pre-dose and 175.9 (43.50) µg/mL at Cycle 5 Day 1 pre-dose.

Out of the 10 subjects who were ADA evaluable for oleclumab, one subject was ADA positive at post baseline only in the Dose 2 group. Two out of 10 durvalumab ADA-evaluable subjects were ADA positive post baseline, both in the Dose 2 group.

Summary of Safety Results

Cohort A Part 1

The median (minimum [min], maximum [max]) duration of exposure to oleclumab and durvalumab in the Dose 1 group was 8.00 (2.0, 40.1) weeks for both treatments. In the Dose 2 group, the median (min, max) duration of exposure to oleclumab and durvalumab was 19.70 (2.0, 42.0) weeks for both treatments.

All subjects had at least one AE and one treatment-related AE, and most subjects had at least one AE of Grade ≥ 3 severity and/or at least one SAE (5 [57.1%] subjects in the Dose 1 group and 7 [100%] subjects in the Dose 2 group). The number of deaths due to AEs and AEs leading to discontinuation of study drug were low in proportion to total AEs (deaths: one [14.3%] subject in the Dose 1 group; discontinuation AEs: one [14.3%] subject in the Dose 1 group and 2 [28.6%] subjects in the Dose 2 group).

The most common AEs (≥ 80% total subjects) were fatigue and nausea (fatigue: 6 [85.7%] subjects in the Dose 1 group and 7 [100%] subjects in the Dose 2 group; nausea: 6 [85.7%] subjects in the Dose 1 group and 6 [85.7%] subjects in the Dose 2 group).

In the Dose 1 group, 5 (71.4%) subjects experienced an adverse event of special interest (AESI) for oleclumab. Four (57.1%) subjects experienced a treatment-related AESI in the category microvascular capillary permeability. Three (42.9%) subjects experienced an AESI for oleclumab in the AESI category thromboembolic events (none were treatment related). In the Dose 2 group, 4 (57.1%) subjects experienced an AESI for oleclumab. Three (42.9%) subjects experienced an AESI in the category microvascular capillary permeability (of which one [14.3%] subject had a treatment-related AESI). Three (42.9%) subjects experienced an AESI for oleclumab in the AESI category thromboembolic events (of which one [14.3%] subject had a treatment-related AESI).

All (14 [100%]) subjects in Cohort A Part 1 died. The majority (13 [92.9%] subjects) of deaths reported were related to the disease under investigation.

Over half the subjects (4 [57.1%]) in Dose 1 group had a treatment-emergent SAE. The majority of subjects (6 [85.7%]) in Dose 2 group had a treatment-emergent SAE. No SAEs were reported in more than 2 subjects.

Adverse events leading to discontinuation of study treatment were pneumonia (one [14.3%] subject) in the Dose 1 group and alanine aminotransferase increased, aspartate aminotransferase increased, blood creatinine increased, and renal failure (one [14.3%] subject each) in the Dose 2 group.

Generally, changes in hematology and clinical chemistry were not considered clinically significant.

There were no concerning safety signals noted in Part 1, and no subjects experienced a dose-limiting toxicity (DLT). The safety profile of oleclumab in combination with durvalumab was considered appropriate to proceed to dose expansion in this patient population.

Cohort A Part 2

In Arm A3, the duration of exposure to durvalumab (median [min, max]: 25.80 [2.3, 120.0]) was the same as that to oleclumab (median [min, max]: 25.80 [2.0, 120.0]). The duration of exposure to oleclumab was similar on Arm A2 (median [min, max]: 24.00 [2.0, 164.1]) compared with that on Arm A3, suggesting that combination of durvalumab with oleclumab did not reduce the planned administration of oleclumab.

Almost every subject experienced an AE (62 [100%] subjects in Arm A1, 37 [97.4%] subjects in Arm A2, and 70 [100%] subjects in Arm A3). Most subjects experienced treatment-related AEs, and the proportion of subjects who experienced treatment-related AEs was similar in all arms (59 [95.2%] subjects in Arm A1, 37 [97.4%] subjects in Arm A2, and 69 [98.6%] subjects in Arm A3). Additionally, most subjects experienced AEs that were serious and/or of ≥ Grade 3 severity, and the proportion of subjects who experienced serious and/or ≥ Grade 3 severity AEs was similar in all treatment arms (53 [85.5%] subjects in Arm A1, 34 [89.5%] subjects in Arm A2, and 63 [90.0%] subjects in Arm A3).

The most common AEs (≥ 40% total subjects) were nausea, fatigue, and diarrhoea, all of which were reported by more subjects in Arm A3 than Arm A1 (nausea: 29 [46.8%] subjects in Arm A1, 26 [68.4%] subjects in Arm A2, and 41 [58.6%] subjects in Arm A3; fatigue: 30 [48.4%] subjects in Arm A1, 25 [65.8%] subjects in Arm A2, and 41 [58.6%] subjects in Arm A3; diarrhoea: 20 [32.2%] subjects in Arm A1, 14 [36.8%] subjects in Arm A2, and 38 [54.3%] subjects in Arm A3). Anaemia, diarrhoea, alopecia, pruritus, rash, back pain, and hypertension were experienced by a greater proportion (> 10% difference between arms) of subjects in Arm A3 compared with those in Arm A1. Constipation, nausea, fatigue, oedema peripheral, and myalgia were experienced by a greater proportion (> 10% difference between arms) of subjects in both Arm A3 and Arm A2 compared with those in Arm A1.

The proportion of subjects with AESIs for oleclumab was greater in Arm A2 (25 [65.8%] subjects) and Arm A3 (43 [61.4%] subjects) than Arm A1 (23 [37.1%] subjects). The most commonly reported AESI categories (≥ 20% total subjects) were microvascular capillary permeability (16 [25.8%] subjects in Arm A1, 16 [42.1%] subjects in Arm A2, and 34 [48.6%] subjects in Arm A3) and thromboembolic events (12 [19.4%] subjects in Arm A1, 9 [23.7%] subjects in Arm A2, and 17 [24.3%] subjects in Arm A3).

The majority (122 [71.8%] subjects) of deaths reported were related to the disease under investigation. A low proportion of subjects in each arm experienced AEs leading to death, and there were no notable differences in AEs with outcome of death between the treatment arms.

A similar proportion of subjects experienced SAEs in Arm A3 (37 [52.9%] subjects) and Arm A1 (34 [54.8%] subjects), and there appeared to be slightly more subjects who experienced SAEs in Arm A2 (24 [63.2%] subjects) than Arm A1. The most common SAE was pyrexia (5 [8.1%] subjects in Arm A1, 3 [7.9%] subjects in Arm A2, and 8 [11.4%]

subjects in Arm A3). Treatment-related SAEs were experienced by a similar proportion of subjects in all 3 treatment arms.

Adverse events leading to discontinuation of study treatment were experienced in a greater proportion of subjects in Arm A3 (17 [24.3%] subjects) and Arm A2 (9 [23.7%] subjects) than in Arm A1 (7 [11.3%] subjects). Peripheral sensory neuropathy and oedema peripheral were amongst the preferred terms (PTs) driving this difference.

Generally, there did not appear to be any notable differences in hematology or clinical chemistry parameter toxicity grades between the 3 treatment arms, but there were more subjects with alanine aminotransferase ≥ 3 × upper limit of normal (ULN) or aspartate aminotransferase ≥ 3 × ULN and total bilirubin ≥ 2 × ULN in Arm A3 (9 [12.9%] subjects) than Arm A1 (5 [8.1%] subjects). A greater proportion of subjects experienced a new > 450 msec single beat value for QT interval corrected for heart rate by Fridericia's formula (QTcF) in Arm A3 (10 [14.7%] subjects) than in Arm A2 (3 [8.1%] subjects) and in Arm A1 (3 [5.0%] subjects).

Cohort B Part 1

The median (min, max) duration of exposure to oleclumab and durvalumab in the Dose 1 group was 16.00 (10.4, 16.0) weeks for both treatments. In the Dose 2 group, the median (min, max) duration of exposure to oleclumab and durvalumab was 15.55 (5.9, 57.7) weeks and 15.15 (7.9, 57.7) weeks, respectively.

All subjects had at least one AE and one treatment-related AE, and most had at least one AE of Grade ≥ 3 severity and/or at least one SAE (all subjects in the Dose 1 group and 6 [75.0%] subjects in the Dose 2 group). The number of deaths due to AEs and AEs leading to discontinuation of study drug were low in proportion to total AEs (no deaths due to AEs; discontinuation AEs: no subjects in the Dose 1 group and 3 [37.5%] subjects in the Dose 2 group).

The most commonly reported (≥ 50% total subjects) AEs were fatigue (2 [66.7%] and 6 [75.0%] subjects in the Dose 1 and Dose 2 group, respectively), nausea (2 [66.7%] and 5 [62.5%] subjects in the Dose 1 and Dose 2 group, respectively), and diarrhoea (one [33.3%] and 5 [62.5%] subjects in the Dose 1 and Dose 2 group, respectively).

In the Dose 1 group, one (33.3%) subject experienced an AESI for oleclumab in the AESI category microvascular capillary permeability. In the Dose 2 group, 4 (50.0%) subjects experienced an AESI for oleclumab. Two (25.0%) subjects experienced an AESI for oleclumab in the AESI category infusion related/hypersensitivity/anaphylactic reaction (both of which had treatment related AESIs), and 3 (37.5%) subjects reported an AESI for oleclumab in the AESI category microvascular capillary permeability (one [12.5%] subject having treatment-related AESIs of localised oedema and oedema peripheral).

All (11 [100%] subjects) deaths reported in Cohort B during Part 1 of the study were related to the disease under investigation.

No SAEs were reported in the Dose 1 group. At the PT level, the reported SAEs in the Dose 2 group were nausea (2 [25.0%] subjects), and vomiting, localised oedema, bacterial infection, biliary tract infection, and failure to thrive (one [12.5%] subject each).

In the Dose 1 group, there were no AEs leading to discontinuation of study treatment. In the Dose 2 group, AEs leading to discontinuation of study treatment were infusion related reaction, platelet count decreased, and neuropathy peripheral (one [12.5%] subject for each PT).

Generally, changes in hematology and clinical chemistry were not considered clinically significant.

There were no concerning safety signals noted in Part 1. One subject experienced a DLT in the Dose 2 group due to a Grade 3 localised oedema and Grade 3 nausea. The safety profile of oleclumab in combination with durvalumab was considered appropriate to begin dose expansion in this patient population if the decision had been to proceed.

Conclusions

- Overall, the safety profile of oleclumab in combination with durvalumab and chemotherapy was consistent with the known safety profiles of the oleclumab, durvalumab, and chemotherapy components in this study. The safety profile would not preclude further development of these combinations.
- The study did not meet its primary efficacy objective to demonstrate a statistically significant improvement in OR when comparing oleclumab in combination with durvalumab and chemotherapy with chemotherapy alone (OR difference 3.8%; 95% CI [-13.2%, 20.7%]; 90% one-sided confidence limit = -7.4; one-sided p = 0.3252).
  - Any difference in OR that was observed was driven by those subjects with high levels of CD73, but, similarly, no significant improvement in terms of OR was observed in that subset of subjects.
  - There was no statistically significant difference in PFS in the overall population (PFS HR 0.719; 95% CI [0.467, 1.105]; p = 0.1307; median 7.5 months in Arm A3 vs 6.7 months in Arm A1), but the CD73 high subgroup did show a statistically significant benefit (PFS HR 0.598; 95% CI [0.366, 0.973]; p = 0.0385; median 5.5 months in Arm A3 vs 5.6 months in Arm A1).
  - Likewise, there was no statistically significant difference in OS in the overall population (OS HR 0.750; 95% CI [0.498, 1.131]; p = 0.1673; median 12.9 months in Arm A3 vs 10.8 months in Arm A1). In the subjects with high CD73 levels, there was a statistically significant benefit (OS HR 0.605; 95% CI [0.377, 0.968];

p = 0.0360; median 12.1 months in Arm A3 vs 9.9 months in Arm A1); however, these results should be interpreted with caution due to the wide CIs, which reflect the small number of subjects and that the study was not powered for this analysis.
For OR, PFS, and OS it was found that there was a difference between Arm A3 and Arm A1 (driven by the subjects in the CD73 high subgroup) for subjects who contributed to the first interim analysis, but no difference between the treatment arms from the subjects enrolled after the first interim analysis. This can be attributed to the fact that the subjects in Arm A1 in the CD73 high subgroup who contributed to the first interim analysis had poorer results than expected. Consequently any statistically significant results observed in this study are not likely to reflect the population as a whole.

- There were no marked differences in oleclumab serum concentrations between Arm A2 and Arm A3, indicating that combination with durvalumab did not affect the PK of oleclumab.
- Development of ADAs to oleclumab and durvalumab was low.