A Phase Ib/II, Open-label, Multicenter Study of Novel Oncology Therapies in Combination with Chemotherapy and Bevacizumab as First-line Therapy in Metastatic Microsatellite-stable Colorectal Cancer (COLUMBIA-1)

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Investigational Product: Novel oncology therapies: durvalumab (MEDI4736) and oleclumab (MEDI9447)

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PROTOCOL SYNOPSIS

TITLE

A Phase Ib/II, Open-label, Multicenter Study of Novel Oncology Therapies in Combination with Chemotherapy and Bevacizumab as First-line Therapy in Metastatic Microsatellite-stable Colorectal Cancer (COLUMBIA-1)

HYPOTHESES

In Part 1, novel oncology therapies plus standard of care (FOLFOX [folinic acid (leucovorin), 5-fluorouracil, oxaliplatin] plus bevacizumab) will demonstrate adequate safety and tolerability in subjects with first-line (1L) metastatic microsatellite-stable (MSS) colorectal cancer (CRC) to permit further evaluation in Part 2.

In Part 2, novel oncology therapies plus standard of care (FOLFOX plus bevacizumab) will demonstrate superior antitumor activity to standard of care alone in subjects with 1L metastatic MSS-CRC.

OBJECTIVES AND ENDPOINTS

Type	Objective	Endpoint
PRIMARY		
Safety	**Part 1:** To evaluate the safety and tolerability profile of FOLFOX + bevacizumab + novel oncology therapy combinations	Incidence of AEs, SAEs, DLTs, laboratory findings, and vital signs
Efficacy	**Part 2:** To compare the efficacy of FOLFOX + bevacizumab + novel oncology therapy combinations versus FOLFOX + bevacizumab	OR per RECIST v1.1
SECONDARY		
Efficacy	**Part 1:** To investigate the preliminary antitumor activity of FOLFOX + bevacizumab + novel oncology therapy combinations	Assessments of antitumor activity include OR, BOR, DoR, DC, PFS-12, and PFS as assessed by RECIST v1.1 and OS
Pharmacokinetics	**Part 1 and 2:** To describe the PK of novel agents **Part 1:** To describe the PK of bevacizumab	**Part 1 and 2:** PK (drug concentration) for novel agents **Part 1:** PK (drug concentration) for bevacizumab
Immunogenicity	**Part 1 and 2:** To describe the immunogenicity of applicable novel agents **Part 1:** To describe the immunogenicity of bevacizumab	**Part 1 and 2:** Incidence of ADA to applicable novel agents **Part 1:** Incidence of ADA to bevacizumab
Safety	**Part 2:** To evaluate the safety and tolerability profile of FOLFOX + bevacizumab + novel oncology therapy combinations	Incidence of AEs, SAEs, laboratory findings, and vital signs
Efficacy	**Part 2:** To compare the efficacy of FOLFOX + bevacizumab + novel oncology therapy combinations versus FOLFOX + bevacizumab	Assessment of antitumor activity include BOR, DoR, DC, PFS-12, and PFS as assessed by RECIST v1.1 and OS
EXPLORATORY		
CCI	[redacted]	[redacted]

CCI

Note: Summaries and analysis for exploratory endpoints may be reported outside the CSR in a separate report.

ADA = antidrug antibody; AE = adverse event; BOR = best overall response; CSR = clinical study report; CCI DC = disease control; DLT = dose-limiting toxicity; DoR = duration of response; FOLFOX = folinic acid (leucovorin), 5-fluorouracil, oxaliplatin; CCI OR = objective response; OS = overall survival; PFS = progression-free survival; PFS-12 = progression-free survival at 12 months; PK = pharmacokinetics; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event; CCI

STUDY DESIGN

Study D910CC00001 is a Phase Ib/II, open-label, multicenter, randomized, multidrug platform study to evaluate the safety and efficacy of standard of care (FOLFOX plus bevacizumab) in combination with novel oncology therapies (durvalumab and oleclumab) in subjects with 1L metastatic MSS-CRC. The study is designed to concurrently evaluate potential novel combinations with clinical promise using a 2-part approach. Part 1 is a Phase Ib study of safety, and Part 2 is a Phase II study of efficacy and safety. The treatment regimens evaluated

in Part 2 will depend on the evaluation of safety outcomes in Part 1. Up to approximately 30 to 40 sites globally will participate in this study.

Following a screening period of up to 28 days, subjects will be centrally assigned (Part 1) or randomized (Part 2) to one of the open study arms. In both study parts, study treatment may be administered until disease progression or any discontinuation criteria are met CCI [redacted]

Safety Run-in (Part 1)

CCI [redacted]

Dose Evaluation Committee (Part 1)

A study-specific Dose Evaluation Committee (DEC; including at a minimum the medical monitor/clinical lead and participating investigators who have enrolled subjects) in accordance with its charter will provide ongoing safety surveillance of Part 1 of the study. This committee may also meet to review data at other time points (eg, in response to adverse events [AEs] assessed as medically relevant by the medical monitor). This committee will be responsible for making recommendations for safety run-in decisions. The DEC will review the totality of all available clinical and laboratory safety and pharmacokinetic (PK) data and all other relevant data prior to establishing safety run-in decisions based on the dose de-escalation rules.

Randomized Phase (Part 2)

Once Part 1 has been completed for a given arm, Part 2 will open for randomization to evaluate the efficacy and safety of an arm with the same treatment regimen. Randomization will be evenly distributed across all open arms (eg, 1:1, 1:1:1) and will be stratified based on location of the primary tumor (right sided vs left sided). After 50 subjects are randomized to the control arm, the control arm will continue to enroll subjects, but the allocation ratio to the different arms may be adjusted via protocol amendment. Enrollment to the control arm will pause if there is no active experimental arm. The exact subsequent allocation ratios across arms will be determined by the sponsor during the conduct of the study.

Safety Review Committee (Part 2)

A Safety Review Committee (SRC) will conduct safety reviews of all enrolled subjects at least twice a year. The SRC may make recommendations regarding continuation, modification, or termination of any study arm for safety concerns. The SRC will also be responsible for making recommendations for investigational product dose selection to ensure subjects maintain adequate exposure (eg, assessment of dose modifications, dose delays, etc) to standard of care treatment (FOLFOX plus bevacizumab). The committee may request additional data (eg, clinical efficacy) as needed. Additional safety reviews may be conducted at the discretion of the SRC.

TARGET SUBJECT POPULATION

Male and female subjects ≥ 18 years of age with metastatic MSS-CRC who have not received prior treatment in the recurrent/metastatic setting (subjects treated with prior adjuvant chemotherapy or radiochemotherapy are acceptable so long as progression was not within 6 months of completing the adjuvant regimen).

TREATMENT GROUPS AND REGIMENS

In both study parts, study treatment may be administered until disease progression or any discontinuation criteria are met. Study treatments are described in the table below.

Part	Arm	Study Treatment
1	S1	FOLFOX + bevacizumab + durvalumab + oleclumab
CCI [redacted]		

E = experimental; FOLFOX = folinic acid (leucovorin), 5-fluorouracil, oxaliplatin; S = safety run-in.

FOLFOX plus bevacizumab: administered as outlined in the protocol per National Comprehensive Cancer Network and European Society for Medical Oncology guidelines; 5-fluorouracil will be administered as infusion only, with no bolus.
Durvalumab (MEDI4736): CCI [redacted] intravenously (IV) CCI [redacted]
Oleclumab (MEDI9447): CCI [redacted] IV CCI [redacted] starting on Cycle 5, Day 1

STATISTICAL METHODS

Sample size:

In Part 1, a minimum of 6 subjects (and up to 12 subjects per dose level of novel agent) will be enrolled to complete the safety run-in. The number of subjects to be enrolled will depend upon the toxicities observed during the conduct of the study.

In Part 2, up to 50 subjects per treatment arm may be enrolled into the study. After 50 subjects are randomized to the control arm, the control arm will continue to enroll subjects, but the allocation ratio may be adjusted via protocol amendment. Enrollment to the control arm will pause if there is no active experimental arm.

New combination therapy arms may be added over time via protocol amendment. Criteria for additional combination arms are described in the main body of the protocol.

Statistical analyses:

Efficacy

The final efficacy analyses will be based on the Intent-to-treat Population (defined as all subjects who receive any investigational product analyzed according to their randomized treatment group). CCI [redacted]

Safety

Safety data, including AEs, serious adverse events (SAEs), laboratory evaluations, vital signs, and electrocardiogram results, will be summarized based on the As-treated population (defined as all subjects who receive any investigational product analyzed according to treatment received). Descriptive statistics will be provided for AEs, SAEs, AE grade (severity), and relationship to study drug(s). AEs will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Descriptive statistics will be provided for the clinical laboratory results and toxicities.

Pharmacokinetics and Immunogenicity

For PK analysis, only subjects who receive at least 1 dose of medicinal product of interest (bevacizumab, durvalumab, or oleclumab) and/or other combination study drug and provide at least 1 post-treatment result will be evaluated. Individual bevacizumab and novel agent concentrations, as applicable, will be tabulated with descriptive statistics.

For immunogenicity assessment, only subjects who receive at least 1 dose of medicinal product of interest (bevacizumab, durvalumab, or oleclumab) and/or other combination study drug and provide a baseline and at least 1 post-treatment antidrug antibody (ADA) result will be evaluated. Immunogenicity results will be analyzed descriptively by summarizing the number and percentage of subjects who develop detectable ADAs to bevacizumab and applicable novel biologic agents. The potential impact of ADAs on PK and safety will be assessed if data allow. Samples confirmed positive for ADAs may also be evaluated for neutralizing antibody activity.

Interim analysis:

CCI

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LIST OF ABBREVIATIONS

Abbreviation or Specialized Term	Definition
1L	first line
2L	second line
5-FU	5-fluorouracil
ADA	antidrug antibodies
AE(s)	adverse event(s)
AESI(s)	adverse event(s) of special interest
ALP	alkaline phosphatase
ALT	alanine transaminase
AMP	adenosine monophosphate
AST	aspartate transaminase
ATP	adenosine triphosphate
BOR	best overall response
CCTG	Canadian Cancer Trials Group
CD	cluster of differentiation
CI(s)	confidence interval(s)
CMH	Cochran-Mantel-Haenszel
CNS	central nervous system
CR	complete response
CRC	colorectal cancer
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTL(s)	cytotoxic T lymphocyte(s)
CTLA-4	cytotoxic T-lymphocyte-associated antigen 4
CCI	CCI
DC	disease control
DCR	disease control rate
DEC	Dose Evaluation Committee
DILI	drug-induced liver injury
DLT(s)	dose-limiting toxicity(ies)
DoR	duration of response
DPD	dihydropyrimidine dehydrogenase

Abbreviation or Specialized Term	Definition
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
ESMO	European Society for Medical Oncology
FAAN	Food Allergy and Anaphylaxis Network
FDA	Food and Drug Administration (United States)
FFPE	formalin-fixed paraffin embedded
FOLFOX	folinic acid (leucovorin), 5-fluorouracil, oxaliplatin
GCP	Good Clinical Practice
HBV	hepatitis B virus
HBsAg	hepatitis B virus surface antigen
HCV	hepatitis C virus
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
CCI	CCI
imAE	immune-mediated adverse event
IgG1	immunoglobulin G1
INR	international normalized ratio
IRB	Institutional Review Board
ITT	intent-to-treat
IV	intravenous(ly)
IVRS	interactive voice response system
IWRS	interactive web response system
mAb	monoclonal antibody
MDSC(s)	myeloid-derived suppressor cell(s)
MRI	magnetic resonance imaging
MSI	microsatellite instability
MSS	microsatellite stable
CCI	CCI
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute

Abbreviation or Specialized Term	Definition
NIAID	National Institute of Allergy and Infectious Disease
NSCLC	non-small cell lung cancer
OR	objective response
ORR	objective response rate
OS	overall survival
PD	progressive disease
PD-1	programmed cell death protein 1
PD-L*x*	programmed cell death ligand-*x*
PFS	progression-free survival
PR	partial response
PK	pharmacokinetic(s)
QTcF	QT interval corrected for heart rate using Fridericia's formula
Q*x*W	every *x* weeks
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	recommended Phase II dose
RPLS	reversible posterior leukoencephalopathy syndrome
SAE(s)	serious adverse event(s)
SARS-CoV2	severe acute respiratory syndrome coronavirus 2
SD	stable disease
SID	subject identification
SRC	Safety Review Committee
TBL	total bilirubin
TGF	transforming growth factor
CC	CCI
CCI	CCI
Treg	Regulatory T cells
TV	target value
ULN	upper limit of normal
UPC	urine protein:creatinine (ratio)
UPM	unit probability mass
USA	United States of America
VEGF	vascular endothelial growth factor

1 INTRODUCTION

Study D910CC00001 is a Phase Ib/II, open-label, multicenter, randomized, multidrug platform study to evaluate the safety and efficacy of standard of care in combination with novel oncology therapies (durvalumab and oleclumab) in subjects with metastatic microsatellite stable (MSS) colorectal cancer (CRC) who have received no prior therapy in the recurrent/metastatic setting. New combination treatment arms can be added during the course of the study via protocol amendment, as novel agents of interest are available for testing in this population of patients (Section 1.6.4).

1.1 Disease Background

Colorectal cancer is the third most commonly diagnosed cancer in males and the second in females worldwide, with an estimated 1.8 million cases and 881000 deaths occurring in 2018 (Bray et al, 2018). In the United States, there were an estimated 140250 new cases of CRC and 50630 deaths in 2018 (Siegel et al, 2018). Approximately 21% of CRC cases are metastatic at diagnosis; 5 year survival is 14% in this population (Howlader et al, 2017). Colorectal cancer represents a molecularly heterogeneous disease characterized by a range of genomic and epigenomic alterations with variable clinical outcomes. Of these, the microsatellite instability (MSI) is caused by a hypermutable phenotype due to loss of DNA mismatch repair mechanisms, and is a key factor in disease prognosis and choice of therapy (Mármol et al, 2017; Sinicrope et al, 2015). About 10% to 15% of CRC cases present with MSI tumors and exhibit sensitivity to anti-programmed cell death protein 1 (PD-1) therapy (Le et al, 2015). However, most CRC (85% to 90% of tumors) is defined as MSS and is currently resistant to monotherapy immune checkpoint blockade (Le et al, 2015).

1.1.1 Immunotherapy

1.1.1.1 Programmed Cell Death Ligand-1

Programmed cell death protein 1, programmed cell death ligand-1 (PD-L1), and PD-L2 are part of a complex system of receptors and ligands that control T-cell activation. Programmed cell death ligand-1 expression helps tumors evade detection and elimination by the immune system (Chen and Mellman, 2013; Juneja et al, 2017; Keir et al, 2008; Ohaegbulam et al, 2015). The binding of PD-L1 to PD-1 on activated T cells delivers an inhibitory signal preventing T cells from killing target tumor cells (Pardoll, 2012; Zou and Chen, 2008; Zou et al, 2016). Ipilimumab (cytotoxic T-lymphocyte-associated protein 4 [CTLA-4] inhibitor) in combination with nivolumab (PD-1 inhibitor) in patients with MSI-high or mismatch repair-deficient metastatic CRC that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan, has received Food and Drug Administration (FDA) accelerated approval (Yervoy® US PI, 2018). Pembrolizumab is FDA approved to treat patients with unresectable or metastatic solid tumors that have been identified as having a biomarker referred to as MSI-high or mismatch repair deficient (Keytruda® US PI, 2018).

1.1.1.2 CD73

Adenosine is a regulatory autocrine and paracrine factor that accumulates in the tumor microenvironment, influencing immune activity, angiogenesis, and metastasis. Upon apoptotic or necrotic cell death, tumor cells release adenosine triphosphate (ATP) into the extracellular space. Adenosine triphosphate has been shown to lead to a pro-inflammatory response. To prevent an immune over activation, tissues express cluster of differentiation (CD)39 and CD73 to enzymatically convert ATP to adenosine, which induces a localized immunosuppressive response through multiple immune cell types. In the extracellular space, CD39 and CD73 in tandem metabolize ATP to adenosine monophosphate (AMP), and AMP to adenosine, respectively, and are a major source of extracellular adenosine. Extracellular adenosine impairs the proliferation and effector function of cytotoxic T lymphocytes (CTLs) while simultaneously contributing to the immunosuppressive effects of both regulatory T cells and myeloid-derived suppressor cells, among others (Vijayan et al, 2017). The rate-limiting step in the generation of extracellular adenosine is the dephosphorylation of AMP by CD73.

One mechanism by which tumors may have evolved to evade the immune system is via overexpression of CD73. Overexpression of CD73 has been associated with poor prognosis in multiple cancer types (Hay et al, 2016; Inoue et al, 2017; Vijayan et al, 2017). In patients with CRC, overexpression of CD73 is an independent biomarker for predicting poor survival (Liu et al, 2012; Wu et al, 2012). It is hypothesized that blocking CD73 activity will reduce adenosine production, thus augmenting host and/or immunotherapy response to tumor.

1.2 Study Drug Background

1.2.1 Durvalumab

Durvalumab is a human immunoglobulin G1 (IgG1) kappa monoclonal antibody (mAb) that blocks the interaction of PD-L1 (but not PD-L2) with PD-1 on T cells and CD80 (B7.1) on immune cells and is engineered to reduce antibody-dependent cell-mediated cytotoxicity and complement activation. Refer to the current durvalumab Investigator's Brochure (IB) for details.

1.2.2 Oleclumab

Oleclumab (MEDI9447) is a human IgG1 lambda mAb that selectively binds to CD73 and inhibits adenosine production; in addition, oleclumab reduces CD73 expression through internalization (Geoghegan et al, 2016; Hay et al, 2016). It contains a triple mutation in the heavy chain constant region for reduced effector function. The enzymatic blockade of CD73 and decreased expression caused by binding of oleclumab to CD73 may lead to increased antitumor immunity. Refer to the current oleclumab IB for details.

1.3 Summary of Nonclinical Experience

A complete summary of nonclinical experience for durvalumab and oleclumab can be found in the IB for each agent.

1.4 Summary of Clinical Experience

A complete summary of clinical experience, including safety, efficacy, and pharmacokinetics (PK), for durvalumab and oleclumab can be found in the IB for each agent. A summary of potential benefits and risks is presented in Section 1.6.

1.5 Rationale for Conducting the Study

Despite advances in chemotherapy regimens in combination with biologics in the treatment of CRC, most patients still progress within 6 months after receiving either first line (1L) or second line (2L) chemotherapy (Saltz et al, 2008; Heinemann et al, 2014; Venook et al, 2017). Furthermore, almost all patients who are beyond 2L treatment progress within 3 months after initiation of their last line of therapy (Grothey et al, 2013; Mayer et al, 2015).

Monotherapy with checkpoint inhibitors in subjects with MSS-CRC has resulted in limited or no antitumor activity. For example, an objective response rate (ORR) of 0% was reported when pembrolizumab 10 mg/kg every 2 weeks (Q2W) was administered to subjects with MSS-CRC (Le et al, 2015). Combining immune checkpoint inhibitors and novel therapies with conventional cytotoxic drugs could theoretically provide durable anticancer responses and hence improve the patients' outcome.

In CRC nonclinical models, 5-fluorouracil (5-FU) and oxaliplatin have been shown to promote immunogenic cell death through calreticulin exposure (Martins et al, 2011), to increase CTL/regulatory T cells (Treg) ratio (Gonzalez-Aparicio et al, 2011), and to deplete circulating myeloid-derived suppressor cells (MDSCs; FOLFOX [folinic acid (leucovorin), 5-FU, oxaliplatin]) (Kanterman et al, 2014; Gonzalez-Aparicio et al, 2011). Further, the immunomodulatory role of vascular endothelial growth factor (VEGF) targeting agents, such as bevacizumab, has also been explored in these colorectal models. Vascular endothelial growth factor A is recognized as a key mediator of the immune response by modulating the expression of PD-1, CTLA-4, and Tim-3 on $CD8^+$ T cells (Voron et al, 2015). Bevacizumab has been demonstrated to deplete Tregs (Terme et al, 2013). Altogether, these nonclinical data suggest that combining durvalumab (anti-PD-L1) with FOLFOX plus bevacizumab may provide complementary benefit in mounting an effective antitumor immunity in patients with CRC.

Checkpoint inhibitors in combination with chemotherapy have been tested in subjects with metastatic CRC. Studies have examined the combination of atezolizumab (an anti-PD-L1 agent) with bevacizumab (Arm A) or atezolizumab with bevacizumab and FOLFOX at standard doses (Arm B) (Bendell et al, 2015), nivolumab with capecitabine and irinotecan

(Khemka et al, 2016), or modified FOLFOX with pembrolizumab (Shahda et al, 2017). All combinations appear to be safe and well tolerated.

A variety of approaches for combining PD-1/PD-L1 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, durvalumab, anti-CTLA-4), immunostimulatory cytokines (eg, interferon-γ), cytotoxic chemotherapy, antiangiogenic inhibitors, and small-molecule molecular-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 I studies; a MedImmune-sponsored study (D419SC00001, unpublished data on file) and a Phase Ib study conducted by the Canadian Cancer Trials Group (CCTG; NCT02537418; Daaboul et al, 2017). The combinations tested were tolerable and manageable. In addition, an ongoing Phase Ib/II trial is evaluating the safety, tolerability, and antitumor activity of durvalumab plus tremelimumab combined with FOLFOX in subjects with untreated, RAS mutation positive metastatic CRC (NCT03202758; Fumet et al, 2018a; Fumet et al, 2018b). After an initial safety run-in of 9 subjects, FOLFOX plus durvalumab and tremelimumab was tolerable with manageable toxicity. Preliminary results have shown encouraging clinical outcome; 4 of 9 subjects had a partial response (PR) and 3 subjects had stable disease (SD). The results of the Phase I study have led to the Phase II study, which is ongoing.

In summary, the preliminary efficacy, safety, and tolerability data generated to date for durvalumab alone, 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 MSS-CRC and the initial promising antitumor activity seen with durvalumab in combination with other immuno-oncology agents in subjects with MSS-CRC and good tolerability, it was decided to evaluate whether this preliminary antitumor activity of durvalumab in combination with other novel oncology therapies could be further improved with acceptable tolerability by adding a standard chemotherapy regimen of FOLFOX with bevacizumab in subjects with 1L MSS-CRC. 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.

1.5.1 Rationale for Inclusion of Durvalumab in Combination with Oleclumab

CD73 is known to contribute to the immunosuppressive effects of both CTLs and myeloid-derived suppressor cells, among others (Vijayan et al, 2017). High protein expression of CD73 is associated with poor outcome in CRC patients (Wu et al, 2012). Nonclinical experiments have shown increased tumor growth inhibition and survival in tumor bearing mice treated with

anti-CD73 antibody in combination with anti-PD-1/PD-L1 antibodies (Hay et al, 2016). Oleclumab selectively binds to CD73, inhibits adenosine production and reduces the CD73 expression. The combination of oleclumab with durvalumab is hypothesized to exert a synergistic effect on the reversal of immune suppression in the tumor microenvironment. Chemotherapeutic agents, including oxaliplatin, induce significant ATP release from tumor cells (Martins et al, 2009). Oleclumab may counteract any downstream adenosine mediated immunosuppressive effects induced by this ATP release. Oleclumab in combination with durvalumab (Study D6070C00001) and in combination with durvalumab and chemotherapy (Study D6070C00005) exhibited a manageable safety profile (see oleclumab IB and Section 1.6.2.3), further supporting exploration of this treatment combination. In addition, preliminary evidence of efficacy has been observed for oleclumab plus durvalumab in subjects with CRC (Study D6070C00001; see oleclumab IB and Section 1.6.1.1).

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.

Detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of durvalumab and each novel oncology therapy may be found in the respective IB for each molecule.

1.6.1 Potential Benefits

1.6.1.1 Durvalumab in Combination with Chemotherapy

An ongoing Phase Ib/II trial is evaluating the safety, tolerability, and antitumor activity of durvalumab plus tremelimumab combined with FOLFOX in subjects with untreated, RAS mutation-positive metastatic CRC (NCT03202758; Fumet et al, 2018a; Fumet et al, 2018b). After an initial safety run-in of 9 subjects, FOLFOX plus durvalumab and tremelimumab was tolerable with manageable toxicity. Preliminary results have shown encouraging clinical outcome; 4 of 9 subjects had a PR and 3 subjects had SD. The results of the Phase I study have led to the Phase II study, which is ongoing.

1.6.1.2 Oleclumab

As of 09 June 2019, 3 clinical studies are currently ongoing with oleclumab: Studies D6070C00001, D6070C00004, and D6070C00005. The safety and clinical activity of durvalumab 10 mg/kg Q2W plus oleclumab 40 mg/kg Q2W in third and fifth line MSS-CRC subjects is being evaluated in Study D6070C00001. Preliminary data suggest that treatment with oleclumab is well tolerated and leads to a reduction in CD73 expression on both tumor and circulating immune cells.

Efficacy data from 111 response-evaluable subjects treated with oleclumab plus durvalumab in the dose-expansion phase of Study D6070C00001, including subjects with CRC, pancreatic adenocarcinoma, and non-small cell lung cancer (NSCLC) showed a confirmed ORR of 2.4% (1 of 42 subjects), 4.8% (2 of 42 subjects), and 11.1% (3 of 27 subjects), respectively, with a disease control rate (DCR) at 8 weeks of 21.4%, 23.8%, and 18.5%, respectively. The duration of response (DoR) was 22.1 months in the subject with CRC, 9.2 and 17.6 months in the 2 subjects with pancreatic adenocarcinoma, respectively, and ranged between 5.5 and 5.6 months in the 3 subjects with NSCLC.

In addition, 11 subjects with metastatic pancreatic adenocarcinoma, in Study D6070C00005, have received CCI (3 subjects) or CCI (8 subjects) oleclumab CCI CCI, CCI durvalumab CCI, and a modified regimen of FOLFOX. The regimen is currently being examined in dose-escalation with no dose-limiting toxicities (DLTs) reported and the combination has been well tolerated so far. Refer to the current oleclumab IB for additional information.

The plan to combine oleclumab with durvalumab, FOLFOX, and bevacizumab (Arm S1 and Arm E1) in the current study is supported by nonclinical and clinical studies that have demonstrated increases in CD73 expression and increases in extracellular ATP in response to chemotherapy (Samanta et al, 2018; Zhao et al, 2015). In addition, nonclinical studies have demonstrated synergistic benefit of chemotherapy with CD73 blockade (Loi et al, 2013). Furthermore, FOLFOX-bevacizumab treatment elicited a decrease in granulocytic MDSCs in 15 of 25 patients with metastatic CRC and was associated with an improved survival outcome (Limagne et al, 2016). Notably, granulocytic MDSCs that expressed high levels of PD-L1, CD39, and CD73 exerted a robust immunosuppressive activity, relative to other myeloid cells present in blood, which could be reversed by blocking the CD39/CD73 and PD1/PD-L1 axes. Therefore, oleclumab with durvalumab combined with FOLFOX and bevacizumab therapy may demonstrate a clinically meaningful benefit and manageable safety profile compared with FOLFOX and bevacizumab alone. The overall benefit-risk profile of the proposed treatment combinations is expected to be favorable for subjects with MSS-CRC, therefore supporting the current study design.

1.6.2 Potential Risks

Monoclonal antibodies directed against immune checkpoint proteins, such as PD-L1, aim to boost endogenous immune responses against tumor cells. By stimulating the immune system, however, there is the potential for adverse effects on normal tissues.

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. These risks are generally events with a potential inflammatory or immune-mediated mechanism and that may require more frequent monitoring and/or unique interventions such as immunosuppressants

and/or endocrine therapy. These immune-mediated effects can occur in nearly any organ system and are most commonly seen as gastrointestinal AEs such as colitis and diarrhea, pneumonitis/interstitial lung disease, hepatic AEs such as liver enzyme elevations, skin events such as rash and dermatitis, and endocrinopathies including hypo- and hyper-thyroidism.

1.6.2.1 Durvalumab Risks

Risks with durvalumab include, but are not limited to, diarrhea/colitis, pneumonitis/interstitial lung disease, endocrinopathies (ie, events of hypophysitis/hypopituitarism, adrenal insufficiency, hyperthyroidism, hypothyroidism, type I diabetes mellitus, and diabetes insipidus), hepatitis/increases in transaminases, nephritis/increases in creatinine, rash/dermatitis, myocarditis, myositis/polymyositis, infusion-related reactions, hypersensitivity reactions, pancreatitis, serious infections, and other rare or less frequent inflammatory events, including neuromuscular toxicities (eg, Guillain-Barré syndrome, myasthenia gravis).

In monotherapy clinical studies, AEs reported at an incidence of ≥ 20% include events such as fatigue, cough, decreased appetite, dyspnea, and nausea. Approximately 10% of subjects discontinued the drug due to an AE. Refer to the current edition of the durvalumab IB for a detailed summary of the monotherapy data, including AEs, serious adverse events (SAEs), and Grade 3 to Grade 5 AEs reported across the durvalumab program.

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

A detailed summary of durvalumab monotherapy AE data can be found in the current edition of the durvalumab IB.

1.6.2.2 Checkpoint Inhibitors in Combination with Chemotherapy

Checkpoint Inhibitors in Combination with Chemotherapy and Bevacizumab

Checkpoint inhibitors in combination with chemotherapy have been tested in subjects with metastatic CRC (Section 1.5). A Phase Ib study evaluated atezolizumab (anti-PD-L1 antibody) with bevacizumab (Arm A) or atezolizumab with bevacizumab and FOLFOX at standard doses (Arm B) (NCT01633970; Bendell et al, 2015). All combinations appeared to be well tolerated with no unexpected toxicities. In a Phase II study (MODUL, NCT02291289) comparing fluoropyrimidine plus bevacizumab versus fluoropyrimidine plus bevacizumab with atezolizumab (Cohort 2) as 1L maintenance therapy, the safety profiles observed were consistent with previous findings with no new safety signals identified (Grothey et al, 2013; Grothey et al, 2018).

Durvalumab in Combination with Chemotherapy with or without Other Immunotherapies

An ongoing Phase Ib/II trial is evaluating the efficacy and safety of durvalumab plus tremelimumab combined with FOLFOX in subjects with untreated, RAS mutation positive metastatic CRC (NCT03202758; ESMO 2019; Fumet et al, 2018a; Fumet et al, 2018b). Subjects receive FOLFOX at standard doses plus durvalumab 750 mg Q2W and tremelimumab 75 mg Q4W. After 6 cycles of FOLFOX, only durvalumab and tremelimumab continue. Nine subjects were enrolled in Phase I. Grade 3-4 treatment-related AEs occurred in 3 of 9 subjects. The most common treatment-related Grade 3-4 AEs were neutropenia and diarrhea. No subjects discontinued due to a drug-related AE. CCI [redacted] he results of the Phase I study have led to the Phase II study, which is ongoing.

Overall, toxicities related to the chemotherapy and to durvalumab and tremelimumab were as expected for these agents.

1.6.2.3 Durvalumab plus Oleclumab

Overall, oleclumab and durvalumab combination therapy has demonstrated an acceptable safety profile (see oleclumab IB). As of 09 June 2019, 135 subjects have received oleclumab and durvalumab combination therapy. Of these, 111 subjects with CRC, pancreatic cancer, and NSCLC were treated with 40 mg/kg oleclumab Q2W plus 10 mg/kg durvalumab Q2W combination therapy in the dose-expansion phase of Study D6070C00001.

Following oleclumab plus durvalumab combination therapy in the dose-expansion phase of Study D6070C00001, 53.2% of subjects (59 of 111) reported a treatment-related AE, with fatigue (14.4%), diarrhea (9.0%), pyrexia and vomiting (6.3% each), and increased aspartate aminotransferase (AST; 5.4%) being the most common (≥ 5.0%). Grade 3 or Grade 4 AEs were reported in 54.1% of subjects (60 of 111), with increased blood alkaline phosphatase (7.2%), increased gamma-glutamyl transferase and increased AST (5.4% each), and pneumonia (4.5%) being the most common (≥ 4.0%). Overall, 15.3% of subjects reported treatment-related Grade 3 or Grade 4 AEs. The rate of treatment-related AEs leading to discontinuation was 7.2%. Three subjects had AEs leading to death. One subject died of a treatment-related SAE of systemic inflammatory response syndrome. The other 2 subjects had fatal AEs of respiratory arrest and pulmonary embolism, respectively, which were considered unrelated to study treatment.

As of 09 June 2019, of 11 subjects with metastatic pancreatic adenocarcinoma in Study D6070C00005, one subject from the oleclumab CCI [redacted] dose cohort experienced DLTs. This subject reported SAEs of nausea (Grade 3; not related to oleclumab), localized edema (Grade 3; related to oleclumab), bacterial infection (Grade 3; not related to oleclumab), and dizziness (Grade 3; not related to oleclumab), of which nausea and localized edema were identified as DLTs. No other DLTs were reported for this combination.

For oleclumab, important potential risks include thrombosis and increased microvascular permeability, and potential risks for oleclumab include arterial ischemic disorder, arterial calcifications, and joint calcifications. These events were determined as potential risks for oleclumab based on clinical findings in individuals with CD73 deficiency and findings in CD73-deficient mice. Additional important potential risks include infusion-related reactions, anaphylaxis, hypersensitivity and serious allergic reactions, and immune complex disease, which are associated with the administration of mAbs. Additional potential risks associated with any intravenous (IV) administration are localized infection, redness, swelling, pain, and induration at the administration site. Given the mode of action of oleclumab, the theoretical risk associated with removing the inhibition of adenosine on the microenvironment favors increased antitumor immunity when combined with durvalumab, as well as the risk of emergence of autoimmune phenomena. For information on all identified and potential risks with oleclumab, refer to the current oleclumab IB. See Section 5.3.3 for adverse events of special interest (AESIs) associated with oleclumab.

1.6.3 Overall Benefit-Risk

In the 1L setting, FOLFOX plus bevacizumab is the recommended standard of care in metastatic CRC per National Comprehensive Cancer Network (NCCN) and European Society for Medical Oncology (ESMO) guidelines (NCCN, 2018; Van Cutsem et al, 2016); further improvement in clinical outcomes may be achieved through combination with novel therapies such as durvalumab and oleclumab. Clinical and nonclinical data to date have shown an acceptable safety profile for oleclumab in combination with durvalumab.

The design of the current study aims to minimize potential risks to subjects and include the protocol inclusion and exclusion criteria (Section 4.1.2 and Section 4.1.3, respectively), restrictions on concomitant medication during the study (Section 4.7), safety monitoring (including review of all safety, PK, and other relevant data by the Dose Evaluation Committee [DEC; Section 3.1.3.3] in Part 1 or Safety Review Committee [SRC; Section 3.1.5.2] in Part 2), toxicity management guidelines (Section 3.1.6 and Appendix H), study stopping criteria (Section 4.1.6), and rules and procedures to add new combination treatment arms (Section 1.6.4). Specific intensive safety monitoring is in place for those risks deemed to be most likely for each of the novel combination therapies. Overall, the benefit-risk assessment for this Phase Ib/II platform study is acceptable.

Of note, the eligibility criteria exclude participants with active severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) infection (see Section 4.1.3, exclusion criteria 1, 8, and 11). In case of an infection while on study, including SARS-CoV2, the general toxicity management guidelines and institutional practice guidelines should be followed.

1.6.4 Criteria for Additional Treatment Arms

Further design elements aim to specifically minimize the risks for subjects allocated to a combination experimental arm. Any new combination treatment arm must adhere to the following elements:

- A rationale for additive or synergistic activity of the potential new candidate agent in combination based on its mechanism of action and/or supported by nonclinical or clinical evidence.
- An established recommended dose for the novel agent(s).
- Description of the safety profile and AESIs for the novel agent alone, in combination with durvalumab, and/or with chemotherapy based on previous clinical studies demonstrating a safety profile that would be considered acceptable for the target population in this study.
- Requirement of a protocol amendment and respective health authority and local Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approvals prior to implementing any new experimental arm.
- Updated informed consent form with relevant information on the new combination experimental arm.

1.6.4.1 Regulatory Amendment for Additional Arms: Europe and Rest of World

The sponsor will provide a substantial amendment for review and approval.

1.6.4.2 Regulatory Amendment for Additional Arms: United States of America

For substantive changes that affect safety, scope, or the scientific quality of the study, the sponsor will provide an amendment to the FDA 30 days in advance of planned enrollment amendment unless the amendment contains changes to eliminate an immediate hazard to subjects. The sponsor will begin enrollment of subjects on new cohorts in the United States only after the 30-day review period is completed and after IRB approval is received.

Protocol changes needed to eliminate an apparent immediate hazard to subjects (eg, closure of an arm for unacceptable toxicity, modification of eligibility or monitoring to mitigate risks) will be implemented immediately. Both FDA and IRBs will subsequently be notified of these changes.

1.7 Research Hypotheses

In Part 1, novel oncology therapies plus standard of care (FOLFOX plus bevacizumab) will demonstrate adequate safety and tolerability in subjects with 1L metastatic MSS-CRC to permit further evaluation in Part 2.

In Part 2, novel oncology therapies plus standard of care (FOLFOX plus bevacizumab) will demonstrate superior antitumor activity to standard of care alone in subjects with 1L metastatic MSS-CRC.

2 OBJECTIVES AND ENDPOINTS

2.1 Primary Objectives and Associated Endpoints

Table 1 Primary Objectives and Associated Endpoints

Type	Objective	Endpoint
Safety	**Part 1:** To evaluate the safety and tolerability profile of FOLFOX + bevacizumab + novel oncology therapy combinations	Incidence of AEs, SAEs, DLTs, laboratory findings, and vital signs
Efficacy	**Part 2:** To compare the efficacy of FOLFOX + bevacizumab + novel oncology therapy combinations versus FOLFOX + bevacizumab	OR per RECIST v1.1

AE = adverse event; DLT = dose-limiting toxicity; FOLFOX = folinic acid (leucovorin), 5-fluorouracil, oxaliplatin; OR = objective response; RECIST v1.1 = Response Evaluation Criteria for Solid Tumors version 1.1; SAE = serious adverse event

2.2 Secondary Objectives and Associated Endpoints

Table 2 Secondary Objectives and Associated Endpoints

Type	Objective	Endpoint
Efficacy	**Part 1:** To investigate the preliminary antitumor activity of FOLFOX + bevacizumab + novel oncology therapy combinations	Assessments of antitumor activity include OR, BOR, DoR, DC, PFS-12, and PFS as assessed by RECIST v1.1 and OS
Safety	**Part 2:** To evaluate the safety and tolerability profile of FOLFOX + bevacizumab + novel oncology therapy combinations	Incidence of AEs, SAEs, laboratory findings, and vital signs
Efficacy	**Part 2:** To compare the efficacy of FOLFOX + bevacizumab + novel oncology therapy combinations versus FOLFOX + bevacizumab	Assessment of antitumor activity include BOR, DoR, DC, PFS-12, and PFS as assessed by RECIST v1.1 and OS
Pharmacokinetics	**Part 1 and 2:** To describe the PK of novel agents **Part 1:** To describe the PK of bevacizumab	**Part 1 and 2:** PK (drug concentration) for novel agents **Part 1:** PK (drug concentration) for bevacizumab
Immunogenicity	**Part 1 and 2:** To describe the immunogenicity of applicable novel agents **Part 1:** To describe the immunogenicity of bevacizumab	**Part 1 and 2:** Incidence of ADA to applicable novel agents **Part 1:** Incidence of ADA to bevacizumab

Table 2 Secondary Objectives and Associated Endpoints

Type	Objective	Endpoint

ADA = antidrug antibody; AE = adverse event; BOR = best overall response; DC = disease control; DoR = duration of response; FOLFOX = folinic acid (leucovorin), 5-fluorouracil, oxaliplatin; OR =objective response; OS = overall survival; PFS = progression-free survival; PFS-12 = progression-free survival at 12 months; PK = pharmacokinetics; RECIST v1.1 = Response Evaluation Criteria for Solid Tumors version 1.1; SAE = serious adverse event.

2.3 Exploratory Objectives and Associated Endpoints

Table 3 Exploratory Objectives and Endpoints

CCI

Table 3 Exploratory Objectives and Endpoints

CCI
CCI

3 STUDY DESIGN

3.1 Description of the Study

3.1.1 Overview

Study D910CC00001 is a Phase Ib/II, open-label, multicenter, randomized, multidrug platform study to evaluate the safety and efficacy of standard of care (FOLFOX plus bevacizumab) in combination with novel oncology therapies (durvalumab and oleclumab) in subjects with 1L metastatic MSS-CRC. The study is designed to concurrently evaluate potential novel combinations with clinical promise using a 2-part approach (Figure 1). Part 1 is a Phase Ib study of safety, and Part 2 is a Phase II study of efficacy and safety. The treatment arms are defined in Table 4, and regimens are described in Section 3.1.2. The treatment regimens evaluated in Part 2 will depend on the evaluation of safety outcomes in Part 1.

Following a screening period of up to 28 days, subjects will be centrally assigned (Part 1) or randomized (Part 2) to one of the open study arms. Information on subject randomization and sample size is provided in Section 4.6.1 and Section 4.8.2, respectively. Up to approximately 30 to 40 sites globally will participate in this study.

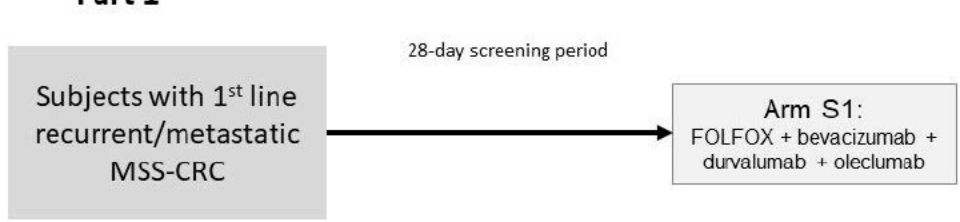
Table 4 Study Arms and Treatments

Part	Arm	Study Treatment
1	S1	FOLFOX + bevacizumab + durvalumab + oleclumab
CCI [redacted]		

E = experimental; FOLFOX = folinic acid (leucovorin), 5-fluorouracil, oxaliplatin; S = safety run-in

In both study parts, study treatment may be administered until disease progression or any discontinuation criteria are met (Section 4.1.6). Mechanisms for post-study access to treatment are described in Section 3.1.7. CCI [redacted]

Figure 1 Study Flow Diagram



E = experimental; FOLFOX = folinic acid (leucovorin), 5-fluorouracil, oxaliplatin; MSS-CRC = microsatellite stable colorectal cancer; S = safety run-in

3.1.2 CCI

CCI

CCI

Figure 2 CCI

CCI

CCI

3.1.3 Safety Run-in (Part 1)

3.1.3.1 CCI

CCI [redacted]

3.1.3.2 CCI

CCI [redacted]

CCI

Table 5 CCI

CCI

3.1.3.3 Dose Evaluation Committee (Part 1)

A study-specific DEC (including at a minimum the medical monitor/clinical lead and participating investigators who have enrolled subjects) in accordance with its charter, will provide ongoing safety surveillance of Part 1 of the study. This committee may also meet to review data at other time points (eg, in response to AEs assessed as medically relevant by the medical monitor). This committee will be responsible for making recommendations for safety run-in decisions. The DEC will review the totality of all available clinical and laboratory safety and PK data and all other relevant data prior to establishing safety run-in decisions based on the dose de-escalation rules. All decisions by this committee will be documented and shared in writing with all participating sites.

3.1.4 Dose-limiting Toxicity (Part 1)

Dose-limiting toxicities will be evaluated during the safety run-in phase (Part 1). The DLT evaluation period is defined as 28 days from the first dose of investigational product (novel therapy). Subjects who do not complete the DLT-evaluation period or did not receive the full prescribed dose of durvalumab and ≥ 75% of the prescribed number of doses of FOLFOX plus bevacizumab and the other novel oncology therapy for reasons other than DLT will be considered non-evaluable for DLT assessment and will be replaced with another subject in the same arm but will still be considered when reviewing toxicity from this arm.

Grading of DLTs will be according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

A DLT will be defined as any Grade 3 or higher toxicity or any of the events listed below that occurs during the 28-day DLT-evaluation period. Toxicity that is clearly and directly related to the primary disease or to another etiology is excluded from this definition. Toxicity that is clearly and directly related to standard treatment (oxaliplatin, 5-FU, and/or bevacizumab) and not related to the novel therapy is excluded from this definition.

The following events will be DLTs:

- Grade 4 immune-mediated adverse event (imAE)
- Grade 3 or Grade 4 noninfectious pneumonitis irrespective of duration
- Grade 3 or Grade 4 noninfectious colitis irrespective of duration
- Liver transaminase elevation:
  - Transaminase elevation > 8 × upper limit of normal (ULN) or total bilirubin (TBL) > 5 × ULN regardless of duration or reversibility
  - Any increase in AST or alanine transaminase (ALT) > 3 × ULN and concurrent increase in TBL > 2 × ULN, regardless of duration or reversibility, where no other reason, other than the investigational product(s), can be found to explain the combination of increases
  - Isolated liver transaminase elevation > 5 × but ≤ 8 × ULN or isolated TBL elevation > 3 × but ≤ 5 × ULN that does not downgrade to Grade 2 or less within 14 days despite optimal management
- Any Grade 3 imAE, including rash, pruritus, or diarrhea (NOTE: this excludes colitis or pneumonitis, as these AEs are already defined above), that does not downgrade to Grade ≤ 2 within 7 days after onset of the event despite maximal supportive care including systemic corticosteroids
- Grade 3 nausea, vomiting, or diarrhea that does not resolve to Grade 2 or less within 3 days of initiation of maximal supportive care
- Grade 3 or Grade 4 neutropenia and/or febrile neutropenia
  - Grade 3 or Grade 4 febrile neutropenia regardless of duration
  - Grade 4 neutropenia, not associated with fever or systemic infection, lasting for > 7 days
  - Grade 3 neutropenia, not associated with fever or systemic infection, that does not improve by at least one grade within 7 days of onset
- Grade 3 or Grade 4 anemia
  - Grade 4 anemia regardless of duration
  - Grade 3 anemia if associated with clinical sequelae or requires transfusion of > 2 units of red blood cell
- Grade 3 or Grade 4 thrombocytopenia
  - Grade 4 thrombocytopenia lasting more than 7 days
  - Grade 3 thrombocytopenia that does not improve by at least one grade within 7 days of onset

- Grade 3 or Grade 4 thrombocytopenia, regardless of duration, associated with Grade 3 or higher hemorrhage or requiring transfusion or invasive intervention

The DLT definition excludes the following conditions:

- Grade 3 fatigue lasting ≤ 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 the symptoms within 14 days after treatment onset.
- Grade 3 inflammatory reaction attributed to a local antitumor response (eg, inflammatory reaction at sites of metastatic disease, lymph nodes) that resolves to ≤ Grade 1 within 30 days after onset
- Concurrent vitiligo or alopecia of any AE grade
- Grade 3 infusion-related reaction: first occurrence and in the absence of steroid prophylaxis that resolves within 12 hours with appropriate clinical management
- Grade 3 or Grade 4 lymphopenia (unless associated with clinical sequelae)
- Isolated Grade 3 electrolyte abnormalities that are not associated with clinical signs or symptoms (eg, hyperlipasemia or hyperamylasemia not associated with clinical signs or symptoms or radiographic features suggestive of pancreatitis) and are reversed with appropriate maximal medical intervention within 7 days
- Grade 3 rigors, chills, or fever lasting < 24 hours with appropriate maximal medical therapy
- Grade 3 diarrhea, nausea, and/or vomiting in the absence of maximal supportive care that responds to therapy per institutional standards and improves by at least 1 grade within 3 days of onset
- Grade 3 hypertension that can be controlled with medical therapy (to < 160/100 mmHg within 7 days)

Immune-mediated AEs are defined as AEs of immune nature (ie, inflammatory) in the absence of a clear alternative etiology. In the absence of clinical abnormality, repeat laboratory testing will be conducted to confirm significant laboratory findings prior to designation as a DLT. An AE not listed above, or an AE meeting the DLT criteria above but occurring outside of the DLT period may be defined as a DLT after consultation with the sponsor and investigators based on the emerging safety profile.

3.1.5 Randomized Phase (Part 2)

Once Part 1 has been completed for a given arm, Part 2 will open for randomization to evaluate the efficacy and safety of an arm with the same treatment regimen. Randomization will be evenly distributed across all open arms (eg, 1:1, 1:1:1) and will be stratified based on location of the primary tumor (right sided vs left sided). After 50 subjects are randomized to the control arm, the control arm will continue to enroll subjects, but the allocation ratio to the different arms may be adjusted via protocol amendment. Enrollment to the control arm will

pause if there is no active experimental arm. The exact subsequent allocation ratios across arms will be determined by the sponsor during the conduct of the study (Section 4.6.1).

3.1.5.1 Interim Analysis (Part 2)

CCI [redacted]

3.1.5.2 Safety Review Committee (Part 2)

An SRC will conduct safety reviews of all enrolled subjects at least twice a year. The SRC may make recommendations regarding continuation, modification, or termination of any study arm for safety concerns. The SRC will also be responsible for making recommendations for investigational product dose selection to ensure subjects maintain adequate exposure (eg, assessment of dose modifications, dose delays, etc) to standard of care treatment (FOLFOX plus bevacizumab). The committee may request additional data (eg, clinical efficacy) as needed. Additional safety reviews may be conducted at the discretion of the SRC.

The SRC will consist of the following:

- External physician not associated with the conduct of the study (SRC Chairperson)
- Principal Investigators from a subset of active investigational sites. The number of sponsor representatives will not exceed the number of Principal Investigators.
- The sponsor study medical monitor, or delegate
- The sponsor Global Safety Physician, or delegate
- The sponsor Study Statistician, or delegate

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

3.1.6 Management of Study Medication Related Toxicities

The following general guidelines should be followed for management of toxicities:

(A) Study drug treatment can be held/omitted in the context of toxicity. Omitted doses will not be administered at a later date. Study treatment may resume when appropriate following the schedule of evaluations.

(B) Study treatment modifications are to be made independently for each study drug, based on the specific types of toxicity that are observed, unless otherwise noted.

Refer to Appendix H for additional details regarding treatment modification and toxicity management. Actions required for any case meeting potential Hy's Law criteria are described in Appendix D.

3.1.6.1 Management of Toxicities Related to Durvalumab-containing Regimens

Subjects who receive oleclumab in combination with durvalumab should follow the durvalumab toxicity management guidelines, which are provided as an Annex to this protocol as described below.

Comprehensive toxicity management guidelines have been developed to assist investigators with the recognition and management of toxicities associated with the use of the immune checkpoint inhibitors durvalumab (PD-L1 inhibitor) and tremelimumab (CTLA-4 inhibitor). Given the similar underlying mechanisms of toxicities observed with these 2 compounds, these durvalumab ± tremelimumab guidelines are applicable to the management of subjects receiving either drug as monotherapy or in combination. Additionally, these guidelines are applicable when either drug is used alone or in combination, and is administered concurrently or sequentially with other anticancer drugs (ie, antineoplastic chemotherapy, targeted agents), as part of a protocol-specific treatment regimen. The toxicity management guidelines provide information for the management of immune-mediated reactions, infusion-related reactions, and non-immune-mediated reactions that may be observed with checkpoint inhibitor monotherapy or combination checkpoint inhibitor regimens, with specific instructions for dose modifications (including discontinuations) and treatment interventions. Investigators are advised, however, to use local practice guidelines and consult local references for the management of toxicities observed with other cancer treatment (Section 3.1.6.2). The most current version of the durvalumab ± tremelimumab toxicity management guidelines, entitled "Dosing Modification and Toxicity Management Guidelines for Immune-Mediated, Infusion-Related, and Non-Immune-Mediated Reactions (MEDI4736 Monotherapy or Combination Therapy with Tremelimumab or Tremelimumab Monotherapy)", is provided to the investigative site as an Annex document and is maintained within the Site Master File. In addition, a version of the current Dosing Modification and Toxicity Management Guidelines is available through the following link: https://tmg.azirae.com. Please contact the study representative for information on how to gain access to this website.

Subjects should be thoroughly evaluated and appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the imAE. Serologic, immunologic, and histologic (biopsy) data, as appropriate, should be used to support an imAE diagnosis. In the absence of a clear alternative etiology, events should be considered potentially immune-related. In addition, there are certain circumstances in which durvalumab should be permanently discontinued. Following the first dose of investigational product, subsequent administration of durvalumab can be modified based on toxicities observed as described in the Dosing Modification and Toxicity Management Guidelines. These guidelines

have been prepared by the sponsor to assist the investigator in the exercise of his/her clinical judgment in treating these types of toxicities. These guidelines apply to AEs considered causally related to a durvalumab-containing regimen by the reporting investigator.

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

3.1.6.2 Management of Toxicities Related to Standard of Care Therapies

Detailed guidelines regarding treatment modification and toxicity management for standard of care therapies are provided in Appendix H. Actions required for any case meeting potential Hy's Law criteria are described in Appendix D.

3.1.7 Post-study Access to Investigational Product(s)

Any subjects still receiving investigational product at the time of the data cutoff (for the final analysis in the clinical study report [CSR]) will be able to continue to receive investigational product, 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) or equivalent program.

- Assessments will revert to the standard of care for each individual site.
- Data will not be entered into the clinical study database after the data cutoff 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.

In the event that product development reaches a point where alternative product supply options become available, then these alternative product supply options will be discussed by AstraZeneca with the Investigator. AstraZeneca will work with the Investigator to transition the participant(s) to alternative supply, where possible.

The sponsor reserves the right to terminate access to investigational product(s) if any of the following occur: a) the marketing application is rejected by the responsible Health Authority; b) the study is terminated due to safety concerns; c) the subject can obtain investigational product(s) from a government sponsored or private health program; or d) therapeutic alternatives become available in the local market.

3.2 Rationale for Dose, Population, and Endpoints

3.2.1 Dose Rationale

3.2.1.1 Durvalumab Dose Rationale

The dose and schedule of durvalumab CCI as monotherapy and in combination therapy has been selected based on PK/pharmacodynamics, safety, and efficacy data from numerous studies. As detailed in the durvalumab IB, a fixed dose of CCI is being used in numerous ongoing studies. Clinical studies across a range of solid tumors found durvalumab 10 mg/kg Q2W and 20 mg/kg Q4W to be well tolerated both in monotherapy and in combination (see Section 5.2.2, durvalumab IB). Durvalumab PK exposures observed in combination therapy were consistent with the observed monotherapy exposures (see Section 5.1, durvalumab IB). Previous studies and PK simulations of durvalumab have indicated a similar area under the concentration curve at steady state (4 weeks) is expected following both 10 mg/kg Q2W and 20 mg/kg Q4W. Additionally, only minor impact of body weight on PK of durvalumab (coefficient of ≤ 0.5) was indicated from these data. Simulation results demonstrated that body weight-based (20 mg/kg Q4W) and fixed dosing (CCI) regimens yield similar median steady-state exposures and variability.

3.2.1.2 Oleclumab Dose Rationale

The oleclumab regimen of CCI was selected based on data from the Phase I Study D6070C00001. In that study, oleclumab doses of 5, 10, 20, and 40 mg/kg Q2W were examined both as a monotherapy and in combination with durvalumab 10 mg/kg Q2W. Oleclumab was well tolerated and there were no observed DLTs either as monotherapy or in combination with durvalumab. Additionally, both oleclumab and durvalumab exposures in combination were comparable to monotherapy exposures. The oleclumab 40 mg/kg Q2W dose was selected for evaluation with durvalumab 10 mg/kg Q2W in the dose-expansion phase of that study.

A fixed dose of oleclumab CCI is currently being explored based on simulations that oleclumab might achieve similar exposures to those observed with the 40 mg/kg Q2W dose schedule. The subsequent CCI schedule at CCI is predicted to result in adequate long-term exposures with median trough concentration above the estimated CD73 saturating concentration of approximately 40 µg/mL (100-fold of estimated Michaelis-Menten constant from the population PK model) to maintain optimal CD73 saturation at steady state.

3.2.2 Rationale for Study Population

CRC is the third most common cancer worldwide and a significant cause of cancer-related mortality (Bray et al, 2018). Approximately 85% of CRC tumors are MSS and minimally responsive to PD-(L)1-targeted agents. Since 2005, the standard of care for 1L metastatic MSS-CRC has been 5-FU doublet chemotherapy (most often FOLFOX) with bevacizumab

(all) or cetuximab (KRAS wild type only). Median overall survival (OS) for 1L metastatic MSS-CRC remains approximately 2 years (Chong et al, 2019; Tran et al, 2011). There is clinical need for improved treatment options for 1L MSS-CRC.

Several reasons may explain why MSS-CRC is poorly immunogenic. First, approximately 40% to 50% of MSS-CRC present a genetic inactivation of the transforming growth factor (TGF) β receptors (TGFBR1 and TGFBR2) or of the SMAD intracellular mediators (SMAD4, SMAD2 and SMAD3). This results in a paradoxical increase in TGFβ (TGFB1) production (Calon et al, 2015) and drives T-cell exclusion (Tauriello et al, 2018). Second, up to 70% of MSS-CRC tumors feature defects in the beta-catenin pathway (eg, activating CTNNB1 or inactivating mutations in Axin1, Axin2, APC1, and APC2), preventing the migration of effector T cells into tumors, via a mechanism of failed Batf3-dendritic cells recruitment (Luke et al, 2016; Spranger et al, 2017; Spranger and Gajewski, 2018). Third, downregulation of MHC-1 impairs the immunosurveillance of tumors. This defect (ie, low or lack of MHC-1 expression) is often observed in colorectal tumors and is associated with poor prognosis (Watson et al, 2006; Simpson et al, 2010). Finally, liver metastases may also be involved in driving the lack of immune response to anti-PD-1/PD-L1 (Tumeh et al, 2017; Paz-Ares et al, 2017). Such findings appear crucial, since up to 65% of patients with metastatic CRC present liver metastases.

FOLFOX plus bevacizumab is the recommended standard of care in 1L metastatic patients per NCCN and ESMO guidelines (NCCN, 2018; Van Cutsem et al, 2016). An increasing body of evidence suggests that combining novel immunotherapies with FOLFOX plus bevacizumab could improve the outcome of patients with CRC. In the CRC setting, FOLFOX has been shown to: (i) promote immunogenic cell death through calreticulin exposure (Martins et al, 2011); (ii) to increase the CTL/Treg ratio (Gonzalez-Aparicio et al, 2011); and (iii) to deplete of circulating MDSCs (Kanterman et al, 2014; Gonzalez-Aparicio et al, 2011). Further, targeting the VEGF pathway with bevacizumab also modulates the immune context of tumors. Indeed, it is recognized that VEGF-A modulates the expression of PD-1, CTLA-4, and Tim-3 on $CD8^+$ T cells (Voron et al, 2015). Further, bevacizumab was described to deplete Tregs (Terme et al, 2013). Finally, the combination of anti-PD-L1 targeting with bevacizumab recently demonstrated improved patient benefit in metastatic NSCLC and advanced hepatocellular carcinoma (Socinski et al, 2018; Stein et al, 2018).

All together, these arguments suggest that combining novel immune oncology assets such as oleclumab plus durvalumab with FOLFOX and bevacizumab, may improve the outcome of metastatic CRC patients by inducing immunogenic tumor cell death, stimulating the innate immune system, and reversing immune suppression within the tumor microenvironment. 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).

3.2.3 Rationale for Endpoint(s)

The primary objective of Part 1 is to evaluate the safety and tolerability of FOLFOX and bevacizumab in combination with novel oncology therapies in subjects with metastatic MSS-CRC. This will be accomplished through confirming the recommended Phase II dose (RP2D) for all combinations tested. The occurrence of DLTs will be used to confirm the RP2D and thus standard safety endpoints, such as AEs, SAEs, clinically meaningful changes from baseline in laboratory parameters, and vital signs will be included in the evaluation. In addition, PK parameters may be considered when confirmed the RP2D, along with emerging safety data.

The primary objective of Part 2 is to compare the efficacy of FOLFOX and bevacizumab plus novel oncology therapy combinations versus FOLFOX plus bevacizumab in subjects with metastatic MSS-CRC. The endpoints for assessment of antitumor activity are those routinely included in oncology studies for the evaluation of clinical response to investigational product and will include objective response (OR) as a primary endpoint, while best overall response (BOR), DoR, disease control (DC), progression-free survival (PFS) per the Response Evaluation Criteria in Solid Tumors (RECIST) v1.1, and OS, will be considered secondary endpoints.

3.2.3.1 CCI

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[redacted]

3.2.3.2 CCI

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4 MATERIALS AND METHODS

4.1 Subjects

4.1.1 Number of Subjects

In Part 1, a minimum of 6 subjects (and up to 12 subjects per dose level of novel agent) will be enrolled to complete the safety run-in. The number of subjects to be enrolled will depend upon the toxicities observed during the conduct of the study.

In Part 2, up to 50 subjects per treatment arm may be enrolled into the study. After 50 subjects are randomized to the control arm, the control arm will continue to enroll subjects, but the allocation ratio may be adjusted at the discretion of the sponsor (Section 4.6.1). Enrollment to the control arm will pause if there is no active experimental arm.

New combination therapy arms may be added over time via protocol amendment (Section 1.6.4). Details regarding the specifics of a new combination arm will be provided via protocol amendment.

4.1.2 Inclusion Criteria

Subjects must meet all of the following criteria:

Informed consent

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

Age

2 Age ≥ 18 years at the time of screening.

Type of subject and disease characteristics

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

4 Subjects must have histologic documentation of advanced or metastatic CRC and:

(a) A documented mutation test during screening and confirmed tumor locations from disease assessment for enrollment.

(b) Subjects must NOT have defective DNA mismatch repair (MSI) as documented by testing. Testing may be performed locally, and prior documentation of this testing is acceptable in lieu of repeating the test. Defective DNA mismatch repair is defined by either:

(i) High-frequency MSI with changes detected in 2 or more panels of microsatellite markers (BAT-25, BAT-26, NR-21, NR-24, or MONO-27), **or**

(ii) Immunohistochemical analysis demonstrating absence of protein expression of any one or more of the following proteins: MLH1, MSH2, MSH6, or PMS2.

(c) Subjects must not have received any prior systemic therapy for recurrent/metastatic disease (prior adjuvant chemotherapy or radiochemotherapy is acceptable so long as progression was not within 6 months of completing the adjuvant regimen).

5 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 the most recent therapy.

(b) Up to 20 subjects per arm at select centers undergoing pre-treatment and on-treatment tumor biopsy must have a non-target, non-lymph node lesion that can be biopsied at acceptable risk as judged by the investigator or a target, non-lymph node lesion that can be biopsied and is ≥ 2 cm in longest diameter. Sites must confirm the nature of the tumor material (fresh vs archived formalin-fixed paraffin embedded [FFPE]) before treatment assignment. Refer to the laboratory manual for details.

6 Subjects must have adequate organ function, as determined by:

(a) Hematological (cannot be met with blood transfusions or growth factor support within 2 weeks of scheduled first dose of study treatment)

(i) Absolute neutrophil count ≥ 1.5×10^9/L

(ii) Platelet count ≥ 100×10^9/L

(iii) Hemoglobin ≥ 9.0 g/dL

(b) Renal

(i) Calculated creatinine clearance by the modification of diet in renal disease equation (Levey et al, 2006) or 24 hour urine creatinine clearance > 40 mL/min

(ii) Urinalysis ≤ 1+ protein. Subjects discovered to have ≥ 2+ proteinuria at baseline must undergo a 24-hour urine collection that must demonstrate < 1 g of protein/24 hours or have a urine protein:creatinine (UPC) ratio < 1.0

(c) Hepatic

(i) TBL ≤ 1.5 × ULN if no demonstrable liver metastases or ≤ 3 ULN in the presence of documented Gilbert's syndrome or liver metastases

(ii) ALT and AST ≤ 2.5 × ULN if no demonstrable liver metastases or ≤ 5 × ULN in the presence of liver metastasis

(d) Coagulation

(i) International normalized ratio (INR) < 1.5 × ULN with the exception of subjects on systemic anticoagulation (see criterion #7)

(ii) Partial thromboplastin time (or activated partial thromboplastin time) < 1.5 × ULN

7 Subjects with medical conditions requiring systemic anticoagulation (eg, atrial fibrillation) are eligible provided that both of the following criteria are met:

- The subject has an in-range INR (usually between 2 and 3) on a stable dose of oral anticoagulant or be on a stable dose of low molecular weight heparin.
- The subject has no active bleeding or pathological condition that carries a high risk of bleeding (eg, tumor involving major vessels or known varices).
- NOTE: Subjects receiving antiplatelet agents including daily prophylactic aspirin (≤ 325 mg/day) are permitted to enroll. In addition, 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 scheduled first dose of study treatment.

Weight

8 Body weight > 35 kg

Lifestyle/Reproduction

9 Females of childbearing potential who are sexually active with a nonsterilized male partner must have used at least one highly effective method of contraception (see Appendix A for definition of females of childbearing potential and for a description of highly effective methods of contraception) from screening through 180 days 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 (except in countries where spermicides are not approved) throughout this period. Cessation of contraception after this point should be discussed with a responsible physician. Periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception. In addition, female subjects must refrain from egg cell donation and breastfeeding while on study and for 180 days after the final dose of investigational product.

10 Nonsterilized male subjects who are sexually active with a female partner of childbearing potential must use a male condom with spermicide (except in countries where spermicides are not approved) from screening through 180 days after receipt of the final dose of investigational product. It is strongly recommended for the female partner of a male subject to also use a highly effective method of contraception throughout this period, as described in Appendix A. In addition, male subjects must refrain from sperm donation while on study and for 180 days after the final dose of investigational product.

4.1.3 Exclusion Criteria

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

Medical conditions

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

2 History of allogeneic organ transplantation.

3 Active or prior documented autoimmune disorders within the past 5 years prior to the scheduled first dose of study treatment. The following are exceptions to this criterion:
   (a) Subjects with vitiligo or alopecia.
   (b) Subjects with hypothyroidism (eg, following Hashimoto syndrome) stable on hormone replacement.
   (c) Any chronic skin condition that does not require systemic therapy.
   (d) Subjects with celiac disease controlled by diet alone.
4 History of venous thrombosis within the past 3 months prior to the scheduled first dose of study treatment.
5 Cardiovascular criteria:
   (a) Presence of acute coronary syndrome including myocardial infarction or unstable angina pectoris, other arterial thrombotic event including cerebrovascular accident or transient ischemic attack or stroke within the past 6 months prior to the scheduled first dose of study treatment.
   (b) New York Heart Association class II or greater congestive heart failure, serious cardiac arrhythmia requiring medication, or uncontrolled hypertension (≥ 160 mmHg systolic and/or ≥ 100 mmHg diastolic, despite appropriate antihypertensive medication).
   (c) History of hypertensive crisis/hypertensive encephalopathy within the past 6 months prior to the scheduled first dose of study treatment.
6 Mean QT interval corrected for heart rate using Fridericia's formula (QTcF) ≥ 470 ms calculated from 3 electrocardiograms (ECGs) obtained within a 5-minute period at least 1 minute apart.
7 No significant history of bleeding events or gastrointestinal perforation:
   (a) History of significant bleeding episodes (eg, hemoptysis, upper or lower gastrointestinal bleeding) within the past 6 months unless the source of bleeding has been resected.
   (b) History of gastrointestinal perforation within the past 12 months prior to the scheduled first dose of study treatment.
8 Uncontrolled intercurrent illness, including but not limited to, ongoing or active infection, interstitial lung disease, serious chronic gastrointestinal conditions associated with diarrhea, or psychiatric illness/social situations that would limit compliance with study requirement, substantially increase risk of incurring AEs or compromise the ability of the patient to give written informed consent.
9 History of another primary malignancy except for:
   (a) Malignancy treated with curative intent and with no known active disease ≥ 5 years prior to the scheduled first dose of study treatment and of low potential risk for recurrence.
   (b) Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease.
   (c) Adequately treated carcinoma in situ without evidence of disease.
10 History of active primary immunodeficiency

11 Active infection including **tuberculosis** (clinical evaluation that includes clinical history, physical examination and radiographic findings, and tuberculosis testing in line with local practice), **hepatitis B** (known positive HBV surface antigen [HBsAg] result), **hepatitis C**, or **human immunodeficiency virus** (positive HIV 1/2 antibodies). NOTE: Subjects with a past or resolved HBV infection (defined as the presence of hepatitis B core antibody [anti-HBc] and absence of HBsAg) are eligible. Subjects positive for hepatitis C virus (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV RNA.

12 Known allergy or hypersensitivity to any of the study drugs or any of the study drug excipients.

13 Any unresolved toxicity NCI CTCAE Grade > 1 from previous anticancer therapy with the exception of alopecia, vitiligo, and the laboratory values defined in the inclusion criteria.

14 History of leptomeningeal disease or cord compression.

15 Untreated central nervous system (CNS) metastases identified either on the baseline brain imaging obtained during the screening period or identified prior to signing the informed consent form. NOTE: Subjects whose brain metastases have been treated may participate provided they show radiographic stability (defined as 2 brain images, both of which are obtained after treatment to the brain metastases. These imaging scans should both be obtained at least 4 weeks apart and show no evidence of intracranial progression). In addition, any neurologic symptoms that developed either as a result of the brain metastases or their treatment must have resolved or be stable either, without the use of steroids for at least 14 days prior to the scheduled first dose of study treatment. Brain metastases will not be recorded as RECIST target lesions at baseline.

16 Lack of physical integrity of the upper gastrointestinal tract, malabsorption syndrome, or inability to take oral medication.

17 Known dihydropyrimidine dehydrogenase (DPD) deficiency. Testing for DPD deficiency must be performed where required by local regulations, using a validated method that is approved by local health authorities.

Prior/concomitant therapy

18 Any concurrent chemotherapy, investigational product, biologic, or hormonal therapy for cancer treatment. Concurrent use of hormonal therapy for non-cancer-related conditions (eg, hormone replacement therapy) is acceptable.

19 Radiotherapy treatment to more than 30% of the bone marrow or with a wide field of radiation within 4 weeks prior to the scheduled first dose of study treatment

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

21 Prior receipt of anti-angiogenics, including, but not limited to, VEGF/VEGF receptor inhibitors.

22 Receipt of live attenuated vaccine within 30 days prior to the scheduled first dose of study treatment.

23 Major surgical procedure, open biopsy, or significant traumatic injury (all as defined by the investigator) within 28 days prior to the scheduled first dose of study treatment, or anticipation of the need for major surgical procedure during the course of the study. NOTE: Local surgery of isolated lesions for palliative intent is acceptable.

24 Current or prior use of immunosuppressive medication within 14 days prior to the scheduled first dose of study treatment. The following are exceptions to this criterion:
   (a) Intranasal, inhaled, topical steroids, or local steroid injections (eg, intra articular injection).
   (b) Steroids as premedication for hypersensitivity reactions (eg, computed tomography [CT] scan premedication or chemotherapy premedication per institutional practice).

Prior/concurrent clinical study experience

25 Participation in another clinical study with an investigational product administered within 28 days prior to the scheduled first dose of study treatment.

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

Other exclusions

27 Female subjects who are pregnant, breastfeeding, or intend to become pregnant during their participation in the study.

28 Involvement in the planning and/or conduct of the study (applies to both sponsor staff and/or staff at the study site).

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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.

A master log of all consented subjects will be maintained at the site and will document all screening failures (ie, subjects who are consented but do not meet study eligibility criteria

and/or are not randomized), including the reason(s) for screening failure. Site completion of the minimal set of screen failure information including demography, screen failure details, eligibility criteria, and any SAE is required.

Subjects who do not meet the criteria for participation in the study (ie, screening failures) may be rescreened (if clinically appropriate). Subjects can be rescreened a single time, but they cannot be re-randomized. Rescreened subjects should be assigned a new SID number. Rescreening should be documented so that its effect on study results, if any, can be assessed. These subjects should have the reason for screen failure recorded in the electronic case report form (eCRF).

Further details regarding randomization are provided in Section 4.6.1.

4.1.5 Withdrawal from the Study

Subjects are free to withdraw their consent to participate in the study (investigational product and assessments) at any time, without prejudice to further treatment. Subjects who withdraw consent will be asked about the reason(s) and the presence of any AEs. If the subject is willing, the subject will be seen and assessed by the investigator. Adverse events will be followed up and all study medications should be returned by the subject. 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 further treatment with investigational product
2 Lost to follow-up
3 Unacceptable toxicity/AE that, in the opinion of the investigator or the sponsor, warrants discontinuation of further dosing or meets criteria for discontinuation from investigational product as defined in the toxicity management guidelines (Section 3.1.6 and Appendix H) or in the local prescribing information for standard of care therapies.
4 Subject is determined to have met one or more of the exclusion criteria or failed to meet all of the inclusion criteria for study participation at study entry and continuing treatment with investigational product might constitute a safety risk.
5 Pregnancy or intent to become pregnant (Section 5.6.2)
6 Initiation of alternative anticancer therapy including another investigational agent
7 Intercurrent illness or medical condition that, in the judgment of the investigator and/or sponsor, warrants discontinuation of further dosing
8 Subject noncompliance (eg, refusal to adhere to visit schedule) that, in the opinion of the investigator or sponsor, warrants withdrawal

9 Confirmed progressive disease (PD) or unconfirmed PD and treatment criteria in the setting of PD are not met (Section 4.1.7)

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

4.1.7 Treatment Beyond Progression

For all subjects, if PD (based on RECIST v1.1) occurs, the subject may continue to be treated with the scheduled regimen assigned after study enrollment until one of the following criteria is met:

- Confirmed PD: The initial assessment of PD by RECIST v1.1 (ie, the unconfirmed PD, defined as the baseline PD assessment) will be confirmed by a repeat evaluation at the next tumor assessment time point, which should be no sooner than 4 weeks but no later than 8 weeks after the previous tumor assessment. If any subsequent tumor assessment time point demonstrates further increase in the tumor burden defined by any of the following: ≥ 5 mm increase in the sum of diameters of target lesions compared to the nadir of the unconfirmed PD assessment; any unequivocal increase in the size of the non-target lesions; or the occurrence of new lesions compared to the nadir of unconfirmed PD; then the subject would be deemed as having confirmed PD.
- Meets any of the investigational product discontinuation criteria (Section 4.1.6)
- Clinical symptoms or signs indicating clinically significant PD such that the benefit-risk ratio of continuing therapy is no longer justified based on the investigator's judgment.
- Decline in ECOG performance status compared to baseline.
- Rapid PD or threat to vital organs/critical anatomical sites (eg, spinal cord compression) requiring urgent alternative medical intervention.

4.1.8 Replacement of Subjects

In the safety run-in phase of the study (Part 1), subjects who do not remain in the study through the DLT-evaluation period for reasons other than DLT (Section 3.1.4) will be considered non-evaluable for DLT assessment and will be replaced with another subject in the same arm.

In the randomized phase of the study (Part 2), withdrawn subjects may not be replaced.

4.1.9 Withdrawal of Informed Consent for Data and Biological Samples

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

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

As collection of the biological samples is an integral part of the study CCI [redacted] if a subject withdraws consent to the use of donated biological samples, then the subject is withdrawn from further study participation.

The Principal Investigator:

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

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

4.2 Schedule of Study Procedures

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.

4.2.1 Enrollment/Screening Period

Table 6 shows all procedures to be conducted at the screening visit.

Table 6 Schedule of Screening Procedures (All Parts)

Study Period	Screening/Baseline
Procedure	**Days -28 to -1**
Written informed consent/assignment of SID number	X
Tumor and Disease Assessments	
History of prior cancer treatment	X
CCI [redacted]	
Disease assessment by RECIST v1.1 (CT or MRI) [a]	X
Brain imaging [a, b]	X

Table 6 Schedule of Screening Procedures (All Parts)

Study Period	Screening/Baseline
Procedure	**Days -28 to -1**
Study Procedures and Examinations	
Demographics	X
Medical 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, pulse rate)	X
Assessment of AEs/SAEs	X
Concomitant medications	X
Safety Labs	
Serum chemistry	X
Hematology	X
Coagulation	X
Thyroid function	X
Urinalysis	X
Serum pregnancy test [e]	X
Hepatitis B and C; HIV	X
CCI	
CCI	

AE = adverse event; BP = blood pressure; CNS = central nervous system; CT = computed tomography; CCI ; DICOM = Digital Imaging and Communications in Medicine; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; HIV = human immunodeficiency virus; MRI = magnetic resonance imaging; MSS = microsatellite stable; SAE = serious adverse event; SID = subject identification

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

[b] Brain MRI to be performed only if CNS involvement is suspected based on the signs and symptoms of individual subjects and only after study eligibility is confirmed, to detect the presence of intracranial metastasis.

[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] ECG will be obtained in triplicate within a 5-minute period at least 1 minute apart.

[e] Females of childbearing potential are required to have a serum pregnancy test within 7 days prior to the first dose of study drug.

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4.2.2 Treatment Period (Part 1)

Table 7 shows all procedures to be conducted during the treatment period in Part 1.

Table 7 Schedule of Treatment Period Procedures Part 1

Cycle #	C1			C2	C3	C4	C5	C6	Continuing
Week #	W1		W2	W3	W5	W7	W9	W11	Q2W unless otherwise noted (± 5d)
Procedure/Study Day #	D1	D2	D8 (+ 2d)	D15 (± 3d)	D29 (± 3d)	D43 (± 3d)	D57 (±3 d)	D71 (±3 d)	
Verify eligibility	X								
Disease Assessments [a]									
Scan (CT/MRI)							X		Q8W through 1 year then Q12W
CEA	X						X		Q8W for 1 year
Study Procedures and Examinations									
Physical exam (focused based on signs/symptoms)	X	X			X		X		Q4W
Weight	X						X		Q4W
ECOG performance status	X						X		Q8W
ECG [b]	X				X		X		Q12W
Vital signs [c]	X	X		X	X	X	X	X	Q2W
Assessment of AEs/SAEs	X	X	X	X	X	X	X	X	Q2W
Concomitant medications	X	X	X	X	X	X	X	X	Q2W
Safety Labs [d]									
Serum chemistry	X [d]		X	X	X	X	X	X	Q2W
Hematology	X [d]			X	X	X	X	X	Q2W
Coagulation	X [d]			X	X	X	X	X	Q2W
Thyroid function tests	X [d]				X		X		Q4W
Urinalysis [e]	X [d]				X		X		Q4W
Pregnancy test [f]	X [d]				X		X		Q8W

Table 7 Schedule of Treatment Period Procedures Part 1

Cycle #	C1			C2	C3	C4	C5	C6	Continuing
Week #	W1		W2	W3	W5	W7	W9	W11	Q2W unless otherwise noted (± 5d)
Procedure/Study Day #	D1	D2	D8 (+ 2d)	D15 (± 3d)	D29 (± 3d)	D43 (± 3d)	D57 (±3 d)	D71 (±3 d)	
Plasma/Serum for PK and Immunogenicity [g]									
Serum for durvalumab PK	X				X				W13, W25, W53
Serum for durvalumab ADA	X				X				W13, W25, W53
Serum for oleclumab PK (S1)	X			X					W13, W25, W53
Serum for oleclumab ADA (S1)	X			X					W13, W25, W53
Serum for bevacizumab PK	X			X					W13, W25, W53
Serum for bevacizumab ADA	X			X					W13, W25, W53
CCI									
CCI									
CCI									
CCI									
Study Drug Administration									
FOLFOX	X			X	X	X	X	X	Q2W

Table 7 Schedule of Treatment Period Procedures Part 1

Cycle #	C1			C2	C3	C4	C5	C6	Continuing
Week #	W1		W2	W3	W5	W7	W9	W11	Q2W unless otherwise noted (± 5d)
Procedure/Study Day #	D1	D2	D8 (+ 2d)	D15 (± 3d)	D29 (± 3d)	D43 (± 3d)	D57 (±3 d)	D71 (±3 d)	
Bevacizumab	X			X	X	X	X	X	Q2W
Durvalumab	X				X		X		Q4W
Oleclumab (S1 only)	X			X	X	X	X		Q4W

ADA = antidrug antibody; AE = adverse event; β-hCG = beta-human chorionic gonadotropin; C = cycle; CEA = carcinoembryonic antigen; CT = computed tomography; CCI [redacted]; D = day; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; FOLFOX = folinic acid (leucovorin), 5-fluorouracil, oxaliplatin; MRI = magnetic resonance imaging; PK = pharmacokinetics; CCI [redacted]; Q*x*W = every *x* weeks; SAE = serious adverse event; W = week.

[a] Disease assessment: brain scans must be performed if brain lesion present at baseline or symptomatic. If post-baseline radiological imaging indicates progressive disease, a separate consent must be signed before continuing treatment.

[b] On C1D1, ECGs will be obtained in triplicate (all 3 within a 5-minute period, at least 1 minute apart) within 30 minutes prior to start of investigational product infusion. At all other time points, a single ECG will be obtained prior to investigational product(s) administration and as clinically indicated.

[c] Vital signs: temperature, blood pressure, and pulse rate will be measured.

[d] If screening laboratory assessments are performed within 3 days prior to C1D1, they do not need to be repeated at D1. All safety laboratory results must be reviewed by the investigator or physician designee prior to administration of study drug.

[e] If bevacizumab is discontinued, urinalysis may be stopped 8 weeks after the last dose of bevacizumab. Assessments may be performed more frequently if clinically indicated.

[f] Females of childbearing potential only. A urine or serum pregnancy test is acceptable; if urine test is positive or equivocal then serum β-hCG testing should be performed for confirmation.

[g] Samples will be collected pre-dose. PK sampling must be within 6 hours prior to start of infusion.

4.2.3 Treatment Period (Part 2)

Table 8 shows all procedures to be conducted during the treatment period in Part 2.

Table 8 Schedule of Treatment Period Procedures (Part 2)

Cycle #	C1	C2	C3	C4	C5	C6	Continuing
Week #	**W1**	**W3**	**W5**	**W7**	**W9**	**W11**	**Q2W unless otherwise noted (± 5d)**
Procedure/Study Day #	**D1**	**D15 (± 3d)**	**D29 (± 3d)**	**D43 (± 3d)**	**D57 (± 3d)**	**D71 (± 3d)**	
Verify eligibility	X						
Randomize (-3 day window)	X						
Disease Assessments [a]							
Scan (CT/MRI)					X		Q8W for 1 year then Q12W
CEA	X				X		Q8W for 1 year
Study Procedures and Examinations							
Physical exam (focused based on signs/symptoms)	X		X		X		Q4W
Weight	X				X		Q4W
ECOG performance status	X				X		Q8W
ECG [b]	X		X		X		Q12W
Vital signs [c]	X	X	X	X	X	X	Q4W
Assessment of AEs/SAEs	X	X	X	X	X	X	Q4W
Concomitant medications	X	X	X	X	X	X	Q4W
Safety Labs [d]							
Serum chemistry	X [d]	X	X	X	X	X	Q2W
Hematology	X [d]	X	X	X	X	X	Q2W
Coagulation	X [d]	X	X	X	X	X	Q2W
Thyroid function tests	X [d]		X		X		Q8W
Urinalysis [e]	X [d]		X		X		Q4W

Table 8 Schedule of Treatment Period Procedures (Part 2)

Cycle #	C1	C2	C3	C4	C5	C6	Continuing
Week #	**W1**	**W3**	**W5**	**W7**	**W9**	**W11**	**Q2W unless otherwise noted (± 5d)**
Procedure/Study Day #	**D1**	**D15 (± 3d)**	**D29 (± 3d)**	**D43 (± 3d)**	**D57 (± 3d)**	**D71 (± 3d)**	
Pregnancy test [f]	X [d]	As clinically indicated					
Serum for PK and Immunogenicity [g]							
Serum for durvalumab PK (except Control 1)	X		X				W13, W25, W53
Serum for durvalumab ADA (except Control 1)	X		X				W13, W25, W53
Serum for oleclumab PK (E1)	X	X					W13, W25, W53
Serum for oleclumab ADA (E1)	X	X					W13, W25, W53
Serum for bevacizumab PK	X	X					W13, W25, W53
CCI [redacted]							
CCI [redacted]							
CCI [redacted]							
CCI [redacted]							
CCI [redacted]							

Table 8 Schedule of Treatment Period Procedures (Part 2)

Cycle #	C1	C2	C3	C4	C5	C6	Continuing
Week #	W1	W3	W5	W7	W9	W11	Q2W unless otherwise noted (± 5d)
Procedure/Study Day #	D1	D15 (± 3d)	D29 (± 3d)	D43 (± 3d)	D57 (± 3d)	D71 (± 3d)	
CCI							
CCI							
CCI							
Study Drug Administration							
FOLFOX	X	X	X	X	X	X	Q2W
Bevacizumab	X	X	X	X	X	X	Q2W
CCI							

ADA = antidrug antibody; AE = adverse event; β-hCG = beta-human chorionic gonadotropin; C = cycle; CEA = carcinoembryonic antigen; CT = computed tomography; CCI; D/d = day; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; FOLFOX = folinic acid (leucovorin), 5-fluorouracil, oxaliplatin; MRI = magnetic resonance imaging; CCI; PK = pharmacokinetics; Q*x*W = every *x* weeks; SAE = serious adverse event; TCRseq = T-cell receptor sequencing; W = week.

[a] Disease assessment: brain scans must be performed if brain lesion present at baseline or symptomatic. If post-baseline radiological imaging indicates progressive disease, a separate consent must be signed before continuing treatment.

[b] On C1D1, ECGs will be obtained in triplicate (all 3 within a 5-minute period, at least 1 minute apart) within 30 minutes prior to start of investigational product infusion. At all other time points, a single ECG will be obtained prior to investigational product(s) administration and as clinically indicated.

[c] Vital signs: temperature, blood pressure, and pulse rate will be measured.

[d] If screening laboratory assessments are performed within 3 days prior to C1D1, they do not need to be repeated at D1. All safety laboratory results must be reviewed by the investigator or physician designee prior to administration of study drug.

[e] If bevacizumab is discontinued, urinalysis may be stopped 8 weeks after the last dose of bevacizumab. Assessments may be performed more frequently if clinically indicated.

[f] Females of childbearing potential only. A urine or serum pregnancy test is acceptable; if urine test is positive or equivocal then serum β-hCG testing should be performed for confirmation.

Table 8 Schedule of Treatment Period Procedures (Part 2)

Cycle #	C1	C2	C3	C4	C5	C6	Continuing
Week #	W1	W3	W5	W7	W9	W11	Q2W unless otherwise noted (± 5d)
Procedure/Study Day #	D1	D15 (± 3d)	D29 (± 3d)	D43 (± 3d)	D57 (± 3d)	D71 (± 3d)	

[g] Samples will be collected pre-dose. PK sampling must be within 6 hours prior to start of infusion.

CCI [redacted]
CCI [redacted]

4.2.4 Follow-up Period

Table 9 shows all procedures to be conducted during the follow-up period.

Table 9 Schedule of Follow-up Procedures (All Parts)

Procedure/Visit Day	End of Treatment Visit	Day 90 Post Last Dose (± 7 days)	6 Months Post Last Dose then Q3Mo (± 14 days)	18 Months Post Last Dose then Q6Mo (± 4 weeks)
Survival Status		X	X	X
Subsequent Anticancer Treatment	X	X	X	X
Disease Assessments (discontinue after confirmed PD or withdrawal of consent)				
Scan (CT/MRI)	X	X	X	X
CEA	X	X		
Study Procedures and Examinations				
Physical exam	X	X		
ECOG performance status	X	X		
ECG	X			
Vital signs	X	X		
Assessment of AEs/SAEs	X	X		
Concomitant medications	X	X		
Safety Labs				
Serum chemistry	X	X		
Hematology	X	X		
Coagulation	X	X		
Thyroid function tests	X	X		
Urinalysis	X	X		
Pregnancy test [a]	X	Q4W starting 8 weeks through 28 weeks post last dose		
Serum for Immunogenicity				
Durvalumab ADA (except Control 1)		X		
Oleclumab ADA (S1 and E1 only)		X		
Bevacizumab ADA		X		
CCI				

Table 9 Schedule of Follow-up Procedures (All Parts)

Procedure/Visit Day	End of Treatment Visit	Day 90 Post Last Dose (± 7 days)	6 Months Post Last Dose then Q3Mo (± 14 days)	18 Months Post Last Dose then Q6Mo (± 4 weeks)
CCI				

ADA = antidrug antibody; AE = adverse event; β-hCG = beta-human chorionic gonadotropin; CEA = carcinoembryonic antigen; CT = computed tomography; CCI ; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; MRI = magnetic resonance imaging; CCI ; PD = progressive disease; Q4W = every 4 weeks; Q*x*Mo = every *x* months; RECIST = Response Evaluation Criteria In Solid Tumors; SAE = serious adverse event.

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

4.3 Description of Study Procedures

4.3.1 Efficacy

Tumor assessments will be based on RECIST v1.1 (Appendix F) and will be performed according to the schedules in Section 4.2. CCI CCI . The assessment schedule also applies to those subjects who continue to receive study therapy in the setting of PD (Section 4.1.7). For those subjects who discontinue study therapy as a result of confirmed PD, disease evaluation will be performed at the end of treatment visit if clinically appropriate (ie, in the absence of rapidly deteriorating clinical status). After discontinuation of investigational product(s), all subjects will complete the end of treatment visit and enter follow-up; disease evaluation will be performed according to the schedule in Table 9. Additional disease assessments may be performed as clinically indicated.

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

Computed Tomography

- CT (contrast preferred) scans of the chest, abdomen, and pelvis should be performed with contiguous cuts in slice thickness of 5 mm or less. Spiral CT should be performed using a 5-mm contiguous reconstruction algorithm. The same imaging device should be used for serial evaluations.
- If CT with contrast is contraindicated, CT without contrast is preferred over MRI. The same method is preferred for all subsequent tumor assessments

Magnetic Resonance Imaging

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

4.3.1.1 CCI

CCI [redacted]

4.3.1.2 Survival Assessments

All subjects will be followed for survival until the end of the study (defined in Section 6.3). Survival information may be obtained via telephone contact with the subject or the subject's family, or by contact with the subject's current physician. The details of first and subsequent therapies for cancer, after discontinuation of treatment, will be collected.

In addition, subjects on treatment or in survival follow-up will be contacted following the data cutoff for the primary analysis and all subsequent survival analyses to provide complete survival data. These contacts should generally occur within 7 days of the data cutoff.

4.3.1.3 CCI

CCI [redacted]

4.3.2 Tumor Samples

CCI

Table 10 CCI

CCI

CCI

4.3.2.1 CCI

CCI

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4.3.2.2 CCI

CCI

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

4.3.3.1 Medical History

A complete medical history will be obtained at screening. Findings from current medical history will be assigned a baseline grade according to the procedure for assessing the intensity of AEs, whenever applicable. As a result, increases in severity of pre-existing conditions during the study will be considered AEs, with resolution occurring when the grade returns to the baseline grade or below.

4.3.3.2 Physical Examinations

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

4.3.3.3 Vital Signs

Vital signs (temperature, blood pressure, and pulse rate) performed according to the schedules in Section 4.2. For all vital sign measurements, subjects should rest for at least 10 minutes in a supine or semi-recumbent position, and all vital sign measurements should be taken prior to any blood draws or other procedures whenever possible.

4.3.3.4 Electrocardiograms

Resting 12-lead ECGs will be recorded as presented in Section 4.2. Electrocardiograms should be obtained after the subject has been in a supine position for 5 minutes and recorded while the subject remains in that position.

In case of clinically significant ECG abnormalities, including a QTcF value ≥ 470 ms, 2 additional 12-lead ECGs should be obtained over a brief period (eg, 30 minutes) to confirm the finding based on the average of all 3 manually overread ECGs by a medically qualified delegate (eg, for initially prolonged QTcF value, the average QTcF value of all 3 manually overread ECGs should be ≥ 470 ms for the QTcF prolongation to be confirmed).

4.3.4 ECOG Performance Status

Performance status as determined by the ECOG scale (Oken et al, 1982) as outlined in Table 11, will be recorded in the eCRF per the schedule in Section 4.2.

Table 11 ECOG Performance Status

Grade	ECOG
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

ECOG = Eastern Cooperative Oncology Group.
Source: Oken et al, 1982

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.

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 (see Section 4.2 for the schedule of tests):

Serum Chemistry

- Albumin
- Amylase
- ALP
- ALT
- AST
- Bicarbonate
- Blood urea nitrogen/urea
- Calcium
- Chloride
- Creatinine
- Creatine phosphokinase
- Gamma-glutamyl transferase
- Glucose
- Lactate dehydrogenase
- Lipase
- Magnesium
- Potassium
- Sodium
- TBL (direct bilirubin should be obtained if TBL > ULN)
- Total protein
- C-reactive protein

ALP = alkaline phosphatase; ALT = alanine transaminase; AST = aspartate transaminase; TBL = total bilirubin; ULN = upper limit of normal

Note for serum chemistry: Tests for AST, ALT, ALP, and TBL must be conducted concurrently and assessed concurrently.

Hematology

- Absolute lymphocyte count
- Absolute neutrophil count
- Hemoglobin
- Platelet count
- White blood cell count

Coagulation

- Activated partial thromboplastin time
- International normalized ratio

Note: If activated partial thromboplastin time is not available, sites may substitute a partial thromboplastin time. If international normalized ratio is not available, sites may substitute a prothrombin time.

Urinalysis

- Blood
- Protein

Note: If urine protein is ≥ 2+ on dipstick urinalysis, UPC ratio (urine protein to urine creatinine) or 24-hour urine collection (protein) will be required.

Pregnancy Test (females of childbearing potential only)

- Urine hCG
- Serum β-hCG (required if urine hCG is equivocal or positive)

hCG = human chorionic gonadotropin

Note: A urine or serum pregnancy test is acceptable; if urine test is positive or equivocal, then serum β-hCG testing should be performed for confirmation.

Other Safety Tests

- Hepatitis B, hepatitis C, and HIV: Active hepatitis B, hepatitis C, and HIV infections are defined by positive serologic test. Subjects positive for HBV infection are eligible if findings are compatible with past or resolved infection (HBsAg negative, anti-HBc positive and anti-HBs positive) or due to vaccination (HBsAg negative, anti-HBc negative and anti-HBs positive). Subjects positive for HCV antibody are eligible only if polymerase chain reaction is negative for HCV RNA.
- Thyroid function tests: TSH, T3, and T4. If TSH is normal, then free T3 or free T4 is not required.

HBc = hepatitis B core; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid stimulating hormone.

4.3.6 Pharmacokinetic Evaluation and Methods

Blood samples will be collected to describe the PK of bevacizumab and novel agents per the schedule of procedures (Section 4.2). Novel agents include durvalumab and oleclumab. See Section 4.2 for collection time points. Measurements will be performed using a validated immunoassay.

4.3.7 Immunogenicity Evaluation and Methods

Blood samples will be collected to describe antidrug antibody (ADA) responses to bevacizumab and applicable novel biologic agents per the schedule of procedures (Section 4.2). Applicable novel agents include durvalumab and oleclumab.

Evaluations will be performed using a validated immunoassay. Tiered analyses will be performed to include screening, confirmatory, and titer assay components, and the positive-negative cut points will be statistically determined from drug-naïve validation samples. Samples may be utilized for further characterization of the ADA response, including possible assessment of neutralizing antibody.

4.3.8 CCI

CCI

4.3.8.1 CCI

CCI

4.3.8.2 CCI

CCI

CCI

4.3.9 CCI

CCI

4.3.9.1 CCI

CCI

4.3.9.2 CCI

CCI

4.3.9.3 CCI

CCI

4.3.9.4 CCI

CCI

4.3.9.5 CCI

CCI

[redacted]

4.3.9.6 CCI

CCI

[redacted]

4.3.9.7 CCI

CCI

[redacted]

4.3.10 Estimate of Volume of Blood to Be Collected

A total of no more than 23.3 mL of blood will be required for all screening tests. No more than approximately 74.3 mL of blood will be drawn at any visit during the treatment period. During the follow-up period, no more than approximately 36.3 mL of blood will be collected at any visit. The total volume to be collected will depend on the treatment arm, laboratory used, and length of a subject's participation in the study. The laboratory manual may be referenced for test volume specifics.

4.4 Study or Study Component Suspension or Termination

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

1 The incidence or severity of AEs in this or other studies indicates a potential health hazard to subjects
2 Subject enrollment is unsatisfactory

3 Non-compliance that might significantly jeopardize the validity or integrity of the study
4 Sponsor decision to terminate development of durvalumab or any of the combination study treatments for this indication
5 Sponsor decision to terminate the study based on a planned futility analysis and/or recommendation from SRC (Section 4.8.8 and Section 3.1.5.2, respectively)

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

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

4.5 Investigational Products

4.5.1 Identity of Investigational Product(s)

The sponsor will provide the investigator(s) with investigational product (Table 12) using designated distribution centers.

Table 12 Identification of Investigational Products

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

HCl = hydrochloride; w/v = weight per volume.

- Durvalumab is supplied in CCI vials CCI [redacted]
- Oleclumab is supplied in CCI vials CCI [redacted]

CCI [redacted] CCI . Drug product should be kept in original packaging until use to prevent prolonged light exposure.

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

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 Handling

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 the sponsor. All unused investigational products will be returned to a sponsor-authorized depot or disposed of upon authorization by the sponsor according to the investigational site policy.

4.5.1.2 Investigational Product Inspection

Each vial selected for dose preparation should be inspected. See Section 4.5.1 for a description of investigational product presentation.

If there are any defects noted with the investigational product, the investigator and site monitor should be notified immediately. Refer to the Product Complaint section for further instructions (Section 4.5.1.7).

4.5.1.3 Durvalumab Dose Preparation and Administration

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 the durvalumab vial to start of administration should not exceed:

- CCI
- CCI

A dose of CCI will be administered using an IV bag containing CCI and delivered through an IV administration set with a 0.2- or 0.22-µm filter. Add CCI durvalumab CCI to the IV bag. The IV bag size should be selected such that the final concentration is within CCI. Mix the bag by gently inverting to ensure homogeneity of the dose in the bag.

Standard infusion time is 1 hour (+ 15 minutes); however, if there are interruptions during infusion, the total allowed infusion time should not exceed 8 hours at room temperature.

For experimental arms that require administration of durvalumab and the combination study drug on the same day, the total infusion time for both study drugs should not exceed 8 hours at room temperature.

Do not coadminister other drugs through the same infusion line. For IV flushing instructions, refer to Section 4.5.1.5.

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

4.5.1.4 Oleclumab Dose Preparation and Administration

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

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

- CCI [redacted]
- CCI [redacted]

No incompatibilities between oleclumab and polyvinylchloride or polyolefin IV bags have been observed.

A dose of CCI [redacted] will be administered using an IV bag containing CCI [redacted] and delivered through an IV administration set with a 0.2- or 0.22-µm filter. Add CCI [redacted] oleclumab CCI [redacted] to the IV bag. The IV bag size should be selected such that the final concentration is within CCI [redacted]. Mix the bag by gently inverting to ensure homogeneity of the dose in the bag.

Standard infusion time for oleclumab is 1 hour (+ 15 minutes); however, if there are interruptions during infusion, the total allowed time should not exceed 4 hours at room temperature. If this duration is met, then the remainder of the dose should be abandoned and should not be completed with a second prepared dose.

See Section 4.5.1.3 for durvalumab administration. In the event of interruptions during infusion for either oleclumab and/or durvalumab on days when both oleclumab and durvalumab are administered, the total infusion duration for both study drugs should not exceed 8 hours. Of the total 8-hour infusion duration, a maximum of 4 hours may correspond to oleclumab infusion.

Do not coadminister other drugs through the same infusion line. For IV flushing instructions, refer to Section 4.5.1.5.

If preparation time exceeds the time limits outlined above, a new dose must be prepared from new vials. Oleclumab does not contain preservatives, and any unused portion must be discarded.

4.5.1.5 Treatment Administration

The first day of dosing with investigational product(s) is considered Week 1, Day 1 in all treatment arms. Where applicable, oleclumab will be administered first, followed by durvalumab, bevacizumab, then FOLFOX per institutional guidelines for administration. A wait period of at least 15 minutes must follow infusions of oleclumab and durvalumab before beginning administration of a subsequent infusion. If infusion reactions are noted during the first infusion of each agent, the wait time may be increased at the discretion of the investigator for subsequent coadministration days.

No specific premedication is required for durvalumab or oleclumab. Details of any premedication or concomitant medication given to manage or prevent AEs should be recorded on the eCRF.

In all treatment arms, flush the IV line with a volume of IV diluent equal to the priming volume of the infusion set used after the contents of the IV bag are fully administered, or complete the infusion according to institutional policy to ensure the full dose is administered.

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.

4.5.1.6 Monitoring of Dose Administration

Subjects will be monitored during and after infusion(s) of investigational product(s). Vital signs will be measured according to the schedules described in Section 4.2.

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

4.5.1.7 Reporting Product Complaints

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

4.5.2 Additional Study Medications

Each standard-of-care agent (folinic acid, 5-FU, oxaliplatin, and bevacizumab) 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. Under certain circumstances when local sourcing is not feasible, a standard-of-care agent will be supplied centrally by the sponsor. This will be labeled with text translated into local languages in accordance with regulatory guidelines. The use of bevacizumab biosimilars is acceptable in regions/countries where their use is approved.

Refer to the Full Prescribing Information for each standard-of-care therapy for further details on product handling, storage, administration/dispensation, etc.

4.5.3 Labeling

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

4.5.4 Storage

All investigational products should be stored in a secure and dry place. Vials of investigational product for parenteral administration should be stored at CCI [redacted] CCI [redacted]. Drug product should be kept in original packaging until use to prevent excessive 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 the sponsor. All unused investigational product will be returned to a sponsor-authorized depot or disposed of upon authorization by the sponsor.

4.6 Treatment Assignment and Blinding

4.6.1 Methods for Assigning Treatment Groups

After eligibility is confirmed, subjects will be centrally assigned (Part 1) or randomized (Part 2) to study treatment using an interactive voice/web response system (IXRS) that will assign the subject depending on open cohorts.

In Part 2, a randomization method with dynamically changing randomization ratios will be employed to account for fluctuation in the number of treatment arms open for randomization over the course of the study. Randomization will be stratified by location of the primary tumor (right sided vs left sided). At the onset, the randomization scheme will use an equal ratio to all study treatment arms open for randomization (eg, if experimental arms are opened sequentially, an experimental arm is added/closed, or enrollment in an experimental arm is suspended). Additionally, the following considerations regarding randomization will apply:

- If there is no experimental arm open for randomization, then randomization will be paused. Any subject who had consented previously and was in screening when the experimental arm(s) was closed due to safety concerns may be allowed to enter into the study but must be allocated to the control arm.
- Once the control arm randomizes 50 subjects, a subsequent randomization scheme may be initiated via protocol amendment to optimize the number of subjects allocated to each arm.
- At any point during the study, the control arm will continue to enroll subjects and have no less than a 30% chance to be randomized in comparison to the active experimental arm that has the lowest randomization ratio in the study.

Investigational product(s) must be administered within 3 days after the treatment arm is assigned. If there is a delay in the administration of investigational product such that it will not be administered within the specified timeframe, the study monitor must be notified immediately.

4.6.2 Methods to Ensure Blinding

This study is not blinded.

4.7 Restrictions During the Study and Concomitant Treatment(s)

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

4.7.1 Permitted Concomitant Medications

Investigators may prescribe concomitant medications or treatments deemed necessary to provide adequate supportive care except for those medications identified as prohibited 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, 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 concomitant medications are prohibited:

- Any investigational anticancer therapy
- Any concurrent chemotherapy, radiotherapy (except palliative radiotherapy), 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.
- Immunosuppressive medications including, but not limited to, methotrexate, azathioprine, and tumor necrosis factor-alpha blockers. The following are exceptions:
  - Use of immunosuppressive medications for the management of investigational product-related AEs, for subjects with contrast allergies, or for chemotherapy premedication as per institutional practice is acceptable.
  - Use of inhaled, intranasal, or topical corticosteroids is permitted.
  - Temporary courses of corticosteroids for treatment of underlying or concurrent illness or in the setting of palliative radiotherapy may be permitted upon discussion with the medical monitor.
- Chronic, daily treatment with high-dose aspirin (> 325 mg/day)
- Live attenuated vaccines during the study through 180 days after the last dose of study drug
- Herbal and natural remedies should be avoided

4.8 Statistical Evaluation

4.8.1 General Considerations

Tabular summaries will be presented by treatment group. Categorical data will be summarized by the number and percentage of subjects in each category. Continuous variables will be summarized by descriptive statistics. Additional details of statistical analyses will be described in the statistical analysis plan. The statistical comparisons will be made between experimental arms and the control, but not between experimental arms.

The Intent-to-treat (ITT) Population is defined as all subjects who receive any investigational product. Subjects will be analyzed according to their randomized treatment group.

The As-treated population is defined as all subjects who receive any investigational product. Subjects will be analyzed according to the treatment received.

The DLT-evaluable Population includes subjects enrolled in the safety run-in phase (Part 1) who receive the full prescribed dose of durvalumab and ≥ 75% of the prescribed number of doses of FOLFOX plus bevacizumab and the other novel oncology therapy during the DLT

evaluation period (defined as 28 days from the first dose of investigational product) or experience any DLT.

The Response-evaluable Population includes subjects from the As-treated population who have a baseline disease assessment, have the opportunity to be followed for at least 8 weeks at the time of the data cutoff (ie, dosed at least 8 weeks prior to the time of the data cutoff), and either has at least one post-baseline disease assessment and/or discontinued treatment due to death or disease progression.

4.8.2 Sample Size

Part 1:

A minimum of 6 subjects (up to 12 subjects per dose level of novel agent) will be enrolled to complete the safety run-in. More subjects may be enrolled if dose de-escalation is needed. CCI

Part 2:

CCI

4.8.3 Efficacy

The final efficacy analyses will be based on the As-treated population for Part 1 and ITT Population for Part 2 as defined in Section 4.8.1. Efficacy analyses for both Part 1 and Part 2 will provide the same or similar summary statistics, but analyses for Part 2 will provide further statistical comparisons between experimental arms and the control arm. Therefore, in this section, only Part 2 analyses are described in detail.

The efficacy analyses will be performed on the following endpoints.

- BOR, defined as the best response (in the order of complete response [CR], PR, SD, PD, and not evaluable) among all overall responses per RECIST v1.1, recorded from randomization/enrollment 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 BOR 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. Tumor response will be based on the programmatically-derived response from the investigator's recorded measurements for target, non-target, and new lesions according to RECIST v1.1.

- OR, defined as the BOR of confirmed CR or confirmed PR per RECIST v1.1.
- DC, defined as the BOR of confirmed CR or confirmed PR, or SD per RECIST v1.1. The DCR at 16 weeks is defined as a BOR of confirmed CR, confirmed PR or having SD with duration of SD lasting at least 16 weeks.
- DoR, defined as the time from the first documentation of a subsequently confirmed OR to the first documentation of a disease progression or death due to any cause, whichever occurs first. Only subjects who have achieved OR (confirmed CR or confirmed PR) will be evaluated for DoR.
- PFS, defined as the time from randomization (first dose date for Part 1) until the first documentation of disease progression or death due to any cause, whichever occurs first, regardless of whether the subject receives subsequent anticancer therapy prior to progression. Subjects who have not progressed at the time of analysis will be censored on the date of their last evaluable tumor RECIST v1.1 assessment. Landmark PFS such as 12-month PFS (PFS-12) will be estimated using the Kaplan-Meier method.
- OS will be determined as the time from randomization (first dose date for Part 1) until death due to any cause. For subjects who are alive at the time of data cutoff, OS will be censored on the last date when subjects are known to be alive.

4.8.3.1 Primary Efficacy Analysis

The primary efficacy endpoint is OR per RECIST v1.1. Objective response rate is defined as the proportion of subjects with OR. The 2-sided 95% confidence intervals (CIs) for ORR will be estimated using the exact binomial distribution. The primary analysis will compare an experimental arm with the control arm using the Cochran-Mantel-Haenszel (CMH) test stratified by the location of the primary tumor. An estimate of the odds ratio in ORR between the experimental arm and the control arm will be reported.

4.8.3.2 Secondary Efficacy Analyses

Secondary efficacy endpoints include BOR, DC, DoR, PFS, and OS. Analyses of secondary endpoints will be performed as follows.

- BOR rate is defined as the proportion of subjects with corresponding BOR. The 2-sided 95% CI of each BOR rate will be provided using an exact probability method.
- DCR is defined as the proportion of subjects with DC. The 2-sided 95% CI of DCR will be provided using an exact probability method. The DCR will be compared between an experimental arm and control arm using the CMH test stratified by the location of the primary tumor.
- DoR will be analyzed using the log-rank test for those subjects with OR in the corresponding analysis populations. The median DoR with 95% CI will be estimated based on the Kaplan-Meier curves.
- PFS according to RECIST v1.1 will be analyzed using the log-rank test stratified by the location of the primary tumor. The median PFS with 95% CI will be estimated based on the Kaplan-Meier curves. PFS-12 will be estimated based on the Kaplan-Meier curves along with their 95% CIs when applicable. An estimate of the difference in PFS-12

between an experimental arm and the control arm will be reported. Comparison of treatment arms for PFS-12 will be performed under complementary log-log transformation of the Kaplan-Meier estimates of PFS-12 (Klein et al, 2007).

- OS will be compared between experimental arms and control arm using the log-rank test stratified by the location of the primary tumor. The median OS with 95% CI will be estimated based on the Kaplan-Meier curves.

4.8.3.3 Exploratory Efficacy Analyses

CCI

[redacted]

4.8.4 Safety

Safety analyses will be based on the As-treated population defined in Section 4.8.1.

4.8.4.1 Analysis of Adverse Events

Summary statistics will be provided for AEs, AEs leading to treatment discontinuation, SAEs, and AE grade, severity, and relationship to study drug(s). AEs will be graded according to NCI CTCAE v5.0 and coded using system organ class and preferred term using the Medical Dictionary for Regulatory Activities preferred term. Specific AEs will be counted once for each subject when calculating rates but will be all presented in total in subject listings.

4.8.4.2 Analysis of Clinical Laboratory Parameters

Summary statistics will be provided for clinical laboratory parameters, physical examinations, vital signs, and ECG. Laboratory abnormalities with toxicity grades according to the NCI CTCAE v5.0 will be derived and summarized.

Laboratory parameters will be assessed at baseline as well as throughout the study. 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 from baseline to the worst post-baseline grade, will be provided for clinical laboratory tests. Also, laboratory parameters will be assessed by presenting tables containing information related to 2-grade (or greater) laboratory shifts.

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 the maximum and minimum post-baseline values.

4.8.4.4 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.

4.8.5 Analysis of Immunogenicity

Subjects who receive at least 1 dose of medicinal product of interest (bevacizumab, durvalumab, or oleclumab) and/or other combination study drug and provide a baseline and at least 1 post-treatment ADA result will be evaluated. Immunogenicity results will be analyzed descriptively by summarizing the number and percentage of subjects who develop detectable ADAs to bevacizumab and applicable novel biologic agents.

The potential impact of ADAs on PK and safety will be evaluated if data allow. Samples confirmed positive for ADAs may also be evaluated for neutralizing antibody activity.

4.8.6 Analysis of Pharmacokinetics

Subjects who receive at least 1 dose of medicinal product of interest (bevacizumab, durvalumab, or oleclumab) and/or other combination study drug and provide at least 1 post-treatment result will be evaluated. Individual bevacizumab and novel agent concentrations, as applicable, will be tabulated with descriptive statistics.

4.8.7 Analyses of Biomarkers

CCI

[redacted]

4.8.8 Interim Analysis

CCI

[redacted]

Figure 3 CCI

5 ASSESSMENT OF SAFETY

5.1 Definition of Adverse Events

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

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

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

5.2 Definition of Serious Adverse Events

An SAE is any AE that:

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

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

5.3 Definition of Adverse Events of Special Interest

An AESI is one of scientific and medical interest specific to understanding of the investigational product and may require close monitoring and rapid communication by the investigator to 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.

5.3.1 Anaphylaxis and Infusion-related Reactions

Infusion-related reactions and hypersensitivity/anaphylactic reactions are considered AESIs. Infusion of biological products is commonly associated with infusion-related reactions. Anaphylaxis and infusion-related reactions 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 of exposure to therapeutic mAbs delivered through IV infusion. These reactions are less common following subsequent exposures. Unlike infusion-related reactions, 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 adverse reactions observed during or shortly after exposure to investigational product and consider the above-mentioned facts prior to making a final diagnosis. For the investigator's convenience and to facilitate consistency in judgments, a copy of the National Institute of Allergy and Infectious Diseases (NIAID) and Food Allergy and Anaphylaxis Network (FAAN) guidance for anaphylaxis diagnosis is provided in Appendix C.

5.3.2 Adverse Events of Special Interest for Durvalumab-containing Regimens

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

If the investigator has any questions regarding an event being an imAE, the investigator should promptly contact the medical monitor.

Adverse events of special interest/imAEs observed with anti-PD-L/PD-1 agents, such as durvalumab, include:

- Pneumonitis
- Hepatitis

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

Further information on all those risks (eg, presenting symptoms) can be found in the current edition of the durvalumab IB. More specific guidelines for their evaluation and treatment are described in detail in Section 3.1.6 and Appendix H. These guidelines have been prepared by the sponsor to assist the investigator in the exercise of his/her clinical judgment in treating these types of toxicities. These guidelines apply to AEs considered causally related to the study drug/study regimen by the reporting investigator.

5.3.3 Adverse Events of Special Interest Associated with Oleclumab

Cardiac Chest Pain, Transient Ischemic Attack, and Thromboembolism

AEs of cardiac chest pain, transient ischemic attack, and thromboembolism are of special interest due to oleclumab potential risks of arterial calcifications, arterial ischemic disorder, and thrombosis. As a result of this potential risk, potential subjects with a history of venous thrombosis in the prior 3 months, or myocardial infarction, stroke, or transient ischemic attack in the prior 6 months are not eligible (Section 4.1.3). These events require urgent medical management, which should be performed according to consensus guidelines developed by the American Heart Association or appropriate local standards of care.

Edema

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

Immune Complex Disease

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

5.4 Recording of Adverse Events

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

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

5.4.1 Time Period for Collection of Adverse Events

AEs and SAEs will be collected from the time of signature of informed consent until at least 90 days after the last dose of study treatment or until initiation of alternative cancer therapy. If an event that starts post the defined safety follow up period noted above is considered to be due to a late onset toxicity to study drug then it should be reported as an AE or SAE as applicable.

All SAEs will be recorded and reported to the sponsor or designee within 24 hours, as indicated in Appendix B. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AE or SAE in former study subjects. However, if the investigator learns of any SAE, including a death, at any time after a patient's last visit and he/she considers the event to be reasonably related to the study treatment or study participation, the investigator should notify the sponsor.

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix B.

5.4.2 Follow-up of Unresolved Adverse Events

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

5.4.3 Deaths

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

- Death clearly the result of disease progression should be reported and documented 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 sponsor representative(s) within the usual timeframes (refer to Section 5.5 for additional information).

5.4.4 Adverse Events Based on Signs and Symptoms

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

5.4.5 Adverse Events Based on Examination and Tests

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

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

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

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

5.4.6 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 $\geq 3 \times$ ULN together with TBL $\geq 2 \times$ ULN will need to be reported as SAEs. Please refer to Appendix D for further instruction on cases of increases in liver biochemistry and evaluation of Hy's Law.

5.4.7 Disease Progression

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

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

New Cancers

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

5.5 Reporting of Serious Adverse Events

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

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

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

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

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

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

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

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

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

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

The reference document for definition of expectedness/listedness is the IB for the novel agents and the European Union Summary of Product Characteristics for standard of care therapies: folinic acid (leucovorin or levoleucovorin), fluorouracil (5-FU), oxaliplatin, and bevacizumab.

5.6 Other Events Requiring Immediate Reporting

5.6.1 Overdose

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

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

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

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

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

5.6.2 Pregnancy

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

Females of childbearing potential must have a negative pregnancy test result at screening to be enrolled in the study and treated with study drug.

5.6.2.1 Maternal Exposure

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

Pregnancy itself is not regarded as an AE unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication.

Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) should be followed up and documented even if the subject was discontinued from the study.

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

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

The same timelines apply when outcome information is available.

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

5.6.2.2 Paternal Exposure

Pregnancy of the subject's partners is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality), occurring from the date of the first dose until 90 days after the last dose of investigational product should, if possible, be followed up and documented.

5.6.3 Medication Error

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

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

Medication error includes situations where an error:

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

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

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

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

- Errors related to or resulting from IVRS/IWRS - including those which lead to one of the above listed events that would otherwise have been a medication error
- Subject accidentally missed drug dose(s), eg, forgot to take medication
- Accidental overdose (will be captured as an overdose)
- Subject failed to return unused medication or empty packaging
- Errors related to background and rescue medication, or standard of care medication in open label studies, even if an AstraZeneca or MedImmune product

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

If a medication error occurs in the course of the study, then the investigator or other site personnel informs the appropriate 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 completed within 1 or 5 calendar days if there is an SAE associated with the medication error (Section 5.5) and within 30 days for all other medication errors. Medication errors should be reported using a medication error report form.

6 STUDY AND DATA MANAGEMENT

6.1 Training of Study Site Personnel

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

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

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

6.2 Monitoring of the Study

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

6.2.1 Source Data

Refer to the clinical study agreement for location of source data.

6.2.2 Study Agreements

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

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

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

6.2.3 Archiving of Study Documents

The investigator follows the principles outlined in the clinical study agreement.

6.3 Study Timetable and End of Study

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

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

The end of the study ("study completion") is defined as the date of the last protocol-specified visit/assessment (including telephone contact) for the last subject in the study (ie, last subject last visit). The end of the study occurs after the last subject has discontinued study treatment and completed any applicable follow-up visit per the schedule of study procedures (Section 4.2), or the date the study is closed by the sponsor, whichever occurs first. Any subjects still receiving investigational product at the time of "study completion" may be able to continue to receive investigational product, as long as, in the investigator's opinion, the subject is deriving clinical benefit and has not fulfilled any discontinuation criteria.

6.4 Data Management

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

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

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

6.5 Medical Monitor Coverage

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

7 ETHICAL AND REGULATORY REQUIREMENTS

7.1 Subject Data Protection

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

7.2 Ethics and Regulatory Review

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

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

The sponsor should approve any substantive modifications to the informed consent form that are needed to meet local requirements.

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

Before the study is initiated, the sponsor will ensure that the national regulatory authority in each country has been notified and their approval has been obtained, as required. The sponsor will provide safety updates/reports according to local requirements, including suspected unexpected serious adverse reactions where relevant, to regulatory authorities, IRB/IEC, and Principal Investigators.

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

7.3 Informed Consent

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

The Principal Investigator(s) at each center will:

- Ensure each subject is given full and adequate oral and written information about the nature, purpose, possible risk, and benefit of the study
- Ensure each subject is notified that they are free to discontinue from the study at any time
- Ensure that each subject is given the opportunity to ask questions and allowed time to consider the information provided
- Ensure each subject provides signed and dated informed consent before conducting any procedure specifically for the study
- Ensure the original, signed informed consent form(s) is/are stored in the investigator's study file
- Ensure a copy of the signed informed consent form 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 informed consent form 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 the sponsor. Any changes must be documented in a study protocol amendment.

For a substantial change to the protocol, the sponsor will distribute amended versions of the protocol to the Principal Investigator(s). Before implementation, amended protocols must be

approved by relevant IRB/IEC (Section 7.2) and reviewed as per local regulatory authority requirements. The IRB/IEC must also approve revisions to the informed consent form, advertising, and any other written information and/or materials resulting from the change to the protocol.

Any non-substantial changes will be communicated to or approved by each IRB/IEC and local regulatory authority per local requirements.

7.5 Audits and Inspections

Authorized representatives of the sponsor, 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, ICH guidelines, and any applicable regulatory requirements. The investigator will contact the sponsor immediately if contacted by a regulatory agency about an inspection at the site.

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9 CHANGES TO THE PROTOCOL

9.1 Protocol Amendment 3

Text revisions resulting from this amendment are incorporated in the body of Protocol Amendment 3. The principal reasons for this amendment were to enable patients to remain on treatment when the study is stopped, and to clarify and reschedule PK and immunogenicity endpoints in Parts 1 and 2 of the study.

There are no changes to the protocol considered to be substantial amendments.

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

1 Corrected minor typographic, grammatical, and formatting issues.

2 Cover page: New medical monitor details added PPD

3 Protocol Synopsis, Objectives and Endpoints (Secondary Pharmacokinetics and Immunogenicity, CCI [redacted]): Updated according to Sections 2.2 and 2.3, respectively, as described below.

4 Section 2.2 (Table 2 - Secondary Objectives and Associated Endpoints, under Objectives), Part 1 and 2: Removed text specifying the PK of novel agents will be described only when used in combination with FOLFOX + bevacizumab. Part 1: Removed text specifying the PK of bevacizumab will be described only when in combination with FOLFOX + novel therapy combinations.

5 Section 2.2 (Table 2 - Secondary Objectives and Associated Endpoints, under Endpoints): Clarified that PK and drug concentrations for novel agents are endpoints in Part 1 and 2. Clarified that PK (drug concentration) for bevacizumab is an endpoint in Part 1.

6 Section 2.2 (Table 2 - Secondary Objectives and Associated Endpoints, under Objectives): Separated statement on objectives into Part 1 and 2, and Part 1. Part 1 and 2: Removed text specifying the immunogenicity of novel agents will be described only when used in combination with FOLFOX + bevacizumab. Part 1: Removed text specifying the immunogenicity of bevacizumab will be only described when in combination with FOLFOX + novel therapy combinations.

7 Section 2.2 (Table 2 - Secondary Objectives and Associated Endpoints, under Endpoints): Separated statement on endpoints into Part 1 and 2, and Part 1. Clarified that the incidence of ADA to novel agents is an endpoint in Part 1 and 2. Clarified that the incidence of ADA to bevacizumab is an endpoint in Part 1.

8 Section 2.3 (Table 3 - CCI [redacted]

9 Section 2.3 (Table 3 - CCI [redacted]

10 Section 2.3 (Table 3 - CCI [redacted]

11 Section 2.3 (Table 3 - CCI [redacted]

12 Section 2.3 (Table 3 - CCI [redacted]

13 Section 3.1.7 (Post-Study Access to Investigational Products[s]): Updated study information clarifying that any subjects still receiving investigational product at the time of the data cutoff will be able to continue to receive investigational product. Specified that the data cutoff refers to the final analysis in the CSR.

14 Section 3.2.3 (Rationale for Endpoint[s]): Added endpoints BOR and DC, and clarified which endpoints are defined as primary or secondary.

15 Section 6.3 (Study Timetable and End of Study): Added that subjects still receiving investigational product at the time of "study completion" may be able to continue to receive investigational product, as long as, in the investigator's opinion, the subject is deriving clinical benefit and has not fulfilled any discontinuation criteria.

9.2 Protocol Amendment 2

Text revisions resulting from this amendment are incorporated in the body of Protocol Amendment 2. The principal reason for this amendment was to clarify study objectives and procedures, and to align safety information with monalizumab, oleclumab, and durvalumab IBs

Substantial changes to the protocol are summarized below:

1 Sections 1.6.2.1 (Durvalumab Risks) and 5.3.2 (Adverse Events of Special Interest for Durvalumab-containing Regimens): Updated per durvalumab IB edition 15.0, including addition of vasculitis, noninfectious meningitis, and noninfectious encephalitis as AESIs.

2 Section 1.6.3 (Overall Benefit-Risk): Added language to discuss subjects with active SARS-CoV2 infection. Added information regarding how subjects should be managed if they develop an active infection while on the study.

3 Section 2.2 (Secondary Objectives and Associated Endpoints), Section 2.3 CCI [redacted]

CCI [redacted]

4 Section 3.1.2 (Treatment Regimen): Specified that for folinic acid therapy, if leucovorin is not available, the use of levoleucovorin at an equivalent dose is acceptable.

5 Section 3.1.5 (Randomized Phase [Part 2]), Section 4.6.1 (Methods for Assigning Treatment Groups): Updated to clarify that the allocation ratio to the different arms may be adjusted via protocol amendment (previously "at the discretion of the sponsor") after 50 subjects are randomized to the control arm. Clarified that the control arm will continue to enroll subjects even after 50 subjects have been enrolled in that arm.

6 Section 3.1.6.1 (Management of Toxicities Related to Durvalumab-containing Regimens [previously titled "Management of Investigational Product Related Toxicities"]): Revised language for toxicity management guidelines per sponsor guidelines and added statement to clarify that subjects who receive oleclumab in combination with durvalumab should follow the durvalumab toxicity management guidelines.

7 Section 4.3.2 (Tumor Samples), Table 10 (Tumor Sample Requirements at Each Time Point), Section 4.3.2.2 (Fresh Tumor Samples): Clarified the requirements for archival and fresh tumor samples. Added language to specify that mandatory biopsies can be waived to ensure subject safety during the SARS-CoV2 pandemic.

8 Section 5.3.1 (Anaphylaxis and Infusion-related Reactions): This section was added and text was moved here from Section 5.3.2 (Adverse Events of Special Interest for Durvalumab-containing Regimens), in order to indicate that it applies to all the biological products used in the study.

9 Section 5.3.3 (Adverse Events of Special Interest Associated with Oleclumab): A section on immune complex disease was added to align with the potential risks of oleclumab.

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

11 Appendix I (Site and Study Closure): Added text to address site and study closure as required in ICH GCP guidelines.

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

1 Cover page: New medical monitor PPD

2 Sections 1.6.1.2 (Oleclumab) and 1.6.2.3 (Durvalumab plus Oleclumab): Updated per oleclumab IB edition 6.0.

3 Section 1.6.2.2 (Checkpoint Inhibitors in Combination with Chemotherapy – Durvalumab in Combination with Chemotherapy with or without Other Immunotherapies) and Section 8 (References): New reference (ESMO 2019) was added.

4 Section 4.1.2 (Inclusion Criteria): The following statement was added to inclusion criteria 9 and 10 "(except in countries where spermicides are not approved)" as spermicides are not approved in all countries.

5 Section 4.1.3 (Exclusion Criteria): Revised Criterion 6 to specify that ECGs will be obtained in triplicate within a 5-minute period at least 1 minute apart (previously 15 minutes at 5 minutes apart) to align with the ECG timing in Table 6 (Schedule of

Screening Procedures [All Parts]) in Section 4.2.1. Revised footnote for ECG in Table 6 to reflect triplicate ECGs are obtained at least 1 minute apart.

6 Section 4.1.7 (Treatment Beyond Progression): Deleted "before completion of the treatment period", as a treatment period is not specified in this protocol.

7 Section 4.5.1.5 (Treatment Administration): Clarified that a wait period of at least 15 minutes must follow infusions of oleclumab and durvalumab before beginning administration of a subsequent infusion.

8 Section 4.5.2 (Additional Study Medications): Clarified that the use of bevacizumab biosimilars is acceptable in regions/countries where their use is approved.

9 Section 4.8.8 CCI [redacted]

9.3 Protocol Amendment 1

Text revisions resulting from this amendment are incorporated in the body of Protocol Amendment 1. The principal reason for this amendment was to address FDA comments on the original protocol.

No changes to the protocol were considered substantial. Changes to the protocol considered to be non-substantial are summarized below.

1 Corrected minor typographic, grammatical, and formatting issues.

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

3 Section 3.1.3 (Safety Run-in [Part 1]): Revised to further clarify that Part 1 will not involve dose escalation.

4 Section 3.1.5.2 (Safety Review Committee [Part 2]): Clarified that the SRC will also be responsible for making recommendations for investigational product dose selection to ensure subjects maintain adequate exposure to standard of care treatment.

5 Section 3.1.6 (Management of Study Medication Related Toxicities):

- Clarified that the toxicity management guidelines provided via the website and Annex to Protocol are applicable to oleclumab.
- Clarified that guidelines regarding treatment modification and toxicity management for standard of care therapies are provided in Appendix H.

Appendix A Contraception Guidance

For females of childbearing potential:

- Females of childbearing potential are defined as those who are not surgically sterile (ie, surgical sterilization includes bilateral tubal ligation, bilateral oophorectomy, or hysterectomy) or those who are not postmenopausal (defined as 12 months with no menses without an alternative medical cause).
- A highly effective method of contraception is defined as one that results in a low failure rate (ie, less than 1% per year) when used consistently and correctly. The acceptable methods of contraception are described in Table A1
- Female subjects must refrain from egg cell donation and breastfeeding while on study and for 180 days after the final dose of investigational product.

Table A1 Highly Effective Methods of Contraception

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

[a] This is also considered a hormonal method.

[b] With appropriate post-vasectomy documentation of surgical success (absence of sperm in ejaculate).

[c] Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of the study and if it is the preferred and usual lifestyle of the subject.

[d] Progestogen-only hormonal contraception, where inhibition of ovulation is not the primary mode of action (eg, minipill), is not accepted as a highly effective method).

Appendix B Additional Safety Guidance

Further Guidance on the Definition of a Serious Adverse Event

Life threatening

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

Hospitalization

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

Important Medical Event or Medical Intervention

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

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

Examples of such events are:

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

Assessment of Severity

Assessment of severity is one of the responsibilities of the investigator in the evaluation of AEs and SAEs. Severity will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.0 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 Grade 5 as defined below.

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

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

Assessment of Relationship

A guide to Interpreting the Causality Question

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

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

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

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

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

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

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

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

Relationship to Protocol Procedures

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

Protocol related: The event occurred due to a procedure/intervention that was described in the protocol for which there is no alternative etiology present in the subject's medical record.

Not protocol related: The event is related to an etiology other than the procedure/ intervention that was described in the protocol (the alternative etiology must be documented in the study subject's medical record).

Appendix C National Institute of Allergy and Infectious Diseases and Food Allergy and Anaphylaxis Network Guidance for Anaphylaxis Diagnosis

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.

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

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

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

D 1 Introduction

This appendix describes the process to be followed 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.

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 sponsor 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.

D 2 Definitions

D 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 alkaline phosphatase (ALP).

D 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, or another drug.

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

D 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 (Section D 2) by reviewing laboratory reports from all previous visits
- Promptly enter the laboratory data into the laboratory eCRF

D 4 Follow-up

D 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.

D 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 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 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

D 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 within 15 calendar days 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 a 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) and follow the sponsor's standard processes

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

- Send the updated SAE (report term 'Hy's Law') according to the sponsor's standard processes.

- The 'Medically Important' serious criterion should be used if no other serious criteria apply
- As there is no alternative explanation for the Hy's Law case, a causality assessment of 'related' should be assigned

If, there is an unavoidable delay of over 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 is 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

D 6 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?

If No: follow the process described in Section D 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 D 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.

D 7 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):806-15.

FDA Guidance for Industry (issued July 2009). Drug-induced liver injury: Premarketing clinical evaluation.

Appendix E CCI

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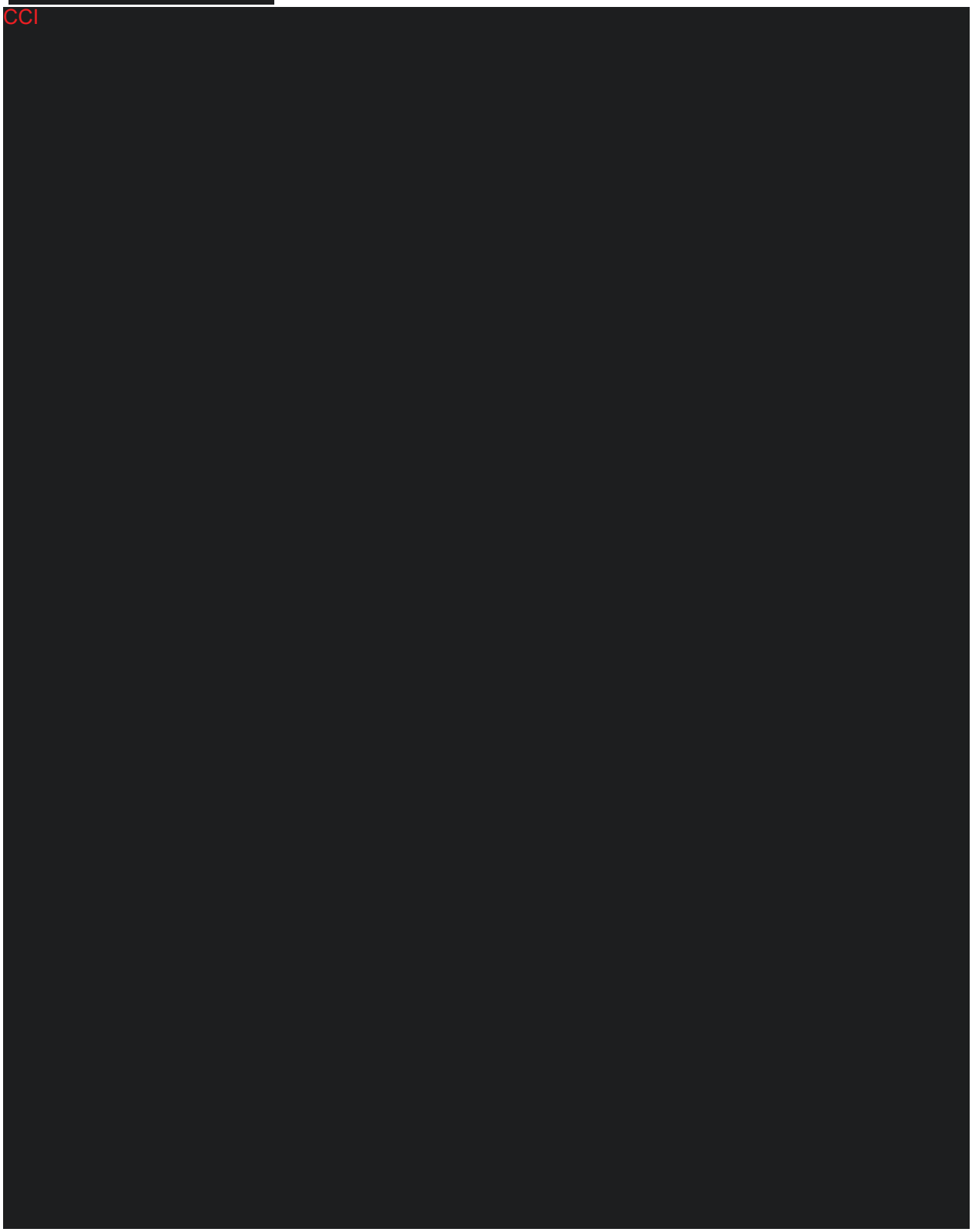

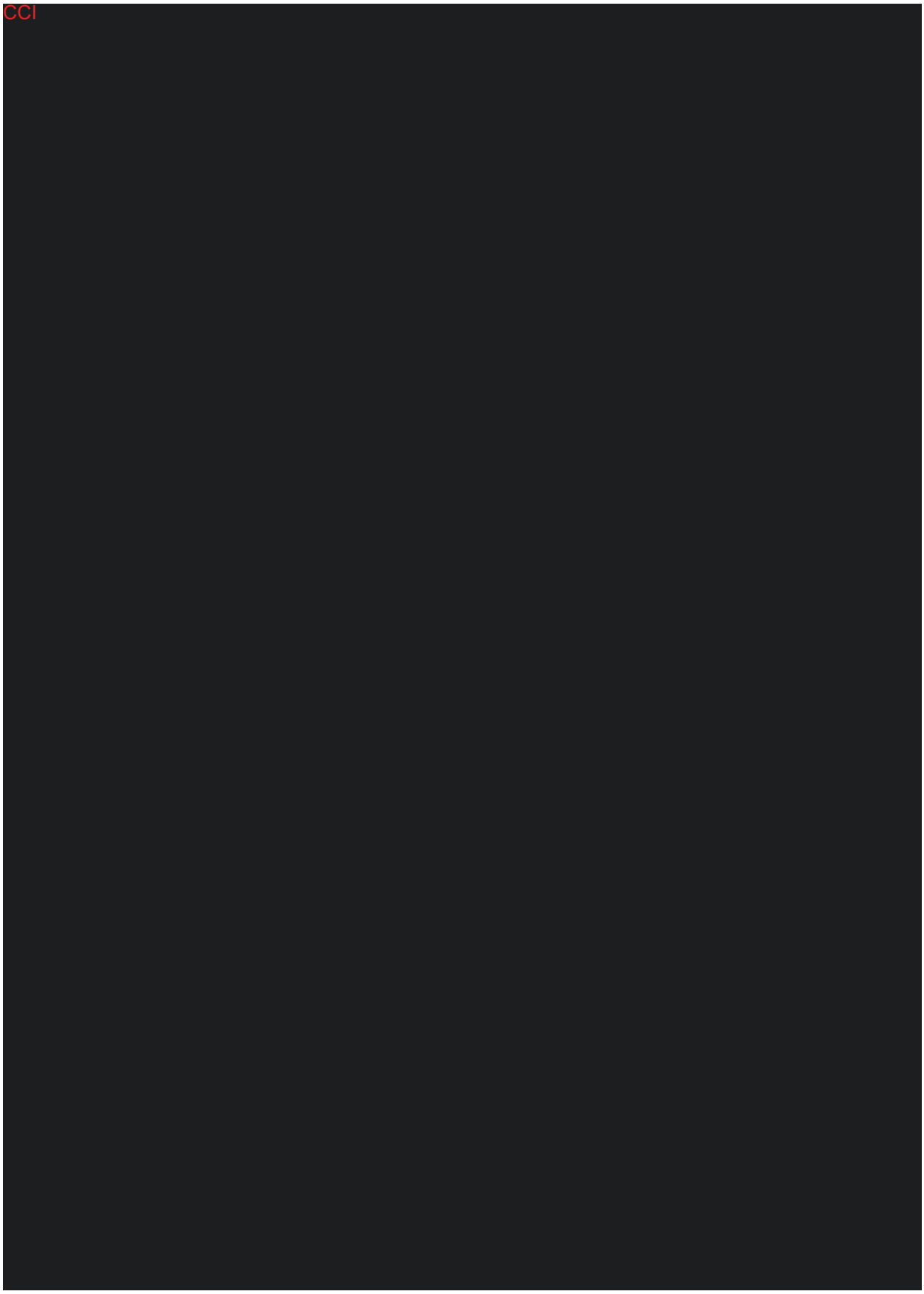
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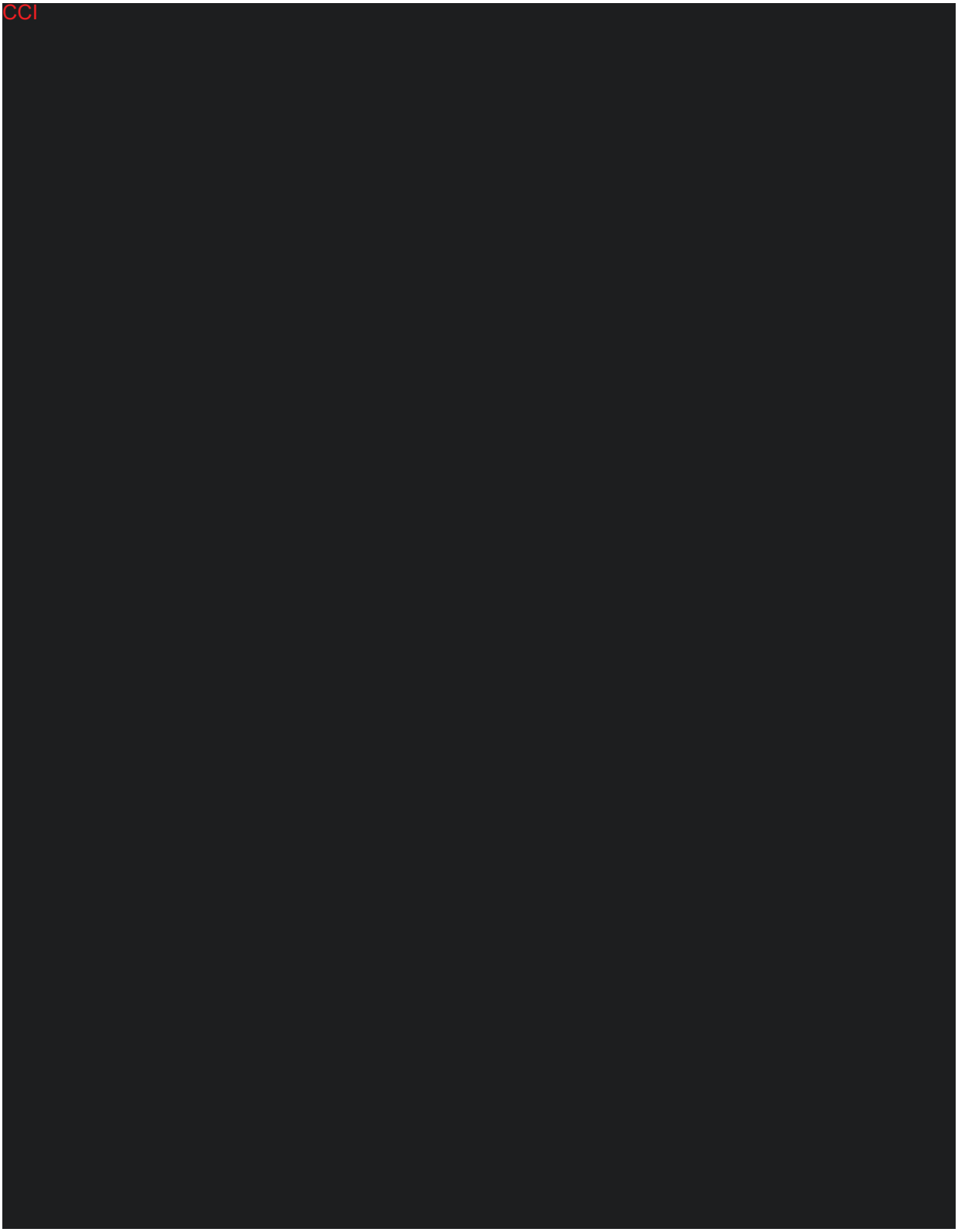
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Appendix F Response Evaluation Criteria in Solid Tumors Version 1.1

F 1 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 examination (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 short axis). Lesions considered truly nonmeasurable include the following: leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, and abdominal masses/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques.
- **Target Lesions -** At baseline, all lesions up to a maximum of 5 lesions total (and a maximum of 2 lesions per organ) representative of all involved organs should be identified as target lesions. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected.
- **Non-target Lesions -** It is possible to record multiple non-target lesions involving the same organ as a single item (eg, "multiple enlarged pelvic lymph nodes" or "multiple liver metastases").
- **New Lesions** - Though only certain new lesion measurements will be included in the tumor burden, all new lesions that can be accurately measured should be recorded. Up to 5 additional target lesions (maximum of 2 additional lesions per organ) may be added to the tumor burden at each postbaseline assessment [redacted] Other new lesions will be included into the non-tumor burden.

F 2 RECIST v1.1 Response Criteria

Evaluation of Target Lesions

- **CR** - Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm (the sum may not be "0" if there are target nodes).
- **PR** - At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.
- **PD** - At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered PD.)
- **SD** - Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum of diameters while on study.

Evaluation of Non-target Lesions

- **CR** - Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis).
- **Non-CR/Non-PD** - Persistence of 1 or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.
- **PD** - Unequivocal progression of existing non-target lesions will be defined as the overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy (Section 4.1.6). In the absence of measurable disease, change in non-measurable disease comparable in magnitude to the increase 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 can nonetheless derive clinical benefit.

Evaluation of Overall Response

For the overall response based on RECIST v1.1, confirmation of CR and PR is required by a repeat, consecutive assessment no less than 4 weeks from the date of first documentation. If a subject discontinues the study due to PD and begins another treatment, a confirmatory scan is not required.

Table F1 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 F1 Evaluation of Overall Response Using RECIST v1.1

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

RECIST v1.1 = Response Evaluation Criteria in Solid Tumors version 1.1.

[a] Defined as no target lesion at baseline.

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

Reference: Eisenhauer et al, 2009

Appendix G CCI

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Table G1 CCI

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Table G1 CCI

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Appendix H Treatment Modification and Toxicity Management

H 1 General Guidelines

If the initiation of a new cycle, or therapy during a cycle, is delayed for ≥ 4 weeks because of investigational product-related toxicity, treatment with FOLFOX may be discontinued. If FOLFOX is discontinued or modified (eg, oxaliplatin is suspended) due to toxicity, subjects may continue on therapy with bevacizumab and/or novel agent(s) only until the subject meets the guidelines for treatment discontinuation (Section 4.1.6).

Immune-related toxicities and chemotherapy-related toxicities are recognized to have different underlying pathophysiology and require different management (Brahmer et al, 2018). To discriminate between them, investigators are invited to perform comprehensive work-up covering both causes in order to direct the appropriate therapeutic interventions (https://tmg.azirae.com). If the toxicities are clearly attributed to chemotherapy or immunotherapy (ie, durvalumab and oleclumab), either chemotherapy or immunotherapy may be delayed or discontinued, and the other may be continued (see Section H 3 for synchronized delay, if applicable). If the causality of toxicity is unclear, both chemotherapy and immunotherapy may be delayed or discontinued. There are no recommended dose reductions for durvalumab or oleclumab.

In the absence of clear alternative etiology, all events should be considered potentially immune-mediated, and the toxicity management guidelines for management of immune-related AEs should be followed (see the Annex to Protocol or https://tmg.azirae.com).

In the event that the novel agent(s) are discontinued or delayed as part of the toxicity management guidance, chemotherapy and bevacizumab may still be administered as scheduled.

H 2 Dose Levels

Table H1 indicates potential dose levels for each of the agents for which dose modifications will be allowed. Dose adjustments of each agent may be made independently based on the specific types of toxicities observed. Only those agents specified in the sections below should be dose reduced.

Table H1 CCI

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Table H1 CCI

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H 3 FOLFOX Dose Modifications

- In the event that toxicities are clearly attributed to chemotherapy, both chemotherapy (5-FU and oxaliplatin) and the regimen containing novel agent(s) may be delayed for up to 7 days; the goal of synchronized delay is to preserve the alignment of chemotherapy and immunotherapy. If chemotherapy cannot be resumed within 7 days after the originally scheduled day, the novel agent(s) may be administered for that cycle.
- If subjects experience a toxicity clearly related to any chemotherapeutic agent necessitating the suspension or the discontinuation of that agent only (eg, neuropathy due to oxaliplatin), then the non-offending chemotherapeutic agent and novel agent(s) may still be continued until the subject meets the guidelines for treatment discontinuation.
- If 5-FU is discontinued, oxaliplatin must also be discontinued.

H 4 Bevacizumab Dose Modifications

- There are no recommended dose reductions
- Temporary suspension is recommended for:
  - Severe infusion reactions (≥ Grade 3; Appendix H 17)
  - At least 4 weeks prior to and after elective surgery (ie, major surgery)
  - Moderate to severe proteinuria (≥ 2 g/24 h; Appendix H 14)
  - Persistent or symptomatic hypertension despite appropriate therapy, as defined in Appendix H 10
- Permanent discontinuation is recommended for:
  - Wound dehiscence and wound healing complications requiring intervention (Appendix H 16)
  - Necrotizing fasciitis
  - Fistula
  - Gastrointestinal perforation (Appendix H 16)
  - Bowel obstruction (≥ Grade 3; Appendix H 16)
  - Intra-abdominal abscess
  - Hypertensive crisis

- Hypertensive encephalopathy
- Serious bleeding/hemorrhage (Appendix H 13)
- Severe arterial thromboembolic events (≥ Grade 3; Appendix H 12)
- Life-threatening (Grade 4) venous thromboembolic events (including pulmonary embolism) (Appendix H 12)
- Nephrotic syndrome or ≥ Grade 3 proteinuria (Appendix H 14)
- Reversible posterior leukoencephalopathy syndrome (RPLS; Appendix H 11)

H 5 FOLFOX/Bevacizumab Hematologic Toxicities

The following dose modifications are based on toxicity experienced during a cycle (ie, after Day 1 of any cycle):

Grade 3 or Grade 4 neutropenia or thrombocytopenia: Skip 5-FU and oxaliplatin.

If counts recover to an absolute neutrophil count ≥ 1.5×10^9/L and platelets ≥ 75×10^9/L, then 5-FU and oxaliplatin may be resumed at one lower dose level for subsequent cycles. Skipped doses are not to be made up (ie, omitted doses will not be administered at a later date).

Febrile neutropenia (defined as absolute neutrophil count < 1.0×10^9/L and temperature ≥ 38.5°C): Skip 5-FU and oxaliplatin. If fever and neutropenia resolve, 5-FU and oxaliplatin may be resumed at one lower dose level for subsequent cycles, provided an absolute neutrophil count ≥ 1.5×10^9/L and platelets ≥ 75×10^9/L. Omitted doses will not be administered at a later date.

Hematopoietic growth factors
Granulocyte-colony stimulating factor (G-CSF) is not recommended as primary prophylaxis, but it can be used in secondary prophylaxis in case of:

- Precedent febrile neutropenia;
- Precedent grade 4 neutropenia lasting 5 days or more;
- More than 2 delays of the planned therapy due to neutropenia.

Anemia: Non-hemolytic ≥ Grade 2 anemia should be managed with blood transfusions or with the administration of erythropoietin, according to institutional guidelines. No dose modification of the chemotherapy or investigational product is required.

NOTE: No bevacizumab, durvalumab, or oleclumab dose modifications will be made for hematologic toxicity.

Continue bevacizumab and novel agent(s), when 5-FU and/or oxaliplatin are skipped for hematologic toxicities.

H 6 FOLFOX/Bevacizumab Gastrointestinal Toxicities

In cases where the toxicity is deemed to be immune related, refer to the toxicity management guidelines annex/website (https://tmg.azirae.com). In cases where toxicity can be reasonably attributed to the chemotherapy and if an immune-related etiology is ruled out, consider the following guidelines. If the investigator is unable to determine which study drug is a more likely cause of the AE (ie, FOLFOX, bevacizumab, or immunotherapeutics), then the treatment management should cover both etiologies.

The following dose modifications are based on toxicity experienced during a cycle (ie, after Day 1 of any cycle):

- For Grade 2 diarrhea, reduce 5-FU one dose level for the subsequent cycles. Oxaliplatin is not reduced. When diarrhea has fully resolved, resume 5-FU at the previous dose level.
- For Grade 3 or Grade 4 diarrhea, skip 5-FU and oxaliplatin. If diarrhea resolves to ≤ Grade 2, then 5-FU and oxaliplatin may be resumed at one lower dose level for subsequent cycles. Omitted doses will not be administered at a later date.

Mucositis: The following dose modifications are based on the grade of mucositis seen on the day of treatment for any day after Day 1 in any cycle.

- For **Grade 2 mucositis**, reduce 5-FU and oxaliplatin one dose level for subsequent cycles. When mucositis has fully resolved, continue 5-FU and oxaliplatin at the previous dose levels.
- For **Grade 3 mucositis**, skip 5-FU and oxaliplatin. If mucositis resolves to ≤ Grade 2, then 5-FU and oxaliplatin may be resumed at one lower dose level for subsequent cycles. Omitted doses will not be administered at a later date. When mucositis has fully resolved, continue 5-FU at the reduced dose level from the previous cycle and resume oxaliplatin at the previous dose level.
- For **Grade 4 mucositis**, skip all protocol therapy. If mucositis resolves to ≤ Grade 2, then 5-FU and oxaliplatin may be resumed at one lower dose level for subsequent cycles. Omitted doses will not be administered at a later date.

Nausea/vomiting: The following dose modifications are based on the grade of nausea and vomiting occurring during a cycle (ie, after Day 1 in any cycle):

- For Grade 3 nausea or vomiting, reduce oxaliplatin one dose level for subsequent cycles.
- For Grade 4 nausea or vomiting, reduce 5-FU and oxaliplatin one dose level for subsequent cycles.

These dose reductions for vomiting and/or nausea should be made only if they persist/occur despite 2 treatments with adequate (combination) antiemetic therapy. See Hesketh et al, 2017 for antiemetic practice guidelines.

No bevacizumab or investigational product dose modifications will be made for diarrhea, mucositis, nausea, or vomiting. Continue bevacizumab when 5-FU and oxaliplatin are skipped for these gastrointestinal toxicities.

H 7 FOLFOX/Bevacizumab Pulmonary Toxicity

In cases where the toxicity is deemed to be immune related, refer to the toxicity management guidelines annex/website (https://tmg.azirae.com). In cases where toxicity can be reasonably attributed to the chemotherapy and if an immune-related etiology is ruled out, consider the following guidelines. If the investigator is unable to determine which study drug is a more likely cause of the AE (ie, FOLFOX, bevacizumab, or immunotherapeutics), then the treatment management should cover both etiologies.

For Grade 2 or worsening pulmonary symptoms unrelated to underlying cancer, investigational product should be held until resolution to Grade 1 or less, and symptoms investigated to rule out a potential immune-related pneumonitis (see https://tmg.azirae.com).

For ≥ Grade 3 cough, dyspnea, hypoxia, pneumonitis, or pulmonary infiltrates unrelated to underlying cancer, skip oxaliplatin, bevacizumab until interstitial lung disease is ruled out. Investigational product should be permanently discontinued; 5-FU may be continued. Discontinue all protocol therapy if interstitial lung disease is confirmed.

H 8 FOLFOX/Bevacizumab Neurotoxicity

In cases where the toxicity is deemed to be immune related, refer to the toxicity management guidelines annex/website (https://tmg.azirae.com). In cases where toxicity can be reasonably attributed to the chemotherapy and if an immune-related etiology is ruled out, consider the following guidelines. If the investigator is unable to determine which study drug is a more likely cause of the AE (ie, FOLFOX, bevacizumab, or immunotherapeutics), then the treatment management should cover both etiologies.

Table H2 Toxicity Scale for the Sensory Neuropathies Associated with Oxaliplatin

Grade	Symptoms
Grade 1	Paresthesias/dysesthesias [a] of short duration that resolve and do not interfere with function.
Grade 2	Paresthesias/dysesthesias [a] interfering with function, but not in activities of daily living.
Grade 3	Paresthesias/dysesthesias [a] with pain or with functional impairment that also interfere with activities of daily living.
Grade 4	Persistent paresthesias/dysesthesias [a] that are disabling or life threatening.

[a] May be cold-induced

For Grade 2 neurotoxicity persisting between treatments: Reduce oxaliplatin by one dose level for subsequent cycles.

For Grade 3 neurotoxicity resolving to ≤ Grade 2 between treatments: Reduce oxaliplatin by one dose level for subsequent cycles.

For recurrent Grade 3 neurotoxicity resolving to ≤ Grade 2 between treatments: Reduce oxaliplatin by one additional dose level for subsequent cycles. Oxaliplatin will not be reduced beyond level –3. If further dose reduction is required for neurotoxicity, oxaliplatin will be discontinued. Subjects should continue to receive other protocol therapy.

For Grade 3 neurotoxicity persisting between treatments: Discontinue oxaliplatin. Subjects should continue to receive other protocol therapy.

For Grade 4 neurotoxicity: Discontinue oxaliplatin. Subjects should continue to receive other protocol therapy.

For pharyngo-laryngeal dysesthesia: Increase the duration of oxaliplatin infusion to 6 hours for all subsequent treatments.

Subjects may also discontinue oxaliplatin following multiple cycles even in the absence of dose-limiting neurotoxicity if, in the physician's judgment, neurotoxicity is likely to become problematic. Subjects should continue to receive other protocol therapy and the oxaliplatin may be reintroduced subsequently.

H 9 FOLFOX Extravasation

Extravasation of oxaliplatin has been associated with necrosis; if extravasation is suspected, the infusion should be stopped, and the drug administered at another site. Extravasation may be treated according to institutional guidelines.

H 10 Bevacizumab Dose Modifications for Hypertension

- For hypertension controlled with medication (to < 160/100 mmHg): Continue bevacizumab.
- For persistent or symptomatic hypertension despite appropriate therapy: skip bevacizumab. If bevacizumab treatment is delayed for more than 4 weeks due to uncontrolled hypertension, discontinue bevacizumab.
- Grade 4 hypertension: Permanently discontinue bevacizumab.

Subjects who skip or discontinue bevacizumab due to hypertension may continue other protocol therapy.

H 11 Bevacizumab Dose Modifications for RPLS

For signs and symptoms suggestive of RPLS (eg, confusion, headache, seizures, cortical blindness) skip bevacizumab. Suspected RPLS should be investigated with MRI as described in Section H 11.1. If diagnosis of RPLS is confirmed, bevacizumab should be permanently discontinued.

If RPLS is ruled out via MRI, the decision on resuming bevacizumab should be based on the nature of the signs/symptoms. For Grade 4 events with likely relationship to bevacizumab, discontinue bevacizumab; for Grade 3 events, bevacizumab may be resumed if toxicities completely resolve within 4 weeks.

Other protocol therapy may be continued at the discretion of the treating physician.

H 11.1 Investigation of RPLS

Reversible posterior leukoencephalopathy syndrome or clinical syndromes related to vasogenic edema of the white matter have been reported in association with bevacizumab therapy. These syndromes have been seen in < 1% of patients to date. Clinical presentations are variable and may include altered mental status, seizure and cortical visual deficit. Hypertension is a common risk factor and was present in most (though not all) patients on bevacizumab who developed RPLS. MRI scans are key to diagnosis and typically demonstrate vasogenic edema (hyperintensity in T2 and FLAIR images and hypointensity in T1 images) predominantly in the white matter of the posterior parietal and occipital lobes; less frequently, the anterior distributions and the gray matter may also be involved. RPLS should be in the differential diagnosis in subjects presenting with unexplained mental status change, visual disturbance, seizure or other CNS findings. RPLS is potentially reversible, but timely correction of the underlying causes, including control of blood pressure and interruption of the offending drug, is important to prevent progression to irreversible tissue damage.

H 12 Dose Modifications for Cardiovascular Toxicities

In cases where the toxicity is deemed to be immune related, refer to the toxicity management guidelines annex/website (https://tmg.azirae.com). In cases where toxicity can be reasonably attributed to the chemotherapy and if an immune-related etiology is ruled out, consider the following guidelines. If the investigator is unable to determine which study drug is a more likely cause of the AE (ie, FOLFOX, bevacizumab, or immunotherapeutics), then the treatment management should cover both etiologies.

Subjects should be carefully monitored for evidence of thromboembolic disease during treatment.

For Grade 3 venous thrombosis or asymptomatic pulmonary embolism: Skip bevacizumab. If the planned duration of full-dose anticoagulation is < 2 weeks, bevacizumab should be held until the full-dose anticoagulation period is over. If the planned duration of full-dose anticoagulation is > 2 weeks, bevacizumab may be resumed during the period of full-dose anticoagulation if all of the following criteria are met:

- The subject must have an in-range INR (usually between 2 and 3) or be on stable dose of low molecular weight heparin prior to restarting bevacizumab treatment;
- The subject must not have pathological conditions that carry high risk of bleeding (eg, tumor involving major vessels);
- The subject must not have had hemorrhagic events while on study.

For Grade 4 or for recurrent/worsening venous thromboembolic events after resumption of bevacizumab: Discontinue all protocol therapy and notify the sponsor medical monitor.

For symptomatic pulmonary embolism, subjects will discontinue all protocol therapy.

Arterial Thrombotic Events

- For Grade 2 arterial thrombotic events not present at baseline or worsened since the initiation of protocol therapy, discontinue bevacizumab. Subjects may continue other protocol therapy.
- For Grade 3 cerebrovascular ischemia, and/or peripheral or visceral arterial ischemia, discontinue bevacizumab. Subjects may continue other protocol therapy.
- For Grade 3 cardiac ischemia/infarction, discontinue all protocol therapy.
- For any Grade 4 arterial thrombotic event, including cerebrovascular ischemia, cardiac ischemia/infarction, peripheral or visceral arterial ischemia, discontinue all protocol therapy.

Myocarditis, Pericarditis, Arrhythmias or Impaired Ventricular Function with Heart Failure Events

- For Grade 3 events, discontinue bevacizumab and investigational product. FOLFOX should be held until resolution to ≤ Grade 1.
- For Grade 4 events, discontinue all protocol therapy.

H 13 Bevacizumab Dose Modifications for Hemorrhage/bleeding

- For Grade 3 hemorrhage/bleeding, discontinue bevacizumab and skip other protocol therapy; once hemorrhage or bleeding resolves, other protocol therapy may be continued at the treating physician's discretion.
- For Grade 4 hemorrhage/bleeding, discontinue all protocol therapy.

H 14 Bevacizumab Dose Modifications for Proteinuria

In cases where the toxicity is deemed to be immune related, refer to the toxicity management guidelines annex/website (https://tmg.azirae.com). In cases where toxicity can be reasonably attributed to the chemotherapy and if an immune-related etiology is ruled out, consider the following guidelines. If the investigator is unable to determine which study drug is a more likely cause of the AE (ie, FOLFOX, bevacizumab, or immunotherapeutics), then the treatment management should cover both etiologies.

- For proteinuria of ≥ 2+: Confirm total urine protein with a 24-hour urine collection or UPC ratio. For 2+ proteinuria, the scheduled dose of bevacizumab may be given while awaiting the results of the 24-hour collection or UPC ratio. For > 2+ proteinuria, skip bevacizumab while awaiting results of the 24-hour urine collection or UPC ratio. Other protocol therapy may be continued.
- If proteinuria is ≥ 2 g/24 hours or UPC ratio ≥ 2.0, skip bevacizumab until urine protein recovers to < 2 g/24 hours or UPC < 2.0, continue other protocol treatment. If bevacizumab is delayed more than 8 weeks due to proteinuria, discontinue bevacizumab.
- If nephrotic syndrome or ≥ Grade 3 proteinuria occurs, discontinue bevacizumab.

H 15 Dose Modifications for Elevated Transaminase and Alkaline Phosphatase Levels

Bevacizumab: After the first incidence of elevated ALT or AST levels or Grade 3 or Grade 4 ALP, which the clinical investigator considers to be related to bevacizumab treatment, bevacizumab should only be resumed after laboratory values have resolved to Grade ≤ 1. Therapy with bevacizumab should be discontinued after the second incidence.

H 16 Other Bevacizumab Toxicities

- For wound dehiscence requiring medical or surgical intervention: Discontinue bevacizumab.
- For any grade gastrointestinal perforation, gastrointestinal leak, or intra-abdominal fistula: Discontinue bevacizumab.
- For bowel obstruction:
  - Grade 1: Subjects who experience partial obstruction not requiring medical intervention may continue on bevacizumab
  - Grade 2: Hold bevacizumab in subjects who experience partial obstruction requiring medical intervention. Resume upon complete resolution
  - Grade 3/4: Discontinue bevacizumab

H 17 Hypersensitivity and Infusion Reactions

Hypersensitivity reactions as well as infusion-related reactions have been reported with anti-PD-(L)1 therapy (Brahmer et al, 2018). Since durvalumab is a human anti-PD-L1 mAb, as with any antibody, allergic reactions following the infusion are possible and can be caused by various mechanisms, including acute anaphylactic (IgE-mediated) and anaphylactoid reactions against the mAb, and serum sickness.

Severe hypersensitivity reactions should be managed according to standard clinical practice. At all sites, 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. The study site must have immediate access to emergency resuscitation teams and equipment in addition to the ability to admit patients to an intensive care unit if necessary.

Serum tryptase or other blood or urine testing relevant to the diagnosis of anaphylaxis may be obtained at the discretion of the Investigator.

Refer to the toxicity management guidelines annex/website (https://tmg.azirae.com) for the management of hypersensitivity and infusion related reactions for immune-related events.

Dose Modifications for Hypersensitivity Reactions (FOLFOX and Bevacizumab Only)

- For Grade 1 hypersensitivity reactions (transient rash, drug fever < 38°C): Decrease the infusion rate by 50% until symptoms resolve, then resume at the initial planned rate.
- For Grade 2 hypersensitivity reactions (urticaria, drug fever ≥ 38°C and/or asymptomatic bronchospasm): Stop infusion. Administer H1 and/or H2 blockers, and/or steroids according to institutional policy. Restart the infusion when symptoms resolve and pretreat before all subsequent doses. Treat according to institutional policy.
- For Grade 3 or Grade 4 hypersensitivity reactions: Stop the infusion. Discontinue all protocol treatment and notify the sponsor medical monitor.

Oxaliplatin-induced Pharyngolaryngeal Dysesthesias

Should a subject develop oxaliplatin-induced pharyngolaryngeal dysesthesia, their oxygen saturation should be evaluated via a pulse oximeter; if normal, an anxiolytic agent may be given, and the subject observed in the clinic until the episode has resolved. Following this toxicity, subjects may continue protocol therapy if it is felt appropriate. A table comparing pharyngo-laryngodysesthesia to platinum hypersensitivity reactions is presented below (Table H3).

Table H3 Comparison of the Symptoms and Treatment of Pharyngo-Laryngodysesthesias and Platinum Hypersensitivity Reactions

Clinical Symptoms	Pharyngo-Laryngeal Dysesthesias	Platinum Hypersensitivity
Dyspnea	present	present
Bronchospasm	absent	present
Laryngospasm	absent	present
Anxiety	present	present
Oxygen saturation	normal	decreased
Difficulty swallowing	present (loss of sensation)	absent
Pruritus	absent	present
Urticaria/rash	absent	present
cold-induced symptoms	yes	no
Blood pressure	normal or increased	normal or decreased
Treatment	anxiolytics, observation in a controlled clinical setting until symptoms abate or at the physician's discretion	oxygen, steroids, epinephrine, bronchodilators; fluids and vasopressors, if appropriate

Bevacizumab Dose Modifications for Infusion Reactions

The initial bevacizumab dose should be administered over a minimum of 90 minutes. If no adverse reactions occur, the second dose should be administered over a minimum of 60 minutes. Again, if no adverse reactions occur, the third and subsequent doses should be administered over a minimum of 30 minutes. If infusion-related adverse reactions occur, subsequent infusions should be administered over the shortest period that is well tolerated. Subjects may receive premedication with diphenhydramine 25 to 50 mg IV or orally 30 minutes prior to bevacizumab if they have previously experienced mild infusion reactions. Acetaminophen premedication may also be used.

H 18 FOLFOX-induced Other Non-Hematologic Toxicities

For all other ≥ Grade 3 non-hematologic toxicities not described above, hold all protocol treatment and monitor toxicity at least weekly. If toxicity resolves to ≤ Grade 1 within 4 weeks, treatment may be resumed, with 5-FU at one lower dose level.

H 19 Dose Modification for Obese Subjects

There is no clearly documented adverse impact of treatment of obese subjects when dosing is performed according to actual body weight. Therefore, all applicable dosing is to be determined solely by the subject's actual weight without any modification. This will eliminate the risk of calculation error and the possible introduction of variability in dose administration.

Failure to use actual body weight in the calculation of drug dosages will be considered a major protocol deviation. Physicians who are uncomfortable with administering chemotherapy dose based on actual body weight should not enroll obese subjects.

Appendix I Site and Study Closure

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include, but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

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