A Phase 1/2 Study of Durvalumab and Monalizumab in Adult Subjects with Select Advanced Solid Tumors

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Investigational Product: Durvalumab and monalizumab (IPH2201)

Sponsor: MedImmune, LLC, a wholly owned subsidiary of AstraZeneca PLC, PPD

Medical Monitor: PPD
PPD , Clinical Development, Early Oncology
PPD

Contract Research Organization: Covance

Protocol History, Date
Original Protocol, 09 December 2015
Amendment 1, 21 January 2016
Amendment 2, 10 January 2018
Amendment 3, 31 August 2018
Amendment 4, 22 February 2019
Amendment 5, 06 December 2019
Amendment 6, 31 May 2021

PROTOCOL SYNOPSIS

TITLE

A Phase 1/2 Study of Durvalumab and Monalizumab in Adult Subjects with Select Advanced Solid Tumors

Rationale for Amendment 2: Due to the preliminary clinical activity signal observed with durvalumab in combination with monalizumab in the microsatellite-stable colorectal cancer (CCI CRC) cohort in Part 2 of the current study, Part 3 (Cohorts A CCI) was added to the current study to evaluate further the combination of durvalumab and monalizumab with standard-of-care chemotherapeutic regimens with and without biologic agents (bevacizumab or cetuximab) in subjects with first-line (1L) or second-line (2L) CCI CRC.

Rationale for Amendment 3: Due to the promising preliminary clinical activity signal observed with monalizumab in combination with cetuximab in subjects with recurrent or metastatic squamous cell carcinoma of the head and neck (NCT02643550; Cohen et al, 2018), Cohort C is being added to Part 3 (Cohorts C1A, C1B, C2A, and C2B) of the current study to understand better the exact mechanism of monalizumab in combination with cetuximab (ie, enhancement of antibody-dependent cellular cytotoxicity or adaptive immune response). This will be achieved by evaluating the combination of monalizumab with cetuximab in subjects with CCI CCI CRC that is CCI (Part 3, Cohort C2B) as well as CCI (Part 3, Cohort C1B). In addition, given the previously observed signal of durvalumab in combination with monalizumab in CCI CRC from Part 2, the current study will also evaluate durvalumab in combination with monalizumab plus cetuximab in subjects with CCI CRC that is CCI (Part 3, Cohort C2A) as well as CCI CCI (Part 3, Cohort C1A).

Rationale for Amendment 4: The primary reasons for the amendment were CCI to revise prior therapy inclusion criteria for subjects in Part 3 C Cohorts to match standard of care practice, and to update the process for identifying and reporting potential Hy's Law and Hy's Law cases.

A high-level overview of the study design, status update for each part of the study, total planned number of subjects, and currently enrolled number of subjects is presented below.

Rationale for Amendment 5: The primary reasons for Amendment 5 were to remove the toxicity modification guidelines to a separate standalone document according to updated Sponsor guideline, to align with other Sponsor guidelines, to allow re-treatment following relapse, and to add Schedules of Procedures for re-treatment.

Rationale for Amendment 6: The primary reasons for Amendment 6 were to: describe the continued treatment and monitoring of subjects still on study treatment at the time of the final data cut off, add study mitigation language to provide sites with measures that may be implemented if a participant is not able to visit a study site to ensure that the clinical trial can continue while minimizing risk to the participant, maintaining compliance with Good Clinical Practice, and minimizing risks to the study integrity; CCI

Tumor Type	Treatment	Status Under Protocol Amendment 6	Total Planned Enrollment	Subjects Enrolled and Treated as of 24 March 2020
CCI				

Tumor Type	Treatment	Status Under Protocol Amendment 6	Total Planned Enrollment	Subjects Enrolled and Treated as of 24 March 2020
CCI [redacted]				
Part 3 (Dose Exploration in CCI CRC)				
1L CCI CRC	Cohort A1: mFOLFOX6, bevacizumab, durvalumab 1500 mg Q4W, and monalizumab 750 mg Q2W	Closed	18	18
	Cohort A2: mFOLFOX6, cetuximab, durvalumab 1500 mg Q4W, and monalizumab 750 mg Q2W	Closed	18	18
	CCI [redacted]			

Tumor Type	Treatment	Status Under Protocol Amendment 6	Total Planned Enrollment	Subjects Enrolled and Treated as of 24 March 2020
CCI				

1L = first-line; CCI mFOLFOX6 = a modified FOLFOX regimen of folinic acid/fluorouracil/oxaliplatin; CCI CRC = CCI colorectal cancer; CCI Q2W = every 2 weeks; Q4W = every 4 weeks; CCI

HYPOTHESIS

Parts 1 and 2: The combination of durvalumab (MEDI4736; anti-programmed death ligand 1 [PD-L1] monoclonal antibody) and monalizumab (IPH2201; anti-NKG2a monoclonal antibody) administered to subjects with select advanced solid tumors will show acceptable safety and tolerability so as to permit further clinical testing in subsequent studies.

Part 3 (Cohorts A CCI): The combination of durvalumab and monalizumab plus chemotherapy with or without a biologic agent (bevacizumab or cetuximab), as clinically indicated, administered to subjects with recurrent or metastatic 1L or 2L CCI CRC will show acceptable safety and tolerability so as to permit further clinical testing in subsequent studies.

Part 3 (Cohorts C1A and C2A): The combination of durvalumab and monalizumab plus cetuximab administered to subjects with CCI CRC that is CCI (C1A) or CCI (C2A) will show acceptable safety (C1A and C2A), tolerability (C1A and C2A), and antitumor activity (C1A only) so as to permit further clinical testing in subsequent studies.

Part 3 (Cohorts C1B and C2B): The combination of monalizumab plus cetuximab administered to subjects with CCI CRC that is CCI (C1B) or CCI (C2B) will show acceptable safety (C1B and C2B), tolerability (C1B and C2B), and antitumor activity (C1B only) so as to permit further clinical testing in subsequent studies.

OBJECTIVES

Primary objective:

Part 1:

To assess safety and tolerability, describe the dose-limiting toxicities (DLTs), and determine the maximum tolerated dose (MTD) or the highest protocol-defined dose level in the absence of establishing an MTD of durvalumab in combination with monalizumab in subjects with advanced solid tumors.

Part 2:

To assess further the safety and tolerability of either the MTD or the highest protocol-defined dose level, in the absence of establishing an MTD, of durvalumab in combination with monalizumab in subjects with selected advanced solid tumors.

Part 3:

Cohorts A CCI : To assess safety and tolerability of durvalumab in combination with monalizumab plus chemotherapy with or without a biologic agent (bevacizumab or cetuximab), as clinically indicated, in subjects with 1L or 2L CCI CRC

Cohorts C1A and C2A: To assess safety (C1A and C2A) and tolerability (C1A and C2A) and evaluate the preliminary antitumor activity (C1A only) of durvalumab in combination with monalizumab plus cetuximab in subjects with CCI CRC that is CCI (C1A) or CCI (C2A)

Cohorts C1B and C2B: To assess safety (C1B and C2B) and tolerability (C1B and C2B) and evaluate the preliminary antitumor activity (C1B only) of monalizumab in combination with cetuximab in subjects with CCI CRC that is CCI (C1B) or CCI (C2B)

Secondary objectives:

1 To evaluate the preliminary antitumor activity of:
- Durvalumab in combination with monalizumab in subjects with advanced solid tumors **(Parts 1 and 2)**
- Durvalumab in combination with monalizumab plus chemotherapy with or without a biologic agent (bevacizumab or cetuximab), as clinically indicated in subjects with 1L or 2L CCI CRC **(Part 3, Cohorts A CCI)**
- Durvalumab in combination with monalizumab plus cetuximab in subjects with CCI CRC that is CCI **(Part 3, Cohort C2A)**
- Monalizumab in combination with cetuximab in subjects with CCI CRC that is CCI **(Part 3, Cohort C2B)**

2 To further evaluate the antitumor activity of:
- Durvalumab in combination with monalizumab plus cetuximab in subjects with CCI CRC that is CCI **(Part 3, Cohort C1A)**
- Monalizumab in combination with cetuximab in subjects with CCI CRC that is CCI **(Part 3, Cohort C1B)**

3 To describe the pharmacokinetics (PK) of:
- Durvalumab and monalizumab when administered in combination in subjects with advanced solid tumors **(Parts 1 and 2)**
- Durvalumab and monalizumab when administered in combination with chemotherapy with or without a biologic agent (bevacizumab or cetuximab), as clinically indicated in subjects with 1L or 2L CCI CRC **(Part 3, Cohorts A CCI)**

- Durvalumab, monalizumab, and cetuximab when administered in combination in subjects with CCI CRC that is CCI **(Part 3, Cohort C1A)**
- Monalizumab and cetuximab when administered in combination in subjects with CCI CRC that is CCI **(Part 3, Cohort C1B)**
- Durvalumab and monalizumab when administered in combination with cetuximab in subjects with CCI CRC that is CCI **(Part 3, Cohort C2A)**
- Monalizumab when administered in combination with cetuximab in subjects with CCI CRC that is CCI **(Part 3, Cohort C2B)**

4 To describe the immunogenicity of:

- Durvalumab and monalizumab when administered in combination in subjects with advanced solid tumors **(Parts 1 and 2)**
- Durvalumab and monalizumab when administered in combination with chemotherapy with or without a biologic agent (bevacizumab or cetuximab), as clinically indicated in subjects with 1L or 2L CCI CRC **(Part 3, Cohorts A** CCI **)**
- Durvalumab, monalizumab, and cetuximab when administered in combination in subjects with CCI CRC that is CCI **(Part 3, Cohort C1A)**
- Monalizumab and cetuximab when administered in combination in subjects with CCI CRC that is CCI **(Part 3, Cohort C1B)**
- Durvalumab and monalizumab when administered in combination with cetuximab in subjects with CCI CRC that is CCI **(Part 3, Cohort C2A)**
- Monalizumab when administered in combination with cetuximab in subjects with CCI CRC that is CCI **(Part 3, Cohort C2B)**

5 To characterize the association between clinical outcomes and pre-treatment protein expression within the tumor microenvironment when

- Durvalumab is administered in combination with monalizumab in subjects with advanced solid tumors **(Parts 1 and 2)**
- Durvalumab is administered in combination with monalizumab plus chemotherapy with or without a biologic agent (bevacizumab or cetuximab), as clinically indicated in subjects with 1L or 2L CCI CRC **(Part 3, Cohorts A** CCI **)**
- Durvalumab is administered in combination with monalizumab plus cetuximab in subjects with CCI CRC that is CCI or CCI **(Part 3, Cohorts C1A and C2A**, respectively)
- Monalizumab is administered in combination with cetuximab in subjects with CCI CRC that is CCI or CCI **(Part 3, Cohorts C1B and C2B**, respectively)

Exploratory objectives:

1 To evaluate additional candidate prognostic/predictive/pharmacodynamic biomarkers when

- Durvalumab is administered in combination with monalizumab in subjects with advanced solid tumors **(Parts 1 and 2)**
- Durvalumab is administered in combination with monalizumab plus chemotherapy with or without a biologic agent (bevacizumab or cetuximab), as clinically indicated in subjects with 1L or 2L CCI CRC **(Part 3, Cohorts A** CCI **)**
- Durvalumab is administered in combination with monalizumab plus cetuximab in subjects with CCI CRC that is CCI or CCI **(Part 3, Cohorts C1A and C2A**, respectively)
- Monalizumab is administered in combination with cetuximab in subjects with CCI CRC that is CCI or CCI **(Part 3, Cohorts C1B and C2B**, respectively)

2 CCI

- CCI

- CCI [redacted]
- CCI [redacted]
- CCI [redacted]

3 To evaluate the effect of the following treatment combinations on disease-related symptoms/functioning/health-related quality of life (HRQoL) and overall health status
   - Durvalumab in combination with monalizumab plus cetuximab in subjects with CCI [redacted] CRC that is CCI [redacted] CCI [redacted]
   - Monalizumab in combination with cetuximab in subjects with CCI [redacted] CRC that is CCI [redacted] CCI [redacted]

STUDY ENDPOINTS

Primary endpoint:

The primary endpoint is safety as assessed by presence of adverse events (AEs), serious adverse events (SAEs), DLTs, abnormal laboratory parameters, vital signs, and electrocardiogram (ECG) results. AEs will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.03.

The primary endpoint for evaluating clinical activity in Part 3 (Cohorts C1A and C1B) is objective response (OR) by investigator assessment per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.

Secondary endpoints:

4 The endpoints for assessment of antitumor activity include OR (primary endpoint for Cohorts C1A and C1B), disease control (DC), duration of response (DoR), and progression-free survival (PFS) by investigator assessment per RECIST v1.1. Overall survival (OS) will also be assessed.

5 The endpoints for assessment of PK include individual subject durvalumab, monalizumab, and cetuximab concentrations in serum at different time points after administration of these agents.

6 The endpoints for assessment of immunogenicity include the number and percentage of subjects who develop detectable anti-drug antibodies (ADAs).

7 CCI [redacted]

Exploratory endpoints:

8 Additional candidate prognostic/predictive/pharmacodynamic biomarkers may include, but are not limited to:

   a. Assessment of T- and natural killer (NK)-cell activation (eg, inducible costimulatory molecule expression) and proliferation (eg, Ki67 expression) measured by flow cytometry in blood, by immunohistochemistry (IHC) in tumors, and by mass spectrometry, DNA/RNA/miRNA (microRNA) assessments (RNAseq, exome sequence, single-cell RNA) in blood and tumors

   b. Assessment of the number and activity of CD8+ effector T cells and NK cells and expression of immunomodulatory proteins (eg, programmed death 1) within tumor biopsies using IHC

   c. CCI [redacted]

   d. CCI [redacted]

   e. CCI [redacted]

      i. CCI [redacted]

ii. CCI
iii. CCI
iv. CCI
v. CCI
vi. CCI
vii. CCI
viii. CCI

9 CCI

10 Clinical outcome assessments include:

a. Descriptive statistics for domain, subscale scores, and individual items at each time point and change from baseline as measured by the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30)
b. Time to deterioration and response status for domain, subscale scores, and individual items as measured by the EORTC QLQ-C30
c. Descriptive statistics for subjects' global impression of change of their overall health status at each time point as measured by the Patient Global Impression of Change
d. Time to deterioration in Eastern Cooperative Oncology Group performance status ≥ 2

STUDY DESIGN

This is a Phase 1/2, multicenter, open-label, study of durvalumab and monalizumab to evaluate safety, tolerability, PK, immunogenicity, pharmacodynamics, and antitumor activity in adult subjects with advanced solid tumor malignancies at approximately 60 sites globally. The study consists of 3 parts: dose escalation (Part 1), dose expansion (Part 2), and dose exploration in CCI CRC (Part 3).

- **Part 1** will evaluate dose escalation of durvalumab in combination with monalizumab in subjects with select advanced solid tumor malignancies.
- **Part 2** will evaluate further the identified dose of durvalumab in combination with monalizumab from Part 1 in subjects with select advanced solid tumor malignancies.
- **Part 3 (Cohorts A CCI)** will evaluate dose exploration of durvalumab in combination with monalizumab and chemotherapy, with or without a biologic agent (bevacizumab or cetuximab), as clinically indicated, in subjects with metastatic 1L or 2L CCI CRC.
- **Part 3 (Cohorts C1 and C2)** will evaluate dose exploration of 1) durvalumab in combination with monalizumab plus cetuximab (Cohorts C1A and C2A) and 2) monalizumab in combination with cetuximab (Cohorts C1B and C2B) in subjects with CCI CRC that is CCI or CCI .

Study treatment will be administered up to 3 years until unacceptable toxicity, documentation of confirmed progressive disease (PD), or documentation of subject withdrawal for another reason. Subjects who continue to receive clinical benefit after 3 years of treatment, will continue to receive the treatment on this study, via a rollover study requiring approval by the responsible Health Authority (HA) and ethics committee, or through another mechanism at the discretion of the sponsor. Tolerability data for all subjects will be evaluated regularly and subjects' clinical response status classified according to RECIST v1.1. All subjects will be followed for survival until the end of study. The end of the study ("study completion") is 5 years after the final subject is enrolled or the date the study is closed by the sponsor, whichever occurs first.

Part 1: Dose Escalation

Subjects with advanced CCI CRC, ovarian cancer, CCI endometrial cancer, cervical cancer, castration-resistant prostate cancer, pancreatic adenocarcinoma and non-small cell lung cancer (NSCLC) will be

enrolled in the dose-escalation part. Subjects in sequential cohorts will receive durvalumab (1500 mg every 4 weeks [Q4W]) in combination with monalizumab at CCI planned dose levels (CCI every 2 weeks [Q2W]). CCI

Escalation to the next dose level will be determined by using a modified toxicity probability interval (mTPI) algorithm, with a target DLT rate of ≥ 33% and an equivalence interval of CCI. A minimum of 3 subjects will be enrolled to a dose level and the maximum number of subjects for each dose level will be capped at 12. A dose level will be considered unsafe if it has an estimated 95% or more probability of exceeding the target DLT rate of ≥ 33% with at least 3 subjects treated at that dose level. Up to 60 subjects could be enrolled in the dose-escalation part to determine MTD. Given that the mTPI algorithm leads to a dose-escalation decision if there is no DLT in the first 3 subjects enrolled in a dose-level cohort, it is expected that the actual sample size observed will be fewer. Subjects will be dosed in a group size of 3. The first 3 subjects enrolled in the escalation part will be enrolled to dose-level Cohort 1. No escalation is allowed unless 3 or more evaluable subjects have been treated and evaluated through the DLT-evaluation period in a dose level. Intermediate dose levels may be explored based on emerging data at the discretion of the sponsor.

The MTD will be determined by isotonic regression analysis applied to DLT rates observed during the dose-escalation part.

In general, an AE will be considered a DLT if it is Grade 3 or higher, considered to be drug-related, and occurs within the DLT-evaluation period (defined as the time from start of the first dose of investigational product [durvalumab and monalizumab] until the planned administration of the second dose of durvalumab and the third dose of monalizumab; this corresponds to 28 days after the first dose of durvalumab and monalizumab or 14 days after the second dose of monalizumab).

Administration of the first dose of investigational product will be staggered by a minimum of 24 hours between the first and second subjects in each dose-escalation cohort. Dose escalation will continue to the next higher dose level after all available safety data and any available PK data from subjects in that dose level and prior dose levels have been reviewed by a study-specific dose-escalation committee (DEC). The sponsor may halt dose escalation prior to determining the MTD based on emerging PK/pharmacodynamic, toxicity or response data. The dose-expansion part may be initiated once the MTD, or highest protocol-defined dose level in the absence of exceeding the MTD, is established in the dose-escalation part of the study.

Following completion of the Q2W dose escalation, an alternate treatment schedule(s) of durvalumab in combination with monalizumab (eg, monalizumab Q4W) may be explored based on PK, pharmacodynamic, safety, and response data. If this were to occur, the first group of 3 to 12 subjects will receive durvalumab in combination with monalizumab at the highest dose level that did not exceed the MTD using the durvalumab (Q4W) and monalizumab (Q2W) schedule. If the MTD is not exceeded at that dose level on a monalizumab Q4W schedule and provided this was not the highest protocol-defined dose, dose escalation may proceed with additional sequential cohorts of 3 to 12 subjects according to the aforementioned dose levels using the same mTPI algorithm.

Ongoing surveillance of pharmacodynamics, PK, clinical safety, and antitumor activity data will be performed throughout the dose-escalation part. Once the dose escalation has completed per the mTPI or the highest protocol-defined dose is evaluated, any dose level showing acceptable safety during dose escalation can be expanded to a total of up to 18 subjects with mandatory pre-treatment and on-treatment tumor biopsies. At the discretion of the sponsor, the expansion at a given dose level may be restricted to a specific tumor type(s) included in the dose-escalation part. These dose-escalation cohort expansions will provide additional PK, pharmacodynamic, and safety data to inform optimal dose-level selection for the dose-expansion part (Part 2) and subsequent clinical studies.

Part 2: Dose Expansion

The dose-expansion part will enroll 4 cohorts of approximately 40 subjects each with recurrent or metastatic CCI CRC, ovarian cancer, endometrial cancer, or NSCLC. The dose level and schedule determined in the dose-

escalation part will be used in the dose-expansion part, as agreed by the study-specific DEC. Additional dose levels not exceeding the MTD may be considered based on clinical and PK/pharmacodynamic data from the dose-escalation part.

Enrollment into dose-expansion cohorts may be discontinued at the discretion of the sponsor should emerging clinical or preclinical data suggest that continued treatment may not be beneficial to a given cohort. During dose expansion, subjects will be monitored for safety using the same DLT criteria employed during dose escalation. CCI

During the dose-expansion part, if a toxicity meeting criterion for discontinuation of treatment with the combination of durvalumab and monalizumab is observed in a subject in the NSCLC cohort, but the subject is receiving clinical benefit, the subject may be considered for monotherapy treatment with durvalumab. In this circumstance, the decision to treat NSCLC patients with monotherapy durvalumab will be based on factors such as known sensitivity/response of the tumor type to durvalumab and require agreement of the sponsor and treating investigator.

Enrollment may proceed up to approximately 40 subjects in the CCI CRC, ovarian, and endometrial expansion cohorts CCI . Enrollment may proceed up to approximately 40 subjects in the NSCLC dose-expansion cohort CCI .

Part 3: Dose Exploration in CCI CRC

Subjects with advanced CCI CRC will be enrolled in the dose-exploration part.

Cohort A CCI Subjects:

Cohort A subjects (ie, Cohorts A1, A2, CCI) must be systemic therapy-naïve in the recurrent/metastatic setting, and CCI must be naïve to irinotecan-containing treatment and must have progressed on an oxaliplatin-containing regimen in the first line of their treatment for recurrent/metastatic cancer. Based on the identified dose for durvalumab in combination with monalizumab from Part 1, subjects will receive durvalumab (1500 mg Q4W) in combination with monalizumab (750 mg Q2W) plus a standard chemotherapy regimen of a modified FOLFOX regimen comprised of folinic acid, fluorouracil, and oxaliplatin (mFOLFOX6 [Cohorts A1, A2, CCI]) CCI in combination with bevacizumab (Cohorts A1 CCI) or cetuximab (Cohorts A2 CCI), CCI .

Initially, up to 6 subjects may be enrolled into each of the 4 chemotherapy cohorts with a biologic agent (Cohorts A1, A2, CCI). Initiation of Cohorts CCI (chemotherapy cohorts without a biologic agent) will be staggered and dependent on emerging safety data from Cohorts A1 and A2, CCI , respectively. Administration of the first dose of investigational products and chemotherapy will be staggered by a minimum of 24 hours between the first and second subjects in all 6 cohorts and no more than 3 of the initial subjects in a given cohort will be dosed within 1 week. Subsequently, subjects may be enrolled continuously without pausing the enrollment for DEC review of aggregate safety data until a total of 6 subjects have been enrolled in a given cohort and observed thru the DLT observation period or > 2 subjects experience a DLT in a particular cohort prior to enrolling 6 subjects. Meetings of the study DEC will be held to review all available safety, PK, pharmacodynamic, immunogenicity, and clinical activity data to determine whether to continue enrollment at the current dose level, dose de-escalate, or stop further evaluation of the combination with chemotherapy, with or without a biologic agent, according to the mTPI algorithm. If the DEC decides to continue at the current dose level after the initial 6 subjects have been enrolled and evaluated for DLTs, enrollment may increase by up to an additional 12 subjects per chemotherapy cohort provided criteria for de-escalation according to the mTPI algorithm are not met at any point based on ongoing assessment of safety. In addition, while enrollment is ongoing, the DEC will review aggregate safety data once a total of 12 or 18 subjects in a given cohort have been enrolled and followed through the DLT-evaluation period.

Cohort C Subjects:

Cohort C subjects (ie, Cohorts C1 and C2) CCI CCI CRC that is CCI (Cohort C1) or CCI (Cohort C2); prior standard chemotherapy must include i) fluoropyrimidines, irinotecan, and oxaliplatin; and ii) an anti-vascular endothelial growth factor (VEGF) monoclonal antibody (mAb; eg, bevacizumab); and iii) subjects in Cohort C2 must not have received prior anti-EGFR therapy (eg, cetuximab or panitumumab naïve).

CCI

CCI

CCI

For all cohorts in Part 3, safety will be monitored on an ongoing basis and aggregate safety data will be reviewed by the DEC at pre-specified intervals as described below. CCI Dose modification of individual chemotherapy agents and/or the biologic agents for the management of toxicity in individual subjects will be allowed as per standard clinical practice CCI .

TARGET SUBJECT POPULATION

In both the dose-escalation and dose-expansion parts of the study, male or female adult subjects ≥ 18 years of age, with select advanced solid tumors who are naïve to immunotherapy (subjects entering Part 1 [dose escalation] may have received prior immunotherapy) and subjects entering Parts 1 and 2 must have received and

have progressed or are refractory to at least one line of standard systemic therapy in the recurrent/metastatic setting, appropriate for the specific tumor type, are eligible.

Subjects with the following tumor types may be enrolled in each part of the study as specified below.

1 CCI CRC
   (a) Part 1 and Part 2: Subjects who have received up to 3 lines of prior systemic therapy.
   (b) Part 3 Cohort A (ie, Cohorts A1, A2 CCI): Subjects must be 1L chemotherapy-naïve in the recurrent/metastatic setting; subjects may have progressed ≥ 6 months after receiving an oxaliplatin chemotherapy regimen in the adjuvant setting.
      (i) Subjects in Cohorts A1 CCI can be enrolled regardless of CCI and location of colon primary tumor.
      (ii) Subjects in Cohort A2 are required to be CCI and have a left-sided colon primary tumor.
   (c) Part 3 CCI : Subjects must have received only 1 line of prior therapy containing oxaliplatin in the recurrent/metastatic setting and must be naïve to treatment containing an irinotecan combination.
      (i) Subjects in CCI can be enrolled regardless of CCI and location of colon primary tumor.
      (ii) Subjects in CCI are required to be CCI .
   (d) Part 3, Cohort C (ie, Cohorts C1A, C1B, C2A, and C2B): Subjects CCI prior standard chemotherapy must include i) fluoropyrimidines, irinotecan, and oxaliplatin; and ii) an anti-VEGF mAb (eg, bevacizumab); and iii) subjects in Cohorts C2A and C2B must not have received prior anti-EGFR therapy (eg, cetuximab or panitumumab naïve).
      (i) Subjects in Cohort C1A and C1B are required to have documented CCI .
      (ii) Subjects in Cohort C2A and C2B are required to be wild type for CCI .
2 Ovarian cancer (Part 1 and Part 2): Subjects may have received up to 3 prior lines of systemic therapy (including standard and investigational therapies) in the recurrent/metastatic setting. All subjects must have previously received and progressed while on or within 6 months of completing a platinum-based regimen.
3 CCI endometrial cancer (Part 1 and Part 2): Subjects who have received up to 2 lines of prior systemic therapy (including standard and investigational therapies) in the recurrent/metastatic setting and whose tumors must NOT have high-frequency microsatellite instability.
4 NSCLC (Part 1 and Part 2): Subjects must have histologically proven, stage IIIb or stage IV NSCLC or recurrent or PD following multi-modal therapy (radiation therapy, surgical resection or definitive chemoradiation) for locally advanced disease. Subjects with known sensitizing EGFR-mutation or anaplastic lymphoma kinase-rearrangement are excluded. All subjects' tumors must be tested and shown to be wild type EGFR and anaplastic lymphoma kinase. Subjects must have received up to 2 lines of systemic therapy (including standard and investigational therapies) in the recurrent/metastatic setting.
5 Cervical cancer, castration-resistant prostate cancer, or pancreatic adenocarcinoma (Part 1 only) – Subjects may have received up to 2 prior lines of systemic therapy for recurrent/metastatic disease. Subjects with castration-resistant prostate cancer must have progressed following therapy with abiraterone or enzalutamide.

INVESTIGATIONAL PRODUCT, DOSAGE, AND MODE OF ADMINISTRATION

In the dose-escalation part of the study, sequential cohorts will receive durvalumab (1500 mg Q4W) in combination with monalizumab at CCI planned dose levels via IV infusion (CCI Q2W). The combination of monalizumab 750 mg Q2W and durvalumab 1500 mg Q4W was deemed safe by the DEC; therefore, these doses and associated regimens will be employed in the dose expansion and exploration parts of the study.

Both durvalumab and monalizumab will be administered over approximately 60 minutes. On dosing days when both durvalumab and monalizumab are administered, durvalumab will be administered first with monalizumab

starting 15 to 30 minutes after the completion of the durvalumab infusion. Ongoing monitoring of potential infusion reactions will be performed and pre-treatment of hypersensitivity and/or adjustment of infusion rate will be allowed as detailed in the protocol.

In the dose-exploration part of the study, subjects will receive study treatment based on prior therapies received CCI (see Target Subject Population):

- In addition to durvalumab and monalizumab combination therapy, Cohort A subjects will also receive a regimen of
  - mFOLFOX6 with bevacizumab (Cohort A1) or
  - mFOLFOX6 with cetuximab (Cohort A2) or
  - CCI .
- CCI
  - CCI
  - CCI
  - CCI
- CCI
- CCI

mFOLFOX6, CCI , and the biologic agent (bevacizumab or cetuximab) will be administered according to standard-of-care prescribing information outlined in this protocol and summarized below:

- mFOLFOX6 (Cohorts A1, A2, CCI): Oxaliplatin 85 mg/m^2 IV infusion on Day 1 plus folinic acid 400 mg/m^2 IV infusion on Day 1 plus fluorouracil 400 mg/m^2 IV bolus on Day 1, followed by 2400 mg/m^2 administered by continuous IV infusion over 46 to 48 hours starting on Day 1; repeat Q2W.
- CCI
- Bevacizumab (Cohorts A1 CCI): 5 mg/kg IV infusion on Day 1 then Q2W.
- Cetuximab (Cohorts A2 CCI): Loading dose of 400 mg/m^2 IV infusion over 2 hours on Day 1, followed by maintenance dose of 250 mg/m^2 IV infusion over 1 hour every week starting on Day 8. The cetuximab regimen may be changed to 500 mg/m^2 IV infusion for approximately 2 hours Q2W after a subject has completed the 28-day DLT-evaluation period, at the investigator's discretion and in accordance with institutional guidelines.
- Cetuximab (Cohorts C1A, C1B, C2A, C2B): 500 mg/m^2 IV infusion over 2 hours on Day 1 then 500 mg/m^2 IV infusion for approximately 2 hours Q2W starting on Day 15.

STATISTICAL ANALYSIS PLAN

Sample Size

CCI Additional subjects may be required if additional cohorts or dosing schedules are explored.

Part 1: In the dose-escalation part, the number of subjects to be enrolled will depend upon the toxicities observed as the study progresses. Following an mTPI dose-escalation design for 5 dose levels, with a minimum of 3 subjects and a maximum of 12 subjects for each dose level, up to 60 evaluable subjects may be enrolled. An additional 6 subjects per dose level may be enrolled, up to a maximum of 18 subjects per dose level to provide additional PK, pharmacodynamic, and safety data.

Part 2: In the dose-expansion part, up to 160 subjects (40 subjects per tumor-type cohort) may be enrolled to obtain preliminary assessment of safety and antitumor activity in each tumor type. Enrollment may proceed up

to approximately 40 subjects in the CRC, ovarian, and endometrial expansion cohorts [redacted]. The observed 0/20 response gives an upper limit of a 1-sided [redacted]% confidence interval (CI) of approximately [redacted]%, which means that a response rate greater than [redacted]% can be ruled out with [redacted]% confidence and hence enrollment would be stopped for lack of desirable response rate.

Enrollment may proceed up to approximately 40 subjects in the NSCLC expansion cohort [redacted]. Observing 1/20 response gives an upper limit of a 1-sided [redacted]% CI of approximately [redacted]%, which means that a response rate greater than [redacted]% can be ruled out with [redacted]% confidence and enrollment would be stopped for lack of desirable response rate.

Part 3 (Cohorts A [redacted]): In Part 3 (dose exploration in [redacted] CRC, Cohorts A1, A2, [redacted]), the number of subjects to be enrolled will depend upon the toxicities observed as the study progresses. Based on an mTPI dose-escalation design for up to 2 dose levels, with a minimum of 3 subjects and a maximum of 12 subjects for each dose level, up to 144 evaluable subjects (ie, 2 dose levels across 6 chemotherapy cohorts with or without a biologic agent) may be enrolled. An additional 6 subjects per dose level may be enrolled, up to a maximum of 18 subjects per dose level (ie, a total of 216 evaluable subjects in 2 dose levels across 6 chemotherapy combination cohorts with or without a biologic agent) to provide additional PK, pharmacodynamic, and safety data.

Part 3 (Cohort C): In Part 3 (dose exploration in [redacted] CRC, Cohorts C1 and C2), up to 100 subjects/cohort may be enrolled in Cohorts C1A and C1B. A total of 100 subjects would provide a width of < [redacted]% between the observed objective response rate and its lower limit of the exact [redacted]% CI.

Up to 40 subjects/cohort may be enrolled in Cohorts C2A and C2B. [redacted]

Statistical Analyses

Safety

The MTD will be determined by isotonic regression analysis (Ji et al, 2010) applied to DLT rates observed during the dose-escalation part. The MTD evaluation will be based on the DLT-evaluable Population, which includes all subjects enrolled in the dose-escalation part who receive investigational product per protocol and complete the safety follow-up through the DLT-evaluation period or who experience any DLT during the DLT- evaluation period.

Safety data, including AEs, SAEs, laboratory evaluations, vital signs, physical examinations, and ECG results will be summarized based on the As-treated Population. The As-treated Population includes all subjects who receive any investigational product. Summary statistics will be provided for AEs, SAEs, AE grade, severity, relationship to investigational products, clinical laboratory parameters, physical examinations, vital signs, and ECG. AEs will be graded according to the NCI CTCAE v4.03 and described by system organ class and preferred term using the Medical Dictionary for Regulatory Activities. Laboratory abnormalities with toxicity grades according to the NCI CTCAE v4.03 will be derived and summarized.

Antitumor activity

The analyses of antitumor activity will be based on the As-treated Population for the nonrandomized cohorts and on the Intent-to-treat (ITT) Population for the randomized cohorts. The ITT Population includes subjects who are randomized, and they will be analyzed according to the treatment group they were randomized to. The rates of OR and DC based on RECIST 1.1 will be summarized with [redacted]% and [redacted]% CIs 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 Response-evaluable Population which includes subjects in the As-treated Population for the nonrandomized cohorts and in the ITT Population for the randomized cohorts, who have at least 1 post-baseline disease assessment, who died from any cause, or who discontinued due to clinical PD prior to any post-baseline tumor assessment.

Pharmacokinetics

Individual concentrations will be tabulated by dose cohort along with descriptive statistics. Individual cetuximab concentrations will also be summarized for Part 3, Cohort C1. 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.

Anti-drug antibodies/immunogenicity

The immunogenic potential of durvalumab and monalizumab 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 evaluating neutralizing capacity of ADAs in the future.

Pharmacodynamic biomarkers

Pharmacodynamic biomarkers will be analyzed descriptively. CD94/NKG2a receptor occupancy will be used to assess the pharmacodynamics of monalizumab.

Interim analysis

For Part 3, Cohorts C1A, C1B, C2A, and C2B, an interim futility analysis will be performed after 20 subjects in each cohort are response-evaluable (including subjects who received the same dose during the DLT evaluation). Enrollment will stop CCI [redacted].

For Part 3, Cohorts C1A and C1B, a subsequent interim futility analysis will be performed after 40 subjects in each cohort are response-evaluable (including subjects who received the same dose during the DLT evaluation). Enrollment will stop CCI [redacted].

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LIST OF ABBREVIATIONS

Abbreviation or Specialized Term	Definition
1L	first-line
2L	second-line
CCI	CCI
ADA	anti-drug antibody
ADCC	antibody-dependent cellular cytotoxicity
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BP	blood pressure
CD	cluster of differentiation
CI	confidence interval
CNS	central nervous system
CR	complete response
CRC	colorectal cancer
CrCl	creatinine clearance
CSP	clinical study protocol
CSR	clinical study report
CT	computed tomography
CCI	CCI
CTL	cytotoxic T lymphocyte
CTLA	cytotoxic T lymphocyte antigen
DC	disease control
DCO	Data cut off
DCR	disease control rate
DEC	dose-escalation committee
DLT	dose-limiting toxicity
DoR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EGFR	epidermal growth factor receptor
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire
Fc	fragment crystallizable
CCI	CCI
FOLFOX	a chemotherapy regimen comprised of folinic acid, fluorouracil, and oxaliplatin

Abbreviation or Specialized Term	Definition
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HCP	Health Care Professional
HLA	human leukocyte antigen
HRQoL	health-related quality of life
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IFNγ	interferon-γ
Ig	Immunoglobulin
IHC	Immunohistochemistry
imAEs	immune-mediated adverse events
INR	international normalized ratio
irAE	immune-related adverse event
IRB	Institutional Review Board
CCI	CCI
IRR	infusion-related reaction
IV	Intravenous
IXRS	interactive voice/web response system
mAb	monoclonal antibody
mFOLFOX6	a modified FOLFOX regimen comprised of folinic acid, fluorouracil, and
MRI	magnetic resonance imaging
CCI	CCI
CCI	CCI
CCI	CCI
MTD	maximum tolerated dose
mTPI	modified toxicity probability interval
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NK	natural killer
NSCLC	non-small cell lung cancer
OR	objective response
ORR	objective response rate
OS	overall survival
PBMC	peripheral blood mononuclear cell
PD	progressive disease
PD-1	programmed death 1
PD-L1	programmed death ligand 1
PFS	progression-free survival
PGIC	Patient Global Impression of Change
PK	pharmacokinetics
PR	partial response

Abbreviation or Specialized Term	Definition
PRO	patient reported outcome
PT	preferred term
Q1W	every week
Q2W	every 2 weeks
Q4W	every 4 weeks
QoL	quality of life
QTcB	QT corrected using Bazett's formula
QTcF	QT corrected using Fridericia's formula
RA	rheumatoid arthritis
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SCCHN	squamous cell carcinoma of the head and neck
SD	stable disease
SID	subject identification
TBL	total bilirubin
TPV	third-party vendor
ULN	upper limit of normal
UPM	unit probability mass
USA	United States of America
VEGF	vascular endothelial growth factor
WFI	water for injection
w/v	weight per volume

1 INTRODUCTION

1.1 Disease Background

Despite considerable advancements made during the last decade, patients with recurrent or metastatic solid tumors including non-small cell lung cancer (NSCLC), colorectal cancer (CRC), endometrial cancer, and ovarian cancer have poor outcomes with currently available therapies. For example, second-line (2L) and third-line (3L) therapies in metastatic CRC are typically irinotecan or epidermal growth factor receptor (EGFR)-targeting monoclonal antibody (mAb) based (Rougier et al, 1998; Van Cutsem et al, 2007). However, anticipated survival with multi-agent combination regimens remains less than 6 months (Peeters et al, 2010). In addition, following initial treatment with systemic chemotherapy, median overall survival (OS) (Rougier et al, 1998) is 12.3 months for NSCLC (Sandler et al, 2006).

1.2 Monalizumab and Durvalumab Background

1.2.1 CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI

CCI

CCI

1.2.2 CCI

CCI

CCI [redacted]

1.2.3 Durvalumab Background

Durvalumab is a human IgG1 kappa mAb directed against human programmed cell death ligand 1 (PD-L1). Durvalumab is expressed in Chinese hamster ovary cells and has an overall molecular weight of approximately 149 kDa. Durvalumab selectively binds human PD-L1 with high affinity and blocks its ability to bind to programmed death 1 (PD-1) and CD80. The fragment crystallizable (Fc) domain of durvalumab contains a triple mutation in the constant domain of the IgG1 heavy chain that reduces binding to the complement component C1q and the Fc gamma receptors responsible for mediating antibody-dependent cell-mediated cytotoxicity (Oganesyan et al, 2008).

1.3 Summary of Nonclinical Experience

1.3.1 Monalizumab Nonclinical Experience

For nonclinical information on monalizumab, refer to the current Investigator's Brochure.

1.3.2 Durvalumab Nonclinical Experience

For nonclinical information on durvalumab, refer to the current Investigator's Brochure.

1.4 Summary of Clinical Experience

Refer to the current Investigator's Brochures for further details of the clinical experience obtained with monalizumab and durvalumab.

1.4.1 Monalizumab Clinical Experience

The safety and tolerability as well as single-dose and multiple-dose pharmacokinetic (PK) and pharmacodynamic properties of monalizumab were initially investigated in patients with active RA (NN8765-3658 trial [completed]). Monalizumab is now being developed for the treatment of various hematologic malignancies and solid tumors as monotherapy or in combination with other drugs. As of 23 April 2018, a total of 383 patients have been treated with monalizumab: 68 patients in the Phase 1 RA study and 315 patients in 7 hematology/oncology studies.

As of 23 April 2018, two studies are completed:

- IPH2201-201 is a monotherapy, open-label, single-arm Phase 1b/2 study, assessing the pre-operative administration of monalizumab in patients with locally advanced resectable squamous cell carcinoma of the oral cavity. CCI [redacted]

- IND.221 is an investigator-sponsored study conducted by the Canadian Cancer Trials Group. It is a dose-ranging study of monalizumab in patients with gynecologic malignancies (ovarian, endometrial, and cervical cancer). This study is completed.

As of 23 April 2018, in addition to the current study (Section 1.4.3), the following 4 studies are ongoing:

- IPH2201-202 is an open-label, Phase 1b/2a study of a combination of monalizumab and ibrutinib in patients with relapsed, refractory, or previously untreated chronic lymphocytic leukemia.
- IPH2201-203 is a Phase 1b/2 study of a combination of monalizumab and cetuximab in subjects with HPV (+) and HPV (-) recurrent or metastatic SCCHN.
- PIRAT-IPC 2015-018 is an investigator-sponsored study conducted by the "Paoli Calmettes Institute" in France. This is an open-label, Phase 1, dose-ranging study of single-dose monalizumab administration in patients following HLA-matched allogeneic hematopoietic stem cell transplantation.
- EORTC-1559-HNCG is an investigator-sponsored study conducted by EORTC. This is a pilot study of personalized biomarker-based treatment strategy or immunotherapy in patients with recurrent/metastatic SCCHN ("UPSTREAM").

1.4.1.1 Oncology Studies

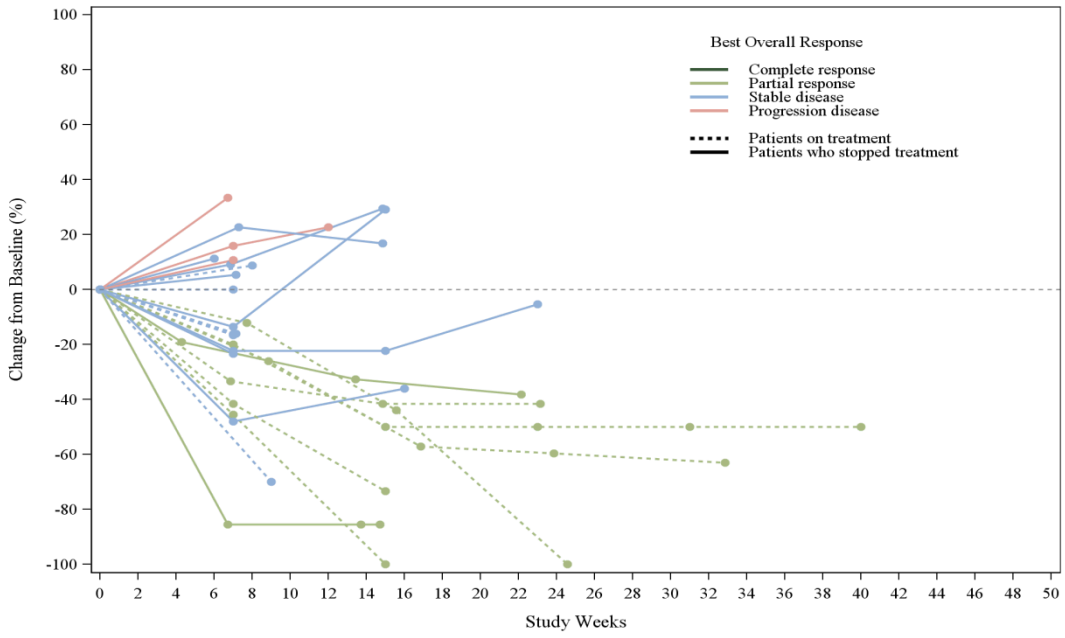
As of 23 April 2018, in hematology/oncology trials, 315 patients have been treated with multiple intravenous (IV) doses of monalizumab at up to 10 mg/kg or 750 mg. Most of the reported adverse events (AEs) were of Grade 1 to 2. There was no obvious dose relationship for AEs. The most frequent (≥ 5%) AEs considered by the investigators as related to monalizumab in monotherapy were headache (23%), nausea (18%), fatigue (16%), vomiting (15%), anorexia (11%), diarrhea, abdominal pain, and sore throat (10% each), myalgia (8%), hot flashes, dry mouth, and other respiratory, thoracic and mediastinal disorders (7% each), blurred vision, dyspnea, and flu like symptoms (5% each). There were no deaths related to treatment. The safety data obtained did not change the overall safety or risk/benefit profile of monalizumab; the data supported continuation of the clinical development of monalizumab for the treatment of various malignancies as monotherapy and combination therapy (Monalizumab Investigator's Brochure).

As of 23 April 2018, 57 subjects with SCCHN have been enrolled in IPH2201-203 and have received monalizumab every 2 weeks (Q2W) at doses of 0.4 to 10 mg/kg in combination with cetuximab every week (Q1W) according the approved labeling. A total of 57 subjects (100%) experienced at least one AE, and 42 subjects (74%) reported at least one AE considered as related to monalizumab or the combination with cetuximab. The most frequently reported treatment-related AEs were fatigue/asthenia (21%), rash and headache (11% each), nausea, hypomagnesemia, and hypophosphatemia (9% each), pyrexia and stomatitis (7% each), dry skin, pruritus, diarrhea, vomiting, decreased appetite, and weight decreased (5% each). Cetuximab-related toxicities (eg skin disorders) did not appear to be exacerbated by

monalizumab. Twenty-four subjects (42%) experienced at least one Grade 3 or Grade 4 AE, of which 7 subjects (12%) had at least one treatment-related event. The most frequent Grade 3 to 4, treatment-related AE was hypophosphatemia, experienced by 3 subjects. Others were fatigue, stomatitis, colitis, interstitial lung disease, and lymphopenia (1 subject each). Three subjects discontinued treatment due to AEs, all of which were reported as serious (one subject experienced interstitial lung disease and colitis; these events occurred in the context of sepsis and were reported as related by the investigator but were considered as not related by the sponsor; one subject with cardiac history experienced dyspnea and atrial fibrillation; one subject experienced tracheostomy malfunction due to progressive disease [PD]). Three subjects (5%) experienced treatment-related serious adverse events (SAEs; one subject experienced interstitial lung disease and colitis which led to treatment discontinuation; one subject experienced hypophosphatemia; and one subject experienced dizziness). No IRRs or treatment-related deaths were reported. The overall safety profile of the combination was manageable and appeared similar to the single agent experience with either agent (Monalizumab Investigator's Brochure).

As of 09 March 2018, 26 subjects were evaluable for efficacy, which included 25 subjects with at least 1 post-baseline assessment and 1 subject who died due to PD at Week 8 without post-baseline assessment: 8 (31%) subjects had a best response of partial response (PR) and 14 (54%) subjects had a best response of stable disease (SD; Figure 1). This response rate is higher than the historical data with single-agent cetuximab in this patient population (objective response rate [ORR] 13%). Refer to Cohen et al, 2018 for additional details.

Figure 1 Study IPH2201-203: Percent Reduction of Target Lesion from Baseline



1.4.2 Durvalumab Clinical Experience

As of the data cut-off (DCO) date (12 July 2018), across the entire clinical development program, approximately 5127 patients have received durvalumab in AstraZeneca or MedImmune-sponsored interventional studies in multiple tumor types, stages of disease, and lines of therapy. Of these, 2229 patients received durvalumab monotherapy, 1573 patients received durvalumab in combination with tremelimumab, and 1325 patients received durvalumab in combination with an investigational and/or an approved product. An estimated 8252 patients are currently enrolled in blinded studies. In addition, 1637 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 total post-marketing exposure to durvalumab to 12 July 2018 was estimated to be approximately 1854 patient-years.

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 the immune checkpoint inhibitor class of agents are thought to be due to the effects of inflammatory cells on specific tissues and could occur in any organ system. Adverse events of special interest (AESIs) and immune-mediated adverse events (imAEs)/immune-related adverse events (irAEs) observed with anti-PD-L1/PD-1 agents such as durvalumab and durvalumab in combination with tremelimumab include pneumonitis, hepatitis, diarrhea/colitis, intestinal perforation, endocrinopathies (hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis/hypopituitarism and type 1 diabetes mellitus), nephritis, rash/dermatitis, pancreatitis, myocarditis, myositis/polymyositis and rare/less frequent imAEs/irAEs including neuromuscular toxicities such as myasthenia gravis and Guillain-Barre syndrome. AESIs of IRRs are also included. AESIs, including imAEs/irAEs reported in AstraZeneca- or MedImmune-sponsored durvalumab studies are defined as AEs that include, but are not limited to, events with a potential inflammatory- or immune-mediated mechanism that may require more frequent monitoring and/or interventions such as corticosteroids, immunosuppressants, and/or endocrine therapy. A number of selected preferred terms (PTs) are used for each AESI category.

In addition, in studies where the data are clean and validated, an adjudication process has been conducted to identify imAEs/irAEs. These are AESIs of special interest (excluding infusion related/hypersensitivity/anaphylactic reaction) consistent with an immune-mediated mechanism that required treatment with systemic corticosteroids, other immunosuppressants, or endocrine therapy and where there was no clear alternate etiology. Serologic, immunologic, and histologic (biopsy) data, as appropriate, were used to support the characterization of an imAE. These AESIs, including imAEs/irAEs, are manageable by available/established treatment guidelines as described in Section 3.1.3.

In the durvalumab clinical program, no tumor types appeared to be associated with unique AEs.

Refer to the current durvalumab Investigator's Brochure for a complete summary of clinical information including safety, efficacy, and PK.

1.4.3 Safety and Efficacy Results from the Current Ongoing Study

Part 1 (Dose-escalation) and Part 2 (Dose-expansion)

CCI [redacted]

CCI [redacted]

CCI

CCI

CCI

Figure 2

Part 3 (Dose exploration in CCI CRC)

CCI

CCI

CCI

CCI

CCI [redacted]

1.5 Rationale for Conducting the Study

Recent nonclinical and clinical research has demonstrated that the immune system is capable of targeting and eliminating cancers. Stimulating an antitumor immune response of the adaptive immune system by activating T cells through inhibition of cytotoxic T-lymphocyte antigen (CTLA)-4 has proven beneficial in patients with advanced metastatic melanoma (Hodi et al, 2010). Similarly, antibodies blocking the PD-1/PD-L1 pathway have demonstrated antitumor activity in multiple tumor types. For example, pembrolizumab and nivolumab have recently been approved for the treatment of melanoma and NSCLC (Dummer et al, 2015; Rizvi et al, 2015a; Weber et al, 2015).

Despite the advances in targeting immune checkpoints such as PD-L1 to treat cancer, there remains an unmet need in many patients with solid tumors.

1.5.1 Rationale for Evaluating Combinations of Durvalumab and Monalizumab with Chemotherapy and/or Biologic Agents

Despite advances in chemotherapy regimens in combination with biologics in the treatment of CCI CRC, a significant number of patients progress within 6 months after receiving either first or 2L chemotherapy. Furthermore, among patients who are beyond 2L treatment, even greater numbers progress within 6 months of their last treatment. Current investigations are now adding immunotherapeutics to chemotherapeutics, targeted therapies, and antiangiogenics to broaden antitumor responses. Immune checkpoint inhibitor therapy can provide durable responses, and using these agents in combination with standard-of-care chemotherapy and/or a biologic agent can theoretically extend this effect, potentially leading to benefit in patients who have a significant clinical unmet need.

Monotherapy with checkpoint inhibitors in subjects with CCI CRC has resulted in limited or no antitumor activity. For example, an ORR of 0% was reported when pembrolizumab 10 mg/kg Q2W was administered to subjects with microsatellite proficient CRC (Le et al, 2015). On the other hand, studies of monotherapy with pembrolizumab 200 mg Q3W or 10 mg/kg Q2W and nivolumab 3 mg/kg Q2W in subjects with microsatellite instability-high CRC or mismatch repair deficient CRC have reported an ORR of 36% for pembrolizumab (FDA, 2017a) and 28% for nivolumab (FDA, 2017b).

Cytotoxic chemotherapy has been shown to modulate the immune response by several mechanisms, such as stimulating T-cell activation via increasing the expression of major histocompatibility complex-1 molecules (Liu et al, 2010), stimulating dendritic cell maturation (Liu et al, 2010), and inducing immunogenic cell death (a form of cell death that induces dendritic cells to stimulate tumor antigen presentation to T cells) (Kroemer et al,

2013), and reducing the immunosuppressive function of regulatory T cells (Zhang et al, 2008) and MDSCs (Kodumudi et al, 2010). Combining durvalumab, a PD-L1 antagonist, with cytotoxic agents may provide complementary benefit in mounting an effective antitumor immunity by promoting antigen presentation, increasing the production of protective T cells, and overcoming immunosuppression in the tumor bed (Mellman et al, 2011). A variety of approaches for combining PD-1 pathway blockers with other agents have been explored over the past few years in an effort to both improve the efficacy of therapy and/or position the treatment regimen for testing in treatment-naïve patients with a variety of cancers. Approaches have included combinations with other checkpoint inhibitors (eg, ipilimumab), immunostimulatory cytokines (eg, interferon-γ [IFNγ]), cytotoxic chemotherapy, anti-angiogenic inhibitors, and small-molecule molecularly targeted therapies, many with promising results and an acceptable toxicity profile (Philips and Atkins, 2015). Data for durvalumab with or without tremelimumab plus standard platinum-based chemotherapy in advanced cancers are being generated from 2 ongoing Phase 1 studies; a MedImmune-sponsored study (D4191SC0001, unpublished data on file) and a Phase 1b study conducted by the Canadian Cancer Trials Group (NCT02537418; Daaboul et al, 2017). The combinations tested were tolerable and manageable.

The combination of immunotherapies and biologic agents may also be beneficial. In metastatic CRC, cetuximab is currently indicated for patients whose tumors do not have CCI [redacted], as retrospective analysis shows that presence of these mutations correlates with lack of clinical benefit (Karapetis et al, 2008). While these data suggest that EGFR pathway inhibition is more important than ADCC in CRC, both mechanisms may contribute. Retrospective analysis of patients with wild type as well as KRAS mutant metastatic CRC, treated with cetuximab, shows a survival advantage for those with high-affinity Fc gamma receptor polymorphisms associated with improved antibody effector function (Liu et al, 2016). Monalizumab, via its effects on NK cells, could potentially enhance the ADCC activity of cetuximab (Ferris et al, 2018; Ochoa et al, 2017; Wang et al, 2015); in turn, cetuximab-mediated tumor cell death could potentially lead to release of tumor antigens and enhance the antitumor immune response along with durvalumab and monalizumab (Ferris et al, 2018). Furthermore, there is evidence suggesting that an anti-angiogenesis agent such as bevacizumab could enhance the antitumor effects of checkpoint inhibitor therapy (Manegold et al, 2017; Wallin et al, 2016).

Checkpoint inhibitors in combination with chemotherapy have been tested in subjects with metastatic CRC. In an open-label Phase 1b study, subjects with refractory, metastatic CRC were treated with atezolizumab (an anti-PD-1 agent) 20 mg/kg Q3W in combination with bevacizumab 15 mg/kg Q3W (Arm A) and a group of oxaliplatin-naïve subjects with metastatic CRC received atezolizumab 14 mg/kg Q2W in combination with bevacizumab 10 mg/kg Q2W and folinic acid, fluorouracil, and oxaliplatin (FOLFOX) at standard doses (Arm B). In Arm A (n=14), Grade 3 to 4 AEs regardless of attribution were 64%, including abdominal pain, hyperbilirubinemia and pneumonia (14% each). In Arm B (n=30), 73% of

subjects had Grade 3 to 4 AEs, including neutropenia (40%), diarrhea (13%), increased ALT (10%) and increased AST (10%). Grade ≥ 3 atezolizumab-related AEs were 7% in Arm A and 20% in Arm B. For subjects with ≥ 1 tumor assessment, the unconfirmed ORR was 8% (1/13) in Arm A and 36% (9/25) in Arm B. The unconfirmed ORR was 44% (8/18) for Arm B first-line (1L) subjects. Minimum follow-up was 1.9 months in Arm A and 2.2 months in Arm B. It was concluded that atezolizumab in combination with bevacizumab with or without FOLFOX was well tolerated with no unexpected toxicities. Clinical activity was observed with both treatment combinations (Bendell et al, 2015).

Another Phase 1b study evaluated nivolumab (3 mg/kg on days 1and 15 every 28-day cycle) in combination with capecitabine (1000 mg orally twice daily days 1 to 5 on, days 6 to 7 off, each 7-day period) and irinotecan (175 mg/m^2 on day 1 every 14 days) in subjects with previously treated, metastatic CRC. Subjects were treated until disease progression or toxicity. All of the 9 subjects for whom data were available had treatment-related AEs (any grade). The most common (> 50% subjects) were fatigue (Grade 1), nausea (Grade 1), and diarrhea (Grade 1). No IRRs were observed. There were no DLTs or study-related SAEs. Of 6 subjects evaluable for best overall response, 1 had a PR for 8 months, 1 had SD for 6 months, 1 had ongoing SD over 3 months, and 3 had disease progression. It was concluded that nivolumab in combination with capecitabine and irinotecan appeared to be safe in subjects with previously treated, metastatic CRC (Khemka et al, 2016).

The mFOLFOX6 chemotherapy regimen in combination with pembrolizumab was evaluated in a Phase 2 study that enrolled subjects with untreated, unresectable CRC. During the safety run-in, 2 patients had Grade 3 febrile neutropenia and 1 had Grade 4 neutropenia. Consequently, the data safety monitoring committee recommended 20% dose reduction of the mFOLFOX6 regimen. Of the 27 evaluable subjects, 36.7% experienced Grade 3-4 toxicity during the median follow-up period of 24 weeks. Febrile neutropenia was not reported during the follow-up period and there was no Grade 5 toxicity observed. Reported responses were 1 CR, 15 PRs, (ORR = 53%) and 14 SD. The authors concluded that combination therapy with mFOLFOX6 and pembrolizumab has acceptable toxicity in subjects with untreated, advanced CRC and clinical activity was demonstrated (Shahda et al, 2017).

In summary, the preliminary efficacy, safety, and tolerability data generated to date for durvalumab alone and in combination with monalizumab, together with early positive signals observed with other PD-1/PD-L1 in combination with chemotherapy support the development of these combination therapies in the treatment of CRC. Based on the known lack of single-agent activity of PD-1/PD-L1 antagonists in CCI CRC and the initial promising antitumor activity seen with durvalumab in combination with the 750-mg dose of monalizumab administered Q2W CCI [redacted] and good tolerability, it was decided to evaluate

whether this preliminary antitumor activity of durvalumab in combination with monalizumab could be further improved with acceptable tolerability by adding a standard chemotherapy regimen of mFOLFOX6 [redacted] with or without bevacizumab or cetuximab in subjects with 1L or 2L [redacted] CRC, respectively.

Based on promising antitumor activity and a favorable safety profile of monalizumab + cetuximab in subjects with recurrent or metastatic SCCHN (8 subjects with PR and 14 subjects with SD out of 26 subjects [summarized in Section 1.4.1.1]) and the preliminary clinical activity of monalizumab + durvalumab in [redacted] CRC (described above) observed in this ongoing study, the combination of monalizumab, durvalumab, and cetuximab and the combination of monalizumab and cetuximab will be evaluated in [redacted] CRC in this study.

Combining durvalumab and monalizumab with standard chemotherapy regimens and/or a biologic agent, as clinically indicated, for the treatment of [redacted] CRC appears to be promising based on the following rationale: 1) the potential to provide enhanced durability in efficacy as seen historically with biological agents in combination with chemotherapy in CRC and emerging data from the [redacted] CRC cohort in the current study with durvalumab and monalizumab combination treatment; 2) the potential for enhanced clinical activity when combining checkpoint blockade with chemotherapy based on experience in the treatment of other solid tumors (eg, NSCLC and triple negative breast cancer); 3) and possible synergy of monalizumab with mAbs that elicit ADCC, such as cetuximab, including the potential to overcome resistance to such mAbs [redacted].

Thus, the combination of a checkpoint inhibitor with a standard chemotherapy regimen and/or a biologic agent has the potential to improve treatment outcomes in settings where there is significant clinical unmet need.

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 Council for Harmonisation (ICH)/Good Clinical Practice (GCP), and applicable regulatory requirements.

1.6.1 Potential Benefits

Emerging data with durvalumab in a monotherapy setting across a range of tumor types (Section 1.4.2), and in combination with tremelimumab in NSCLC, demonstrate encouraging clinical activity.

In the presence of monalizumab, CD94/NKG2a+ NK and T cells may kill target cells that also express ligands for activating receptors on the effector cell. Such activating ligands are generally not expressed on healthy cells and tissues but can be induced in transformed or infected cells or cells undergoing proliferative stress, such as in chronic inflammatory conditions. Hence, monalizumab does not induce the killing of healthy cells, but has been

shown to enhance killing of tumor cells and cells at sites of chronic inflammation. The antitumor activity of monalizumab has been demonstrated experimentally ex vivo, with malignant cell lines or fresh leukemic cells of patients, as well as in vivo in non-obese diabetic severe combined immunodeficiency mice infused with human NK cells and inoculated with patient leukemic cells (Ruggeri et al, 2016)

The combination of durvalumab and monalizumab has the opportunity to utilize both the innate and adaptive immune system to target tumor cells through potentially complementary mechanisms. Furthermore, using these agents in combination with standard-of-care chemotherapy and/or a biologic agent has the potential to enhance the antitumor effect. The encouraging preliminary safety and efficacy results from the current study are summarized in Section 1.4.3 and the rationale for evaluating a treatment regimen of durvalumab in combination with monalizumab plus a standard chemotherapy regimen and/or a biologic agent is presented in Section 1.5.1. The rationale for the study design and starting doses is described in Section 3.2. The results from this study will inform the design of future studies of the combination of durvalumab and monalizumab.

1.6.2 Summary of Risks

Immune-mediated reactions/immune-related adverse events (imAEs/irAEs), also considered to be AESIs, are important risks of immune checkpoint inhibitors, and are being closely monitored in clinical studies with durvalumab monotherapy and combination therapy. Risks with durvalumab include, but are not limited to, diarrhea/colitis, intestinal perforation, pneumonitis/interstitial lung disease, endocrinopathies (hypothyroidism, hyperthyroidism, type I diabetes mellitus, hypophysitis, and adrenal insufficiency), hepatitis/increases in transaminases, nephritis/increases in creatinine, pancreatitis/increases in amylase and lipase, rash/dermatitis, myocarditis, myositis/polymyositis, and other rare or less frequent inflammatory events including neurotoxicities, IRRs, hypersensitivity reactions, and infections/serious infections. See Section 5.3 for a summary of risks that are considered AESIs with durvalumab.

CCI [redacted]

With regard to the potential risks of treatment with the durvalumab/monalizumab combination plus standard chemotherapy and/or a biologic agent, experience with the biologics cetuximab and bevacizumab combined with chemotherapy suggests the following as some of the theoretical risks: cytopenia, a need for transfusion support, an increased risk of infection, gastrointestinal AEs (ie, nausea, vomiting and diarrhea), stomatitis, mucositis, electrolyte imbalance, acute cholinergic syndrome, peripheral sensory neuropathy, cold-induced

paresthesias, renal dysfunction, skin disorders (ie, rash and palmar/plantar erythrodysesthesia), alopecia, hypertension, bleeding, thrombosis, infusion reactions, laryngopharyngeal dysesthesia, cardiotoxicity (eg, for coronary vasospasm) and liver and pulmonary toxicity (eg, for pneumonitis/interstitial lung disease).

These AESIs, including imAEs/irAEs, are manageable by available/established treatment guidelines as described in the toxicity management guidelines (see Section 3.1.3).

For information on all identified and potential risks with durvalumab and monalizumab, refer to the current Investigator's Brochure for each respective agent.

1.7 Research Hypotheses

1.7.1 Primary Hypothesis

Parts 1 and 2: The combination of durvalumab (MEDI4736; anti-programmed death ligand 1 [PD-L1] mAb) and monalizumab (anti-CD94/NKG2a mAb) administered to subjects with select advanced solid tumors will show acceptable safety and tolerability so as to permit further clinical testing in subsequent studies.

Part 3 (Cohorts A CCI): The combination of durvalumab and monalizumab plus chemotherapy with or without a biologic agent (bevacizumab or cetuximab), as clinically indicated, administered to subjects with recurrent or metastatic 1L or 2L CCI CRC will show acceptable safety and tolerability so as to permit further clinical testing in subsequent studies.

Part 3 (Cohorts C1A and C2A): The combination of durvalumab and monalizumab plus cetuximab administered to subjects with CCI CRC that is CCI (C1A) or CCI (C2A) will show acceptable safety (C1A and C2A), tolerability (C1A and C2A), and antitumor activity (C1A only) so as to permit further clinical testing in subsequent studies.

Part 3 (Cohorts C1B and C2B): The combination of monalizumab plus cetuximab administered to subjects with CCI CRC that is CCI (C1B) or CCI (C2B) will show acceptable safety (C1B and C2B), tolerability (C1B and C2B), and antitumor activity (C1B only) so as to permit further clinical testing in subsequent studies.

1.7.2 Secondary Hypotheses

The combination of durvalumab and monalizumab will demonstrate antitumor activity.

2 OBJECTIVES AND ENDPOINTS

2.1 Primary Objective and Associated Endpoints

Table 1 Primary Objectives and Associated Endpoints

Type	Objective	Endpoint
Safety	**Part 1**: To assess safety and tolerability, describe the DLTs, and determine the MTD or the highest protocol-defined dose level in the absence of establishing an MTD of durvalumab in combination with monalizumab in subjects with advanced solid tumors	• AEs • SAEs • DLTs • Abnormal laboratory parameters, vital signs, and ECG results
	Part 2: To assess further the safety and tolerability of either the MTD or the highest protocol-defined dose level, in the absence of establishing an MTD, of durvalumab in combination with monalizumab in subjects with selected advanced solid tumors	
	Part 3 (Cohorts A [redacted]): To assess safety and tolerability of durvalumab in combination with monalizumab plus chemotherapy with or without a biologic agent (bevacizumab or cetuximab), as clinically indicated, in subjects with 1L or 2L [redacted] CRC **Part 3 (Cohorts C1A and C2A):** To assess safety and tolerability of durvalumab in combination with monalizumab plus cetuximab in subjects with [redacted] CRC that is [redacted] (C1A) or [redacted] (C2A) **Part 3 (Cohorts C1B and C2B):** To assess safety and tolerability of monalizumab in combination with cetuximab in subjects with [redacted] CRC that is [redacted] (C1B) or [redacted] (C2B)	
Clinical activity	**Part 3 (Cohort C1A):** To evaluate the antitumor activity of durvalumab in combination with monalizumab plus cetuximab in subjects with [redacted] CRC that is [redacted] **Part 3 (Cohort C1B):** To evaluate the antitumor activity of monalizumab in combination with cetuximab in subjects with [redacted] CRC that is [redacted]	OR by investigator assessment per RECIST v1.1

1L = first-line; 2L = second-line; [redacted] AE = adverse event; DLT = dose-limiting toxicity; ECG = electrocardiogram; EGFR = epidermal growth factor receptor; mAb = monoclonal antibody; [redacted] CRC = [redacted] colorectal cancer; MTD = maximum tolerated dose; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; OR = objective response; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event; VEGF = vascular endothelial growth factor.

NOTE: Part 1 is dose escalation, Part 2 is dose expansion, and Part 3 is dose exploration in [redacted] CRC.

NOTE: Cohort A subjects must be systemic therapy-naïve in the recurrent/metastatic setting. [redacted] subjects must be naïve to irinotecan-containing treatment and must have progressed on an oxaliplatin-containing regimen in the first line of their treatment for recurrent/metastatic cancer. Cohort C subjects [redacted] prior standard chemotherapy must include i) fluoropyrimidines, irinotecan, and oxaliplatin; and ii) an anti-VEGF mAb (eg, bevacizumab); and iii) subjects in Cohort C2 must not have received prior anti-EGFR therapy (eg, cetuximab or panitumumab naïve).

2.2 Secondary Objectives and Associated Endpoints

Table 2 Secondary Objectives and Associated Endpoints

Type	Objective	Endpoint
Clinical activity	**Parts 1 and 2:** To evaluate the preliminary antitumor activity of durvalumab in combination with monalizumab in subjects with advanced solid tumors	• OR, DC, DoR, PFS by investigator assessment per RECIST v1.1 • OS
	Part 3 (Cohorts A CCI): To evaluate the preliminary antitumor activity of durvalumab in combination with monalizumab plus chemotherapy with or without a biologic agent (bevacizumab or cetuximab), as clinically indicated, in subjects with 1L or 2L CCI CRC **Part 3 (Cohort C2A):** To evaluate the antitumor activity of durvalumab in combination with monalizumab plus cetuximab in subjects with CCI CRC that is CCI **Part 3 (Cohort C2B):** To evaluate the antitumor activity of monalizumab in combination with cetuximab in subjects with CCI CRC that is CCI	
	Part 3 (Cohort C1A): To further evaluate the antitumor activity of durvalumab in combination with monalizumab plus cetuximab in subjects with CCI CRC that is CCI **Part 3 (Cohort C1B):** To further evaluate the antitumor activity of monalizumab in combination with cetuximab in subjects with CCI CRC that is CCI	• DC, DoR, PFS by investigator assessment per RECIST v1.1 • OS
PK	**Parts 1 and 2:** To describe the PK of durvalumab and monalizumab when administered in combination in subjects with advanced solid tumors	• Individual subject durvalumab, monalizumab, and cetuximab concentrations in serum at different time points after administration of these agents will be summarized
	Part 3 (Cohorts A CCI): To describe the PK of durvalumab and monalizumab when administered in combination with chemotherapy with or without a biologic agent (bevacizumab or cetuximab), as clinically indicated, in subjects with 1L or 2L CCI CRC **Part 3 (Cohorts C1A and C1B):** To describe the PK of the following when administered in combination in subjects with CCI CRC that is CCI • Durvalumab, monalizumab, and cetuximab (C1A) • Monalizumab and cetuximab (C1B) **Part 3 (Cohorts C2A and C2B):** To describe the PK of the following when administered in combination with cetuximab in subjects with CCI CRC that is CCI • Durvalumab and monalizumab (C2A)	

Table 2 Secondary Objectives and Associated Endpoints

Type	Objective	Endpoint
	• Monalizumab (C2B)	
Immuno-genicity	**Parts 1 and 2:** To describe the immunogenicity of durvalumab and monalizumab when administered in combination in subjects with advanced solid tumors	CCI
	Part 3 (Cohorts A CCI): To describe the immunogenicity of durvalumab and monalizumab when administered in combination with chemotherapy with or without a biologic agent (bevacizumab or cetuximab), as clinically indicated, in subjects with 1L or 2L CCI CRC **Part 3 (Cohorts C1A and C1B):** To describe the immunogenicity of the following when administered in combination in subjects with CCI CRC that is CCI • Durvalumab, monalizumab, and cetuximab (C1A) • Monalizumab and cetuximab (C1B) **Part 3 (Cohorts C2A and C2B):** To describe the immunogenicity of the following when administered in combination with cetuximab in subjects with CCI CRC that is CCI • Durvalumab and monalizumab (C2A) • Monalizumab (C2B)	
CCI	CCI	CCI
	CCI	

1L = first-line; 2L = second-line; CCI CCI DC = disease control;
DoR = duration of response; EGFR = epidermal growth factor receptor; CCI
mAb = monoclonal antibody; CCI CRC = CCI colorectal cancer; OR = objective response;
OS = overall survival; CCI PFS = progression-free survival;
PK = pharmacokinetic(s); RECIST = Response Evaluation Criteria in Solid Tumors; VEGF = vascular endothelial growth factor.

NOTE: Part 1 is dose escalation, Part 2 is dose expansion, and Part 3 is dose exploration.

NOTE: Cohort A subjects must be systemic therapy-naïve in the recurrent/metastatic setting. CCI subjects must be naïve to irinotecan-containing treatment and must have progressed on an oxaliplatin-containing regimen in the first line of their treatment for recurrent/metastatic cancer. Cohort C subjects CCI prior standard chemotherapy must include i) fluoropyrimidines, irinotecan, and oxaliplatin; and ii) an anti-VEGF mAb (eg, bevacizumab); and iii) subjects in Cohort C2 must not have received prior anti-EGFR therapy (eg, cetuximab or panitumumab naïve).

See Figure 3 for a description of the cohorts.

2.3 Exploratory Objectives and Associated Endpoints

Table 3 Exploratory Objectives and Associated Endpoints

Type	Objective	Endpoint
Prognostic/ Predictive/ Pharmacodynamic	**Parts 1 and 2:** To evaluate additional candidate prognostic/ predictive/ pharmacodynamic biomarkers when durvalumab is administered in combination with monalizumab in subjects with advanced solid tumors	• Assessment of T- and NK-cell activation (eg, inducible costimulatory molecule expression) and proliferation (eg, Ki67 expression) measured by flow cytometry in blood, by IHC in tumors and by mass spectrometry, DNA/ RNA/ miRNA assessments (RNAseq, exome sequence, scRNA) in blood and tumors • Assessment of the number and activity of CD8+ effector T and NK cells and expression of immunomodulatory proteins (eg, PD-1) within tumor biopsies using IHC CCI
	Part 3 (Cohorts A CCI): To evaluate additional candidate prognostic/ predictive/ pharmacodynamic biomarkers when durvalumab is administered in combination with monalizumab plus chemotherapy with or without a biologic agent (bevacizumab or cetuximab), as clinically indicated, in subjects with 1L or 2L CCI CRC **Part 3 (Cohorts C1A and C2A):** To evaluate additional candidate prognostic/ predictive/ pharmacodynamic biomarkers when durvalumab is administered in combination with monalizumab plus cetuximab in subjects with CCI CRC that is CCI (C1A) or CCI (C2A) **Part 3 (Cohorts C1B and C2B**): To evaluate additional candidate prognostic/ predictive/ pharmacodynamic biomarkers when monalizumab is administered in combination with cetuximab in subjects with CCI CRC that is CCI (C1B) or CCI (C2B)	

Table 3 Exploratory Objectives and Associated Endpoints

Type	Objective	Endpoint
		CCI
CCI	CCI	CCI
	CCI	

Table 3 Exploratory Objectives and Associated Endpoints

Type	Objective	Endpoint
Clinical outcome assessments	CCI To evaluate the effect of treatment with durvalumab in combination with monalizumab plus cetuximab on disease-related symptoms/ functioning/ HRQoL and overall health status in subjects with CCI CRC that is CCI CCI To evaluate the effect of treatment with monalizumab in combination with cetuximab on disease-related symptoms/ functioning/ HRQoL and overall health status in subjects with CCI CRC that is CCI	• Descriptive statistics for domain, subscale scores, and individual items at each time point and change from baseline as measured by EORTC QLQ-C30 • Time to deterioration and response status for each domain, subscale and individual items as measured by EORTC QLQ-C30 • Descriptive statistics for subject's global impression of change of their overall health status at each time point as measured by PGIC • Time to deterioration in ECOG performance status ≥ 2

1L = first-line; 2L = second-line; CCI CD = cluster of differentiation; CRC = colorectal cancer; CCI CCI ECOG = Eastern Cooperative Oncology Group; CCI EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; CCI CCI CCI CCI CCI IHC = immunohistochemistry; CCI mAb = monoclonal antibody; miRNA = microRNA; CCI CCI NK = natural killer; CCI PBMC = peripheral blood mononuclear cell; PD-1 = programmed death 1; PGIC = Patient Global Impression of Change; scRNA = single-cell RNA; VEGF = vascular endothelial growth factor.

NOTE: Part 1 is dose escalation, Part 2 is dose expansion, and Part 3 is dose exploration in CCI CRC.

NOTE: Cohort A subjects must be systemic therapy-naïve in the recurrent/metastatic setting. CCI subjects must be naïve to irinotecan-containing treatment and must have progressed on an oxaliplatin-containing regimen in the first line of their treatment for recurrent/metastatic cancer. Cohort C subjects CCI prior standard chemotherapy must include i) fluoropyrimidines, irinotecan, and oxaliplatin; and ii) an anti-VEGF mAb (eg, bevacizumab); and iii) subjects in Cohort C2 must not have received prior anti-EGFR therapy (eg, cetuximab or panitumumab naïve).

See Figure 3 for a description of the cohorts.

3 STUDY DESIGN

3.1 Description of the Study

3.1.1 Overview

This is a Phase 1/2, multicenter, open-label, study of durvalumab and monalizumab to evaluate the safety, tolerability, PK, immunogenicity, pharmacodynamics, and antitumor activity in adult subjects with advanced solid tumor malignancies at approximately 60 sites globally. The study consists of 3 parts: dose escalation (Part 1), dose expansion (Part 2), and dose exploration in CCI CRC (Part 3).

- **Part 1** will be dose escalation of durvalumab in combination with monalizumab in subjects with select advanced solid tumor malignancies.
- **Part 2** will evaluate further the identified dose of durvalumab in combination with monalizumab from Part 1 in subjects with select advanced solid tumor malignancies.
- **Part 3 (Cohorts A [redacted])** will evaluate dose exploration of durvalumab in combination with monalizumab and chemotherapy with or without a biologic agent (bevacizumab or cetuximab), as clinically indicated, in subjects with metastatic 1L or 2L [redacted] CRC.
- **Part 3 (Cohorts C1 and C2)** will evaluate dose exploration of 1) durvalumab in combination with monalizumab plus cetuximab (Cohorts C1A and C2A) and 2) monalizumab in combination with cetuximab (Cohorts C1B and C2B) in subjects with [redacted] CRC that is [redacted] or [redacted].

In Part 1 (dose escalation), subjects with recurrent or metastatic [redacted] CRC, ovarian cancer, [redacted] endometrial cancer, cervical cancer, castration-resistant prostate cancer, pancreatic adenocarcinoma, or NSCLC will be enrolled. In Part 2 (dose expansion), subjects with [redacted] CRC, ovarian cancer, [redacted] endometrial cancer, or NSCLC will be enrolled. In Part 3 (dose exploration), subjects with [redacted] CRC will be enrolled. See Figure 3 for a description of the cohorts.

Refer to Section 1.5.1 for a discussion of the rationale for adding a chemotherapy regimen with or without a biologic agent and Section 3.1.3.1 for information on chemotherapy dose modification.

Tolerability data for all subjects will be evaluated regularly and subjects' clinical response status classified according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. All subjects will be followed for survival until the end of study (Section 6.3). During the dose-expansion phase, if a subject with NSCLC experiences a toxicity that meets the criteria for treatment discontinuation (Sections 4.1.6 and 4.1.7), but the subject is receiving clinical benefit, the subject may be considered for monotherapy treatment with durvalumab. In this circumstance, the decision to treat subjects with monotherapy durvalumab is based on its known efficacy in NSCLC patients and will require agreement between the sponsor and treating investigator. For a subject receiving durvalumab monotherapy, the same study assessments as for combination therapy should be followed (except for continued sampling for monalizumab PK and immunogenicity) (Table 9 and Table 14).

Part 1: Dose Escalation

In the dose-escalation part of the study, sequential cohorts will receive durvalumab in combination with monalizumab at 1 of the 4 planned dose levels described in Figure 3. The dose-escalation part will utilize a modified toxicity probability interval (mTPI) algorithm (Ji et al, 2010), which employs a simple beta-binomial Bayesian model. Decision rules are based on calculating the unit probability mass (UPM) of three intervals corresponding to underdosing, proper dosing, and overdosing in terms of toxicity. The three dosing intervals are associated

with three different dose-escalation decisions. The underdosing interval corresponds to a dose escalation (E), overdosing corresponds to a dose de-escalation (D), and proper dosing corresponds to staying at the current dose (S). Given an interval and a probability distribution, the UPM of that interval is defined as the probability of the interval divided by the length of the interval. The mTPI design calculates the UPMs for the three dosing intervals, and the one with the largest UPM implies the corresponding dose-finding decision. The design for the dose-escalation part of the study uses a target DLT rate of ≥ 33% and an equivalence interval of CCI for dose-escalation/de-escalation decisions as well as MTD determination. A dose level will be considered unsafe, with no additional subjects enrolled at that dose level, if it has an estimated 95% or more probability of exceeding the target DLT rate of ≥ 33% (ie, P [DLT ≥ 33%|data] > 95%) with at least 3 subjects treated at that dose level.

A minimum of 3 subjects will be enrolled to a dose level cohort and evaluated for a dose-escalation/de-escalation decision (unless unacceptable toxicity is encountered prior to enrollment of 3 subjects), but the maximum number of subjects for each dose-level cohort will be capped at 12. Thus, based on 5 dose-level cohorts, a maximum of 60 subjects could be enrolled in the dose-escalation part. Given that mTPI leads to a dose-escalation decision if there is no DLT in the first 3 subjects enrolled in a dose-level cohort, it is expected that the actual sample size will be fewer.

Subjects will be dosed in a group size of three. The first 3 subjects enrolled in the escalation part will be enrolled to dose-level Cohort 1. No escalation is allowed unless 3 or more evaluable subjects have been treated and evaluated through the DLT-evaluation period in a dose level.

Ongoing surveillance of pharmacodynamics, PK, clinical safety, and antitumor activity data will be performed throughout the dose-escalation part. Once the dose escalation has completed per the mTPI or the highest protocol-defined dose is evaluated, any dose level showing acceptable safety during dose escalation can be expanded to a total of up to 18 subjects with mandatory pre-treatment and on-treatment tumor biopsies. At the discretion of the sponsor, the expansion at a given dose level may be restricted to a specific tumor type(s) included in the dose-escalation part. These dose-escalation cohort expansions will provide additional PK, pharmacodynamic, and safety data to inform optimal dose-level selection for the dose-expansion part and subsequent clinical studies.

Part 2: Dose Expansion

The dose-expansion part will enroll 4 cohorts of approximately 40 subjects each with recurrent or metastatic CCI CRC, ovarian cancer, CCI endometrial cancer, or NSCLC. The dose level and schedule determined in the dose-escalation part will be used in the dose-expansion part, as agreed by the study-specific DEC. Additional dose levels not exceeding the MTD may be considered based on clinical and PK/pharmacodynamic data from the dose-escalation part.

Part 3: Dose Exploration in CCI CRC

Subjects with advanced CCI CRC will be enrolled in the dose-exploration part.

Cohorts A CCI: Cohort A subjects (ie, Cohorts A1, A2, CCI) must be systemic therapy-naïve in the recurrent/metastatic setting, and CCI must be naïve to irinotecan-containing treatment and must have progressed on an oxaliplatin-containing regimen in the first line of their treatment for recurrent/metastatic cancer. Based on the identified dose for durvalumab in combination with monalizumab from Part 1, subjects will receive durvalumab (1500 mg Q4W) in combination with monalizumab (750 mg Q2W) plus a standard chemotherapy regimen of mFOLFOX6 (Cohorts A1, A2, CCI) CCI in combination with bevacizumab (Cohorts A1 CCI) or cetuximab (Cohorts A2 CCI) CCI.

Cohort C: Cohort C subjects (ie, Cohorts C1 and C2) CCI CCI CRC that is CCI (Cohort C1) or CCI (Cohort C2); prior standard chemotherapy must include i) fluoropyrimidines, irinotecan, and oxaliplatin; and ii) an anti-vascular endothelial growth factor (VEGF) mAb (eg, bevacizumab); and iii) subjects in Cohort C2 must not have received prior anti-EGFR therapy (eg, cetuximab or panitumumab naïve). CCI

The study flow is presented in Figure 3.

Figure 3 Study Flow Diagram

Part 3: Dose exploration in CCI CRC

Cohort and Chemotherapy or Biologic Regimen	Durvalumab Dose	Monalizumab Dose	Number of Subjects[d]
A1: mFOLFOX6 + bevacizumab	1500 mg Q4W	750 mg Q2W	Up to 18
A2: mFOLFOX6 + cetuximab	1500 mg Q4W	750 mg Q2W	Up to 18

CCI

CRC = colorectal cancer; CCI EGFR = epidermal growth factor receptor; CCI mAb = monoclonal antibody; mFOLFOX6 = folinic acid/fluorouracil/oxaliplatin; CCI CCI CCI CCI CCI CCI Q2W = every 2 weeks; Q4W = every 4 weeks; CCI VEGF = vascular endothelial growth factor.

CCI

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

3.1.2 Treatment Regimen

Subjects will be treated in the dose-escalation (Part 1 [Section 3.1.2.1]), dose-expansion (Part 2 [Section 3.1.2.2]), or dose-exploration (Part 3 [Section 3.1.2.3]) part of the study (Section 3.1.1).

Both durvalumab and monalizumab will be administered over approximately 60 minutes via IV infusion. On dosing days when both durvalumab and monalizumab are administered, durvalumab will be administered first with monalizumab starting 15 to 30 minutes after the completion of the durvalumab infusion.

- In addition to the combination of durvalumab and monalizumab, subjects enrolled in Part 3 Cohorts A CCI will also receive a standard Q2W regimen of folinic acid, fluorouracil, and oxaliplatin or irinotecan (mFOLFOX6 CCI respectively) with or without

bevacizumab or cetuximab, as clinically indicated according to local prescribing guidelines (Section 3.1.2.3).

- CCI [redacted]
- CCI [redacted]

Study treatment will be administered up to 3 years until unacceptable toxicity, documentation of confirmed PD, or documentation of subject withdrawal for another reason (Section 4.1.6). Study treatment may be continued beyond PD or following relapse if the subject meets the criteria described in Sections 4.1.7 and 4.1.8.

Subjects who continue to receive clinical benefit after 3 years of treatment will continue to receive the treatment on this study, via a rollover study requiring approval by the responsible Health Authority (HA) and ethics committee, or through another mechanism at the discretion of the sponsor. The sponsor reserves the right to terminate access to study treatment if any of the following occur:

- The marketing application is rejected by the responsible HA.
- The study is terminated due to safety concerns.
- The subject can obtain medication from a government-sponsored or private health program.
- Therapeutic alternatives become available in the local market.

3.1.2.1 Part 1: Dose Escalation

CCI [redacted]

Dose escalation will continue to the next higher dose-level cohort after all available safety data and any available PK data from subjects in that dose level and prior dose levels have been reviewed by a study-specific DEC. The sponsor may halt dose escalation prior to determining the MTD based on emerging PK/pharmacodynamic, toxicity, or response data.

Intermediate dose levels of durvalumab in combination with monalizumab may also be evaluated based on available data.

CCI [redacted]

CCI [redacted] If the MTD is not exceeded at that dose level on a monalizumab Q4W schedule and provided this was not the highest protocol-defined dose, dose escalation may proceed with additional sequential cohorts of 3 to 12 subjects according to the mTPI algorithm.

Rules for Dose Escalation and Determination of MTD

1 The MTD will be determined based on assessment of DLT (see below in this section) according to the mTPI algorithm (Table 4) during the DLT-evaluation period. Subjects who do not meet criteria for DLT-evaluable Population will be replaced at the same dose level (Section 4.8.1). Subjects will be followed for safety throughout the study. If late-emerging AEs (occurring after the DLT-evaluation period) are observed, these events will be considered by the DEC during data reviews for dose-escalation decisions. All toxicities will be thoroughly reviewed with a study-specific DEC, prior to proceeding with a dose-escalation or dose de-escalation decision. The MTD will be determined by isotonic regression analysis (Ji et al, 2010) applied to the DLT rates observed during the dose-escalation part.

2 Administration of the first dose of investigational product will be staggered by a minimum of 24 hours between the first and second subjects in each dose-level cohort. Intra-subject dose escalation will not be allowed.

3 A minimum of 3 subjects will be enrolled in each dose-level cohort unless unacceptable toxicity is encountered prior to enrollment of the third subject which would require dose de-escalation per the mTPI design.

4 At the highest protocol-specified dose level, enrollment may be stopped if no DLTs are observed in the first 3 evaluable subjects.

5 Upon completion of the dose escalation per the mTPI design, additional subjects (up to a total of 18 per dose level) may be enrolled at any dose level considered safe as defined in the mTPI algorithm for further evaluation of safety, PK/pharmacodynamics, and response.

6 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, pharmacodynamics, biomarker, safety, or response data.

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

Table 4 Durvalumab Treatment Modification and Toxicity Management Guidelines for Immune-related Adverse Events Level

Number of Subjects with Toxicities	Number of Subjects Treated at Current Dose											
	1[a]	2[a]	3	4	5	6	7	8	9	10	11	12
0	E	E	E	E	E	E	E	E	E	E	E	E
1	D	S	S	S	S	E	E	E	E	E	E	E
2		DU	D	S	S	S	S	S	S	S	E	E
3			DU	DU	D	D[b]	S	S	S	S	S	E[c]
4				DU	DU	DU	D	D	S	S	S	D[c]
5					DU	DU	DU	DU	DU	D	S	D[c]
6						DU	DU	DU	DU	DU	DU	D
7							DU	DU	DU	DU	DU	DU
8								DU	DU	DU	DU	DU
9									DU	DU	DU	DU
10										DU	DU	DU
11											DU	DU
12												DU

D = de-escalate to the next lower dose level; DU = current dose is unacceptably toxic; E = escalate to the next higher dose level; S = stay at the current dose level.

Note: Target toxicity (%) ≥ 33% and equivalence interval = CCI Sample size cap for each dose level = 12 subjects.

[a] The columns indicating the actions based on data from 1 or 2 subjects are included to reflect the completeness of the modified toxicity probability interval (mTPI) design. However, in this study, a minimum of 3 subjects will be enrolled at each dose level, unless unacceptable toxicity is seen.

[b] The original mTPI algorithm was S for this case and is modified to D as the observed DLT rate is 50%.

[c] The original mTPI algorithm was S for these cases and is modified to either E or D according to whether the observed dose-limiting toxicity (DLT) rate is < or ≥ the target toxicity of ≥ 33%, respectively.

Source: Modified from Ji et al, 2010.

Dose-limiting Toxicity

The period for DLT evaluation is defined as the time from start of the first dose of investigational product (durvalumab and monalizumab) until the planned administration of the second dose of durvalumab and the third dose of monalizumab and planned chemotherapy; this corresponds to 28 days after the first dose of durvalumab and monalizumab plus chemotherapy or 14 days after the second dose of monalizumab plus chemotherapy. Subjects who do not remain in the study or require dose modifications in the chemotherapy or the biologic component (Part 3, dose exploration) during the DLT-evaluation period, for reasons other than 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.

Grading of DLTs will be according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.03. Toxicity that is clearly and directly related to the primary disease or to another etiology is excluded from this definition. A DLT will be defined during the dose-escalation part as any durvalumab- or monalizumab-related Grade 3 or higher toxicity (with modifications or exceptions noted below) that occurs during the DLT-evaluation period. All DLTs must be documented as AEs. The following will be considered DLTs:

- Any Grade ≥ 3 noninfectious colitis irrespective of duration
- Any Grade ≥ 3 noninfectious pneumonitis irrespective of duration
- Liver transaminase elevation ≥ 5 × but ≤ 8 × upper limit of normal (ULN) that does not downgrade to Grade 2 within 7 days after onset with optimal medical management including systemic corticosteroids
- Any Grade 4 imAE/irAE, excluding colitis or pneumonitis, that does not downgrade to Grade 2 within 7 days after the onset of the event despite optimal medical management including systemic corticosteroids or does not downgrade to ≤ Grade 1 within 14 days
- Any Grade 3 or higher clinically significant (ie, requiring dose modification or dose delay of > 7 days to permit resolution) non-hematologic toxicity that occurs during the DLT-evaluation period
- Transaminase elevation > 8 × ULN or total bilirubin (TBL) > 5 × ULN will be considered a DLT regardless of duration or reversibility
- Any increase in AST or ALT ≥ 3 × ULN and concurrent increase in TBL ≥ 2 × ULN, where no other reason can be found to explain the combination of increases, eg, elevated serum alkaline phosphatase (ALP) indicating cholestasis, viral hepatitis, another drug (Hy's Law [HL] criteria) will be considered a DLT
- Thrombocytopenia
  - Grade 3 or 4 thrombocytopenia, regardless of duration, associated with Grade 3 or higher hemorrhage
  - Grade 4 thrombocytopenia ≥ 7 days (Part 3 Cohorts A CCI subjects only)
  - Grade 4 thrombocytopenia regardless of duration (excluding Part 3 Cohorts A CCI subjects)
  - Grade 3 thrombocytopenia that does not improve by at least 1 grade within 7 days (excluding Part 3 Cohorts A CCI subjects)
- Neutropenia and/or febrile neutropenia
  - Grade 4 febrile neutropenia of any duration
  - Grade 3 febrile neutropenia lasting ≥ 5 days while receiving maximal supportive care (Part 3 Cohorts A CCI subjects only)
  - Grade 3 febrile neutropenia regardless of duration or reversibility (excluding Part 3 Cohorts A CCI subjects)

  - Grade 4 neutropenia lasting > 7 days (Part 3 Cohorts A [redacted] subjects)
  - Grade 3 or 4 neutropenia that is not associated with fever or systemic infection or that does not improve by at least 1 grade within 7 days (excluding Part 3 Cohorts A [redacted] subjects).
- 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

The definition of DLT for all subjects (except as noted below) excludes the following conditions:

- Grade 3 fatigue for < 7 days
- Grade 3 endocrine disorder (thyroid, pituitary, and/or adrenal insufficiency) that is managed with or without systemic corticosteroid therapy and/or hormone replacement therapy with resolution of symptoms within 14 days of AE onset
- Grade 3 inflammatory reaction attributed to a local antitumor response (eg, inflammatory reaction at sites of metastatic disease, lymph nodes, etc) that resolves to ≤ Grade 1 within 30 days after onset
- Concurrent vitiligo or alopecia of any AE grade
- Isolated Grade 3 electrolyte abnormalities that are not associated with clinical signs or symptoms and are reversed with appropriate maximal medical intervention within 7 days of onset
- Grade 3 or 4 asymptomatic elevation in serum amylase or lipase that are not associated with either clinical signs or symptoms or radiographic features suggestive of pancreatitis
- Grade 3 IRR (first occurrence and in the absence of steroid prophylaxis) that resolves within 6 hours of onset with appropriate clinical management
- Grade 3 rigors or chills lasting < 6 hours that respond to optimum medical therapy
- Grade 3 fever lasting ≤ 24 hours with or without medical therapy
- Grade 3 or 4 lymphopenia (unless clinically significant)
- Grade 3 diarrhea, nausea or vomiting in the absence of premedication that responds to therapy per institutional standards and improves by at least 1 grade within 3 days after onset.
- Grade 4 diarrhea, nausea or vomiting will be a DLT regardless of duration or reversibility
- Grade 3 hypertension that can be controlled with medical therapy

Additional Information Regarding Dose-limiting Toxicity Criteria

[redacted]

CCI [redacted]

Abnormal Laboratory Results

In the absence of associated clinical signs or symptoms, isolated abnormal laboratory tests not specifically described above will not be considered as DLTs unless they are considered clinically significant (ie, requiring dose modification or dose delay of > 7 days to permit resolution of treatment-related toxicity).

Adverse Events not Defined Above

imAEs/irAEs are defined as AEs of immune nature (ie, inflammatory) in the absence of a clear alternative etiology. While the rules for adjudicating DLTs in the context of dose escalation are specified above, an AE not listed above or occurring outside the DLT window may be defined as a DLT after a consultation with the sponsor and investigators, based on the emerging safety profile.

During dose expansion in all tumor groups and dose exploration in CCI [redacted] CRC, subjects will be monitored for safety according to the same criteria employed during dose escalation. CCI [redacted]

3.1.2.2 Part 2: Dose Expansion

The dose-expansion part of the study may be initiated at the sponsor's discretion once the MTD, or highest protocol-defined dose level in the absence of exceeding the MTD, is established in the dose-escalation part of the study. In the dose-expansion part, subjects will receive durvalumab and monalizumab at the dose level and treatment schedule determined in the dose-escalation part. Additional dose levels not exceeding the MTD may be considered based on clinical and PK/pharmacodynamic data from the dose-escalation part.

Enrollment into dose-expansion cohorts may be discontinued at the discretion of the sponsor should emerging clinical or preclinical data suggest that continued treatment may not be beneficial to a given cohort. During dose expansion, subjects will be monitored for safety using the same DLT criteria employed during dose escalation. CCI [redacted]

Enrollment may proceed up to approximately 40 subjects in the CCI [redacted] CRC, ovarian cancer, and endometrial expansion cohorts CCI [redacted]

CCI . Enrollment may proceed up to approximately 40 subjects in the NSCLC expansion cohort CCI .

3.1.2.3 Part 3: Dose Exploration in CCI CRC

Subjects with advanced CCI CRC will be enrolled in the dose-exploration part.

Cohorts A CCI : Cohort A subjects (ie, Cohorts A1, A2, CCI) must be systemic therapy-naïve in the recurrent/metastatic setting and CCI must be naïve to irinotecan-containing treatment and must have progressed on an oxaliplatin-containing regimen in the first line of their treatment for recurrent/metastatic cancer. Based on the identified dose for durvalumab in combination with monalizumab from Part 1, subjects will receive durvalumab (1500 mg Q4W) in combination with monalizumab (750 mg Q2W) plus a standard chemotherapy regimen of mFOLFOX6 (Cohorts A1, A2, CCI) CCI in combination with bevacizumab (Cohorts A1 CCI) or cetuximab (Cohorts A2 CCI) CCI .

Cohort C: Cohort C subjects (ie, Cohorts C1 and C2) CCI CCI CRC that is CCI (Cohort C1) or CCI (Cohort C2); prior standard chemotherapy must include i) fluoropyrimidines, irinotecan, and oxaliplatin; and ii) an anti-VEGF mAb (eg, bevacizumab); and iii) subjects in Cohort C2 must not have received prior anti-EGFR therapy (eg, cetuximab or panitumumab naïve). CCI

The chemotherapy and biologic component (bevacizumab or cetuximab, when clinically indicated) should be prescribed according to local practice but the starting dose, sequence and days of administration for these standard-of-care regimens should not be modified unless there is toxicity, in order to maintain consistency across the subjects enrolled in the study. The recommended regimens are as follows.

The mFOLFOX6 treatment (Cohorts A1, A2, CCI) should contain:

- Oxaliplatin 85 mg/m^2 administered by IV infusion on Day 1
- Folinic acid 400 mg/m^2 administered by IV infusion on Day 1
- Fluorouracil 400 mg/m^2 administered by IV bolus on Day1 followed by 2400 mg/m^2 administered by continuous IV infusion over 46 to 48 hours starting on Day 1.

CCI [redacted]

- CCI [redacted]
- CCI [redacted]
- CCI [redacted]

The above chemotherapy regimens will be administered Q2W.

The biologic regimens are described below:

- For Cohorts A1 CCI [redacted], bevacizumab (5 mg/kg IV infusion) will be administered on Day 1, then Q2W according to institutional guidelines.
- For Cohorts A2 CCI [redacted], cetuximab loading dose (400 mg/m^2 IV infusion over 2 hours) will be administered on Day 1, then maintenance dose (250 mg/m^2 IV infusion over 1 hour) Q1W will be administered starting on Day 8. The cetuximab regimen may be changed to 500 mg/m^2 IV infusion for approximately 2 hours Q2W after a subject has completed the 28-day DLT-evaluation period, at the investigator's discretion and in accordance with institutional guidelines (Benson et al, 2018; Pfeiffer et al, 2008; Tabernero et al, 2008).
- For Cohorts C1A, C1B, C2A, and C2B, cetuximab (500 mg/m^2 IV infusion over 2 hours) will be administered on Day 1 then 500 mg/m^2 IV infusion for approximately 2 hours Q2W starting on Day 15 in accordance with institutional guidelines (Benson et al, 2018; Pfeiffer et al, 2008; Tabernero et al, 2008).

Treatment will be administered as described below for specific cohorts:

- Part 3 Cohorts A CCI [redacted]: Durvalumab will be administered first with monalizumab starting 15 to 30 minutes after the completion of the durvalumab infusion. Following an observation period of 15 to 30 minutes post end of monalizumab infusion, the infusion of the premedication and biologic component or chemotherapy can begin.
  - Infusion of the biologic agent, when clinically indicated, should be prior to the chemotherapy according to standard practice.
  - The pre-medications for chemotherapy should be administered within 1 hour prior to the start of chemotherapy.
- CCI [redacted]
- CCI [redacted]

Safety will be monitored on an ongoing basis and aggregate safety data will be reviewed by the de-escalation committee at pre-specified intervals as described below. CCI [redacted]

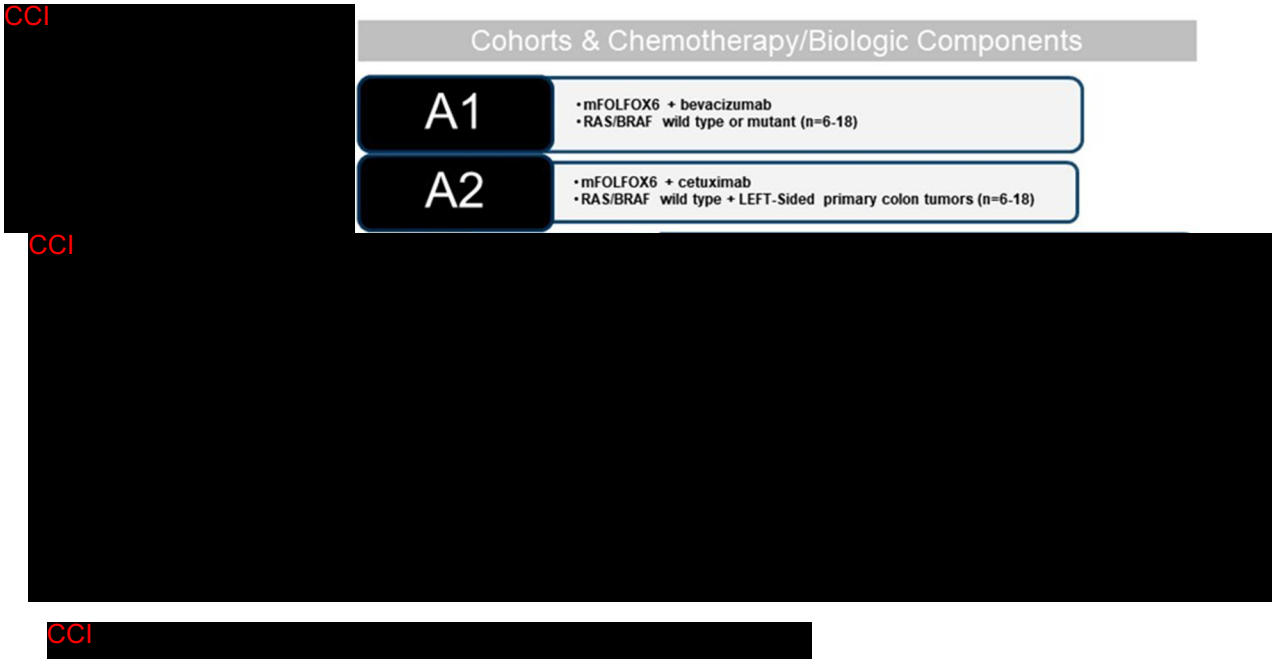
- CCI [redacted]
- CCI [redacted]
- Dose modification of individual chemotherapy agents and/or the biologic agents for the management of toxicity in individual subjects will be allowed as per standard clinical practice CCI [redacted]

Cohort A CCI [redacted] Subjects

Initially, up to 6 subjects may be enrolled into each of the 4 chemotherapy cohorts with a biologic agent (Cohorts A1, A2, CCI [redacted]). Initiation of Cohorts CCI [redacted] (chemotherapy cohorts without a biological agent) will be staggered and dependent on emerging safety data from Cohorts A1 and A2, CCI [redacted] respectively. Administration of the first dose of investigational products and chemotherapy will be staggered by a minimum of 24 hours between the first and second subjects in all 6 cohorts and no more than 3 of the initial subjects in a given cohort will be dosed within 1 week. Subsequently, subjects may be enrolled continuously without pausing the enrollment for DEC review of aggregate safety data until a total of 6 subjects have been enrolled in a given cohort and observed through the DLT-evaluation period or > 2 subjects experience a DLT in a particular cohort prior to enrolling 6 subjects. Meetings of the study DEC will be held to review all available safety, PK, pharmacodynamic, immunogenicity, and clinical activity data to determine whether to continue enrollment at the current dose level, dose de-escalate, or stop further evaluation of the combination with chemotherapy with or without a biologic agent according to the mTPI algorithm. If the DEC decides to continue at the current dose level after the initial 6 subjects have been enrolled and evaluated for DLTs, enrollment may increase by up to an additional 12 subjects per chemotherapy with or without a biologic agent cohort provided criteria for de-escalation according to the mTPI algorithm are not met at any point based on ongoing assessment of safety. In addition, while enrollment is ongoing, the DEC will review aggregate safety data once a total of 12 or 18 subjects in a given cohort have been enrolled and followed through the DLT-evaluation period.

The design of study Part 3 is depicted in Figure 4 for Cohorts A CCI [redacted].

Figure 4 Study Part 3 (Dose Exploration) Flow Diagram for Cohorts A CCI



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Cohort C Subjects

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Figure 5 CCI

CCI

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[redacted]

3.1.3 Management of Study Medication Related Toxicities

No dose reductions are permitted for durvalumab or monalizumab. However, doses may be held/omitted in the context of toxicity. Omitted doses will not be administered at a later date. Both hematologic and non-hematologic toxicities will be graded according to the NCI CTCAE v4.03. AEs for which a cause other than durvalumab or monalizumab can be clearly attributed will not require a dose delay.

Dosing will not be interrupted or discontinued for a laboratory toxicity that is deemed not to be clinically significant.

Treatment modifications and toxicity management guidelines for durvalumab and the toxicity management guidelines for monalizumab are provided within the Site Master File. For marketed study medications, please refer to the local product information for guidance on toxicity management.

3.1.3.1 Chemotherapy and Biologic Agent Dose Modification

When a study treatment is partly or wholly delayed or withheld, the sites should follow their standard local prescribing practice and consider following the guidelines described below:

- If chemotherapy and/or the biologic agent (bevacizumab or cetuximab) is withheld because of toxicity for more than 2 cycles (approximately 28 days), the chemotherapy and/or biologic component of study treatment is to be discontinued. However, if durvalumab and/or monalizumab are not implicated in the toxicity resulting in chemotherapy or biologic agent discontinuation, then durvalumab and/or monalizumab can be continued. **NOTE:** The approximate 28-day time period begins on the day that the next cycle of study treatment should have been administered but was withheld for toxicity.
- If fluorouracil and folinic acid administration is delayed, irinotecan or oxaliplatin treatment is also to be delayed, although monalizumab and durvalumab administration can be continued without delay at the discretion of the investigator and sponsor.

- If fluorouracil and folinic acid treatment is to be discontinued, irinotecan, biologic agent, durvalumab and monalizumab can be administered but not oxaliplatin when using the mFOLFOX6 regimen.
- If irinotecan or oxaliplatin administration is to be delayed, fluorouracil and folinic acid treatment should also be delayed, although the biologic component, monalizumab and durvalumab administration can continue without delay.
- If irinotecan or oxaliplatin administration is to be discontinued, fluorouracil, folinic acid, biologic agent, monalizumab, and durvalumab administration can continue.
- If monalizumab and durvalumab are discontinued (ie, in the setting of a Grade 3-4 IRR or immune-mediated toxicity), treatment on study with CCI [redacted] mFOLFOX6 along with the biologic agent can continue.
- No folinic acid dose reductions are to be implemented; however, it should always be withheld when fluorouracil is to be held.
- If a dose is reduced because of toxicity, it is not to be re-escalated to the starting level. However, subjects who require multiple-dose reductions during a cycle can, at the investigator's discretion, begin the following cycle at 1 dose level higher than the final dose level during that cycle.

Chemotherapy dose modifications are presented in the table below. Dose modifications of each agent are to be made independently, based on the specific types of toxicity observed. If a dose reduction exceeding that represented by Dose Level -3 is required for any agent, that agent is to be discontinued.

	Dose Level			
Intravenous Agent	**Initial Dose**	**-1**	**-2**	**-3**
Irinotecan	180 mg/m^2	150 mg/m^2	120 mg/m^2	100 mg/m^2
Oxaliplatin	85 mg/m^2	68 mg/m^2	51 mg/m^2	34 mg/m^2
Fluorouracil bolus	400 mg/m^2	200 mg/m^2	0 mg/m^2	0 mg/m^2
Fluorouracil infusion (over 46-48 hours)	2400 mg/m^2	2000 mg/m^2	1600 mg/m^2	1200 mg/m^2

Bevacizumab

- There are no recommended dosage reductions.
- Temporary suspension is recommended for severe infusion reactions, at least 4 weeks prior to (and after) elective surgery, in moderate-to-severe proteinuria (ie, consider holding treatment when proteinuria ≥ 2 g/24 hours), or in patients with severe hypertension that is not controlled with medical management.
- Permanent discontinuation is recommended in patients who develop wound dehiscence and wound healing complications requiring intervention, necrotizing fasciitis, fistula (gastrointestinal and nongastrointestinal), gastrointestinal perforation, intra-abdominal abscess, hypertensive crisis, hypertensive encephalopathy, serious bleeding/hemorrhage,

severe arterial thromboembolic event, life-threatening (Grade 4) venous thromboembolic events (including pulmonary embolism), nephrotic syndrome, or PRES.

Cetuximab

- Infusion reactions, Grade 1 or 2: Reduce the infusion rate by 50% and continue to use prophylactic antihistamines
- Grade 3 or 4: Immediately and permanently discontinue
- Pulmonary toxicity:
  - Acute onset or worsening pulmonary symptoms: Hold treatment
  - Interstitial lung disease: Permanently discontinue
- Skin toxicity, mild to moderate: No dosage modification required
- Acneiform rash, severe (Grade 3 or 4):
  - First occurrence: Delay cetuximab infusion 1 to 2 weeks
    - If improvement, continue at a dose of 250 mg/m^2 if on Q1W regimen or 500 mg/m^2 if on Q2W regimen
    - If no improvement, discontinue therapy
  - Second Occurrence: Delay cetuximab infusion 1 to 2 weeks
    - If improvement, continue at reduced dose of 200 mg/m^2 if on Q1W regimen or 400 mg/m^2 if on Q2W regimen
    - If no improvement, discontinue therapy
  - Third occurrence: Delay cetuximab infusion 1 to 2 weeks
    - If improvement, continue at reduced dose of 150 mg/m^2 if on Q1W regimen or 300 mg/m^2 if on Q2W regimen
    - If no improvement, discontinue therapy
  - Fourth occurrence: Discontinue therapy.

3.2 Study Design and Dose Rationale

3.2.1 Dose Rationale

3.2.1.1 Rationale for Monalizumab Dosing

As of 23 April 2018, 68 patients with RA have been exposed to IV or subcutaneous doses of monalizumab and 315 patients with cancer have been exposed to multiple IV doses of monalizumab. To date, the clinical data indicate no safety concerns for single or multiple doses of monalizumab up to 10 mg/kg IV and up to 4 mg/kg subcutaneously.

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CCI [redacted]

3.2.1.2 Rationale for Durvalumab Dosing

The dose and schedule for durvalumab monotherapy were selected based on 2 sets of data: (1) the safety analysis of doses (0.1, 0.3, 1.0, 3.0, and 10 mg/kg Q2W) administered in Study CD-ON-MEDI4736-1108 (a Phase 1/2 study to evaluate the safety, tolerability, and PK of IV durvalumab given as monotherapy in subjects with advanced solid tumors; and (2) PK profile simulations for durvalumab administered using 10 mg/kg Q2W and 20 mg/kg Q4W schedules.

After evaluation of the PK data from subjects enrolled in Study CD-ON-MEDI4736-1108, durvalumab exhibited nonlinear (dose-dependent) PK consistent with target-mediated drug disposition. Linear PK was observed at doses of 3 mg/kg and higher and is consistent with near complete target suppression, as reflected in target trough plasma concentrations of drug > 100 µg/mL. This trough concentration is supported by soluble PD-L1 suppression data. Furthermore, the 10 mg/kg Q2W dose was not associated with any DLTs in the dose-escalation phase and was, therefore, selected for further evaluation in the dose-expansion phase of Study CD-ON-MEDI4736-1108.

A population PK model was developed using durvalumab monotherapy data from Phase 1 of Study CD-ON-MEDI4736-1108 (N = 292; doses = 0.1 to 10 mg/kg Q2W or 15 mg/kg every 3 weeks; solid tumors) (Song et al, 2015). This population PK model adequately described monotherapy PK data and was utilized to predict expected PK exposures following 20 mg/kg Q4W dosing regimens (none of the monotherapy studies explored Q4W regimens). PK simulations indicate that a similar overall exposure as represented by area under the concentration-time curves (4 weeks) is expected following both 10 mg/kg Q2W and 20 mg/kg Q4W regimens. However, median maximum observed concentration at steady state is expected to be higher with 20 mg/kg Q4W (approximately 1.5 fold) and median trough concentration at steady state is expected to be higher with 10 mg/kg Q2W (approximately 1.25 fold).

Population PK analysis indicated only minor impact of body weight on PK of durvalumab (coefficient of ≤ 0.5). The impact of body weight-based (10 mg/kg Q2W) and fixed dosing (750 mg Q2W) of durvalumab was evaluated by comparing predicted steady state PK concentrations (5th, median and 95th percentiles) using the population PK model. A fixed

dose of 750 mg was selected to approximate 10 mg/kg (based on median body weight of ~75 kg). A total of 1000 patients were simulated using body weight distribution of 40 to 120 kg. Simulation results demonstrate that body weight-based and fixed dosing regimens yield similar median steady state PK concentrations with slightly less overall between-subject variability with fixed dosing regimen.

Similar findings have been reported by others (Ng et al, 2006; Wang et al, 2009; Zhang et al, 2012; Narwal et al, 2013). 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 antibodies (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-subject variability in PK/pharmacodynamics parameters (Zhang et al, 2012).

A fixed dosing approach is preferred by the prescribing community due to ease of use and reduced dosing errors. Given expectation of similar PK exposure and variability, a fixed dosing regimen is considered appropriate. Based on average body weight of 75 kg, a fixed dose of 1500 mg Q4W durvalumab (equivalent to 20 mg/kg Q4W) is included in the current study. This dose is equivalent to 10 mg/kg Q2W, which has an acceptable safety profile (Section 1.4.2).

3.2.1.3 Rationale for the Combination of Monalizumab and Durvalumab

In the current ongoing study of monalizumab in combination with durvalumab in subjects with solid tumors (D419NC00001), dose escalation is complete. CCI [redacted] The combination of monalizumab 750 mg Q2W and durvalumab 1500 mg Q4W was deemed safe by the DEC; therefore, these doses and associated regimens will be employed in the dose expansion and exploration parts of the study (Section 1.4.3).

3.2.1.4 Rationale for Cetuximab Dosing

The cetuximab regimen to be administered in Part 3 Cohorts A2 CCI [redacted] (400 mg/m^2 initial dose followed by 250 mg/m^2 Q1W starting on Day 8) is per the cetuximab label. The 500 mg/m^2 Q2W cetuximab regimen to be administered in combination with durvalumab and monalizumab in Part 3 Cohorts A2 CCI [redacted] (optional after the DLT-evaluation), C1A, and C2A, and in combination with monalizumab in Cohorts C1B and C2B is per institutional practice and NCCN guidelines (Benson et al, 2018; Pfeiffer et al, 2008; Tabernero et al, 2008). The treatment regimen is detailed in Section 3.1.2.3.

3.2.2 Rationale for Study Population

The tumor types included in this study were selected based on unmet clinical need and underlying tumor biology. In both the dose-escalation (Part 1) and dose-expansion (Part 2) parts of the study, subjects with advanced solid tumors who have progressed or are refractory to at least 1 line of standard therapy will be enrolled. These populations are thought to

represent an unmet clinical need as currently available treatment options provide limited benefit.

All tumor types chosen for the dose-escalation and dose-expansion parts of the study have been shown to overexpress HLA-E, the ligand of CD94/NKG2a, and therefore may be appropriate for monalizumab treatment (Section 1.1). Emerging clinical data have demonstrated that PD-1/PD-L1 targeting agents may be clinically active among several tumor types (NSCLC, endometrial cancer, or high-grade serous epithelial ovarian cancer) selected for the expansion part (Le et al, 2015; Rizvi et al, 2015b; Disis et al, 2015). Initial clinical development of the combination of durvalumab and monalizumab will focus on these 4 indications with unmet clinical need and biological rationale for targeting both the PD-L1 and CD94/NKG2a pathways. CCI [redacted]
Specifically, in the NSCLC population, durvalumab has shown that clinical activity correlates with tumoral PD-L1 expression where ORR was higher in patients whose tumors are PD-L1-positive as compared to those whose tumors are PD-L1-negative (Rizvi et al, 2015b). This study will evaluate the impact of PD-L1 expression on the clinical activity of the combination of durvalumab and monalizumab by enrolling both PD-L1-positive and PD-L1-negative NSCLC subjects.

Based on the known lack of single-agent activity of PD-1/PD-L1 antagonists in CCI [redacted] CRC and the initial promising antitumor activity seen with durvalumab in combination with the 750-mg dose of monalizumab administered Q2W in subjects with CCI [redacted] CRC in the dose-escalation and dose-expansion parts of the study (see summary in Section 1.4.3) and good tolerability, it was decided to evaluate whether this preliminary antitumor activity of durvalumab in combination with monalizumab could be further improved with acceptable tolerability by adding a standard chemotherapy regimen of mFOLFOX6 CCI [redacted] with or without bevacizumab or cetuximab in subjects with either 1L or 2L CCI [redacted] CRC, respectively. Acceptable tolerability profiles for PD-1/PD-L1 targeting drugs in combination with chemotherapeutic agents have been reported in other clinical studies of patients with metastatic CRC (Bendell et al, 2015; Shahda et al, 2017; Khemka et al, 2016).

Furthermore, based on promising antitumor activity and favorable safety profile of monalizumab + cetuximab in subject with recurrent or metastatic SCCHN (see summary in Section 1.4.1.1) and the preliminary clinical activity of monalizumab + durvalumab in CCI [redacted] CRC (described in Section 1.4.3) observed in this ongoing study, the combination of monalizumab, durvalumab, and cetuximab and the combination of monalizumab and cetuximab in CCI [redacted] CRC will be evaluated in Part 3 of this study. There is a strong rationale for combining cetuximab and monalizumab, alone and with durvalumab, in CCI [redacted] CRC, regardless of mutational status, as these agents target three distinct, interconnected aspects of the antitumor immune response: 1) Cetuximab promotes tumor cell killing, antigen release, and cytokine production via ADCC (a mechanism that is not dependent on CCI [redacted]

CCI); 2) monalizumab may enhance the activity of cetuximab by promoting NK activity; 3) addition of durvalumab may overcome suppression of the resulting adaptive immune response (Ferris et al, 2018).

For patients with refractory, metastatic CRC, there is a significant clinical unmet need for better treatment regimens than those currently available, as reported in Section 1.5.1.

3.2.3 Rationale for Dose-escalation Algorithm

The mTPI design used in the dose-escalation part is a model-based algorithm for dose-escalation/de-escalation decisions that incorporates data from all dose levels. The design maintains the practical considerations of the 3+3 design (minimal parametric assumptions regarding toxicity, and pre-determined dose-escalation/de-escalation rules with no in-trial modeling required), while improving reliability in determining the MTD according to a pre-specified target toxicity. Simulation work has demonstrated improved operating characteristics with respect to both reliability and safety (Ji et al, 2010). Given that the dose-escalation design will provide evidence-based support for the dose-expansion cohorts, an approach that has higher likelihood of identifying the true MTD is favored, and minimizes the likelihood of having to change the dose based on emerging data during the dose-expansion part.

The mTPI algorithm used during the dose-escalation part (Part 1) will be used during the dose-exploration part (Part 3).

3.2.4 Rationale for Endpoints

The primary objectives of the study are to determine the safety, MTD or the highest protocol-defined dose in the absence of establishing an MTD. The occurrence of DLTs will be used to establish the MTD and thus the standard safety endpoints, such as AEs, SAEs, and deaths, will be included in the safety evaluation. As durvalumab in combination with monalizumab will be administered on a repeated dosing schedule, the development of anti-drug antibodies (ADAs) and its potential effect on the endpoints related to safety, PK, and clinical activity will also be assessed. Furthermore, the dose-exploration part of the study (Part 3) will determine whether a standard chemotherapy regimen and/or a biologic agent can be added to the combination of durvalumab and monalizumab with acceptable safety and PK, and improved clinical activity.

The endpoints for assessment of antitumor activity are those routinely included in oncology studies and will include OR (primary endpoint for Part 3 Cohorts C1A and C1B), DC, duration of response (DoR), and progression-free survival (PFS), by investigator assessment per RECIST v1.1, as well as OS.

The PK of durvalumab is being examined to determine the effect of monalizumab on durvalumab PK parameters. Conversely, the PK of monalizumab is being examined to

determine the effect of durvalumab on monalizumab PK parameters. In Part 3, Cohorts C1A and C1B, the PK of cetuximab is being examined to determine the effect of durvalumab and monalizumab on cetuximab PK parameters.

CCI [redacted]

CCI [redacted]

Target engagement of monalizumab will be assessed through CD94/NKG2a receptor occupancy. These will allow the extent to which each drug interacts with their target at each dose to be assessed. T-cell and NK-cell proliferation and activation may also be assessed to determine the effects drug target engagement has on cell function. CCI [redacted] Cetuximab is an EGFR inhibitor. The expression of EGFR will be evaluated in subjects treated with cetuximab to detect whether subjects with an increased pathway engagement will be more likely to respond to treatment. CCI [redacted] Changes in circulating protein levels of IFNγ and other proteins associated with immune cell activation may also be assessed as potential indicators of patient response.

3.3 Study Mitigation During Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis

The guidance given below supersedes instructions provided elsewhere in this clinical study protocol (CSP) and should be implemented only during cases of civil crisis, natural disaster, or public health crisis (eg, during quarantines and resulting site closures, regional travel restrictions, and considerations if site personnel or study subjects become infected with SARS-CoV-2 or similar pandemic infection), which would prevent the conduct of study-related activities at study sites, thereby compromising the study site staff or the subject's ability to conduct or participate in the study. The investigator or designee should

contact the study sponsor representative to discuss whether the mitigation plans below should be implemented.

To ensure continuity of the clinical study during a civil crisis, natural disaster, or public health crisis, changes may be implemented to ensure the safety of study subjects, maintain compliance with Good Clinical Practice, and minimize risks to study integrity.

Where allowable by local health authorities, ethics committees, healthcare provider guidelines (eg, hospital policies) or local government, these changes may include the following options:

- Obtaining consent/assent for the mitigation procedures (note, in the case of verbal consent/assent, the Informed Consent Form (ICF) should be signed at the subject's next contact with the study site).
- Home or Remote visit: Performed by a site-qualified Health Care Professional (HCP) or HCP provided by a third-party vendor (TPV).
- Telemedicine visit: Remote contact with the subjects using telecommunications technology, including phone calls, virtual or video visits, and mobile health devices.

For further details on study conduct during civil crisis, natural disaster, or public health crisis, refer to Section 10.6.

4 MATERIALS AND METHODS

4.1 Subjects

4.1.1 Number of Subjects

CCI [redacted]

- CCI [redacted]
- CCI [redacted]
- CCI [redacted]
- CCI [redacted]

CCI [redacted]

CCI [redacted]

Table 5 Study Overview and Status Update

Tumor Type	Treatment	Status Under Protocol Amendment 6	Total Planned Enrollment	Subjects Enrolled and Treated as of 24 March 2020
CCI [redacted]				
Part 3 Dose Exploration in CCI CRC				
1L CCI CRC	Cohort A1: mFOLFOX6, bevacizumab, durvalumab 1500 mg Q4W, and monalizumab 750 mg Q2W	Closed	18	18
	Cohort A2: mFOLFOX6, cetuximab, durvalumab 1500 mg Q4W, and monalizumab 750 mg Q2W	Closed	18	18
	CCI [redacted]			
CCI [redacted]				

Table 5 Study Overview and Status Update

Tumor Type	Treatment	Status Under Protocol Amendment 6	Total Planned Enrollment	Subjects Enrolled and Treated as of 24 March 2020
CCI [redacted]				

1L = first-line; CCI [redacted] mFOLFOX6 = a modified FOLFOX regimen of folinic acid/fluorouracil/oxaliplatin; CCI [redacted]; CCI [redacted] CRC = CCI [redacted] colorectal cancer; CCI [redacted] QW2 = every 2 weeks; QW4 = every 4 weeks; CCI [redacted]

CCI [redacted]

4.1.2 Inclusion Criteria

Subjects must meet all of the following criteria:

1 Written and signed informed consent and any locally required authorization (eg, Health Insurance Portability and Accountability Act in the United States of America [USA]) obtained from the subject/legal representative prior to performing any protocol-related procedures, including screening evaluations

2 Age ≥ 18 years at the time of study entry

3 In the dose-escalation part, subjects must have histologic documentation of advanced recurrent or metastatic CCI CRC, NSCLC, CCI endometrial cancer, high-grade serous epithelial ovarian cancer (including fallopian tubal carcinoma and peritoneal carcinoma), cervical cancer, castration-resistant prostate cancer, or pancreatic adenocarcinoma.

4 In the dose-expansion part, subjects must have histologic documentation of advanced recurrent or metastatic CCI CRC, NSCLC, CCI endometrial cancer, or high-grade serous epithelial ovarian cancer (including fallopian tubal carcinoma and peritoneal carcinoma).

5 Subjects entering Parts 1 and 2 (escalation and expansion) must have received and have progressed or are refractory to at least one line of standard systemic therapy in the recurrent/metastatic setting, appropriate for the specific tumor type. In addition, subjects must meet all of the tumor specific criteria below, with documented progression from previous therapy at study entry. Interval progression between two lines of therapy defines separate lines of therapy. Both standard and investigational treatments will count as lines of therapy when determining eligibility.

   For all tumor types: No evidence of partial small bowel obstruction or small bowel obstruction within 4 weeks prior to the first scheduled dose of study treatment, and ability to maintain weight and hydration with oral intake only, without requirement for IV or supplemental enteral nutrition or hydration (ie, no G-tubes, J-tubes, total parenteral nutrition, or hydration requirements). Subjects with active/ongoing paracentesis are excluded.

   (a) Ovarian:

      (i) Subjects may have received up to 3 prior lines of systemic therapy for recurrent/metastatic disease. All subjects must have previously received and progressed while on or within 6 months of completing a platinum-based regimen.
      In dose expansion, approximately equal numbers of subjects will be enrolled from the following two groups: 1 to 2 versus 3 prior lines of treatment in the recurrent/metastatic setting

   (b) CCI CRC:

      (i) All subjects need to have a documented mutation test during screening and confirmed tumor locations from disease assessment for enrollment

      (ii) CRC cancers must NOT have a defective DNA mismatch repair (microsatellite instability) documented by testing. Testing may be done locally, and prior documentation of this testing is acceptable in lieu of running the test again. Defective DNA mismatch repair is defined by either:

* High-frequency microsatellite instability with changes detected in 2 or more panels of microsatellite markers (BAT-25, BAT-26, NR-21, NR-24, or MONO-27),
  OR
* Immunohistochemical analysis demonstrating absence of protein expression of any one or more of the following proteins: MLH1, MSH2, MSH6, or PMS2

(iii) Subjects entering Part 1 and Part 2 may have received up to 3 prior lines of systemic therapy for recurrent/metastatic disease

* In Part 2 (dose expansion), approximately equal numbers of subjects will be enrolled from the following two groups: 1 to 2 versus 3 prior lines of treatment in the recurrent/metastatic setting

(iv) The following inclusion criteria apply to subjects entering Part 3 (by Cohort):

Prior therapy criteria

* Part 3, Cohorts A1, A2, CCI : subjects must be 1L chemotherapy-naïve in the recurrent/metastatic setting; subjects may have progressed ≥ 6 months after receiving an oxaliplatin chemotherapy regimen in the adjuvant setting.
* CCI [redacted]
* Part 3, Cohorts C1A, C1B, C2A, C2B: subjects CCI [redacted]

  Prior standard chemotherapy in the recurrent/metastatic setting must include **ALL** of the following agents:

  -- Fluoropyrimidines, irinotecan and oxaliplatin
  -- An anti-VEGF mAb (eg, bevacizumab)

-- Subjects in Cohorts C2A and C2B must not have received prior anti-EGFR therapy (eg, cetuximab or panitumumab naïve).

Subjects must have progressed based on imaging during or within 3 months of the last administration of each standard chemotherapy.

Subjects who have withdrawn from standard treatment due to unacceptable toxicity warranting discontinuation of treatment and precluding retreatment with the same agent prior to progression of disease will also be eligible to enter the study.

Subjects who had received adjuvant chemotherapy and had recurrence during or within 6 months of completion of the adjuvant chemotherapy are allowed to count the adjuvant therapy as 1 regimen of chemotherapy.

Disease pathology criteria

* Part 3, Cohorts A1 CCI : subjects can be enrolled regardless of CCI and location of colon primary tumor.
* Part 3, Cohort A2: subjects are required to be CCI and have a left-sided colon primary tumor. CCI
* CCI
* CCI
* Part 3, Cohorts C1A and C1B: subjects are required to have documented CCI . CCI
* Part 3, Cohorts C2A and C2B: subjects are required to be CCI . CCI

Bevacizumab criteria

* Part 3, Cohorts A1 CCI where bevacizumab is the biologic component:

  The subject has adequate coagulation function as defined by international normalized ratio (INR) < 1.5 × ULN and a partial thromboplastin time (or activated partial thromboplastin time) < 1.5 ULN if not receiving anticoagulation therapy. Subjects on full-dose anticoagulation must be on a stable dose (minimum duration 14 days) of oral or parenteral (eg, low molecular weight heparin) anticoagulant therapy and if on oral anticoagulation with coumarin derivatives, must have an INR < 3 and have no clinically significant active bleeding (defined as Grade 2 or higher hemorrhage within

14 days prior to first dose of study treatment) or pathological condition that carries a high risk of bleeding (eg, intact primary tumor with a history of clinically significant bleeding, or tumor involving major vessels or known esophageal varices).

NOTE: Subjects with a venous thrombosis are permitted to enroll, including subjects on newer oral anticoagulants (eg, apixaban, rivaroxaban, dabigatran, etc), provided they are clinically stable, asymptomatic, and adequately treated with anticoagulation in the opinion of the investigator for at least 3 months prior to the first dose of study treatment.

The subject's urinary protein is < 1+ on dipstick or routine urinalysis; if urine protein > 2+, a 24-hour urine must be collected and must demonstrate < 1000 mg of protein in 24 hours to allow participation in the study.

(c) NSCLC: Subjects must have histologically proven, stage IIIb or IV NSCLC or recurrent or PD following multi-modal therapy (radiation therapy, surgical resection or definitive chemo radiation) for locally advanced disease.

(i) Subjects may have received up to 2 prior lines of systemic therapy for recurrent/metastatic disease. Prior therapies must have included a platinum-based regimen.

(ii) Maintenance therapy following platinum doublet-based chemotherapy will not be considered a separate line of therapy.

(iii) Prior platinum-containing adjuvant, neoadjuvant, or definitive chemoradiation therapy given for locally advanced disease is considered 1L therapy only if recurrent (local or metastatic) disease developed within 6 months of completing therapy. Subjects with recurrent disease > 6 months must also have progressed after a subsequent platinum-based chemotherapy regimen given to treat the recurrence.

(iv) PD-L1 status will be prospectively determined by IHC prior to enrollment in the dose-expansion part. A minimum of 10 of the initial 20 NSCLC subjects enrolled must have PD-L1+ tumors. Similarly, if enrollment in the NSCLC cohort continues up to approximately 40 subjects, a minimum of 20 subjects must have PD-L1+ tumors.

(v) Subjects with known sensitizing EGFR-mutation or anaplastic lymphoma kinase-rearrangement are excluded. All subjects' tumors must be tested and shown to be wild type EGFR (by IHC or sequencing) and anaplastic lymphoma kinase (by IHC, fluorescence in-situ hybridization, or sequencing) in a Clinical Laboratory Improvement Amendments certified lab in the USA. Countries outside the USA must use one of the methods mentioned for EGFR-mutation and anaplastic lymphoma kinase-rearrangement testing that has regulatory approval in the country the subject is being enrolled.

(d) CCI endometrial cancer:

(i) Subjects may have received up to 2 prior lines of systemic therapy for recurrent/metastatic disease.

(ii) CCI [redacted]

(e) Cervical cancer, castration-resistant prostate cancer, or pancreatic adenocarcinoma (dose-escalation part only): Subjects may have received up to 2 prior lines of systemic therapy for recurrent/metastatic disease. Subjects with castration-resistant prostate cancer must have progressed following therapy with abiraterone or enzalutamide.

6 Tumor tissue requirements are as follows:

(a) CCI [redacted]

(b) The initial 20 subjects in each dose-expansion cohort must have at least one lesion amenable to biopsy and must provide a pre-treatment biopsy during the Screening Period, and, if clinically feasible, during Week 9. If a given dose-expansion cohort is expanded beyond the initial 20 subjects, additional subjects must consent to provide an archival tumor sample from a biopsy collected within 1 year prior to first dose of study drug or must provide a pre-treatment biopsy during the Screening Period. If clinically feasible, all dose-expansion subjects must provide a biopsy during Week 9.

(c) Subjects in Part 3 must consent to provide an archival tumor sample from a biopsy collected within 1 year prior to the first dose of study treatment or must provide a pre-treatment biopsy during the Screening Period.

(d) For subjects with CRC, the microsatellite stability testing pathology report will be available to the sponsor at screening.

7 Subjects must have at least one lesion that is measurable by RECIST v1.1 (Eisenhauer et al, 2009).

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

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

8 Eastern Cooperative Oncology Group (ECOG) Performance Score of 0 or 1

9 As of Week 1 Day 1, subjects with central nervous system (CNS) metastases must have been treated and must be asymptomatic and meet the following:

(a) No concurrent treatment, inclusive of but not limited to surgery, radiation, and/or corticosteroids

(b) At least 28 days after CNS treatment, clinically stable with no symptoms of CNS metastasis or sequelae of radiation and at least 14 days since last dose of corticosteroids
NOTE: Subjects with clinical symptoms or cord compression or with leptomeningeal disease are excluded from the study

10 Adequate organ function as determined by:

(a) Hematological (criteria i – iii cannot be met with recent blood transfusions or require ongoing growth factor support within 2 weeks of starting study treatment):

(i) Absolute neutrophil count ≥ 1.5 × 10^9/L (1,500/mm3)

(ii) Platelet count ≥ 100 × 10^9/L (100,000/mm3)

(iii) Hemoglobin ≥ 9.0 g/dL within first 2 weeks prior to first dose of study treatment

(b) Renal:
Calculated creatinine clearance* (CrCl) or 24 hour urine CrCl > 50 mL/min

**Cockcroft-Gault formula will be used to calculate CrCl*

(c) Hepatic:

(i) TBL ≤ 1.5 × ULN; for subjects with documented/suspected Gilbert's syndrome, bilirubin ≤ 3 × ULN

(ii) AST and ALT ≤ 2.5 × ULN (AST/ALT can be up to 5 × ULN in the presence of liver metastasis, but cannot be associated with elevated bilirubin)

(iii) Subjects with Gilbert's syndrome are not permitted to enroll in Part 3, CCI [redacted]. Thus, subjects with a known history of or clinical evidence of Gilbert's syndrome and those known to have the genotype UGT1A1*28/*28 are to be excluded from these cohorts.

11 Females of childbearing potential who are sexually active with a nonsterilized male partner must use at least one highly effective method of contraception from screening, and must agree to continue using such precautions for 6 months after the final dose of investigational product. 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 birth control.

(a) 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 postmenopausal (defined as 12 months with no menses without an alternative medical cause).

(b) 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 6.

(c) Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she must inform her treating physician immediately.

(d) Female subjects must refrain from egg cell donation and breastfeeding while on study and for 6 months after the final dose of investigational product.

12 Nonsterilized male subjects who are sexually active with a female partner of childbearing potential must use a male condom with spermicide from Day 1 through 6 months after receipt of the final dose of investigational product. It is strongly recommended for the female partner of a male subject to also us an effective method of contraception throughout this period (Table 6). In addition, male subjects must refrain from sperm donation while on treatment and for 6 months after the final dose of investigational product.

Table 6 Highly Effective Methods of Contraception

Intrauterine Methods	Hormonal Methods
• Copper T intrauterine device • Levonorgestrel-releasing intrauterine system) or implant (eg, Mirena ®) [a]	• Implants • Hormone injection • Intravaginal devices • Combined pill • Minipill • Patch

[a] This is also considered a hormonal method.

4.1.3 Exclusion Criteria

1 Prior treatment with immunotherapy agents, including, but not limited to: tumor necrosis factor receptor superfamily agonists or checkpoint inhibitors or NK-cell inhibitors including agents targeting KIR, PD-1, PD-L1, CTLA-4, OX40, CD27, CD137 (4-1BB), CD357 (GITR), and CD40. Prior treatment with antitumor vaccines may be permitted upon discussion with the medical monitor. NOTE: Subjects who have received prior anti-PD-1, anti-PD-L1 or anti-CTLA-4 immunotherapy may be enrolled in Part 1 if they meet the following criteria:

   (a) Must not have experienced a toxicity that led to permanent discontinuation of prior immunotherapy.

   (b) All AEs while receiving prior immunotherapy must have completely resolved or resolved to baseline prior to screening for this study.

   (c) Must not have experienced a ≥ Grade 3 immune-related AE or an immune-related neurologic or ocular AE of any grade while receiving prior immunotherapy. NOTE: Subjects with endocrine AE of ≤ Grade 2 are permitted to enroll if they are stably maintained on appropriate replacement therapy and are asymptomatic.

   (d) Must not have required the use of additional immunosuppression other than corticosteroids for the management of an AE, not have experienced recurrence of an AE if re-challenged, and not currently require maintenance doses of > 10 mg prednisone or equivalent per day.

2 Prior participation in clinical studies that include durvalumab alone or in combination, where the study has registrational intent and the analyses for the primary endpoint have not yet been completed

3 Known allergic reaction to any component of durvalumab, monalizumab, or any component of the chemotherapy regimens and biologics that will be administered in Part 3.

4 Concurrent enrollment in another clinical study, unless it is an observational (non-interventional) clinical study or the follow-up period of an interventional study.

5 Receipt of any conventional or investigational anticancer therapy within 4 weeks prior to the first dose of study treatment.

6 Any concurrent chemotherapy, immunotherapy, biologic or hormonal therapy for cancer treatment. Concurrent use of hormones for non-cancer-related conditions (eg, insulin for diabetes and hormone replacement therapy) is acceptable. Local treatment (eg, by local surgery or radiotherapy) of isolated lesions for palliative intent is acceptable beyond the DLT-evaluation period with prior consultation and in agreement with the medical monitor.

7 Receipt of live attenuated vaccines within 30 days prior to the first dose of study treatment. Subjects, if enrolled, should not receive live or live attenuated vaccine during the study and 30 days after the last dose of investigational products.

8 Unresolved toxicities from prior anticancer therapy, defined as having not resolved to NCI CTCAE v4.03 Grade 0 or 1 with the exception of alopecia and laboratory values listed per the inclusion criteria. Subjects with irreversible toxicity that is not reasonably expected to be exacerbated by the study drug may be included (eg, hearing loss) after consultation with the medical monitor.

9 Current or prior use of immunosuppressive medication within 14 days before the first dose. The following are exceptions to this criterion:
   (a) Intranasal, inhaled, topical steroids or local steroid injections (eg, intra-articular injection), OR
   (b) Systemic corticosteroids at physiologic doses not to exceed 10 mg/day of prednisone or equivalent, OR
   (c) Steroids as premedication for hypersensitivity reactions (eg, computed tomography [CT] scan premedication).
   (d) Premedication with steroids for chemotherapy and biologic components in Part 3.
10 History of primary immunodeficiency or allogeneic transplantation.
11 Active or prior documented autoimmune or inflammatory disorders (including inflammatory bowel disease [eg, colitis or Crohn's disease], diverticulitis [with the exception of diverticulosis], systemic lupus erythematosus, Sarcoidosis syndrome, or Wegener syndrome [granulomatosis with polyangiitis, Graves' disease, rheumatoid arthritis, hypophysitis, uveitis, etc]). 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
   (c) Any chronic skin condition that does not require systemic therapy
   (d) Subjects without active disease in the last 5 years may be included but only after consultation with the study physician
   (e) Subjects with celiac disease controlled by diet alone.
12 Uncontrolled concurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, active peptic ulcer disease or gastritis, or psychiatric illness/social situations that would limit compliance with study requirement, substantially increase risk of incurring AEs from durvalumab and monalizumab, or compromise the ability of the subject to give written informed consent.
13 Major surgery (as defined by the investigator) within 28 days prior to first dose of study treatment or still recovering from prior surgery. Local surgery of isolated lesions for palliative intent is acceptable.
14 Positive test results for human immunodeficiency virus, acute hepatitis A, active hepatitis B, or C.
15 Females who are pregnant, lactating, or intend to become pregnant during their participation in this study.
16 Other invasive malignancy within 2 years except for noninvasive malignancies such as cervical carcinoma in situ, non-melanomatous carcinoma of the skin or ductal carcinoma in situ of the breast that has/have been surgically cured. Subjects with localized malignancy that was treated with curative intent (eg, localized breast cancer, prostate cancer) and who remain disease free and are considered of low likelihood for recurrence may be enrolled on a case-by-case basis with prior discussion and in agreement with the sponsor's medical monitor.

17 Any condition that, in the opinion of the investigator or sponsor, would interfere with evaluation of the investigational product or interpretation of subject safety or study results.

18 The following exclusion criteria apply to subjects enrolling in Part 3, Cohorts A1 CCI , in which bevacizumab will be the biologic component:

(a) Subjects with a history of uncontrolled hereditary or acquired bleeding or thrombotic disorders.

(b) The subject has undergone subcutaneous venous access device placement ≤ 7 days prior to the first dose of study treatment.

(c) The subject has had a serious nonhealing wound, ulcer, or bone fracture ≤ 28 days prior to first dose of study treatment.

(d) The subject has an elective or planned major surgery to be performed during the course of the study.

(e) The subject has experienced a Grade 3 or higher bleeding event ≤ 3 months prior to first dose of study treatment.

(f) The subject has either peptic ulcer disease associated with a bleeding event, or known active diverticulitis.

(g) The subject experienced any of the following during 1L therapy with a bevacizumab-containing regimen: an arterial thrombotic/thromboembolic event, Grade 4 hypertension, Grade 3 proteinuria, a Grade 3-4 bleeding event or bowel perforation.

19 Subjects enrolling in Part 3, CCI , must not have experienced a toxicity that led to permanent discontinuation of prior therapy with cetuximab.

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 voice/web response system [IXRS]), 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 the randomized Part 3 Cohorts C1 and C2, subjects who complete all screening procedures and meet the eligibility criteria will proceed to randomization. The site will access the IXRS system on or prior to the subject's Week 1 Day 1 visit and a unique randomization number will be provided. Treatment should start no more than 3 working days after being randomized. Subjects cannot be re-randomized.

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.

Subjects who fail to meet the inclusion/exclusion criteria (ie, screening failures) should not receive investigational product/or be randomized.

4.1.5 Withdrawal from the Study

Subjects are at any time free to withdraw from the study (investigational product and assessments), without prejudice to further treatment (withdrawal of consent). Such subjects will always be asked about the reason(s) and the presence of any AEs. If possible, they will be seen and assessed by an investigator. AEs will be followed.

4.1.5.1 Withdrawal from Treatment

If a subject withdraws consent to further treatment, they will not receive any further investigational product(s), but may continue with further study observation. Subjects who decline to return to the site for evaluations will be offered follow-up by phone according to the schedule in Section 4.2.3 as an alternative. If a subject withdraws from further participation in the study, then no further study visits or data collection should take place.

4.1.5.2 Withdrawal of Consent

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
2 Withdrawal of consent from further treatment with investigational product
3 Lost to follow-up
4 An AE that, in the opinion of the investigator or the sponsor, contraindicates further dosing
5 Any AE that meets criteria for discontinuation from investigational product (refer to Section 3.1.3 for toxicity management guidelines) and refer to Section 3.1.3.1 for instructions on when to discontinue the biologic agents). (If a subject is receiving clinical benefit, monotherapy treatment with durvalumab can be considered for NSCLC subjects, see Section 4.1.7.)
6 Subject did not meet one or more inclusion criteria or was 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
7 Pregnancy or intent to become pregnant
8 Subject noncompliance that, in the opinion of the investigator or sponsor, warrants withdrawal (eg, refusal to adhere to scheduled visits)
9 Initiation of alternative anticancer therapy including another investigational agent
10 Confirmation of PD 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)

11 Investigator determination that the subject is no longer benefiting from the treatment regimen

Subjects who are permanently discontinued from receiving investigational product will be followed for safety per Section 5.4, including the collection of any protocol-specified blood specimens, survival and subsequent anticancer treatment. If a subject withdraws consent, is lost to follow-up or is administered subsequent therapy, follow-up visits are no longer required. Subjects who decline to return to the site for evaluations and/or receive subsequent anticancer therapy, must be offered follow-up by phone per Table 14 as an alternative to obtain survival information as well as information on additional subsequent anticancer treatment.

4.1.7 Treatment Beyond Progression

For all subjects, if PD (based on RECIST v1.1) occurs, the subject may continue study treatment until one of the following criteria is met:

1 Confirmed PD: An initial assessment of PD by RECIST v1.1 will be confirmed by a repeat evaluation at the next tumor assessment time point, but no sooner than 4 weeks later. If any subsequent tumor assessment time point shows ≥ 20% increase in the overall tumor burden (the sum of diameters of target lesions and new lesions), when compared to the initial PD assessment (the sum of diameters of target lesions and new lesions), the subject would be deemed as having confirmed PD and must be discontinued.
2 Meets any of the other investigational product discontinuation criteria (Section 4.1.6)
3 Clinical symptoms or signs indicating clinically significant PD such as the benefit-risk ratio of continuing therapy is no longer justified.
4 Decline in ECOG performance status indicating rapid decline.
5 Rapid PD or threat to vital organs/critical anatomical sites (eg, spinal cord compression) requiring urgent alternative medical intervention, and/or continuation of study therapy would prevent institution of such intervention.

Subjects must provide separate consent to continue treatment when progression is first detected.

4.1.8 Re-treatment Following Relapse

A subject who has been treated for a minimum of 2 years and continues to experience CR, PR, or SD as demonstrated by radiographic measures may be considered for treatment discontinuation. Data from other immunotherapy studies suggest that subjects who initially derive clinical benefit from immunotherapy can derive benefit again once the subject has PD while off therapy (Wolchok et al, 2013; Hamid et al, 2013).

Subjects who progress during the first 52 weeks after the last dose of study treatment will be eligible for re-treatment with the protocol-defined experimental medicines (same dose and schedule) as at the time of discontinuation, after consultation and in agreement with the

sponsor. The investigator may consider standard-of-care chemotherapy backbone with the experimental agent(s) as appropriate for the subject at time of re-treatment. The criteria listed below must not apply:

1 Meets any of the investigational product discontinuation criteria (see Section 4.1.6);
2 ECOG performance status > 2;
3 Rapid PD or threat to vital organs/critical anatomical sites (eg, spinal cord compression) requiring urgent alternative medical intervention.
4 Subject has had severe/refractory irAE or development of new autoimmune condition that, in the investigator's opinion, poses undue risk to the subject.

This option for re-treatment will be limited to one occasion and will apply only if the subject has not received any other anticancer treatment for their disease following study-treatment discontinuation. The study protocol must still be active, ie, the final database lock has not yet occurred. The subject will need to follow the schedule of study procedures as described in Section 4.2.2. Subjects must also be re-consented.

4.1.9 Replacement of Subjects

In the dose-escalation part, a minimum of 3 evaluable subjects is required unless unacceptable toxicity is seen in a dose-level cohort. For a dose-level cohort that has less than 3 evaluable subjects, subjects who do not meet the criteria for the DLT-evaluable Population (Section 4.8.1) will be replaced. Subjects who fail DLT evaluation in the dose-exploration part, for reasons other than a DLT, will be replaced as necessary to obtain at least 6 evaluable subjects. Subjects enrolled in the dose-expansion part will not be replaced.

4.1.10 Withdrawal of Informed Consent for Data and Biological Samples

Biological Samples Obtained for the Main Study

Study data are protected by the use of an SID number, which is a number specific to the subject. The investigator is in control of the information that is needed to connect a study sample to a subject. A subject's consent to the use of data does not have a specific expiration date, but the subject may withdraw consent at any time by notifying the investigator. If consent is withdrawn, any samples collected prior to that time may still be given to and used by the sponsor but no new data or samples will be collected unless specifically required to monitor safety of the subject.

Samples Obtained for Genetic Research or Future Research

Samples obtained for genetic research or future research will be labeled with a sample identification number linked to the SID number but will not be labeled with personal identifiers such as the subject's name. If the subject withdraws consent for participating in the genetic research or future research, the sponsor will locate the subject's sample and destroy it.

The coding of samples and results is to ensure that these research results are kept confidential by keeping the subject's identity and these results separate.

This study involves the collection of biological samples, such as blood and samples of body tissue. These samples will be used to evaluate the presence of study drug, immune cells, proteins, CCI [redacted] in your tumor cells. This is different from genetic research looking at the DNA that is inherited from a patients' parents, since it is a test evaluating how a patient's cancer developed. Medimmune will be evaluating these changes to determine how the drugs are working and if there are situations in which the drugs work best. These biological samples will be used to conduct the main study and are not part of what is usually referred to as genetic research.

If the subject consents to have his/her samples used for genetic research or future research, this additional research may not start immediately and may start at any time during the storage period. The subject's sample(s), CCI [redacted] will be stored by the sponsor with similar samples from other subjects at a secure central laboratory. The subject's samples will not be kept for more than 25 years after the end of the study in which they were collected. If the subject chooses not to allow his/her study samples to be used for genetic research or future research, the samples will be destroyed by the sponsor once they are no longer required for the main study.

CCI [redacted]

In this case only the remaining sample(s) will be destroyed

4.2 Schedule of Study Procedures

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. The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) and Patient Global Impression of Change (PGIC) questionnaire are being implemented in CCI [redacted] these should be completed prior to any other study procedures that day; see Section 4.3.3 for instructions regarding these assessments.

4.2.1 Enrollment/Screening Period

Table 7 shows all procedures to be conducted at screening/baseline. Screening procedures will be conducted within 28 days prior to the first dose of investigational product. The screening period may be extended an additional 7 days for subjects requiring prospective testing for tumoral PD-L1 expression.

Table 7 Schedule of Screening/Baseline Procedures

Study Period	Screening/Baseline
Procedure	**Days -28 to -1**
Written informed consent/ assignment of SID number	X
Verify eligibility criteria	X
Tumor and disease assessments	
History of prior cancer treatment	X
Disease assessment by RECIST v1.1 (CT or MRI) [a]	X
Brain imaging [a, b]	X
Study procedures and examinations	
Demographics (including age, sex, race, ethnicity)	X
Medical history (including smoking history) and prior imaging [c]	X
Physical examination (including height and weight)	X
ECOG performance status	X
12-lead ECG [d]	X
Vital signs (including temperature, BP, respiratory rate, pulse rate)	X
Assessment of AEs/SAEs	X
Concomitant medications	X
Laboratory tests	
Serum chemistry	X
Hematology	X
Coagulation parameters	X
Thyroid function	X
Urinalysis [e]	X
Serum pregnancy test	X
Hepatitis A, B and C; HIV-1	X
Other laboratory tests and assays	
Archival tumor sample [f]	X
Fresh tumor biopsy [f]	X
Flow cytometry	X
CCI [redacted]	

Table 7 Schedule of Screening/Baseline Procedures

Study Period	Screening/Baseline
Procedure	**Days -28 to -1**
Circulating soluble factors (serum)	X
Circulating soluble factors (plasma)	X
PBMC collection	X
CCI	
Stool sample (Part 3, Cohorts C1A, C1B, C2A, and C2B only)	X [g]

AE = adverse event; BP = blood pressure; CT = computed tomography; CCI ; DICOM = Digital Imaging and Communications in Medicine; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; HIV = human immunodeficiency virus; CCI ; MRI = magnetic resonance imaging; CCI PBMC = peripheral blood mononuclear cells; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event; SID = subject identification.

[a] Previous scans for baseline disease and brain imaging that were performed within 6 weeks of dosing and meet the protocol requirements do not need to be repeated.

[b] All subjects must receive a brain scan during the Screening Period.

[c] 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.

[d] At screening, a single ECG will be obtained.

[e] If urine protein > 2+, a 24-hour urine must be collected and must demonstrate < 1000 mg of protein in 24 hours to allow participation in the study.

[f] For the initial subjects in each dose-escalation cohort, archival tumor from the subject should be collected. If not available, a fresh biopsy must be performed. Additional subjects enrolled in a dose-escalation cohort while the pharmacodynamics are further investigated, must have at least one lesion amenable to biopsy and must provide a pre-treatment biopsy during the screening period. Fresh biopsies are required for the initial 20 subjects in each dose-expansion cohort. If enrollment in each dose-expansion cohort proceeds beyond 20 subjects, archival tumor obtained within 1 year of enrollment or fresh biopsy obtained during screening is required. In Part 3, archival tumor sample obtained within 1 year of enrollment or fresh biopsy obtained during screening is required.

[g] The stool sample can be collected anytime during screening, up to and including Day 1, provided it is collected prior to administration of the first dose of study drug(s).

4.2.2 Treatment Period

Procedures to be conducted during the treatment period presented in Table 8 for Weeks 1 to 26 and in Table 9 for Weeks 27 to End of Treatment. At study visits when subjects do not receive investigational product, all of the pre-treatment assessments will be performed. The procedures presented in Table 8 for Weeks 1 to 26 and in Table 9 for Weeks 27 to End of Treatment should also be followed for NSCLC subjects receiving durvalumab monotherapy.

CCI

For subjects undergoing re-treatment following relapse, procedures to be conducted are presented in Table 12 and Table 13.

Considerations when scheduling and conducting study visits:

- The timing of ECGs and vital sign assessments should be such that it allows the blood draw (eg, PK blood sample) to occur at the exact nominal time. The EORTC QLQ-C30 and PGIC questionnaire, is being implemented in CCI [redacted]; these should be completed prior to any other study procedures that day; see Section 4.3.3 for instructions regarding these assessments.
- All protocol required samples are collected predose unless otherwise indicated.
- All dosing visits are to be scheduled based on the date of Week 1 Day 1 dosing.
- Future dosing visits are not to be recalibrated based on actual dosing dates unless approved by the sponsor.
- Subjects are to receive durvalumab and/or monalizumab (and if applicable chemotherapy and/or biologic) within a 5-day visit window (7-day visit window if the Q4W monalizumab schedule is investigated). The following guidelines should be followed as applicable:
  - If doses are not received within these visit windows, and the sponsor has not approved recalibration (see bullet above), the dose must be omitted and subjects should receive the next planned dose according to the schedule established at Week 1 Day 1.
  - In the event of scheduling shifts within the 5-day visit window, sequential doses of durvalumab and/or monalizumab (and if applicable bevacizumab and cetuximab [Q2W dosing schedules]) (eg, dose 1, dose 2) must not be administered less than 10 days apart.
  - In the event of scheduling shifts within the 5-day visit window, sequential doses of cetuximab (Q1W dosing schedule) (eg, dose 1, dose 2) must not be administered less than 6 days apart.
  - In the event of scheduling shifts within the 5-day visit window, sequential doses of chemotherapy (eg, dose 1, dose 2) must not be administered less than 14 days apart.
- Disease assessment scans do not need to be performed on the same day as dosing and can be performed within a 7-day window of the dosing day.
- If any subject experiences a toxicity related to investigational product, the management guidelines provided in Section 3.1.3 should be followed.

Table 8 Schedule of Treatment Period Study Procedures Weeks 1 to 26

Study Period	Treatment Period: Weeks 1 to 26														
Week/Day	**W1 D1**	**W1 D2**	**W2 D1**	**W3 D1**	**W5 D1**	**W7 D1**	**W9 D1**	**W11 D1**	**W13 D1**	**W15 D1**	**W17 D1**	**W19 D1**	**W21 D1**	**W23 D1**	**W25 D1**
Procedure/Study Day	**1**	**2**	**8**	**15**	**29**	**43**	**57**	**71**	**85**	**99**	**113**	**127**	**141**	**155**	**169**
Enrollment	X														
Tumor and disease assessments															
Disease assessment by RECIST v1.1[CCI] (CT or MRI and brain imaging [if metastasis found at baseline or symptomatic]) [a]							X				X				X
Fresh tumor biopsy [b]							X (± 7D)								
Study procedures and examinations															
Physical examination	X [c]	X			X		X		X		X		X		X
ECOG performance status	X [c]						X[o]				X				X
[CCI]															
PGIC (Part 3, Cohorts C1A and C1B only)					X		X		X		X		X		X
Vital signs [d]	X	X		X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG [e]	X						X				X				X
Assessment of AEs/SAEs [l]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications [l]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory tests															
Serum chemistry [l]	X [c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology	X [c]			X	X		X		X		X		X		X

Table 8 Schedule of Treatment Period Study Procedures Weeks 1 to 26

Study Period	Treatment Period: Weeks 1 to 26														
Week/Day	**W1 D1**	**W1 D2**	**W2 D1**	**W3 D1**	**W5 D1**	**W7 D1**	**W9 D1**	**W11 D1**	**W13 D1**	**W15 D1**	**W17 D1**	**W19 D1**	**W21 D1**	**W23 D1**	**W25 D1**
Procedure/Study Day	**1**	**2**	**8**	**15**	**29**	**43**	**57**	**71**	**85**	**99**	**113**	**127**	**141**	**155**	**169**
Coagulation parameters	X [c]			X	X		X		X		X		X		X
Thyroid function tests	X [c]				X		X		X		X		X		X
Urinalysis	X [c]				X		X		X		X		X		X
Urine or serum pregnancy test	X				X		X		X		X		X		X
Carcinoembryonic antigen for colorectal cancer and CA-125 for ovarian/endometrial cancer [f]	X						X[o]								X
Pharmacokinetics															
Durvalumab PK (not applicable for Part 3 Cohorts C1B and C2B)	X [g]			X	X		X[o]		X [g]						X
Monalizumab PK [h]	X [g]	X [h]		X [h]	X [h]		X [h, o]		X [g, h]						X [h]
Cetuximab PK (Part 3, Cohorts C1A and C1B only)	X[g]			X	X		X[o]		X[g]	X					
Other laboratory tests and assays															
CD94/NKG2a receptor occupancy	X	X							X						
Durvalumab immunogenicity (not applicable for Part 3 Cohorts C1B and C2B)	X				X				X						X
Monalizumab immunogenicity [h]	X				X				X [h]						X [h]
Cetuximab immunogenicity (Part 3, Cohorts C1A and C1B only)	X				X		X[o]		X						
Flow cytometry	X		X	X	X		X								

Table 8 Schedule of Treatment Period Study Procedures Weeks 1 to 26

Study Period	Treatment Period: Weeks 1 to 26														
Week/Day	**W1 D1**	**W1 D2**	**W2 D1**	**W3 D1**	**W5 D1**	**W7 D1**	**W9 D1**	**W11 D1**	**W13 D1**	**W15 D1**	**W17 D1**	**W19 D1**	**W21 D1**	**W23 D1**	**W25 D1**
Procedure/Study Day	**1**	**2**	**8**	**15**	**29**	**43**	**57**	**71**	**85**	**99**	**113**	**127**	**141**	**155**	**169**
CCI [redacted]															
Circulating soluble factors (serum)	X								X						
Circulating soluble factors (plasma)	X		X	X	X		X				X				X
PBMC collection	X	X		X	X		X								X
CCI [redacted]															
Stool sample (Part 3, Cohorts C1A, C1B, C2A, and C2B only)							X [p]								
Blood sample for future analysis [m]	X														
Study treatment administration															
Durvalumab administration (Q4W dosing schedule; not applicable for Part 3 Cohorts C1B and C2B) [i]	X				X		X		X		X		X		X
Monalizumab administration (Q2W dosing schedule) [i]	X			X	X	X	X	X	X	X	X	X	X	X	X
Chemotherapy administration (Part 3 Cohorts A1-CCI [redacted] only; Q2W dosing schedule) [j,k]	X			X	X	X	X	X	X	X	X	X	X	X	X
Bevacizumab (Part 3, Cohorts A1 CCI [redacted] only; Q2W dosing schedule) [k]	X			X	X	X	X	X	X	X	X	X	X	X	X
Cetuximab (Part 3, Cohorts A2 CCI [redacted] only; Q1W dosing schedule) [k,l,n]	X		X	W3: X	W4: X	W5: X	W6: X	W7: X	W8: X	W9: X	W10: X	W11: X	W12: X	W13: X	W14: X
				W15: X	W16: X	W17: X	W18: X	W19: X	W20: X	W21: X	W22: X	W23: X	W24: X	W25: X	W26: X

Table 8 Schedule of Treatment Period Study Procedures Weeks 1 to 26

Study Period	Treatment Period: Weeks 1 to 26														
Week/Day	**W1 D1**	**W1 D2**	**W2 D1**	**W3 D1**	**W5 D1**	**W7 D1**	**W9 D1**	**W11 D1**	**W13 D1**	**W15 D1**	**W17 D1**	**W19 D1**	**W21 D1**	**W23 D1**	**W25 D1**
Procedure/Study Day	**1**	**2**	**8**	**15**	**29**	**43**	**57**	**71**	**85**	**99**	**113**	**127**	**141**	**155**	**169**
Cetuximab (Part 3, Cohorts C1A, C1B, C2A, and C2B only; Q2W dosing schedule) [k, l, n]	X			X	X	X	X	X	X	X	X	X	X	X	X

AE = adverse event; CT = computed tomography; CCI [redacted]; D = day; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOI = end of infusion; CCI [redacted] CCI [redacted] CCI [redacted] CCI [redacted], MRI = magnetic resonance imaging; PBMC = peripheral blood mononuclear cells; PGIC = Patient Global Impression of Change; PK = pharmacokinetic; Q1W = every week; Q2W = every 2 weeks; Q4W = every 4 weeks; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event; W = week.

Note: On treatment days, evaluations and sample collections should be conducted prior to administration of durvalumab/monalizumab unless otherwise indicated. On nontreatment days, all of the pre-treatment assessments will be performed.

[a] If post-baseline radiological imaging indicates progressive disease, a separate consent must be signed before the subject may continue treatment.

[b] As clinically feasible, for subjects in dose escalation participating in pharmacodynamics expansion and for subjects in dose expansion who provided a fresh pre-treatment biopsy. As clinically feasible, subjects in Part 3 (dose exploration) who provided a fresh pre-treatment biopsy are encouraged to provide a biopsy at Week 9.

[c] If tests are performed within 3 days prior to Week 1, Day 1, they do not need to be repeated. All safety laboratory results must be reviewed by the investigator or physician designee prior to administration of the scheduled dose of investigational product.

[d] Vital signs (temperature, blood pressure, pulse rate, and respiratory rate) will be measured on durvalumab and monalizumab treatment days according to the following schedule: within 30 minutes prior to the start of durvalumab and monalizumab infusion, approximately every 15 minutes during durvalumab and monalizumab infusion, at EOI of durvalumab and monalizumab, and at approximately 30 and 60 minutes post EOI of monalizumab. On Week1, Day 1, an additional 2-hour (± 15 minutes) post monalizumab EOI vital sign measurement will be required, while for Part 3 a 15- to 30-minute observation period would be sufficient prior to infusion of pre-medication for the biologic agent or chemotherapy but vital sign collection should continue approximately every 30 minutes up to 2 hours after Monalizumab infusion. For subsequent doses, the additional 2-hour observation period will not be required unless clinically indicated (eg, subject experiences an infusion-related reaction).

[e] On Week 1, Day 1, ECGs will be obtained in triplicate (all 3 within a 5-minute time period, at least 1 minute apart) within 30 minutes prior to start of durvalumab infusion, within 30 minutes post EOI of monalizumab, and between 2 and 6 hours post EOI of monalizumab. At all other time points, a single ECG will be obtained prior to investigational product(s) administration and as clinically indicated.

[f] Sample to be taken prior to administration of investigational product.

[g] One predose sample will be collected prior to start of durvalumab infusion and an EOI (within 10 minutes) sample collected after the end of the durvalumab infusion and after the end of the monalizumab infusion. For subjects in Cohort C1A, an EOI (within 10 minutes) sample will also be collected after the end of the cetuximab infusion. For subjects in Cohort C1B, one predose sample will be collected prior to start of monalizumab infusion and an EOI (within 10 minutes) sample collected after the end of the monalizumab infusion and after the end of the cetuximab infusion. Post-dose PK samples are not applicable if the investigational product is not administered.

[h] For subjects who continue in the study on durvalumab monotherapy (Section 3.1.1), a sample for monalizumab PK and immunogenicity should be taken 90 days (± 7 days) after the last dose of monalizumab. Further samples for monalizumab PK and immunogenicity are not required.

[i] On study days when both durvalumab and monalizumab are administered, durvalumab will be administered first and the infusion duration will be approximately 60 minutes. The monalizumab infusion will start approximately 15 to 30 minutes post EOI of durvalumab and the infusion will be administered over approximately 60 minutes.

[j] Infusion times for the biologic agent and chemotherapy should be according to the respective institutional guidelines. The biologic agent or chemotherapy regimen will be administered within 1 hour post end of the monalizumab infusion. The pre-medications for the biologic agent or chemotherapy can be administered after the 15- to 30-minute observation period post end of the monalizumab infusion.

[k] During the days when the biologic agent and chemotherapy are administered, there should only be a 15- to 30-minute observation period post end of the monalizumab infusion, after which either pre-medication for the biologic agent or chemotherapy, or chemotherapy/biologic agent infusion can start.

[l] The following should be assessed on the days of cetuximab administration: serum chemistry, all AEs, and concomitant medications.

[m] Additional baseline blood samples will also be collected in a 10-mL red top tube in order to have serum samples collected at baseline for future analysis, which includes, but is not limited to an autoimmune work-up (refer to the Laboratory Manual for the processing of this sample).

[n] Cohorts A2 [redacted]: Cetuximab loading dose (400 mg/m^2 IV infusion over approximately 2 hours) will be administered on Day 1, then maintenance dose (250 mg/m^2 IV infusion over approximately 1 hour) Q1W will be administered starting on Day 8. The cetuximab regimen may be changed to 500 mg/m^2 IV infusion for approximately 2 hours Q2W after a subject has completed the 28-day DLT-evaluation period, at the investigator's discretion and in accordance with institutional guidelines.
Cohorts C1A, C1B, C2A, and C2B: Cetuximab (500 mg/m^2 IV infusion over approximately 2 hours) will be administered on Day 1 then 500 mg/m^2 IV infusion for approximately 2 hours Q2W starting on Day 15.

[o] Assessment is optional if the subject is discontinuing treatment at the scheduled W9 D1 visit.

[p] Second stool sample can be collected ± 2 weeks from the W9 D1visit.

Table 9 Schedule of Treatment Period Study Procedures Weeks 27 to End of Treatment

Study Period	Treatment Period: Weeks 27 to End of Treatment													
Week/Day	**W27 D1**	**W29 D1**	**W31 D1**	**W33 D1**	**W35 D1**	**W37 D1**	**W39 D1**	**W41 D1**	**W43 D1**	**W45 D1**	**W47 D1**	**W49 D1**	**W51 D1**	**Cont.[h]**
Procedure/Study Day	**D183**	**D197**	**D201**	**D225**	**D239**	**D253**	**D267**	**D281**	**D295**	**D309**	**D323**	**D337**	**D351**	**Cont.**
Tumor and disease assessments														
Disease assessment by RECIST v1.1 CCI (CT or MRI and brain imaging [if metastasis found at baseline or symptomatic]) [a]				X				X				X		W57 D1 (D393) then Q26W [i]
Study procedures and examinations														
Physical examination		X		X		X		X		X		X		Q4W
ECOG performance status				X				X				X		W57 D1 (D393) then Q8W
CCI														
PGIC (Part 3, Cohorts C1A and C1B only)				X				X				X		W57 D1 (D393) then Q8W
Vital signs [b]	X	X	X	X	X	X	X	X	X	X	X	X	X	Q2W
12-lead ECG				X				X				X		
Assessment of AEs/SAEs [f]	X	X	X	X	X	X	X	X	X	X	X	X	X	Q2W
Concomitant medications [f]	X	X	X	X	X	X	X	X	X	X	X	X	X	Q2W
Laboratory tests														
Serum chemistry [f]	X	X	X	X	X	X	X	X	X	X	X	X	X	Q4W
Hematology		X		X		X		X		X		X		Q4W
Coagulation parameters		X		X		X		X		X		X		

Table 9 Schedule of Treatment Period Study Procedures Weeks 27 to End of Treatment

Study Period	Treatment Period: Weeks 27 to End of Treatment													
Week/Day	**W27 D1**	**W29 D1**	**W31 D1**	**W33 D1**	**W35 D1**	**W37 D1**	**W39 D1**	**W41 D1**	**W43 D1**	**W45 D1**	**W47 D1**	**W49 D1**	**W51 D1**	**Cont.[h]**
Procedure/Study Day	**D183**	**D197**	**D201**	**D225**	**D239**	**D253**	**D267**	**D281**	**D295**	**D309**	**D323**	**D337**	**D351**	**Cont.**
Thyroid function tests		X		X		X		X		X		X		Q12W
Urinalysis		X		X		X		X		X		X		Q12W
Urine or serum pregnancy test		X		X		X		X		X		X		Q4W
Study treatment administration														
Durvalumab administration (Q4W dosing schedule; not applicable for Part 3 Cohorts C1B and C2B) [c]		X		X		X		X		X		X		Q4W
Monalizumab administration (Q2W dosing schedule)[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	Q2W
Chemotherapy administration (Part 3 Cohorts A1-CCI only; Q2W dosing schedule) [de]	X	X	X	X	X	X	X	X	X	X	X	X	X	Q2W
Bevacizumab (Part 3, Cohorts A1 CCI only; Q2W dosing schedule) [e]	X	X	X	X	X	X	X	X	X	X	X	X	X	Q2W
Cetuximab (Part 3, Cohorts A2 CCI only; Q1W dosing schedule) [e, f, g]	W27 / W28	W29 / W30	W31 / W32	W33 / W34	W35 / W36	W37 / W38	W39 / W40	W41 / W42	W43 / W44	W45 / W46	W47 / W48	W49 / W50	W51 / W52	Q1W
	X / X	X / X	X / X	X / X	X / X	X / X	X / X	X / X	X / X	X / X	X / X	X / X	X / X	
Cetuximab (Part 3, Cohorts C1A, C1B, C2A, and C2B only; Q2W dosing schedule) [efg]	X	X	X	X	X	X	X	X	X	X	X	X	X	Q2W

AE = adverse event; CT = computed tomography; D = day; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOI = end of infusion; CCI EOT = end of treatment; CCI ; MRI = magnetic resonance imaging; PGIC = Patient Global Impression of Change; Q1W = every week; Q2W = every 2 weeks; Q4W = every 4 weeks; Q8W = every 8 weeks; Q12W = every 12 weeks; Q26W = every 26 weeks; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event; W = week.

Note: On treatment days, evaluations and sample collections should be conducted prior to administration of durvalumab unless otherwise indicated.

[a] If a post-baseline radiological imaging indicates progressive disease, a separate consent must be signed before the subject may continue treatment.

[b] Vital signs (temperature, blood pressure, pulse rate, and respiratory rate) will be measured on durvalumab and monalizumab treatment days according to the following schedule: within 30 minutes prior to the start of durvalumab and monalizumab administration, approximately every 15 minutes during durvalumab and monalizumab administration, at the EOI of durvalumab and monalizumab, and at approximately 30 and 60 minutes post EOI of monalizumab.

[c] On days when durvalumab and monalizumab are administered together, durvalumab will be administered first and the infusion duration will be approximately 60 minutes. The monalizumab infusion will start approximately 15 to 30 minutes post EOI of durvalumab and the infusion will be administered over approximately 60 minutes.

[d] Infusion times for chemotherapy can be per the respective institutional guidelines. The chemotherapy regimen will be administered within 1 hour post end of the monalizumab infusion. The pre-medications for chemotherapy or biologic agent can begin after the 15- to 30-minute observation period post end of the monalizumab infusion.

[e] During the days when the biologic agent and chemotherapy are administered, there should only be a 15- to 30-minute observation period post end of the monalizumab infusion, after which either pre-medication for the biologic agent or chemotherapy, or chemotherapy/biologic agent infusion can start.

[f] The following should be assessed on the days of cetuximab administration: serum chemistry, all AEs, and concomitant medications.

[g] Cohorts A2 CCI : Cetuximab loading dose (400 mg/m^2 IV infusion over approximately 2 hours) will be administered on Day 1, then maintenance dose (250 mg/m^2 IV infusion over approximately 1 hour) Q1W will be administered starting on Day 8. The cetuximab regimen may be changed to 500 mg/m^2 IV infusion for approximately 2 hours Q2W after a subject has completed the 28-day DLT-evaluation period, at the investigator's discretion and in accordance with institutional guidelines.
Cohorts C1A, C1B, C2A, and C2B: Cetuximab (500 mg/m^2 IV infusion over approximately 2 hours) will be administered on Day 1 then 500 mg/m^2 IV infusion for approximately 2 hours Q2W starting on Day 15.

[h] Procedures can be performed as clinically indicated/more frequently if considered necessary by the investigator.

[i] Imaging can be performed more frequently if required by Institutional Guidelines or if clinically indicated.

Table 10 CCI

CCI

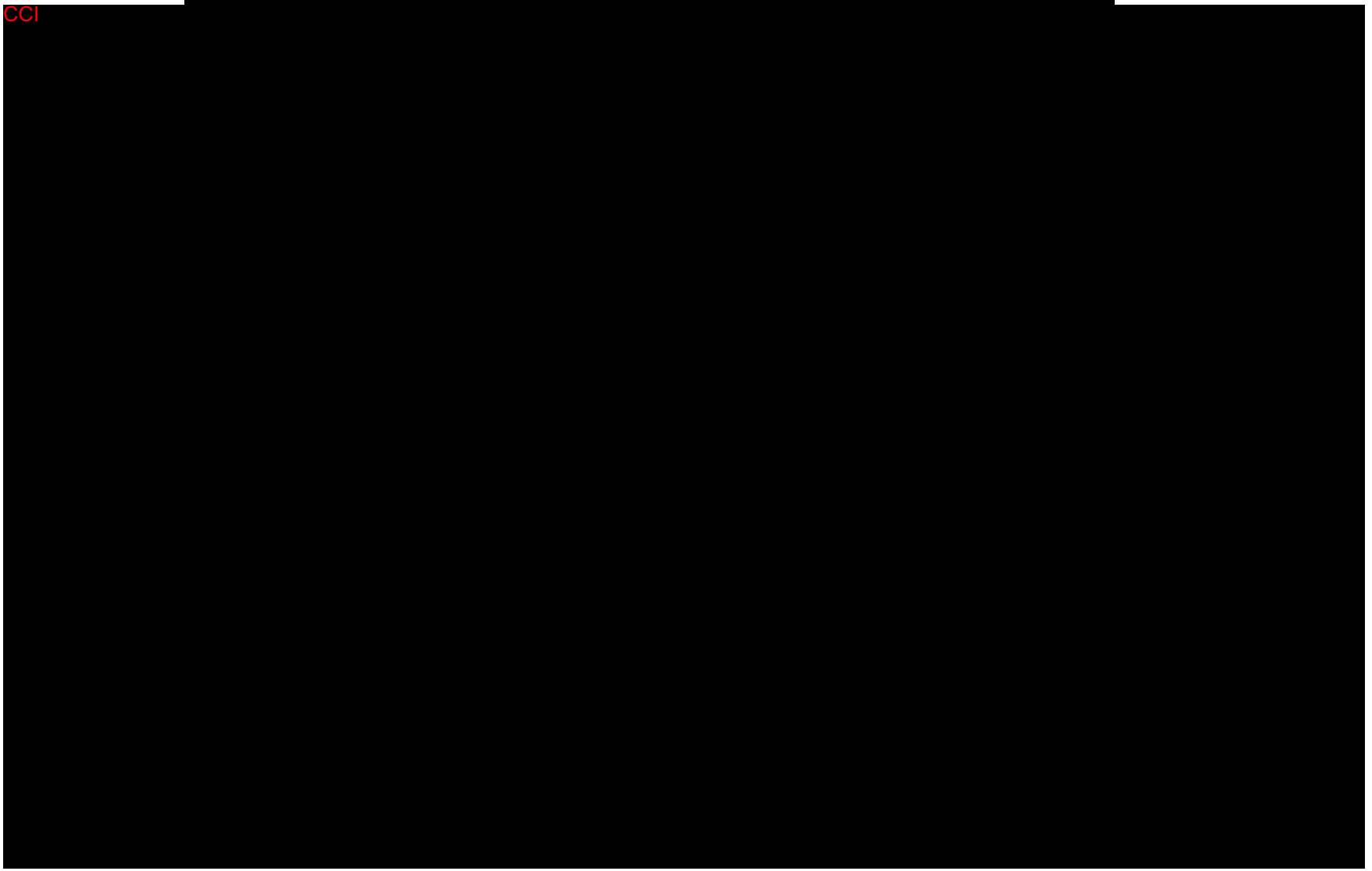

Table 10 CCI

CCI


CCI

Table 11 CCI

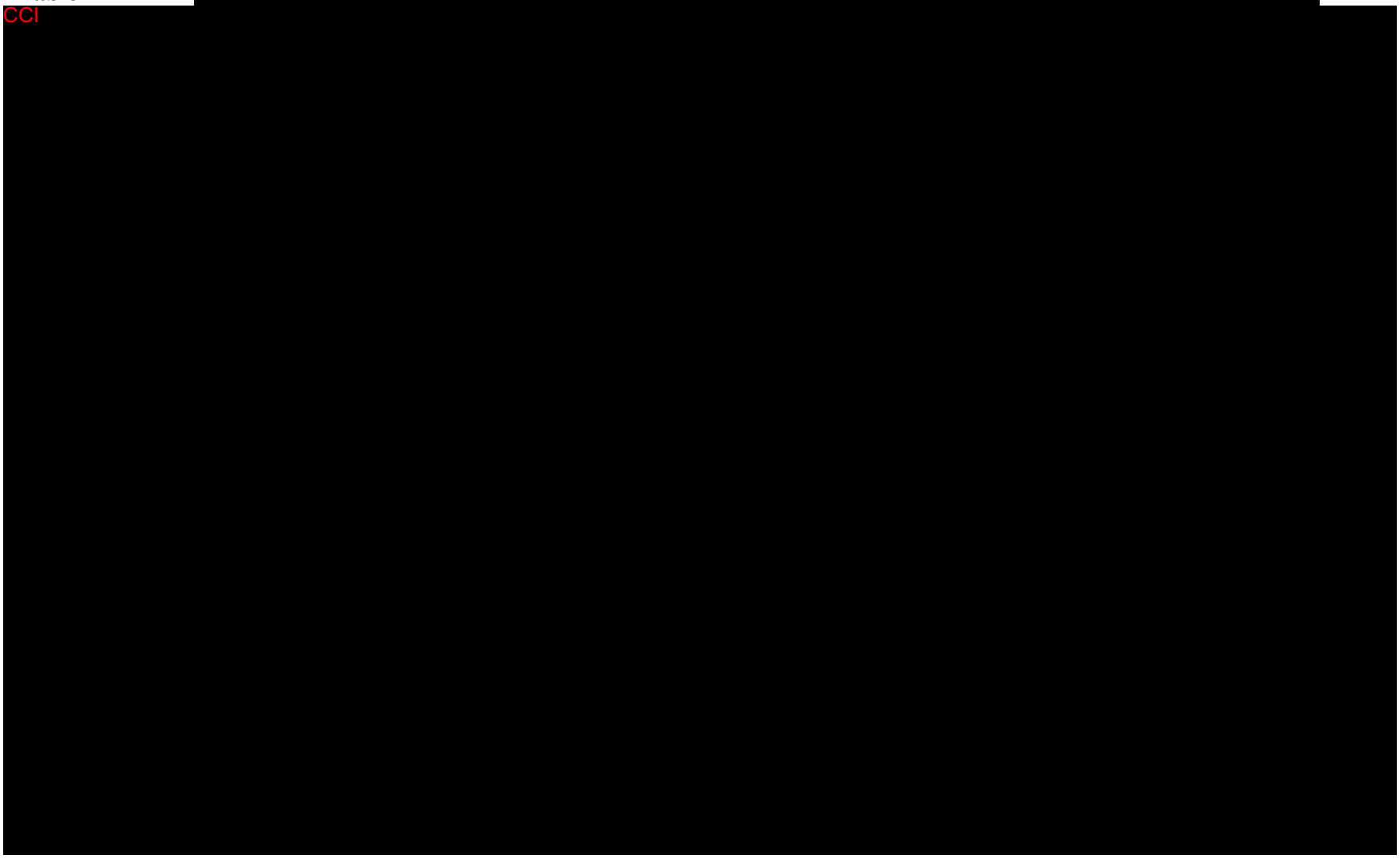

Table 11 CCI

CCI

Table 12 Schedule of Treatment Period Study Procedures for Re-treatment after Relapse – Re-treatment Weeks 1 to 26

Study Period	Re-treatment Period: Re-treatment Weeks 1 to 26														
Week/Day	**Re-baseline [a]**	**RW1 D1**	**RW2 D1**	**RW3 D1**	**RW5 D1**	**RW7 D1**	**RW9 D1**	**RW11 D1**	**RW13 D1**	**RW15 D1**	**RW17 D1**	**RW19 D1**	**RW21 D1**	**RW23 D1**	**RW25 D1**
Written Informed Consent	X														
Enrollment		X													
Tumor and disease assessments															
Disease assessment by RECIST v1.1 CCI (CT or MRI and brain imaging [if metastasis found at baseline or symptomatic]) [b]		X [c]					X				X				X
Study procedures and examinations															
Physical examination	X	X [c]			X		X		X		X		X		X
ECOG performance status	X	X [c]					X				X				X
Vital signs [d]	X	X		X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG [e,]	X	X					X [k]				X [k]				X [k]
Assessment of AEs/SAEs [i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications [i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory tests															
Serum chemistry [i, k]	X	X [c]	X [k]	X [k]	X [k]	X [k]	X [k]	X [k]	X [k]	X [k]	X [k]	X [k]	X [k]	X [k]	X [k]
Hematology [k]	X	X [c]		X [k]	X [k]		X [k]		X [k]		X [k]		X [k]		X [k]
Coagulation parameters	X	X [c]		X [k]	X [k]		X [k]		X [k]		X [k]		X [k]		X [k]
Thyroid function tests	X	X [c]			X [k]		X [k]		X [k]		X [k]		X [k]		X [k]
Urinalysis	X	X [c]			X [k]		X [k]		X [k]		X [k]		X [k]		X [k]

Table 12 Schedule of Treatment Period Study Procedures for Re-treatment after Relapse – Re-treatment Weeks 1 to 26

Study Period	Re-treatment Period: Re-treatment Weeks 1 to 26														
Week/Day	**Re-baseline [a]**	**RW1 D1**	**RW2 D1**	**RW3 D1**	**RW5 D1**	**RW7 D1**	**RW9 D1**	**RW11 D1**	**RW13 D1**	**RW15 D1**	**RW17 D1**	**RW19 D1**	**RW21 D1**	**RW23 D1**	**RW25 D1**
Urine or serum pregnancy test	X	X			X		X		X		X		X		X
Study treatment administration															
Durvalumab administration (Q4W dosing schedule; not applicable for Part 3 Cohorts C1B and C2B) [f]		X			X		X		X		X		X		X
Monalizumab administration (Q2W dosing schedule) [f]		X		X	X	X	X	X	X	X	X	X	X	X	X
Chemotherapy administration (Part 3 Cohorts A1-CCI only; Q2W dosing schedule) [g,h]		X		X	X	X	X	X	X	X	X	X	X	X	X
Bevacizumab (Part 3, Cohorts A1 CCI only; Q2W dosing schedule) [h]		X		X	X	X	X	X	X	X	X	X	X	X	X
Cetuximab (Part 3, Cohorts A2 CCI only; Q1W dosing schedule) [h,i,j]		X	X	RW 3: X; RW 4: X; RW 5: X; RW 6: X; RW 7: X; RW 8: X; RW 9: X; RW 10: X; RW 11: X; RW 12: X; RW 13: X; RW 14: X; RW 15: X; RW 16: X; RW 17: X; RW 18: X; RW 19: X; RW 20: X; RW 21: X; RW 22: X; RW 23: X; RW 24: X; RW 25: X; RW 26: X											
Cetuximab (Part 3, Cohorts C1A, C1B, C2A, and C2B only; Q2W dosing schedule) [h, i, j]		X		X	X	X	X	X	X	X	X	X	X	X	X

AE = adverse event; CT = computed tomography;; D = day; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOI = end of infusion; CCI; MRI = magnetic resonance imaging; Q1W = every week; Q2W = every 2 weeks; Q4W = every 4 weeks; RECIST = Response Evaluation Criteria in Solid Tumors; RW = re-treatment week; SAE = serious adverse event.

Note: On treatment days, evaluations and sample collections should be conducted prior to administration of durvalumab/monalizumab unless otherwise indicated. On nontreatment days, all of the pre-treatment assessments will be performed.

[a] Re-baseline procedures to be conducted within 28 days of initiation of re-treatment

[b] If post-baseline radiological imaging indicates progressive disease, a separate consent must be signed before the subject may continue treatment.

[c] If tests are performed within 3 days prior to re-treatment Week 1, Day 1, they do not need to be repeated. All safety laboratory results must be reviewed by the investigator or physician designee prior to administration of the scheduled dose of investigational product.

[d] Vital signs (temperature, blood pressure, pulse rate, and respiratory rate) will be measured on durvalumab and monalizumab treatment days according to the following schedule: within 30 minutes prior to the start of durvalumab and monalizumab infusion, approximately every 15 minutes during durvalumab and monalizumab infusion, at EOI of durvalumab and monalizumab, and at approximately 30 and 60 minutes post EOI of monalizumab. On Week1, Day 1, an additional 2-hour (± 15 minutes) post monalizumab EOI vital sign measurement will be required, while for Part 3 a 15- to 30-minute observation period would be sufficient prior to infusion of pre-medication for the biologic agent or chemotherapy but vital sign collection should continue approximately every 30 minutes up to 2 hours after Monalizumab infusion. For subsequent doses, the additional 2-hour observation period will not be required unless clinically indicated (eg, subject experiences an infusion-related reaction).

[e] On Week 1, Day 1, ECGs will be obtained in triplicate (all 3 within a 5-minute time period, at least 1 minute apart) within 30 minutes prior to start of durvalumab infusion, within 30 minutes post EOI of monalizumab, and between 2 and 6 hours post EOI of monalizumab. At all other time points, a single ECG will be obtained prior to investigational product(s) administration and as clinically indicated.

[f] On study days when both durvalumab and monalizumab are administered, durvalumab will be administered first and the infusion duration will be approximately 60 minutes. The monalizumab infusion will start approximately 15 to 30 minutes post EOI of durvalumab and the infusion will be administered over approximately 60 minutes.

[g] Infusion times for the biologic agent and chemotherapy should be according to the respective institutional guidelines. The biologic agent or chemotherapy regimen will be administered within 1 hour post end of the monalizumab infusion. The pre-medications for the biologic agent or chemotherapy can be administered after the 15- to 30-minute observation period post end of the monalizumab infusion.

[h] During the days when the biologic agent and chemotherapy are administered, there should only be a 15- to 30-minute observation period post end of the monalizumab infusion, after which either pre-medication for the biologic agent or chemotherapy, or chemotherapy/biologic agent infusion can start.

[i] The following should be assessed on the days of cetuximab administration: serum chemistry, all AEs, and concomitant medications.

[j] Cohorts A2 CCI : Cetuximab loading dose (400 mg/m^2 IV infusion over approximately 2 hours) will be administered on Day 1, then maintenance dose (250 mg/m^2 IV infusion over approximately 1 hour) Q1W will be administered starting on Day 8. The cetuximab regimen may be changed to 500 mg/m^2 IV infusion for approximately 2 hours Q2W after a subject has completed the 28-day DLT-evaluation period, at the investigator's discretion and in accordance with institutional guidelines.
Cohorts C1A, C1B, C2A, and C2B: Cetuximab (500 mg/m^2 IV infusion over approximately 2 hours) will be administered on Day 1 then 500 mg/m^2 IV infusion for approximately 2 hours Q2W starting on Day 15.

[k] Procedures can be performed as clinically indicated/less frequently if considered appropriate by the investigator or if not required by Institutional Guidelines with a minimum at the beginning of each cycle and at the end of treatment.

Table 13 Schedule of Treatment Period Study Procedures for Re-treatment after Relapse – Re-treatment Weeks 27 to End of Treatment

Study Period	Treatment Period: Re-treatment Weeks 27 to End of Treatment													
Week/Day	**RW27 D1**	**RW29 D1**	**RW31 D1**	**RW33 D1**	**RW35 D1**	**RW37 D1**	**RW39 D1**	**RW41 D1**	**RW43 D1**	**RW45 D1**	**RW47 D1**	**RW49 D1**	**RW51 D1**	**Cont.[i]**
Tumor and disease assessments														
Disease assessment by RECIST v1.1 CCI (CT or MRI and brain imaging [if metastasis found at baseline or symptomatic]) [a]				X				X				X		RW57 D1 (D393) then Q26W [i]
Study procedures and examinations														
Physical examination		X		X		X		X		X		X		Q4W
ECOG performance status				X				X				X		RW57 D1 (D393) then Q8W
Vital signs [b]	X	X	X	X	X	X	X	X	X	X	X	X	X	Q2W
12-lead ECG [h]				X				X				X		
Assessment of AEs/SAEs [f]	X	X	X	X	X	X	X	X	X	X	X	X	X	Q2W
Concomitant medications [f]	X	X	X	X	X	X	X	X	X	X	X	X	X	Q2W
Laboratory tests														
Serum chemistry [f, h]	X	X	X	X	X	X	X	X	X	X	X	X	X	Q4W
Hematology [h]		X		X		X		X		X		X		Q4W
Coagulation parameters [h]		X		X		X		X		X		X		
Thyroid function tests [h]		X		X		X		X		X		X		Q12W
Urinalysis [h]		X		X		X		X		X		X		Q12W
Urine or serum pregnancy test		X		X		X		X		X		X		Q4W

Table 13 Schedule of Treatment Period Study Procedures for Re-treatment after Relapse – Re-treatment Weeks 27 to End of Treatment

Study Period	Treatment Period: Re-treatment Weeks 27 to End of Treatment																								
Week/Day	RW27 D1		RW29 D1		RW31 D1		RW33 D1		RW35 D1		RW37 D1		RW39 D1		RW41 D1		RW43 D1		RW45 D1		RW47 D1		RW49 D1		RW51 D1		Cont.[i]
Study treatment administration																											
Durvalumab administration (Q4W dosing schedule; not applicable for Part 3 Cohorts C1B and C2B) [c]			X				X				X				X				X				X				Q4W
Monalizumab administration (Q2W dosing schedule) [c]	X		X		X		X		X		X		X		X		X		X		X		X		X		Q2W
Chemotherapy administration (Part 3 Cohorts A1-CCI only; Q2W dosing schedule) [d, e]	X		X		X		X		X		X		X		X		X		X		X		X		X		Q2W
Bevacizumab (Part 3, Cohorts A1 CCI only; Q2W dosing schedule) [e]	X		X		X		X		X		X		X		X		X		X		X		X		X		Q2W
Cetuximab (Part 3, Cohorts A2 CCI only; Q1W dosing schedule) [e, f, g]	RW 27	RW 28	RW 29	RW 30	RW 31	RW 32	RW 33	RW 34	RW 35	RW 36	RW 37	RW 38	RW 39	RW 40	RW 41	RW 42	RW 43	RW 44	RW 45	RW 46	RW 47	RW 48	RW 49	RW 50	RW 51	RW 52	Q1W
	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Cetuximab (Part 3, Cohorts C1A, C1B, C2A, and C2B only; Q2W dosing schedule) [e, f, g]	X		X		X		X		X		X		X		X		X		X		X		X		X		Q2W

AE = adverse event; CT = computed tomography; D = day; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOI = end of infusion; CCI MRI = magnetic resonance imaging; Q1W = every week; Q2W = every 2 weeks; Q4W = every 4 weeks; Q8W = every 8 weeks; Q12W = every 12 weeks; Q26W = every 26 weeks; RECIST = Response Evaluation Criteria in Solid Tumors; RW = re-treatment week; SAE = serious adverse event.

Note: On treatment days, evaluations and sample collections should be conducted prior to administration of durvalumab unless otherwise indicated.

[a] If a post-baseline radiological imaging indicates progressive disease, a separate consent must be signed before the subject may continue treatment.

[b] Vital signs (temperature, blood pressure, pulse rate, and respiratory rate) will be measured on durvalumab and monalizumab treatment days according to the following schedule: within 30 minutes prior to the start of durvalumab and monalizumab administration, approximately every 15 minutes during durvalumab and monalizumab administration, at the EOI of durvalumab and monalizumab, and at approximately 30 and 60 minutes post EOI of monalizumab.

[c] On days when durvalumab and monalizumab are administered together, durvalumab will be administered first and the infusion duration will be approximately 60 minutes. The monalizumab infusion will start approximately 15 to 30 minutes post EOI of durvalumab and the infusion will be administered over approximately 60 minutes.

[d] Infusion times for chemotherapy can be per the respective institutional guidelines. The chemotherapy regimen will be administered within 1 hour post end of the monalizumab infusion. The pre-medications for chemotherapy or biologic agent can begin after the 15- to 30-minute observation period post end of the monalizumab infusion.

[e] During the days when the biologic agent and chemotherapy are administered, there should only be a 15- to 30-minute observation period post end of the monalizumab infusion, after which either pre-medication for the biologic agent or chemotherapy, or chemotherapy/biologic agent infusion can start.

[f] The following should be assessed on the days of cetuximab administration: serum chemistry, all AEs, and concomitant medications.

[g] Cohorts A2 CCI : Cetuximab loading dose (400 mg/m^2 IV infusion over approximately 2 hours) will be administered on Day 1, then maintenance dose (250 mg/m^2 IV infusion over approximately 1 hour) Q1W will be administered starting on Day 8. The cetuximab regimen may be changed to 500 mg/m^2 IV infusion for approximately 2 hours Q2W after a subject has completed the 28-day DLT-evaluation period, at the investigator's discretion and in accordance with institutional guidelines.
Cohorts C1A, C1B, C2A, and C2B: Cetuximab (500 mg/m^2 IV infusion over approximately 2 hours) will be administered on Day 1 then 500 mg/m^2 IV infusion for approximately 2 hours Q2W starting on Day 15.

[h] Procedures can be performed as clinically indicated/more frequently if considered necessary by the investigator.

[i] Imaging can be performed more frequently if required by Institutional Guidelines or if clinically indicated.

4.2.3 Follow-up Period

Table 14 shows all procedures to be conducted during the end of treatment visit and follow-up period. Subjects will complete the end of treatment visit within 14 days of the last dose of investigational product (either last dose of durvalumab and monalizumab treatment, or last dose of durvalumab, if the subject receives durvalumab monotherapy).

CCI [redacted] All subjects are to complete the end of treatment visit, all follow-up visits, and be contacted for survival status/subsequent anticancer treatment in accordance with Table 14. If a subject discontinues from treatment and moves onto alternative anticancer treatment, the follow-up visits will no longer be required; however, survival follow-up assessments and collection of subsequent anticancer treatment information would be required as indicated in Table 14, unless the subject withdraws consent for further follow-up. Survival follow-up will continue until the End of Study as described in Section 6.3.

Table 14 Schedule of Follow-up Procedures

Study Period	Follow-up Period				
Procedure / Study Day or Month	End of Treatment (EOT) Visit	Day 30 Post Last Dose ± 3 Days	Day 90 Post Last Dose ± 7 Days [h]	Q3M After Day 90 Post Last Dose up to Month 12 Post Last Dose ± 7 Days [h]	Q6M After Month 12 Post Last Dose ± 14 Days [h]
Disease assessments					
Disease assessment by RECIST v1.1CCI (CT or MRI and brain imaging [if metastasis found at baseline or symptomatic]) [a]	X		X	X	X
Optional fresh tumor biopsy (when clinically feasible)	X				
Subsequent anticancer therapy [b]		X	X	X	X
Survival status		X	X	X	X
Study procedures and examinations					
Physical examination	X	X	X		
ECOG performance status			X	X	X
CCI					
PGIC (Part 3, Cohorts C1A and C1B only)	X [c]		X	X [d]	X [d]
Vital signs	X	X	X		
12-lead ECG e	X		X		
Assessment of AEs/SAEs	X	X	X		
Concomitant medications	X	X	X		
Laboratory tests					
Serum chemistry	X	X	X		
Hematology	X	X	X		

Table 14 Schedule of Follow-up Procedures

Study Period	Follow-up Period				
Procedure / Study Day or Month	**End of Treatment (EOT) Visit**	**Day 30 Post Last Dose ± 3 Days**	**Day 90 Post Last Dose ± 7 Days [h]**	**Q3M After Day 90 Post Last Dose up to Month 12 Post Last Dose ± 7 Days [h]**	**Q6M After Month 12 Post Last Dose ± 14 Days [h]**
Coagulation parameters	X	X	X		
Thyroid function tests	X	X	X		
Urinalysis	X	X	X		
Urine pregnancy test	X				
Pharmacokinetics					
Durvalumab PK (not applicable for Part 3 Cohorts C1B and C2B)			X		
Monalizumab PK			X [f]		
Cetuximab PK (Part 3, Cohorts C1A and C1B only)		X			
Other laboratory tests					
CD94/NKG2a receptor occupancy			X		
Durvalumab immunogenicity (not applicable for Part 3 Cohorts C1B and C2B)			X		
Monalizumab immunogenicity			X [f]		
Cetuximab immunogenicity (Part 3, Cohorts C1A and C1B only)		X			
Flow cytometry	X [g]				
CCI					
Circulating soluble factors (plasma)	X [g]	X			
PBMC collection	X [g]				

Table 14 Schedule of Follow-up Procedures

Study Period	Follow-up Period				
Procedure / Study Day or Month	End of Treatment (EOT) Visit	Day 30 Post Last Dose ± 3 Days	Day 90 Post Last Dose ± 7 Days [h]	Q3M After Day 90 Post Last Dose up to Month 12 Post Last Dose ± 7 Days [h]	Q6M After Month 12 Post Last Dose ± 14 Days [h]
CCI					

AE = adverse event; CT = computed tomography; CCI ; DCO = data cut off; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; CCI EOT = End of Treatment; CCI ; MRI = magnetic resonance imaging; CCI PBMC = peripheral blood mononuclear cells; PD = progressive disease; PGIC = Patient Global Impression of Change; PK = pharmacokinetic; Q3M = every 3 months; Q6M = every 6 months; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event.

[a] Disease assessments after the EOT Visit are not required for subjects discontinuing due to PD. The last dose disease assessment is not required if it has been < 28 days since the last disease assessment.

[b] When a subject receives subsequent treatment for disease after study end, follow-up will be terminated, no further scans or assessment is required other than survival information and information about their subsequent anticancer therapy, if subject permits.

CCI

[e] A single ECG will be obtained.

[f] For subjects who continue in the study on durvalumab monotherapy (Section 3.1.1), a sample for monalizumab PK and immunogenicity should be taken 90 days (± 7 days) after the last dose of monalizumab. Further samples for monalizumab PK are not required.

[g] Assessments should be performed if EOT occurs at the scheduled Week 9 visit.

[h] Follow-up assessments at Day 90, Q3M, and Q6M will only occur prior to DCO. After DCO, only follow-up of SAEs, overdoses, and pregnancies will continue until 90 days post last dose.

4.3 Description of Study Procedures

4.3.1 Antitumor Activity

Tumor assessments will be based on RECIST v1.1 (Eisenhauer et al, 2009) and will be performed according to the schedule presented in Section 4.2. All subjects will be followed for survival according to the schedule in Table 14 through the end of the study.

Sites will be required to store electronic copies of all scans, and the sponsor will arrange for centralized storage of all imaging data. All imaging assessments, including unscheduled visit scans, will be collected on an ongoing basis and sent to the sponsor or designee for storage.

The centralized storage of imaging data would be for possible independent centralized third-party blinded review of disease assessments. At the discretion of the sponsor, an independent central review of all scans used in the assessment of tumors by RECIST v1.1 CCI may be conducted. Guidelines for imaging collection and storage will be provided in a separate document. The management of subjects will be based solely upon the results of assessment conducted by the investigator based on RECIST v1.1 per protocol.

All tumor assessments should include the following evaluations: physical examination (with photograph and measurement of skin lesions as applicable), and cross-sectional imaging using CT or magnetic resonance imaging (MRI) scan.

Chest, abdomen, and pelvis CT/MRI scans are required at baseline for all subjects. Pelvic scans are not required post baseline for NSCLC tumor types if tumor lesions were not identified at baseline. For all other tumor types, pelvic scans are required at all post-baseline time points regardless of presence of tumor lesions at baseline.

All subjects must receive a brain CT/MRI scan during the Screening Period. Post-screening, if the subject has CNS metastases, a brain CT/MRI is required at each post-baseline assessment. If a subject becomes neurologically symptomatic during treatment outside of the setting where the subject has known CNS metastases, a brain CT/MRI is required.

The preferred method of systemic 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.

4.3.1.1 Tumor Evaluations

Physical examination

Lesions detected by physical examination will only be considered measurable if superficial, eg, skin nodules and palpable lymph nodes. Documentation by color photography, including ruler, is recommended for estimating the size of skin lesions.

CT scan

- CT scans 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.
- CT scans of hepatic tumors should be collected in the hepatic arterial, portal venous, and delayed phases.

MRI scans

MRI scans are acceptable for measurement of lesions provided that the same anatomical plane is used for serial assessments. If possible, the same imaging device should be used for serial evaluations. MRI scans of hepatic tumors should be performed in the precontrast, hepatic arterial, portal venous and delayed phases.

Measurability of Tumor Lesions

Tumor lesions will be categorized as follows:

- Measurable Lesions - Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:
  - 10 mm by CT scan (irrespective of scanner type) and MRI (no less than double the slice thickness and a minimum of 10 mm)
  - 10 mm caliper measurement by clinical exam (when superficial)
  - Malignant lymph nodes are considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm)
- 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 in short axis). Lesions considered truly nonmeasurable include the following: leptomeningeal disease, ascites, pleural/pericardial effusion, and inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.
- Target Lesions - 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 on the electronic case report form (eCRF; eg, “multiple enlarged pelvic lymph nodes” or “multiple liver metastases”).

4.3.1.2 Evaluation of Response by Response Evaluation Criteria in Solid Tumors

Tumor response will be assessed by RECIST v1.1.

Evaluation of Target Lesions

- Complete Response - 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 - At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.
- Progressive Disease - 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 may be considered progression.)
- Stable Disease - 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 - Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10 mm in short axis).
- Non-complete Response/Non-PD - Persistence of one or more non- target lesion(s) and/or maintenance of tumor marker level above the normal limits.
- Progressive Disease - 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. 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 v1.1. Considering the unique response kinetics that have been observed with immunotherapy, new lesions may not represent true disease progression. In the absence of rapid clinical deterioration, subjects may continue to receive study treatment until confirmed PD (Section 4.1.7).

Evaluation of Overall Response

Confirmation of CR, PR, as well as PD is required by a repeat, consecutive assessment no less than 4 weeks from the date of first documentation. If the next protocol-scheduled scan is due within 2 weeks after the confirmatory scan was obtained, the protocol-scheduled scan does not need to be done. Treatment of subjects may continue between the initial assessment of PD and confirmation of PD (which is not required by RECIST v1.1; see Section 4.1.7). These subjects may continue to receive durvalumab in combination with monalizumab 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 durvalumab in combination with monalizumab and provide a more complete evaluation of durvalumab in combination with monalizumab antitumor activity than would be seen with conventional response criteria.

Table 15 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 Evaluation of Overall Response at a Single Time Point by RECIST V1.1

Target Lesions	Non-target Lesions	New Lesions	Overall Response
Complete response	Complete response	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 [b]	No	Partial response
Stable disease	Non-progressive disease and not evaluable [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 or No	Progressive disease
Any	Progressive disease	Yes or No	Progressive disease
Any	Any	Yes	Progressive disease
No target lesion [a]	Unequivocal progressive disease	Yes or No	Progressive disease
No target lesion [a]	Any	Yes	Progressive disease

RECIST = Response Evaluation Criteria in Solid Tumors.

[a] Defined as no target lesions at baseline.

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

4.3.1.3 CCI

CCI

CCI

CCI

Table 16 CCI

Table 16 CCI

CCI

Table 16 CCI

CCI

4.3.2 Tissue Biopsies

4.3.2.1 Fresh Tissue Biopsies

CCI Subjects enrolled in each dose-escalation cohort while the pharmacodynamics are further investigated, must have at least one lesion amenable to biopsy and must provide a pre-treatment biopsy during the Screening Period, and, if clinically feasible, during Week 9.

The initial 20 subjects in each dose-expansion cohort must have at least 1 lesion amenable to biopsy and must provide a pre-treatment biopsy. If a given dose-expansion cohort is expanded beyond the initial 20 subjects, additional subjects must consent to provide an archival tumor sample from a biopsy collected within 1 year prior to first dose of study drug or must provide

a pre-treatment biopsy during the Screening Period. If clinically feasible, all dose-expansion subjects must provide a biopsy during Week 9.

Subjects in each dose-exploration in CCI CRC cohort must consent to provide an archival tumor sample from a biopsy collected within 1 year prior to the first dose of study treatment or must provide a pre-treatment biopsy during the Screening Period. If clinically feasible, all dose-exploration subjects who provided a fresh biopsy during screening are encouraged to provide an on-treatment biopsy during Week 9.

As noted, fresh tumor biopsies will be obtained on Week 9 Day 1 (± 7 days) if clinically feasible (ie, repeat biopsy does not pose unacceptable medical risk to a subject as determined by the investigator). Additional biopsies may also be performed if clinically indicated (eg, for mixed responses). For subjects requiring serial image-guided core needle tumor biopsy, those biopsies will be performed according to institutional practice.

For fresh tumor biopsies, the tumor lesion should not be used as a RECIST target lesion, unless there are no other tumors suitable for biopsy. If a RECIST target lesion is used for biopsy, the lesion must be ≥ 2 cm in longest diameter. If clinically practical, at each fresh tumor biopsy time point, subjects will undergo 4 core biopsies. The first and third core biopsies will be placed in formalin and processed for formalin-fixed, paraffin-embedded blocks, while the second and fourth core biopsies (if available) will be immediately frozen in liquid nitrogen or equivalent method and then stored at -80°C (-112°F). In exceptional cases, excisional or punch biopsies are permitted and may be substituted for the core biopsies if sufficiently large (4 mm or greater in diameter).

CCI Tumor samples from subjects with endometrial cancer may be tested for mismatch repair deficiency.

Tumor biopsies will be stored at MedImmune or an appropriate vendor selected by MedImmune. Core (tumor) biopsies may be used for correlative studies such as IHC, tumor mutation analysis, CCI proteomic, and immunodiversity. Additional details for sample collection, processing, storage, and shipment will be provided in the Laboratory Manual.

4.3.2.2 Archival Tumor Samples

CCI If a given dose-expansion cohort is expanded beyond the initial 20 subjects, additional subjects must consent to provide an archival tumor sample from a biopsy collected within 1 year prior to first dose of study drug or must provide a pre-treatment biopsy during the Screening Period. Subjects in each dose-exploration in CCI CRC cohort must consent to

provide an archival tumor sample from a biopsy collected within 1 year prior to the first dose of study treatment or must provide a pre-treatment biopsy during the Screening Period. Archival tumor samples must be formalin fixed and embedded in paraffin blocks for IHC CCI [redacted]

4.3.3 Patient Reported Outcomes CCI [redacted]

A patient-reported outcome (PRO), a type of clinical outcome assessment, is an umbrella term referring to all outcomes and symptoms that are directly reported by the patient. PROs have become a significant endpoint when evaluating effectiveness of treatments in cancer clinical studies and regulatory decision making (Kluetz et al, 2018). In addition to assessing OS and other clinical endpoints in oncology clinical trials, it is important to assess the treatment impact on disease-related symptoms, functioning (eg, physical function), and other health-related quality of life (HRQoL) of the subject and thereby aid understanding of how clinical benefit relates to subject well-being and experience, and for making a comprehensive benefit-risk assessment. Moreover, PROs assist in the documentation of what specific symptoms and impacts are most important to subjects and how these relate to clinical outcomes.

To evaluate the impact of study treatment on disease-related symptoms and functioning/HRQoL and overall health status, the following PROs will be administered in this study:

- European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) v3.0
- Patient Global impression of Change (PGIC)

The EORTC QLQ-C30 was selected as the primary PRO for the study because it has good conceptual coverage of disease-related symptoms and impacts in the target patient population. Additionally, the EORTC QLQ-C30 is widely used in cancer clinical trials including CRC trials to characterize treatment effect from the patient perspective (Overman et al, 2017). Secondly, the PGIC is a single-item PRO questionnaire included to assess a subject's perception of his or her overall change in health status since the start of study drug(s) administration.

Subjects will complete the PRO assessments by using an electronic PRO (ePRO) tablet device at the study site. Each site must allocate the responsibility for the administration of the ePRO tablet devices to a specific individual (eg, a research nurse or study coordinator), and, if possible, assign a back-up person to cover for that individual if he or she is absent.

The PRO questionnaires will:

- be completed by the subjects to the best of their ability using an ePRO tablet device at the site.
- take approximately 10 to 15 minutes for each subject to complete the questionnaires, hence the burden to the subject is low.
- be administered according to the schedules in Section 4.2.

The following best practice guidelines should be followed when collecting PRO data using the ePRO tablet device:

- The research nurse or appointed site staff must explain the value and relevance of participation to the subjects and inform them that these questions are being asked to find out from them directly how they feel. This can help motivate subjects to comply with data collection. The research nurse or appointed site staff should also stress that the information is confidential. Therefore, if the subject has any medical problems, he or she should discuss them with the doctor or research nurse separately from the ePRO assessment.
- The research nurse or appointed site staff must train the subject on how to use the ePRO device using the materials and training provided by the ePRO vendor and provide guidance on whom to call if there are problems with the device.
- PRO questionnaires must be completed in private and prior to any other study procedures (following informed consent) and before interaction with study staff, laboratory assessments (eg, blood draw), treatment administration, and before discussion of disease assessments and progress to avoid biasing the subject's responses to the questions.
- The EORTC QLQ-C30 should always be completed before the PGIC questionnaire.
- The research nurse or appointed site staff must remind subjects that there are no right or wrong answers and must avoid introducing bias by not clarifying items.
- The subject should not receive help from relatives, friends, or clinic staff to answer the PRO questionnaires.
- Site staff must not read or complete the PRO questionnaires on behalf of the subject. If the subject is unable to read the questionnaire (eg, is blind or illiterate), that subject should be exempted from completing PRO questionnaires but may still participate in the study. It should be documented that the subject exempted in this regard.
- The study nurse or appointed site staff must administer questionnaires available in the language that the subject speaks and understands. Questions should not be read in an available language and translated into another language for the subject.
- The research nurse or appointed site staff must monitor compliance; minimizing missing data is a key aspect of study success. Compliance must be checked at each study visit.
- If the subject cannot complete the questionnaire, the reason for this should be provided in the ePRO device.
- It is vital that the ePRO reporting is initiated as specified in the study plan to capture the effect of study treatment.

Data from the PRO assessments will not be made available to the treating physicians throughout the study. Patients should be informed of this and counseled through multiple channels that they should contact their healthcare provider for any concerning symptoms they experience any time during their care.

4.3.3.1 European Organization for Research and Treatment of Cancer Quality of Life Questionnaire

The EORTC QLQ-C30 is a self-administered PRO questionnaire and is to be completed by the subject without the assistance of the investigational site personnel. Questions are grouped into:

- 5 multi-item functional scales
  - Physical (5 items)
  - Role (2 items)
  - Cognitive (2 items)
  - Emotional (4 items)
  - Social (2 items)
- 3 multi-item symptom scales
  - Fatigue (3 items)
  - Pain (2 items)
  - Nausea/vomiting (2 items)
- Global measure of health status/quality of life (QoL) scale (2 items).
- 5 single-item measures assessing additional symptoms commonly reported by cancer patients
  - Dyspnea
  - Loss of appetite
  - Insomnia
  - Constipation
  - Diarrhea
- 1 single-item measure concerning the perceived financial impact of the disease

All but 2 questions have 4-point scales: “Not at all,” “A little,” “Quite a bit,” and “Very much.” The 2 questions concerning global health status and QoL have 7-point scales with ratings ranging from “Very poor” to “Excellent.” For each of the 15 domains (9 multiple-item scales and 6 single-item scales), final scores are transformed such that they range from 0 to 100, where higher scores indicate greater functioning, greater HRQoL, or greater level of symptoms (Aaronson et al, 1993). The EORTC QLQ-C30 questionnaire will be scored

according to the established scoring manual by the developer. Refer to Section 10.5.1 for a copy of the questionnaire.

4.3.3.2 Patient Global Impression of Change

The PGIC is a single-item PRO questionnaire included to assess how a subject perceives his or her overall change in health status since the start of study drug(s) administration. Subjects will select a single response from the following seven response options: Very Much Improved; Much Improved; Minimally Improved; No Change; Minimally Worse; Much Worse; and Very Much Worse. The PGIC is useful in characterizing the overall impact of the treatment. Refer to Section 10.5.2 for a copy of the questionnaire.

4.3.4 Medical History, Physical Examination, Electrocardiogram, ECOG Performance Status, Weight, and Vital Signs

4.3.4.1 Medical History and Physical Examination

Physical examinations will be performed according to institutional guidelines on study days noted in Section 4.2, and will include assessments of weight and height (Screening only).

Findings from medical history and physical examination shall be given a baseline grade. Increases in severity of pre-existing conditions during the study will be considered AEs, with resolution occurring when the grade returns to the prestudy grade or below.

4.3.4.2 Electrocardiograms

A single electrocardiogram (ECG) will be obtained during the Screening Period (Section 4.2.1). ECGs will be obtained during the treatment period according to the schedules in Section 4.2.2. On Day 1 of Week 1, ECGs will be obtained in triplicate (all 3 within a 5-minute time period, at least 1 minute apart) as indicated in Table 8 and Table 10. At all other time points during the treatment period, a single ECG will be obtained prior to investigational product(s) administration and as clinically indicated (Section 4.2.2). During the follow-up period, a single ECG will be obtained according to the schedule in Section 4.2.3.

In case of clinically significant ECG abnormalities, including an ECG that demonstrates a QT corrected using Fridericia's formula (QTcF) value > 500 milliseconds, 2 additional 12-lead ECGs should be obtained over a brief period (eg, 30 minutes) to confirm prolongation by a medically-qualified person based on the average of manually over-read QTcF values from 3 individual ECGs.

The same recorder will be used for each subject at each time point, if possible. Date and time settings should be checked at the start of each study day.

Skin preparation should be thorough and electrode positions should be according to standard 12-lead ECG placement.

The investigator may add extra 12-lead ECG safety assessments if there are any abnormal findings or if the investigator considers it is required for any other safety reason.

Paper tracings will be used for local management. In addition, digital copies of ECGs may be held by a central ECG provider and stored for potential independent analysis during or at the end of the study at the sponsor's discretion. The independent review will not replace the local review by the investigator or other medically-qualified designee. Clinical interpretation and management of subjects for all ECGs will be done locally.

4.3.4.3 ECOG Performance Status

Performance status as determined by the ECOG scale (Oken et al, 1982; Table 17) will be recorded in the eCRF per the schedule in Section 4.2.

Table 17 Eastern Cooperative Oncology Group Performance Status

Grade	Performance Status Criteria
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work or office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

4.3.4.4 Vital Signs

Vital signs include temperature, blood pressure (BP), pulse rate, and respiratory rate will be measured on study days noted in Section 4.2.

4.3.5 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. Urinalysis, chemistry and hematology samples will be analyzed at the local site laboratories. The carcinoembryonic antigen and CA-125 samples will be analyzed by a central laboratory. The tumor sample for subjects with endometrial cancer will be sent for microsatellite instability testing by a central laboratory.

Clinical laboratory safety tests including serum pregnancy 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 according to the schedules of procedures in Section 4.2.

Serum Chemistry

• Calcium	• Lipase
• Chloride	• Gamma-glutamyl transferase (GGT)
• Magnesium	• Lactate dehydrogenase (LDH)
• Potassium	• Uric acid
• Sodium	• Creatinine
• Bicarbonate	• Blood urea nitrogen (BUN)
• Aspartate aminotransferase (AST)	• Glucose
• Alanine aminotransferase (ALT)	• Albumin
• Alkaline phosphatase (ALP)	• Total protein
• Total bilirubin	• Triglycerides
• Direct bilirubin	• Cholesterol
• Indirect bilirubin	• Amylase

Notes for serum chemistries:
Tests for AST, ALT, ALP, direct bilirubin, indirect bilirubin, and total bilirubin must be conducted concurrently and assessed concurrently. Direct and indirect bilirubin are needed only if total bilirubin is not within normal range. If the clinical laboratory does not perform both direct bilirubin and indirect bilirubin, it is acceptable to assess one rather than both of these parameters.
Urea is an acceptable alternative if BUN is not routinely tested.

Hematology

• White blood cell count with differential (neutrophils, lymphocytes, monocytes, eosinophils, and basophils)	• Platelet count
• Hemoglobin	

Coagulation

• Prothrombin time	• International normalized ratio (INR)
• Activated partial thromboplastin time (APTT)	• Fibrinogen

Urinalysis

• Color	• Glucose
• Appearance	• Ketones
• Specific gravity	• Blood
• pH	• Bilirubin
• Protein	

Pregnancy Test (females of childbearing potential only)

• Urine human chorionic gonadotropin (hCG)	• Serum beta-hCG

Thyroid Function Tests

• Thyroid-stimulating hormone (TSH)	• Free triiodothyronine (T3)
• Free thyroxine (T4)	

Other Safety Tests

- Hepatitis A antibody, hepatitis B surface antigen, hepatitis C antibody
- Human immunodeficiency virus antibodies
- Additional baseline blood samples will also be collected in a 10-mL red top tube in order to have serum samples collected at baseline for future analysis, which includes, but is not limited to an autoimmune work up (refer to the Laboratory Manual for the processing of this sample).

4.3.6 Pharmacokinetic Evaluation and Methods

Measurement of durvalumab, monalizumab, and cetuximab concentrations in serum will be performed using validated immunoassays.

Details for collection, aliquoting, storage, and shipment of serum samples for PK evaluations are presented in a separate Laboratory Manual.

Blood samples for measurement of durvalumab, monalizumab, and cetuximab concentrations in serum will be collected in samples taken according to the schedules of procedures presented in Section 4.2.

4.3.7 Immunogenicity Evaluation and Methods

Validated electrochemiluminescence assays using a Meso Scale Discovery platform will be used for the determination of ADA to durvalumab, monalizumab, and cetuximab in human serum.

Details for collection, aliquoting, storage, and shipment of serum samples for ADA evaluations are presented in a separate Laboratory Manual.

Blood samples for detection of durvalumab, monalizumab, and cetuximab ADA in serum will be collected in samples obtained according to the schedules of procedures presented in Section 4.2.

4.3.8 CCI

CCI [redacted]

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4.3.9 Estimate of Volume of Blood to be Collected

A total of approximately 56 mL of blood will be collected during the initial screening 28-day period for all screening tests. No more than 77.5 mL of blood will be drawn for any one protocol visit during treatment. During the end of treatment/follow-up period, no more than approximately 44.5 mL of blood will be collected at any one follow-up visit. The total volume to be collected will depend on the length of a subject's participation in the study.

4.4 CCI

CCI

1 CCI

2 CCI

3 CCI

4 CCI

5 CCI

CCI

CCI

4.5 Investigational Products

4.5.1 Identity of Investigational Product(s)

MedImmune will provide the investigator(s) with investigational product (Table 18) using designated distribution centers.

Table 18 Identification of Investigational Products

Investigational Product	Provider	Concentration and Formulation as Supplied
Durvalumab (MEDI4736)	MedImmune	Supplied as a vialed solution containing 500 mg (nominal) durvalumab per vial. The solution contains 50 mg/mL durvalumab, 26 mM histidine/histidine HCl, 275 mM trehalose dihydrate, 0.02% (w/v) polysorbate 80, at pH 6.0 and density of 1.054 g/mL. The label-claim volume is 10 mL.
Monalizumab (IPH2201) CCI [redacted]	MedImmune	CCI [redacted]
Monalizumab (IPH2201) CCI [redacted]	MedImmune	CCI [redacted]
Cetuximab (Part 3 Cohorts C1A and C1B only)	Merck Serono	Supplied as a vialed solution containing 500 mg (nominal) cetuximab per vial. The solution contains 5 mg/mL cetuximab, sodium chloride, glycine, polysorbate 80, citric acid monohydrate, sodium hydroxide, and WFI. The label-claim volume is 100 mL.

HCl = hydrochloride; WFI = water for injection; w/v = weight per volume.

CCI [redacted]

Commercially available 0.9% (weight per volume [w/v]) saline or 5% (w/v) dextrose will be supplied by each site.

4.5.1.1 Investigational Product Inspection

Until Study-defined DCO: Investigational products will be supplied to the site in vials in coded kits. Each kit has a unique number that is printed on all labels within the kit (ie, the outer carton label and the label of each vial within the carton). Select the IXRS-assigned number of vials of investigational product required to prepare the subject's dose.

After Study-defined DCO: IXRS will no longer be utilized after the DCO. Sites will manually order investigational product from AstraZeneca.

Each vial selected for dose preparation should be inspected. If there are any defects noted with the investigational product(s), the investigator and site monitor should be notified immediately. Refer to the Product Complaint section (Section 4.5.1.5) for further instructions.

Durvalumab

Durvalumab will be supplied in 10-mL vials as a sterile, clear to opalescent, colorless to slightly yellow solution, free from visible particles, containing 500 mg (nominal) durvalumab per vial.

CCI [redacted]

CCI [redacted]

CCI [redacted]

Cetuximab

Cetuximab will be supplied in 100-mL vials as a solution containing 500 mg (nominal) cetuximab per vial.

4.5.1.2 Investigational Product Dose Preparation and Administration

Durvalumab

The dose of durvalumab 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 a durvalumab vial to start of administration must not exceed:

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

If the final product is stored at both refrigerated and ambient temperatures, the total time must not exceed 24 hours.

A dose of 1500 mg (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 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 mL (ie, 1500 mg) of durvalumab 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.

If the subject's weight falls to ≤ 30 kg, weight-based dosing at 20 mg/kg will be administered using an IV bag size such that the final concentration is within 1 to 15 mg/mL. Fixed dosing of 1500 mg IV durvalumab Q4W may resume once the subject's weight is > 30 kg.

Standard infusion time is 1 hour; however, if there are interruptions, the total allowed time must not exceed 8 hours at room temperature.

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

The IV line will be flushed according to local practices to ensure the full dose is administered. Infusion time does not include the final flush time.

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

CCI [redacted]

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- CCI
- CCI

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CCI

Cetuximab

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

Cetuximab is being provided by MedImmune only for those subjects enrolled in Cohorts C1A and C1B, as it is being administered off-label at a dose of 500 mg/m^2 in this study. Cetuximab will be sourced locally by study sites for all other cohorts where it is required. The cetuximab infusion, if applicable, will start 15 to 30 minutes after the end of the monalizumab infusion.

NOTE: The concentration of cetuximab provided for this study is 5 mg/mL, 100 mL (500 mg/vial).

The prepared dose of cetuximab will be administered through a 0.2 to 0.22-µm filter via an infusion pump or syringe pump. Since cetuximab is only compatible with sterile sodium

chloride (0.9%) solution for injection, it must not be mixed with other intravenously applied medicinal products. A separate infusion line must be used for the infusion, and the line must be flushed with sterile sodium chloride (0.9%) solution for injection at the end of infusion.

Cetuximab 5 mg/mL is compatible with

- polyethylene, ethyl vinyl acetate or polyvinyl chloride bags
- polyethylene, polyurethane, ethyl vinyl acetate, polyolefin thermoplastic, or polyvinyl chloride infusion sets
- polypropylene syringes for syringe pump

Cetuximab 5 mg/mL is chemically and physically stable for up to 48 hours at 25°C, if the solution is prepared as described hereafter. However, since it does not contain any antimicrobial preservative or bacteriostatic agent, it is intended for immediate use. Care must be taken to ensure aseptic handling when preparing the infusion. Cetuximab 5 mg/mL must be prepared as follows:

For administration with infusion pump (diluted with sterile sodium chloride [0.9%] solution):
Take an infusion bag of adequate size of sterile sodium chloride (0.9%) solution. Calculate the required volume of cetuximab. Remove an adequate volume of the sodium chloride solution from the infusion bag, using an appropriate sterile syringe with a suitable needle. Draw up the required volume of cetuximab from a vial. Transfer the cetuximab into the prepared infusion bag. Repeat this procedure until the calculated volume has been reached. Connect the infusion line and prime it with the diluted cetuximab before starting the infusion. Use a gravity drip or an infusion pump for administration.

For administration with infusion pump (undiluted):
Calculate the required volume of cetuximab. Take an appropriate sterile syringe (minimum 50 mL) and attach a suitable needle. Draw up the required volume of cetuximab from a vial. Transfer the cetuximab into a sterile evacuated container or bag. Repeat this procedure until the calculated volume has been reached. Connect the infusion line and prime it with cetuximab before starting the infusion.

For administration with a syringe pump:
Calculate the required volume of cetuximab. Take an appropriate sterile syringe and attach a suitable needle. Draw up the required volume of cetuximab from a vial. Remove the needle and put the syringe into the syringe pump. Connect the infusion line to the syringe and start the infusion after priming the line with cetuximab or sterile sodium chloride (0.9%) solution. Repeat this procedure until the calculated volume has been infused.

All infusions of 500 mg/m^2 cetuximab should be over approximately 2 hours. Alternatively, subsequent Q1W infusions of 250 mg/m^2 cetuximab may be administered for approximately 1 hour. An infusion rate of 10 mg/min must not be exceeded.

4.5.1.3 Treatment Administration

The first day of dosing is considered Day 1. Dose preparation and administration instructions are provided in Section 4.5.1.2. Durvalumab will be administered first. The monalizumab infusion will start 15 to 30 minutes after the end of the durvalumab infusion. Infusion of the pre-medication for cetuximab may begin following an observation of 15 to 30 minutes post end of monalizumab infusion and will be followed 30 minutes later by the cetuximab infusion, if applicable. 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 an IV infusion.

4.5.1.4 Monitoring of Dose Administration

Subjects will be monitored prior to, during, and after infusion of durvalumab and monalizumab. Monitoring of subjects receiving cetuximab infusion will be performed per label. Vital signs (temperature, BP, pulse rate, and respiratory rate) will be measured according to the schedule in Section 4.2.

As with any mAb, 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.

Primary prophylaxis against IRRs is not permitted during this study in order to avoid obscuring potential safety signals and enable a future assessment regarding whether premedication should be required for all subjects in future studies. Antihistamines or steroids can be administered per label prior to cetuximab infusion. However, at the discretion of the investigator, secondary prophylaxis (ie, prevention of IRR following initial episode) is appropriate and will be permitted with the following recommended regimen: acetaminophen (eg, 650 to 1000 mg) and diphenhydramine (eg, 12.5 to 25 mg) administered approximately 30 minutes prior to the start of infusion of durvalumab and monalizumab. Consideration can be given to premedicating with nonsedating antihistamines (eg, cetirizine) at the discretion of the investigator. At the discretion of the investigator, administration of IV doses of meperidine (eg, 10 to 25 mg) and promethazine (eg, 12.5 to 25 mg) or their equivalents just prior to the start of infusion of durvalumab and monalizumab is permitted. Investigators may administer steroids at their discretion as clinically indicated and per their institution’s guidelines.

Pre-treatment medications may need to be repeated during the course of the infusion; therefore, this should be taken into consideration when deciding on the dosage of the pre-treatment medications.

In the event of a Grade ≤ 2 IRR, the infusion rate of durvalumab or monalizumab may be decreased by 50% or interrupted until resolution of the event (up to 4 hours) and re-initiated at 50% of the initial rate until completion of the infusion. In subjects experiencing Grade ≤ 2 IRR, subsequent infusions may be administered at 50% of the initial rate. If the IRR is Grade 3 or higher in severity, treatment with durvalumab and monalizumab will be discontinued.

4.5.1.5 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.

4.5.2 Additional Study Medications

4.5.2.1 Standard-of-Care Chemotherapy/Biologic Agents

Each standard-of-care agent (mFOLFOX6, CCI , bevacizumab, and cetuximab [excluding Part 3 Cohorts C1A and C1B]) 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 Benson et al, 2018 and Van Cutsem et al, 2016 for treatment guidelines for the management of patients with metastatic CRC. Under certain circumstances when local sourcing is not feasible, a standard-of-care agent will be supplied centrally by AstraZeneca. This will be labeled with local language translated text in accordance with regulatory guidelines.

4.5.3 Labeling

Labels for the investigational product will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines. The label will fulfill GMP Annex 13 requirements for labeling. Label text will be translated into local languages, as required.

4.5.4 Storage

Store durvalumab, monalizumab, and cetuximab at 2°C to 8°C (36°F to 46°F). Do not freeze. All investigational products should be kept in a secure and dry place. Investigational product must 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.

4.6 Treatment Assignment and Blinding

4.6.1 Methods for Assigning Treatment Groups

Part 1, Part 2, and Part 3 (Cohorts A1[redacted])

Each subject who meets the eligibility criteria will be assigned open-label investigational product.

An IXRS will be used for assignment of unblinded investigational product.

The time between enrollment and the initiation of treatment should be as short as possible and no more than 1 business day. 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.

Part 3 (Cohorts C1A, C1B, C2A, and C2B)

An IXRS will be used for randomization to a treatment group and assignment of unblinded investigational product. A subject is considered randomized into the study when the investigator notifies the IXRS that the subject meets eligibility criteria and provides the location of the primary CRC tumor and baseline ALP level of the subject; the IXRS provides the assignment of unblinded investigational product to the subject.

Randomizations of the C1 and C2 cohorts, respectively, will be stratified by the location of the primary tumor and baseline ALP levels.

- The location of the primary tumor is classified as left-sided, right-sided, or transverse.
- Baseline ALP level is classified as high (> 1.0 × ULN) or low (≤1.0 × ULN). Local laboratories can define their own ULN values as long as they do not deviate dramatically from 160 U/L, a typical benchmark ULN value for ALP.

4.6.2 Methods for Ensuring Blinding

This is an open-label study.

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 end of the clinical phase of the study (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, and treatment with antibiotics, growth factors, anti-emetics, anti-diarrheals, and analgesics, and other care as deemed appropriate, and in accordance with their institutional guidelines.

4.7.2 Prohibited Concomitant Medications

Subjects must be instructed not to take any medications, including over-the-counter products, without first consulting with the investigator.

The following medications are considered exclusionary during the study. The sponsor must be notified if a subject receives any of these during the study.

1 Any investigational anticancer therapy.
2 Any concurrent chemotherapy (other than per protocol chemotherapy), radiotherapy (except palliative radiotherapy after consultation with the medical monitor), immunotherapy, biologic or hormonal therapy for cancer treatment. Concurrent use of hormones for noncancer-related conditions (eg, insulin for diabetes and hormone replacement therapy) is acceptable.
3 Immunosuppressive medications including, but not limited to methotrexate, azathioprine, and tumor necrosis factor-α blockers are prohibited. The following are exceptions to this criterion:
   (a) Use of immunosuppressive medications for the management of investigational product-related AEs.
   (b) Systemic corticosteroids at physiologic doses not to exceed 10-12 mg/day of prednisone or its equivalent.
   (c) Use of inhaled, topical, intranasal corticosteroids or local steroid injections (eg, intra-articular injection).
   (d) Temporary uses of corticosteroids for concurrent illnesses (eg, food allergies, CT scan contrast hypersensitivity, etc) or as premedication for subjects receiving chemotherapy are acceptable upon discussion with the medical monitor. **NOTE:** Steroids should not be given concomitantly or used for premedication prior to the immune-oncologic infusions.
4 Live attenuated vaccines during the study through 30 days after the last dose of investigational product.
5 Herbal and natural remedies should be avoided. Drugs with laxative properties for constipation should be used with caution through 90 days after the last day of study treatment.

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.

The analysis populations are defined as following:

Population	Description
Intent-to-treat (ITT) population	The ITT population includes subjects who are randomized. Subjects will be analyzed according to the treatment group they were randomized to. The ITT population is only applicable for the randomized cohorts.
As-treated population	The As-treated population includes subjects who receive any investigational products. Subjects will be analyzed according to the treatment they actually received. The As-treated Population will be used to evaluate baseline characteristics as well as all endpoints for the safety and efficacy profiles.
Response-evaluable population	The Response-evaluable population includes subjects in the As-treated population for the nonrandomized cohorts and in the ITT Population for the randomized cohorts, who have at least 1 post-baseline disease assessment, who died from any cause, or who discontinued due to clinical progressive disease prior to any post-baseline tumor assessment.
DLT-Evaluable population	The DLT-Evaluable Population includes all subjects enrolled in the dose-escalation part who receive at least 1 dose of investigational products and complete the safety follow-up through the DLT-evaluation period or experience any DLT during the DLT-evaluation period.

4.8.2 Sample Size

CCI [redacted] Additional subjects may be required if additional cohorts or treatment schedules are explored.

4.8.2.1 Part 1 (Dose Escalation)

In Part 1 (dose escalation), the number of subjects to be enrolled will depend upon the toxicities observed as the study progresses. With a minimum of 3 subjects and a maximum of 12 subjects enrolled for each dose level, up to 60 subjects may be enrolled following an mTPI design for 5 planned dose levels. An additional 6 subjects per dose level may be enrolled, up to a maximum of 18 subjects per dose level to provide additional PK, pharmacodynamic, and safety data. Additional subjects could be required if other dose levels or alternate treatment schedules are explored.

4.8.2.2 Part 2 (Dose Expansion)

In Part 2 (dose expansion), up to 160 subjects (approximately 40 subjects per tumor-type cohort) may be enrolled to obtain preliminary assessment of safety and antitumor activity in each tumor type. Enrollment may proceed up to approximately 40 subjects in the CRC, ovarian, and endometrial expansion cohorts CCI [redacted]. The observed 0/20 response gives an upper limit of a 1-sided CCI [redacted]% confidence interval (CI) of approximately CCI [redacted]%, which means that a response rate greater than CCI [redacted]% can be ruled out with CCI [redacted]% confidence and hence enrollment would be stopped for lack of desirable response rate. Enrollment may proceed up to approximately 40 subjects in the NSCLC expansion cohort CCI [redacted]

CCI Observing 1/20 response gives an upper limit of a 1-sided CCI% CI of approximately CCI%, which means that a response rate greater than CCI% can be ruled out with CCI% confidence and hence enrollment would be stopped for lack of desirable response rate. CCI Table 19 provides the estimated ORR and its CCI% CI based on the exact probability method for a range of possible responses out of 20 and 40 subjects, respectively.

4.8.2.3 Part 3 (Dose Exploration in CCI CRC)

In Part 3 (dose exploration, Cohorts A1, A2, CCI), the number of subjects to be enrolled will depend upon the toxicities observed as the study progresses. Based on an mTPI dose-escalation design for 2 dose levels, with a minimum of 3 subjects and a maximum of 12 subjects for each dose level, up to 144 evaluable subjects (ie, 2 dose levels across 6 chemotherapy combination cohorts with or without a biologic agent) may be enrolled. An additional 6 subjects per dose level may be enrolled, up to a maximum of 18 subjects per dose level (ie, a total of 216 evaluable subjects in 2 dose levels across 6 chemotherapy combination cohorts with or without a biologic agent) to provide additional PK, pharmacodynamic, and safety data.

In Part 3 (dose exploration, Cohorts C1 and C2), up to 100 subjects/cohort may be enrolled in Cohorts C1A and C1B. A total of 100 subjects would provide a width of < CCI% between the observed ORR and its lower limit of the exact CCI% CI. Up to 40 subjects/cohort may be enrolled in Cohorts C2A and C2B. CCI

Table 19 provides the estimated ORR and its CCI% CI based on the exact probability method for a range of possible responses out of 20 and 40 subjects, respectively.

Table 19 Estimated Objective Response Rate and CCI% Confidence Interval Out of 20 and 40 Subjects, Respectively

Sample Size	Number (%) of Responses						
20	2 (10)	4 (20)	6 (30)	8 (40)	10 (50)	12 (60)	14 (70)
Lower limit of CCI% CI	CCI%	CCI%	CCI%	CCI%	CCI%	CCI%	CCI%
Upper limit of CCI% CI	CCI%	CCI%	CCI%	CCI%	CCI%	CCI%	CCI%
40	4 (10)	8 (20)	12 (30)	16 (40)	20 (50)	24 (60)	28 (70)
Lower limit of CCI% CI	CCI%	CCI%	CCI%	CCI%	CCI%	CCI%	CCI%
Upper limit of CCI% CI	CCI%	CCI%	CCI%	CCI%	CCI%	CCI%	CCI%

CI = confidence interval.

Table 20 provides the estimated ORR and the CCI% CI based on the exact probability method for a range of possible responses out of 100 subjects.

Table 20 Observed Objective Response Rate with CCI% Confidence Interval

Cohort	Number of subjects	Number of Responses	ORR (%)	2-sided exact CCI% CI (%)	
C1 CCI	100	10	10	CCI	CCI
	100	11	11		
	100	15	15		
	100	17	17		
	100	23	23		
	100	25	25		

CI = confidence interval; ORR = objective response rate.

For Cohort C1 CCI CCI CRC, with a total of 100 subjects, there is a CCI% chance of observing at least CCI responses (an ORR of CCI% with the lower limit of the exact CCI% CI excluding a historical response rate of CCI%), if the true ORR is CCI%.

4.8.3 Efficacy

4.8.3.1 Antitumor Activity

The following endpoints will be analyzed. More details will be provided in the statistical analysis plan.

- OR is defined as best overall response of confirmed CR or confirmed PR according to RECIST 1.1 guidelines. 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/or randomization until progression, or the last evaluable disease assessment in the absence of PD prior to the initiation of subsequent anticancer therapy or discontinuation from 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 1 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 CCI% CI and CCI% CI will be estimated using the exact binomial distribution.
- 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 DCO 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 (subjects achieving SD will be included in the disease control rate (DCR) if they maintain SD for ≥ 8 weeks [± 7 days]) based on RECIST 1.1 guidelines. The DCR will be estimated by the proportion of DC, and its CCI% CI and CCI% CI will be estimated using the exact binomial distribution.

- PFS will be measured from the start of treatment/or randomization with investigational product 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 DCO 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.
- The OS will be determined as the time from the start of treatment/or randomization with investigational product until death due to any cause. For subjects who are alive at the time of DCO, 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.
- Efficacy analyses will be based on the As-treated population according to RECIST v1.1 per investigator assessment for the nonrandomized cohorts and on the ITT population according to RECIST v1.1 per investigator assessment for the randomized cohorts. Additional supportive analyses may be conducted in the ITT population according to RECIST v1.1 per Blinded Independent Central Review to inform internal program decisions and/or for potential interactions with regulatory agencies for future development.
- Additional analyses of antitumor activity may be conducted in the Response-evaluable population.

4.8.4 Safety

The MTD will be determined by isotonic regression analysis (Ji et al, 2010) applied to the DLT rates observed during the dose-escalation part. MTD evaluation will be based on the DLT-evaluable population, which includes all subjects enrolled in the dose-escalation part who receive study treatment per protocol and complete the safety follow-up through the DLT-evaluation period or who experience any DLT during the DLT-evaluation period.

4.8.4.1 Analysis of Adverse Events

Summary statistics will be provided for AEs, SAEs, and AE grade, severity, and relationship to study drug, clinical laboratory parameters, physical examinations, vital signs, and ECG. AEs will be graded according to NCI CTCAE v4.03 and described by system organ class using the Medical Dictionary for Regulatory Activities PT. At each level of subject summarization, a subject will be counted once using the highest grade and level of causality if one or more occurrences of the same system organ class/PT is reported.

4.8.4.2 Analysis of Clinical Laboratory Parameters

Laboratory abnormalities with toxicity grades according to the NCI CTCAE v4.03 will be derived and summarized. Frequencies of maximum observed grade will be presented for each laboratory parameter as well as the rates of subjects with Grade 3-4 toxicities. A shift table, presenting the 2-way frequency tabulation for baseline and post-baseline grade at scheduled

time of evaluation as well as the worst post-baseline grade, will be provided for clinical laboratory tests.

4.8.4.3 Analysis of Vital Signs

Descriptive statistics will be provided for the vital signs measurements 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.

4.8.4.4 Analysis of Electrocardiograms

ECG parameters (PR, QRS, QT, QTc corrected according to Bazett's formula [QTcB], and QTcF) will be summarized using descriptive statistics for actual values and for changes from baseline by treatment arm by scheduled time of evaluation including end of treatment visit as well as for the maximum post-baseline values. The QTcF will be considered as the primary correction method to assess subject cardiac safety.

The notable ECG interval values in maximum absolute QTcF and QTcB intervals (new > 450 milliseconds, new > 480 milliseconds, new > 500 milliseconds) and the maximum absolute uncorrected QT intervals (new > 500 milliseconds) over all post-baseline evaluations, as well as in QTcF and QTcB maximum changes from baseline (> 30 and > 60 milliseconds) over all post-baseline evaluations will be summarized by treatment. "New" means the category of the QTc abnormality was not present at baseline and became present at least one post-baseline ECG assessment.

4.8.4.5 Analysis of ECOG Performance Status

Descriptive statistics will be provided for the ECOG performance status assessments and changes from baseline by scheduled time of evaluation and by treatment arm including end of treatment visit.

4.8.5 Analysis of Patient Reported Outcomes (Part 3, Cohort C1 only)

4.8.5.1 Analysis of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire

The EORTC QLQ C-30 is described in Section 4.3.3.1 and a sample questionnaire is provided in Section 10.5.1. Domain, subscale, and individual item scores will be summarized descriptively at each time point. At each post-baseline assessment, the change in symptoms/ functioning/global health status score from baseline will be calculated for each domain, subscale, and item, and summarized using descriptive statistics. Additional exploratory analysis will be conducted to assess time to deterioration and response status for domains, subscales and individual items as measured by the EORTC QLQ-C30. Further details will be provided in the statistical analysis plan.

EORTC Scoring and Handling Missing Data: The EORTC QLQ-C30 consists of 30 questions that can be combined to produce 5 functional scales (physical, role, cognitive,

emotional, and social), 3 symptom scales (fatigue, pain, and nausea/vomiting), and health status/QoL scale. The EORTC QLQ-C30 will be scored according to the EORTC QLQ-C30 Scoring Manual by the developer (Fayers et al, 2001). An outcome variable consisting of a score from 0 to 100 will be derived for each of the symptom scales, each of the functional scales, and the global measure of health status scale in the EORTC QLQ-C30 according to the EORTC QLQ-C30 Scoring Manual. Higher scores on the global measure of health status and functional scales indicate better health status/function, but higher scores on symptom scales represent greater symptom severity. For each subscale, if < 50% of the subscale items are missing, then the subscale score will be divided by the number of non-missing items and multiplied by the total number of items on the subscales (Fayers et al, 2001). If at least 50% of the items are missing, then that subscale will be treated as missing. Missing single items are treated as missing. The reason for any missing questionnaire will be identified and recorded.

Compliance rate summarizing PRO completion at each visit will be tabulated.

4.8.5.2 Analysis of Patient Global Impression of Change

The PGIC questionnaire is described in Section 4.3.3.2 and a sample questionnaire is provided in Section 10.5.2. Response on the PGIC will be summarized descriptively as number of subjects and corresponding percentages for each category in the questionnaire at each visit.

Compliance rate summarizing PRO completion at each visit will be tabulated.

4.8.6 Analysis of Immunogenicity

Only subjects who receive at least 1 dose of durvalumab and/or monalizumab, and provide at least 1 post-treatment sample, will be evaluated. The immunogenic potential of durvalumab and monalizumab will be assessed by summarizing the number and percentage of subjects who develop detectable ADAs. The immunogenic potential of cetuximab will also be assessed for Part 3, Cohorts C1A and C1B 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 evaluating neutralizing capacity of ADAs in the future.

4.8.7 Analysis of Pharmacokinetics

Only subjects who receive at least 1 dose of durvalumab and/or monalizumab, and provide at least 1 post-treatment sample, will be evaluated. Individual durvalumab and monalizumab concentrations will be tabulated by dose cohort along with descriptive statistics. Individual cetuximab concentrations will also be summarized for Part 3, Cohorts C1A and C1B.

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.

4.8.8 Analysis of Pharmacodynamic Biomarkers

Analysis of pharmacodynamics biomarkers will be descriptive. CCI [redacted] Changes in numbers and percentages of T cells and NK cells will be assessed in peripheral blood as well as the number and percentage of NK and T cells expressing activation and proliferation markers.

Summaries and analyses for exploratory pharmacodynamics/biomarkers may be reported outside the clinical study report (CSR) in a separate report.

4.8.9 Interim Analysis

For Part 3, Cohorts C1A, C1B, C2A, and C2B, an interim futility analysis will be performed after 20 subjects in each cohort are response-evaluable (including subjects who received the same dose during the DLT evaluation). Enrollment will stop CCI [redacted]. The observed 1/20 response gives an upper limit of a 1-sided CCI [redacted]% CI of approximately CCI [redacted]%, which means that a response rate greater than CCI [redacted]% can be ruled out with CCI [redacted]% confidence and hence enrollment would be stopped for lack of desirable response rate.

For Part 3, Cohorts C1A and C1B, a subsequent interim futility analysis will be performed after 40 subjects in each cohort are response-evaluable (including subjects who received the same dose during the DLT evaluation). Enrollment will stop CCI [redacted]. The observed 3/40 response gives an upper limit of a 1-sided CCI [redacted]% CI of approximately CCI [redacted]%, which means that a response rate greater than CCI [redacted]% can be ruled out with CCI [redacted]% confidence and hence enrollment would be stopped for lack of desirable response rate.

5 ASSESSMENT OF SAFETY

5.1 Definition of Adverse Events

The ICH Guideline for GCP E6(R1) defines an AE as: Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

An AE includes, but is not limited to any clinically significant worsening of a subject's pre-existing condition. 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 count increased). Abnormal laboratory values that are not, in the investigator's opinion, medically significant and do not require intervention should not be reported as AEs.

Adverse events may be treatment emergent (ie, occurring after initial receipt of investigational product) or non-treatment emergent. A non-treatment-emergent AE is any new sign or symptom, disease, or other untoward medical event that begins after written informed consent has been obtained but before the subject has received investigational product.

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.

Adverse Events Associated with 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. Events that are unequivocally due to disease progression should not be reported as an AE during the study. Death clearly resulting from disease progression should not be reported as an SAE (see reporting guidelines in Section 5.4.3).

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

5.2 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 collecting additional information by the investigator to the sponsor. 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.

All AESIs should be recorded in the eCRF within 24 hours. In addition, AESIs that are also SAEs should be reported to MedImmune Patient Safety within 24 hours. Instructions to the site on how to record (in the eCRF) and report SAEs is provided in Section 5.4 and Section 5.5, respectively. The AESIs for this study are defined below.

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/irAE 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/irAE diagnosis. Appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the imAE/irAE.

If the investigator has any questions in regards to an AE being an imAE/irAE, the investigator should promptly contact the Study Physician.

AESIs observed with durvalumab include:

- Diarrhea/colitis and intestinal perforation
- Pneumonitis/interstitial lung disease
- Hepatitis/transaminase increases
- Endocrinopathies (ie, events of hypophysitis, hypopituitarism, adrenal insufficiency, hyper- and hypothyroidism, and type I diabetes mellitus)

- Rash/dermatitis
- Nephritis/blood creatinine increases
- Pancreatitis/serum lipase and amylase increases
- Myocarditis
- Myositis/polymyositis
- Neuropathy/neuromuscular toxicity (eg, Guillain-Barre 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 and rheumatological events.

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

Further information on these risks (eg, presenting symptoms) can be found in the current version of the durvalumab Investigator's Brochure. More specific guidelines for their evaluation and treatment are described in detail Section 3.1.3.

5.4 Recording of Adverse Events

Adverse events will be recorded on the eCRF using a recognized medical term or diagnosis that accurately reflects the event. Adverse events 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 the sponsor (Section 5.5). Refer to 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 in the SAE Report Form.

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. Infusion-related reactions are commonly observed during or shortly after the first time 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 durvalumab and monalizumab, 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 in order 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.

5.4.1 Time Period for Collection of Adverse Events

AEs and SAEs will be collected from time of signature of informed consent, throughout the treatment period and including the follow-up period until 90 days after last treatment.

5.4.2 Follow-up of Unresolved Adverse Events

Any AEs that are unresolved at the subject's last visit 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. Updates regarding SAEs that were ongoing at the time of the subject's completion of study participation should be submitted to the study representative using a paper SAE follow-up form.

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 in the 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 the appropriate sponsor representative(s) or designee within the usual timeframes.

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 towards 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 (SUSAR) 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 Investigator's Brochure and/or will notify the IRB/IEC, if appropriate according to local requirements.

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

If any SAE occurs during the course of the study, the investigator other site personnel will inform the appropriate sponsor representative(s) within one day; ie, immediately but no later than 24 hours of when he or she becomes aware of it. The designated sponsor representative works with the investigator to ensure that all the necessary information is provided to the sponsor 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 will 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 of when he or she becomes aware of it.

Once the investigator 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 the SAE to the appropriate sponsor representative by telephone. The sponsor representative will advise the investigator/study site personnel how to proceed.

5.6 Other Events Requiring Immediate Reporting

5.6.1 Overdose

An overdose in this study is defined as a subject receiving a dose of investigational product that is greater than the dose that was intended to be given,

- 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 with a MedImmune investigational product occurs during the course of the study, then the investigator or other site personnel inform appropriate sponsor representatives immediately, or no later than 24 hours of when he or she becomes aware of it.

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.

5.6.2 Potential Hy's Law and Hy's Law

Cases where a subject shows elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT ≥ 3 × ULN together with TBL ≥ 2 × ULN will need to be reported as SAEs. Refer to Section 10.4 for further instruction on cases of increases in liver biochemistry and evaluation of Hy's Law.

5.6.3 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to the sponsor.

5.6.3.1 Maternal Exposure

Women of childbearing potential in this study who are sexually active with a nonsterilized male partner are required to use two forms of contraception as described in the inclusion criteria. Pregnancy should be avoided for at least 6 months after receiving investigational product or until the subject completes participation in the study, whichever is longer. 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 for 2 weeks post-birth and documented even if the subject was discontinued from the study.

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

The designated sponsor representative works with the investigator to ensure that all relevant information is provided within 1 or 5 calendar days for SAEs (Section 5.5) and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

The outcome of any conception occurring from the date of the first investigational product administration until 12 weeks after the last investigational product administration should be

followed up and documented. Information on the pregnancy of a subject's partner must be obtained directly from the subject's partner. Therefore, prior to obtaining information about the pregnancy, the investigator must obtain the consent of the subject's partner.

5.6.3.2 Paternal Exposure

Nonsterilized male study subjects who are sexually active with a female partner of childbearing potential must use condoms and a spermicide from Day 1 through the end of the study follow-up period.

Male subjects should refrain from fathering a child or donating sperm during the study and for 12 weeks following the last dose.

Pregnancy of the subject's partner is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) should if possible be followed up for 2 weeks post-birth and documented.

5.7 Safety Management During the Study

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

A MedImmune safety review committee provides safety surveillance, guidance, and oversight for all clinical development studies in which MedImmune has sponsor accountabilities. Committee members include, but are not limited to, appropriate representatives from Patient Safety, Clinical Development, and Regulatory Affairs. The committee reviews protocol-specific safety data and assesses changes to the benefit/risk profile of the molecule during early phases of development. Based on review of safety data, the committee may suspend enrollment or subject dosing in clinical studies, request modification of study documents, or take other actions as deemed necessary.

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 CSP 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 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 CSP and the Clinical Study Agreement, the terms of CSP 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

The study started in March 2016 and the last subject was enrolled in March 2020. The DCO in support of final database lock will occur approximately 19 months after the last subject recruited who was administered the first dose of investigational product.

Data analysis will be performed, and a CSR will be written based on this final database lock.

Any subjects still receiving investigational product at the time of this DCO will be able to continue to receive investigational product within the current study, as long as, in the investigator's opinion, the subject is deriving clinical benefit and has not fulfilled any discontinuation criteria. This continued treatment period may be managed by the study team or the sponsor's Post Analysis and Reporting Team [PART] program

During this continued treatment period:

- Assessments will revert to the standard of care for each individual site.
- Data will not be entered into the clinical study database after the DCO date.
- Subjects will continue to be monitored for SAEs, overdoses, and pregnancies only, and these will be reported up to 90 days after the last dose of investigational product using paper-based SAE reporting. SAE data will be entered into the sponsor's global safety database.
- The IXRS system will be closed at DCO, and sites will manually order investigational product.
- The investigational product accountability information must still be collected until all subjects have completed treatment, and investigational product dispensation and reconciliation will be handled by the study site at each subject's visit.
- After the DCO for the CSR and database lock is completed, individual study sites will be closed once their final subject completes the 90-day follow-up visit.

6.4 Data Management

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

A Web Based Data Capture system will be used for data collection and query handling. The investigator will ensure that data are recorded on the eCRFs as specified in the study protocol and in accordance with the 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.

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 CSP 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 a TPV.

7 ETHICAL AND REGULATORY REQUIREMENTS

7.1 Subject Data Protection

The ICF will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation. Data (clinical and biological samples) from this study may be used and may be combined with results from other studies for additional scientific-related research, based on agreement from the subject as defined in the ICF.

MedImmune will not provide individual genotype results to subjects, any insurance company, any employer, their family members, general physician or any other third party, unless required to do so by law.

Extra precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the subject. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a subject. For example, in the case of a medical emergency, a MedImmune Medical Monitor or an investigator might know a subject's identity and also have access to his or her genetic data. Also Regulatory authorities

may require access to the relevant files, though the subject's medical information and the genetic files would remain physically separate.

7.2 Ethics and Regulatory Review

An IRB/IEC should 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 investigator will ensure the distribution of these documents to the applicable IRB/IEC, and to the study site staff.

The opinion of the IRB/IEC should be given in writing. The investigator should submit the written approval to MedImmune before enrollment of any subject into the study.

The IRB/IEC should approve all advertising used to recruit subjects for the study.

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

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

Before enrollment of any subject into the study, the final study protocol, including the final version of the ICF, is approved by the national regulatory authority or a notification to the national regulatory authority is done, according to local regulations.

MedImmune will handle the distribution of any of these documents to the national regulatory authorities.

MedImmune will provide Regulatory Authorities, IRB/IEC and Principal Investigators with safety updates/reports according to local requirements, including suspected unexpected serious adverse reactions, where relevant.

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

7.3 Informed Consent

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.

If there are any substantial changes to the study protocol, then these changes will be documented in a study protocol amendment and where required in a new version of the study protocol.

The amendment is to be approved by the relevant IRB/IEC and if applicable, also the national regulatory authority approval, before implementation. Local requirements are to be followed for revised protocols.

MedImmune will distribute any subsequent amendments and new versions of the protocol to each Principal Investigator(s). For distribution to IRB/IEC see Section 7.2.

If a protocol amendment requires a change to a site's ICF, MedImmune and the site's IRB/IEC are to approve the revised ICF before the revised form is used.

If local regulations require, any administrative change 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

All changes described below have been incorporated into the current version of the protocol.

9.1 Protocol Amendment 6

Text revisions resulting from this amendment are incorporated in the body of Protocol Amendment 6. The primary reasons for Amendment 6 were to: describe the continued treatment and monitoring of subjects still on study treatment at the time of the final data cut off (DCO), add study mitigation language to provide sites with measures that may be implemented if a participant is not able to visit a study site to ensure that the clinical trial can continue while minimizing risk to the participant, maintaining compliance with Good Clinical Practice (GCP), and minimizing risks to the study integrity; CCI [redacted]

Major changes to the protocol are summarized below:

1 Section 3.1.3 (Management of Study Medication Related Toxicities): Section 3.1.3 was updated to remove the link to the TMG portal, which has been decommissioned.

2 Section 3.3 (Study Mitigation During Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis); Section 10.6 (Changes Related to Mitigation of Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis): The impact of COVID-19 has highlighted the risk to continuity of clinical trials during times of study disruption, whether by civil crisis, natural disaster, or public health crisis. These sections summarize and detail, respectively, the measures that may be implemented if a participant is not able to visit a study site to ensure that the clinical trial can continue while minimizing risk to the participant, maintaining compliance with GCP, and minimizing risks to study integrity. These changes will only be initiated at a time of study disruption.

3 CCI [redacted]

4 Section 6.3 (Study Timetable and End of Study): This section was updated to define study milestones and to confirm procedures for DCO, database lock, and clinical study report production. This change was made to provide additional clarity.

Minor changes to the protocol are summarized below:

5 Updated change to front page to reflect change in personnel.

6 Updated Synopsis to align with changes in the body of the protocol.

7 Section 2.2 (Table 2: Secondary Objectives and Associated Endpoints); Section 2.3 (Table 3: Exploratory Objectives and Associated Endpoints): CCI [redacted]

8 Section 4.1.1 (Number of Subjects): Table 5 was updated to include the most current enrollment numbers.

9 Section 4.5.1 (Identity of Investigational Products): Table 18 was updated to provide additional clarity on the durvalumab and monalizumab investigational product provided in this study.

10 Section 4.5.1.1 (Investigational Product Inspection); Section 6.3 (Study Timetable and End of Study): These sections were updated to confirm that the use of interactive voice/web response system (IXRS) will not continue after the time of DCO. Details of how to obtain supplies of investigational product once IXRS is decommissioned were added to Section 4.5.1.1. In addition, details on the presentation of monalizumab according to vial size were updated to provide additional clarity.

11 Section 4.5.1.2 (Dose Calculation) was removed as not required since fixed doses are used, and all relevant information is provided in the following section.

12 Section 4.5.1.2, formerly Section 4.5.1.3 (Investigational Product Dose Preparation and Administration): This section was updated to provide separate instructions for the different vial sizes of monalizumab to provide additional clarity and to clarify storage conditions.

13 Throughout, correction of grammatical and typographical errors.

9.2 Protocol Amendment 5

Text revisions resulting from this amendment are incorporated in the body of Protocol Amendment 5. The primary reasons for Amendment 5 were to remove the toxicity modification guidelines to a separate standalone document according to updated Sponsor guideline, to align with other Sponsor guidelines, to allow re-treatment following relapse, and to add Schedules of Procedures for re-treatment.

Major changes to the protocol are summarized below.

1 Section 1.4.2 (Durvalumab Clinical Experience); Section 1.4.3 (Safety and Efficacy Results from the Current Ongoing Study); Section 1.6.2 (Summary of Risks); Section 4.1.6 (Discontinuation of Investigational Product); Section 4.2.2 (Treatment Period); Section 5.3 (Definition of Adverse Events of Special Interest): The location of information detailing management of study medication-related toxicities has been removed from these sections and reference made to Section 3.1.3 for details.

2 Section 1.4.3 (Safety and Efficacy Results from the Current Ongoing Study); Section 1.6.2 (Summary of Risks); Section 3.1.3 (Management of Study Medication Related Toxicities); Section 4.1.6 (Discontinuation of Investigational Product); Section 4.2.2

(Treatment Period): Information detailing management of study medication-related toxicities for monalizumab has been removed from these sections and reference made to Section 3.1.3 for details.

3 Section 1.6.2 (Summary of Risks): Information detailing risks for monalizumab has been updated to include the identified risk of infusion related reactions and a theoretical risk of immune-mediated events (including, but not limited to pancreatic, hepatic, renal, lung, skin, musculoskeletal, and endocrine disorders). Other potential risks for monalizumab are related to hypersensitivity, including anaphylaxis and serious allergic reactions, and immune complex disease.

4 Section 3.1.3 (Management of Study Medication Related Toxicities); Section 10.2 (Management of Study Medication Related Toxicities): Section 10.2 was removed, and Section 3.1.3 was updated to confirm that study medication-related toxicities for durvalumab is to be maintained within the Site Master File. In addition, a version of the current Toxicity Management Guidelines is available through the following link: https://tmg.azirae.com. Details for management of study medication-related toxicities for monalizumab and marketed drugs were added to Section 3.1.3.

5 Section 3.1.2 (Treatment Regimen); Section 4.1.8 (Treatment on Relapse); Section 4.2.2 (Treatment Period): Subjects who progress during the first 52 weeks after the last dose of study treatment will be eligible for re-treatment with the protocol-defined experimental medicines (same dose and schedule) as at the time of discontinuation, after consultation and in agreement with the Sponsor. The Investigator may consider standard-of-care chemotherapy backbone with the experimental agent(s) as appropriate for the subject at time of re-treatment. The following criteria must not apply: Meets any of the investigational product discontinuation criteria; ECOG performance status > 2; Rapid PD or threat to vital organs/critical anatomical sites (eg, spinal cord compression) requiring urgent alternative medical intervention; Subject has had severe/refractory irAE or development of new autoimmune condition that, in the investigator's opinion, poses undue risk to the subject. This option for re-treatment will be limited to one occasion and will apply only if the subject has not received any other anticancer treatment for their disease following study-treatment discontinuation. The study protocol must still be active, ie, the final database lock has not yet occurred. The subject will need to follow the schedule of study procedures as described in Section 4.2.2. Subjects must also be re-consented.

6 Section 3.1.2.3 (Part 3: Dose Exploration in CCI CRC), Section 4.2.2 (Treatment Period; Table 8 Footnote n and Table 9 Footnote g), and Section 4.5.1.3 (Investigational Product Dose Preparation and Administration): The infusion time for all infusions of cetuximab at a dose of 500 mg/m^2 was updated to approximately 2 hours in line with prescribing information.

7 Section 4.1.2 (Inclusion Criteria; Table 6: Highly Effective Methods of Contraception): Intravaginal devices was added as an effective method of contraceptive and clarification of intrauterine devices was made in line with updated Sponsor guidance.

8 Section 4.2.2 (Treatment Period - Table 9 Schedule of Treatment Period Procedures Weeks 27 to End of Treatment): To reduce the burden on the study subjects, from week 57 onwards, the number of assessments for disease assessment (from Q8W to Q26W), 12-lead ECG (not required unless clinically indicated), serum chemistry (from Q2W to

Q4W), coagulation parameters (not required unless clinically indicated), and thyroid function tests (from Q4W to Q12W) have been reduced in number or ceased after consideration of data obtained to date. The statement that procedures can be performed as clinically indicated/more frequently if considered necessary by the Investigator or if required by Institutional Guidelines was added to allow for additional assessments if deemed necessary.

9 Section 4.8.1 (General Considerations): The definition of the ITT population was amended to include any subject who had been randomized, according to new Sponsor guidelines.

10 Section 4.8.3.1 (Antitumor Activity): The time window for the scans for disease activity was amended from ± 3 days to ± 7 days in line with the time provided in Table 14 (Schedule of Follow-up Assessments) and RECIST 1.1 guidelines.

11 Section 5.1 (Definition of Adverse Events; Adverse Events Associated with Disease Progression): The clarification that events which are unequivocally due to disease progression should not be reported as AEs during the study was added to prevent overreporting of AEs.

12 Section 5.5 (Reporting of Serious Adverse Events): This section was updated to ensure that country-specific regulatory reporting requirements for SAEs are met, according to updated Sponsor guidelines.

13 Section 5.6.3.1 (Maternal Exposure) and Section 5.6.3.2 (Paternal Exposure): The timeframe for follow up of the outcome of pregnancies of 2 weeks post-birth was added for clarification.

Minor changes to the protocol are summarized below.

14 Updated synopsis to align with changes in the body of the protocol.

15 Throughout the document the abbreviation irAEs for immune-related adverse events has been expanded to include imAE (immune -modulated AEs) and both terms are presented together as imAEs/irAEs since these will be considered in the same way.

16 Title Page; Section 10.1 (Signatures): The name of the Sponsor signatory and medical monitor was updated to reflect the change in personnel.

17 Section 1.4.1 (Monalizumab Clinical Experience): Data cut-off date was reiterated within the section for clarification.

18 Section 3.1.2.3 CCI [redacted]; The subject description for Cohorts C1 and C2 was amended to include second-line subjects in line with the description provided below that patients had to have failed at least 1 but no more than 2 prior lines of therapy. This description was changed from a note to a footnote letter.

19 Section 3.1.2.3 (Part 3: Dose Exploration in CCI [redacted] CRC); Section 4.5.1.4 (Treatment Administration): Clarification was made that following an observation period of 15 to 30 minutes post end of monalizumab infusion, the infusion of the premedication for cetuximab may begin and will be followed 30 minutes later by the cetuximab infusion.

20 Section 3.1.3 (Management of Study Medication Related Toxicities): It was confirmed that the local product information should be used for guidance on toxicity management for marketed study medications.

21 Section 4.3.5 (Clinical Laboratory Tests; Other Safety Tests): Hepatitis A antibody was added to list of tests as previously omitted in error.

22 Section 4.5.1.1 (Investigational Product Inspection): The requirement for the durvalumab solution to be practically free from visible particles was removed for clarification.

23 Section 4.5.1.3 (Investigational Product Dose Preparation and Administration): The infusion time for cetuximab at a dose 250 mg/m^2 was added as previously omitted in error, the requirement for the dose of durvalumab to be allowed to equilibrate at room temperature before use was removed as not required, the acceptability of polyethylene and polypropylene tubing for monalizumab infusion was removed as these tubes have not been assessed.

24 Section 4.5.4 (Storage): The term "secondary packaging" was replaced by the term "original packaging" as clarification of requirement.

9.3 Protocol Amendment 4

Text revisions resulting from this amendment are incorporated in the body of Protocol Amendment 4. The primary reasons for the amendment were CCI [redacted] to revise prior therapy inclusion criteria for subjects in Part 3 C Cohorts to match standard-of-care practice, and to update the process for identifying and reporting potential Hy's Law and Hy's Law cases. Major changes to the protocol are summarized below.

1 Updated synopsis to align with changes in the body of the protocol.

2 Sections 1.4.1.1 (Rheumatoid Arthritis Study [NN8765-3658]) and 1.6.2 (Summary of Risks): Removed summary of RA study (Section 1.4.1.1 and second paragraph in Section 1.6.2); this information is provided in the monalizumab Investigator's Brochure.

3 Section 1.4.2 (Durvalumab Clinical Experience): Updated the clinical data as of the durvalumab Investigator's Brochure version 13.0.

4 Section 1.4.3 (Safety and Efficacy Results from the Current Ongoing Study): Updated the clinical data as of the data cut-off date of 02 January 2019.

5 Section 1.6.2 (Summary of Risks): In the first paragraph, added text on the risks for durvalumab. Although already listed previously in Section 1.4.2 (Durvalumab Clinical Experience), the risks were also included in Section 1.6.2 for clarity.

6 Sections 2.1 (Primary Objectives and Associated Endpoints), 2.2 (Secondary Objectives and Associated Endpoints), 2.3 (Exploratory Objectives and Associated Endpoints), 3.1.1 (Overview), and 3.1.2.3 (Part 3: Dose Exploration in CCI CRC): Revised footnotes and text regarding prior therapy for Cohort C subjects to be consistent with the change in inclusion criterion 5b (iv) in Section 4.1.2 (Inclusion Criteria) described below.

7 Section 2.2 (Secondary Objectives and Associated Endpoints), 3.2.4 (Rationale for Endpoints), 4.3.8 CCI [redacted], and 4.8.8 (Analysis of

Pharmacodynamic Biomarkers): In Table 2 (Secondary Objectives and Associated Endpoints), revised language for predictive endpoints to include EGFR and clarified that the endpoints include "but are not limited to CCI in pre-treatment tumor biopsies". The corresponding objective for these endpoints was revised as "To characterize the association between clinical outcomes and pre-treatment protein expression within the tumor microenvironment". As cetuximab is an EGFR inhibitor, EGFR expression will be evaluated in subjects treated with cetuximab to detect whether subjects with an increased pathway engagement will be more likely to respond to treatment. The rationale for this endpoint was added to Section 3.2.4, and text in Sections 4.3.8 and 4.8.8 was revised to include EGFR.

8 Section 2.3 (Exploratory Objectives and Associated Endpoints): In Table 3 (Exploratory Objectives and Associated Endpoints) revised CCI as described below:

CCI

9 Section 3.1.2.1 (Part 1: Dose Escalation): Under the subheading "Dose-limiting Toxicity", DLT criteria for Grade 3 or 4 neutropenia were revised to "Grade 3 or 4 neutropenia that is **not** associated with fever or systemic infection…" (bold indicates added text). Grade 3 or 4 neutropenia that is associated with fever or systemic infection is already covered by febrile neutropenia DLT criteria.

10 CCI

11 Section 4.1.1 (Number of Subjects): Updated Table 5 (Study Overview and Status Update) as of the data cut-off date of 02 January 2019.

12 Section 4.1.2 (Inclusion Criteria): Inclusion criterion 5b (iv) (Prior Therapy Criteria) for subjects in Part 3 Cohorts C1A, C1B, C2A, and C2B was revised to match standard-of-care practice to require that subjects CCI CCI must have contained fluoropyrimidines, irinotecan, oxaliplatin, and an anti-VEGF inhibitor (eg, bevacizumab) in the recurrent/metastatic setting. The change to allow at least 1 prior line of therapy was made so that subjects who have progressed after receiving FOLFOXIRI or equivalent fluoropyrimidine regimen, which contains oxaliplatin and irinotecan as first-line treatment, may qualify for enrollment in the study (previously, subjects were required to have received only 2 prior lines of treatment which must have contained fluoropyrimidines, irinotecan, and oxaliplatin). The requirement for prior treatment with bevacizumab was added to ensure subjects have received all standard-of- care agents prior to enrollment. Additionally the following criteria were added:

(a) Clarified that subjects must have progressed based on imaging during or within 3 months of the last administration of each standard chemotherapy.

(b) Added criterion to allow subjects who were intolerant to standard treatment to qualify for enrollment in the study.

(c) Clarified that subjects who had received adjuvant chemotherapy and had recurrence during or within 6 months of completion are allowed to count the adjuvant therapy as 1 regimen.

13 Sections 4.2.1 (Enrollment/Screening Period) and 4.2.2 (Treatment Period): Moved stool sample assessment at Week 1, Day 1 in Table 8 (Schedule of Treatment Period Study Procedures Weeks 1 to 26) to Screening/baseline in Table 7 (Schedule of Screening/Baseline Procedures) and added footnote that the sample can be collected anytime during screening, up to and including Day 1, provided it is collected prior to administration of the first dose of study drug(s).

14 Section 4.2.2 (Treatment Period) and Table 9 (Schedule of Treatment Period Study Procedures Weeks 27 to End of Treatment): A statement regarding timing of disease assessment scans was added in Section 4.2.2 to clarify that scans can be performed within a 7-day window of the dosing day. In Table 9, the frequency for the assessments of ECG, coagulation parameters, and thyroid function tests after Week 51 ("Cont" column) was revised in Protocol Amendment 3. However, due to oversight, these changes were not listed in the Summary of Changes for Protocol Amendment 3 and are thus noted here:

(a) The frequency for ECG assessment was revised to "W57 D1 (D393) then Q12W" in Protocol Amendment 3 (Q8W in Protocol Amendment 2).

(b) The frequency for coagulation parameters was revised to "Q8W" in Protocol Amendment 3 (Q4W in Protocol Amendment 2).

(c) The frequency for urinalysis was revised to "Q12W" in Protocol Amendment 3 (Q4W in Protocol Amendment 2).

15 Section 4.5.1 (Identity of Investigational Products) and Table 16 (Identification of Investigational Products), and Sections 4.5.1.1 (Investigational Product Inspection), 4.5.1.2 (Dose Calculation), CCI [redacted]

16 Section 4.5.1.3 (Investigational Product Dose Preparation and Administration): The following revisions were made:

(a) Removed requirement that IV administration filter be in-line for durvalumab, monalizumab, and cetuximab to allow flexibility for clinical sites.

(b) For durvalumab and monalizumab, added statement that for treatment arms that require administration of durvalumab and monalizumab on the same day, the total infusion time for both study drugs should not exceed 8 hours at room temperature (with a maximum of 4 hours for the durvalumab infusion). This statement was added to limit the combination infusion time since instructions for each drug permit up to 8 hours per infusion.

17 Section 4.5.4 (Storage): Added storage information for cetuximab.

18 Section 5.6.2 (Potential Hy's Law and Hy's Law): Revised section heading from "Hepatic Function Abnormality" to "Potential Hy's Law and Hy's Law" and added requirement to report these cases as SAEs to align with revised MedImmune requirements.

19 Section 7.1 (Ethical Conduct of the Study): Removed this section as this information is already stated in Section 1.6 (Benefit-Risk and Ethical Assessment). Subsequent sections were renumbered accordingly.

20 Section 7.1 (Subject Data Protection), previously number Section 7.2: Revised to align with preferred MedImmune standard language.

21 Section 10.1 (Signatures): Updated sponsor signature information.

22 Section 10.5 (Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law): Updated to align with revised MedImmune requirements.

9.4 Protocol Amendment 3

Text revisions resulting from this amendment are incorporated in the body of Protocol Amendment 2. The primary reason for this Amendment was to update the clinical experience for monalizumab and to add treatment cohorts in Part 3 for subjects with CCI CRC that is CCI or CCI. Due to the preliminary clinical activity signal observed with durvalumab in combination with monalizumab in the CCI CRC cohort in Part 2 of this study, Part 3 (Cohorts A CCI) was added under Amendment 2 to evaluate further the combination of durvalumab and monalizumab with standard-of-care chemotherapeutic regimens with and without biologic agents (bevacizumab or cetuximab) in subjects with 1L or 2L CCI CRC. Due to the promising preliminary clinical activity signal observed with monalizumab in combination with cetuximab in subjects with recurrent or metastatic SCCHN (NCT02643550; Cohen et al, 2018), Cohort C is being added to Part 3 (Cohorts C1A, C1B, C2A, and C2B) of the current study under Amendment 3 to understand better the exact mechanism of monalizumab in combination with cetuximab (ie, enhancement of ADCC or adaptive immune response). This will be achieved by evaluating the combination of monalizumab with cetuximab in subjects with CCI CRC that is CCI (Part 3, Cohort C2B) as well as CCI (Part 3, Cohort C1B). In addition, given the previously observed signal of durvalumab in combination with monalizumab in CCI CRC from Part 2, this study will also evaluate durvalumab in combination with monalizumab plus cetuximab in subjects with CCI CRC that is CCI (Part 3, Cohort C2A) as well as CCI (Part 3, Cohort C1A. Major changes to the protocol are summarized below.

1 Title: The study title was revised to reflect that the study is Phase 1/2 (previously Phase 1) and IPH2201 was changed to monalizumab. This change is also reflected in the signature pages.

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

3 Tables and figures were renumbered sequentially throughout the protocol CCI

4 Section 1.4.1 (Monalizumab Clinical Experience): Updated per most recent Monalizumab Investigator's Brochure.

5 Section 1.4.1.2 (Oncology Studies) and Figure 1 (Study IPH2201-203: Percent Reduction of Target Lesion from Baseline): Added clinical efficacy for IPH2201-203 as of 09 March 2018. Added Figure 1.

6 Section 1.4.3 (Safety and Efficacy Results from the Current Ongoing Study) and Figure 2 CCI [redacted] Updated clinical experience for the current study as of the data cut-off date of 23 April 2018 and per most recent Monalizumab Investigator's Brochure. Updated title and data for Figure 2 (previously numbered Figure 1.4.3-1).

7 Section 1.5.1 (Rationale for Evaluating Combinations of Durvalumab and Monalizumab with Chemotherapy and/or Biologic Agents): Section renamed (previously "Rationale for evaluating durvalumab in combination with monalizumab and chemotherapy with or without a biologic agent") and revised to include rationale for evaluating the combination of durvalumab and monalizumab plus cetuximab and the combination of monalizumab plus cetuximab in subjects with CCI [redacted] or CCI [redacted] CRC.

8 Section 1.7.1 (Primary Hypothesis): Added primary hypothesis for Part 3, C Cohorts.

9 Section 2 (Objectives and Endpoints): Revised to present objectives and endpoints in tabular format. Added primary, secondary, and exploratory objectives and endpoints for Part 3, Cohorts C1 and C2. Specified primary and secondary endpoints for antitumor activity per RECIST v1.1 to be "by investigator assessment". Revised exploratory endpoints as described below:

CCI [redacted]

10 Sections 3.1.1 (Study Design - Overview), Figures 3 (Study Flow Diagram) and 5 (Study Part 3 [Dose Exploration] Flow Diagram for Cohorts C1 and C2), CCI [redacted]

CCI [redacted] Details for Cohorts C1 and C2 were added to Figure 3 (previously numbered Figure 3.1.1-1). CCI [redacted] The number of sites was revised to 60 (previously 30).

11 Sections 3.1.1 (Study Design - Overview), 3.1.2 (Treatment Regimen) and 3.2.5 (Post Study Access to Therapy): Moved text stating that subjects will receive treatment until unacceptable toxicity, documentation of PD, or subject withdrawal to Section 3.1.2 and specified maximum time of treatment in the study as 3 years. Moved text regarding post study access in Section 3.2.5 (section now deleted) to Section 3.1.2 and revised time period for treatment to 3 years (previously 2 years).

12 Section 3.1.2.1 (Part 1: Dose Escalation): The following revisions were made:

- Under the subheading "Dose-limiting Toxicity", revised bulleted list to specify Cohorts A CCI [redacted] subjects where Part 3 is designated as these are applicable to subjects who are receiving chemotherapy.
- Revised first sentence of last paragraph to include dose exploration to "During dose expansion **and dose exploration in** CCI [redacted] **CRC**, subjects will be monitored for safety according to the same criteria employed during dose **escalation**" (bold indicates added text).

13 Section 3.1.2.3 (Part 3: Dose Exploration in CCI [redacted] CRC): For Cohorts A2 CCI [redacted] revised text to specify that the first infusion of cetuximab is over 2 hours and subsequent infusions of 250 mg/m^2 are over 1 hour and that the cetuximab regimen may be changed to 500 mg/m^2 IV infusion over 1 hour Q2W after a subject has completed the 28-day DLT-evaluation period, at the investigator's discretion and in accordance with institutional guidelines.

14 Section 3.1.3.1 (Chemotherapy and Biologic Agent Dose Modification): Under cetuximab, the following revisions were made:

- Revised criteria for infusion reactions to specify that infusion rate be reduced by 50% for Grade 1 or 2 infusion reactions and permanently discontinued for Grade 3 or 4 infusion reactions to align with the label.
- Revised dose modification for acneiform rash to include details for subjects who receive the cetuximab 500 mg/ m^2 Q2W regimen. Specifically,
  - Under first occurrence, revised first bullet to "If improvement, continue at a dose of 250 mg/m^2 **if on Q1W regimen or 500 mg/m^2 if on Q2W regimen"** (bold indicates added text).
  - Under second occurrence, revised first bullet to "If improvement, continue at reduced dose of 200 mg/m^2 **if on Q1W regimen or 400 mg/m^2 if on Q2W regimen"** (bold indicates added text).
  - Under third occurrence, revised first bullet to "If improvement, continue at reduced dose of 150 mg/m^2 **if on Q1W regimen or 300 mg/m^2 if on Q2W regimen"** (bold indicates added text).

15 Section 3.2.1.3 (Rationale for the Combination of Monalizumab and Durvalumab) and 3.2.1.4 (Rationale for Cetuximab Dosing): Added Section 3.2.1.3 with rationale for monalizumab/durvalumab combination dose used in dose expansion (Part 2) and dose exploration (Part 3). Added Section 3.2.1.4 with rationale for cetuximab regimen used in dose exploration (Part 3).

16 Section 3.2.2 (Rationale for Study Population): Added rationale for dose exploration of durvalumab and monalizumab plus cetuximab in subjects with CCI CRC that is CCI [redacted] or CCI [redacted]

17 Section 3.2.4 (Rationale for Endpoints): Revised text in second paragraph to specify "by investigator assessment" for OR, DC, DoR, and PFS and to clarify OR as primary endpoint for Part 3, Cohort C1. Added statement that cetuximab PK is being examined for Part 3 (Cohorts C1A and C1B) in third paragraph.

18 Section 4.1.1 (Number of Subjects): CCI [redacted] with addition of Table 5 (subsequent table numbers reordered).

19 Section 4.1.2 (Inclusion Criteria): The following revisions were made:

(a) Clarified that the first sentence of inclusion criterion 5, requiring at least one prior line of standard systemic therapy in the recurrent/metastatic setting, applies to subjects entering Parts 1 and 2.

(b) Moved criterion 5a (ii), which specified that subjects with ovarian cancer must not have evidence of partial small bowel obstruction or small bowel obstruction within 4 weeks prior to the first scheduled dose of study treatment, to number 5 as this criterion is applicable for all tumor types (previously only specific for ovarian cancer).

(c) For inclusion criteria 5b (ii) and 5d (ii): Clarified that testing for microsatellite instability may be done locally and prior documentation of this testing is acceptable in lieu of running the test again.

(d) Under criterion 5b (iv), revised inclusion criteria for subjects in Part 3 A1 CCI [redacted] to specify INR < 3 for subjects on "oral anticoagulation **with coumarin derivatives** and must have and INR< 3 and have no significant active bleeding (defined as **Grade 2 or higher hemorrhage within** 14 days **prior to first dose of study treatment**"). Under "Note", revised text to "Subjects with a venous thrombosis are permitted to enroll **including subjects on newer oral anticoagulants (eg, apixaban, rivaroxaban, dabigatran, etc)** provided they are clinically stable, asymptomatic, and adequately treated with anticoagulation in the opinion of the investigator **for at least 3 months prior to the first dose of study treatment**", bold indicates added text. The change was made to distinguish parameters applicable for subjects on coumarin derivatives versus newer oral anticoagulants.

(e) CCI [redacted]

(f) Under criterion 5b (iv), added specific inclusion criteria for Cohorts C1 and C2.

(g) For inclusion criterion 6b, revised time period for archival tumor sample to 1 year, previously 6 months.

(h) Added inclusion criterion 6c that subjects in dose-exploration cohorts (Part 3) must consent to provide an archival tumor sample from a biopsy collected within 1 year prior to the first dose of study drug or must provide a pre-treatment biopsy during the Screening Period.

(i) Removed inclusion criterion 7c that specified results of imaging up to 6 months prior to screening are to be made available to the sponsor as this is not required for inclusion in the study.

20 Section 4.1.3 (Exclusion Criteria): The following revisions were made:

(a) Removed the text "major surgery ≤ 28 days prior to first dose of study treatment" from exclusion criterion 18b, as this is already stated in exclusion criterion 13.

(b) Added exclusion criterion 19 that subjects enrolling in Part 3, CCI must not have experienced a toxicity that led to permanent discontinuation of prior therapy with cetuximab.

21 Section 4.1.4 (Subject Enrollment and Randomization): Added paragraph with details for subjects enrolled in the randomized portion of the study (Part 3 Cohorts C1 and C2) and revised section title to included randomization.

22 Section 4.2.1 (Enrollment/Screening Period): The following revisions were made to Table 7 (Schedule of Screening/Baseline Procedures [formerly Table 4.2.1-1]):

(a) For disease assessments, added footnote to allow subjects to use previous scans for baseline disease and brain imaging that were performed within 6 weeks of dosing and meet the protocol requirements.

(b) Included smoking history and added "and prior imaging" to the assessment for medical history, with a footnote that 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 if allowed by country, to collect data on tumor kinetics.

(c) Specified coagulation parameters as a separate row for clarification that prothrombin time, APTT, INR and fibrinogen are collected under coagulation panel.

(d) CCI

(e) Added assessment of serum for circulating soluble factors as both serum and plasma will be collected.

(f) In the footnote for archival tumor biopsy, revised the time period for archival tumor sample to 1 year, previously 6 months and added a statement that in Part 3, archival tumor sample from within 1 year of enrollment or fresh biopsy is required.

23 Section 4.2.2 (Treatment Period), Table 8 (Schedule of Treatment Study Procedures Weeks 1 to 26 [formerly Table 4.2.2-1]), Table 9 (Schedule of Treatment Study Procedures Weeks 27 to End of Treatment [formerly Table 4.2.2-2]), Table 10 (Schedule of Treatment Study Procedures Weeks 1 to 25 for Monalizumab Q4W [formerly Table 4.2.2-3]), and Table 11 (Schedule of Treatment Study Procedures Weeks 26 to End of Treatment for Monalizumab Q4W [formerly Table 4.2.2-4]): The following revisions were made:

(a) Revisions were made in the text of Section 4.2.2 to clarify scheduling and conducting study visits. A statement was added that PRO questionnaires will be implemented for subjects in CCI [redacted] with cross-reference to Section 4.3.3 for additional instructions.

(b) Table 8: The following revisions were made:

(i) Added PRO assessments for Part 3, CCI [redacted].

(ii) Added assessment for ECG at W17 D1 to correct omission.

(iii) Added assessment for hematology sample at Day 15.

(iv) Specified coagulation parameters as a separate row for clarification that prothrombin time, APTT, INR and fibrinogen are collected under coagulation panel.

(v) For durvalumab PK and immunogenicity, specified that this is not applicable for Part 3 Cohorts C1B and C2B. Revised PK footnote to include details for cetuximab sample in these cohorts.

(vi) Added assessment for cetuximab PK and cetuximab immunogenicity in Part 3 Cohorts C1A and C1B.

(vii) Removed assessment for soluble PD-L1 as this will not be measured.

(viii) Removed the W25 D1 assessment for flow cytometry.

(ix) CCI [redacted]

(x) Added assessment of serum for circulating soluble factors as both serum and plasma will be collected.

(xi) Added stool sample for Part 3 Cohorts C1A, C1B, C2A, and C2B only.

(xii) Added assessment of blood sample for future analysis at the Week 1 Day 1 visit with footnote that additional blood samples will also be collected at baseline for future analysis including but not limited to an autoimmune work-up.

(xiii) For durvalumab administration, specified that this is not applicable for Cohorts C1B and C2B.

(xiv) For chemotherapy administration, specified that this is applicable for Cohorts A1 CCI [redacted].

(xv) Added footnote for the cetuximab Q1W regimen with dose and regimen for subjects in Cohorts A2 CCI [redacted] who can switch to Q2W after DLT-evaluation period per investigator's discretion and in accordance with institutional guidelines.

(xvi) Added row for cetuximab administration (Q2W) for subjects in Cohorts C1A, C1B, C2A, and C2B with footnote to specify the details for the Q2W regimen and additional columns for dosing on W4 and W26.

(xvii) Revised footnote for tumor biopsy at Week 9 Day 1 to clarify that this is also for subjects in dose exploration who provided a fresh pre-treatment biopsy.

(xviii) Revised footnote for infusion duration of monalizumab and durvalumab to be "approximately 60 minutes", previously "60 minutes (± 5 minutes)".

(xix) Added footnote for Week 9, Day 1 assessments of ECOG, CA for CRC/CA-125, durvalumab PK, monalizumab PK, cetuximab PK, and cetuximab

ADA that these assessments may be optionally collected if the subject is discontinuing treatment at the scheduled Week 9 Day 1 visit.

(c) Table 9: The following revisions were made:

(i) Revised format of the table to specify specific visits from W27 D1 to EOT for clarity. The cetuximab dosing for Part 3, Cohorts A2 CCI was removed for W26 as included in Table 8.

(ii) Added column for W1 for cetuximab Part 3, Cohorts A2 CCI, QW schedule.

(iii) Added PRO assessments for Part 3, Cohorts C1A and C1B.

(iv) Specified coagulation parameters as a separate row for clarification that prothrombin time, APTT, INR and fibrinogen are collected under coagulation panel.

(v) For durvalumab administration, specified that this is not applicable for Cohorts C1B and C2B.

(vi) For chemotherapy administration, specified that this is applicable for Cohorts A1–CCI.

(vii) Revised cetuximab administration to be Q2W for subjects in Cohorts A2, CCI C1A, C1B, C2A, and C2B with footnote with details for the Q1W and Q2W regimens and that subjects in Cohorts A2 CCI on Q1W schedule can switch to Q2W after DLT-evaluation period per investigator's discretion and in accordance with institutional guidelines.

(viii) Revised footnote for infusion duration of monalizumab and durvalumab to be "approximately 60 minutes", previously "60 minutes (± 5 minutes)".

(d) Table 10: The following revisions were made:

(i) Added assessment for ECG at W17 D1 to correct omission.

(ii) Specified coagulation parameters as a separate row for clarification that prothrombin time, APTT, INR and fibrinogen are collected under coagulation panel.

(iii) Removed assessment for soluble PD-L1 as this will not be measured.

(iv) Removed the W25 D1 assessment for flow cytometry.

(v) CCI

(vi) Added additional assessment for circulating soluble factors to specify both serum and plasma will be collected.

(vii) Added assessment of blood sample for future analysis at the Week 1 Day 1 visit with footnote that additional blood samples will also be collected at baseline for future analysis including but not limited to an autoimmune work-up.

(viii) Revised footnote for tumor biopsy at Week 9 Day 1 to clarify that this is also for subjects in dose exploration who provided a fresh pre-treatment biopsy.

(ix) Revised footnote for infusion duration of monalizumab and durvalumab to be "approximately 60 minutes", previously "60 minutes (± 5 minutes)".

(x) Added footnote for Week 9, Day 1 assessments of ECOG, durvalumab PK, monalizumab PK, and CD94/NKG2a receptor occupancy that these assessments

may be optionally collected if the subject is discontinuing treatment at the scheduled Week 9 Day 1 visit.

(e) Table 11: The following revisions were made:

(i) Revised format of the table to specify specific visits from W29 D1 to EOT for clarity.

(ii) Specified coagulation parameters as a separate row for clarification that prothrombin time, APTT, INR and fibrinogen are collected under coagulation panel.

(iii) Revised footnote for infusion duration of monalizumab and durvalumab to be "approximately 60 minutes", previously "60 minutes (± 5 minutes)".

24 Section 4.2.3 (Follow-up Period) and Table 12 (Schedule of Follow-up Procedures formerly Table 4.2.3-1): The following revisions were made:

(a) Added PRO assessments for Part 3, Cohorts C1A and C1B.

(b) Specified coagulation parameters as a separate row for clarification that prothrombin time, APTT, INR and fibrinogen are collected under coagulation panel.

(c) For durvalumab PK and immunogenicity, specified that this is not applicable for Part 3 Cohorts C1B and C2B.

(d) Added assessment for cetuximab PK and cetuximab immunogenicity in Part 3 Cohorts C1A and C1B.

(e) Added assessments for plasma for flow cytometry, CCI [redacted], circulating soluble factors (plasma), PBMC, and CCI [redacted] with a footnote that the assessments should be performed if EOT occurs at the scheduled Week 9 visit.

25 Sections 4.3.2.1 (Fresh Tissue Biopsies) and 4.3.2.2 (Archival Tumor Samples): Added text that subjects in dose-exploration cohorts (Part 3) must consent to provide an archival tumor sample from a biopsy collected within 1 year prior to the first dose of study drug or must provide a pre-treatment biopsy during the Screening Period and if clinically feasible, dose-exploration subjects who provided a fresh biopsy during screening are encouraged to provide a biopsy during Week 9.

26 Section 4.3.3 (Patient Reported Outcomes [Part 3, Cohorts C1A and C1B Only]): Added new section with details of PRO assessments. Subsequent sections were renumbered accordingly.

27 Section 4.3.4.2 (Electrocardiograms [formerly Section 4.3.3.1]): First paragraph revised to align with Section 4.2. Added paragraph to specify that digital copies of ECGs can be held centrally and stored for potential independent analysis.

28 Section 4.3.5 (Clinical Laboratory Tests [formerly Section 4.3.4]): The following revisions were made:

– Moved thyroid function test from "Serum Chemistry" to "Thyroid Function Tests" as it is not part of the serum chemistry panel.

– In the note under "Serum Chemistry", added text to clarify that direct and indirect bilirubin are only needed if total bilirubin is not within normal range and that it is acceptable to assess one rather than both indirect and direct bilirubin. Added note to clarify that urea is an acceptable alternative if BUN is not routinely tested.

- Moved APTT and fibrinogen from “Hematology” to “Coagulation” for clarification.
- Under “Other Safety Tests”, added bullet for additional baseline blood samples for future analysis including, but not limited to, an autoimmune work-up.

29 Section 4.3.8 CCI [redacted] CCI [redacted]

30 Section 4.3.9 (Estimate of Volume of Blood to be Collected [formerly Section 4.3.8]): Revised blood volume estimates for screening period to 56 mL (previously 44 mL), for treatment period to 77.5 mL (previously 64 mL), and for follow-up period to 44.5 mL (previously 36 mL) to be consistent with the changes to the study procedures.

31 Section 4.5 (Investigational Products): This section was reorganized for clarity and to include cetuximab as investigational product for Part 3 Cohorts C1A and C1B. The following revisions were made:

(a) Section 4.5.1 (Identity of Investigation Products) and Table 16 (Identification of Investigational Products [formerly Table 4.5.1-1]): In Table 16, added cetuximab as investigational product for Part 3 Cohorts C1A and C1B. Deleted redundant text below the table.

(b) Section 4.5.1.1 (Investigational Product Inspection [formerly Section 4.5.1.3]): Added details for cetuximab.

(c) Section 4.5.1.2 (Dose Calculation): Added dose calculation for cetuximab.

(d) Section 4.5.1.3 (Investigational Product Dose Preparation and Administration [formerly Section 4.5.1.1]): The section was revised to include dose preparation and administration instructions. The dose preparation and administration instructions for durvalumab were updated. Reconstitution procedure for monalizumab was added. Details for cetuximab were added.

(e) Section 4.5.1.4 (Treatment Administration): Redundant text was deleted. Details for cetuximab were added.

(f) Section 4.5.1.5 (Monitoring of Dose Administration): A statement was added in the first paragraph that monitoring of the cetuximab infusion will be performed per the label. A statement was added in the third paragraph that antihistamines or steroids can be administered per label prior to cetuximab infusion.

32 Section 4.6.1 (Methods for Assigning Treatment Groups): Added details for the randomization and stratification of subjects enrolled in Part 3 Cohorts C1 and C2.

33 Section 4.7.2 (Prohibited Concomitant Medication): Revised number 5 to clarify that all herbal and natural remedies should be avoided (previously, “herbal and natural remedies that may have immune-modulating effects should not be given concurrently unless agreed by the sponsor”).

34 Section 4.8.1 (General Considerations): Added definitions for ITT population and Response-evaluable population.

35 Section 4.8.2 (Sample Size) and Table 19 (Observed Objective Response Rate with CCI % Confidence Interval): CCI [redacted] Created numbered subheadings for Part 1 (Section 4.8.2.1), Part 2 (Section 4.8.2.2), and Part 3 (Section 4.8.2.3). Under Section 4.8.2.3 (Dose Exploration) added Table 19 for Cohort C1 and details for Part 3 C1 and C2 Cohorts.

36 Section 4.8.3.1 (Antitumor Efficacy): Added bullet that efficacy analyses are based on the As-treated population for the non-randomized cohorts and on the ITT for the randomized cohorts according to RECIST v1.1 by investigator assessment and that additional supportive analyses may be conducted in the ITT population according to RECIST v1.1 per Blinded Independent Central Review to inform internal program decisions and/or for potential interactions with regulatory agencies for future development.

37 Section 4.8.5 (Analysis of Patient Reported Outcomes [Part 3, Cohort C1 only]): Added new section with details for the analysis of PRO. Subsequent sections were renumbered accordingly.

38 Section 4.8.9 (Interim Analysis [formerly Section 4.8.8]): Added details for the interim analyses for Part 3, Cohorts C1 and C2.

39 Section 8: Revised references.

40 Section 10.6 (Appendix 7 [Patient Reported Outcomes]): Added new section with questionnaires for collection of PRO data.

9.5 Protocol Amendment 2

Text revisions resulting from this amendment are incorporated in the body of Protocol Amendment 2. Major changes to the protocol are summarized below.

1 Synopsis: Updated to align with the body of the protocol.

2 Section 1.4 (Summary of Clinical Experience): Previous content replaced with summary clinical experience information from the current versions of the durvalumab and monalizumab Investigator's Brochures and added a section on safety and efficacy data from the current study.

3 Section 1.5 (Rationale for Conducting the Study): Added a subsection providing the rationale for evaluating durvalumab in combination with monalizumab and chemotherapy plus bevacizumab or cetuximab.

4 Section 1.7.1 (Primary Hypothesis): Revised to include durvalumab in combination with monalizumab and chemotherapy plus bevacizumab or cetuximab administered to subjects with CCI [redacted] colorectal cancer.

5 Section 2 (Objectives and Endpoints): Revised to include the use of chemotherapy plus bevacizumab or cetuximab with the durvalumab/monalizumab combination.

6 Section 3 (Study Design): Revised to include the addition of the dose-exploration part of the study (Part 3) in which subjects with advanced CCI [redacted] CRC will be treated with the combination of durvalumab and monalizumab and a chemotherapy regimen (mFOLFOX6 CCI [redacted] plus cetuximab or bevacizumab. As a consequence of the addition of Part 3

to the study and to assist in differentiating the 3 treatment parts, the dose escalation phase is now referred to as Part 1 and the dose-expansion phase is referred to as Part 2.

(a) Revised the bulleted list of DLTs and non-DLTs.

(b) Added Section 3.1.3.1 on chemotherapy and biologic agent dose modification.

(c) Section 3.2.2: Added rationale for the new dose-exploration part of the study (Part 3).

7 Section 4.1.2 (Inclusion Criteria): added specific inclusion criteria that must be met by subjects enrolling in Part 3.

8 Section 4.1.3 (Exclusion Criteria): Added to criterion 1: "Subjects who have received prior immunotherapy treatment may be enrolled in Part 1 (dose escalation) on a case-by-case basis with the agreement of the sponsor." Added to criterion 3: "…or any component of the chemotherapy regimens that will be administered in Part 3."

9 Section 4.1.9 (Consent for Data and Biological Samples): Added a study-specific explanation of how collected biological samples will be used to the subsection on Genetic Research.

10 Section 4.3.1.3 CCI [redacted]

11 Section 4.5 (Investigational Products): Revised instructions on preparation and administration of investigational products.

12 Section 4.8.2 (Sample Size): Updated to include a description of the sample size for the new dose-exploration part of the study (Part 3).

13 Section 5.3 (Definition of Adverse Events of Special Interest): Added rash and infusion-related /hypersensitivity/anaphylactic reactions to the list of AESIs.

14 Section 8 (References): Added citation details for the following references, which have been used to support information added to Section 1.5.1: Bendell et al, 2015; Daaboul et al, 2017; FDA, 2017a; FDA, 2017b; Giantonio et al, 2007; Khemka et al, 2016; Kroemer et al, 2013; Liu et al, 2010; Mayer et al, 2015; Mellman et al, 2011; Muntasell et al, 2017; Pfirschke et al, 2016; Philips and Atkins, 2015; Postow et al, 2015; Ruggeri et al, 2016; CCI [redacted] Shahda et al, 2017; Van Cutsem et al, 2012; Van Cutsem et al, 2016; Wallin et al, 2016; Wang et al, 2015; Zhang et al, 2012.

15 Section 10.2 Appendix 2 (Management of Study Medication Related Toxicities): Replaced with an updated version.

9.6 Protocol Amendment 1

Text revisions resulting from this amendment are incorporated in the body of Protocol Amendment 1. Major changes to the protocol are summarized below.

1 Synopsis: Updated to align with the body of the protocol.

2 Section 3.1.1 (Overview of the Study): Added a statement, per the Agency's request, to indicate that additional dose levels not exceeding the MTD may be considered based on clinical PK/pharmacodynamic data from the dose-escalation phase.

3 Section 3.1.2.2 (Dose-limiting Toxicity): Revised this section as follows per the Agency's request:

(a) Added text to the definition of DLT to indicate that Grade 3 or 4 laboratory abnormalities requiring hospitalization for the management of toxicities will be considered a DLT.

(b) Added text to the definition of DLT to indicate that any delay in monalizumab dosing due to a treatment-related AE will be considered a DLT.

(c) Removed the following statement: In the event of protocol permitted treatment delay of the second dose of monalizumab, the DLT period will be extended such that subjects are followed for 14 days after the second dose of monalizumab.

(d) Added the following exclusions to the DLT criteria:

(e) Grade 3 nausea/vomiting or Grade 4 vomiting in the absence of maximal medical therapy that resolves in 3 days

(f) Grade 3 hypertension that can be controlled with medical therapy

4 Section 3.1.2.3 (Dose Expansion): Added a statement, per the Agency's request, to indicate that additional dose levels not exceeding the MTD may be considered based on clinical PK/pharmacodynamic data from the dose-escalation phase.

5 Section 4.1.2 (Inclusion Criteria): Revised this section as follows per the Agency's request:

(a) Criterion 5a.i: Revised to require advanced ovarian cancer subjects to have previously received and progressed while on or within 6 months of completing a platinum-based regimen.

(b) Criterion 5e: Revised to require metastatic castration-resistant prostate cancer subjects to have progressed from either abiraterone or enzalutamide.

6 Section 10.2 (Appendix 2 - Management of Study Medication Related Toxicities): Revised this section, per the Agency's request, to require permanent discontinuation of study drugs if the immune-mediated neurotoxicities are not resolved to ≤ Grade 1 within 14 days.

10 APPENDICES

10.1 Signatures

Sponsor Signature(s)

A Phase 1/2 Study of Durvalumab and Monalizumab in Adult Subjects with Select Advanced Solid Tumors

I agree to the terms of this protocol.

Signature and date: _____CCI_____

PPD

PPD, Clinical Development, Early Oncology

PPD

Office: PPD

Email: PPD

Signature of Principal Investigator

A Phase 1/2 Study of Durvalumab and Monalizumab in Adult Subjects with Select Advanced Solid Tumors

I, the undersigned, have reviewed this protocol and all amendments, and I agree to conduct this protocol in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with the International Conference on Harmonisation guidelines on Good Clinical Practice, any applicable laws and requirements, and any conditions required by a regulatory authority and/or Institutional Review Board/Independent Ethics Committee (IRB/IEC).

I understand that the protocol may not be modified without written approval of the sponsor. All changes to the protocol must be submitted to the applicable regulatory authority and IRB/IEC, and must be approved by the IRB/IEC prior to implementation except when necessary to eliminate immediate hazards to the subjects or when the change(s), as deemed by the sponsor, involves only logistical or administrative changes. Documentation of IRB/IEC approval must be sent to the sponsor immediately upon receipt.

Signature and date: _____

Name and title: _____

Address including postal code: _____

_____

Telephone number: _____

Site/Center Number (if available) _____

This document contains confidential information, which should not be copied, referred to, released, or published without written approval from MedImmune or AstraZeneca. Investigators are cautioned that the information in this protocol may be subject to change and revision.

10.2 Additional Safety Guidance

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 (NCI CTCAE) <<indicate version number as V4.03 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 (mild)	An event 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 (moderate)	An event 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 (severe)	An 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 (life threatening)	An event, and/or its immediate sequelae, that is associated with an imminent risk of death.
Grade 5 (fatal)	Death (loss of life) 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

Relationship to Investigational Product

The investigator is required to provide an assessment of relationship of AEs and SAEs to the investigational product.

An event will be considered "not related" to use of the investigational product if any of the following tests are met:

- An unreasonable temporal relationship between administration of the investigational product and the onset of the event (eg, the event occurred either before, or too long after, administration of the investigational product for it to be considered product-related)
- A causal relationship between the investigational product and the event is biologically implausible (eg, death as a passenger in an automobile accident)
- A clearly more likely alternative explanation for the event is present (eg, typical adverse reaction to a concomitant drug and/or typical disease-related event)

Individual AE/SAE reports will be considered "related" to use of the investigational product if the "not related" criteria are not met.

"Related" implies that the event is considered to be "associated with the use of the drug" meaning that there is "a reasonable possibility" that the event may have been caused by the product under investigation (ie, there are facts, evidence, or arguments to suggest possible causation).

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 and Allergy Anaphylaxis Network Guidance for Anaphylaxis Diagnosis

National Institute of Allergy and Infectious Disease and Food and Allergy 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 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) Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP
   (b) Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline

References

Sampson HA, Muñoz-Furlong A, Campbell RL, Adkinson FN Jr, Bock SA, Branum A, et al. Second symposium on the definition and management of anaphylaxis: Summary report -- Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol. 2006;117:391-7.

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 in order to identify and appropriately report potential Hy's Law cases and Hy's Law cases. 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 1.1 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.

All sources of laboratory data are appropriate for the determination of potential Hy's Law and Hy's Law events; this includes samples taken at scheduled study visits and other visits including all local laboratory evaluations even if collected outside of the study visits.

The investigator will also review AE data (for example, for AEs that may indicate elevations in liver biochemistry) for possible potential Hy's Law events.

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 ≥ 3 × ULN **together with** TBL ≥ 2 × 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 ≥ 3 × ULN **together with** TBL ≥ 2 × 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, 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 ≥ 3 × ULN
- AST ≥ 3 × ULN
- TBL ≥ 2 × 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 eCRF

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:

- Notify the sponsor study representative who will then inform the central study team.
- Within 1 day of potential Hy's Law criteria being met, the investigator will report the case as an SAE of potential Hy's Law; serious criteria 'Important medical event' and causality assessment 'yes/related' according to clinical study protocol process for SAE reporting.

The Medical Monitor contacts the investigator, to provide guidance, discuss and agree on an approach for the study subjects' follow-up (including any further laboratory testing) 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. Complete follow-up SAE Form as required.
- Investigate the etiology of the event and perform diagnostic investigations as discussed with the Medical Monitor.
- Complete the relevant eCRF Modules as information becomes available.

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.

As soon as possible 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, to ensure timely analysis and reporting to health authorities per local requirements from the date potential Hy's Law criteria were met. 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.

Where 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 an SAE:

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate eCRF
- If the alternative explanation is an AE/SAE, update the previously submitted potential Hy's Law SAE and AE eCRFs accordingly with the new information (reassessing event term; causality and seriousness criteria) following 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:

- Send the updated SAE (report term 'Hy's Law') according to 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 15 calendar days 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:

- Provide any further update to the previously submitted SAE of 'Potential Hy's Law' (report term now 'Hy's Law case'), ensuring causality assessment is related to the investigational product and seriousness criteria are medically important, according to the clinical study protocol process for SAE reporting
- 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 still met. Update the previously submitted potential Hy's Law SAE report following clinical study protocol process for SAE reporting, according to the outcome of the review, and amend the reported term if an alternative explanation for the liver biochemistry elevations is determined

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

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 for reporting potential Hy's Law as an SAE.

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 for reporting potential Hy's Law as an SAE.

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.

10.4.8 Laboratory Tests

To evaluate the underlying etiology of potential Hy's Law cases, relevant laboratory tests will be performed as outlined in Section 4.3.5. Additional laboratory assessments may be performed as clinically indicated.

REFERENCES

Aithal GP, Watkins PB, Andrade RJ, Larrey D, Molokhia M, Takikawa H, et al. Case definition and phenotype standardization in drug-induced liver injury. Clin Pharmacol Ther. 2011;89(6):806-815.

FDA Guidance for Industry (issued July 2009) 'Drug-induced liver injury: Premarketing clinical evaluation':

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

10.5 Patient Reported Outcomes

10.5.1 European Organization for Research and Treatment of Cancer Quality of Life Questionnaire

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: ____
Your birthdate (Day, Month, Year): ____
Today's date (Day, Month, Year): 31 ____

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

Specimen

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

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Specimen

10.5.2 Patient Global Impression of Change

PATIENT GLOBAL IMPRESSION OF CHANGE

Since the start of the treatment I have received in this study, my overall health status is:

Please tick (√) one box only:

- □ Very Much Improved
- □ Much Improved
- □ Minimally Improved
- □ No Change
- □ Minimally Worse
- □ Much Worse
- □ Very Much Worse

10.6 Changes Related to Mitigation of Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis

Note: Changes below should be implemented only during study disruptions due to any of or a combination of civil crisis, natural disaster, or public health crisis (eg, during quarantines and resulting site closures, regional travel restrictions, and considerations if site personnel or study subjects become infected with SARS-CoV-2 or similar pandemic infection) during which subjects may not wish to or may be unable to visit the study site for study visits. These changes should only be implemented if allowable by local/regional guidelines and following notification from the Sponsor and instructions on how to perform these procedures will be provided at the time of implementation.

Please note that during civil crisis, natural disaster, or public health crisis, some study assessments and procedures may not be conducted due to international or local policies or guidelines, hospital or clinic restrictions, and other measures implemented to ensure the patient's safety. If in doubt, please contact the AstraZeneca Study Physician.

10.6.1 Reconsent/reassent of Study Subjects During Study Interruptions

During study interruptions, it may not be possible for the subjects to complete study visits and assessments on site and alternative means for carrying out the visits and assessments may be necessary, eg, remote visits. Reconsent/reassent should be obtained for the alternative means of carrying out visits and assessments and should be obtained prior to performing the procedures described in Sections 10.6.2 to 10.6.4. Local and regional regulations and/or guidelines regarding reconsent of study subjects should be checked and followed. Reconsent/reassent may be verbal if allowed by local and regional guidelines (note, in the case of verbal reconsent/reassent, the Informed Consent Form should be signed at the subject's next contact with the study site). Visiting the study sites for the sole purpose of obtaining reconsent/reassent should be avoided.

10.6.2 Home or Remote Visit to Replace On-site Visit (where applicable)

A qualified Health Care Professional (HCP) from the study site or third-party vendor service will visit the subject's home or other remote location as per local standard operating procedures, as applicable. Supplies will be provided for a safe and efficient visit. The qualified HCP will be expected to collect information per the clinical study protocol.

10.6.3 Telemedicine Visit to Replace On-site Visit (where applicable)

In this appendix, the term 'telemedicine visit' refers to remote contact with the subject using telecommunications technology, including phone calls, virtual or video visits, and mobile health devices.

During a civil crisis, natural disaster, or public health crisis, on-site visits may be replaced by a telemedicine visit if allowed by local/regional guidelines. Having a telemedicine contact with the subjects will allow adverse events and concomitant medication to be reported and documented.

10.6.4 Data Capture During Telemedicine or Home/Remote Visits

Data collected during telemedicine visits will be collected from the subject by a HCP.

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