Statistical Analysis Plan

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

Protocol Number: D419NC00001

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List of Abbreviations

Abbreviation	Definition
1L	first-line
2L	second-line
CCI	CCI
AE	adverse event
ALP	alkaline phosphatase
BOR	best overall response
CI	confidence interval
CR	complete response
CRC	colorectal cancer
DC	disease control
DCR	disease control rate
DEC	dose-escalation committee
DLT	dose-limiting toxicity
DoR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire
CCI	CCI
FOLFOX	a chemotherapy regimen comprised of folinic acid, fluorouracil and oxaliplatin
HLA	human leukocyte antigen
imAE	immune-mediated adverse events
IV	intravenous
IXRS	interactive voice/web response system
mFOLFOX6	a modified FOLFOX regimen comprised of folinic acid, fluorouracil and oxaliplatin
CCI	CCI
CCI	CCI
MTD	maximum tolerated dose
mTPI	modified toxicity probability interval
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NE	not evaluable
NK	natural killer
NSCLC	non-small cell lung cancer

Abbreviation	Definition
OR	objective response
ORR	objective response rate
OS	overall survival
PD	progressive disease
PD-L1	programmed death ligand 1
PFS	progression-free survival
PGIC	Patient Global Impression of Change
PK	pharmacokinetics
PR	partial response
PRO	Patient Reported Outcome
PT	preferred term
Q2W	every 2 weeks
Q4W	every 4 weeks
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
CCI	CCI
SD	stable disease
SPP	statistical programming plan
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
UPM	unit probability mass

1 INTRODUCTION

This document describes the statistical analysis methodology for protocol D419NC00001, a Phase 1/2 study of durvalumab (MEDI4736; anti-programmed death ligand 1 [PD-L1] monoclonal antibody) in combination with monalizumab (anti-NKG2a monoclonal antibody) in adult subjects with selected solid tumors. The main portion of this document details the statistical summaries relating to each study objective and describes the general conventions and definitions that will be used. In addition, a set of table templates and specifications will be included in a statistical programming plan (SPP) to complement this document.

2 STUDY OVERVIEW

2.1 Study Objectives

2.1.1 Primary Study Objective(s)

Part 1:

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

Part 2:

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

Part 3:

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

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

Cohorts C1B and C2B: To assess safety (C1B and C2B) and tolerability (C1B and C2B) and evaluate the preliminary antitumor activity (C1B only) of monalizumab in combination

with cetuximab in subjects with CCI CRC that is CCI (C1B) or CCI CCI (C2B)

2.1.2 Secondary Study Objectives

1. To evaluate the preliminary antitumor activity of:
   - Durvalumab in combination with monalizumab in subjects with advanced solid tumors **(Parts 1 and 2)**
   - Durvalumab in combination with monalizumab plus chemotherapy with or without a biologic agent (bevacizumab or cetuximab), as clinically indicated in subjects with 1L or 2L CCI CRC **(Part 3, Cohorts A CCI)**
   - Durvalumab in combination with monalizumab plus cetuximab in subjects with CCI CRC that is CCI **(Part 3, Cohort C2A)**
   - Monalizumab in combination with cetuximab in subjects with CCI CRC that is CCI **(Part 3, Cohort C2B)**
2. To further evaluate the antitumor activity of:
   - Durvalumab in combination with monalizumab plus cetuximab in subjects with CCI CRC that is CCI **(Part 3, Cohort C1A)**
   - Monalizumab in combination with cetuximab in subjects with CCI CRC that is CCI **(Part 3, Cohort C1B)**
3. To describe the pharmacokinetics (PK) of:
   - Durvalumab and monalizumab when administered in combination in subjects with advanced solid tumors **(Parts 1 and 2)**
   - Durvalumab and monalizumab when administered in combination with chemotherapy with or without a biologic agent (bevacizumab or cetuximab), as clinically indicated in subjects with 1L or 2L CCI CRC **(Part 3, Cohorts A CCI)**
   - Durvalumab, monalizumab, and cetuximab when administered in combination in subjects with CCI CRC that is CCI **(Part 3, Cohort C1A)**
   - Monalizumab and cetuximab when administered in combination in subjects with CCI CRC that is CCI **(Part 3, Cohort C1B)**
   - Durvalumab and monalizumab when administered in combination with cetuximab in subjects with CCI CRC that is CCI **(Part 3, Cohort C2A)**
   - Monalizumab when administered in combination with cetuximab in subjects with CCI CRC that is CCI **(Part 3, Cohort C2B)**
4. To describe the immunogenicity of:

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

5. To characterize the association between clinical outcomes and pre-treatment protein expression within the tumor microenvironment when
   - Durvalumab is administered in combination with monalizumab in subjects with advanced solid tumors **(Parts 1 and 2)**
   - Durvalumab is administered in combination with monalizumab plus chemotherapy with or without a biologic agent (bevacizumab or cetuximab), as clinically indicated in subjects with 1L or 2L CCI CRC **(Part 3, Cohorts A CCI)**
   - Durvalumab is administered in combination with monalizumab plus cetuximab in subjects with CCI CRC that is CCI or CCI **(Part 3, Cohorts C1A and C2A**, respectively)
   - Monalizumab is administered in combination with cetuximab in subjects with CCI CRC that is CCI or CCI **(Part 3, Cohorts C1B and C2B**, respectively)

2.1.3 Exploratory Study Objectives

1. To evaluate additional candidate prognostic/predictive/pharmacodynamic biomarkers when
   - Durvalumab is administered in combination with monalizumab in subjects with advanced solid tumors **(Parts 1 and 2)**

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

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

2.2 Study Design

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

Part 1 will evaluate dose escalation of durvalumab in combination with monalizumab in subjects with select advanced solid tumor malignancies.

Part 2 will evaluate further the identified dose of durvalumab in combination with monalizumab from Part 1 in subjects with select advanced solid tumor malignancies.

Part 3 (Cohorts A CCI) will evaluate dose exploration of durvalumab in combination with monalizumab and chemotherapy, with or without a biologic agent (bevacizumab or cetuximab), as clinically indicated, in subjects with metastatic 1L or 2L CCI CRC.

Part 3 (Cohorts C1 and C2) will evaluate dose exploration of 1) durvalumab in combination with monalizumab plus cetuximab (Cohorts C1A and C2A) and 2) monalizumab in combination with cetuximab (Cohorts C1B and C2B) in subjects with CCI CRC that is CCI or CCI .

Part 1: Dose-escalation phase

In the dose-escalation phase of the study, sequential cohorts will receive durvalumab in combination with monalizumab at 1 of the 4 planned dose levels as described in Figure 2.2.2-1. The dose-escalation phase will utilize a modified toxicity probability interval (mTPI) algorithm (Ji et al, 2010), which employs a simple beta-binomial Bayesian model. Decision rules are based on calculating the unit probability mass (UPM) of three intervals corresponding to underdosing, proper dosing, and overdosing in terms of toxicity. The three dosing intervals are associated with three different dose-escalation decisions. The under dosing interval corresponds to a dose escalation (E), overdosing corresponds to a dose de-escalation (D), and proper dosing corresponds to staying at the current dose (S). Given an interval and a probability distribution, the UPM of that interval is defined as the probability of the interval divided by the length of the interval. The mTPI design calculates the UPMs for the three dosing intervals, and the one with the largest UPM implies the corresponding dose-finding decision. The design for the dose-escalation phase of the study uses a target DLT rate of ≥ 33% and an equivalence interval of CCI for dose-escalation/de-escalation decisions as well as MTD determination. A dose level will be considered unsafe, with no additional subjects enrolled at that dose level, if it has an estimated 95% or more probability of exceeding the target DLT rate of 33% (ie, P [DLT > 33%|data] > 95%) with at least 3 subjects treated at that dose level.

A minimum of 3 subjects will be enrolled to a dose level cohort and evaluated for a dose-escalation/de-escalation decision per mTPI algorithm (see Table 2.2.2-1) unless

unacceptable toxicity is encountered prior to enrollment of 3 subjects, but the maximum number of subjects for each dose level cohort will be capped at 12.

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

Ongoing surveillance of pharmacodynamics, PK, clinical safety, and antitumor activity data will be performed throughout the dose-escalation part. Once the dose escalation has completed per the mTPI or the highest protocol defined dose is evaluated, any dose level showing acceptable safety during dose escalation can be expanded to a total of up to 18 subjects with mandatory pre-treatment and on-treatment tumor biopsies.

Table 2.2.2-1 Durvalumab Treatment Modification and Toxicity Management Guidelines for Immune-related Adverse Events

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

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

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

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

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

[c] The original mTPI algorithm was S for these cases and is modified to either E or D according to whether the observed DLT rate is $<$ or $\geq$ the target toxicity of 33%, respectively.

Source: Modified from Ji et al, 2010.

Part 2: Dose-expansion phase

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

agreed by the study-specific dose-escalation committee. Additional dose levels not exceeding the MTD may be considered based on clinical and PK/pharmacodynamic data from the dose-escalation part.

Part 3: Dose Exploration in CCI CRC

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

Cohort A CCI Subjects:

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

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

while enrollment is ongoing, the DEC will review aggregate safety data once a total of 12 or 18 subjects in a given cohort have been enrolled and followed through the DLT evaluation period.

Cohort C Subjects:

Cohort C subjects (ie, Cohorts C1 and C2) CCI [redacted] CCI CRC that is CCI [redacted] (Cohort C1) or CCI [redacted] (Cohort C2). CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

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

The study flow is presented in Figure 2.2.2-1. More detailed study flow for Cohort A CCI is presented in Figure 2.2.2-2 whereas Cohort C in Figure 2.2.2-3.

Figure 2.2.2-1 Study Flow Diagram

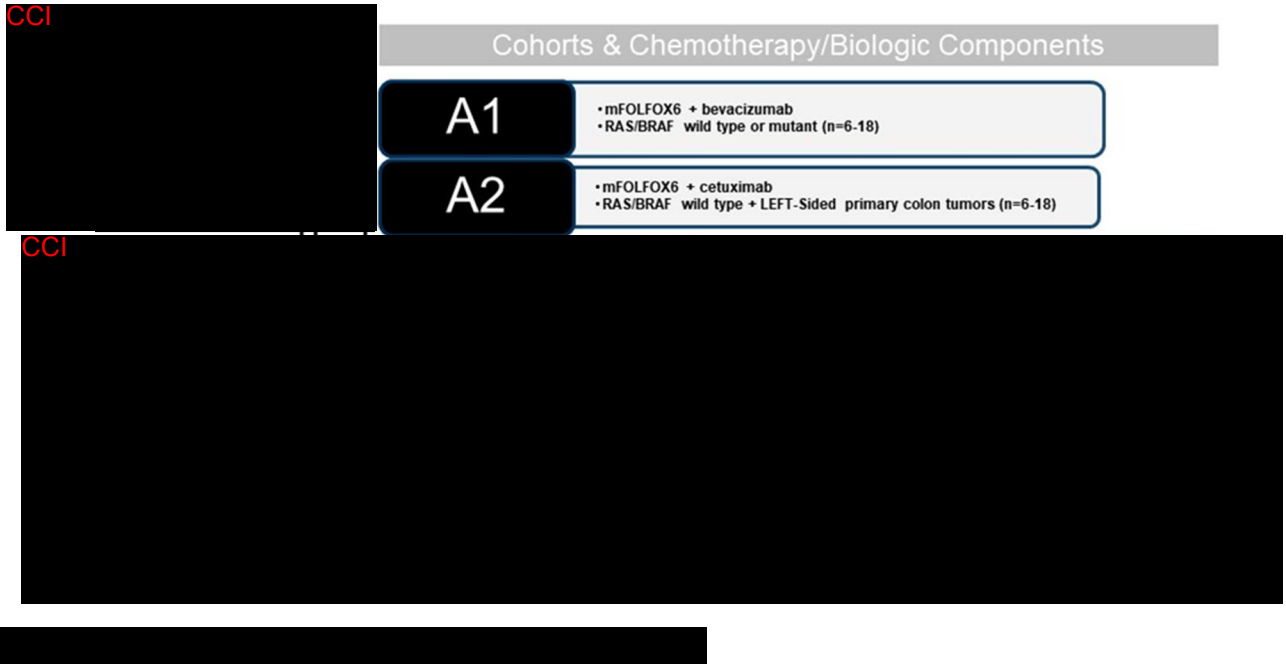
Part 3: Dose exploration in CCI CRC			
Cohort and Chemotherapy or Biologic Regimen	**Durvalumab Dose**	**Monalizumab Dose**	**Number of Subjects[d]**
A1: mFOLFOX6 + bevacizumab	1500 mg Q4W	750 mg Q2W	Up to 18
A2: mFOLFOX6 + cetuximab	1500 mg Q4W	750 mg Q2W	Up to 18
CCI			

CRC = colorectal cancer; CCI mFOLFOX6 = folinic acid/fluorouracil/oxaliplatin; CCI Q2W = every 2 weeks; Q4W = every 4 weeks; CCI

CCI

CCI

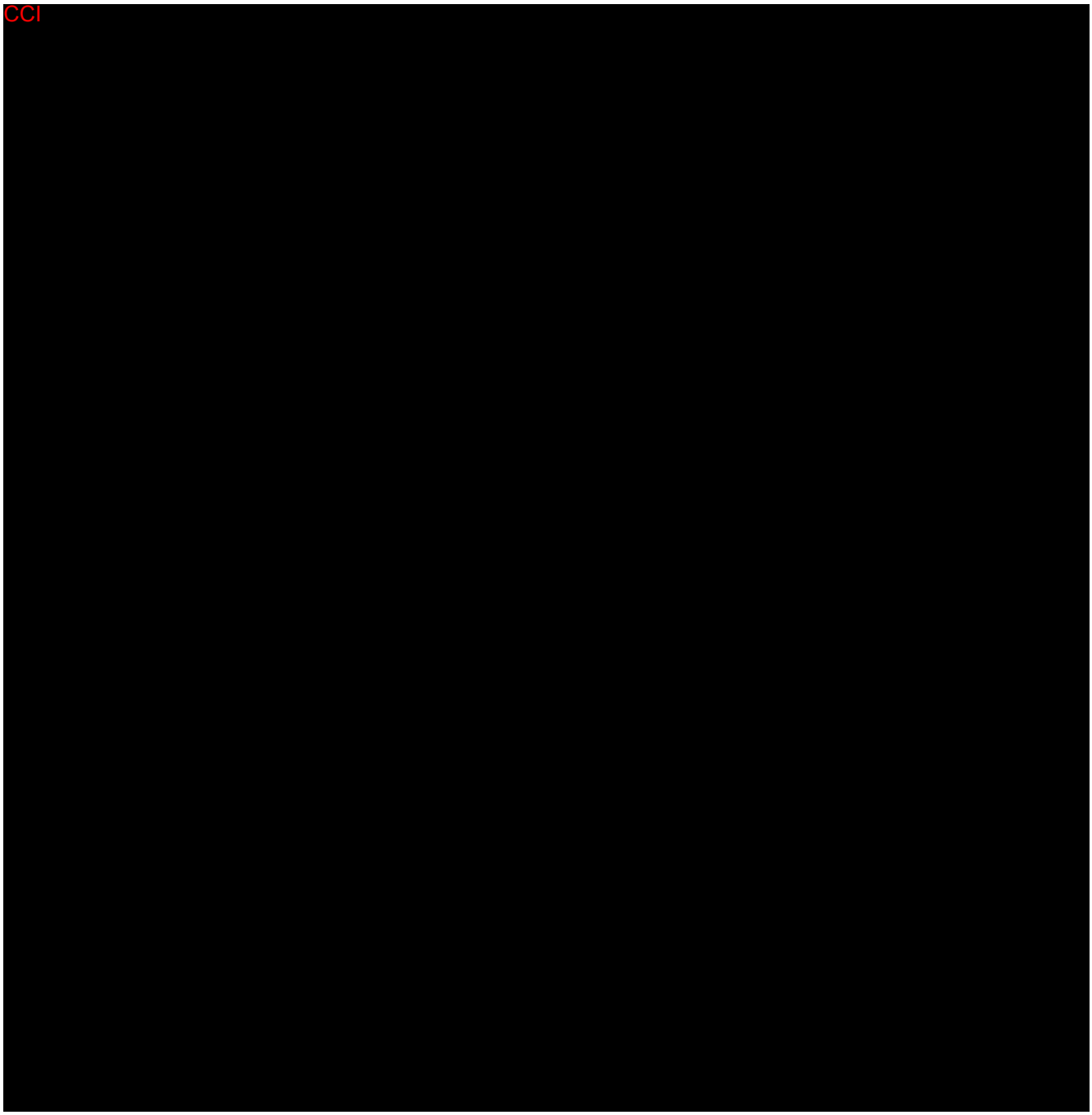
Figure 2.2.2-2 Study Part 3 (Dose Exploration) Flow Diagram for Cohorts A CCI



1

CCI

Figure 2.2.2-3 CCI



2.3 Treatment Assignment and Blinding

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

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

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

CCI [redacted]

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

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

2.4 Sample Size

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

In Part 1 (dose escalation), the number of subjects to be enrolled will depend upon the toxicities observed as the study progresses. With a minimum of 3 subjects and a maximum of 12 subjects enrolled for each dose level, up to 60 subjects may be enrolled following an mTPI design for 5 planned dose levels. An additional 6 subjects per dose level may be

enrolled, up to a maximum of 18 subjects per dose level to provide additional PK, pharmacodynamic, and safety data. Additional subjects could be required if other dose levels or alternate treatment schedules are explored.

In Part 2 (dose expansion), up to 160 subjects (approximately 40 subjects per tumor-type cohort) may be enrolled to obtain preliminary assessment of safety and antitumor activity in each tumor type. Enrollment may proceed up to approximately 40 subjects in the CRC, ovarian, and endometrial expansion cohorts [redacted]. The observed 0/20 response gives an upper limit of a 1-sided [redacted]% confidence interval (CI) of approximately [redacted]%, which means that a response rate greater than [redacted]% can be ruled out with [redacted]% confidence and hence enrollment would be stopped for lack of desirable response rate. Enrollment may proceed up to approximately 40 subjects in the NSCLC expansion cohort [redacted]. Observing 1/20 response gives an upper limit of a 1-sided [redacted]% CI of approximately [redacted]%, which means that a response rate greater than [redacted]% can be ruled out with [redacted]% confidence and hence enrollment would be stopped for lack of desirable response rate. [redacted] Table 2.4-1 provides the estimated ORR and its [redacted]% CI based on the exact probability method for a range of possible responses out of 20 and 40 subjects, respectively.

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

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

Table 2.4-1 Estimated Objective Response Rate and CCI% Confidence Interval Out of 20 and 40 Subjects, Respectively

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

CI = confidence interval.

Table 2.4-2 provides the estimated ORR and the CCI% CI based on the exact probability method for a range of possible responses out of 100 subjects.

Table 2.4-2 Observed Objective Response Rate with CCI% Confidence Interval

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

CI = confidence interval; ORR = objective response rate.

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

3 STATISTICAL METHODS

3.1 General Considerations

All data of interest will be provided in data listings sorted by dose level, subject number, and date collected where appropriate. All tabular summaries will be presented by dose level (in dose escalation phase), tumor type (in dose expansion phase), and/or combination treatment regimen (in dose exploration phase) as appropriate. Categorical data will be summarized by

the number and percentage of subjects falling within each category. In general, continuous variables will be summarized by descriptive statistics including mean, standard deviation, median, minimum, and maximum.

All available data will be used and thus, missing data will not be imputed. Subjects with missing data for a parameter will be excluded from the summary of this parameter. Unless specified otherwise, baseline values will be defined as the last valid assessment prior to the first administration of any study treatment.

Data analyses will be conducted using the SAS® System version 9.3 or higher (SAS Institute Inc., Cary, NC). The analytical results generated from SAS programs will be validated according to AstraZeneca/MedImmune SAS programming standards and validation procedures.

3.2 Analysis Populations

The analysis populations are defined in Table 3.2-1. Analyses relating to efficacy will be conducted on As-treated population for cohorts without randomization whilst on ITT population for randomized cohorts unless otherwise specified. Additional efficacy analyses can be conducted on Response-evaluable population as necessary. Analyses pertaining to safety will be conducted on As-treated population unless otherwise specified.

Table 3.2-1 Analysis Populations

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

3.3 Study Subjects

3.3.1 Subject Disposition and Completion Status

A summary of subjects treated at each dose level will be provided. In addition, summaries using the number and percent of subjects that completed or discontinued treatment and the reasons for discontinuation will be provided.

Summary of subject status at the end of study and the reasons for ending study will be provided as well.

The end of study mortality summary will include subjects who are dead at the end of study and their cause of death (adverse event, disease under investigation, or other).

3.3.2 Demographics and Baseline Characteristics

Baseline disease characteristics will be summarized for the As-treated population besides Cohort C where summary will be based on ITT population. Demographic information such as sex, age, race, ethnicity, weight, height, and body mass index will be summarized. Tumor history including histology, stage, etc. at the time of diagnosis and at study entry will be summarized.

The summary for prior anticancer treatment will include the number and percent of subjects by treatment category (systemic therapy, radiation, cancer related surgery, stem cell/bone marrow transplant, other), number of previous regimens, and best response (complete response, partial response, stable disease, progressive disease, not evaluable, not applicable) to the most recent line of therapy.

3.3.3 Study Drug Exposure

The total durvalumab duration of exposure, and total monalizumab duration of exposure will be summarized by descriptive statistics. The duration of exposure is defined as

- last dose date plus 14 (Q2W) or 28 (Q4W) days minus first dose date for subjects on treatment.

- minimum of (date of death plus 1 day, data cutoff date plus 1 day, last dose date plus 14 (Q2W) or 28 (Q4W) days) minus first dose date for subjects who discontinued treatment

Dose intensity and relative dose density of durvalumab and monalizumab will be summarized by descriptive statistics. The details of the dose intensity calculation will be provided in the SPP.

The use of subsequent alternative cancer treatment after the discontinuation of study treatment will be summarized by the type of treatment.

3.3.4 Concomitant Medications

The number and percentage of subjects who took concomitant medications will be summarized for the As-treated population. The listings of concomitant medications will include all concomitant medications taken on or after the date of first dose of investigational product(s) or any concomitant medication started prior to first dose of investigational product(s) that continued beyond the date of first dose of investigational product(s).

3.4 Efficacy Analyses

3.4.1 Efficacy Endpoint(s) and Analyses

The efficacy endpoints include best overall response (BOR); objective response (OR); disease control (DC); time to response (TTR); duration of response (DoR); progression-free survival (PFS); overall survival (OS); and change from baseline in tumor size. The efficacy endpoints will be summarized based on the As-treated population for non-randomized cohorts. As randomization takes place in Cohort C, efficacy endpoints in Cohort C will be summarized per ITT population instead of As-treated population. In addition, for time-to-event efficacy endpoints the calculation starts at date of randomization instead of date of first treatment for Cohort C.

Efficacy analyses will be based on an application of RECIST 1.1(Eisenhauer et al, 2009) according to investigator assessed tumor measurements.

3.4.1.1 Best Overall Response

Best overall response (BOR) will be based on all post-baseline disease assessments that occur prior to the initiation of alternative anticancer therapy during the initial treatment period. BOR will be summarized with the number and percentage of subjects for the following categories: complete response (CR); partial response (PR); stable disease (SD); progressive disease (PD); and non-evaluable (NE). If retreatment is permitted following relapse, a BOR will be reported separately for the retreatment period.

In order to assign a best overall response of SD, at least 8 weeks must elapse from the first dose of treatment (or randomization) to the disease assessment of SD. The requirement of 8 weeks will allow for the protocol-defined disease assessment window of 7 days. Confirmation of PR and CR is required and must occur no fewer than 4 weeks after initial

documentation of PR or CR and with no evidence of progression between the initial and CR/PR confirmation visit.

3.4.1.2 Objective Response

Objective response rate (ORR) is defined as the proportion of subjects with a BOR of confirmed CR or confirmed PR. ORR will be estimated and its CCI % and CCI % CI using the exact binomial method will be calculated. Subjects that have missing overall response assessments will be considered non-responders, and will therefore be counted in the denominator, but not in the numerator of ORR.

3.4.1.3 Disease Control

Disease control rate (DCR) is defined as the proportion of subjects with a BOR of confirmed CR, confirmed PR, or SD. DCR will be estimated with CCI % and CCI % CI using the exact binomial method.

3.4.1.4 Time to Response

Time to response (TTR) is defined as the time from the first dose of study treatment (or randomization) until the first documentation of a subsequently confirmed objective response.

Only subjects who have achieved objective response (confirmed CR or confirmed PR) will be evaluated for TTR. TTR is defined as follows:

TTR = Date of first disease response – Date of the first dose of the study treatment (or randomization) + 1.

The median TTR and its CCI % CI will be assessed using the Kaplan-Meier method.

3.4.1.5 Duration of Response

Duration of response (DoR) is defined as the time from the first documentation of a subsequently confirmed objective response until the first documentation of disease progression or death due to any cause, whichever occurs first. Only subjects who have achieved objective response (confirmed CR or confirmed PR) will be evaluated for DoR. DoR is defined as follows:

DoR = Date of PD/death or censoring – Date of first disease response + 1.

The rule of DoR censoring is the same as the PFS censoring rule as given in Table 3.4-1. The median DoR and its CCI % CI will be estimated using the Kaplan-Meier method.

3.4.1.6 Progression-free Survival

Progression-free survival (PFS) is defined as the time from the first dose of the study treatment (or randomization) until the first documentation of a disease progression or death due to any cause, whichever occurs first. The definition of PFS (and censoring rules) is presented in Table 3.4-1.

Table 3.4-1 Summary of Censoring Guidelines for PFS

Situation	Date of PD/Death or Censoring	PFS Outcome
Documented Progressive Disease (PD)	Date of earliest sign of PD	Progressed
No PD or death at time of analysis or lost to follow-up	Date of last adequate progression-free disease assessment	Censored
Death or PD immediately after ≥ 2 consecutive missed or non-evaluable disease assessments	Date of the first dose of the study treatment (or randomization) or last progression-free disease assessment prior to missed or non-evaluable assessments, whichever occurred last	Censored
Initiation of alternative anticancer therapy	Date of last adequate progression-free disease assessment prior to initiation of alternative anticancer therapy	Censored
No tumor assessment at baseline and no evidence of PD at first post-baseline disease assessment, or no tumor assessment post-first dose, and no death prior to second scheduled post-baseline disease assessment	Date of the first dose of the study treatment (or randomization)	Censored

The date of PD will be the first date at which any objective diagnostic test provides data indicating PD. Specifically, the date of PD will be the earliest of the following 3 dates:

- Date of PD as indicated by target lesions: If PD is triggered by a change in sum of diameters of target lesions, and the dates of evaluation of the target lesions vary for the same assessment, assign the first evaluation date among target lesions.
- Date of PD as indicated by non-target lesions: If the dates of evaluation of the non-target lesions vary for the same assessment, assign the first evaluation date for which any non-target lesion exhibits a status of Unequivocal Progression.
- Date of PD as indicated by new lesions: If multiple new lesions are identified and the dates of evaluation for the new lesions vary for the same assessment, assign the first evaluation date for which any new lesion is detected.

PFS will be calculated as following:

PFS = Date of PD/death or censoring – Date of the first dose of the study treatment (or randomization) + 1.

The median PFS and its CCI % CI will be estimated using the Kaplan-Meier method.

3.4.1.7 Overall Survival

Overall survival (OS) is defined as the time from the first dose of study treatment (or randomization) until death due to any cause. Subjects who are alive at the end of study or lost to follow-up will be censored for OS at the last date when the subjects were known to be alive. OS is defined in months as follows:

OS = Date of death or censoring – Date of the first dose of study treatment (or randomization) + 1.

The median OS and its CCI % CI will be estimated using the Kaplan-Meier method.

3.4.1.8 Change from Baseline in Tumor Sizes

The percent change from baseline in target tumor will be calculated at each adequate post-baseline disease assessment. It will be presented by subject using spider plots. The best percent change from baseline in target tumor is defined as the largest reduction or smallest increase (in the case where a reduction does not occur) from baseline observed over all post-baseline disease assessments (prior to initiation of subsequent anticancer therapy) and will be presented using waterfall plots.

3.4.2 Additional Analyses of the Efficacy Endpoints

The landmark PFS and OS may be calculated at time points of interest (for example, 6 months, 12 months, etc.) where clinically meaningful depending on the disease setting of each cohort. The landmark PFS and OS will be obtained through Kaplan-Meier method.

3.4.3 Handling of Dropouts and Missing Data

Guidance regarding the handling of dropouts and missing data and censoring will apply uniformly to all efficacy analyses resulting from an application of RECIST 1.1 to investigator assessed tumor measurements. For investigator reported outcomes, analyses will present outcomes reported by the investigator without consideration of missing data or censoring rules. In general, subjects not classifiable under the RECIST 1.1 response categories due to

insufficient data or early death will be classified as non-evaluable for BOR, but will be counted in the denominator of all response rate calculations.

MISSING DATA AT BASELINE

If a subject has missing lesion data at baseline, the subject will be classified as non-evaluable for BOR and censored at the date of the first dose of study treatment (or randomization) for PFS unless the subject dies prior to the second scheduled post-baseline disease assessment in which case the death date will qualify as a PFS event.

MISSING DATA AT A DISEASE ASSESSMENT

If a subject has a missing tumor measurement at a disease assessment for 1 or more target lesions, the sum of diameters (longest for non-nodal lesions, short axis for nodal lesions) will be reported for the remaining target lesions. These data will be used to indicate radiologic disease progression if the sum of diameters for the observed lesions increases at least 20% from the nadir sum of diameters of all lesions and demonstrates at least a 5 mm absolute increase from the nadir sum of diameters of all lesions, in spite of the missing data (or if other criteria for PD are met). If a subject has a missing tumor status at a disease assessment for 1 or more non-target lesions, radiologic disease progression will be determined if the remaining non-target lesions qualitatively demonstrate unequivocal progression (or if other criteria for PD are met). If a subject has a missing tumor measurement at some assessment(s) for 1 or more target or a missing tumor status at some assessment(s) for 1 or more non-target lesions and criteria for PD are not otherwise met, an overall response of non-evaluable will be assigned for the assessment(s).

MISSING DISEASE ASSESSMENT(S)

If a subject has two or more consecutive completely missed or non-evaluable assessments followed immediately by death or an assessment showing radiologic disease progression, then the subject will be censored for PFS. PFS will be censored at the date of the first dose of study treatment (or randomization) or the last progression-free disease assessment prior to the missed or non-evaluable assessments, whichever occurred last. If a subject has two or more consecutive missed or non-evaluable assessments followed by an assessment showing no radiologic disease progression, then the assumption will be that the subject did not progress during the missed or non-evaluable assessments.

3.4.4 Subgroup Analyses

There is no subgroup analysis being planned.

3.4.5 Exploratory Efficacy Analyses

No exploratory efficacy analyses are planned.

3.5 Patient Reported Outcomes

No analyses pertaining to Patient Reported Outcomes are planned.

3.6 Pharmacodynamic Endpoint(s) and Analyses

CCI [redacted]

3.7 Other Additional Analyses

Not applicable.

3.8 Safety Analyses

3.8.1 MTD Evaluation

The Maximum Tolerated Dose (MTD) evaluation will be based on the DLT evaluable population. After the escalation phase is completed, final DLT rates at each dose level will be estimated by isotonic regression (Ji et al, 2010) if any DLT is observed. The weighted least squares regression model will assume monotonic non-decreasing DLT rates with increasing dose and use the empirical (observed) DLT rates at each dose level as responses and dose level sample sizes as weights, along with the pool adjacent violators algorithm (PAVA) to estimate the DLT rate at each dose level using available software (e.g., Cytel EAST or the function pava() from the R package 'ISO'). Given the DLT estimates for each dose level, the MTD will be selected from all tried dose levels that have not been previously declared to be unsafe (P[DLT>33%|data] > 95%) with a DU decision according to the mTPI decision table). With this constraint, the MTD will be determined as the dose level with the DLT estimate closest to the target toxicity level of 30%.

In the case of dose levels with estimated toxicity of equal distance (tied dose levels) from the target toxicity of 30%, the following approach will be used (Ji et al, 2010): among all tied dose levels the highest dose level with target toxicity ≤ 33% will be selected, unless all tied dose levels have estimated toxicity > 33%, in which case the lowest dose level will be selected.

The number and percentage of subjects with DLT will also be presented by dose level in cohorts where dose escalation/de-escalation is evaluated.

3.8.2 Adverse Events and Serious Adverse Events

Adverse events will be coded by MedDRA (use most recent version at study start), and graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.03. The incidence, severity and relationship to study investigational product(s) will be summarized. Specific adverse events will be counted once for each subject for calculating percentages. In addition, if the same adverse event occurs multiple times within a particular subject, the highest severity and level of relationship observed will be reported. If any associations of interest between adverse events and baseline characteristics are observed, additional stratified results may be presented. All treatment-emergent adverse events will be summarized overall, as well as categorized by MedDRA System Organ Class and Preferred Term.

Treatment-emergent adverse event (TEAE) is defined as events present at baseline that worsen in severity after administration of study drug or events absent at baseline that emerge after administration of study drug.

The number and percentage of subjects reporting TEAEs will be reported by frequencies of preferred terms, MedDRA SOC, grade of adverse events, relatedness to the investigational product(s). Similar analysis will also be performed for serious adverse events. TEAEs data will be listed, and a standalone TEAEs listing may be provided for subjects who enter the re-treatment period.

3.8.3 Adverse Events of Special Interest, Adverse Events of Possible Interest, and Immune-mediated Adverse Events

Adverse events of special interest (AESI), adverse events of possible interest (AEPI), and immune-mediated adverse events (imAE) will be identified and summarized following the latest durvalumab global imAE characterization charter at the time of study close-out preparation.

3.8.4 Deaths and Treatment Discontinuations due to Adverse Events

AEs that result in permanent discontinuation of investigational product(s) or death will be summarized descriptively.

3.8.5 Clinical Laboratory Evaluation

Data listings will be provided for the clinical laboratory results and changes from baseline by scheduled time of evaluation including end of treatment visit.

Laboratory parameters will be assessed at baseline as well as throughout the study. Frequencies of worst observed Grade 0-4 toxicity, as defined by NCI CTCAE version 4.03, will be presented for each laboratory parameter where numeric grading criteria are available. The analysis will present worst grade observed and the rates of subjects with Grade 3-4 toxicity.

In addition, laboratory parameters will be assessed by presenting tables containing information related to 2-grade (or greater) laboratory shifts from baseline.

3.8.6 Other Safety Evaluations

3.8.6.1 Vital Signs

Vital signs will be assessed at baseline and throughout the study. Descriptive statistics will be provided for the vital signs measurements and changes from baseline to scheduled time of evaluation, including end of treatment visit as well as for the maximum and minimum post-baseline values.

3.8.6.2 Electrocardiogram

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

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

3.8.6.3 ECOG Performance Status

Eastern Cooperative Oncology Group (ECOG) performance status will be assessed at baseline as well as throughout the study. ECOG will be summarized by study visit and will include descriptive statistics for the value of the parameters and the changes from baseline.

3.8.7 Subgroup Analyses

No subgroup analyses are planned.

3.9 Immunogenicity

Immunogenicity of durvalumab and monalizumab (and cetuximab for cohorts specified in the protocol) will be assessed as specified in protocol section 4.2. The number of subjects in each treatment group showing an immunological response to durvalumab and monalizumab (and cetuximab for cohorts specified in the protocol) will be summarized by study visit. In the summary, all post-dose immunogenicity results will also be summarized under "Any Visit" category. A subject will be counted as having a detectable antibodies at "Any Visit", if the subject has detectable antibodies at any post-dose visit. The subject will be counted as not having detectable antibodies at "Any Visit" if all post-dose immunogenicity assessments have no respective antibody.

All valid assay results from subjects who receive any study drug will be included in immunogenicity summaries. All subjects with titer information will be shown in the data listing.

3.10 Pharmacokinetics

Pharmacokinetics population: subjects who receive at least 1 dose of durvalumab and/or monalizumab, and provide at least 1 post-treatment sample, will be evaluated.

Individual durvalumab, monalizumab and cetuximab serum concentrations will be listed by cohort, dose level and visit. Summary statistics of the serum concentrations will be tabulated by cohort, dose level and visit.

A population PK analysis may also be performed using data from this study to evaluate the effect of covariates on PK variability, but will be reported separately from the CSR.

4 INTERIM ANALYSIS

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

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

5 REFERENCES

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6 VERSION HISTORY

Version	Date	Summary of Changes	Reason for Change
1.0	18Apr2016	Initial document	Initial document
2.0	07Dec2021	• Include relevant contents revised or added through all of the protocol amendments occurring after the last approved version of SAP.	Protocol Amendments

SIGNATURE PAGE

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