A Phase 1b/2 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

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Durvalumab

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PROTOCOL SYNOPSIS

TITLE

A Phase 1b/2 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

HYPOTHESIS

The combination of oleclumab (anti-cluster of differentiation [CD]73) with or without durvalumab (anti-programmed cell death ligand-1 [PD-L1]) plus chemotherapy will demonstrate adequate safety, tolerability, and antitumor activity in subjects with metastatic pancreatic ductal adenocarcinoma (PDAC) that has been previously untreated or has progressed following gemcitabine-based chemotherapy.

OBJECTIVES AND STUDY ENDPOINTS

Primary objectives and endpoints:

Part 1 (Dose Escalation)

- To assess the safety and tolerability of oleclumab plus durvalumab in combination with chemotherapy administered in subjects with metastatic PDAC
  - Dose-limiting toxicities (DLTs), incidence of adverse events (AEs) and serious adverse events (SAEs), and clinically meaningful changes from baseline in clinical laboratory parameters, vital signs, and electrocardiogram (ECG) results

Part 2 (Dose Expansion)

- 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 first-line (1L) metastatic PDAC
  - Objective response (OR) according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 (v1.1)
- To evaluate the preliminary antitumor activity of oleclumab with or without durvalumab in combination with a modified regimen of leucovorin, 5-fluorouracil (5-FU) and oxaliplatin (mFOLFOX) compared to mFOLFOX administered in subjects with second-line (2L) metastatic PDAC
  - OR according to RECIST v1.1

Secondary objectives and endpoints:

Part 1 (Dose Escalation)

- 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 disease control (DC) according to RECIST v1.1
- 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 (Dose Expansion)

- 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 and clinically meaningful changes from baseline in clinical laboratory parameters, vital signs, and ECG results
- 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

- Overall survival (OS); progression-free survival (PFS), duration of response (DoR), and DC according to RECIST v1.1

- 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
- 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

Part 1 (Dose Escalation) and Part 2 (Dose Expansion)

- To assess the immunogenicity of oleclumab and durvalumab in combination with chemotherapy administered in subjects with metastatic PDAC
  - Development of detectable anti-drug antibodies (ADAs) following oleclumab and durvalumab
- To determine the pharmacokinetic (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

Exploratory objectives and endpoints:

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STUDY DESIGN

This is a Phase 1b/2, multicenter, open-label, dose-escalation and dose-expansion study to assess the safety, preliminary antitumor activity, immunogenicity, and PK of oleclumab with or without durvalumab in combination with chemotherapy administered in subjects with metastatic PDAC. Subjects with previously untreated metastatic PDAC (1L metastatic PDAC) will be enrolled in Cohort A. Subjects with metastatic PDAC previously treated with gemcitabine-based chemotherapy (without exposure to 5-FU, capecitabine, or oxaliplatin; 2L metastatic PDAC) will be enrolled in Cohort B. The study consists of 2 parts, dose escalation (Part 1) and dose expansion (Part 2).

Part 1 (Dose Escalation)

During Part 1, dose escalation of oleclumab will be performed in combination with durvalumab and chemotherapy (gemcitabine + nab-paclitaxel for subjects with 1L metastatic PDAC [Cohort A]; mFOLFOX for subjects with 2L metastatic PDAC [Cohort B]) to determine either the maximum tolerated dose (MTD) or the highest protocol-defined dose for each regimen. Subjects will be enrolled in cohorts to be treated with increasing dose levels of oleclumab with the potential to be treated at a lower dose level. A single dose level for durvalumab and chemotherapy will be used in combination with oleclumab. The Dose-escalation Committee will monitor subjects for DLTs during the 28-day DLT-evaluation period and will make decisions for enrollment of additional subjects at a dose level, dose escalation to the next dose level, or dose de-escalation. Dose escalation will begin with enrollment of at least 3 subjects (and up to 6 subjects) at Dose Level 1. If no DLTs are observed in a cohort of 3 to 6 evaluable subjects, then dose escalation to the next higher dose cohort will be permitted after review of all available safety data. If 1 subject in a dose-level cohort of 3 or more evaluable subjects experiences a DLT, that dose-level cohort will be expanded to a total of 6 subjects. If no more than 1 of 6 subjects in the dose-level cohort experiences a DLT, dose escalation will continue to the next higher dose-level cohort. If ≥ 2 subjects in a dose-level cohort experience a DLT, the MTD will be exceeded and no further subjects will be enrolled into that dose-level cohort. If this occurs, the preceding dose-level cohort will be evaluated for the MTD and a total of 6 subjects will be treated at the preceding dose level if not already expanded. If ≤ 1 of 6 subjects experiences a DLT at the preceding dose level, then this dose level will be the MTD. If the MTD is exceeded at the starting dose level, then a lower dose level of oleclumab (dose level -1) may be evaluated.

Part 2 (Dose Expansion)

Once the recommended Phase 2 dose (RP2D) for a cohort has been identified, enrollment into Part 2 dose expansion may proceed. Cohorts A and B may be opened for enrollment at the discretion of the sponsor independently of each other.

During Part 2 (dose expansion), the RP2D of oleclumab identified in Part 1 for each regimen will be evaluated with or without durvalumab in combination with chemotherapy. Subjects enrolled in Part 2 will be stratified according to tumoral expression of CD73 by immunohistochemistry (IHC) and randomized to a treatment arm. Subjects in Cohort A (1L metastatic PDAC) will be 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) will be randomized 1:1:1 to one of 3 treatment arms: mFOLFOX (Arm B1); oleclumab + mFOLFOX (Arm B2); or oleclumab + durvalumab + mFOLFOX (Arm B3). There will be no crossover between treatment arms.

TARGET SUBJECT POPULATION

Subjects ≥ 18 years of age diagnosed with histologically or cytologically confirmed pancreatic adenocarcinoma. Subjects with previously untreated metastatic PDAC (1L metastatic PDAC) will be enrolled in Cohort A. Subjects with metastatic PDAC previously treated with gemcitabine-based chemotherapy (without exposure to 5-FU, capecitabine, or oxaliplatin [if considered a line of therapy]; 2L metastatic PDAC) will be enrolled in Cohort B.

TREATMENT GROUPS AND REGIMENS

Up to approximately 339 subjects will be enrolled in this study: up to approximately 24 subjects in Part 1 (dose escalation) and up to approximately 315 subjects in Part 2 (dose expansion). All subjects in both cohorts will be treated until disease progression (and the treatment criteria in the setting of progressive disease are not met), intolerable toxicity, withdrawal of subject consent, or another discontinuation criterion is met.

Any study subject still receiving investigational product at the time of data entry cut-off will continue to receive investigational product 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 is deriving clinical benefit and has not fulfilled any treatment discontinuation criteria.

Part 1 (Dose Escalation)

Up to approximately 24 subjects will be enrolled in Part 1 (dose escalation): 9 to approximately 12 subjects with 1L metastatic PDAC will be enrolled in Cohort A and 9 to approximately 12 subjects with 2L metastatic PDAC will be enrolled in Cohort B and treated with increasing dose levels of oleclumab. A single dose level for durvalumab and chemotherapy (gemcitabine/nab-paclitaxel for Cohort A; mFOLOX for Cohort B) will be used in combination with oleclumab as detailed below.

- Oleclumab at one of 3 dose levels:
  - Dose level -1 (3-6 subjects): CCI every 2 weeks (Q2W) for 4 doses, then every 4 weeks (Q4W); if the MTD is exceeded at the starting dose level (Dose Level 1)
  - Dose level 1 (3-6 subjects) CCI Q2W for 4 doses, then Q4W (starting dose level)
  - Dose level 2 (6 subjects): CCI Q2W for 4 doses, then Q4W (highest planned dose level)
- Durvalumab CCI IV Q4W
- Cohort A: Gemcitabine CCI IV and nab-paclitaxel CCI IV on Days 1, 8, and 15 and then repeated on a Q4W schedule
- Cohort B: mFOLFOX on Days 1 and 15 and then repeated on a Q4W schedule: oxaliplatin CCI IV; leucovorin CCI IV; 5-FU CCI IV bolus followed by 5-FU CCI administered by continuous IV infusion over 46 to 48 hours

Part 2 (Dose Expansion)

Up to approximately 315 subjects will be enrolled in Part 2 (dose expansion), up to approximately 210 subjects in Cohort A and up to approximately 105 subjects in Cohort B. Subjects will be stratified by CD73 expression level and randomized 1:1:1 to one of 3 treatment arms per cohort (approximately 70 subjects per treatment arm in Cohort A; approximately 35 subjects per treatment arm in Cohort B). The dose level for oleclumab will be determined during Part 1 (dose escalation). The dose and treatment regimens for durvalumab and chemotherapy are the same as in dose escalation. The treatment arms for each cohort are detailed below:

- Cohort A
  - Arm A1 (70 subjects): gemcitabine/nab-paclitaxel
  - Arm A2 (70 subjects): oleclumab and gemcitabine/nab-paclitaxel
  - Arm A3 (70 subjects): oleclumab, durvalumab, and gemcitabine/nab-paclitaxel
- Cohort B
  - Arm B1 (35 subjects): mFOLFOX
  - Arm B2 (35 subjects): oleclumab and mFOLFOX
  - Arm B3 (35 subjects): oleclumab, durvalumab, and mFOLFOX

STATISTICAL METHODS

Sample size: Up to approximately 339 subjects will be enrolled in the study: up to approximately 24 subjects in Part 1, Dose Escalation and up to approximately 315 subjects in Part 2, Dose Expansion (up to approximately 210 subjects in Cohort A and up to approximately 105 subjects in Cohort B).

Statistical analyses:

Efficacy:

The efficacy analyses of antitumor activity will be based on the intent-to-treat (ITT) population (defined as all subjects who are randomized and receive any amount of investigational product, analyzed according to randomized treatment assignment). The rates of OR and DC based on RECIST v1.1 will be summarized with 95% confidence interval based on the exact binomial distribution. Time-to-event endpoints (DoR, PFS, and OS) will be analyzed using the Kaplan-Meier method. Additional analyses of antitumor activity may be conducted in the as-treated population (defined as all subjects who receive any investigational product analyzed according to treatment received).

Safety:

Safety data, including DLTs, AEs, SAEs, laboratory evaluations, vital signs, and ECG results will be summarized based on the as-treated population (defined as all subjects who receive any investigational product analyzed according to treatment received). Descriptive statistics will be provided for AEs, SAEs, AE grade (severity), and relationship to investigational product(s), clinical laboratory parameters, vital signs, and ECG results. AEs will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03. Descriptive statistics will be provided for the clinical laboratory results and changes from baseline by scheduled time of evaluation and by treatment arm including end of treatment visit as well as for the maximum and minimum post-baseline values. Laboratory abnormalities will be graded according to the NCI CTCAE version 4.03, if applicable. Frequencies of worst observed grade will be presented for each laboratory parameter as well as the rates of subjects with Grade 3-4 toxicities.

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Immunogenicity and Pharmacokinetics:

Only subjects who receive at least 1 dose of oleclumab and/or durvalumab and provide at least 1 post-treatment sample will be evaluated.

For each cohort, the immunogenic potential of combinations will be assessed by summarizing the number and percentage of subjects who develop detectable ADAs. The impact of ADAs on PK will be assessed if data allow. Samples will be collected for potentially evaluating the neutralizing capacity of ADAs in the future.

Individual oleclumab and durvalumab concentrations will be tabulated by dose cohort along with descriptive statistics. Non-compartmental PK data analysis will be performed from each dose cohort with scheduled PK sample collection where data allow. Relevant descriptive statistics of non-compartmental PK parameters will be provided and may include: area under concentration-time curve, maximum observed concentration (C_{max}), time to reach C_{max}, clearance, volume of distribution, and terminal half-life.

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Interim Analysis:

An interim analysis will be performed when approximately 30 subjects in each treatment arm of Part 2 Cohort A have been dosed and reach the data cut-off criteria (ie, subjects who have a baseline disease assessment, have been dosed at least 16 weeks prior to the time of the data cut-off, and have at least 1 post-baseline disease assessment and/or discontinued treatment due to death or disease progression). Randomization may be paused during the interim analysis before the decision is made. If the futility criteria are met for an experimental arm, further enrollment to that arm will be stopped.

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LIST OF ABBREVIATIONS

Abbreviation or Specialized Term	Definition
δ	delta
1L	first-line
2L	second-line
5-FU	5-fluorouracil
ADA	anti-drug antibody
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AMP	adenosine monophosphate
AST	aspartate aminotransferase
ATP	adenosine triphosphate
AUC	area under concentration-time curve
CAP	College of American Pathologists
CD	cluster of differentiation
CI	confidence interval
CLIA	Clinical Laboratory Improvement Amendments
C_{max}	maximum observed concentration
CNS	central nervous system
CR	complete response
CRC	colorectal cancer
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating tumor DNA
CTLA-4	cytotoxic T-lymphocyte associated protein-4
DC	disease control
DCR	disease control rate
DEC	Dose-escalation Committee
DLT	dose-limiting toxicity
DoR	duration of response
ECG	electrocardiogram

Abbreviation or Specialized Term	Definition
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
CCI [redacted]	CCI [redacted]
CCI [redacted]	CCI [redacted]
CCI [redacted]	[redacted]
FOLFOX	leucovorin, 5-fluorouracil, and oxaliplatin
FOLFIRI	5-fluorouracil and liposomal irinotecan
FOLFIRINOX	leucovorin, 5-fluorouracil, irinotecan, and oxaliplatin
FTIH	first-time-in-human
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
HCl	hydrochloride
HMGB1	high-mobility group box 1
CCI [redacted]	[redacted]
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IFN-γ	interferon-gamma
Ig	immunoglobulin
IHC	immunohistochemical
ILD	interstitial lung disease
imAE	immune-mediated adverse event
IRB	Institutional Review Board
CCI [redacted]	CCI [redacted]
IRR	infusion-related reactions
IRT	Interactive Response Technology
IV	intravenous(ly)
mAb	monoclonal antibody
mFOLFOX	modified regimen of leucovorin, 5-fluorouracil, and oxaliplatin
MRI	magnetic resonance imaging

Abbreviation or Specialized Term	Definition
MSS	microsatellite stable
MTD	maximum tolerated dose
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NSCLC	non-small cell lung cancer
OR	objective response
ORR	objective response rate
OS	overall survival
PD	progressive disease
PD-1	programmed cell death-1
PD-L1	programmed cell death ligand-1
PDAC	pancreatic ductal adenocarcinoma
PFS	progression-free survival
PK	pharmacokinetic(s)
PR	partial response
CCI	[redacted]
Q2W	every 2 weeks
Q4W	every 4 weeks
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SD	stable disease
SID	subject identification
SIRS	systemic inflammatory response syndrome
SRC	Safety Review Committee
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	terminal half-life
TBL	total bilirubin
TMA	tumor tissue microarray
t_{max}	time to reach C_{max}
TNBC	triple negative breast cancer
TV	target value
ULN	upper limit of normal
V_d	volume of distribution
w/v	weight/volume

1 INTRODUCTION

1.1 Disease Background

Pancreatic cancer constitutes about 2.4% of all cancers worldwide but accounts for 4% of all cancer-related deaths (GLOBOCAN, 2012). Overall, it is the seventh most common cause of death from cancer for both men and women (GLOBOCAN, 2012). In 2000, there were approximately 216,400 new cases of pancreatic cancer globally with 213,500 reported deaths from the disease (Parkin et al, 2001). By 2012, the number of new cases had increased to 337,972 with 330,391 estimated deaths worldwide (GLOBOCAN, 2012). The high mortality rate is a testament to the aggressiveness of this disease and is further compounded by the lack of effective therapies. Given both the increasing incidence and lethality of this disease, it is essential that novel effective therapies are developed to reduce human suffering and death.

Pancreatic ductal adenocarcinoma (PDAC) is a malignancy with an extremely poor prognosis, as exemplified by a 1-year survival rate of approximately 18% for all stages of the disease and an estimated 5-year survival rate of less than 4% (Hidalgo et al, 2015). At the time of diagnosis, approximately 50% to 60% of PDAC patients have metastatic disease, and approximately 30% to 40% have locally advanced disease not amenable to resection (Gillen et al, 2010). This underscores the unmet medical need for more effective therapies for PDAC patients, especially in the metastatic setting.

1.1.1 Chemotherapy in Pancreatic Ductal Carcinoma

Combination chemotherapy is the mainstay of treatment for first-line (1L) and second-line (2L) metastatic PDAC. The regimens typically utilized in the 1L setting include 1) gemcitabine + nab-paclitaxel, 2) leucovorin, 5-fluorouracil (5-FU), irinotecan and oxaliplatin (FOLFIRINOX), 3) gemcitabine + capecitabine, and 4) gemcitabine + docetaxel + capecitabine. In patients with good performance status, gemcitabine + nab-paclitaxel is one of the most commonly prescribed regimens globally. In patients with poor performance status, gemcitabine monotherapy is typically used. The regimens containing more than 2 active agents typically resulted in slightly higher response rates and median overall survival (OS) but at the expense of increased toxicity. The most commonly used of these is FOLFIRINOX with an objective response rate (ORR) of 32% and a median OS of 11.1 months (Conroy et al, 2011). In contrast, gemcitabine + nab-paclitaxel has an ORR of 23% and a median OS of 8.5 months but a more favorable safety profile (Von Hoff et al, 2013).

The regimens typically utilized in 2L PDAC patients that received a gemcitabine-based therapy in the 1L include 5-FU + liposomal irinotecan (FOLFIRI) or a modified regimen of leucovorin, 5-FU, and oxaliplatin (mFOLFOX) for patients with good performance status. Patients with poor performance status typically receive single-agent 5-FU or best supportive care only. In a 3-arm, randomized, open-label study, liposomal irinotecan + 5-FU had an ORR of 7.7% versus 0.8% for the leucovorin + 5-FU arm and demonstrated a statistically

significant improvement in median OS of 6.1 months versus 4.2 months (Merrimack Pharmaceuticals, 2015). There have been multiple studies of mFOLFOX where the ORR has ranged from 0% to 7% with median OS between 3.4 to 5.1 months (Pelzer et al, 2011; Yoo et al, 2009). Given the differing safety profiles of the 2 regimens, many clinicians have continued to favor the use of mFOLFOX in the 2L setting for patients with good performance status that received gemcitabine-based therapy in 1L.

1.1.2 Immunotherapy

Recently, checkpoint inhibitors (programmed cell death-1 [PD-1]/ programmed cell death ligand-1 [PD-L1] and cytotoxic T-lymphocyte associated protein-4 [CTLA-4] inhibitors) have shown significant antitumor activity and become the standard-of-care for multiple tumor types. Due to their non-redundant mechanism of action (Pardoll, 2012), targeting both PD-L1 and CTLA-4 pathways simultaneously might have additive or synergistic activity in terms of tumor response. However, durvalumab (PD-L1 inhibitor) or tremelimumab (CTLA-4 inhibitor) monotherapy and in combination therapy did not show meaningful clinical activity in 2L metastatic PDAC subjects (O'Reilly et al, 2018).

1.1.3 Immunotherapy in Combination with Chemotherapy

Immunotherapy in combination with chemotherapy has shown the potential for additive or synergistic effects on clinical response across multiple tumor types even when the immunotherapy effect by itself was minimal such as in colorectal cancer (CRC).

In a Phase 1b, open-label, 2-arm study, atezolizumab (PD-L1 inhibitor) + bevacizumab (a vascular endothelial growth factor inhibitor) in refractory metastatic CRC patients (Arm A) and atezolizumab + bevacizumab + (leucovorin, 5-FU, and oxaliplatin [FOLFOX]) in oxaliplatin-naive metastatic CRC patients (Arm B) were evaluated. The unconfirmed ORR was 8% (1/13) in Arm A and 36% (9/25) in Arm B for subjects with ≥1 tumor assessment. The unconfirmed ORR was 44% (8/18) for Arm B 1L subjects. It was concluded that there were no unexpected toxicities and that clinical activity was demonstrated in both treatment regimens (Bendell et al, 2015).

In a Phase 2 study, pembrolizumab (PD-L1 inhibitor) in combination with mFOLFOX was evaluated in subjects with untreated, unresectable CRC. The study reported outcomes were 1 complete response (CR), 15 partial responses (PRs), (ORR = 53%) and 14 stable disease (SD). The authors concluded that the combination had an acceptable safety profile in subjects with untreated advanced CRC and that clinical activity was encouraging (Shahda et al, 2017).

In a Phase 2, open-label study of chemotherapy-naïve subjects with non-small cell lung cancer (NSCLC), subjects received 4 cycles of pembrolizumab 200 mg plus carboplatin area under concentration-time curve (AUC) 5 mg/mL per min and pemetrexed 500 mg/m^2 every 3 weeks followed by pembrolizumab for 24 months and indefinite pemetrexed maintenance therapy or

4 cycles of carboplatin and pemetrexed alone followed by indefinite pemetrexed maintenance therapy (Langer et al, 2016). Fifty-five percent (33/60) subjects in the pembrolizumab plus chemotherapy group achieved an objective response (OR) compared with 29% (18/63) subjects treated with chemotherapy alone (p=0·0016). Based on the results of this study, this is now an approved therapy in the United States.

In addition, preliminary clinical data of gemcitabine and nab-paclitaxel combined with durvalumab and tremelimumab in 11 subjects with metastatic PDAC showed an ORR of 73% and disease control rate (DCR) of 100%. The findings compare favorably with the ORR and DCR observed with a current standard-of-care, gemcitabine and nab-paclitaxel (ORR 29%, DCR 80%). These preliminary data suggest synergistic activity despite the lack of clinical activity for the combination of durvalumab and tremelimumab in metastatic PDAC subjects but await confirmation in a larger cohort of subjects with a randomized control, which is ongoing. The majority of adverse events (AEs) observed in the combination regimen were related to chemotherapy and were low grade (Renouf et al, 2018).

In summary, the available clinical activity and safety data support further development of immunotherapy combined with chemotherapy to leverage potential additive or synergistic effects in the treatment of metastatic PDAC.

1.1.4 CD73

Adenosine is a regulatory autocrine and paracrine factor that accumulates in the tumor microenvironment, influencing immune activity, angiogenesis, and metastasis. Upon apoptotic or necrotic cell death, tumor cells release adenosine triphosphate (ATP) into the extracellular space. ATP has been shown to lead to a pro-inflammatory response. To prevent an immune reaction stimulated by cell death, tissues express cluster of differentiation (CD)39 and CD73 to enzymatically convert ATP to adenosine, which induces a localized immunosuppressive response through pleotropic effects upon multiple immune cell types. In the extracellular space, CD39 and CD73 in tandem metabolize ATP to adenosine monophosphate (AMP), and AMP to adenosine, respectively, and are a major source of extracellular adenosine. The rate-limiting step in the generation of extracellular adenosine is the dephosphorylation of AMP by CD73.

One mechanism by which tumors may have evolved to evade the immune system is via overexpression of CD73. Overexpression of CD73 has been associated with poor prognosis in multiple cancer types (Inoue et al, 2017; Lu et al, 2013; Turcotte et al, 2015; Wang et al, 2012; Yang et al, 2013; Yu et al, 2015). It is hypothesized that targeted immunotherapy to inhibit CD73 activity will reduce adenosine production, thus augmenting host and/or immunotherapy response to tumor.

In-vitro and in-vivo studies conducted by Zhao et al investigated the impact of anticancer therapies including gemcitabine on the induction of immunogenic cell death. The authors found that gemcitabine effectively inhibited tumor growth by inducing immunogenic cell death in pancreatic cancer, and that it increased both ATP and high-mobility group box 1 (HMGB1) release (Zhao et al, 2015). Furthermore, an in-vitro study by Samanta, et al demonstrated that for multiple chemotherapeutic agents and multiple triple negative breast cancer (TNBC) cell lines, chemotherapy induced hypoxia-inducible factor-dependent coordinated transcriptional activation of PD-L1, CD47, and CD73 expression. Cell surface expression of PD-L1 and/or CD73 on TNBC cells enables them to induce anergy or apoptosis of effector T cells with a concomitant increase in regulatory T cells in the tumor microenvironment, thereby impairing adaptive antitumor immunity (Samanta et al, 2018). Taken together, the results of these preclinical studies suggest that chemotherapy can increase extracellular ATP and increase CD73 and PD-L1 expression supporting the combination of immunotherapy targeting CD73 and/or PD-L1 with chemotherapy to improve efficacy.

Immunohistochemical (IHC) analysis of tumor tissue microarrays (TMAs) for CD73 expression has demonstrated that there are tumor histologies enriched for prevalence of high tumoral CD73 expression, with highest prevalence in pancreatic TMAs. Therefore, anti-CD73 immunotherapy that targets adenosine-mediated immunosuppression might improve the prognosis of PDAC patients when used in combination with other anticancer therapies.

1.2 Oleclumab and Durvalumab Background

Oleclumab (investigational name MEDI9447) and durvalumab are briefly described below. Refer to the current Investigator's Brochures (IBs) for details.

1.2.1 Oleclumab Background

MedImmune is pursuing development of oleclumab as a potential anticancer therapy for patients with advanced solid tumors. Oleclumab is a human immunoglobulin (Ig) G1 lambda (IgG1λ) monoclonal antibody (mAb) that selectively binds to CD73 and inhibits adenosine production from CD73-associated ectonucleotidase activity and leads to a reduction in CD73 expression due to both internalization of the receptor and shedding of the extracellular domain. It contains a triple mutation in the heavy chain constant region for reduced effector function. Extracellular adenosine contributes to the immunosuppressive effects of both cytotoxic T lymphocytes and myeloid-derived suppressor cells, among others. The enzymatic blockade of CD73 and decreased expression caused by binding of oleclumab to CD73 may lead to increased antitumor immunity.

1.2.2 Durvalumab Background

MedImmune has developed durvalumab as a potential anticancer therapy for the treatment of multiple tumor types. Durvalumab is a human Ig G1 kappa (IgG1κ) mAb that blocks the

interaction of PD-L1 (but not programmed cell death ligand-2) with PD-1 on T-lymphocyte (T cells) and CD80 (B7.1) on immune cells and is engineered to reduce antibody-dependent cell-mediated cytotoxicity and complement activation.

1.3 Summary of Nonclinical Experience

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1.3.2 Durvalumab Nonclinical Experience

Refer to the current durvalumab IB for a complete summary of nonclinical experience.

1.4 Summary of Clinical Experience

Clinical experience with oleclumab and durvalumab is briefly described below. Refer to the current IBs for a complete summary of clinical information that includes safety, efficacy, and pharmacokinetics (PK).

1.4.1 Oleclumab Clinical Experience

1.4.1.1 Study D6070C00001

Study D6070C00001 is a first-time-in-human (FTIH), Phase 1, multicenter, open-label, dose-escalation, and dose-expansion study of oleclumab to be administered as a single agent or in combination with durvalumab in adult subjects with selected advanced solid tumors. As of the 09 June 2019 data cut-off, the monotherapy and combination therapy dose-escalation phases were completed with a total enrollment of 42 subjects and 24 subjects, respectively. In this study, subjects received oleclumab 5, 10, 20, and 40 mg/kg given IV every 2 weeks (Q2W) as monotherapy and in combination with durvalumab 10 mg/kg Q2W in the dose-escalation phase. The combination therapy dose-expansion phase is ongoing with a total of 111 subjects enrolled, including 42 subjects with CRC, 42 subjects with PDAC, and 27 subjects with epidermal growth factor receptor mutant NSCLC. Based on analysis of safety, PK, and preliminary efficacy in Study D6070C00001, a recommended Phase 2 dose (RP2D) of oleclumab 40 mg/kg (3000 mg in a 75-kg individual) Q2W was selected.

Oleclumab Monotherapy (Dose-escalation Phase)

Among the 42 subjects with advanced CRC and PDAC who were treated with oleclumab monotherapy, 39 subjects (92.9%) experienced at least 1 AE and 23 subjects (54.8%) experienced at least 1 treatment-related AE. The most frequently reported AEs (in ≥ 15% of total subjects, regardless of causality) were fatigue (40.5%), anemia and abdominal pain (23.8% each), dyspnea and decreased appetite (21.4% each), vomiting (19.0%), and pyrexia (16.7%). There were no clinically meaningful trends in incidence of AEs across dose groups. The most frequently reported treatment-related AEs (in ≥ 5% total subjects) were fatigue (16.7%) and nausea and anemia (9.5% each).

Three subjects (7.1%) reported at least 1 treatment-related Grade 3 or Grade 4 AE (events of increased amylase, increased gamma-glutamyl transferase (GGT), increased lipase, and hyperglycemia). Fifteen subjects (35.7%) experienced serious adverse events (SAEs). Three subjects (7.1%) experienced the SAE of ascites; this was the only SAE reported by more than 1 subject. None of the SAEs were considered treatment-related. Three subjects (7.1%) discontinued treatment due to events of cholangitis, metastases to central nervous system (CNS), and pulmonary embolism. None of these events were considered treatment-related. Five of the 42 subjects (11.9%) reported at least 1 adverse event of special interest (AESI). Four subjects (9.5%) had peripheral edema and 1 subject (2.4%) had pulmonary embolism.

A total of 32 (76.2%) subjects died on study; 3 of these deaths were reported while subjects were on treatment (death was the reason for end of treatment). One subject who died on treatment had a fatal AE of small intestinal obstruction; this death was not considered related to treatment with oleclumab. All other deaths were due to the disease under study. There were no dose-limiting toxicities (DLTs) reported during the oleclumab monotherapy dose-escalation phase, and the maximum tolerated dose (MTD) was not reached.

Oleclumab and Durvalumab Combination Therapy (Dose-escalation Phase)

Twenty-four subjects with advanced CRC and PDAC were treated with oleclumab and durvalumab combination therapy in the dose-escalation phase. All 24 subjects experienced AEs, and 13 subjects (54.2%) experienced at least 1 treatment-related AE. The most frequently reported AEs (in ≥ 15% of total subjects, regardless of causality) were fatigue and vomiting (29.2% each), abdominal pain (20.8%), and nausea (16.7%). There were no clinically meaningful trends in incidence of AEs across dose groups. The most frequently reported treatment-related AEs (in ≥ 10% of total subjects) were fatigue (25.0%) and nausea, increased aspartate aminotransferase (AST), and vomiting (12.5% each).

Five subjects (20.8%) reported at least 1 treatment-related Grade 3 or Grade 4 AE (events of thrombocytopenia [1 subject], increased alanine aminotransferase (ALT) [1 subject], increased AST [2 subjects], hyperglycemia [1 subject], and headache [1 subject]). Ten subjects (41.7%) experienced SAEs. Pulmonary embolism (2 subjects) was the only SAE experienced by more

than 1 subject. One subject reported a treatment-related SAE of thrombocytopenia. Two subjects (8.3%) discontinued treatment due to events of increased ALT, increased AST, increased blood alkaline phosphatase (ALP), and increased blood bilirubin. One of these 2 subjects experienced events that were considered treatment-related (increased AST and increased blood bilirubin). Five of the 24 subjects (20.8%) experienced at least 1 AESI. Peripheral edema and pulmonary embolism were the only AESIs reported in > 1 subject (2 subjects each).

A total of 19 (79.2%) subjects died on study; 2 of these deaths were reported while subjects were on treatment. One subject who died on treatment had a fatal AE of renal failure considered unrelated to study treatment by the investigator. All other deaths were due to the disease under study. There were no DLTs reported during the oleclumab and durvalumab combination therapy dose-escalation phase, and the MTD was not reached.

Oleclumab and Durvalumab Combination Therapy (Dose-expansion Phase)

Safety

Among the 111 subjects treated with oleclumab and durvalumab combination therapy in the dose-expansion phase of the study, 104 subjects (93.7%) experienced at least 1 AE, and 59 subjects (53.2%) experienced at least 1 treatment-related AE. The most frequently reported AEs by preferred term (in ≥ 15% of total subjects, regardless of causality) were fatigue (28.8%), nausea (18.9%), abdominal pain and vomiting (18.0% each), constipation (17.1%), increased AST (16.2%), and pyrexia and diarrhea (15.3% each). There were no clinically meaningful patterns in the incidence of AEs across expansion cohorts. The most frequently reported treatment-related AEs (in ≥ 5% of total subjects) were fatigue (14.4%), diarrhea (9.0%), pyrexia and vomiting (6.3% each), and increased AST (5.4%).

A total of 15.3% of subjects reported at least 1 treatment-related Grade 3 or Grade 4 AE. The following treatment-related Grade 3 or Grade 4 AEs were reported in 2 subjects each: hepatitis, increased AST, increased blood ALP, and increased lipase. Overall, 45.9% of subjects experienced at least 1 SAE. The most frequently reported SAEs (> 2% subjects) were ascites, pneumonia, and vomiting (4.5% each), abdominal pain and pulmonary embolism (3.6% each), and pleural effusion and sepsis (2.7% each). Eight (7.2%) of these subjects experienced SAEs that were considered treatment-related. The treatment-related SAE of hepatitis (1.8%) was the only treatment-related SAE reported in more than 1 subject. Overall, 7.2% of subjects experienced AEs leading to discontinuation of treatment with oleclumab and durvalumab; hepatitis (1.8%) was the only such event that occurred in more than 1 subject. Both cases of hepatitis were considered treatment-related. Another subject experienced a treatment-related AE of fatigue that led to discontinuation of treatment. A fourth subject discontinued treatment due to a treatment-related fatal SAE of systemic inflammatory response syndrome (SIRS; a narrative for this subject is provided in the oleclumab IB). Twenty-five of the 111 subjects (22.5%) reported at least 1 AESI. The most common AESIs

(≥ 2% of expansion total) reported were peripheral edema (10.8%), pulmonary embolism (6.3%) and deep vein thrombosis (3.6%).

A total of 66 subjects (59.5%) died on study; 4 subjects died while on treatment. The majority of deaths occurred due to the disease under study (56.8%). Of the 66 subjects who died, 3 subjects had AEs leading to death. Of the 3 subjects who had AEs leading to death, 1 subject died of a treatment-related SAE of SIRS, and the other 2 subjects died of AEs that were considered unrelated to study treatment.

Clinical Activity

As of the 09 June 2019 data cut-off date, the ORR (confirmed) in the PDAC cohort (n = 42) was 4.8% (95% confidence interval [CI]: 0.6%, 16.2%). The DCR (8 weeks) in this cohort was 23.8% (95% CI: 12.1%, 39.5%). The median OS in the PDAC cohort was 6.3 months.

As of the 09 June 2019 data cut-off date, the ORRs (confirmed) in the CRC cohort (n = 42) and NSCLC cohort (n = 18) were 2.4% (95% CI: 0.1%, 12.6%) and 11.1% (95% CI: 2.4%, 29.2%), respectively. The DCRs (8 weeks) in the CRC and NSCLC cohorts were 21.4% (95% CI: 10.3%, 36.8%) and 18.5% (95% CI: 6.3%, 38.1%), respectively.

1.4.1.2 Study D6070C00005

As of 09 June 2019, 75 subjects with PDAC have been enrolled in the following cohorts of the current ongoing study (D6070C00005):

- Dose escalation – Cohort A
  - Dose 1 - Oleclumab [CCI] + durvalumab + gemcitabine + nab-paclitaxel ([CCI])
  - Dose 2 - Oleclumab [CCI] + durvalumab + gemcitabine + nab-paclitaxel ([CCI])
- Dose escalation – Cohort B
  - Dose 1 - Oleclumab [CCI] + durvalumab + mFOLFOX ([CCI])
  - Dose 2 - Oleclumab [CCI] + durvalumab + mFOLFOX ([CCI])
- Dose expansion – Cohort A
  - Arm A1 – gemcitabine + nab-paclitaxel ([CCI])
  - Arm A2 – Oleclumab [CCI] + gemcitabine + nab-paclitaxel ([CCI])
  - Arm A3 – Oleclumab [CCI] g + durvalumab + gemcitabine + nab-paclitaxel ([CCI])

Dose Escalation - Cohort A

[CCI]

CCI

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

1.4.2 Durvalumab Clinical Experience

As of the data cut-off date of 12 July 2019, approximately 8817 patients have received durvalumab as monotherapy or in combination with other anticancer agents in AstraZeneca or MedImmune-sponsored interventional studies in multiple tumor types, stages of disease, and lines of therapy. An estimated 8343 patients have been randomized to the various treatment/comparator arms in sponsor-blinded studies. In addition, 2482 patients have participated in the durvalumab Early Access Program (Study D4194C00002) for patients with locally advanced, unresectable NSCLC whose disease has not progressed following platinum-based chemoradiation therapy. The cumulative global post-marketing patient exposure to durvalumab (10 mg/kg) to 30 June 2019 has been estimated to be approximately 12385 patient-years. Durvalumab has been approved in bladder and lung cancer in a number of countries. Details on the safety profile of durvalumab are briefly summarized below.

The safety profile of durvalumab as monotherapy and combined with other anticancer agents is consistent with the pharmacology of the target and other agents in the immune checkpoint inhibitor class. Most adverse drug reactions seen with this class of agents are thought to be

due to effects of inflammatory cells on specific tissues and could occur in any organ system. Safety data pooled from 8 durvalumab monotherapy studies included 2769 patients who received a durvalumab dose of 10 mg/kg Q2W or 20 mg/kg Q4W.

- Overall, AEs reported in ≥ 15% of patients, regardless of causality, were fatigue, decreased appetite, cough, nausea, dyspnea, constipation, and diarrhea. . The most common treatment-related AEs reported in ≥ 5% of patients were fatigue (13.5%), diarrhea (8.1%), hypothyroidism (8.1%), pruritus (7.0%), nausea (6.7%), decreased appetite (6.6%), and rash (6.2%).
- AEs of Grade 3 or higher considered related to durvalumab were reported in 11.6% of patients: 9.9% of patients had Grade 3 events, 1.0% of subjects had Grade 4 events, and 0.6% of subjects had Grade 5 (fatal) events. Grade 3 or 4 treatment-related AEs occurring in ≥ 0.5% patients were fatigue (1.1%), increased GGT (0.8%), pneumonitis (0.7%), and increased AST (0.6%). The only Grade 5 events considered related to durvalumab occurring in ≥ 2 patients were pneumonitis (6 patients [0.2%]) and respiratory failure (2 patients [< 0.1%]).
- A total of 9.4% of patients discontinued from study treatment due to an AE. The most common events leading to treatment discontinuation were pneumonitis (1.2%), pneumonia (0.6%), dyspnea (0.4%), general physical health deterioration (0.3%), and interstitial lung disease (ILD), radiation pneumonitis, sepsis, and anemia (0.2% each); all other discontinuation events occurred in ≤ 4 patients.
- A total of 6.5% of patients had SAEs that were considered related to durvalumab. The most common treatment-related SAEs were pneumonitis (1.2%), pneumonia, diarrhea, and ILD (0.3% each), colitis, infusion-related reaction (IRR), and fatigue (0.2% each), and dyspnea, radiation pneumonitis, acute kidney injury, adrenal insufficiency, increased AST, dehydration, hypothyroidism, nausea, nervous system disorder, and thrombocytopenia (0.1% each).

The majority of treatment-related AEs were manageable with dose delays, symptomatic treatment and, in the case of events suspected to have an immune basis, the use of established treatment guidelines for immune-mediated toxicity (Section 3.1.4).

1.5 Rationale for Conducting the Study

Pancreatic ductal adenocarcinoma is a highly morbid disease with a high mortality due to a lack of effective therapies. According to global clinical practice guidelines (National Comprehensive Cancer Network and European Society for Medical Oncology), gemcitabine plus nab-paclitaxel and mFOLFOX are preferred treatment regimens for 1L and 2L metastatic PDAC, respectively. However, the effectiveness of these regimens remains limited. Preclinical in-vitro and in-vivo studies found that gemcitabine effectively inhibited tumor growth by inducing immunogenic cell death in pancreatic cancer, and that it increased ATP and HMGB1 release (Zhao et al, 2015). Another preclinical study demonstrated that for multiple chemotherapeutic agents and multiple TNBC cell lines, chemotherapy induced transcriptional activation of PD-L1, CD47, and CD73 expression. Cell surface expression of

PD-L1 and/or CD73 on TNBC cells enables them to induce anergy or apoptosis of effector T cells with a concomitant increase in regulatory T cells in the tumor microenvironment, thereby impairing adaptive antitumor immunity (Samanta et al, 2018). These preclinical studies suggest that chemotherapy can increase extracellular ATP and increase CD73 and PD-L1 expression supporting the combination of immunotherapy targeting CD73 and/or PD-L1 with chemotherapy to improve efficacy.

1.6 Benefit-Risk and Ethical Assessment

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with International Conference on Harmonisation (ICH)/Good Clinical Practice (GCP), and applicable regulatory requirements.

1.6.1 Potential Risks

There are currently no identified risks for oleclumab. The important potential risks for oleclumab include thrombosis and increased microvascular permeability, and potential risks for oleclumab include arterial ischemic disorder. Additional important potential risks include IRRs, anaphylaxis, hypersensitivity or allergic reactions, and immune complex disease, which are associated with the administration of mAbs. Additional potential risks associated with any IV administration are localized infection, redness, swelling, pain, and induration at the administration site. For information on all identified and potential risks with oleclumab, refer to the current oleclumab IB.

Identified risks with durvalumab include, but are not limited to, pneumonitis/ILD, hepatitis, diarrhea/colitis, endocrinopathies (ie, events of hypophysitis/hypopituitarism, thyroiditis, adrenal insufficiency, hypothyroidism, hyperthyroidism, type 1 diabetes mellitus [which may present with diabetic ketoacidosis], and diabetes insipidus), nephritis, rash/dermatitis (including pemphigoid), myocarditis, myositis/polymyositis, myasthenia gravis, immune thrombocytopenia, IRRs, pancreatitis, and encephalitis. Potential risks include hypersensitivity reactions and anaphylaxis, subcutaneous injection site reactions, immunogenicity, cytokine release syndrome, other infections, and other rare or less frequent immune-mediated AEs (including, but not limited to Guillain-Barre Syndrome, pericarditis, sarcoidosis, uveitis, cholangitis sclerosing, immune-mediated cystitis, and other events involving the eye, skin, haematological, rheumatological events, vasculitis, and non-infectious

meningitis). For information on all identified and potential risks with durvalumab, refer to the current durvalumab IB.

Durvalumab plus oleclumab and oleclumab as a monotherapy have been well tolerated to date in Study D6070C00001. The majority of AEs have been low grade and not related to treatment. There are no significant overlapping toxicities with chemotherapy based on either the safety profile or the mechanisms of action of the investigational products.

The design of the current study aims to minimize potential risks to subjects based on the protocol inclusion and exclusion criteria, restrictions on concomitant medication during the study, safety monitoring (including review of all safety, PK, and other relevant data by the Dose-escalation Committee [DEC]), toxicity management guidelines, starting dose selection, dose escalation scheme, and stopping criteria. Specific intensive safety monitoring is in place for those risks deemed to be most likely.

1.6.2 Potential Benefits

Metastatic PDAC is a disease with an extremely poor prognosis, which underscores the need for novel therapies for this patient population.

In Study CD ON-MEDI4736-1108, a Phase 1 multi-arm expansion study of durvalumab in subjects with solid tumors, preliminary efficacy data for subjects with pancreatic cancer showed 2 CR/PRs in 30 evaluable subjects with unselected PD-L1 status and 2 CR/PRs in 19 evaluable subjects with PD-L1 low/negative status (defined as tumor cells < 25%; Durvalumab IB). Study D4198C00001 (ALPS), a Phase 2 study of durvalumab in 2L PDAC subjects, showed 2 unconfirmed PRs in 33 evaluable subjects (O'Reilly et al, 2018).

The safety and clinical activity of durvalumab 10 mg/kg plus oleclumab 40 mg/kg Q2W in 2L and 3L PDAC subjects is being evaluated in Study D6070C00001. The preliminary data suggest that treatment with oleclumab is well-tolerated and leads to a reduction in CD73 expression on both tumor and circulating immune cells. As of the 09 June 2019 data cut-off, 42 subjects with PDAC received the combination therapy in the dose-expansion cohort. The ORR (confirmed) was 4.8% (95% CI: 0.6%, 16.2%) and included 1 subject with CR and 1 subject with PR. The DCR (8 weeks) was 23.8% (95% CI: 12.1%, 39.5%). As of 09 June 2019, the median OS in this cohort was 6.3 months. These data acquired in the 2-3L metastatic pancreatic setting compare well with the active standard-of-care being 5FU-Onyvide (OS = 6.1 months) and provide a strong rationale for investigating further the oleclumab-containing regimens in pancreatic cancer. Refer to Section 1.4.1 and the current oleclumab IB for additional information.

The plan to combine oleclumab with or without durvalumab with gemcitabine and nab-paclitaxel (Cohort A) and mFOLFOX (Cohort B) in the current study is supported by preclinical and clinical studies which have demonstrated increases in CD73 expression and

increases in extracellular ATP in response to chemotherapy (Samanta et al, 2018; Zhao et al, 2015). In addition, preclinical studies have demonstrated synergistic benefit of chemotherapy with CD73 blockade (Loi et al, 2013). Therefore, oleclumab with or without durvalumab combined with gemcitabine and nab-paclitaxel or mFOLFOX therapy may demonstrate a clinically meaningful benefit and manageable safety profile compared with gemcitabine and nab-paclitaxel or mFOLFOX. The overall benefit-risk profile of the proposed treatment combinations is expected to be favorable for subjects with PDAC, therefore supporting the current study design.

1.7 Research Hypotheses

The combination of oleclumab (anti-CD73) with or without durvalumab (anti-PD-L1) plus chemotherapy will demonstrate adequate safety, tolerability, and antitumor activity in subjects with metastatic PDAC that has been previously untreated or has progressed following gemcitabine-based chemotherapy.

2 OBJECTIVES AND ENDPOINTS

2.1 Primary Objective(s) and Associated Endpoints

Table 1 (2.1-1) Primary Objective(s) and Associated Endpoints

Type	Objective	Endpoint
Safety	Part 1: 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 clinical laboratory parameters, vital signs, and ECG results
Clinical Activity	Part 2: 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: 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

1L = first-line; 2L = second-line; AE = adverse event; ECG = electrocardiogram; DLT = dose-limiting toxicity; mFOLFOX = modified regimen of leucovorin, 5-fluorouracil and oxaliplatin; OR = objective response; PDAC = pancreatic ductal adenocarcinoma; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event; v = version
Note: Part 1 is dose escalation and Part 2 is dose expansion.

2.1.1 Secondary Objectives and Associated Endpoints

Table 2 (2.1.1-1) Secondary Objective(s) and Associated Endpoints

Type	Objective	Endpoint
Safety	Part 2: 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
Clinical Activity	Part 1: 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
	Part 1: 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: 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: 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: 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
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

Table 2 (2.1.1-1) Secondary Objective(s) and Associated Endpoints

Type	Objective	Endpoint
Pharmaco kinetics	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

1L = first-line; 2L = second-line; ADA = anti-drug antibody; AE = adverse event; CD = cluster of differentiation; DC = disease control; 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 = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event; v = version.
Note: Part 1 is dose escalation and Part 2 is dose expansion.

2.1.2 CCI [redacted]

Table 3 (2.1.2-1) CCI [redacted]

CCI [redacted]		

Table 3 (2.1.2-1) CCI

CCI

CCI

3 STUDY DESIGN

3.1 Description of the Study

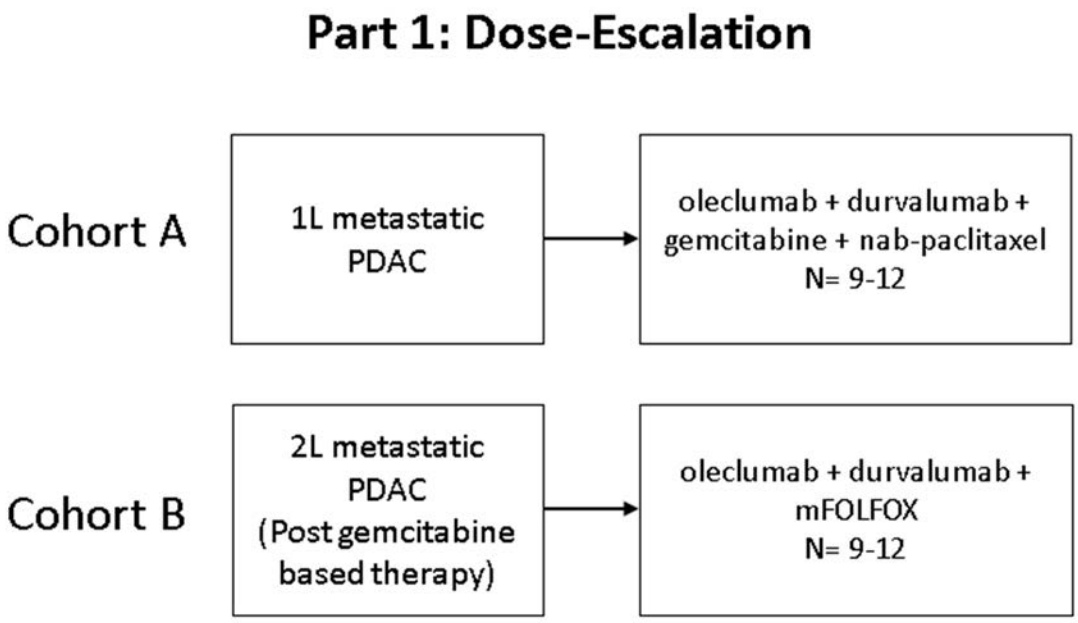
3.1.1 Overview

This is a Phase 1b/2, multicenter, open-label, dose-escalation and dose-expansion study to assess the safety, preliminary antitumor activity, immunogenicity, and PK of oleclumab with or without durvalumab in combination with chemotherapy administered in subjects with metastatic PDAC. Subjects with previously untreated metastatic PDAC (1L metastatic PDAC) will be enrolled in Cohort A. Subjects with metastatic PDAC previously treated with

gemcitabine-based chemotherapy (without exposure to 5-FU, capecitabine, or oxaliplatin; 2L metastatic PDAC) will be enrolled in Cohort B. The study consists of 2 parts, dose escalation (Part 1) and dose expansion (Part 2). All subjects in both cohorts will be treated until disease progression, intolerable toxicity, withdrawal of subject consent, or another discontinuation criterion is met.

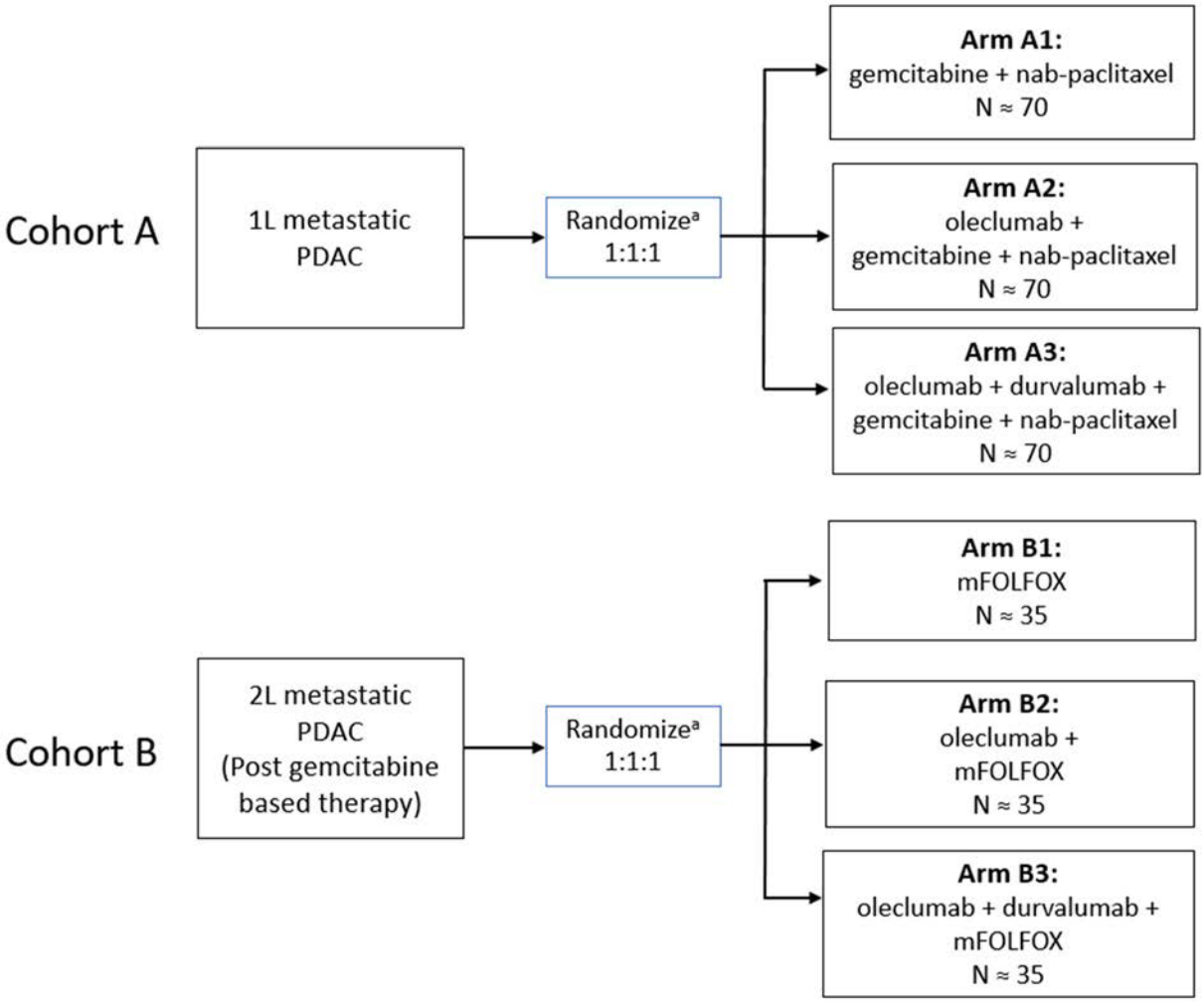
Up to approximately 339 subjects will be enrolled in this study at approximately 30 sites globally: up to approximately 24 subjects in Part 1 (dose escalation) and up to approximately 315 subjects in Part 2 (dose expansion). The study flow diagram is presented in Figure 1 (3.1.1-1) for Part 1 (dose escalation) and in Figure 2 (3.1.1-2) for Part 2 (dose expansion).

Figure 1 (3.1.1-1) Study Flow Diagram (Part 1: Dose Escalation)



1L = first-line; 2L = second-line; mFOLFOX = modified regimen of leucovorin, 5-fluorouracil, and oxaliplatin; N = number; PDAC = pancreatic ductal adenocarcinoma.

Figure 2 (3.1.1-2) Study Flow Diagram (Part 2: Dose Expansion)



1L = first-line; 2L = second-line; CD = cluster of differentiation; mFOLFOX = modified regimen of leucovorin, 5-fluorouracil and oxaliplatin; N = number; PDAC = pancreatic ductal adenocarcinoma.
[a] Stratification for CD73.

For Cohort A, an interim analysis will be performed when approximately 30 evaluable subjects in each treatment arm have been dosed and reach the data cut-off criteria. Refer to Section 4.8.7 for additional details.

The endpoints to be measured in this study are described in Section 2.

3.1.1.1 Part 1: Dose Escalation

During Part 1, dose escalation of oleclumab will be performed in combination with durvalumab and chemotherapy (gemcitabine + nab-paclitaxel for subjects with 1L metastatic PDAC [Cohort A]; mFOLFOX for subjects with 2L metastatic PDAC [Cohort B]) to determine either the MTD or the highest protocol-defined dose for each regimen.

Subjects will be enrolled in cohorts to be treated with increasing dose levels of oleclumab with the potential to be treated at a lower dose level. A single dose level for durvalumab and chemotherapy will be used in combination with oleclumab (see Section 3.1.2.1). Dose escalation will begin with enrollment of at least 3 subjects (and up to 6 subjects) at Dose Level 1 (Table 4 (3.1.1.1-1)). The DEC (Section 3.1.3.1) will monitor subjects for DLTs during the DLT-evaluation period as defined in Section 3.1.3.3. Enrollment of additional subjects at a dose level, dose escalation to the next dose level, or dose de-escalation will progress according to the rules outlined in Section 3.1.3.2. If the MTD is exceeded at the starting dose level, then a lower dose level of oleclumab CCI (dose level -1) may be evaluated (Table 4 (3.1.1.1-1)).

Table 4 (3.1.1.1-1) Oleclumab Dose Levels for Evaluation in Part 1 (Dose Escalation)

Agents	Dose Level -1 N = 3-6 subjects	Dose Level 1 [a] N = 3-6 subjects	Dose Level 2 N = 6 subjects
Oleclumab (Cohorts A and B)	CCI Q2W × 4 then Q4W	CCI Q2W × 4 then Q4W	CCI Q2W × 4 then Q4W

IV = intravenously; Q2W = every 2 weeks; Q4W = every 4 weeks.
[a] Starting dose level.

3.1.1.2 Part 2: Dose Expansion

Once the RP2D for a cohort has been identified, enrollment into Part 2 dose expansion may proceed. Cohorts A and B may be opened for enrollment at the discretion of the sponsor independently of each other. Refer to Section 3.1.3.1 for details on ongoing safety surveillance.

During Part 2 (dose expansion), the RP2D of oleclumab identified in Part 1 for each regimen will be evaluated with or without durvalumab in combination with chemotherapy (see Section 3.1.2.2). Subjects enrolled in Part 2 will be stratified according to tumoral expression of CD73 by IHC and randomized to a treatment arm.

Subjects in Cohort A (1L metastatic PDAC) will be randomized 1:1:1 to one of 3 treatment arms:

- Arm A1: gemcitabine + nab-paclitaxel or
- Arm A2: oleclumab + gemcitabine + nab-paclitaxel or
- Arm A3: oleclumab + durvalumab + gemcitabine + nab-paclitaxel

Subjects in Cohort B (2L metastatic PDAC) will be randomized 1:1:1 to one of 3 treatment arms:

- Arm B1: mFOLFOX or
- Arm B2: oleclumab + mFOLFOX or
- Arm B3: oleclumab + durvalumab + mFOLFOX

There will be no crossover between treatment arms.

3.1.2 Treatment Regimen

The treatment arms and regimens are detailed in Section 3.1.2.1 for Part 1 (dose escalation) and in Section 3.1.2.2 for Part 2 (dose expansion). All treatment will be administered beginning on Day 1 until confirmed radiological progressive disease (PD) unless there is unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met.

If any chemotherapeutic agent is discontinued due to treatment-related toxicity, oleclumab with or without durvalumab and any non-responsible chemotherapeutic agent may continue at the investigator's discretion when toxicity resolves to Grade 2 or less.

Note: If the investigator feels a subject is ready to restart the other non-responsible treatments prior to the chemotherapeutic toxicity resolving to Grade 2 or less, MedImmune should be consulted for an exception to this rule.

All subjects will be followed for survival until the end of the study (defined as the last expected visit of the last subject on study, approximately 2 years after the last subject begins treatment with investigational product or when the sponsor stops the study, whichever occurs earlier [Section 6.3]).

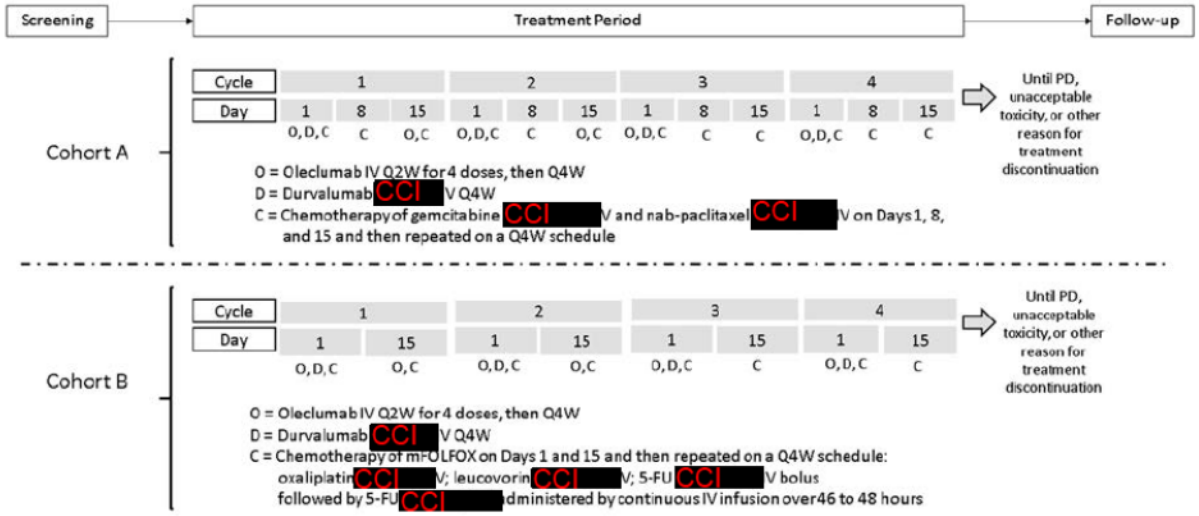
At the conclusion of the study, subjects who continue to demonstrate clinical benefit will be eligible to receive investigational product via a rollover study requiring approval by the responsible Health Authority and ethics committee or through another mechanism at the discretion of the sponsor. The sponsor reserves the right to terminate access to investigational product if any of the following occur: a) the marketing application is rejected by the responsible Health Authority; b) the study is terminated due to safety concerns; c) the subject can obtain investigational product from a government-sponsored or private health program; or d) therapeutic alternatives become available in the local market.

3.1.2.1 Part 1: Dose Escalation

In Part 1 (dose escalation), subjects will be enrolled in either Cohort A or B and receive the following treatment as detailed below and presented in Figure 3 (3.1.2.1-1).

- Cohort A:
  - Oleclumab at one of 3 dose levels (CCI, CCI, or CCI) IV Q2W for 4 doses, then Q4W and
  - Durvalumab CCI Q4W and
  - Gemcitabine CCI and nab-paclitaxel CCI IV on Days 1, 8, and 15 and then repeated on a Q4W schedule
- Cohort B:
  - Oleclumab at one of 3 dose levels (CCI, CCI, or CCI Q2W for 4 doses, then Q4W and
  - Durvalumab CCI Q4W and
  - mFOLFOX on Days 1 and 15 and then repeated on a Q4W schedule: oxaliplatin CCI; leucovorin CCI; 5-FU CCI bolus followed by 5-FU CCI administered by continuous IV infusion over 46 to 48 hours

Figure 3 (3.1.2.1-1) Treatment Regimen for Part 1 (Dose Escalation)



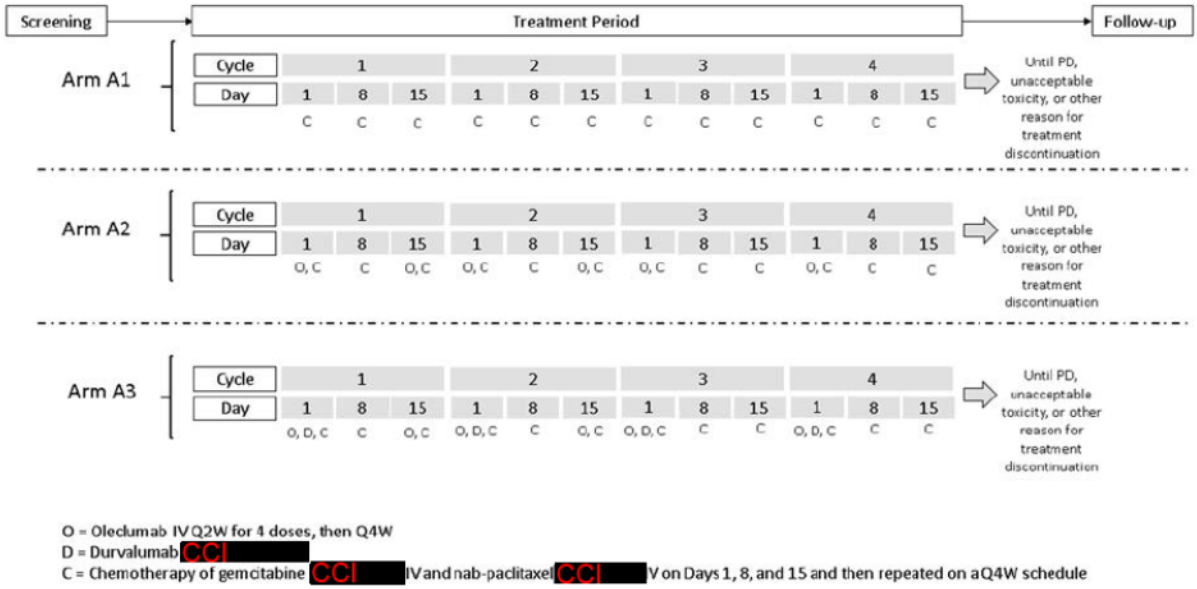
5-FU = 5-fluorouracil; IV = intravenously; mFOLFOX = modified regimen of leucovorin, 5-FU, and oxaliplatin; PD = progressive disease; Q2W = every 2 weeks; Q4W = every 4 weeks.
Note: A cycle = 28 days.

3.1.2.2 Part 2: Dose Expansion

In Part 2 (dose expansion), subjects will be enrolled in either Cohort A or B and will be randomized 1:1:1 to one of 3 treatment arms per cohort as detailed below and presented in Figure 4 (3.1.2.2-1) for subjects enrolled in Cohort A and in Figure 5 (3.1.2.2-2) for subjects enrolled in Cohort B. The dose level for oleclumab will be determined during Part 1 (dose escalation).

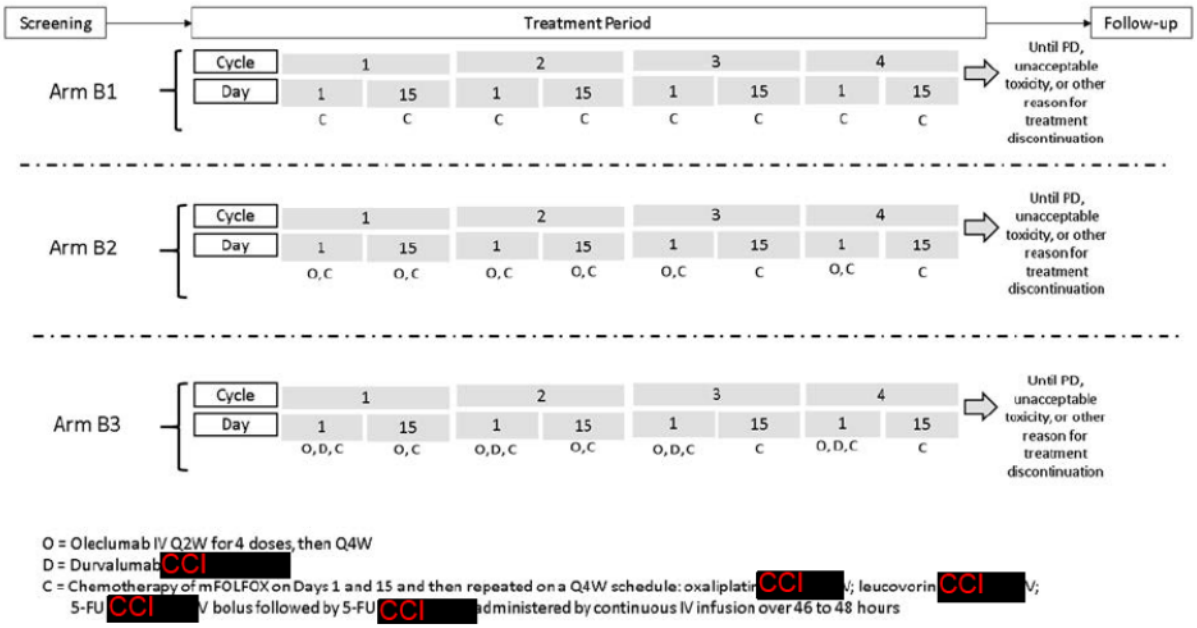
- Cohort A
  - Arm A1
    - Gemcitabine CCI and nab-paclitaxel CCI on Days 1, 8, and 15 and then repeated on a Q4W schedule
  - Arm A2
    - Oleclumab IV Q2W for 4 doses, then Q4W and
    - Gemcitabine CCI and nab-paclitaxel CCI on Days 1, 8, and 15 and then repeated on a Q4W schedule
  - Arm A3
    - Oleclumab IV Q2W for 4 doses, then Q4W and
    - Durvalumab CCI Q4W and
    - Gemcitabine CCI and nab-paclitaxel CCI on Days 1, 8, and 15 and then repeated on a Q4W schedule
- Cohort B
  - Arm B1
    - mFOLFOX on Days 1 and 15 and then repeated on a Q4W schedule: Oxaliplatin CCI leucovorin CCI; 5-FU CCI bolus followed by 5-FU CCI administered by continuous IV infusion over 46 to 48 hours
  - Arm B2
    - Oleclumab IV Q2W for 4 doses, then Q4W and
    - mFOLFOX on Days 1 and 15 and then repeated on a Q4W schedule: Oxaliplatin CCI leucovorin CCI; 5-FU CCI bolus followed by 5-FU CCI administered by continuous IV infusion over 46 to 48 hours
  - Arm B3
    - Oleclumab IV Q2W for 4 doses, then Q4W and
    - Durvalumab CCI Q4W and
    - mFOLFOX on Days 1 and 15 and then repeated on a Q4W schedule: Oxaliplatin CCI; leucovorin CCI; 5-FU CCI bolus followed by 5-FU CCI administered by continuous IV infusion over 46 to 48 hours

Figure 4 (3.1.2.2-1) Treatment Regimen for Cohort A (Arms A1, A2, and A3) in Part 2 (Dose Expansion)



IV = intravenously; PD = progressive disease; Q2W = every 2 weeks; Q4W = every 4 weeks.
Note: A cycle = 28 days.

Figure 5 (3.1.2.2-2) Treatment Regimen for Cohort B (Arms B1, B2, and B3) in Part 2 (Dose Expansion)



5-FU = 5-fluorouracil; IV = intravenously; mFOLFOX = modified regimen of leucovorin, 5-FU, and oxaliplatin; PD = progressive disease; Q2W = every 2 weeks; Q4W = every 4 weeks.
Note: A cycle = 28 days.

3.1.3 Dose Escalation, Cohort Progression, Dose-limiting Toxicity, and Safety Review

3.1.3.1 Dose-escalation Committee (Part 1, Dose Escalation)

Subjects will be followed for safety during Part 1 of the study. A study-specific DEC (including at a minimum the sponsor medical monitor/clinical lead and all participating investigators who have enrolled subjects in that dose level) will provide ongoing safety surveillance of the study, with regularly scheduled reviews of safety and other relevant data. This committee may also meet to review data at other time points (eg, in response to AEs assessed as medically relevant by the medical monitor). This committee will be responsible for dose-escalation or dose de-escalation decisions and recommendations regarding further conduct of the study during Part 1. All decisions by this committee will be documented and shared with all participating sites in writing.

3.1.3.2 Rules for Dose Escalation and Cohort Progression (Part 1)

In Part 1 of this study, durvalumab and oleclumab in combination with chemotherapy will be explored. The following rules will be applicable to dose escalation in Cohorts A and B.

1 The MTD will be determined based on the assessment of DLTs during the DLT-evaluation period (Section 3.1.3.3). Subjects who do not meet the criteria for the DLT-evaluable population will be replaced (Section 4.1.8).

2 Administration of the first dose of investigational product must be staggered by a minimum of 24 hours for the first 2 subjects in each cohort. Intra-subject dose escalation will not be allowed. Intra-subject dose de-escalation of oleclumab or durvalumab will not be allowed.

3 A minimum of 3 subjects (up to 6 subjects) will be enrolled in each dose-level cohort. If no DLTs are observed in a cohort of 3 to 6 evaluable subjects, then dose escalation may occur.

4 If 1 subject in a dose-level cohort of 3 or more evaluable subjects experiences a DLT, that dose-level cohort will be expanded to a total of 6 subjects. If no more than 1 of 6 subjects in the dose-level cohort experiences a DLT, dose escalation will continue to the next higher dose-level cohort.

5 If ≥ 2 subjects in a dose-level cohort experience a DLT, the MTD will be exceeded and no further subjects will be enrolled into that dose level cohort. If this occurs, the preceding dose-level cohort will be evaluated for the MTD and a total of 6 subjects will be treated at the preceding dose level if not already expanded. If ≤ 1 of 6 subjects experiences a DLT at the preceding dose level, then this dose level will be the MTD.

6 If ≥ 2 subjects in the first dose cohort experience a DLT, then no further subjects will be enrolled into that dose-level cohort. A dose de-escalation (Dose Level -1) will then be evaluated for the MTD in 6 subjects.

7 If the highest protocol-defined dose level is reached and no DLTs are observed in a minimum of 3 evaluable subjects, the sponsor will expand the highest protocol-defined dose level to 6 subjects. If ≤ 1 of 6 subjects experiences a DLT, then the highest protocol-defined dose level may be selected for further evaluation in Part 2.

8 At the discretion of the sponsor, dose escalation may be stopped before an MTD is reached. In this case, an expanded cohort dose may be chosen based on an assessment of PK, pharmacodynamic, biomarker, safety, and antitumor activity data.

9 Dose escalation proceeds independently between the cohorts of this study.

3.1.3.3 Dose-limiting Toxicity

DLTs will be evaluated during Part 1 (dose escalation) for both Cohorts A and B. The period for DLT-evaluation will be from the first dose of all study treatments through Day 28. Subjects who do not complete the DLT-evaluation period or did not receive all planned doses of oleclumab, durvalumab, or chemotherapy during this time for reasons other than a DLT will be considered non-evaluable for DLT assessment and will be replaced with another subject at the same dose level, but will still be considered when reviewing toxicity from this cohort (Sections 4.1.8 and 4.8.1). Grading of DLTs will be according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE version 4.03).

A DLT will be defined as any Grade 3 or higher toxicity or any of the events listed below that occurs during the DLT-evaluation period. Toxicity that is clearly and directly related to the primary disease, chemotherapy alone, or to another etiology will not be considered DLTs. The following will be DLTs:

- Immune-mediated adverse events (imAEs)
  - Any Grade 4 imAE (excluding asymptomatic lipase and/or amylase elevation)
  - Any ≥ Grade 3 colitis
  - Any ≥ Grade 3 nausea, vomiting, or diarrhea that does not resolve to Grade 2 or less within 3 days of the initiation of maximal supportive care
  - Any ≥ Grade 3 pneumonitis or ILD
  - Any Grade 2 pneumonitis or ILD for which the symptomatology does not resolve within 7 days of the initiation of maximal supportive care
- Anemia
  - Grade 4 anemia of any duration
  - Grade 3 anemia if associated with clinical sequelae or requires transfusion of > 2 units of red blood cells
- Thrombocytopenia
  - Grade 4 thrombocytopenia ≥ 7 days

  - Grade 3 or 4 thrombocytopenia, regardless of duration, associated with Grade 3 or higher hemorrhage
- Neutropenia and/or febrile neutropenia
  - Grade 4 febrile neutropenia of any duration
  - Grade 3 febrile neutropenia lasting ≥ 5 days while receiving maximal supportive care
  - Grade 4 neutropenia lasting > 7 days
- Liver function tests
  - Isolated Grade 3 liver transaminase elevation or isolated Grade 3 total bilirubin (TBL) that does not downgrade to Grade 1 or less within 14 days after onset with optimal medical management, including systemic corticosteroids.
  - Isolated Grade 4 liver transaminase elevation or TBL regardless of duration.
  - Any increase in AST or ALT > 3 × upper limit normal (ULN) and concurrent increase in TBL > 2 × ULN (Hy's Law) without evidence of cholestasis or alternative explanations (eg, viral hepatitis, disease progression in the liver)
- Any other toxicity that is greater than that at baseline, is clinically significant and/or unacceptable and is judged to be a DLT by the DEC

A DLT excludes the following:

- Grade 3 endocrine disorder (thyroid, pituitary, and/or adrenal insufficiency) that is managed with or without systemic corticosteroid therapy and/or hormone replacement therapy
- Grade 3 inflammatory reaction attributed to a local antitumor response (eg, inflammatory reaction at sites of metastatic disease, lymph nodes, etc) that resolved to Grade 1 or less within 30 days
- Concurrent vitiligo or alopecia of any AE grade
- Isolated laboratory changes of any grade without clinical sequelae or clinical significance that are not defined as a DLT above

Immune-mediated AEs are defined as AEs of an immune nature (ie, inflammatory) in the absence of a clear alternative etiology. In the absence of clinical abnormality, repeat laboratory testing will be conducted to confirm significant laboratory findings prior to designation as a DLT.

3.1.3.4 Safety Review Committee (Part 2, Dose Expansion)

A Safety Review Committee (SRC) will conduct safety reviews of all enrolled subjects approximately every 3 months. The SRC may make recommendations regarding continuation, modification, or termination of any study arm for safety concerns. The SRC may request

additional data as needed. Additional safety reviews may be conducted at the discretion of the SRC.

The SRC will include, but is not limited to, the following:

- SRC Chairperson (MedImmune/AstraZeneca Clinical Lead)
- Study Medical Monitor
- Global Safety Physician
- Principal Investigators from a subset of active investigational sites (3-5). The number of sponsor representatives will not exceed the number of Principal Investigators.
- Study Statistician
- SRC coordinator

The Clinical Development Scientist, Patient Safety Scientist, and other delegates may also be invited as appropriate. Other internal and external experts may be consulted by the SRC as necessary. The membership, roles, responsibilities, and details on the process flow/communication plan are provided in the SRC Charter.

3.1.4 Management of Study Medication Related Toxicities

The following general guidance should be followed for management of toxicities.

- Treat each of the toxicities with maximum supportive care (including holding the agent or agents suspected of causing the toxicity if required). The use of growth factors according to local practice will be allowed.
- Subjects should be thoroughly evaluated to rule out any alternative etiology (eg, disease progression, concomitant medications, and infections).
- If the toxicities are clearly attributed to chemotherapy or immune therapy, either chemotherapy or immune therapy can be delayed or discontinued, and the other one may be continued. If the causality of toxicity is unclear, both chemotherapy and immune therapy should be delayed or discontinued.
- In the event that toxicities are clearly attributed to chemotherapy, both chemotherapy (gemcitabine and nab-paclitaxel or 5-FU and oxaliplatin) and the regimen comprised of durvalumab and oleclumab should be delayed for up to 7 days; the goal of synchronized delay is to preserve the alignment of chemotherapy and immunotherapy. If chemotherapy cannot be resumed within 7 days after the originally scheduled day, the durvalumab and oleclumab may be administered for that cycle.
- If subjects experience a toxicity clearly related to any chemotherapeutic agent necessitating the permanent discontinuation of that agent only (eg, neuropathy due to oxaliplatin), then the non-offending chemotherapeutic agent, durvalumab and oleclumab may still be continued until the subject meets the guidelines for treatment discontinuation.

- In the absence of clear alternative etiology, all events should be considered potentially immune-mediated, and the toxicity management guidelines detailed below should be followed.
- In the event that durvalumab and oleclumab is discontinued or delayed as part of the toxicity management guidance, chemotherapy may still be administered as scheduled. If durvalumab or oleclumab is delayed, then both agents must be delayed.

If unsure how to manage a subject, please contact the study medical monitor to discuss individual cases. All toxicities will be graded according to NCI CTCAE version 4.03.

3.1.4.1 Management of Oleclumab-Related Toxicities

Guidelines for management of immune-mediated reactions, IRRs, and non-immune-mediated reactions for oleclumab are provided in the toxicity management guidelines in Section 10.9.

3.1.4.2 Management of Durvalumab-Related Toxicities

Comprehensive toxicity management guidelines have been developed to assist investigators with the recognition and management of toxicities associated with the use of the immune-checkpoint inhibitors durvalumab (PD-L1 inhibitor) and tremelimumab (CTLA-4 inhibitor). Given the similar underlying mechanisms of toxicities observed with these 2 compounds, these durvalumab ± tremelimumab guidelines are applicable to the management of patients receiving either drug as monotherapy or in combination. Additionally, these guidelines are applicable when either drug is used alone or in combination and is administered concurrently or sequentially with other anticancer drugs (ie, antineoplastic chemotherapy, targeted agents), as part of a protocol specific treatment regimen. The toxicity management guidelines provide information for the management of immune-mediated reactions, IRRs, and non-immune mediated reactions that may be observed with checkpoint inhibitor monotherapy or combination checkpoint inhibitor regimens, with specific instructions for dose modifications (including discontinuations) and treatment interventions. Investigators are advised however to use local practice guidelines and consult local references for the management of toxicities observed with other cancer treatment (Section 3.1.4.3). The most current version of the durvalumab ± tremelimumab toxicity management guidelines, entitled "Dosing Modification and Toxicity Management Guidelines for Immune-Mediated, Infusion-Related, and Non-Immune Mediated Reactions (MEDI4736 Monotherapy or Combination Therapy with Tremelimumab or Tremelimumab Monotherapy)", is provided to the investigative site as an Annex document and is maintained within the Site Master File. In addition, a version of the current Dosing Modification and Toxicity Management Guidelines is available through the following link: https://tmg.azirae.com. Please contact the study representative for information on how to gain access to this website.

Patients should be thoroughly evaluated and appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the imAE. Serologic, immunologic, and histologic (biopsy) data, as appropriate, should be used to support an imAE

diagnosis. In the absence of a clear alternative etiology, events should be considered potentially immune related. In addition, there are certain circumstances in which durvalumab should be permanently discontinued. Following the first dose of investigational product, subsequent administration of durvalumab can be modified based on toxicities observed as described in the Dosing Modification and Toxicity Management Guidelines. These guidelines have been prepared by the sponsor to assist the Investigator in the exercise of his/her clinical judgment in treating these types of toxicities. These guidelines apply to AEs considered causally related to durvalumab containing regimen by the reporting investigator.

Dose reductions are not permitted. In case of doubt, the investigator should consult with the medical monitor.

3.1.4.3 Management of Chemotherapy Related Toxicities

Toxicities related to chemotherapy should be managed by following institutional local standard-of-care guidelines including dose omission, dose modification, and discontinuation of therapy.

Hematologic Events

For hematologic toxicities (eg, neutropenia and thrombocytopenia), management of the toxicity, including dose modifications or growth factor support, should be performed according to the local standard practice.

Non-hematologic Events

For non-hematologic toxicities (eg, peripheral neuropathy, cutaneous toxicity, gastrointestinal toxicity such as mucositis or diarrhea), management of the toxicity, including dose omissions, modifications, and discontinuations, should be performed according to the local standard practice.

Abnormal Hepatic Function

Chemotherapy should only be administered if hepatic function is within the local or institutional parameters specified for administration. Hepatic toxicity from taxanes may occur but is uncommon. Therefore, hepatic dysfunction that occurs while the subject is on study should prompt an evaluation to determine the cause, including the possibility of progressive metastatic disease and hepatotoxicity from concurrent medications. In the case of subjects who are receiving oleclumab with or without durvalumab, immune-mediated hepatitis should be considered and managed according to the toxicity management guidelines in the absence of a clear alternative etiology (Section 3.1.4).

3.2 Rationale for Dose, Population, and Endpoints

3.2.1 Dose Rationale

3.2.1.1 Oleclumab and Durvalumab Dose Rationale

The oleclumab starting dose of CCI Q2W × 4 then Q4W (equivalent to CCI Q2W × 4 then Q4W in a 75 kg individual) was selected based on the available clinical safety, tolerability, efficacy, and PK data from the ongoing Phase 1 Study D6070C00001. In this study oleclumab doses of CCI, and CCI Q2W were examined both as a monotherapy and in combination with durvalumab CCI Q2W. Oleclumab was well tolerated and there were no observed DLTs either as monotherapy or in combination with durvalumab (Section 1.4.1). The oleclumab CCI Q2W dose (equivalent to the oleclumab CCI Q2W fixed dose for a 75 kg individual) was identified for evaluation with durvalumab CCI Q2W in the dose-expansion phase of this study (Study D6070C00001).

The target dose of CCI Q2W × 4 was chosen with the intent to achieve exposures for the initial 70 days similar to those observed at CCI Q2W dose in Study D6070C00001 where clinical activity has been observed and CD73 is expected to have been inhibited maximally. Subsequently, a Q4W schedule at CCI is predicted to result in adequate long-term exposures with the predicted median trough of CCI The predicted trough concentration is above the estimated CD73 saturating concentration of approximately CCI (100-fold of estimated Michaelis-Menten constant [K_m] from the population PK model) to maintain optimal CD73 saturation at steady state. At the CCI Q4W maintenance dose level, the predicted median steady state trough concentration at CCI will maintain adequate concentrations during the majority of the dosing interval. Oleclumab CCI is one dose level below the highest monotherapy and combination weight-based doses that have been tested and declared tolerable in the FTIH Study D6070C00001. Therefore, oleclumab CCI × 4 then Q4W has been selected as the starting dose to be used in combination with durvalumab and standard-of-care chemotherapy. A fixed dose of oleclumab CCI × 4 then Q4W (equivalent to CCI × 4 then Q4W) is included as Dose Level -1, if needed.

The dose and schedule of durvalumab CCI Q4W in combination with oleclumab was selected based on PK/pharmacodynamics, safety and efficacy data from numerous studies containing durvalumab. As detailed in Table 46 (Durvalumab IB, edition 12), a fixed dose of CCI Q4W (equivalent to CCI) is being investigated in numerous ongoing studies. This dose was found to be well tolerated both in monotherapy (Section 5.2.2.1; Durvalumab IB, edition 12,) and in combination (Sections 5.2.2.2 to 5.2.2.6; Durvalumab IB, edition 12). Durvalumab PK exposures observed in combination therapy were consistent with the observed monotherapy exposures (Table 4; Durvalumab IB, edition 12). Similarly, in the ongoing FTIH Phase 1 study (Study D6070C00001), durvalumab CCI Q2W (equivalent to 750 mg), administered in combination with oleclumab at CCI Q2W, was well

tolerated without any DLTs (Section 1.4.1). Also, both durvalumab and oleclumab exposures in combination did not show any differences as compared to monotherapy exposures.

Previous studies and PK simulations of durvalumab have indicated that a similar AUC at steady state (4 weeks) is expected following both 10 mg/kg Q2W and CCI Q4W. As such, durvalumab CCI Q4W is considered to be equivalent to durvalumab CCI Q2W currently being utilized in the ongoing FTIH Phase 1 study (Study D6070C00001). Considering all the available PK, safety and tolerability data, a CCI Q4W dose of durvalumab is proposed in combination with oleclumab and chemotherapy to potentially derive the maximum benefit.

Rationale for Fixed Doses of Immunotherapy

Many published articles have previously reported a similarity of exposures following either fixed or body size-based dosing of mAbs (Narwal et al, 2013; Ng et al, 2006; Wang et al, 2009; Zhang et al, 2012). Wang and colleagues investigated 12 mAbs and found that fixed and body size-based dosing perform similarly, with fixed dosing being better for 7 of 12 mAbs (Wang et al, 2009). In addition, they investigated 18 therapeutic proteins and peptides and showed that fixed dosing performed better for 12 of 18 in terms of reducing the between-patient variability in PK/pharmacodynamics parameters (Zhang et al, 2012). A fixed dosing approach is also preferred by the prescribing community due to ease of use and reduced dosing errors. Given the expectation of similar PK exposure and variability, it is considered feasible to switch to fixed dosing regimens. Based on average body weight of 75 kg, the fixed dose of CCI Q4W durvalumab (equivalent to CCI Q4W) and the fixed doses of oleclumab CCI Q2W × 4 then Q4W (equivalent to CCI Q2W × 4 then Q4W) and oleclumab CCI Q2W × 4 then Q4W (equivalent to CCI Q2W × 4 then Q4W) are included in the current study.

3.2.1.2 Rationale for Doses of Chemotherapy

The standard-of-care agents being administered either alone or in combination with oleclumab with or without durvalumab will be dosed according to standard practice for the regimens. The treatment regimens are detailed in Section 3.1.2.

3.2.2 Rationale for Study Population

Durvalumab or tremelimumab monotherapy and in combination have shown modest antitumor activity in the 2L metastatic PDAC population. However, the combination regimen of these 2 agents with gemcitabine and nab-paclitaxel demonstrates clinical activity in the 1L metastatic PDAC population. In addition, oleclumab in combination with durvalumab has shown clinical activity in 2L and 3L PDAC. Therefore, oleclumab plus durvalumab combined with gemcitabine and nab-paclitaxel may potentially offer benefit to subjects with previously untreated metastatic PDAC.

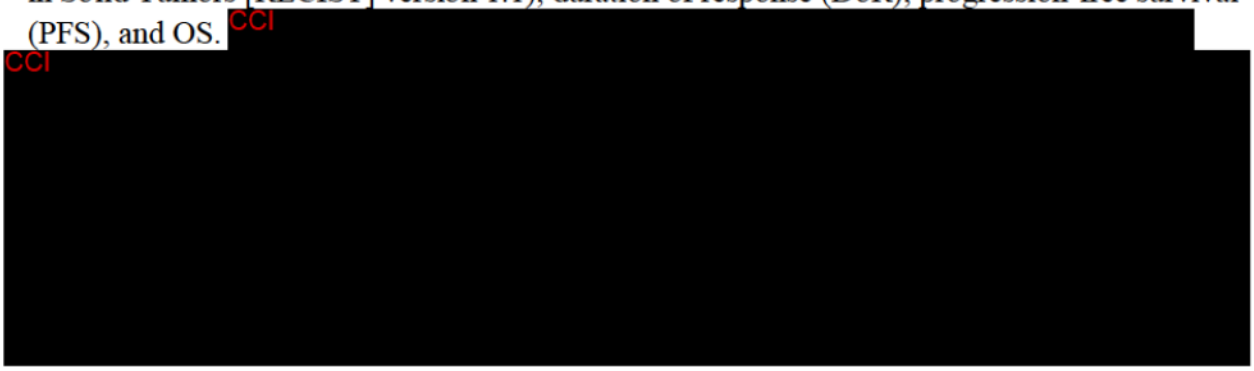
Durvalumab plus tremelimumab combined with gemcitabine and nab-paclitaxel was tolerable in the 1L metastatic PDAC population. The majority of AEs were low grade and not related to treatment. AEs ≥ Grade 3 in severity were mostly caused by chemotherapy and all were reversible and manageable. Oleclumab in combination with durvalumab was tolerable in the 2L+ metastatic PDAC population. The study design aims to minimize potential risks and to ensure that intensive monitoring, including early safety assessment via the dose escalation, is in place for those risks deemed to be most likely based on prior experience with the investigational products (including durvalumab, oleclumab, and chemotherapy agents).

PDAC is a malignancy with an extremely poor prognosis and metastatic PDAC is particularly aggressive and lethal even in the context of treatment with current therapeutic options. Therefore, PDAC represents a significant unmet medical need and underlines the need for novel therapies for this patient population. The combination of oleclumab plus gemcitabine and nab-paclitaxel or oleclumab and durvalumab plus gemcitabine and nab-paclitaxel proposed in this study for subjects with 1L metastatic PDAC may demonstrate a meaningful clinical benefit and a manageable safety profile compared with gemcitabine and nab-paclitaxel. The combination of oleclumab plus mFOLFOX or oleclumab and durvalumab plus mFOLFOX proposed in this study for subjects with 2L metastatic PDAC may demonstrate a meaningful clinical benefit and a manageable safety profile compared with mFOLFOX.

3.2.3 Rationale for Endpoint(s)

The primary aim of this study is to determine the safety and efficacy of oleclumab with or without durvalumab in combination with standard-of-care chemotherapy combinations in subjects with metastatic PDAC. Thus, the study will initially identify the MTD or highest protocol-defined dose in the absence of establishing an MTD and assess the antitumor activity for all combinations for which a confirmed safe dose is established. The occurrence of DLTs will be used to establish the MTD and thus the standard safety endpoints, such as AEs and SAEs, will be included in the evaluation.

The endpoints for assessment of antitumor activity are those routinely included in oncology studies and will include OR and disease control (DC) (based on Response Evaluation Criteria in Solid Tumors [RECIST] version 1.1), duration of response (DoR), progression-free survival (PFS), and OS. CCI



The PK parameters for oleclumab, durvalumab, and selected chemotherapies that will be determined for the secondary objective may include one or more of the following: maximum observed concentration (C_{max}), time to reach C_{max} (t_{max}), AUC, clearance, apparent volume of distribution (V_d), and terminal half-life ($t_{1/2}$) if the data allow as well as others if deemed important. As durvalumab and oleclumab will be administered on a repeating dosing schedule, the development of anti-drug antibody (ADA) and its potential effect on safety, pharmacodynamics, PK, and antitumor activity will also be assessed.

As CD73 has been shown to be prognostic and is the direct target of one of the agents utilized in this study, the correlation between CD73 expression and clinical outcome as assessed by ORR, DCR, DoR, PFS, and OS will be evaluated.

3.2.4 Rationale for Stratification Factors (Part 2 [Dose Expansion])

CD73 expression has been associated with poor prognosis and worse OS in numerous malignancies including CRC (Liu et al, 2012; Wu et al, 2012), TNBC (Loi et al, 2013), renal cell carcinoma (Yu et al, 2015), gastric cancer (Lu et al, 2013), high-grade serous ovarian cancer (Turcotte et al, 2015), and head and neck squamous cell carcinoma (Ren et al, 2016).


. Subjects in Part 2 will be required to submit either archival or fresh tumor biopsy samples for CD73 IHC testing during screening. These results will be required for stratified randomization to achieve balanced representation of the 3 treatment arms in each of these strata, thereby minimizing the likelihood of undue bias on treatment comparisons at the end of the study. The randomization will be stratified by CD73 expression level (see Section 4.6.1).

4 MATERIALS AND METHODS

4.1 Subjects

4.1.1 Number of Subjects

Up to approximately 339 subjects will be enrolled in this study: up to approximately 24 subjects in Part 1 (dose escalation) and up to approximately 315 subjects in Part 2 (dose expansion).

4.1.2 Inclusion Criteria

1 Age ≥ 18 years at the time of screening or age of consent according to law.

2 Written informed consent and any locally required authorization (eg, data privacy) obtained from the subject prior to performing any protocol-related procedures, including screening evaluations.

3 Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.

4 Weight ≥ 35 kg.

5 Subjects diagnosed with histologically or cytologically confirmed pancreatic adenocarcinoma:

   (a) For Cohort A: Subjects must not have received systemic therapy for metastatic pancreatic adenocarcinoma. If subjects received prior neoadjuvant or adjuvant chemotherapy and progressed within 6 months of the last dose, then this should be considered as a prior line of systemic therapy.

   (b) For Cohort B: Subjects must have received and radiologically progressed on only 1 prior line of systemic therapy for metastatic pancreatic adenocarcinoma. This must have been a gemcitabine-based regimen and may not have contained 5-FU, capecitabine, or oxaliplatin (if considered a line of therapy) as any of the components. If subjects received prior neoadjuvant or adjuvant chemotherapy and progressed within 6 months of the last dose, then this should be considered as a prior line of systemic therapy.

6 Subjects must have at least 1 measurable lesion according to RECIST version 1.1.

   (a) A previously irradiated lesion can be considered a target lesion if the lesion is well defined, measurable per RECIST, and has clearly progressed.

   (b) Subjects must have a non-target lesion that can be biopsied at acceptable risk (if biopsy is required for enrollment) as judged by the investigator, or if no other lesion is suitable for biopsy, then a RECIST target lesion used for biopsy must be ≥ 2 cm in longest diameter.

7 All subjects must consent to providing archival tumor specimens (core biopsies or larger resection, no fine-needle aspiration samples) for correlative biomarker studies and CD73 expression testing for stratification if tumor tissue is available. If archival specimen (≤ 12 months old) is not available, subjects must consent to a fresh biopsy.

8 Adequate organ and marrow function as defined in Table 5 (4.1.2-1).

Table 5 (4.1.2-1) Criteria for Adequate Organ and Marrow Function

	Parameter	Value
Hematological	Hemoglobin [a]	≥ 9 g/dL
	Absolute neutrophil count [a]	≥ 1,500 µ/L
	Platelet count [a]	≥ 100,000 µ/L
Hepatic	Total bilirubin	Cohort A: ≤ 1.5 × ULN Cohort B: ≤ 1.5 × ULN if no demonstrable liver metastases
		Cohort B: ≤ 3 × ULN is allowed in the presence of documented Gilbert's syndrome or liver metastases
	Alanine transaminase and Aspartate transaminase	≤ 2.5 × ULN if no demonstrable liver metastases
		≤ 5 × ULN in the presence of liver metastases
	Albumin	≥ 3 g/dL
Renal	Calculated creatinine clearance [b]	≥ 40 mL/minute

ULN = upper limit normal.

[a] Hematological criteria cannot be met with ongoing or recent blood transfusions (within 14 days prior to the scheduled first dose of study treatment) or require growth factor support (within 21 days prior to the scheduled first dose of study treatment).

[b] As determined by Cockcroft-Gault (using actual body weight) or 24-hour urine creatinine clearance.

9 Females of childbearing potential who are sexually active with a nonsterilized male partner must use at least 1 highly effective method of contraception (see Section 10.1 for definition of females of childbearing potential and for a description of highly effective methods of contraception) from screening to 180 days after the final dose of study treatment. It is strongly recommended for the male partner of a female subject to also use male condom plus spermicide throughout this period. Cessation of contraception after this point should be discussed with a responsible physician. Periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception.

10 Nonsterilized male subjects who are sexually active with a female partner of childbearing potential must use a male condom with spermicide from screening to 180 days after receipt of the final dose of study treatment. It is strongly recommended for the female partner of a male subject to also use a highly effective method of contraception throughout this period, as described in Section 10.1. In addition, male subjects must refrain from sperm donation while on study and for 180 days after the final dose of study treatment.

4.1.3 Exclusion Criteria

Any of the following would exclude the subject from participation in the study:

1 Receipt of any conventional or investigational anticancer therapy within 21 days or palliative radiotherapy within 14 days prior to the scheduled first dose of study treatment.

2 Prior receipt of any immune-mediated therapy including, but not limited to, other anti-CTLA-4, anti-PD-1, anti-PD-L1 antibodies and agents targeting CD73, CD39, or adenosine receptors, excluding therapeutic anticancer vaccines.

3 Concurrent enrollment in another therapeutic clinical study. Enrollment in observational studies will be allowed.

4 Any toxicity (excluding alopecia) from prior standard therapy that has not been completely resolved to baseline at the time of consent. Subjects with NCI CTCAE version 4.03 Grade 1 or 2 toxicities that are deemed stable or irreversible can be enrolled on a case-by-case basis with prior consultation and agreement with the medical monitor.

5 Subjects with a history of venous thrombosis within the past 3 months prior to the scheduled first dose of study treatment. NOTE: Subjects with thrombosis due to mechanical obstruction by the tumor that is found incidentally and is asymptomatic and does not require therapy may be enrolled at the investigator's discretion and should be closely monitored.

6 Subjects with prior history of myocardial infarction, transient ischemic attack, or stroke within the past 3 months prior to the scheduled first dose of study treatment.

7 Active or prior documented autoimmune disorders within the past 3 years prior to the scheduled first dose of study treatment. The following are exceptions to this criterion:

   (a) Subjects with vitiligo or alopecia.

   (b) Subjects with hypothyroidism (eg, following Hashimoto syndrome) stable on hormone replacement or psoriasis not requiring systemic treatment.

   (c) Any chronic skin condition that does not require systemic therapy.

   (d) Subjects with celiac disease controlled by diet alone.

8 Subjects with confirmed human immunodeficiency virus (even if viral load is undetectable), chronic or active hepatitis B or C, or active hepatitis A.

9 History of primary immunodeficiency, solid organ transplantation, or active tuberculosis. In settings where there is a clinical or radiographic evidence of tuberculosis, active disease must be excluded prior to enrollment.

10 Other invasive malignancy within 2 years. Noninvasive malignancies (ie, cervical carcinoma in situ, in situ prostate cancer, non-melanomatous carcinoma of the skin, ductal carcinoma in situ of the breast that has been surgically cured) are excluded from this definition.

11 Known allergy or hypersensitivity to investigational product formulations.

12 Uncontrolled intercurrent illness including, but not limited to ongoing or active infection requiring antibiotic therapy, uncontrolled hypertension, bleeding diatheses, or psychiatric illness/social situations that would limit compliance with study requirements, substantially increase risk of incurring AEs, or compromise the ability of the subject to give written informed consent.

13 Any history of leptomeningeal disease or cord compression.

14 Untreated CNS metastatic disease. Note: Subjects previously treated for CNS metastases that are radiographically and neurologically stable for at least 28 days and do not require corticosteroids (of any dose) for CNS symptomatic management for at least 14 days prior to the scheduled first dose of study treatment will be eligible.

15 Current or prior use of immunosuppressive medication within 14 days prior to the scheduled first dose of study treatment. The following are exceptions to this criterion:

(a) Intranasal, topical, inhaled corticosteroids or local steroid injections (eg, intra-articular injection).

(b) Systemic corticosteroids at physiologic doses not to exceed 10 mg/day of prednisone or equivalent.

(c) Steroids as premedication for hypersensitivity reactions (eg, computed tomography [CT] scan premedication).

16 Receipt of live, attenuated vaccine within 28 days prior to the scheduled first dose of study treatment (Note: Subjects, if enrolled, should not receive live vaccine during the study and 180 days after the last dose of study treatment). Vaccination with an inactivated vaccine is permitted at any time.

17 Major surgery (as defined by the investigator) within 28 days prior to scheduled first dose of study treatment or still recovering from prior surgery. Local procedures (eg, placement of a systemic port, core needle biopsy, and prostate biopsy) are allowed if completed at least 24 hours prior to the administration of the first dose of study treatment.

18 Females who are pregnant, lactating, or intend to become pregnant during their participation in the study.

19 Subjects who are involuntarily incarcerated or are unable to willingly provide consent or are unable to comply with the protocol procedures.

20 Any condition that, in the opinion of the investigator, would interfere with safe administration or evaluation of the investigational products or interpretation of subject safety or study results.

21 Known allergy or hypersensitivity to gemcitabine, nab-paclitaxel, oxaliplatin, leucovorin, or 5-FU.

4.1.4 Subject Enrollment and Randomization

Study participation begins (ie, a subject is "enrolled") once written informed consent is obtained. Once informed consent is obtained, a subject identification (SID) number will be assigned by a central system (eg, an Interactive Response Technology [IRT]), and the screening evaluations may begin to assess study eligibility (inclusion/exclusion) criteria. The SID number will be used to identify the subject during the screening process and throughout study participation, if applicable.

For Part 2 (dose expansion), once the subject is confirmed to be eligible, the investigator or suitably trained delegate will perform randomization in IRT. The system will randomize the eligible subject to 1 of the 3 treatment arms. Subjects will begin treatment on Cycle 1 Day 1. Treatment should start no more than 3 working days after being randomized. Subjects must not be randomized and treated unless all eligibility criteria have been met. If the subject is ineligible and not randomized, the IRT should be contacted to withdraw the subject in the system.

A master log of all consented subjects will be maintained at the site and will document all screening failures (ie, subjects who are consented but do not meet study eligibility criteria and/or are not randomized), including the reason(s) for screening failure. Site completion of the minimal set of screen failure information including demography, screen failure details, eligibility criteria, and any SAE are required.

Subjects who do not meet the criteria for participation in the study (ie, screening failures) may be rescreened. Subjects can be rescreened a single time, but they cannot be re-randomized. Rescreened subjects should be assigned a new subject number. However, rescreening should be documented so that its effect on study results, if any, can be assessed.

These subjects should have the reason for screen failure recorded in the electronic case report form (eCRF).

4.1.5 Withdrawal from the Study

Subjects are free to withdraw their consent to participate in the study (investigational product and assessments) at any time, without prejudice to further treatment. Subjects who withdraw consent will be asked about the reason(s) and the presence of any AEs. If the subject is willing, the subject will be seen and assessed by the investigator and AEs will be followed up. If a subject withdraws from further participation in the study, then no further study visits or data collection should take place.

4.1.6 Discontinuation of Investigational Product

An individual subject will not receive any further investigational product if any of the following occur in the subject in question:

1 Withdrawal of consent from the study or from further study treatment by subject
2 Unacceptable toxicity/AE that in the opinion of the investigator or MedImmune, warrants discontinuation of further dosing or meets criteria for discontinuation from investigational product as defined in Section 3.1.3.3 and Section 3.1.4
3 Lack of clinical activity or clinical benefit to the subject, in the opinion of the investigator
4 Confirmed or unconfirmed PD and the treatment criteria in the setting of PD are not met (ie, absence of clinical symptoms or signs indicating clinically significant PD; no decline in ECOG performance status indicating rapid decline; AND absence of rapid PD or threat to vital organs/critical anatomical sites requiring urgent alternative medical intervention)
5 Initiation of alternative anticancer therapy including another investigational agent
6 Intercurrent illness which, in the judgment of the investigator, would significantly affect assessments of clinical status
7 Lost to follow-up
8 Pregnancy (Section 5.6.2) or intent to become pregnant
9 Subject is determined to have met one or more of the exclusion criteria for study participation at study entry and continuing treatment with investigational product might constitute a safety risk.
10 Subject noncompliance (eg., refusal to adhere to visit schedule) that, in the opinion of the Investigator or MedImmune, warrants withdrawal

Subjects who are permanently discontinued from receiving investigational product will be followed for protocol-specified assessments including follow-up of any AEs unless consent is withdrawn from further study participation (Section 4.1.5) or the subject is lost to follow-up.

4.1.7 Treatment Beyond Progression

Subjects in all treatment arms may continue receiving their originally assigned treatment, at the investigator's discretion, after the first overall time point assessment of PD by RECIST version 1.1 until PD is confirmed on a follow-up scan (confirmed radiological PD). A confirmatory scan is required following the assessment of PD by RECIST version 1.1, preferably at the next scheduled visit and no earlier than 4 weeks after the immediate previous assessment of PD.

For all subjects who are treated through progression the investigator should ensure that the subject does not have any significant, unacceptable, or irreversible toxicities that indicate that continuing treatment will not further benefit the patients. Subjects with unconfirmed radiologic PD who are eligible to continue receiving their assigned treatment will be made aware of the potential benefits and risks of continuing treatment in the setting of PD and must provide a separate written informed consent prior to treatment.

The criteria for continuing treatment despite RECIST version 1.1-defined progression are as follows:

- There is absence of clinical symptoms or signs indicating clinically significant disease progression accompanied by a decline of more than 1 in WHO/ECOG performance status.
- There is absence of rapid disease progression or threat to vital organs or critical anatomical sites (eg, CNS metastasis, respiratory failure due to tumor compression, or spinal cord compression) requiring urgent alternative medical intervention (concurrent radiation treatment is not permitted). **NOTE:** If a subject requires palliative radiation for isolated progression at an immunologically privileged site (eg, brain) while maintaining disease control outside the CNS, consult MedImmune for an exception to this rule: protocol therapy will need to be held prior to and during the radiation.

Subjects with confirmed radiological PD may continue to receive their assigned treatment at the discretion of the investigator (following consultation with MedImmune) as long as they are gaining clinical benefit; collection of additional scans subsequent to confirmed radiological PD will continue according to the original imaging schedule.

Subjects who MedImmune and the investigator determine may not continue treatment after PD will be followed up for survival. Subjects who have discontinued treatment due to toxicity or symptomatic deterioration will be followed up until radiological PD and for survival. Subjects who have commenced subsequent anticancer therapy will be followed up only for survival.

4.1.8 Replacement of Subjects

In Part 1 (dose escalation) subjects who do not complete the DLT-evaluation period as defined in Section 3.1.3.3 will be considered non-evaluable for DLT assessment and will be replaced with another subject at the same dose level.

Subjects enrolled in Part 2 (dose expansion) will not be replaced.

4.1.9 Withdrawal of Informed Consent for Data and Biological Samples

MedImmune ensures that biological samples are returned to the source or destroyed at the end of a specified period as described in the informed consent.

If a subject withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed, and the action documented. If samples are already analyzed, MedImmune is not obliged to destroy the results of this research.

As collection of the biological samples (CCI [redacted]) is an integral part of the study, then the subject is withdrawn from further study participation.

The Principal Investigator:

- Ensures subjects' withdrawal of informed consent to the use of donated samples is notified immediately to MedImmune.
- Ensures that biological samples from that subject, if stored at the study site, are immediately identified, disposed of/destroyed, and the action documented.
- Ensures the organization(s) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed, the action documented and the signed document returned to the study site.
- Ensures that the subject and MedImmune are informed about the sample disposal.

MedImmune ensures the organization(s) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed and the action documented and returned to the study site.

4.2 Schedule of Study Procedures

4.2.1 Enrollment/Screening Period

Table 6 (4.2.1-1) shows all procedures to be conducted at the screening visit.

Whenever vital signs, 12-lead ECGs, and blood draws are scheduled for the same nominal time, the blood draws should occur last. The timing of the first 2 assessments should be such that it allows the blood draw (eg, PK blood sample) to occur at the proper nominal time.

Table 6 (4.2.1-1) Schedule of Screening Procedures (Part 1 [Dose Escalation] and Part 2 [Dose Expansion])

Procedure	Screening Visit 1 Day -28 to Day -1
Written informed consent/ assignment of SID number	X
Demographics (age, race, and ethnicity)	X
Medical history (including smoking, prior therapies and prior imaging) [a]	X
Verify eligibility criteria	X
Assessment of AEs/SAEs	X
Concomitant medications	X
Physical examination (full)	X
Height and weight	X
Vital signs	X
ECG (in triplicate)	X

Table 6 (4.2.1-1) Schedule of Screening Procedures (Part 1 [Dose Escalation] and Part 2 [Dose Expansion])

Procedure	Screening Visit 1 Day -28 to Day -1
ECOG performance status	X
Local Laboratory Assessments	
Clinical chemistry	X
Hematology	X
TSH and free T4 (If TSH is normal then free T4 is not required)	X
CCI	C
C-reactive protein	X
Lipid panel	X
Urinalysis	X
Pregnancy test, serum β-HCG [b]	X
Coagulation parameters (aPTT and INR) [c]	X
Hepatitis B, C; HIV-1	X
Disease Evaluation [d]	
Contrasted CT (preferred) of the chest, abdomen and pelvis	X
MRI (preferred) scan of brain if clinical concern for brain metastases	X
Central Laboratory Assessments	
CCI	C
CCI	C
CCI	C
CCI	C
Tumor biopsy [e]	X
CCI	C

AE = adverse event; aPTT = activated partial thromboplastin time; β-hCG = beta-human chorionic gonadotropin; CCI CT = computed tomography; CCI ; DICOM = Digital Imaging and Communications in Medicine; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; HIV-1= human immunodeficiency virus-1; INR = international normalized ratio; MRI = magnetic resonance imaging; SAE = serious adverse event; SID = subject identification; T4 = thyroxine; THS = thyroid-stimulating hormone.

[a] If allowed by country: Prior imaging includes raw imaging data (eg DICOM) of a previous disease assessment that has been performed between 4 weeks and 6 months prior to baseline scan obtained during screening.

[b] Females of childbearing potential only.

[c] If INR is not available, the sites may substitute a prothrombin time.

[d] Disease assessments obtained prior to informed consent as part of standard-of-care treatment but within 28 days of first dose may be submitted instead if the collection meets the study requirements, otherwise repeat scans should be obtained.

[e] All subjects must consent to providing archival tumor specimens for correlative biomarker studies and CD73 expression testing for stratification if tumor tissue is available. If archival tissue is not available or if the archival tissue was taken over 12 months ago, then subjects must consent to and provide a fresh biopsy as part of screening prior to first dose of study treatment.

4.2.2 Treatment Period

All procedures to be conducted during the treatment period are shown in Table 7 (4.2.2-1) for Cohort A and in Table 8 (4.2.2-2) for Cohort B.

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Table 7 (4.2.2-1) Schedule of Treatment Period Study Procedures (Cohort A: Part 1 [Dose Escalation] and Part 2 [Dose Expansion])

	Cycle 1			Cycle 2			Cycle 3			Cycle 4			Cycle 5			Cycle 6 and subsequent cycles		
	28-day cycle: Window for each assessment after Cycle 1 Day 1 is ±3 days, window for tumor assessment ±7 days																	
Procedure	**D1**	**D8**	**D15**	**D1**	**D8**	**D15**	**D1**	**D8**	**D15**	**D1**	**D8**	**D15**	**D1**	**D8**	**D15**	**D1**	**D8**	**D15**
Targeted physical examination (based on symptoms) and at other visits as clinically indicated	X			X						X						D1 Q2 cycles starting with C6		
Weight	D1 of each cycle																	
Vital signs [a]	All visits																	
ECG (in triplicate) [b]	X									X						C8 D1 only		
ECOG performance status	X			X						X						D1 Q2 cycles starting with C6		
CCI [redacted]																		
Concomitant medications	All Visits																	
Assessment of AEs/SAEs	All Visits																	
Disease Evaluation																		
Disease assessment (scans)	Acquire scans Q8W ± 7 days for the first 48 weeks and then Q12W ± 7 days thereafter relative to the date of first dose until confirmed radiological progression, unless not clinically feasible. This imaging schedule MUST be followed regardless of any delays in dosing																	
Local Laboratory Assessments [c]																		
Clinical chemistry	X [d]	X	X	X		X	X			X			X			X		
Hematology	X [d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Table 7 (4.2.2-1) Schedule of Treatment Period Study Procedures (Cohort A: Part 1 [Dose Escalation] and Part 2 [Dose Expansion])

	Cycle 1			Cycle 2			Cycle 3			Cycle 4			Cycle 5			Cycle 6 and subsequent cycles		
	28-day cycle: Window for each assessment after Cycle 1 Day 1 is ±3 days, window for tumor assessment ±7 days																	
Procedure	**D1**	**D8**	**D15**	**D1**	**D8**	**D15**	**D1**	**D8**	**D15**	**D1**	**D8**	**D15**	**D1**	**D8**	**D15**	**D1**	**D8**	**D15**
TSH and free T4 (If TSH is normal then free T4 is not required)	X [d]			X			X			X			D1 Q2 cycles starting with C5					
CCI																		
Urinalysis	X [d]						X						D1 Q2 cycles starting with C5					
Pregnancy test [e]	X	As clinically indicated																
Coagulation parameters (aPTT and INR) [f]	As clinically indicated																	
Pharmacokinetics [g]																		
Serum for oleclumab PK (Part 1 and Arms A2 and A3)	X			X			X			X			D1 Q3 cycles starting with C5 through C11					
Serum for durvalumab PK (Part 1 and Arm A3)	X			X			X			X			D1 Q3 cycles starting with C5 through C11					
Plasma for gemcitabine PK	X									X								
Plasma for nab-paclitaxel PK	X									X								
Central Laboratory Assessments [c]																		
Serum for oleclumab ADA (Part 1 and Arms A2 and A3)	X			X			X						D1 Q3 cycles starting with C5					

Table 7 (4.2.2-1) Schedule of Treatment Period Study Procedures (Cohort A: Part 1 [Dose Escalation] and Part 2 [Dose Expansion])

	Cycle 1			Cycle 2			Cycle 3			Cycle 4			Cycle 5			Cycle 6 and subsequent cycles		
	28-day cycle: Window for each assessment after Cycle 1 Day 1 is ±3 days, window for tumor assessment ±7 days																	
Procedure	**D1**	**D8**	**D15**	**D1**	**D8**	**D15**	**D1**	**D8**	**D15**	**D1**	**D8**	**D15**	**D1**	**D8**	**D15**	**D1**	**D8**	**D15**
Serum for durvalumab ADA (Part 1 and Arm A3)	X			X			X						D1 Q3 cycles starting with C5					
CCI																		
CCI																		
CCI																		
Treatment Administration																		
Oleclumab (Part 1 and Arms A2 and A3)	X		X	X		X	X			X			X			X		
Durvalumab (Part 1 and Arm A3)	X			X			X			X			X			X		
Gemcitabine	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Nab-paclitaxel	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

ADA = anti-drug antibody(ies); AE = adverse event; aPTT = activated partial thromboplastin time; β-hCG = beta-human chorionic gonadotropin; C = cycle; CCI ; CCI D = day; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; CCI ; CCI = CCI ; INR = international normalization ratio; PK = pharmacokinetic(s); SAE = serious adverse event; Q2 = every 2; Q3 = every 3; Q8W = every 8 weeks; Q12W = every 12 weeks; T4 = thyroxine; TSH = thyroid-stimulating hormone.

[a] Vital signs: On days of investigational product administration, vital signs will be measured according to the collection times in Table 10 (4.3.3-1).
[b] ECGs: On days of investigational product administration, ECGs will be measured according to the collection times in Table 11 (4.3.3-2).
[c] Local and Central Labs: Assessments will be collected prior to administration of any investigational product. All safety laboratory results must be reviewed by the investigator or physician designee prior to administration of any investigational product.
[d] If screening assessments have been performed within the 5 days prior to Cycle 1 Day 1 (Days -5 to -1), then assessment does not need to be performed on Cycle 1 Day 1 pre-dose.
[e] Pregnancy test: For women of childbearing potential only. A urine or serum pregnancy test is acceptable, if urine test is positive or equivocal then serum β-hCG testing should be performed for confirmation. Women of childbearing potential are required to have a pregnancy test within 7 days prior to the first dose of study treatment. Pregnancy test may occur on Cycle 1 Day 1, but results must be available and reviewed by the treating physician or investigator prior to administration of any investigational product.
[f] Coagulation tests: aPTT and INR – only performed at screening and as clinically indicated. If INR is not available, the sites may substitute a prothrombin time.
[g] PK samples: Serum samples for oleclumab and durvalumab PK will be collected pre-dose (within 90 minutes prior to start of infusion) and 10 minutes (± 5 minutes) post end of the respective infusion. Plasma samples for gemcitabine and nab-paclitaxel will be collected pre-dose (within 90 minutes prior to start of infusion) and 10 minutes (± 5 minutes) post end of the respective infusion for first dose of Cycles 1 and 4.

Table 8 (4.2.2-2) Schedule of Treatment Procedures (Cohort B: Part 1 [Dose Escalation] and Part 2 [Dose Expansion])

	Cycle 1		Cycle 2		Cycle 3		Cycle 4		Cycle 5		Cycle 6 and subsequent cycles	
	28-day cycle: Window for each assessment after Cycle 1 Day 1 is ±3 days, window for tumor assessment ±7 days											
Procedure	**D1**	**D15**	**D1**	**D15**	**D1**	**D15**	**D1**	**D15**	**D1**	**D15**	**D1**	**D15**
Targeted physical examination (based on symptoms) and at other visits as clinically indicated	X		X				X				D1 Q2 cycles starting with C6	
Weight	D1 of each cycle											
Vital signs [a]	All visits											
ECG (in triplicate) [b]	X						X				C8 D1 only	
ECOG performance status	X		X				X				D1 Q2 cycles starting with C6	
CCI [redacted]	[redacted]											
CCI [redacted]	[redacted]											
Concomitant medications	All visits											
Assessment of AEs/SAEs	All visits											
Disease Evaluation												
Disease assessment (scans)	Acquire scans Q6W ± 7 days for the first 24 weeks and then Q8W ± 7 days thereafter relative to the date of first dose until confirmed radiological progression, unless not clinically feasible. This imaging schedule MUST be followed regardless of any delays in dosing.											
Local Laboratory Assessments [c]												
Clinical chemistry	X [d]	X	X	X	X		X		X		X	
Hematology	X [d]	X	X	X	X	X	X	X	X	X	X	X

Table 8 (4.2.2-2) Schedule of Treatment Procedures (Cohort B: Part 1 [Dose Escalation] and Part 2 [Dose Expansion])

	Cycle 1		Cycle 2		Cycle 3		Cycle 4		Cycle 5		Cycle 6 and subsequent cycles	
	28-day cycle: Window for each assessment after Cycle 1 Day 1 is ±3 days, window for tumor assessment ±7 days											
Procedure	**D1**	**D15**	**D1**	**D15**	**D1**	**D15**	**D1**	**D15**	**D1**	**D15**	**D1**	**D15**
TSH and free T4 (If TSH is normal then free T4 is not required)	X [d]		X		X		X		D1 Q2 cycles starting with C5			
CA19-9	X [d]		X		X		X		D1 Q2 cycles starting with C5			
Urinalysis	X [d]				X				D1 Q2 cycles starting with C5			
Pregnancy test [e]	X	As clinically indicated										
Coagulation parameters (aPTT and INR) [f]	As clinically indicated											
Pharmacokinetics [g]												
Serum for oleclumab PK (Part 1 and Arms B2 and B3)	X		X		X		X		D1 Q3 cycles starting with C5 through C11			
Serum for durvalumab PK (Part 1 and Arm B3)	X		X		X		X		D1 Q3 cycles starting with C5 through C11			
Central Laboratory Assessments [c]												
Serum for oleclumab ADA (Part 1 and Arms B2 and B3)	X		X		X				D1 Q3 cycles starting with C5			
Serum for durvalumab ADA (Part 1 and Arm B3)	X		X		X				D1 Q3 cycles starting with C5			
CCI [redacted]												

Table 8 (4.2.2-2) Schedule of Treatment Procedures (Cohort B: Part 1 [Dose Escalation] and Part 2 [Dose Expansion])

	Cycle 1		Cycle 2		Cycle 3		Cycle 4		Cycle 5		Cycle 6 and subsequent cycles	
	28-day cycle: Window for each assessment after Cycle 1 Day 1 is ±3 days, window for tumor assessment ±7 days											
Procedure	**D1**	**D15**	**D1**	**D15**	**D1**	**D15**	**D1**	**D15**	**D1**	**D15**	**D1**	**D15**
Whole blood for gene expression profiling	X	X	X									
Treatment Administration												
Oleclumab (Part 1 and Arms B2 and B3)	X	X	X	X	X		X		X		X	
Durvalumab (Part 1 and Arm B3)	X		X		X		X		X		X	
Oxaliplatin	X	X	X	X	X	X	X	X	X	X	X	X
5-FU/leucovorin	X	X	X	X	X	X	X	X	X	X	X	X

ADA = anti-drug antibody(ies); AE = adverse event; aPTT = activated partial thromboplastin time; β-hCG = beta-human chorionic gonadotropin; C = cycle; CCI ; CCI ; D = day; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; CCI ; CCI ; INR =international normalization ratio; PK = pharmacokinetic(s); Q2 = every 2; Q3 = every 3;Q6W = every 6 weeks; Q8W = every 8 weeks; SAE = serious adverse event; T4 = thyroxine; TSH = thyroid-stimulating hormone.

[a] Vital signs: On days of investigational product administration, vital signs will be measured according to the collection times in Table 10 (4.3.3-1).

[b] ECGs: On days of investigational product administration, ECGs will be measured according to the collection times in Table 11 (4.3.3-2).

[c] Local and Central Labs: Assessments will be collected prior to administration of any investigational product. All safety laboratory results must be reviewed by the investigator or physician designee prior to administration of any investigational product.

[d] If screening assessments have been performed within the 5 days prior to Cycle 1 Day 1 (Days -5 to -1), then assessment does not need to be performed on Cycle 1 Day 1 pre-dose.

[e] Pregnancy test: For women of childbearing potential only. A urine or serum pregnancy test is acceptable, if urine test is positive or equivocal then serum β-hCG testing should be performed for confirmation. Women of childbearing potential are required to have a pregnancy test within 7 days prior to the first dose of study treatment. Pregnancy test may occur on Cycle 1 Day 1, but results must be available and reviewed by the treating physician or investigator prior to administration of any investigational product.

[f] Coagulation tests: aPTT and INR – only performed at screening and as clinically indicated. If INR is not available the sites may substitute a prothrombin time.

[g] PK samples: Serum samples for oleclumab and durvalumab PK will be collected pre-dose (within 90 minutes prior to start of infusion) and 10 minutes (± 5 minutes) post end of the respective infusion.

4.2.3 Follow-up Period

Table 9 (4.2.3-1) shows all procedures to be conducted during the follow-up period.

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Table 9 (4.2.3-1) Schedule of Follow-up Procedures (Part 1 [Dose Escalation] and Part 2 [Dose Expansion])

Procedure	Follow-up Period	
	FUP-1	FUP-n
	4 Weeks Post Last Dose (± 7 Days)	Q8W (± 7 days) Starting 12 Weeks Post Last Dose
Clinical Assessments		
Physical examination (abbreviated, symptom-directed)	X	
Weight	X	
Vital signs	X	
ECG (in triplicate)	X	Only FUP-2
ECOG performance status	X	
CCI		
Concomitant medications	X	
Assessment of AEs/SAEs	X	Only FUP-2
Follow-up for survival and subsequent anticancer treatment (telephone contact if visits are discontinued)		X
Local Laboratory Assessments		
Clinical chemistry	X	
Hematology	X	
TSH and free T4 (If TSH is normal then free T4 is not required)	X	
CCI		

Table 9 (4.2.3-1) Schedule of Follow-up Procedures (Part 1 [Dose Escalation] and Part 2 [Dose Expansion])

Procedure	Follow-up Period	
	FUP-1	FUP-n
	4 Weeks Post Last Dose (± 7 Days)	Q8W (± 7 days) Starting 12 Weeks Post Last Dose
Lipid panel	X	
Pregnancy test [b]	X	Q4W starting 8 weeks through 28 weeks post last dose
Urinalysis	X	
Disease Evaluation		
Disease assessment (scans) [a]	For Cohort A: Acquire scans Q8W ± 7 days for the first 48 weeks and then Q12W ± 7 days thereafter relative to the date of first dose until confirmed radiological progression, unless not clinically feasible For Cohort B: Acquire scans Q6W ± 7 days for the first 24 weeks and then Q8W ± 7 days thereafter relative to the date of first dose until confirmed radiological progression, unless not clinically feasible	
Central Laboratory Assessments		
Serum for oleclumab PK (Part 1 and Arms A2, A3, B2, and B3)		Only FUP-2
Serum for oleclumab ADA (Part 1 and Arms A2, A3, B2, and B3)		Only FUP-2
Serum for durvalumab PK (Part 1 and Arms A3 and B3)		Only FUP-2
Serum for durvalumab ADA (Part 1 and Arms A3 and B3)		Only FUP-2
CCI [redacted]		

ADA = anti-drug antibody; AE = adverse event; β-hCG = beta-human chorionic gonadotropin; CCI [redacted]; CCI [redacted]; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; CCI [redacted] CCI [redacted] FUP = follow-up; PK = pharmacokinetic; Q6W = every 6 weeks; Q8W = every 8 weeks; Q12W = every 12 weeks; SAE = serious adverse event; T4 = thyroxine; THS = thyroid-stimulating hormone.

[a] Only for subjects who discontinued for reasons other than progressive disease.

[b] Females of childbearing potential only. Urine pregnancy tests will be performed either on site or at home; the study site will contact the subject by phone to obtain results for tests performed at home. If urine test is positive or equivocal then serum β-hCG testing should be performed for confirmation.

4.3 Description of Study Procedures

4.3.1 Efficacy

The primary assessment of tumor response will be based on RECIST version 1.1 (Eisenhauer et al, 2009); see Section 10.7) and will be performed according to the schedules in Section 4.2. All images will be collected and stored for possible future central re-analysis. The assessment schedule also applies to those subjects who continue to receive study therapy in the setting of PD (Section 3.1.2). For those subjects who discontinue study therapy as a result of confirmed PD, disease evaluation will be performed at the end of treatment visit if clinically appropriate (ie, in the absence of rapidly deteriorating clinical status). After discontinuation of investigational product(s), all subjects will complete the end of treatment visit and enter follow-up; disease evaluation will be performed according to the schedule in Table 9(4.2.3.-1). Additional disease assessments may be performed as clinically indicated.

Tumor assessments may include the following evaluations: cross-sectional imaging using CT or magnetic resonance imaging (MRI) scan of the chest, abdomen, pelvis; and brain. CT or MRI scan of the chest, abdomen, and pelvis will be performed with each disease assessment for all subjects. Additionally, CT or MRI scan of the brain will be performed at screening for all subjects with clinical concern for brain metastasis. Any subjects with brain metastases at screening or any subjects who develop neurologic or other clinical symptoms that warrant imaging must also have brain imaging with each disease assessment. The preferred method of disease assessment is CT with contrast; if CT with contrast is contraindicated, CT without contrast is preferred over MRI. The preferred method for CNS imaging is MRI; if CT scan is performed, CT with contrast is required. The same method is preferred for all subsequent tumor assessments.

Computed tomography scan

- CT (contrast preferred) scans of the chest, abdomen, and pelvis should be performed with contiguous cuts in slice thickness of 5 mm or less. Spiral CT should be performed using a 5-mm contiguous reconstruction algorithm. The same imaging device should be used for serial evaluations.

Magnetic resonance imaging scan

- MRI scan of the chest, abdomen, and pelvis is acceptable for measurement of lesions provided that the same anatomical plane is used for serial assessments.
- In case of MRI, measurements will be preferably performed in the axial (transverse) plane on contrast-enhanced T1-weighted images. However, there are no specific sequence recommendations.

4.3.1.1 CCI

CCI

[redacted]

4.3.2 CCI

CCI

[redacted]

CCI

4.3.2.1 CCI

4.3.2.2 CCI

CCI

[redacted]

4.3.3 Medical History and Physical Examination, Electrocardiogram, Weight, and Vital Signs

Medical History

Medical history will be collected at screening. Based on findings from medical history, ongoing current conditions will be given a baseline grade according to the procedure for AEs. Increases in severity of pre-existing conditions during the study will be considered AEs, with resolution occurring when the grade returns to the pre-study grade or below.

Physical Examinations

Physical examinations will be performed according to the schedules in Section 4.2. A complete physical examination will be performed at screening and should include assessments of the head, eyes, ears, nose, and throat, respiratory, cardiovascular, gastrointestinal, musculoskeletal, neurological, psychiatric, dermatological, hematologic/lymphatic, endocrine systems, and weight to 0.1 kg; and height (at screening only). Abbreviated symptom-directed physical examinations will be conducted at subsequent visits post dosing.

Vital Signs

Vital signs (temperature, blood pressure, pulse rate, and respiratory rate) will be measured according to the schedules in Section 4.2. Collection times during the treatment period are detailed below in Table 10 (4.3.3-1). For all vital sign measurements, subjects should rest for at least 10 minutes in a supine or semi-recumbent position, and all vital sign measurements should be taken prior to any blood draws or other procedures whenever possible.

Table 10 (4.3.3-1) Collection Times for Vital Signs During the Treatment period

Treatment Arm	Oleclumab		Durvalumab		Chemotherapy [a]	
	Pre-dose	EOI	Pre-dose	EOI	Pre-dose	EOI
A1 and B1	NA	NA	NA	NA	Within 30 minutes	Within 15 minutes
A2 and B2	Within 30 minutes	Within 15 minutes	NA	NA	Same as oleclumab EOI or within 30 minutes on chemotherapy only dosing days	Within 15 minutes
Part 1, A3, and B3	Within 30 minutes	Within 15 minutes	Same as oleclumab EOI	Within 15 minutes	Same as oleclumab or durvalumab EOI or within 30 minutes on chemotherapy only dosing days	Within 15 minutes

5-FU = 5-fluorouracil; EOI = end of infusion; NA = not applicable.
[a] Excludes 5-FU continuous infusion.

Electrocardiograms

According to the schedules in Section 4.2, 12-lead ECGs will be obtained by the site in triplicate (all 3 within a 5-minute time period) after the subject has been in supine or semi-recumbent rest for 10 minutes. Collection times during the treatment period are detailed below in Table 11 (4.3.3-2).

In case of clinically significant ECG abnormalities including an ECG that demonstrates a QTcF value > 500 msec, 2 additional 12-lead ECGs should be obtained over a brief period (eg, 30 minutes) to confirm prolongation based on the average QTcF value manually over-read by a medically qualified person.

Table 11 (4.3.3-2) Collection Times for Electrocardiograms During the Treatment period

Treatment Arm	Oleclumab		Durvalumab		Chemotherapy [a]	
	Pre-dose	EOI	Pre-dose	EOI	Pre-dose	EOI
A1 and B1	NA	NA	NA	NA	Within 30 minutes	Within 15 minutes
A2 and B2	Within 30 minutes	Within 15 minutes	NA	NA	Same as oleclumab EOI or within 30 minutes on chemotherapy only dosing days	Within 15 minutes
Part 1, A3, and B3	Within 30 minutes	Within 15 minutes	Same as oleclumab EOI	Within 15 minutes	Same as oleclumab or durvalumab EOI or within 30 minutes on chemotherapy only dosing days	Within 15 minutes

5-FU = 5-fluorouracil; EOI = end of infusion; NA = not applicable.
[a] Excludes 5-FU continuous infusion.

4.3.4 Clinical Laboratory Tests

A Laboratory Manual will be provided to the sites that specifies the procedures for collection, processing, storage, and shipment of samples, as well as laboratory contact information, specific to this clinical research study.

Clinical laboratory safety tests will be performed in a licensed clinical laboratory. Urine pregnancy tests may be performed at the site using a licensed test (dipstick). Abnormal laboratory results should be repeated as soon as possible (preferably within 24 to 48 hours).

The following clinical laboratory tests will be performed (see Section 4.2 for the schedules of tests):

Serum/Plasma Chemistry

• Sodium	• ALT
• Potassium	• Total bilirubin (A direct bilirubin should be obtained if total bilirubin is > ULN)
• Bicarbonate	• ALP
• Blood urea nitrogen	• Albumin
• Creatinine	• Gamma-glutamyl transpeptidase
• Glucose	• Total protein
• Calcium	• Lactate dehydrogenase
• Magnesium	• Amylase
• AST	• Lipase

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; ULN = upper limit normal

Note for serum/plasma chemistry: Tests for AST, ALT, ALP, and total bilirubin must be conducted concurrently and assessed concurrently.

Lipid Panel

• Total Cholesterol	• Triglycerides

Hematology

• White blood cells count	• Absolute monocyte count
• Absolute neutrophil count	• Hemoglobin
• Absolute lymphocyte count	• Platelet count

Urinalysis

• Protein	• Blood
• Ketones	• If abnormal, then microscopy including WBC/HPF, RBC/HPF

HPF = high power field; RBC = red blood cells; WBC = white blood cells.

Pregnancy Test (females of childbearing potential only)

• Urine hCG	• Serum β-hCG (at screening only and if a urine hCG is equivocal or positive during the remainder of the study)

β-hCG = beta-human chorionic gonadotropin; hCG = human chorionic gonadotropin.

Other Safety Tests

- Coagulation tests: activated partial thromboplastin time and international normalized ratio. If international normalized ratio is not available the sites may substitute a prothrombin time.
- Hepatitis B testing: hepatitis B surface antigen, hepatitis B surface antibody, hepatitis B core antibody, IgM hepatitis B core antibody. If hepatitis B core (total) antibody testing is unavailable, then the hepatitis B core IgG and IgM should both be obtained instead. If a test is not locally available, then standard local practice for assessing hepatitis B status should be utilized. If screening tests are positive, a HBV-DNA test should be obtained to assess infection status.
- Hepatitis C antibody. If screening antibody is positive, a HCV-RNA tests should be performed to assess infection status.
- Human immunodeficiency virus-1 antibody.
- Thyroid function tests: thyroid-stimulating hormone (TSH) and free thyroxine (T4). Note: If TSH is normal then free T4 is not required.
- C-reactive protein.

4.3.5 Pharmacokinetic Evaluation and Methods

Blood will be collected to evaluate PK of oleclumab and durvalumab in serum (see Section 4.2 for collection time points). The PK of oleclumab and durvalumab in serum will be measured utilizing a validated assay.

Blood samples will be collected for determination of nab-paclitaxel and gemcitabine concentration in plasma (see Section 4.2 for collection time points). Plasma samples will be analyzed using appropriate bioanalytical methods. Details of sample processing, handling, shipment, and storage are provided in the Laboratory Manual. Full details of the analytical methods used will be described in separate bioanalytical reports.

4.3.6 Immunogenicity Evaluation and Methods

Blood samples will be collected to evaluate ADA responses to oleclumab and durvalumab in serum (see Section 4.2 for collection time points). These evaluations will be performed utilizing a validated immunoassay method.

4.3.7 CCI

CCI [redacted]

4.3.8 CCI

The subject's consent to the use of donated biological samples is mandatory.

CCI [redacted]

CCI

[redacted]

CCI

CCI

Details regarding specimen collection, processing, and testing will be provided in the Laboratory Manual.

CCI

[redacted]

CCI [redacted]

[redacted]

[redacted]

[redacted].

4.3.8.1 Storage, Re-use and Destruction of Biological Samples

Samples will be stored for a maximum of 15 years from the date of the Last Subject's Last Visit, after which they will be destroyed. The results of this biomarker research will be reported either in the clinical study report (CSR) itself or as an addendum, or separately in a scientific report or publication. The results of this biomarker research may be pooled with biomarker data from other studies with the study drug to generate hypotheses to be tested in future research.

4.3.9 Estimate of Volume of Blood Be Collected

A total of no more than 70 mL (15 teaspoons) of blood will be required for all screening tests. No more than 50 mL (12 teaspoons) of blood will be drawn on any visit day after screening. The total volume to be collected will depend on the number of doses administered and the length of follow-up.

4.4 Study or Study Component Suspension or Termination

MedImmune reserves the right to temporarily suspend or permanently terminate this study or any component of the study at any time. The reasons for temporarily suspending or permanently terminating the study may include but are not limited to the following:

1 The incidence or severity of AEs in this or other studies indicates a potential health hazard to subjects
2 Subject enrollment is unsatisfactory
3 Noncompliance that might significantly jeopardize the validity or integrity of the study

4 Sponsor decision to terminate development of the investigational product for this indication

5 Sponsor decision to terminate the study based on a planned futility analysis

If MedImmune determines that temporary suspension or permanent termination of the study or component of the study is required, MedImmune will discuss the reasons for taking such action with all participating investigators (or head of the medical institution, where applicable). When feasible, MedImmune will provide advance notice to all participating investigators (or head of the medical institution, where applicable) of the impending action.

If the study or component of the study is suspended or terminated for safety reasons, MedImmune will promptly inform all investigators, heads of the medical institutions (where applicable), and/or institutions conducting the study. MedImmune will also promptly inform the relevant regulatory authorities of the suspension/termination along with the reasons for such action. Where required by applicable regulations, the investigator or head of the medical institution must inform the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) promptly and provide the reason(s) for the suspension/termination. If the study or component of the study is suspended for safety reasons and it is deemed appropriate by MedImmune to resume the study or component of the study, approval from the relevant regulatory authorities (and IRBs/IECs when applicable) will be obtained prior to resuming the study.

4.4.1 Continued Treatment at Study Completion

Any study subject still receiving investigational product at the time of data entry cut-off will continue to receive investigational product 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 is deriving clinical benefit and has not fulfilled any treatment discontinuation criteria (Section 4.1.6). The duration of treatment will be until disease progression, withdrawal or until continued treatment is unfeasible. During this continued treatment period after data cut-off for analysis of final study data, assessments will revert to the standard of care for each individual site.

Following the data cut-off for the final analysis of the study data, the IRT will be closed and the investigational product dispensation will be manually ordered by the study site. The investigational product accountability information must continue to be maintained and collected by the study site until all the site's study subjects permanently complete receipt of investigational product.

Data expected on and after the data cut-off for the final analysis of the study data will not be entered into the clinical study database by sites. During a study subject's continued treatment period after data cut-off for analysis of final study data, SAEs, overdoses, and pregnancies

will be reported using paper-based CRFs until 28 days after the study subject's last dose of investigational product. Reported SAE data will be entered by the sponsor into the sponsor's global safety database.

Individual sites will be closed after safety database lock has occurred and site's final study subject completes the 12-week follow-up visit. The continued treatment period after data cut-off for analysis of final study data will remain available to study subjects until treatment discontinuation, which is defined as the date of the last study subject's 12-week follow-up visit.

4.5 Investigational Products

4.5.1 Identity of Investigational Product(s)

MedImmune will provide the investigator(s) with investigational product (Table 12 (4.5.1-1) using designated distribution centers.

Table 12 (4.5.1-1) Identification of Investigational Products

Investigational Product	Manufacturer	Concentration and Formulation as Supplied
Oleclumab (MEDI9447)	MedImmune	CCI [redacted]
Durvalumab (MEDI4736)	MedImmune	

w/v = weight/volume.

CCI [redacted]

CCI [redacted]

CCI [redacted]

Each investigational product kit has a unique number that is printed on all labels within the kit (ie, the outer carton label and the label of each container within the carton). Each carton and vial is labeled with the same unique sequence number range.

The investigator's or site's designated investigational product manager is required to maintain accurate investigational product accountability records. Upon completion of the study, copies of investigational product accountability records will be returned to MedImmune. All unused investigational products will be returned to a MedImmune-authorized depot or disposed of upon authorization by MedImmune according to the investigational site policy. All investigational products should be kept in a secure and dry place. Vials should be stored at 2°C to 8°C (refrigerated) and must not be frozen. Drug product should be kept in original packaging until use to prevent prolonged light exposure.

4.5.1.1 Investigational Product Inspection

Each vial selected for dose preparation should be inspected.

If any defects are noted with the investigational product(s), the investigator and site monitor should be notified immediately. Refer to the Product Complaint section (Section 4.5.1.6) for further instructions.

During the inspection if the solution is turbid or if any discoloration, or particulates are observed, the site monitor should be notified immediately and the vial(s) should be stored in QUARANTINE at refrigerated (2°C to 8°C [36°F to 46°F]) temperature for drug accountability and potential future inspection.

After removing the required number of vials for oleclumab (MEDI9447) dose preparation (2 vials for the CCI [redacted] dose; 3 vials for the CCI [redacted] dose; 6 vials for the CCI [redacted] dose) from the carton container, the carton should be immediately returned to storage at 2°C to 8°C (36°F to 46°F).

4.5.1.2 Oleclumab (MEDI9447) IV Bag Preparation and Administration

The oleclumab (MEDI9447) doses must be prepared by the investigator's or site's designated investigational product manager using aseptic technique.

Total time from needle puncture of the oleclumab (MEDI9447) vial to the start of administration should not exceed:

- 24 hours at 2°C to 8°C (36°F to 46°F)
- 4 hours at room temperature

No incompatibilities between oleclumab (MEDI9447) and polyvinylchloride or polyolefin bags have been observed.

For subjects > 30 kg in weight, doses of CCI (in the event of a de-escalation), CCI, and CCI will be administered using an IV bag containing 0.9% (w/v) saline, with a final oleclumab (MEDI9447) concentration ranging from 1.5 to 30 mg/mL, and delivered through an IV administration set with a 0.2- or 0.22-µm filter. Add 15 mL (ie, CCI dose), 30 mL (ie, CCI dose), or 60.0 mL (ie, CCI dose) of oleclumab (MEDI9447)) to the IV bag. The IV bag size should be selected such that the final concentration is within 1.5 to 30 mg/mL. Mix the bag by gently inverting to ensure homogeneity of the dose in the bag.

Oleclumab (MEDI9447) will be administered at room temperature (approximately 20 to 25°C) by controlled infusion into a peripheral or central vein. Standard infusion time for oleclumab (MEDI9447) is 1 hour (+ 15 minutes); however, if there are interruptions during infusion, the total allowed infusion time should not exceed 4 hours at room temperature.

Do not co-administer other drugs through the same infusion line.

Flush the IV line with a volume of IV diluent equal to the priming volume of the infusion set used after the contents of the IV bag are fully administered, or complete the infusion according to institutional policy to ensure the full dose is administered and document if the line was not flushed.

If either preparation time or infusion time exceeds the time limits, a new dose must be prepared from new vials. Oleclumab (MEDI9447) does not contain preservatives, and any unused portion must be discarded.

4.5.1.3 Durvalumab (MEDI4736) IV Bag Preparation and Administration

The dose of durvalumab (MEDI4736) for administration must be prepared by the investigator's or site's designated investigational product manager using aseptic technique.

Total time from needle puncture of the durvalumab (MEDI4736) vial to the start of administration should not exceed:

- 24 hours at 2°C to 8°C (36°F to 46°F)
- 4 hours at room temperature

A dose of CCI (for subjects > 30 kg in weight) will be administered using an IV bag containing 0.9% (w/v) saline or 5% (w/v) dextrose, with a final durvalumab (MEDI4736) concentration ranging from 1 to 15 mg/mL, and delivered through an IV administration set with a 0.2- or 0.22-µm filter. Add 30.0 mL of durvalumab (MEDI4736) (ie, CCI of

durvalumab [MEDI4736]) to the IV bag. The IV bag size should be selected such that the final concentration is within 1 to 15 mg/mL. Mix the bag by gently inverting to ensure homogeneity of the dose in the bag.

Durvalumab (MEDI4736) IV infusion will start no less than 15 minutes after the end of oleclumab (MEDI9447) infusion. Standard infusion time for durvalumab (MEDI4736) is 1 hour (+15 minutes); however, if there are interruptions during infusion, the total allowed infusion time should not exceed 8 hours at room temperature.

Do not co-administer other drugs through the same infusion line.

Flush the IV line with a volume of IV diluent equal to the priming volume of the infusion set used after the contents of the IV bag are fully administered, or complete the infusion according to institutional policy to ensure the full dose is administered and document if the line was not flushed.

If either preparation time or infusion time exceeds the time limits, a new dose must be prepared from new vials. Durvalumab (MEDI4736) does not contain preservatives, and any unused portion must be discarded.

4.5.1.4 Treatment Administration

The first day of dosing is considered Day 1. Dose preparation and administration instructions are provided in Section 4.5.1.2 for oleclumab (MEDI9447) and in Section 4.5.1.3 for durvalumab (MEDI4736). All therapies will be administered on the same day. For Part 1 (dose escalation), the order of the administration will be: oleclumab (MEDI9447), durvalumab (MEDI4736), and then chemotherapy according to institutional practice. For Part 2 (dose expansion), the same order of administration should be followed for all therapies that are to be administered based upon the randomized arm.

Chemotherapy infusion times are listed below:

- Nab-paclitaxel CCI administered by IV infusion over 30 to 40 minutes followed by gemcitabine CCI administered by IV infusion over 30 to 40 minutes, and according to institutional practice
- Oxaliplatin CCI and leucovorin CCI administered by IV infusion over 2 hours, followed by 5-FU CCI IV bolus, then 5-FU CCI administered by continuous IV infusion over 46 to 48 hours, and according to institutional practice

No specific premedication is required for oleclumab (MEDI9447) or durvalumab (MEDI4736). Subjects should receive standard premedication according to the standard local practice for each chemotherapy. Details of any premedication or concomitant medication given to manage or prevent AEs should be recorded on the eCRF.

A physician must be present at the site or immediately available to respond to emergencies during all administrations of investigational product. Fully functional resuscitation facilities should be available. Investigational product must not be administered via IV push or bolus but as a slow IV infusion. The entire content of each IV bag will be infused using an infusion pump.

4.5.1.5 Monitoring of Dose Administration

Subjects will be monitored during and after infusion of investigational product. Vital signs will be measured according to the schedules described in Section 4.2.2 and collection times in Table 10 (4.3.3-1).

Management of oleclumab or durvalumab-related toxicities are described in Section 3.1.4. Acetaminophen and/or an antihistamine (eg, diphenhydramine) may be administered at the discretion of the investigator. If the IRR is severe or prolonged, methylprednisolone 100 mg (or the equivalent) should be administered as well. Investigators may administer steroids at their discretion as clinically indicated and per their institution's guidelines. The medical monitor should be informed if steroids are utilized for management of an IRR.

As with any biologic product, allergic reactions to dose administration are possible. Therefore, appropriate drugs and medical equipment to treat acute anaphylactic reactions must be immediately available, and study personnel must be trained to recognize and treat anaphylaxis.

4.5.1.6 Reporting Product Complaints

Any defects with the investigational product must be reported *immediately* to the MedImmune Product Complaint Department by the site with further notification to the site monitor. All defects will be communicated to MedImmune and investigated further with the Product Complaint Department. During the investigation of the product complaint, all investigational product must be stored at labeled conditions unless otherwise instructed.

MedImmune contact information for reporting product complaints:

Email: productcomplaints@medimmune.com

Phone: +1-301-398-2105
+1-877-MEDI-411 (+1-877-633-4411)

Fax: +1-301-398-8800

Mail: MedImmune
Attn: Product Complaint Department
One MedImmune Way,
Gaithersburg, MD USA 20878

4.5.2 Additional Study Medications

Each standard-of-care agent (gemcitabine, nab-paclitaxel, and mFOLFOX [leucovorin, 5-FU, and oxaliplatin]) will be sourced as commercially available material/locally sourced, prescribed according to local regulations, and will be administered according to prescribing information or treatment guidance in general use by the investigating site. Please refer to Tempero et al, 2017 and Ducreux et al, 2015 treatment guidelines for the management of patients with metastatic PDAC. Under certain circumstances when local sourcing is not feasible, a standard-of-care agent will be supplied centrally by MedImmune. This will be labeled with text translated into local languages in accordance with regulatory guidelines.

4.5.3 Labeling

Labels for the investigational product will be prepared in accordance with Good Manufacturing Practice and local regulatory guidelines. Label text will be translated into local languages, as required.

4.5.4 Storage

Investigational product vials are stored at 2°C to 8°C (36°F to 46°F) and must not be frozen. Drug product should be kept in original packaging until use to prevent prolonged light exposure.

4.5.5 Treatment Compliance

Investigational product is administered by study site personnel, who will monitor compliance.

4.5.6 Accountability

The investigator's or site's designated investigational product manager is required to maintain accurate investigational product accountability records. Upon completion of the study, copies of investigational product accountability records will be returned to MedImmune. All unused investigational product will be returned to a MedImmune-authorized depot or disposed of upon authorization by MedImmune.

For details of accountability during the continued treatment period after data cut-off for analysis of final study data, see Section 4.4.1.

4.6 Treatment Assignment and Blinding

4.6.1 Methods for Assigning Treatment Groups

Subjects enrolled in Part 1 (dose escalation) who meet the eligibility criteria will be assigned open-label investigational product.

In Part 2 (dose expansion), an IRT will be used for randomization to a treatment group and assignment of open-label investigational product. A subject is considered randomized into the study when the investigator notifies the IRT that the subject meets eligibility criteria and provides the CD73 expression status of the subject, and the IRT provides the assignment of open-label investigational product to the subject.

Subjects in Cohort A will be randomized using a 1:1:1 ratio to receive either 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 will be randomized using a 1:1:1 ratio to receive either mFOLFOX (Arm B1), oleclumab + mFOLFOX (Arm B2) or oleclumab + durvalumab + mFOLFOX (Arm B3).

The randomization will be stratified by CD73 expression level:

[redacted]

In Part 2 (dose expansion), investigational product must be administered within 3 working days of the initial treatment assignment. If there is a delay in the administration of investigational product such that it will not be administered within the specified timeframe, the study monitor must be notified immediately.

4.6.2 Methods to Ensure Blinding

This study is not blinded.

4.7 Restrictions During the Study and Concomitant Treatment(s)

The investigator must be informed as soon as possible about any medication taken from the time of screening until the final study visit. Any concomitant medication(s), including herbal preparations, taken during the study will be recorded in the eCRF.

4.7.1 Permitted Concomitant Medications

Investigators may prescribe concomitant medications or treatments deemed necessary to provide adequate supportive care except for those medications identified as "excluded" as listed in Section 4.7.2. Specifically, subjects should receive full supportive care during the

study, including transfusions of blood and blood products, growth factor support, and treatment with antibiotics, anti-emetics, anti-diarrheals, and analgesics, and other care as deemed appropriate, and in accordance with their institutional guidelines. Palliative radiotherapy is allowed during the study upon discussion with the medical monitor.

4.7.2 Prohibited Concomitant Medications

Other than the medications described above, use of concomitant medications including over-the-counter medications, herbal supplements, vitamins, etc is discouraged. Subjects must be instructed not to take any medications, including over-the-counter products, without first consulting with the investigator. The following concomitant medications are prohibited:

- Any investigational anticancer therapy
- Any concurrent chemotherapy, radiotherapy (except palliative radiotherapy), immunotherapy, biologic or hormonal therapy for cancer treatment.
- Immunosuppressive medications including, but not limited to systemic corticosteroids at doses exceeding 10 mg/day of prednisone or equivalent, methotrexate, azathioprine, and tumor necrosis factor-alpha blockers. Use of immunosuppressive medications for the management of investigational product-related AEs, in subjects with contrast allergies, or as premedication prior to chemotherapy, is acceptable. In addition, use of inhaled and intranasal corticosteroids is permitted. Temporary courses of corticosteroids for treatment of underlying or concurrent illness or in the setting of palliative radiotherapy may be permitted upon discussion with the medical monitor.
- Live attenuated vaccines during the study through 180 days after the last dose of both drugs
- Cannabinoids (oleclumab treatment arms only)
- Herbal and natural remedies should be avoided

4.8 Statistical Evaluation

4.8.1 General Considerations

Tabular summaries will be presented by treatment group. Categorical data will be summarized by the number and percentage of subjects in each category. Continuous variables will be summarized by descriptive statistics. Additional details of statistical analyses will be described in the statistical analysis plan.

Study populations are defined below.

- The intent-to-treat (ITT) population is defined as all subjects who are randomized and receive any amount of investigational product, analyzed according to randomized treatment assignment. All analyses will be performed on the ITT population unless otherwise specified.

- The as-treated population is defined as all subjects who receive any investigational product analyzed according to treatment received.
- The DLT-evaluable population is defined as all subjects enrolled in Part 1 (dose escalation) who receive all planned doses of oleclumab, durvalumab, and chemotherapy during the DLT-evaluation period (defined in Section 3.1.3.3) and complete the safety follow-up through the DLT-evaluation period or experience any DLT.

4.8.2 Sample Size

Up to approximately 339 subjects will be enrolled in the study: up to approximately 24 subjects in Part 1, Dose Escalation and up to approximately 315 subjects in Part 2, Dose Expansion (approximately 210 subjects in Cohort A and approximately 105 subjects in Cohort B).

Part 1 (Dose Escalation)

CCI

Table 13 (4.8.2-1) CCI

CCI

DLT = dose-limiting toxicity.

Part 2 (Dose Expansion)

In Part 2 (dose expansion), up to approximately 315 subjects will be enrolled to obtain preliminary assessment of safety and antitumor activity in each cohort:

- 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)

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4.8.3 Efficacy

The efficacy analyses of antitumor activity will be based on the ITT population (defined in Section 4.8.1). The rates of OR and DC based on RECIST version 1.1 will be summarized with 95% CI based on the exact binomial distribution. Time-to-event endpoints (DoR, PFS, and OS) will be analyzed using the Kaplan-Meier method. Additional analyses of antitumor activity may be conducted in the as-treated population (defined in Section 4.8.1). Additional details will be provided in the statistical analysis plan. The following efficacy endpoints will be analyzed.

4.8.3.1 Primary Efficacy Analysis

The primary efficacy endpoint is OR. OR is defined as best overall response of confirmed CR or confirmed PR according to RECIST version 1.1. The best overall response is defined as the best response (in the order of CR, PR, SD, PD, and not evaluable) among all overall responses recorded from the start of treatment with investigational product until objective documentation of PD, or the last evaluable disease assessment in the absence of PD prior to the initiation of subsequent anticancer therapy or end of the study, whichever occurs first. The best overall response of CR or PR must be confirmed, which means a response of CR/PR is recorded at a visit and confirmed by repeat imaging not less than 28 days (4 weeks) after the visit when the response was first observed with no evidence of progression between the initial and CR/PR confirmation visit. The ORR will be estimated by the proportion of OR, and its 95% CI will be estimated using the exact binomial distribution. Comparison of arms for ORR will be obtained from Cochran-Mantel-Haenszel test.

4.8.3.2 Additional Analyses of the Primary Endpoint

If applicable, analysis of ORR by CD73 expression at baseline as measured by IHC in archival and/or fresh tumor biopsies may be conducted.

4.8.3.3 Secondary Efficacy Analyses

Secondary efficacy endpoints include DoR, DC, PFS, and OS.

- DoR is defined as the duration from the first documentation of OR to the first documented disease progression or death due to any cause, whichever occurs first. For subjects who are alive and progression-free at the time of data cut-off for analysis, DoR will be censored at the last tumor assessment date. The DoR will only be evaluated for the subgroup of subjects with an OR using the Kaplan-Meier method.
- DC is defined as CR, PR, or SD (if subjects maintain SD for ≥ 8 weeks [± 3 days]). DC will be analyzed by estimating the DCR, defined as the proportion of subjects with DC and its 2-sided 95% CIs using an exact probability method.
- PFS is defined as the time from randomization until the first documentation of disease progression or death due to any cause, whichever occurs first. For subjects who are alive and progression-free at the time of data cut-off for analysis, PFS will be censored at the last tumor assessment date. The Kaplan-Meier method (Kaplan and Meier, 1958) will be used to estimate the PFS curve and the PFS rate at time points of interest.
- OS is defined as the time from randomization until death due to any cause. For subjects who are alive at the time of data cut-off, OS will be censored on the last date when subjects are known to be alive. The Kaplan-Meier method will be used to estimate the OS curve and the OS rate at time points of interest.

4.8.3.4 CCI

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4.8.4 Safety

4.8.4.1 Analysis of Safety Endpoints

Safety data, including DLTs, AEs, SAEs, laboratory evaluations, vital signs, and ECG results will be summarized based on the as-treated population. Descriptive statistics will be provided for AEs, SAEs, AE grade (severity), and relationship to investigational product(s), clinical laboratory parameters, vital signs, and ECG results. AEs will be graded according to the NCI CTCAE version 4.03.

Descriptive statistics will be provided for the clinical laboratory results and changes from baseline by scheduled time of evaluation and by treatment arm including end of treatment visit as well as for the maximum and minimum post-baseline values. Laboratory abnormalities will be graded according to the NCI CTCAE version 4.03, if applicable. Frequencies of worst observed grade will be presented for each laboratory parameter as well as the rates of subjects with Grade 3-4 toxicities.

4.8.4.2 CCI

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4.8.4.3 CCI

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CCI [redacted]

4.8.5 Analysis of Immunogenicity/Pharmacokinetics

Only subjects who receive at least 1 dose of oleclumab and/or durvalumab and provide at least 1 post-treatment sample will be evaluated.

For each cohort, the immunogenic potential of combinations will be assessed by summarizing the number and percentage of subjects who develop detectable ADAs. The impact of ADAs on PK will be assessed if data allow. Samples will be collected for potentially evaluating the neutralizing capacity of ADAs in the future.

Individual oleclumab and durvalumab concentrations will be tabulated by dose cohort along with descriptive statistics. Non-compartmental PK data analysis will be performed from each dose cohort with scheduled PK sample collection where data allow. Relevant descriptive statistics of non-compartmental PK parameters will be provided and may include: AUC, C_{max}, t_{max}, clearance, V_d. and $t_{1/2}$.

4.8.6 CCI [redacted]

CCI [redacted]

CCI

[redacted]

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4.8.7 Interim Analysis

Interim analysis comparing experimental arms with control will be performed in Part 2 Cohort A using a joint Bayesian predictive probability, which allows for interim analysis of the delta (δ), or difference, of the ORR between experimental and control arms (Lee and Liu, 2008; Pulkstenis et al, 2017). For interim futility analyses, a response is defined as either a confirmed or unconfirmed CR or PR per RECIST v1.1.

An interim analysis will be performed when approximately 30 subjects in each treatment arm of Part 2 Cohort A have been dosed and reach the data cut-off criteria (ie, subjects who have a baseline disease assessment, have been dosed at least 16 weeks prior to the time of the data cut-off, and have at least 1 post-baseline disease assessment and/or discontinued treatment due to death or disease progression). Randomization may be paused during the interim analysis before the decision is made.

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5 ASSESSMENT OF SAFETY

5.1 Definition of Adverse Events

An AE is the development of any untoward medical occurrence in a subject or clinical study subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (eg, an abnormal laboratory finding), symptom (eg, nausea, chest pain), or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

The term AE is used to include both serious and nonserious AEs and can include a deterioration of a pre-existing medical occurrence. An AE may occur at any time, including run-in or washout periods, even if no study treatment has been administered.

Elective treatment or surgery or preplanned treatment or surgery (that was scheduled prior to the subject being enrolled into the study) for a documented pre-existing condition that did not worsen from baseline is not considered an AE (serious or nonserious). An untoward medical event occurring during the prescheduled elective procedure or routinely scheduled treatment should be recorded as an AE or SAE.

5.2 Definition of Serious Adverse Events

An SAE is any AE that:

- Results in death
- Is immediately life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect in offspring of the subject
- Is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above

Medical or scientific judgment should be exercised in deciding whether expedited reporting is appropriate in this situation. Examples of medically important events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalizations, or development of drug dependency or drug abuse.

5.3 Definition of Adverse Events of Special Interest

An AESI is one of scientific and medical interest specific to understanding of the investigational product and may require close monitoring and rapid communication by the investigator to MedImmune. An AESI may be serious or nonserious. The rapid reporting of AESIs allows ongoing surveillance of these events in order to characterize and understand them in association with the use of this investigational product.

5.3.1 Anaphylaxis and Infusion-related Reactions

Infusion of biological products is commonly associated with IRRs. Anaphylaxis and IRRs have some common manifestations and may be difficult to distinguish from each other. IRRs are commonly observed during or shortly after the first time of exposure to therapeutic mAbs delivered through IV infusion. These reactions are less common following subsequent exposures. Unlike IRRs, anaphylaxis is a rare event, usually occurring after subsequent exposure to an antigen, and it is most commonly accompanied by severe systemic, skin and/or mucosal reactions. The investigator is advised to carefully examine symptoms of adverse reactions observed during or shortly after exposure to oleclumab and durvalumab, and consider the above-mentioned facts prior to making a final diagnosis. Reactions occurring at the time of or shortly after subsequent infusions of investigational product are to be judged by the investigator at his/her own discretion. For the investigator's convenience and to facilitate consistency in judgments, a copy of the National Institute of Allergy and Infectious Disease and Food and Allergy Anaphylaxis Network guidance for anaphylaxis diagnosis is provided in Section 10.3.

Refer to Section 3.1.4 for guidelines for management of subjects with hypersensitivity (including anaphylactic reaction) and IRRs. In the event of an IRR, the site should document which medications have been infused at the time of onset of the IRR in addition to signs and symptoms.

5.3.2 Adverse Events of Special Interest for Oleclumab

5.3.2.1 Cardiac Chest Pain, Transient Ischemic Attack, and Thromboembolism

AEs of cardiac chest pain, transient ischemic attack, and thromboembolic events are of special interest due to oleclumab potential risks of arterial ischemic disorder, and thrombosis. Because of this potential risk, potential subjects with a history of myocardial infarction, stroke, transient ischemic attack, or thromboembolism in the prior 3 months are not eligible (see Section 4.1.3). These events require urgent medical management, which should be performed according to consensus guidelines developed by the American Heart Association or appropriate local standards of care.

5.3.2.2 Edema

Edema (eg, pulmonary or peripheral) is regarded as AESI due to oleclumab potential risks of increased microvascular permeability. For subjects who develop ≥ Grade 3 edema, doses should be omitted as per Section 3.1.4, and therapy may be discontinued at the discretion of the investigator.

5.3.2.3 Immune Complex Disease

The immune system can respond to foreign protein, even to humanized mAb by producing human-anti-human antibodies, which may result in formation of immune complexes and their deposition in blood vessels, joints, and glomeruli causing symptomatic disease (eg, vasculitis, glomerulonephritis, arthritis, serum sickness). Subjects will be monitored clinically and for the presence of ADAs. Subjects who experience an AE suspected to be immune complex-related will discontinue treatment. Immune complex disease will be managed in accordance with standard-of-care.

5.3.3 Adverse Events of Special Interest for Durvalumab

AESIs for durvalumab include but are not limited to events with a potential inflammatory or immune-mediated mechanism and which may require more frequent monitoring and/or interventions such as steroids, immunosuppressants, and/or hormone replacement therapy. These AESIs are being closely monitored in clinical studies with durvalumab monotherapy and combination therapy. An imAE is defined as an AE that is associated with drug exposure and is consistent with an immune-mediated mechanism of action and where there is no clear alternate etiology. Serologic, immunologic, and histologic (biopsy) data, as appropriate, should be used to support an imAE diagnosis. Appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the imAE.

If the investigator has any questions in regards to an AE being an imAE, the investigator should promptly contact the medical monitor.

AESIs/imAEs observed with anti-PD-L1/PD-1 agents such as durvalumab include:

- Pneumonitis
- Hepatitis
- Diarrhea/colitis
- Intestinal perforation
- Endocrinopathies (ie, events of hypophysitis/hypopituitarism, type 1 diabetes mellitus, adrenal insufficiency, hyperthyroidism, and hypothyroidism)
- Nephritis
- Rash/dermatitis
- Myocarditis
- Myositis/polymyositis
- Pancreatitis
- Rare/less frequent imAEs including neuromuscular toxicities (eg, Guillain-Barre syndrome and myasthenia gravis)
- Other inflammatory responses that are rare/less frequent with a potential immune-mediated etiology include, but are not limited to, pericarditis, sarcoidosis, uveitis, and other events involving the eye, skin, hematological events, rheumatological events, vasculitis, non-infectious meningitis, and non-infectious encephalitis. It is possible that events with an inflammatory or immune mediated mechanism could occur in nearly all organs.

In addition, IRRs and hypersensitivity/anaphylactic reactions with a different underlying pharmacological etiology are also considered AESIs (Section 5.3.1).

Further information on these risks (eg, presenting symptoms) can be found in the current version of the durvalumab IB. More specific guidelines for their evaluation and treatment are described in detail in in the Dose Modification and Toxicity Management Guidelines (refer to Section 3.1.4).

5.4 Recording of Adverse Events

AEs will be recorded on the eCRF using a recognized medical term or diagnosis that accurately reflects the event. AEs will be assessed by the investigator for severity, relationship to the investigational product, possible etiologies, and whether the event meets criteria of an SAE and therefore requires immediate notification to MedImmune (see Section 5.5). See Section 5.2 for the definition of SAEs and Section 10.2 for guidelines for assessment of severity and relationship.

If an AE evolves into a condition that meets the regulatory definition of "serious," it will be reported on the SAE Report Form.

5.4.1 Time Period for Collection of Adverse Events

AEs will be collected from time of signature of informed consent throughout the treatment period and including the follow-up period 12 weeks post last dose.

All SAEs will be recorded from the time of informed consent.

5.4.2 Follow-up of Unresolved Adverse Events

Any AEs that are unresolved at the subject's last AE assessment or other assessment/visit as appropriate in the study are followed up by the investigator for as long as medically indicated, but without further recording in the eCRF. MedImmune retains the right to request additional information for any subject with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

5.4.3 Deaths

All deaths that occur during the study, including the protocol-defined follow-up period must be reported as follows:

- Death clearly the result of disease progression should be reported and documented on the statement of death eCRF but should not be reported as an SAE.
- Where death is not due (or not clearly due) to disease progression, the AE causing the death must be reported as an SAE within 24 hours. The report should contain a comment regarding the co-involvement of disease progression, if appropriate, and should assign main and contributory causes of death.
- Deaths with an unknown cause should always be reported as an SAE. A post-mortem (autopsy) may be helpful in the assessment of the cause of death, and if performed, a copy of the post-mortem results should be forwarded to MedImmune representative(s) within the usual timeframes (refer to Section 5.5 for additional information).

5.4.4 Adverse Events Based on Signs and Symptoms

All AEs spontaneously reported by the subject or reported in response to the open question from the study site staff: *'Have you had any health problems since the previous visit/you were last asked?'*, or revealed by observation will be collected and recorded in the eCRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

5.4.5 Adverse Events Based on Examination and Tests

The results from the protocol-mandated laboratory tests and vital signs will be summarized in the CSR. An abnormal laboratory finding (including ECG finding) that requires medical intervention by the investigator, or a finding judged by the investigator as medically significant should be reported as an AE. If clinical sequelae are associated with a laboratory abnormality, the diagnosis or medical condition should be reported (eg, renal failure, hematuria) not the laboratory abnormality (eg, elevated creatinine, urine red blood cell increased).

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible, the reporting investigator uses the clinical, rather than the laboratory term (eg, anemia versus low hemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE

Deterioration of a laboratory value, which is unequivocally due to disease progression, should not be reported as an AE/SAE.

5.4.6 Hy's Law

Cases where a subject shows elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT $\geq 3 \times$ ULN together with TBL $\geq 2 \times$ ULN should be reported as SAEs (Section 5.5). Please refer to Appendix 10.4 for further instruction on cases of increases in liver biochemistry and evaluation of Hy's Law.

5.4.7 Disease Progression

Disease progression can be considered as a worsening of a subject's condition attributable to the disease for which the investigational product is being studied. It may be an increase in the severity of the disease under study and/or increases in the symptoms of the disease. The development of a new metastasis or progression of existing metastasis related to the primary cancer under study should not be considered an AE. Death clearly resulting from disease progression should not be reported as an SAE (see reporting guidelines in Section 5.4.3).

The term disease progression should not be reported as an AE or SAE, however, medically significant individual events and/or laboratory abnormalities associated with disease progression (see definition of disease progression above) that fulfill the AE or SAE definition should be reported.

New Cancers

The development of a new cancer should be regarded as an SAE. New cancers are those that are not the primary reason for the administration of the investigational product and have been identified after the subject's inclusion in the study. New metastatic lesion(s) of the subject's known cancer should not be reported as a new cancer.

5.5 Reporting of Serious Adverse Events

Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a study intervention under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/IECs, and investigators.

For all studies except those utilizing medical devices investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the IB and/or will notify the IRB/IEC, if appropriate according to local requirements.

All SAEs have to be reported, whether or not considered causally related to the investigational product, or to the study procedure(s). All SAEs will be recorded in the eCRF.

If any SAE occurs in the course of the study, then investigators or other site personnel must inform the appropriate sponsor representative(s) within 1 day, ie, immediately but no later than 24 hours after becoming aware of the event.

The designated study representative works with the investigator to ensure that all the necessary information is provided to the sponsor's Patient Safety data entry site within 1 calendar day of initial receipt for fatal and life-threatening events and within 5 calendar days of initial receipt for all other SAEs.

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform sponsor representatives of any follow-up information on a previously reported SAE within 1 calendar day, ie, immediately but no later than 24 hours after becoming aware of the event.

Once the investigators or other site personnel indicate an AE is serious in the electronic data capture (EDC) system, an automated email alert is sent to inform the designated sponsor representative(s).

If the EDC system is not available, then the investigator or other study site personnel reports an SAE to the appropriate sponsor representative by telephone. The sponsor representative will advise the investigator/study site personnel how to proceed.

For details of SAE reporting during the continued treatment period after data cut-off for analysis of final study data, see Section 4.4.1.

The reference document for definition of expectedness/listedness is the IB for the AstraZeneca/MedImmune drug and the local country label for the active comparator product (chemotherapy drugs).

5.6 Other Events Requiring Immediate Reporting

5.6.1 Overdose

An overdose is defined as a subject receiving a dose of investigational product in excess of that specified in the IB, unless otherwise specified in this protocol.

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the eCRF and on the Overdose eCRF module.
- An overdose without associated symptoms is only reported on the Overdose eCRF module.

If an overdose on a MedImmune investigational product occurs during the course of the study, then the investigator or other site personnel should inform the appropriate sponsor representatives immediately, but no later than 24 hours after becoming aware of the event.

The designated sponsor representative works with the investigator to ensure that all relevant information is provided to the sponsor's Patient Safety data entry site.

For overdoses associated with an SAE, the standard reporting timelines apply; see Section 5.5. For other overdoses (ie, those not associated with an AE or SAE), reporting must occur within 30 days.

For details of overdose reporting during the continued treatment period after data cut-off for analysis of final study data, see Section 4.4.1.

5.6.2 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to the sponsor except if the pregnancy is discovered before the study subject has received any study drug.

For details of pregnancy reporting during the continued treatment period after data cut-off for analysis of final study data, see Section 4.4.1.

5.6.2.1 Maternal Exposure

If a subject becomes pregnant during the course of the study, investigational product should be discontinued immediately.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be followed up and documented even if the subject was discontinued from the study.

If any pregnancy occurs during the course of the study, then the investigator or other site personnel will inform the appropriate sponsor representatives within 1 day, ie, immediately but **no later than 24 hours** after becoming aware of the event.

The designated study representative works with the investigator to ensure that all relevant information is provided to the sponsor's Patient Safety data entry site within 1 or 5 calendar days for SAEs (see Section 5.5) and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

The pregnancy reporting module in the eCRF is used to report the pregnancy and the pregnancy outcome module is used to report the outcome of the pregnancy.

5.6.2.2 Paternal Exposure

Pregnancy of the subject's partners is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality), occurring from the date of the first dose until 180 days after the last dose of investigational product should, if possible, be followed up and documented.

5.6.3 Medication Error

For the purposes of this clinical study, a medication error is an unintended failure or mistake in the treatment process for a MedImmune study drug that either causes harm to the subject or has the potential to cause harm to the subject.

A medication error is not lack of efficacy of the drug, but rather a human- or process-related failure while the drug is in control of the study site staff or subject.

Medication error includes situations where an error:

- Occurred
- Was identified and intercepted before the subject received the drug
- Did not occur, but circumstances were recognized that could have led to an error

Examples of events to be reported in clinical studies as medication errors:

- Drug name confusion (ie, instead of receiving the investigational product, the subject received a drug that has a similar-sounding name)
- Dispensing error, eg, medication prepared incorrectly, even if it was not actually given to the subject
- Drug not administered as indicated, for example, wrong route or wrong site of administration
- Drug not taken as indicated, eg, tablet dissolved in water when it should be taken as a solid tablet
- Drug not stored as instructed, eg, kept in the refrigerator when it should be at room temperature
- Wrong subject received the medication (excluding IRT errors)
- Wrong drug administered to subject (excluding IRT errors)

Examples of events that **do not** require reporting as medication errors in clinical studies:

- Errors related to or resulting from IRT - including those which lead to one of the above listed events that would otherwise have been a medication error
- Accidental overdose (will be captured as an overdose)
- Errors related to background and rescue medication, or standard-of-care medication in open-label studies, even if an AstraZeneca or MedImmune product

Medication errors are not regarded as AEs but AEs may occur as a consequence of the medication error.

If a medication error occurs in the course of the study, then the investigator or other site personnel informs the appropriate MedImmune representatives within 1 day, ie, immediately but no later than 24 hours of when he or she becomes aware of it.

The designated MedImmune representative works with the investigator to ensure that all relevant information is completed within 1 or 5 calendar days if there is an SAE associated with the medication error (see Section 5.5) and within 30 days for all other medication errors. Medication errors should be reported using a Medication Error Report Form.

6 STUDY AND DATA MANAGEMENT

6.1 Training of Study Site Personnel

Before the first subject is entered into the study, a MedImmune representative will review and discuss the requirements of the protocol and related documents with the investigational staff and also train them in any study-specific procedures and system(s) utilized.

The Principal Investigator will ensure that appropriate training relevant to the study is given to all of these staff, and that any new information relevant to the performance of this study is forwarded to the staff involved.

The Principal Investigator will maintain a record of all individuals involved in the study (medical, nursing, and other staff).

6.2 Monitoring of the Study

During the study, a MedImmune representative will have regular contacts with the study site, including visits to:

- Provide information and support to the investigator(s).
- Confirm that facilities remain acceptable.
- Confirm that the investigational team is adhering to the protocol, that data are being accurately and timely recorded in the eCRFs, that biological samples are handled in accordance with the Laboratory Manual, and that study drug accountability checks are being performed.
- Perform source data verification (a comparison of the data in the eCRFs with the subject's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating subjects. This will require direct access to all original records for each subject (eg, clinic charts).
- Ensure withdrawal of informed consent to the use of the subject's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented, and reported to the subject.

The MedImmune representative will be available between visits if the investigator(s) or other staff at the center needs information and advice about the study conduct.

6.2.1 Source Data

Refer to the Clinical Study Agreement for location of source data.

6.2.2 Study Agreements

The Principal Investigator at each/the center should comply with all the terms, conditions, and obligations of the Clinical Study Agreement, or equivalent, for this study. In the event of any

inconsistency between this protocol and the Clinical Study Agreement, the terms of protocol shall prevail with respect to the conduct of the study and the treatment of subjects and in all other respects, not relating to study conduct or treatment of subjects, the terms of the Clinical Study Agreement shall prevail.

Agreements between MedImmune and the Principal Investigator must be in place before any study-related procedures can take place, or subjects are enrolled.

6.2.3 Archiving of Study Documents

The investigator follows the principles outlined in the Clinical Study Agreement.

6.3 Study Timetable and End of Study

An individual subject will be considered to have completed the study if the subject was followed through their last protocol-specified visit/assessment (including telephone contact), regardless of the number of doses of investigational product that was received.

Subjects will be considered not to have completed the study if consent was withdrawn or the subject was lost to follow-up (see Sections 4.1.5 and 4.1.6).

The end of the study ("study completion") is defined as the date of the last protocol-specified visit/assessment (including telephone contact) for the last subject in the study. This date will be approximately 2 years after the last subject begins treatment or when the sponsor stops the study, whichever occurs earlier. A final data cut-off for the primary analysis will occur at this time.

6.4 Data Management

Data management will be performed by MedImmune Data Management staff or other party according to the Data Management Plan.

An EDC system will be used for data collection and query handling. The investigator will ensure that data are recorded in the eCRFs as specified in the study protocol and in accordance with the eCRF instructions provided.

The investigator ensures the accuracy, completeness, and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement. The investigator will sign the completed eCRFs. A copy of the completed eCRFs will be archived at the study site.

Data will not be entered into the EDC system after the final data cut-off (see Section 4.4.1). During a study subject's continued treatment period after data cut-off for analysis of final study data, SAEs, overdoses, and pregnancies will be reported using paper-based CRFs until

28 days after the study subject's last dose of investigational product. Reported SAE data will be entered by the sponsor into the sponsor's global safety database.

6.5 Medical Monitor Coverage

Each subject will be provided with contact information for the Principal Investigator. In addition, each subject will receive a toll-free number intended to provide the subject's physician access to a medical monitor 24 hours a day, 7 days a week in the event of an emergent situation where the subject's health is deemed to be at risk. In this situation, when a subject presents to a medical facility where the treating physician or health care provider requires access to a physician who has knowledge of the investigational product and the clinical study protocol and the Principal Investigator is not available, the treating physician or health care provider can contact a medical monitor through this system, which is managed by the sponsor.

7 ETHICAL AND REGULATORY REQUIREMENTS

7.1 Subject Data Protection

Each subject will be assigned a SID to ensure that personally identifiable information is kept separate from the study data. Subject data that are relevant to the trial, eg, demographic information, physical or mental health condition, diagnosis, comorbidities, laboratory test results, etc. will only be collected with the subject's informed consent. The ICF will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that describes how subject data will be collected, used, and distributed in compliance with relevant data protection and privacy legislation.

7.2 Ethics and Regulatory Review

The IRB/IEC responsible for each site must review and approve the final study protocol, including the final version of the ICF and any other written information and/or materials to be provided to the subjects. The IRB/IEC must also approve all advertising used to recruit subjects for the study. The investigator is responsible for submitting these documents to the applicable IRB/IEC, and distributing them to the study site staff.

The opinion of the IRB/IEC must be given in writing. The investigator must provide a copy of the written approval to MedImmune before enrollment of any subject into the study.

MedImmune should approve any substantive modifications to the ICF that are needed to meet local requirements.

If required by local regulations, the protocol must be re-approved by the IRB/IEC annually.

Before the study is initiated, MedImmune will ensure that the national regulatory authority in each country has been notified and their approval has been obtained, as required. MedImmune will provide safety updates/reports according to local requirements, including SUSARs where relevant, to regulatory authorities, IRB/IEC, and principal investigators.

Each Principal Investigator is responsible for providing reports of any serious and unexpected adverse drug reactions from any other study conducted with the investigational product to the IRB/IEC. MedImmune will provide this information to the Principal Investigator so that he/she can meet these reporting requirements.

7.3 Informed Consent

Informed consent of each subject will be obtained through a written and verbal explanation process that addresses all elements required by ICH/GCP. MedImmune will develop a core ICF for use by all investigators in the clinical study. MedImmune must approve any modifications to the ICF that are needed to meet local requirements.

The Principal Investigator(s) at each center will:

- Ensure each subject is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study.
- Ensure each subject is notified that they are free to discontinue from the study at any time.
- Ensure that each subject is given the opportunity to ask questions and allowed time to consider the information provided.
- Ensure each subject provides signed and dated informed consent before conducting any procedure specifically for the study.
- Ensure the original, signed ICF(s) is/are stored in the investigator's Study File.
- Ensure a copy of the signed ICF is given to the subject.
- Ensure that any incentives for subjects who participate in the study as well as any provisions for subjects harmed as a consequence of study participation are described in the ICF that is approved by an IRB/IEC.

7.4 Changes to the Protocol and Informed Consent Form

Study procedures will not be changed without the mutual agreement of the Principal Investigator and MedImmune. Any changes must be documented in a study protocol amendment.

For a substantial change to the protocol, MedImmune will distribute amended versions of the protocol to the Principal Investigator(s). Before implementation, amended protocols must be approved by the relevant IRB/IEC (see Section 7.2) and reviewed as per local regulatory authority requirements. The IRB/IEC must also approve revisions to the ICF, advertising, and any other written information and/or materials resulting from the change to the protocol.

Any non-substantial changes will be communicated to or approved by each IRB/IEC.

7.5 Audits and Inspections

Authorized representatives of MedImmune, a regulatory authority, or an IRB/IEC may perform audits or inspections at the center, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents, to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, GCP, guidelines of the ICH, and any applicable regulatory requirements. The investigator will contact MedImmune immediately if contacted by a regulatory agency about an inspection at the site.

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9 CHANGES TO THE PROTOCOL

9.1 Protocol Amendment 3

Text revisions resulting from this amendment are incorporated in the body of Protocol Amendment 3. The principal reason for this amendment is to allow any study subject still receiving investigational product at the time of the data entry cut-off to continue to receive investigational product within the current study through a continued treatment period.

Substantial changes to the protocol are summarized below.

1 Section 4.4.1 (Continued Treatment at Study Completion): New section describing the continued treatment period for subjects still receiving investigational product at the time of data entry cut-off. A summary of Section 4.4.1 has also been added to the protocol synopsis.
2 Sections 1.6.1 (Potential Risks) and 5.3.2.1 (Cardiac Chest Pain, Transient Ischemic Attack, and Thromboembolism): The known and potential risks for oleclumab and durvalumab were updated in line with the most recent information.

Changes to the protocol considered to be non-substantial are summarized below.

1 Section 6.5 (Medical Monitor Coverage): Text was updated to indicate the system for contacting a medical monitor when the Principal Investigator is not available will be managed by the sponsor, not a third-party vendor as previously.
2 Sections 4.5.6 (Accountability), 5.5 (Reporting of Serious Adverse Events), 5.6.1 (Overdose), 5.6.2 (Pregnancy), and 6.4 (Data Management): Cross references to the new Section 4.4.1 (Continued Treatment at Study Completion) were added where relevant.
3 Section 6.3 (Study Timetable and End of Study): Text was added clarifying the point of the data cut-off for the primary analysis.

9.2 Protocol Amendment 2

Text revisions resulting from this amendment are incorporated in the body of Protocol Amendment 2. The principal reason for this amendment is to revise Section 10.9 (previously numbered 10.10) to reflect guidelines to follow for oleclumab-related toxicities. The toxicity management guidelines for durvalumab are to be maintained within the Site Master File and through the following link: https://tmg.azirae.com. Additionally, the sample size for Cohort A (Part 2 [Dose Expansion]) was increased to 70 subjects per treatment arm (previously 60 subjects per treatment arm) due to a drop-out rate of approximately 20% (previously estimated as 10%).

Substantial changes to the protocol are summarized below.

1 Section 1.6.1 (Potential Risks): Revised arterial calcifications and arterial ischemic disorder to potential risks for oleclumab (previously important potential risks) per oleclumab IB edition 6.0. Revised risks for durvalumab per durvalumab IB ed 15.0.

2 Sections 3.1.1 (Overview), 4.1.1 (Number of Subjects), 4.8.2 (Sample Size), and Figure 2 (3.1.1-2; Study Flow Diagram [Part 2: Dose Expansion]): Revised to reflect a sample size of 70 subjects per treatment arm (previously 60 subjects per treatment arm) for Cohort A (Part 2 [Dose Expansion]).

3 Section 3.1.4.1 (Management of Oleclumab-Related Toxicities) and 10.9 (Oleclumab Dosing Modification for Toxicity Management [previously numbered 10.10]): Revised toxicity management guidelines in Section 10.9 to reflect guidelines to follow for oleclumab-related toxicities.

4 Section 3.1.4.2 (Management of Durvalumab-Related Toxicities): Added new section with information regarding toxicity management guidelines for durvalumab. The toxicity management guidelines for durvalumab are to be maintained within the Site Master File and through the following link: https://tmg.azirae.com. The durvalumab toxicity management guidelines should be followed for subjects who receive durvalumab in combination with oleclumab. Renumbered subsequent sections accordingly.

5 Section 4.1.7 (Treatment Beyond Progression): Added statement in the second paragraph that subjects with unconfirmed radiologic PD who are eligible to continue receiving their assigned treatment will be made aware of the potential benefits and risks of continuing treatment in the setting of PD and must provide a separate written informed consent prior to treatment.

6 Section 4.2.3 (Follow-up Period): Added assessment for pregnancy testing Q4W starting 8 weeks through 28 weeks post last dose during follow-up in Table 9 (4.2.3-1; Schedule of Follow-up Procedures [Part 1 (Dose Escalation) and Part 2 (Dose Expansion)]). Clarified in the footnote that urine pregnancy tests will be performed either on site or at home, and the study site will contact the subject by phone to obtain results for tests performed at home. The frequency of the pregnancy testing was updated to align with contraception requirements in the inclusion criteria and the Summary of Product Characteristics for the chemotherapy drugs.

7 Sections 4.5.1.2 (Oleclumab [MEDI9447] IV Bag Preparation and Administration) and 4.5.1.3 (Durvalumab [MEDI4736] IV Bag Preparation and Administration): Revised to require that subject weight is > 30 kg for fixed dosing of oleclumab and durvalumab due to endotoxin levels.

8 Section 5.3.3 (Adverse Events of Special Interest for Durvalumab): Added AESIs of vasculitis, non-infectious meningitis, and non-infectious encephalitis per durvalumab IB ed 15.0.

9 Section 5.5 (Reporting of Serious Adverse Events): Updated this section to ensure that country-specific regulatory reporting requirements for SAEs are met, according to updated sponsor guidelines.

Changes to the protocol considered to be non-substantial are summarized below.

1 Title page: Updated medical monitor and added NCT and EudraCT numbers.
2 Synopsis: Updated to align with changes to the body of the protocol.
3 Sections 1.4.1.1 (Study D6070C00001), 1.4.1.2 (Study D6070C00005), and 1.6.2 (Potential Benefits): Updated clinical experience per oleclumab IB edition 6.0.
4 Section 1.4.2 (Durvalumab Clinical Experience): Updated clinical experience per durvalumab IB edition 15.0.
5 Section 10.1 (Signatures): Removed signature appendix from the protocol. Renumbered subsequent appendices accordingly.

9.3 Protocol Amendment 1

Text revisions resulting from this amendment are incorporated in the body of Protocol Amendment 1. The principal reason for this amendment is to revise Part 2 of the study design to include an additional 30 subjects per treatment arm in Cohort A and add an interim analysis for Cohort A. The reason for the change in study design for Part 2 Cohort A was based on increasing the power of the study, the higher than expected drop-out rate, and the positive results of safety and efficacy of the oleclumab and durvalumab combination seen in the FTIH Study D6070C00001. Additionally, the sample size for Part 2 Cohort B was increased to 35 subjects per treatment arm (previously 30 subjects) to account for the higher than expected drop-out rate seen in Cohort A.

Substantial changes to the protocol are summarized below.

1 Section 3.1.1 (Overview), Figure 2 (3.1.1-2) (Study Flow Diagram [Part 2: Dose Expansion]), Sections 4.1.1 (Number of Subjects), 4.8.2 (Sample Size), and 4.8.7 (Interim Analysis): Revised Part 2 of the study design as detailed below.
   (a) Part 2 Cohort A: Revised number of subjects to include an additional 30 subjects per treatment arm (now up to 60 subjects per treatment arm). Revised significance level to 0.10 (previously 0.15) and increased power to 77% (previously 66%) in Section 4.8.2. Added an interim analysis in Section 4.8.7 when approximately 30 evaluable subjects in each treatment arm have been dosed and reach the data cut-off criteria.

(b) Part 2 Cohort B: Revised the sample size to 35 subjects per treatment arm. Revised significance level to 0.10 (previously 0.15), revised difference in ORR to 20% (previously 15%), and increased power to 72% (previously 63%) in Section 4.8.2.

(c) Updated total number of subjects in the study to account for additional subjects in Part 2 Cohorts A and B.

2 Section 3.1.3.4 (Safety Review Committee): Added SRC to provide details regarding ongoing safety surveillance of subjects during the randomization phase of the study.

Changes to the protocol considered to be non-substantial are summarized below.

1 Title page: Updated medical monitor.

2 Synopsis: Updated to align with changes to the body of the protocol.

3 Renumbered tables and figures sequentially to align with MedImmune house style. Previous table and figure numbers are noted in parentheses.

4 Section 1.4.1 (Oleclumab Clinical Experience): Updated clinical experience for Study D6070C00001 and added clinical experience for Study D6070C00005 per oleclumab IB edition 5.1.

5 Section 1.4.2 (Durvalumab Clinical Experience): Updated clinical experience per durvalumab IB edition 14.0.

6 Section 1.6.2 (Potential Benefits): Updated clinical activity observed in the PDAC cohort in Study D6070C00001 per oleclumab IB edition 5.1.

7 Section 4.1.2 (Inclusion Criteria): For Criterion 8, Table 5 (4.1.2-1) (Criteria for Adequate Organ and Marrow Function), clarified that TBL $\leq 3 \times$ ULN in presence of documented Gilbert's syndrome or liver metastases is allowed only for subjects in Cohort B, as nab-paclitaxel cannot be given to subjects in Cohort A unless TBL $\leq 1.5 \times$ ULN.

8 Section 4.1.3 (Exclusion Criteria): Revised as detailed below.

(a) Criterion 5: Clarified that subjects with thrombosis due to mechanical obstruction by the tumor that is found incidentally and is asymptomatic and does not require therapy may be enrolled at the investigator's discretion and should be monitored closely.

(b) Criterion 21: Added exclusion criterion for subjects with known allergy or hypersensitivity to gemcitabine, nab-paclitaxel, oxaliplatin, leucovorin, or 5-FU.

9 Section 4.2.2 (Treatment Period), Table 7 (4.2.2-1) (Schedule of Treatment Period Study Procedures [Cohort A: Part 1 (Dose Escalation) and Part 2 (Dose Expansion)]), and Table 8 (4.2.2-2) (Schedule of Treatment Period Study Procedures [Cohort B: Part 1 (Dose Escalation) and Part 2 (Dose Expansion)]): Clarified ±3-day treatment window applies to visits after Cycle 1 Day 1.

10 Section 4.3.4 (Clinical Laboratory Tests): Revised subheading for "Serum Chemistry" to "Serum/Plasma Chemistry" for clarification.

11 Section 4.3.8 (Biomarker Evaluation and Methods): Added statement to clarify that CD73 expression will be determined in a CAP/CLIA laboratory using a validated, fully automated, IHC assay to clarify methodology for analysis of CD73 expression.

12 Section 4.5.1 (Identity of Investigational Products): Revised appearance of durvalumab to "clear to opalescent, colorless to slightly yellow liquid, free from visible particles" (previously "free from or practically free from visible particles") for consistency with the Summary of Product Characteristics.

13 Sections 4.5.1 (Identity of Investigational Products) and 4.5.4 (Storage): Clarified that drug products should be kept in original (previously "secondary") packaging until use to prevent prolonged (previously "excessive") light exposure.

14 Sections 4.5.1.2 (Oleclumab [MEDI9447] IV Bag Preparation and Administration) and 4.5.1.3 (Durvalumab [MEDI4736] IV Bag Preparation and Administration): Revised as detailed below.

   (a) Section 4.5.1.2: Revised oleclumab instructions to allow a new oleclumab dose to be prepared if the infusion time exceeds 4 hours similar to durvalumab (previously stated that the oleclumab dose had to be abandoned in this case).

   (b) Sections 4.5.1.2 and 4.5.1.3: Removed requirement that the filter be in-line for oleclumab and durvalumab to allow flexibility for clinical sites. Added a + 15-minute window to the 1-hour oleclumab and durvalumab infusion times to allow flexibility for the clinical sites and time to flush the IV line.

15 Section 4.5.1.4 (Treatment Administration): Added infusion times for chemotherapy.

16 Section 4.7.2 (Prohibited Concomitant Medications): Revised as detailed below.

   (a) Clarified that the use of immunosuppressive medication as premedication prior to chemotherapy is allowed.

   (b) Added cannabinoids as prohibited concomitant medication for oleclumab treatment arms due to interaction between cannabinoids and adenosine pathway.

17 Section 4.8.3.1 (Primary Efficacy Analysis): Comparison of arms for ORR will be obtained from Cochran-Mantel-Haenszel test (previously Chi square or Fisher's exact test).

18 Section 5.3.2.3 (Immune Complex Disease): Deleted "and with confirmed presence of ADAs". Subjects who experience an AE suspected to be immune complex-related will discontinue treatment; confirmation of the presence of ADAs is not required as ADA testing is not performed in real-time.

19 Section 10.1 (Signatures [previously numbered Section 9.1]): Updated sponsor signature.

10 APPENDICES

10.1 Contraception Guidance

For females of childbearing potential:

- Females of childbearing potential are defined as those who are not surgically sterile (ie, surgical sterilization includes bilateral tubal ligation, bilateral oophorectomy, or hysterectomy) or those who are not postmenopausal (defined as 12 months with no menses without an alternative medical cause).
- A highly effective method of contraception is defined as one that results in a low failure rate (ie, less than 1% per year) when used consistently and correctly. The acceptable methods of contraception are described in Table 14 (9.2-1).
- Female subjects must refrain from egg cell donation and breastfeeding while on study and for 180 days after the final dose of investigational product.

Table 14 (9.2-1) Highly Effective Methods of Contraception

Barrier Methods	Hormonal Methods
• Intrauterine device • Intrauterine hormone-releasing system (UIS) [a] • Bilateral tubal occlusion • Vasectomized partner [b] • Sexual abstinence [c]	Combined (estrogen and progestogen containing hormonal contraception) ° Oral (combined pill) ° Injectable ° Transdermal (patch) Progestogen-only hormonal contraception associated with inhibition of ovulation [d] ° Injectable ° Implantable ° Intravaginal

[a] This is also considered a hormonal method.
[b] With appropriate post-vasectomy documentation of surgical success (absence of sperm in ejaculate).
[c] Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of the study and if it is the preferred and usual lifestyle of the subject.
[d] Progestogen-only hormonal contraception, where inhibition of ovulation is not the primary mode of action (eg, minipill), is not accepted as a highly effective method).

10.2 Additional Safety Guidance

Further Guidance on the Definition of a Serious Adverse Event

Life-threatening

'Life-threatening' means that the subject was at immediate risk of death from AE as it occurred or it is suspected that use or continued use of the product would result in the subject's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (eg, hepatitis that resolved without hepatic failure).

Hospitalization

Outpatient treatment in an emergency room is not in itself a serious AE, although the reasons for it may be (eg, bronchospasm, laryngeal edema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the subject was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important Medical Event or Medical Intervention

Medical and scientific judgment should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life-threatening or result in death, hospitalization, disability or incapacity but may jeopardize the subject or may require medical intervention to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgment must be used.

Examples of such events are:

- Angioedema not severe enough to require intubation but requiring IV hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (eg, neutropenia or anemia requiring blood transfusion) or convulsions that do not result in hospitalization
- Development of drug dependency or drug abuse

Assessment of Severity

Assessment of severity is one of the responsibilities of the investigator in the evaluation of AEs and SAEs. Severity will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03 as provided in below. The

determination of severity for all other events not listed in the CTCAE should be made by the investigator based upon medical judgment and the severity categories of Grade 1 to 5 as defined below.

Grade 1	An event of mild intensity that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
Grade 2	An event of moderate intensity that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the subject.
Grade 3	A severe event that requires intensive therapeutic intervention. The event interrupts usual activities of daily living, or significantly affects the clinical status of the subject.
Grade 4	An event, and/or its immediate sequelae, that is associated with an imminent risk of death.
Grade 5	Death as a result of an event.

It is important to distinguish between serious criteria and severity of an AE. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 5.2. A Grade 3 AE need not necessarily be considered an SAE. For example, a Grade 3 headache that persists for several hours may not meet the regulatory definition of an SAE and would be considered a nonserious event, whereas a Grade 2 seizure resulting in a hospital admission would be considered an SAE.

Assessment of Relationship

A guide to Interpreting the Causality Question

The investigator is required to provide an assessment of relationship of AEs and SAEs to the investigational product. The following factors should be considered when deciding if there is a "reasonable possibility" that an AE may have been caused by the investigational product.

- Time Course. Exposure to suspect investigational product. Has the subject actually received the suspect investigational product? Did the AE occur in a reasonable temporal relationship to the administration of the suspect investigational product?
- Consistency with known investigational product profile. Was the AE consistent with the previous knowledge of the suspect investigational product (pharmacology and toxicology) or products of the same pharmacological class? OR could the AE be anticipated from its pharmacological properties?

- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect investigational product?
- No alternative cause. The AE cannot be reasonably explained by another etiology such as the underlying disease, other drugs, or other host or environmental factors.
- Re-challenge experience. Did the AE reoccur if the suspected investigational product was reintroduced after having been stopped? MedImmune would not normally recommend or support a re-challenge.
- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship?

In difficult cases, other factors could be considered such as:

- Is this a recognized feature of overdose of the investigational product?
- Is there a known mechanism?

Causality of 'related' is made if following a review of the relevant data, there is evidence for a 'reasonable possibility' of a causal relationship for the individual case. The expression 'reasonable possibility' of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship.

The causality assessment is performed based on the available data including enough information to make an informed judgment. With limited or insufficient information in the case, it is likely that the event(s) will be assessed as 'not related'.

Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

Relationship to Protocol Procedures

The investigator is also required to provide an assessment of relationship of SAEs to protocol procedures on the SAE Report Form. This includes nontreatment-emergent SAEs (ie, SAEs that occur prior to the administration of investigational product) as well as treatment-emergent SAEs. A protocol-related SAE may occur as a result of a procedure or intervention required during the study (eg, blood collection, washout of an existing medication). The following guidelines should be used by investigators to assess the relationship of SAEs to the protocol:

Protocol related:	The event occurred due to a procedure/intervention that was described in the protocol for which there is no alternative etiology present in the subject's medical record.
Not protocol related:	The event is related to an etiology other than the procedure/ intervention that was described in the protocol (the alternative etiology must be documented in the study subject's medical record).

10.3 National Institute of Allergy and Infectious Disease and Food Allergy and Anaphylaxis Network Guidance for Anaphylaxis Diagnosis

National Institute of Allergy and Infectious Disease and Food Allergy and Anaphylaxis Network define anaphylaxis as a serious allergic reaction that is rapid in onset and may cause death. They recognize 3 categories of anaphylaxis, with criteria designated to capture from 80% of cases (category 1) to > 95% of all cases of anaphylaxis (for all 3 categories).

1 Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula) AND AT LEAST ONE OF THE FOLLOWING
   (a) Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow (PEF), hypoxemia)
   (b) Reduced blood pressure (BP) or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)
2 Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
   (a) Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)
   (b) Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   (c) Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)
   (d) Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)
3 Reduced BP after exposure to known allergen for that patient (minutes to several hours):
   (a) Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline

Reference: Sampson et al, 2006

10.4 Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law

10.4.1 Introduction

This appendix describes the process to be followed to identify and appropriately report cases of Hy's Law. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries. Specific guidance on managing liver abnormalities can be found in Section 3.1.4 of the protocol.

During the course of the study, the investigator will remain vigilant for increases in liver biochemistry. The investigator is responsible for determining whether a subject meets potential Hy's Law criteria at any point during the study.

The investigator participates, together with MedImmune clinical project representatives, in review and assessment of cases meeting potential Hy's Law criteria to agree whether Hy's Law criteria are met. Hy's Law criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than drug-induced liver injury (DILI) caused by the investigational product.

The investigator is responsible for recording data pertaining to potential Hy's Law/Hy's Law cases and for reporting AEs and SAEs according to the outcome of the review and assessment in line with standard safety reporting processes.

10.4.2 Definitions

10.4.2.1 Potential Hy's Law

AST or ALT $\geq 3 \times$ ULN **together with** TBL $\geq 2 \times$ ULN at any point during the study following the start of investigational product irrespective of an increase in ALP.

10.4.2.2 Hy's Law

AST or ALT $\geq 3 \times$ ULN **together with** TBL $\geq 2 \times$ ULN, where no other reason, other than the investigational product, can be found to explain the combination of increases; eg, elevated ALP indicating cholestasis, viral hepatitis, or another drug.

For potential Hy's Law and Hy's Law, the elevation in transaminases must precede or be coincident with (ie, on the same day) the elevation in TBL, but there is no specified timeframe within which the elevations in transaminases and TBL must occur.

10.4.3 Identification of Potential Hy's Law Cases

In order to identify cases of potential Hy's Law, it is important to perform a comprehensive review of laboratory data for any subject who meets any of the following identification criteria in isolation or in combination:

- ALT $\geq 3 \times$ ULN
- AST $\geq 3 \times$ ULN
- TBL $\geq 2 \times$ ULN

The investigator will, without delay, review each new laboratory report and if the identification criteria are met will:

- Notify the sponsor study representative
- Determine whether the subject meets potential Hy's Law criteria (see Section 10.4.2) by reviewing laboratory reports from all previous visits
- Promptly enter the laboratory data into the laboratory case report form (CRF)

10.4.4 Follow-up

10.4.4.1 Potential Hy's Law Criteria Not Met

If the subject does not meet potential Hy's Law criteria the investigator will:

- Inform the study representative that the subject has not met potential Hy's Law criteria.
- Perform follow-up on subsequent laboratory results according to the guidance provided in the study protocol.

10.4.4.2 Potential Hy's Law Criteria Met

If the subject does meet potential Hy's Law criteria the investigator will:

- Determine whether potential Hy's Law criteria were met at any study visit prior to starting study treatment (see Section 10.4.6)
- Notify the sponsor study representative who will then inform the study team

The medical monitor contacts the investigator, to provide guidance, discuss and agree an approach for the study subjects' follow-up and the continuous review of data. Subsequent to this contact the investigator will:

- Monitor the subject until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated.
- Investigate the etiology of the event and perform diagnostic investigations as discussed with the medical monitor.

- If at any time (in consultation with the medical monitor) the potential Hy's Law case meets serious criteria, report it as an SAE using standard reporting procedures.

10.4.5 Review and Assessment of Potential Hy's Law Cases

The instructions in this section should be followed for all cases where potential Hy's Law criteria are met.

No later than 3 weeks after the biochemistry abnormality was initially detected, the medical monitor will contact the investigator in order to review available data and agree on whether there is an alternative explanation for meeting potential Hy's Law criteria other than DILI caused by the investigational product. The medical monitor and Global Safety Physician will also be involved in this review together with other subject matter experts as appropriate.

According to the outcome of the review and assessment, the investigator will follow the instructions below.

If there is an agreed alternative explanation for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE:

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate CRF
- If the alternative explanation is an AE/SAE, record the AE /SAE in the CRF accordingly and follow the sponsor's standard processes

If it is agreed that there is **no** explanation that would explain the ALT or AST and TBL elevations other than the investigational product:

- Report an SAE (report term 'Hy's Law') according to the sponsor's standard processes.
  - The 'Medically Important' serious criterion should be used if no other serious criteria apply
  - As there is no alternative explanation for the Hy's Law case, a causality assessment of 'related' should be assigned

If, there is an unavoidable delay of over 3 weeks in obtaining the information necessary to assess whether or not the case meets the criteria for Hy's Law, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Report an SAE (report term 'Potential Hy's Law') applying serious criteria and causality assessment as per above

- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether Hy's Law criteria are met. Update the SAE report according to the outcome of the review

10.4.6 Actions Required When Potential Hy's Law Criteria Are Met Before and After Starting Study Treatment

This section is applicable to subjects with liver metastases who meet potential Hy's Law criteria on study treatment having previously met potential Hy's Law criteria at a study visit prior to starting study treatment.

At the first on study treatment occurrence of potential Hy's Law criteria being met, the investigator will:

- Determine if there has been a significant change in the subjects' condition compared with the last visit where potential Hy's Law criteria were met
  - If there is no significant change no action is required
  - If there is a significant change notify the study representative, who will inform the central study team, then follow the subsequent process described in Section 10.4.4.2

A 'significant' change in the subject's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST, or TBL) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the investigator, this may be in consultation with the medical monitor if there is any uncertainty.

10.4.7 Actions Required for Repeat Episodes of Potential Hy's Law

This section is applicable when a subject meets potential Hy's Law criteria on study treatment and has already met potential Hy's Law criteria at a previous on study treatment visit.

The requirement to conduct follow-up, review, and assessment of a repeat occurrence(s) of potential Hy's Law is based on the nature of the alternative cause identified for the previous occurrence.

The investigator should determine the cause for the previous occurrence of potential Hy's Law criteria being met and answer the following question:

- Was the alternative cause for the previous occurrence of potential Hy's Law criteria being met found to be the disease under study eg, chronic or progressing malignant disease, severe infection, or liver disease, or did the subject meet potential Hy's Law criteria prior to starting study treatment and at their first on study treatment visit as described in Section 10.4.6?

If **No**: follow the process described in Section 10.4.4.2.

If **Yes**:

Determine if there has been a significant change in the subject's condition compared with when potential Hy's Law criteria were previously met:

- If there is no significant change no action is required
- If there is a significant change follow the process described in Section 10.4.4.2

A 'significant' change in the subject's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST, or TBL) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the investigator; this may be in consultation with the medical monitor if there is any uncertainty.

10.5 Genetic Research

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Inclusion criteria

For inclusion in this genetic research, subjects must fulfill all of the inclusion criteria described in the main body of the Clinical Study Protocol **and**:

- Provide informed consent for the genetic sampling and analyses.

Exclusion criteria

Exclusion from this genetic research may be for any of the exclusion criteria specified in the main study or any of the following:

- Non-leukocyte depleted whole blood transfusion in 120 days of genetic sample collection

Discontinuation of subjects from this genetic research

Specific reasons for discontinuing a subject from this genetic research are:

Withdrawal of consent for genetic research: Subjects may withdraw from this genetic research at any time, independent of any decision concerning participation in other aspects of the main study. Voluntary discontinuation will not prejudice further treatment. Procedures for discontinuation are outlined in Section 4.1.9 of the protocol.

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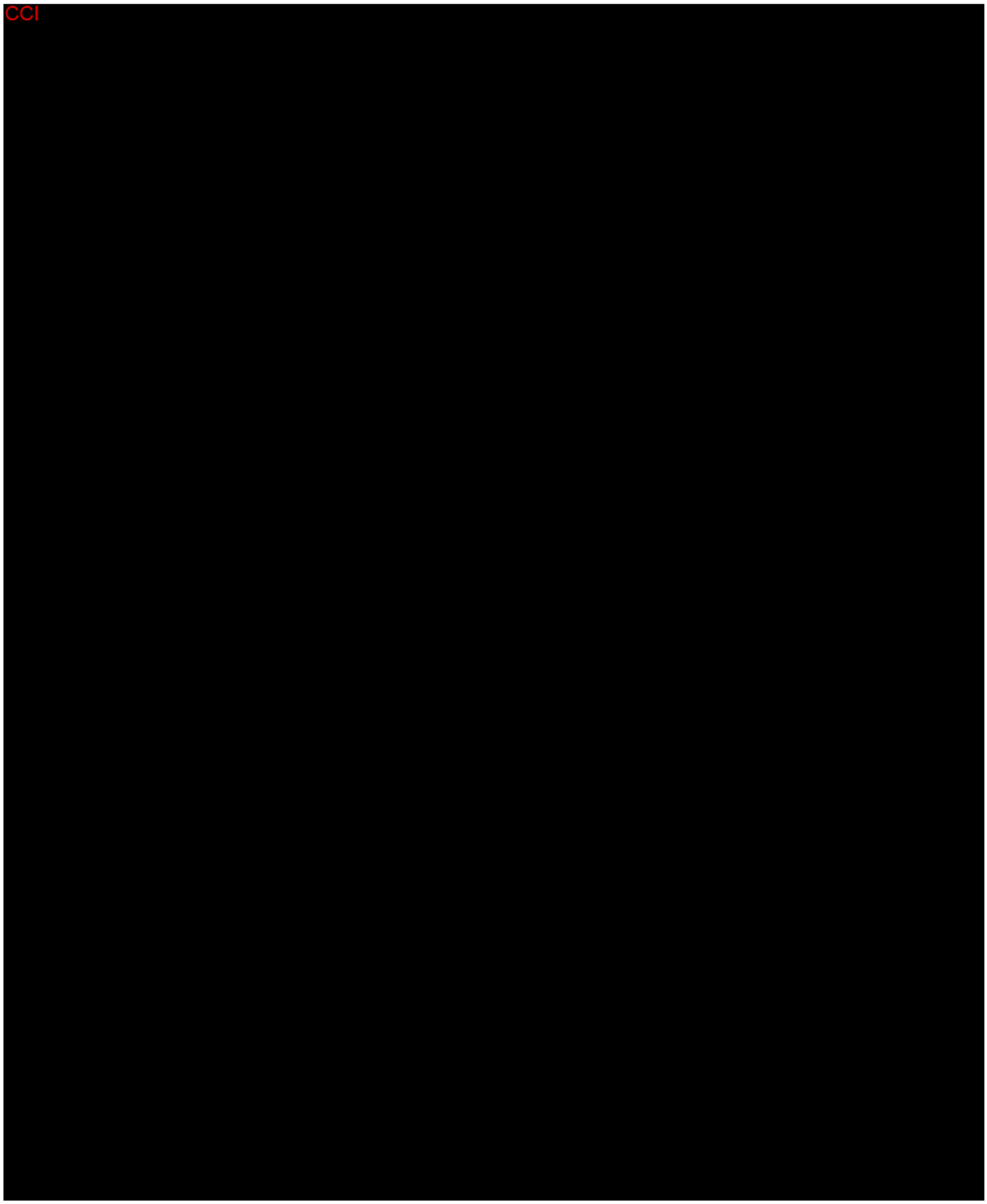
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10.6 CCI

10.6.1 CCI

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10.6.2 CCI

10.7 Response Evaluation Criteria in Solid Tumors Version 1.1

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- **Nonmeasurable Lesions** - Nonmeasurable lesions are defined as all other lesions (or sites of disease), including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis). Lesions considered truly nonmeasurable include the following: leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, and abdominal masses/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques.
- **Target Lesions** - At baseline, all lesions up to a maximum of 5 lesions total (and a maximum of 2 lesions per organ) representative of all involved organs should be identified as target lesions. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected.
- **Non-target Lesions** - It is possible to record multiple non-target lesions involving the same organ as a single item (eg, "multiple enlarged pelvic lymph nodes" or "multiple liver metastases").
- **New Lesions** - CCI [redacted]

RECIST Version 1.1 Response Criteria

Evaluation of Target Lesions

- **Complete Response (CR)** - Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm (the sum may not be "0" if there are target nodes).
- **Partial Response (PR)** - At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

- **Progressive Disease (PD)** - At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered PD.)
- **Stable Disease (SD)** - Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum of diameters while on study.

Evaluation of Non-target Lesions

- **Complete Response (CR)** - Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis).
- **Non-complete response/Non-progressive disease (Non-CR/Non-PD)** - Persistence of 1 or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.
- **Progressive Disease (PD)** - Unequivocal progression of existing non-target lesions will be defined as the overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy (see Sections 4.1.6 and 4.1.7). In the absence of measurable disease, change in nonmeasurable disease comparable in magnitude to the increase that would be required to declare PD for measurable disease. Examples include an increase in a pleural effusion from 'trace' to 'large,' an increase in lymphangitic disease from localized to widespread.

Appearance of New Lesions

The appearance of new lesions is considered PD according to RECIST version 1.1. Considering the unique response kinetics that have been observed with immunotherapy, new lesions can nonetheless derive clinical benefit (Borghaei et al, 2015). In the absence of rapid clinical deterioration, subjects may continue to receive study therapy if investigators consider that subjects continue to benefit from treatment (see Section 4.1.7).

Evaluation of Overall Response

CCI [redacted] If a subject discontinues the study due to PD and begins another treatment, a confirmatory scan is not required. Treatment of subjects may continue between the initial assessment of PD and confirmation of PD (which is not required by RECIST version 1.1). These subjects may continue to receive study therapy beyond confirmed PD in accordance with Section 4.1.7 and if investigators consider that subjects continue to receive benefit from treatment. In the

absence of clinical deterioration, such modifications to the RECIST may discourage the early discontinuation of treatment and provide a more complete evaluation of study therapy antitumor activity than would be seen with conventional response criteria.

Table 15 (9.8-1) provides overall responses for all possible combinations of tumor responses in target and non-target lesions with or without the appearance of new lesions.

Table 15 (9.8-1) Evaluation of Overall Response using RECIST v1.1

Target Lesions	Non-target Lesions	New Lesions	Overall Response
Complete response	Complete response (or no non-target lesion)	No	Complete response
No target lesion [a]	Complete response	No	Complete response
Complete response	Not evaluable [b]	No	Partial response
Complete response	Non-complete response / non-progressive disease	No	Partial response
Partial response	Non-progressive disease and not evaluable (or no non-target lesion) [b]	No	Partial response
Stable disease	Non-progressive disease and not evaluable (or no non-target lesion) [b]	No	Stable disease
Not all evaluated	Non-progressive disease	No	Not evaluable
No target lesion [a]	Not all evaluated	No	Not evaluable
No target lesion [a]	Non-complete response / non-progressive disease	No	Non-complete response / non-progressive disease
Progressive disease	Any	Yes/No	Progressive disease
Any	Progressive disease	Yes/No	Progressive disease
Any	Any	Yes	Progressive disease
No target lesion [a]	Unequivocal progressive disease	Yes/No	Progressive disease
No target lesion [a]	Any	Yes	Progressive disease

RECIST = Response Evaluation Criteria in Solid Tumors; v = version.

[a] Defined as no target lesion at baseline.

[b] Not evaluable is defined as either when no or only a subset of lesion measurements are made at an assessment.

Reference: Eisenhauer et al, 2009

CCI [redacted]

CCI [redacted]

CCI [redacted]

Table 16 (9.9-1) CCI [redacted]

CCI [redacted]

Table 16 (9.9-1) CCI [redacted]

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10.9 Oleclumab Dosing Modification for Toxicity Management

Table 17 (9.10-1) Oleclumab Dosing Modification and Toxicity Management Guidelines for Immune-mediated Reactions – General Considerations

General Considerations	
Dose Modifications	**Toxicity Management**
Drug administration modifications of study drug/study regimen will be made to manage potential immune-related AEs based on severity of treatment-emergent toxicities graded per NCI CTCAE v4.03 (unless otherwise indicated). In addition to the criteria for permanent discontinuation of study drug/study regimen based on CTC grade/severity (see below), permanently discontinue study drug/study regimen for the following conditions: ° Inability to reduce corticosteroid to a dose of ≤10 mg of prednisone per day (or equivalent) **within 12 weeks** of the start of the imAE. ° Grade 3 recurrence of a previously experienced treatment-related imAE following resumption of dosing. Grade 1 No dose modification Grade 2 Hold study drug/study regimen dose until resolution to Grade ≤1. If toxicity worsens, then treat as Grade 3 or Grade 4. Study drug/study regimen can be resumed once event improves to Grade ≤1 after completion of steroid taper to prednisone dose equivalent of ≤10 mg/day. Grade 3 Hold study drug/study regimen dose until resolution to Grade ≤1. If toxicity worsens, then treat as Grade 4. Study drug/study regimen can be resumed once event improves to Grade ≤1 after completion of steroid taper to prednisone dose equivalent of ≤10 mg/day. Grade 4 Permanently discontinue study drug/study regimen. Note: For Grade ≥2 asymptomatic amylase or lipase levels, study drug/study regimen may be continued, and continue to monitor patient closely for symptoms or signs of pancreatitis. Note: Study drug/study regimen should be permanently discontinued in Grade 3 events with high likelihood for morbidity and/or mortality – eg, myocarditis, or other similar events. Similarly, consider whether study drug/study regimen should be permanently discontinued in Grade 2 events with high likelihood for morbidity and/or mortality – eg, myocarditis, or other similar events – when they do not	It is recommended that management of imAEs follows the guidelines presented in this table: ° It is possible that events with an inflammatory or immune-mediated mechanism could occur in nearly all organs. ° Patients should be thoroughly evaluated to rule out any alternative etiology (eg, disease progression, concomitant medications, and infections) to a possible immune-mediated event. In the absence of a clear alternative etiology, all such events should be managed as if they were immune related. General recommendations follow. ° Symptomatic and topical therapy should be considered for low-grade (Grade 1 or 2) events. ° For severe (Grade ≥3) or persistent (>3 to 5 days) low-grade (Grade 2) events, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. ° Some events with high likelihood for morbidity and/or mortality – eg, myocarditis, or other similar events – should progress rapidly to high dose IV corticosteroids (methylprednisolone at 2 to 4 mg/kg/day) even if the event is Grade 2, and if clinical suspicion is high and/or there has been clinical confirmation. Consider, as necessary, discussing with the study medical monitor, and promptly pursue specialist consultation. ° If symptoms recur or worsen during corticosteroid tapering (28 days of taper), increase the corticosteroid dose (prednisone dose 2 to 4 mg/kg/day PO or IV equivalent) until stabilization or improvement of symptoms, then resume corticosteroid tapering at a slower rate (>28 days of taper). ° More potent immunosuppressives such as TNF inhibitors (eg, infliximab) should be considered for events not responding to systemic steroids, with the exception of immune-mediated hepatitis (wherein, alternates such as mycophenolate mofetil should be considered). Progression to use of more potent immunosuppressives should proceed more rapidly in events with

Table 17 (9.10-1) Oleclumab Dosing Modification and Toxicity Management Guidelines for Immune-mediated Reactions – General Considerations

General Considerations	
Dose Modifications	**Toxicity Management**
rapidly improve to Grade <1 upon treatment with systemic steroids and following full taper. Note: There are some exceptions to permanent discontinuation of study drug for Grade 4 events (ie, hyperthyroidism, hypothyroidism, Type 1 diabetes mellitus, adrenal insufficiency, hypophysitis) that have been controlled with hormone-replacement or other appropriate therapy and the patient is clinically stable as per investigator or treating physician's clinical judgment.	high likelihood for morbidity and/or mortality – eg, myocarditis, or other similar events – when these events are not responding to systemic steroids. ° With long-term steroid and other immunosuppressive use, consider need for *Pneumocystis jirovecii* pneumonia (PJP, formerly known as *Pneumocystis carinii* pneumonia) prophylaxis, gastrointestinal protection, and glucose monitoring. ° Discontinuation of study drug/study regimen is not mandated for Grade 3/Grade 4 inflammatory reactions attributed to local tumor response (eg, inflammatory reaction at sites of metastatic disease and lymph nodes). Continuation of study drug/study regimen in this situation should be based upon a benefit-risk analysis for that patient.

AE = adverse event; CTC = Common Toxicity Criteria; CTCAE = Common Terminology Criteria for Adverse Events; imAE = immune-mediated adverse event; IV = intravenous; NCI = National Cancer Institute; PJP = *Pneumocystis jirovecii* pneumonia (formerly known as *Pneumocystis carinii* pneumonia); PO = by mouth; TNF = tumor necrosis factor.

Table 18 (9.10-3) Oleclumab Dosing Modification and Toxicity Management Guidelines for Infusion-related Reactions

Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
Any Grade	General Guidance	For Any Grade: ° Manage per institutional standard at the discretion of investigator. ° Monitor patients for signs and symptoms of infusion-related reactions (eg, fever and/or shaking chills, flushing and/or itching, alterations in heart rate and blood pressure, dyspnea or chest discomfort, or skin rashes) and anaphylaxis (eg, generalized urticaria, angioedema, wheezing, hypotension, or tachycardia).
Grade 1 or 2	For Grade 1: The infusion rate of study drug/study regimen may be decreased by 50% or temporarily interrupted until resolution of the event. For Grade 2: The infusion rate of study drug/study regimen may be decreased 50% or temporarily interrupted until resolution of the event. Subsequent infusions may be given at 50% of the initial infusion rate.	For Grade 1 or 2: ° Acetaminophen and/or antihistamines may be administered per institutional standard at the discretion of the investigator. ° Consider premedication per institutional standard prior to subsequent doses. ° Steroids should not be used for routine premedication of Grade ≤2 infusion reactions.
Grade 3 or 4	For Grade 3 or 4: Permanently discontinue study drug/study regimen.	For Grade 3 or 4: ° Manage severe infusion-related reactions per institutional standards (eg, IM epinephrine, followed by IV diphenhydramine and ranitidine, and IV glucocorticoid).

CTCAE = Common Terminology Criteria for Adverse Events; IM = intramuscular; IV = intravenous; NCI = National Cancer Institute.

Table 19 (9.10-4) Oleclumab Dosing Modification and Toxicity Management Guidelines for Non-immune-mediated Reactions

Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
Any Grade	Note: Dose modifications are not required for AEs not deemed to be related to study treatment (ie, events due to underlying disease) or for laboratory abnormalities not deemed to be clinically significant.	Treat accordingly, as per institutional standard.
Grade 1	No dose modifications.	Treat accordingly, as per institutional standard.
Grade 2	Hold study drug/study regimen until resolution to ≤Grade 1 or baseline.	Treat accordingly, as per institutional standard.
Grade 3	Hold study drug/study regimen until resolution to ≤Grade 1 or baseline. For AEs that downgrade to ≤Grade 2 within 7 days or resolve to ≤Grade 1 or baseline within 14 days, resume study drug/study regimen administration. Otherwise, discontinue study drug/study regimen.	Treat accordingly, as per institutional standard.
Grade 4	Discontinue study drug/study regimen (Note: For Grade 4 labs, decision to discontinue should be based on accompanying clinical signs/symptoms, the investigator's clinical judgment, and consultation with the sponsor.).	Treat accordingly, as per institutional standard.

AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; NCI = National Cancer Institute.

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