

# **Ludwig Institute for Cancer Research**

## **Statistical Analysis Plan**

**A Phase 1/2 Study of Combination Immunotherapy and mRNA Vaccine in Subjects with Non-small Cell Lung Cancer (NSCLC)**

**Protocol Number**

**LUD2014-012-VAC**

**NCT03164772**

**Amendment 9.1, 01-SEP-2020**

**SAP Version**

**3.0 (09DEC2020)**

Prepared By:

**Advanced Clinical**

10 Parkway North, Suite 350

Deerfield, IL 60015

## TABLE OF CONTENTS

<b>1.0</b>	<b>PURPOSE</b> .....	<b>1</b>
<b>2.0</b>	<b>OVERALL STUDY DESIGN AND OBJECTIVES</b> .....	<b>1</b>
2.1	Trial Objectives .....	1
2.2	Study Endpoints .....	2
2.3	Trial Design and Trial Procedures .....	3
2.4	Treatments and Assignment to Treatments.....	4
2.5	Determination of Sample Size.....	4
<b>3.0</b>	<b>GENERAL ANALYSIS CONVENTIONS</b> .....	<b>5</b>
3.1	General Conventions.....	5
3.2	Trial Periods.....	5
3.3	Visit Windows.....	6
3.4	Baseline .....	6
<b>4.0</b>	<b>ANALYSIS POPULATIONS</b> .....	<b>6</b>
4.1	Intent-to-Treat Population .....	6
4.2	Per-Protocol Population (Clinical Efficacy).....	6
4.3	Per-Protocol Population (DLT Assessments) .....	7
<b>5.0</b>	<b>SUBJECT DISPOSITION</b> .....	<b>7</b>
<b>6.0</b>	<b>DEMOGRAPHIC AND BASELINE CHARACTERISTICS</b> .....	<b>8</b>
6.1	Demographic Characteristics .....	8
6.2	Medical History.....	8
6.3	Prior and Concomitant Medications and Procedures .....	9
<b>7.0</b>	<b>EFFICACY ANALYSIS</b> .....	<b>9</b>
7.1	Response Rate .....	9
7.2	Objective Response Rate (ORR) .....	9
7.3	Disease Control Rate (DCR) .....	10
7.4	Progression-free Survival (PFS) .....	10
7.5	Overall Survival (OS) .....	11
7.6	Duration of Response (DoR).....	11
7.7	Analysis of Time to Event (TTE) Variables.....	11
<b>8.0</b>	<b>TRIAL DRUG EXPOSURE AND COMPLIANCE</b> .....	<b>12</b>

<b>9.0</b>	<b>SAFETY ANALYSIS .....</b>	<b>12</b>
9.1	Adverse Events .....	12
9.1.1	Treatment-Emergent Adverse Events.....	13
9.1.2	Adverse Events of Special Interest (AESIs) .....	15
9.2	Clinical Laboratory Data .....	15
9.3	Vital Signs and Weight.....	17
9.4	Electrocardiograms.....	17
9.5	ECOG Performance.....	18
9.6	Physical Examinations.....	18
9.7	Pregnancy Testing.....	18
<b>10.0</b>	<b>EXPLORATORY ANALYSIS .....</b>	<b>18</b>
<b>11.0</b>	<b>STATISTICAL/ANALYTICAL ISSUES.....</b>	<b>19</b>
11.1	Handling of Dropouts or Missing Data.....	19
11.2	Safety Data Handling.....	19
11.3	Coding Dictionaries.....	20
11.4	Pooling of Centers in Multi-Center Trials.....	20
11.5	Multiple Comparisons/Multiplicity .....	20
11.6	Examination of Subgroups .....	20
11.7	Interim Analysis and Data Monitoring .....	20
<b>12.0</b>	<b>QUALITY CONTROL .....</b>	<b>20</b>
<b>13.0</b>	<b>TABLES AND LISTING CONVENTIONS .....</b>	<b>21</b>
<b>14.0</b>	<b>REFERENCES .....</b>	<b>22</b>
<b>15.0</b>	<b>RECORD RETENTION .....</b>	<b>22</b>
<b>16.0</b>	<b>CHANGE HISTORY .....</b>	<b>23</b>
<b>17.0</b>	<b>APPENDICES.....</b>	<b>24</b>
17.1	Appendix A: Study Flowchart.....	24
17.2	Appendix B: Drug Administrative Schedules per Cycle.....	27

## ACRONYMS

Below is the list of acronyms that will be used throughout this document.

<b>Abbreviation</b>	<b>Definition</b>
AE	adverse event
AESI	adverse event of special interest
CI	confidence intervals
CR	Complete response
CTCAE V.4.03	Common Terminology Criteria for Adverse Events v. 4.03
CTLA-4	Cytotoxic T lymphocyte-associated antigen 4
DNA	Deoxyribonucleic Acid
DCR	Disease Control Rate
DLT	Dose limiting toxicity
DoR	Duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
FFPE	Formalin-fixed paraffin-embedded
GCP	Good Clinical Practice
ICH	International Conference on Harmonization
ILD	Interstitial lung disease
irRECIST	Immune-related Response Evaluation Criteria in Solid Tumors
MedDRA	Medical Dictionary for Regulatory Activities
NCI CTCAE	National Cancer Institute Common Terminology Criteria for
NSCLC	Non-small cell lung cancer
ORR	Objective Response Rate
OS	Overall survival
PBMC	Peripheral blood mononuclear cell
PD	Progressive disease
PD-L1	Programmed death ligand 1
PFS	Progression free survival
PR	Partial response
Q4W	Every 4 weeks
RECIST	Response Evaluation Criteria in Solid Tumors
RCD	Recommended combination dose
RNA	Ribonucleic Acid
SAE	Serious Adverse Event
SD	Stable disease
TEAE	Treatment Emergent Adverse Event
TIL	tumor-infiltrating lymphocyte
TME	Tumor microenvironment

## 1.0 PURPOSE

This SAP describes the methods to be used in the analysis of trial data from clinical protocol “A Phase 1/2 Study of Combination Immunotherapy and mRNA Vaccine in Subjects with Non-small Cell Lung Cancer (NSCLC)” in order to answer the trial objective(s), and is based on Amendment 9.1 of the trial protocol (LUD2014-012-VAC), dated 01 September 2020.

Populations for analysis, data handling rules, statistical methods, and formats for data presentation are described within this document. The statistical analyses and summary tabulations described in this SAP will provide the basis for the results sections of the CSR for this trial. The SAP outlines any differences in data analysis methods relative to those planned in the trial protocol. Any changes to the data analysis methods after the SAP is finalized will be described in the CSR.

## 2.0 OVERALL STUDY DESIGN AND OBJECTIVES

### 2.1 Trial Objectives

This study will evaluate the safety and efficacy of the addition of a vaccine therapy (BI 1361849, previously known as CV9202) to 1 or 2 checkpoint inhibitors (durvalumab and tremelimumab) for NSCLC. The study has two phases; the dose evaluation phase and the dose expansion phase. In the dose expansion phase, there are two cohorts as follows:

Arm A: mRNA Vaccine [BI 1361849 (formerly CV9202)] + anti-PD-L1 [durvalumab]

Arm B: mRNA Vaccine [BI 1361849] + anti-PD-L1 [durvalumab] + anti-CTLA-4 [tremelimumab].

The primary trial objectives are:

- Dose evaluation Phase: To evaluate safety and tolerability, including Dose Limiting Toxicities (DLTs) and Recommended Combination Dose (RCD) of a combination immunotherapy with durvalumab or durvalumab and tremelimumab together with an RNA vaccine BI 1361849.
- Expansion Phase: To evaluate safety and tolerability of a combination immunotherapy with durvalumab or durvalumab and tremelimumab together with an RNA vaccine BI 1361849.

The secondary trial objective is:

- To evaluate the clinical efficacy of the combination immunotherapy for all subjects in both the dose evaluation and the dose expansion phases.

The exploratory trial objective is:

- To evaluate Biologic Activity and the effects on tumor microenvironment, and immune response for all subjects in both the dose evaluation and the dose expansion phases.

## 2.2 Study Endpoints

### Primary Endpoints

The primary endpoint of the combination therapy of durvalumab and tremelimumab are:

- Dose- Limiting Toxicities (DLTs). DLTs are defined as any adverse events that are possibly, probably, or definitely related to the administration of durvalumab, tremelimumab, or BI 1361849 components. This applies to Dose Evaluation subjects during the DLT Evaluation period.
- Safety and tolerability evaluated using CTCAE 4.03.
- Recommended Combination Dose (RCD) determined in Dose Evaluation Phase.

The safety endpoints for this study include:

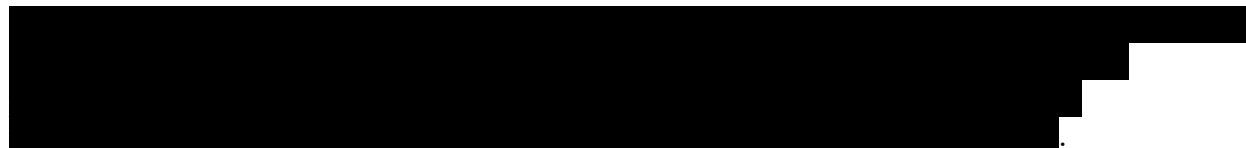
- Treatment-emergent adverse events (TEAEs) and serious AEs (SAEs)
- Clinical laboratory tests (hematology and chemistry)
- Vital signs and weight measurements
- ECG
- ECOG performance status evaluation
- Any other medically indicated assessments, including subject interviews
- All safety analyses will be reported separately for Arm A and Arm B

The Clinical efficacy endpoints will be assessed by irRECIST and RECIST 1.1 and will include:

- Objective Response rate (ORR) at 8 and 24 weeks. ORR is defined as the percentage of subjects meeting criteria of Complete Response (CR) or Partial Response (PR) over a period of at least 4 weeks.
- Duration of Response (DoR). DoR is defined as the interval between the date of earliest determination of CR or PR to the date of earliest determination of PD, or to the date of death, if PD does not occur.
- Disease Control rate (DCR). DCR is defined as the percentage of subjects meeting criteria of Stable Disease (SD), PR, or CR over a period of at least 4 weeks.
- Progressive Free Survival (PFS) at 8 and 24 weeks. PFS is defined as the interval between the date of first dose to the date of earliest determination of Progressive Disease

(PD), or to the date of death, if PD does not occur. Week 8 corresponds to Cycle 3 Day 1 and Week 24 corresponds to Cycle 7 Day 1.

- Overall Survival (OS). OS is defined as the interval between the date of first dose until the date of death or the date of last follow-up.
- All efficacy analyses will be reported separately for Arm A and Arm B.



### 2.3 Trial Design and Trial Procedures

This is an open-label multicenter 2-arm study to evaluate the safety and preliminary efficacy of the addition of a vaccine therapy to 1 or 2 checkpoint inhibitors for NSCLC:

- Arm A: mRNA Vaccine [BI 1361849 (formerly CV9202)] + anti-PD-L1 [durvalumab].
- Arm B: mRNA Vaccine [BI 1361849] + anti-PD-L1 [durvalumab] + anti-CTLA-4 [tremelimumab].

For each arm of the study, there is a *dose evaluation phase* in which the Recommended Combination Dose (RCD) is determined according to a standard 3 + 3 design. For Arm A, the RCD of BI 1361849 + durvalumab is determined. The starting dose of durvalumab is 1500 mg with possible de-escalation to 750 mg; the dose for BI 1361849 remains constant at 12 x 80 ug. The 1500 mg Q4W dosing of durvalumab is recommended only for subjects with > 30kg body weight. Subjects with a body weight  $\leq$  30 kg are not eligible for enrollment in the current study. If a subject's body weight drops to  $\leq$  30 kg while on the study, the subject will receive weight-based dosing equivalent to 20 mg/kg of durvalumab as long as the body weight remains  $\leq$  30 kg. When the weight improves to >30 kg, the subject may return to fixed dosing of durvalumab 1500 mg.

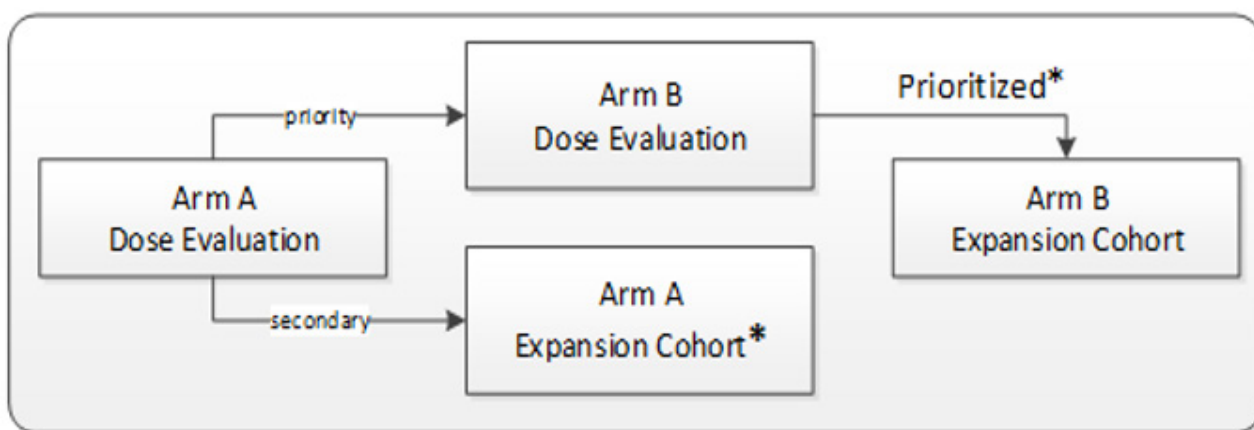
For Arm B, the RCD of BI 1361849 + durvalumab from Arm A with the addition of tremelimumab 75 mg is evaluated. There is no dose escalation/de-escalation for Arm B; if there is unacceptable toxicity in Arm B, the arm will be discontinued as presented in Figure 1.

The *dose evaluation phase* is followed by an *expansion phase*, in which the cohort at the RCD for each arm is expanded to 20 subjects (inclusive of the subjects from the dose evaluation cohort i.e., 14 subjects will be added to the 6 treated at the RCD in the dose evaluation phase for each arm (A and B).

## 2.4 Treatments and Assignment to Treatments

Enrollment will start in the Arm A dose evaluation cohorts in a sequential fashion. After the RCD is determined for Arm A, enrollment will start for the dose evaluation of Arm B and for the Arm A Expansion Cohort, whereby no randomizations will be performed. Any new subject will be assigned to the Arm B dose evaluation cohort, unless no slot is available, in which case the subject will be assigned to the Arm A Expansion Cohort. After the dose evaluation and safety review for Arm B is complete, enrollment into the Arm B Expansion Cohort Group will be prioritized over Arm A.

Figure 1: Enrollment Schema for Arms A and B



\* After the dose evaluation and safety review for Arm B is complete, enrollment into the Arm B Expansion Cohort will be prioritized over Arm A.

## 2.5 Determination of Sample Size

The dose evaluation phase will utilize a standard 3 + 3 design for Arms A and B, which will result in the enrollment of 6 to 18 subjects.

In the expansion phase, 20 subjects per arm are thought to provide sufficient data to adequately identify essential safety and preliminary efficacy signals. Therefore, up to 14 additional subjects will be added to the 6 subjects treated at the RCD in each arm (A and B).

The sample size  $n=20$  for the expansion phase is deemed to provide sufficient precision for the estimation of incidence of adverse events as estimated by the Clopper Pearson confidence intervals (CI) for incidence of adverse events.

Overall, approximately 56 subjects will be enrolled in up to 8 sites in the US. The enrollment period will take approximately 24 months.



### 3.0 GENERAL ANALYSIS CONVENTIONS

#### 3.1 General Conventions

Data collected in this study will be documented using summary tables and subject data listings. Continuous endpoints will be summarized using descriptive statistics, e.g. number of subjects, mean, median, standard deviation, minimum and maximum values. The mean and median will be reported to 1 decimal place more than the level of precision of the data being reported and the SD will be reported to 2 decimal places more than the level of precision of the data being reported, unless otherwise noted. Categorical endpoints will be presented in frequency tables with number and percentage of observations for each level.

All efficacy analyses will be presented separately for Arm A and Arm B. Tumor Response will be summarized and analyzed descriptively. A 95% Confidence Interval based on the binomial distribution will be constructed for the estimated PFS rate and ORR at 8 and 24 weeks and DCR.

The number and percentage of subjects who died or had a confirmed progression, who survived without a confirmed progression, and who were lost to follow up (unknown survival and/or progression status) will be summarized.

PFS rate at 8 and 24 weeks and the corresponding 95% CIs will be calculated based on Kaplan-Meier product limit estimates and will be displayed along with the corresponding number of subjects at risk. (Note – this may include OS as well)

PFS and OS will be summarized using the 25th percentile, Median, and 75th percentile as well as the minimum and maximum survival time, calculated by Kaplan-Meier method, and will be displayed graphically.

The ORR, DCR and DOR will be summarized descriptively and a 95% Confidence Interval based on binomial distribution will be presented.

#### 3.2 Trial Periods

The overall length of study per subject is up to 15 months; comprising of 12 months for treatment and three months for on study follow-up. The screening period is up to one month prior to first drug administration.

Study drug will be administered over 12 cycles with a cycle length of 28 days. The study drugs used in this study will be administered per cycle as shown in Appendix B.

The overall length of the study is 39 months. However the length of the survival post study follow-up is up to five years from initiation of treatment.

### 3.3 Visit Windows

The allowed visit windows are defined as shown in Table 1. Visits will be analyzed per the eCRF collection.

Table 1: Visit Windows

Visit Name	Allowed window (Cycle Day $\pm$ Window)
Screening	Day -28 to -1
Weeks 2, 3, 5, 6, 7, 9, 11, 13, 14	+/- 2 day
Weeks 17, 21, 25, 27	+/- 3 day
Week 28	+/- 2 day
Weeks 29, 33, 37, 39, 41, 45	+/- 3 day
Week 46	+/- 2 day
On study Follow-up	28 (+/-4) days post last dose 42 (+/-4) days post last dose 91 (+/-7) days post last dose
Post Study Follow-up	Every 6 months until 5 years

Note: Visit days are defined from baseline (Cycle 1, Day 1 visit).

Vaccinations may have to be delayed to allow for recovery of AEs prior to continuation of vaccine treatment. After the delayed vaccination all subsequent vaccinations must be continued within the schedule relative to the first vaccination presented in the flow chart.

### 3.4 Baseline

Unless specified otherwise, baseline measurements will be the most recent value prior to receiving the first dose of study medication.

## 4.0 ANALYSIS POPULATIONS

### 4.1 Intent-to-Treat Population

The Intent-To-Treat (ITT) Population is defined as all subjects who receive at least one dose of any of the study drugs. This population will be used for safety and efficacy analyses.

### 4.2 Per-Protocol Population (Clinical Efficacy)

The Per-Protocol (PP) Population (Clinical Efficacy) is defined as all subjects who received at least 75% of the scheduled doses of durvalumab and tremelimumab and at least 4 of the 5 BI 1361849 vaccinations over the first 2 cycles, as well as, respective disease assessments (irRECIST or RECIST, clinical progression or death), without major protocol violations. Efficacy analyses will also be presented for PP population.

### 4.3 Per-Protocol Population (DLT Assessments)

The Per-Protocol (PP) Population (DLT Assessments) is defined as follows:

- All subjects in the dose escalation who experience a DLT at any time during the DLT Evaluation Period (as defined in Section 3.1.9 of the protocol).
- All subjects with no DLT who receive at least 75% of the scheduled doses of durvalumab and tremelimumab and at least 4 of the 5 BI 1361849 vaccinations over the first 2 cycles as well as respective safety assessments without major protocol violations during the DLT Evaluation Period .

## 5.0 SUBJECT DISPOSITION

Subject disposition will be summarized overall for all subjects who entered the study in a disposition table (i.e., signed the informed consent for the study). In addition, the number of subjects in each population (ITT and PP) and subjects that were removed from a population will be summarized. The number and proportion of subjects who complete the study, as well as those who discontinue the study will be summarized along with the reason for discontinuation.

Primary reason for treatment termination include the following criteria:

- Withdrawal of consent for further treatment
- Pregnancy or intent to become pregnant
- DLT at any time
- Progressive disease requiring alternative systemic treatment
- Significant protocol violation or noncompliance that, in the opinion of the Investigator or Sponsor, warrants withdrawal
- Development of intercurrent, non-cancer-related illnesses or complications that prevent either continuation of therapy or regular follow-up
- Best medical interest of the subject (at the discretion of the Investigator)

Primary reason for study discontinuation include the following criteria:

- Best medical interest of the subject at the discretion of the Investigator
- Initiation of alternative anticancer therapy (marketed or investigational)
- Withdrawal of consent for all follow-up
- Lost to follow-up
- Death

Subject disposition data will also be presented in data listings.

## 6.0 DEMOGRAPHIC AND BASELINE CHARACTERISTICS

### 6.1 Demographic Characteristics

Demographic and baseline characteristics at study entry (Screening/baseline visit which will occur up to one month before start of treatment) will be summarized for the ITT and PP Populations.

Demographic and baseline variables to be summarized include:

- Continuous variables
  - Age (years) at time of consent
  - Height (cm) at screening
  - Weight (kg) at screening
  - Body mass index (BMI) ( $\text{kg}/\text{m}^2$ ) at screening
- Categorical variables
  - Gender
  - Race
  - Ethnicity

Demographic and baseline characteristics by subject will be presented in a table and data listings.

### 6.2 Medical History

Medical History was collected at the Screening/Baseline visit. Medical history, including any ongoing and significant conditions or diseases that stopped at or prior to informed consent, must be elicited from each subject during screening. The medical history shall include a complete review of systems, past medical and surgical histories, and any allergies.

The frequency count and percentage of subjects experiencing any medical conditions will be tabulated by system organ classifications (SOC) and preferred term (PT). If a preferred term or system organ class was reported more than once for a subject, the subject would only be counted once in the incidence for that preferred term or system organ class.

Medical history data will also be listed for Safety Population.

### 6.3 Prior and Concomitant Medications and Procedures

Prior medications and procedures include any medication or non-drug therapy or procedure taken or performed within 30 days prior to screening and before the first dose of study drug. Prior medications will be coded using the World Health Organization Drug Dictionary [10].

Concomitant medications are all medications, other than the study drug, taken on or after the first day of study drug dose through 30 days after end of treatment. Concomitant medications and procedures will be coded using the World Health Organization Drug Dictionary.

Medications that started before the first dose of study drug and were ongoing on the date of the first dose will be considered concomitant medications.

The number and proportion of the subjects who took each medication, or had qualifying concomitant procedures, will be tabulated by the ATC-2 level and preferred name for concomitant medications. A subject will only be counted once within each ATC-2 code and within each preferred name.

Prior and concomitant medications will also be listed for ITT.

## 7.0 EFFICACY ANALYSIS

Tumor Response will be summarized and analyzed descriptively for each arm for the ITT and PP populations.

### 7.1 Response Rate

- Responses at Week 8 and Week 24 will be presented. The Number and Percent of subjects in each category (Complete Response, Partial Response, Stable Disease, Progressive Disease or Not Evaluable) will be presented.
- Best Overall Response (BOR) will also be presented. In the determination of BOR, any subsequent scans on or after the date of a clinical progression will be ignored.

### 7.2 Objective Response Rate (ORR)

- Objective Response Rate (ORR) is defined as the percentage of subjects meeting criteria of Complete Response (CR) or Partial Response (PR).
- To be assigned a status of a CR or PR, changes in tumor measurements must be confirmed by repeat assessments that must be performed at least 4 weeks after the criteria for response are first met. If a response is not confirmed, it is considered stable disease.
- If a subject had clinical progression (CP), any recorded response (CR or PR) after the date of CP will be considered invalid.

- Subjects who drop out prior to having a response assessment (including clinical progression) for ORR will be considered as non-responders and they will be included in the denominator when calculating the proportion.
- A 95% Confidence Interval based on binomial distribution will be constructed for the estimated ORR at 8 and 24 weeks.

### 7.3 Disease Control Rate (DCR)

- Disease Control Rate (DCR) is defined as the percent of subjects with Stable Disease (SD), Partial Response (PR) and Complete Response (CR).
- Subjects who drop out prior to meeting the responder criteria for DCR will be considered as non-responders.
- A 95% Confidence Interval based on binomial distribution will be constructed for the estimated DCR at 8 and 24 weeks.

### 7.4 Progression-free Survival (PFS)

- PFS is the interval between the date of first dose to the date of earliest determination of Progressive Disease (PD) (including clinical progression), or to the date of death, if PD does not occur.
- Subjects without documentation of progression at the time of the analysis will be censored at the date of last response assessment.
- Subjects with no tumor response assessment will be censored at the start date of the treatment.
- Subjects who discontinued treatment or withdrew from the study for reasons other than documented PD (including clinical progression) or death will be censored at the date of last response assessment prior to discontinuation or withdrawal.

Descriptive analyses of PFS, at Week 8, Week 24 and Overall, will include the following:

- Number and percentage of subjects that died or had a progressive disease or clinical progression,
- Number and percentage of subjects censored:
  - Number and percentage of subjects lost to follow up (unknown survival and/or progression status)
  - Number and percent of subjects survived without progression
  - Number and percentage of subjects missing tumor response assessment.

- Number and percent of subjects with initiation of alternative therapy.
- The 25<sup>th</sup> percentile, Median and 75<sup>th</sup> percentile and the maximum and minimum PFS at Week 8, Week 24 and Overall and the corresponding 95% CIs will be displayed.
- PFS rate at Week 8, Week 24 and Overall and the corresponding 95% CIs will be displayed.

### 7.5 Overall Survival (OS)

- The interval between the date of first dose until the date of death or the date of last follow-up will be calculated.
- The OS rate, including the 95% CI, will be presented. Duration of follow-up will also be presented. OS will also be updated at yearly intervals during the Post Study Follow-up and can be provided as addendums to the final report.
- Subjects who are still alive will be censored on the date of last follow-up. Every effort will be made to follow subjects for OS after they discontinue the study.
- OS will be summarized using the 25<sup>th</sup> percentile, Median, and 75<sup>th</sup> percentile as well as the minimum and maximum survival time, calculated by Kaplan-Meier method, and will be displayed graphically

### 7.6 Duration of Response (DoR)

- Duration of response (DOR) will be calculated interval between the date of earliest determination of CR or PR to the date of first PD, clinical progression or death whatever occurs first. Patients who had a response and did not lose it subsequently and were alive will be censored at the time of last available tumor assessment.
- $DOR \text{ in weeks} = (\text{Earlier of Date of PD or death} - \text{date of first response} + 1) / 7$
- The median DOR with 2-sided 95% confidence intervals will be presented for subjects who have a confirmed CR or PR at 8 and 24 weeks.

### 7.7 Analysis of Time to Event (TTE) Variables

Progression Free Survival (PFS), OS and DoR will be analyzed using the Kaplan-Meier product limit estimates along with the corresponding number of subjects at risk. The Duration of follow-up (in months) will be analyzed using the Reverse Kaplan-Meier product limit estimation method.

For all time to event analyses the number of events, number censored, 25<sup>th</sup> percentile, median, 75<sup>th</sup> percentile, corresponding 95% CIs as well as the minimum and maximum survival time will be presented in tables. In addition, survival curves will be presented graphically.

## 8.0 TRIAL DRUG EXPOSURE AND COMPLIANCE

Extent of treatment exposure to durvalumab, will be assessed for each of the two study arms. Durvalumab exposure (Arms A and B) will be summarized by the following parameters:

- Duration of durvalumab treatment (week), calculated as:  $(\text{Last dose date} - \text{first dose date} + 1) / 7$
- Number of durvalumab doses
- Total durvalumab dose (mg), defined as the sum of the actual doses (mg) administered
- Number of subjects with durvalumab dose de-escalated (only in Arm A)

Tremelimumab exposure (Arm B) will be summarized by the following parameters:

- Duration of Tremelimumab treatment (week), calculated as:  $(\text{Last dose date} - \text{first dose date} + 1) / 7$
- Number of tremelimumab doses
- Total Tremelimumab dose (mg), defined as the sum of the actual doses (mg) administered

BI 1361849 exposure (Arms A and B) will be summarized by the following parameters:

- Duration of BI 1361849 treatment (week), calculated as:  $(\text{Last dose date} - \text{first dose date} + 1) / 7$
- Number of doses
- Total BI 1361849 dose ( $\mu\text{g}$ ), defined as the sum of the actual doses (mg) administered

## 9.0 SAFETY ANALYSIS

### 9.1 Adverse Events

Adverse events (AEs) will be coded using MedDRA v20 or later and will be classified by System Organ Class (SOC) and preferred term (PT).

Severity of AEs will be assessed according to CTCAE (v4.03).

Prior AEs are those occurring after subject sign off the informed consent and before the administration of the first dose of study treatment.

Drug-relatedness to the study drugs is captured in five categories as follows:

- Definitely related (The AE is clearly related to the investigational agent)



- Probably related (The AE is likely related to the investigational agent)
- Possibly related (The AE may be related to the investigational agent)
- Unlikely related (The AE is doubtfully related to the investigational agent)
- Unrelated (The AE is clearly not related to the investigational agent)

TEAEs are considered as related to the study drug if entered as definitely, probably or possibly related to study drug as assessed by the Investigator. If a subject has multiple occurrences of the same system organ class (SOC) or preferred term, then only the most severe event will be summarized in the tables for that SOC and preferred term.

### 9.1.1 Treatment-Emergent Adverse Events

Treatment-emergent adverse events (TEAEs) are defined as any AEs that started after dosing or worsened in severity after dosing.

An overall AE summary for number of subjects will be presented for the following categories:

- Any Adverse Event
- Any TEAE
- Any Deaths within the AE reporting period
- Any study drug-related adverse event (TRAE) (i.e., related to durvalumab, tremelimumab and/or vaccine)
  - Any durvalumab related TRAE
  - Any tremelimumab related TRAE
  - Any vaccine related TRAE
- Any TEAE  $\geq$  CTCAE Grade 3
- Any TRAE  $\geq$  CTCAE Grade 3
- Any treatment-emergent Serious AEs (SAEs)
- Any Serious TRAEs
- Any TEAE leading to treatment (durvalumab, tremelimumab, and/or vaccine) discontinuation
  - Related to durvalumab
  - Related to tremelimumab
  - Related to vaccine

The following events will be tabulated by SOC and PT. Summaries will be sorted by decreasing frequency of PT within SOC which is sorted alphabetically.

- TEAEs by SOC and PT
- TEAEs by PT frequency only
- Treatment-emergent SAEs
- Treatment-related AEs
  - Durvalumab related
  - Tremelimumab related
  - Vaccine related
- Treatment-related SAEs
- TEAEs leading to treatment (durvalumab, tremelimumab, and/ or vaccine) discontinuation
  - Durvalumab discontinuation
  - Tremelimumab discontinuation
  - Vaccine discontinuation
- DLTs

A summary of TEAEs by SOC, PT and maximum severity, sorted by decreasing frequency of PT within SOC which is sorted alphabetically, will also be provided for:

- TEAEs
- TEAEs  $\geq$  CTCAE Grade 3
- Treatment related AEs
  - Durvalumab related
  - Tremelimumab related
  - Vaccine related
- TRAEs  $\geq$  CTCAE Grade 3

In tabulation by severity grade,

- For a given SOC, only the most severe SOC for each subject will be included.
- For a given PT, only the most severe PT for each subject will be included.

The following listings will be provided:

- All AEs (flag TEAE)

- DLTs
- SAEs
- TEAEs leading to study treatment discontinuation
- TEAEs leading to study drug (durvalumab or tremelimumab) dose modifications
- Deaths in the AE reporting period

#### **9.1.2 Adverse Events of Special Interest (AESIs)**

AESIs will not be separately presented in this analysis.

#### **9.2 Clinical Laboratory Data**

Clinical Laboratory data (chemistry, hematology, coagulation, and urinalysis) will be collected as specified in the study flowchart in section 3.2 of the protocol.

The Clinical lab tests are summarized in Table 3 below.

**Table 3. Clinical Laboratory Tests**

Clinical Chemistry	Hematology	Coagulation	Urinalysis
Alanine transaminase (ALT)	Hematocrit	Activated partial thromboplastin time (aPTT)	Albumin
Albumin	Hemoglobin	Prothrombin time (PT)	Bilirubin
Alkaline phosphatase	Mean cellular volume (MCV)	INR	Blood/Hemoglobin
Aspartate aminotransferase (AST)	Mean corpuscular hemoglobin (MCH)		Glucose
Blood Urea Nitrogen (BUN)	Mean corpuscular hemoglobin concentration (MCHC)		Ketones
Calcium	Mean Platelet Volume (MPV)		White Blood Cells
Carbon Dioxide (CO <sub>2</sub> )	Platelet count		Nitrite
Chloride	Red blood cell (RBC) count		pH
Creatinine	RBC Distribution Width (RDW)		Protein
Glucose	White blood cell (WBC) count		Red Blood Cells
Lactate Dehydrogenase (LDH)	Differential (% and absolute count for each) including:		Specific gravity
Magnesium	Basophils		Urobilinogen
Potassium	Eosinophils		Color
Sodium	Lymphocytes		Turbidity
Total bilirubin	Monocytes		
Total Protein	Neutrophils		
Lipase			
Amylase			
Free T3			
Free T4			
TSH			

**The clinical lab data will be presented in tables and listings as follows:**

- All laboratory results will be presented in the listings.

- Abnormal laboratory values with their clinical significance status will be presented in a listing.
- Urinalysis data, differentials (%), and RDW will be presented in listings only
- Magnesium, MCV, MCH, MCHC, MPV, differentials (absolute count), aPTT, PT, and INR will be presented in listings and summary tables but NOT in shift tables.
- The remaining analytes will be presented in listings, summary tables and shift tables

**The following summaries will be presented:**

- Overall values by time point utilizing continuous descriptive statistics for each arm and cohort.
- For categorical parameters, the n and percentage will be displayed for each arm and cohort.
- Frequencies and percentages for the shifts in these categories (i.e., low to normal, low to high, high to low, etc.) from baseline to each post-treatment assessment time point. For each continuous laboratory parameter, results will be categorized as low, normal, or high based on the laboratory normal ranges. Frequencies and percentages will be presented by Arm A and Arm B and overall Safety population for the shifts in these categories from baseline to selected post-treatment assessment time points (e.g., low to normal, low to high, high to low). Percentages for the shift tables will be calculated based on the number of subjects who had results for both baseline and the corresponding post-treatment assessment time point.
- For continuous parameters, descriptive statistics will be presented for the changes from baseline to each selected post-treatment assessment time point.

### 9.3 Vital Signs and Weight

Subjects will be monitored before, during and after tremelimumab and durvalumab infusion with assessment of vital signs as presented in section 6.5 of the protocol.

- Descriptive statistics will be presented each timepoint.
- Descriptive statistics will also be presented for the changes in vital signs from baseline to each post-treatment assessment time point.

### 9.4 Electrocardiograms

12-Lead ECG will be completed at screening/baseline visit, Day 1 of cycles 1, 2, 4, 6, 8, 10 and 12 and the +28 day post last treatment visit.

- Baseline and post-baseline assessments will be classified as normal, abnormal – not clinically significant, or abnormal – clinically significant. The baseline value will be the pre-dose assessment for each formulation, and the post-baseline value will be the worst post-baseline assessment for each formulation.

- ECG data will be presented in a data listing.

### 9.5 ECOG Performance

ECOG performance will be evaluated on a 6-point scale from grade 0-5. ECOG PS assessments will be summarized overall by time point utilizing descriptive statistics. ECOG performance status will be taken except on Cycle 2 Day 8, Cycle 4 Day 8, Cycle 7 Day 22, Cycle 12 Day 8, and the post study follow-up.

- ECOG PS assessments will also be summarized as categorical variable by timepoint with the n and percentage being displayed for each arm or indication-specific cohort.

### 9.6 Physical Examinations

A full physical examination will be performed at screening/baseline. There will also be targeted physical examinations at other timepoints except on Cycle 2 Day 8, Cycle 4 Day 8, Cycle 7 Day 22, Cycle 12 Day

8, and the post study follow-up.

- Continuous and categorical variables at baseline and various timepoints will be summarized using descriptive statistics.
- Clinically significant changes from baseline to postbaseline time points will be summarized using descriptive statistics.

### 9.7 Pregnancy Testing

Serum pregnancy testing (when applicable) is required prior to dosing up to 1 week before start of treatment. Pregnancy testing is also done on Day 1 of Cycles 1, 3, 5, 7, 9, 11, and On Study Follow-up Days +28 and +91 Days. Also, all subjects of childbearing potential who withdraw from study must have a serum pregnancy test done at the End of Study visit, unless it was done within 7 days prior to the End of Study Visit.

- The results of pregnancy testing (Yes/No) will be summarized for every applicable timepoint with the n and percentage being displayed for each arm or cohort.

## 10.0 EXPLORATORY ANALYSIS



Per Protocol Amendment 9.1, some of the biological assessment tests will no longer be applicable. Hence, some blood sample collections for immune monitoring were discontinued as indicated in the study flow chart.

## 11.0 STATISTICAL/ANALYTICAL ISSUES

### 11.1 Handling of Dropouts or Missing Data

In the dose evaluation phase, subjects who are not fully evaluable for DLT per section 4.1.2 of the protocol may be replaced.

Subjects who are not fully evaluable for the PFS rate and ORR may be replaced.

All available data will be presented on the data listings as collected.

Algorithms for imputing partial or missing dates related to AEs and prior/concomitant medications are shown below in Table 4.

**Table 4 Imputation Rules for Partially Missing Dates**

Variable	Missing Day	Missing Day, Month	Missing Day, Month, Year
Date of Last Therapy/Date of Initial Diagnosis	Assign 1	Assign January 1 if prior to date of informed consent, otherwise use date of informed consent	Missing (do not impute)
Adverse Event/Medication Start Date	Assign first day of month unless it is the month of first dose of study medication. Otherwise, assign date of first dose of study medication.	Assign January 1 unless the year is year of first dose of study medication. Otherwise, assign date of first dose of study medication.	Assign date first dose of study medication.
Adverse Event/Medication End Date	Assign the last day of the month or end of study date, whichever is earlier.	Assign December 31 or end of study date, whichever is earlier.	If ongoing, end date is missing. Otherwise, assign end of study date.

### 11.2 Safety Data Handling

Adverse event toxicity grade will be classified using NCI-CTCAE Version 4.03 criteria (Grade 1 – Grade 5). If a subject has multiple occurrences of the same system organ class (SOC) or

preferred term, then only the most severe event will be summarized in the tables for that SOC and preferred term. Adverse events of  $\geq$ Grade 3 will also be summarized. A missing toxicity grade will not be imputed.

The AE analysis will be repeated for SAEs and AEs leading to dose reduction or discontinuation.

### **11.3 Coding Dictionaries**

Medical history, AEs, and concurrent procedures will be coded using Medical Dictionary for Regulatory Activities (MedDRA V20). Prior and concomitant medications will be coded using the World Health Organization Drug Dictionary (WhoDrugDDEB2\_201703).

### **11.4 Pooling of Centers in Multi-Center Trials**

There will be no pooling of centers.

### **11.5 Multiple Comparisons/Multiplicity**

No adjustments for multiple comparisons or multiplicity will be made.

### **11.6 Examination of Subgroups**

No subgroup analysis will be performed in this study.

### **11.7 Interim Analysis and Data Monitoring**

Interim Safety Reviews will be performed to assess DLTs in the dose evaluation cohorts for determination of RCD. Interim analyses may be performed to analyze the 8- and 24-week endpoints.

## **12.0 QUALITY CONTROL**

All data displays and analyses will adhere to the International Conference on Harmonisation (ICH) Harmonized Tripartite Guideline: Structure and Content of Clinical Study Reports (ICH Topic E3). The clinical monitor will verify that the clinical study is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCPs, and any applicable regulatory requirements.

Ludwig Institute for Cancer Research (LICR) or their designee will review all tables, listings, and figures prior to final database lock. Final SAS datasets, programs and outputs will be transferred to LICR at project completion.



### 13.0 TABLES AND LISTING CONVENTIONS

Mock-ups for statistical tables and listings will be provided. Final formats for the statistical tables and listings may deviate from these mock-ups upon agreement with LICR. Footnotes will be used as needed to clarify the information that is presented in the tables and listings. Unless otherwise requested by LICR, the term ‘subject’ will be used in all tables and listings, in accordance with CDISC standards.

The numbering of tables, figures and listings will be in the following order:

Table 14.x.y.z, Figures 15.x.y.z, Listings 16.x.y.z.

The general layout of tables and listings will be as follows:

Ludwig Institute for Cancer Research.

Protocol: LUD2014-012-VAC

Clinical Study Report

Page x of y

Run Date: DDMMYY \_HH:MM

Listing 16.2\_x (or Table 14.x\_x)

<Title>

<Population>

Col 1 Col 2 Col 3 etc.

---

---

---

<Any footnotes>

File Name: <pathname for SAS program>

All tables and listings will use landscape orientation. Margins will be at least 2.0 cm at the top and bottom and at least 0.8 cm on the left and right, excluding headers and footers, in accordance

with electronic Common Technical Document (eCTD) guidelines. Font will be Courier New, unless otherwise specified, with an 8-point font size in most cases. Page numbering will be sequential within each table, listing, and figure. Column headers should be in initial capital letters. Units for numeric data will be included when appropriate.

Tables and data listings will be created from different SAS programs. A single program may produce multiple tables or multiple data listings from the same dataset (e.g., all clinical chemistry data listings may be generated by a single program).

## 14.0 REFERENCES

1. Cancer Research Institute. Cancerresearchorg <http://www.cancerresearch.org/cancer-immunotherapy/impacting-all-cancers/lung-cancer> Accessed 03 March 2016.
2. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009;45(2):228-47.
3. Bohnsack O, Ludajic K, Hoos A. Adaptation of the immune-related response criteria: irRECIST. *Annals of Oncology ESMO 2014 Poster*. 2014;25 (Suppl 4):iv361-iv72.
4. Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. Published: November 27, 2017. National Cancer Institute, National Institutes of Health. U.S. Department of Health and Human Services.
5. International Conference on Harmonization (ICH, 1996) E6 Guideline for Good Clinical Practice
6. International Conference on Harmonization (ICH, 1997) E8 Guideline: General Considerations for Clinical Trials
7. Medical Dictionary for Regulatory Activities (MedDRA), Version 20.
8. World Health Organization (WHO) Drug Dictionary (WhoDrugDDEB2\_201703).

## 15.0 RECORD RETENTION

Records related to the activities listed in this plan will be retained according to AC SOP AD-005.

**16.0 CHANGE HISTORY**

<b>Version</b>	<b>Date</b>	<b>Description of Changes</b>
0.1	07OCT2019	First draft version
0.2	10OCT2019	Current version. First version delivered to LICR by AC
0.3	01NOV2019	Revised by AC, Sent to LICR
0.4	14NOV2019	Version 0.3 Revised by AC, Version 0.4 sent to LICR
1.0	12DEC2019	Final version
1.1	20AUG2020	<ol style="list-style-type: none"> <li>1. Section 7 revised to better expound on BOR, PFS, DOR</li> <li>2. Clinical Laboratory Data (Section 9.2 revised to reflect intended analysis)</li> <li>3. Section 9.3 (Urinalysis) deleted as it is covered in Section 9.2</li> <li>4. Section 3.4 inserted to explain baseline measurements</li> </ol>
2.0	15SEP2020	Alignment with protocol Amendment version 9.1 (01SEP2020) Revisions to Section 7 as updated in version 1.1 and to align with mock shells,
2.1	02DEC2020	Phase 2 tumor types in Section 9.2 changed to Arm A and Arm B (irRECIST or RECIST, clinical progression or death) inserted in the definition of per protocol analysis population to emphasize disease assessments methods
3.0	09DEC2020	Final version

**17.0 APPENDICES**
**17.1 Appendix A: Study Flowchart**

LUD2014-012-VAC Study Flowchart	Screening / Baseline	Treatment (each cycle = 4 weeks)											
		Cycle 1			Cycle 2			Cycle 3		Cycle 4		Cycle 5	Cycle 6
Study Week		1	2	3	5	6 <sup>j</sup>	7	9	11	13	14 <sup>j</sup>	17	21
Cycle Day		1	8 (±2)	15 (±2)	1 (±2)	8 (±2)	15 (±2)	1 (±2)	15 (±2)	1 (±2)	8 (±2)	1 (±3)	1 (±3)
Cumulative Study Day	Up to 1 month before Tx start	1	8	15	29	36	43	57	71	85	92	113	141
<b>Treatment</b>													
Durvalumab (Arms A and B)		X			X			X		X		X	X
Tremelimumab (Arm B)		X			X			X		X			
BI 1361849 - 6 components (Arms A and B)		X	X	X	X		X	X	X	X		X	X
<b>Tumor and Disease Assessments</b>													
Disease Staging (date/stage at 1st diagnosis and at study entry)	X												
Disease Assessment by irRECIST/RECIST <sup>a</sup>	X							X				X	
<b>Study Procedures and Examinations</b>													
Eligibility Assessment and Informed Consent (IC) <sup>h</sup>	X												
Demographics (incl. DoB; sex; height; race; ethnicity)	X												
Medical history	X												
Physical Exam (incl. weight and ECOG Perf Status) <sup>b</sup>	X	X	X	X	X		X	X	X	X		X	X
12-Lead ECG <sup>a</sup>	X	X			X					X			X
Vital Signs (T, HR, BP, RR) <sup>e</sup>	X	X	X	X	X		X	X	X	X		X	X
Concomitant Medication(s)/ Procedure(s)	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events (starting or worsening after IC) <sup>f</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X
<b>Specimens for Routine Laboratory Procedures</b>													
Blood Hematology (complete blood count, differential, platelets) <sup>a</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X
Chemistry (glucose, BUN, creat., Na, K, Cl, CO <sub>2</sub> , Ca, Mg, protein, albumin, Tbili., AST, ALT, ALP, LDH) <sup>a</sup>	X	X	X	X	X		X	X	X	X		X	X
Chemistry cont. (Free T3, Free T4, TSH) <sup>a</sup>	X	X	X	X	X		X	X	X	X		X	X
Chemistry cont. (Amylase and lipase) <sup>a</sup>	X	X	X	X	X		X	X	X	X		X	X
Urinalysis <sup>a,c</sup>	X	X			X			X		X		X	X
Coagulation parameters <sup>a,d</sup>	X												
Serum pregnancy test (Urine test only on Day 1) <sup>a</sup>	Up to 1 week before Tx start	X						X				X	
<b>Specimens for Other Peripheral Blood Assays</b>													
Blood for exosomal profiling <sup>a</sup>		X			X								
Blood for PaxGene RNA and DNA <sup>a,k</sup> Note: Discontinued per Amendment 9.1		X				X <sup>j</sup>					X <sup>j</sup>		
Blood (PBMC and plasma) for flow cytometry and biological assays <sup>a,i,k</sup> Note: Discontinued per Amendment 9.1		X				X <sup>j</sup>					X <sup>j</sup>		
Blood for humoral responses and other biomarkers <sup>a,k</sup> Note: Discontinued per Amendment 9.1		X				X <sup>j</sup>					X <sup>j</sup>		
<b>Tumor Biopsy</b>													
Biopsy or FFPE slides for tumor microenvironment <sup>g</sup>	X						X						
<b>Long Term Follow-up</b>													
Overall Survival													
Progression Free Survival													

LUD2014-012-VAC Study Flowchart (cont.)	Treatment (each cycle = 4 weeks)										On Study Follow-up <sup>f,k</sup>			Post Study Follow-up			
	Cycle 7			Cycle 8		Cycle 9		Cycle 10		Cycle 11		Cycle 12			Last Study Drug Dose +28 (±4) days	Last Study Drug Dose +42 (±4) days	Last Study Drug Dose +91 (±7) days End of Study
Study Week	25	27	28 <sup>l</sup>	29	33	37	39	41	45	46							
Cycle Day	1 (±3)	15 (±3)	22(±2)	1 (±3)	1 (±3)	1 (±3)	15 (±3)	1 (±3)	1 (±3)	8 (±2)							
Cumulative Study Day	169	183	190	197	225	253	267	281	309	316							
<b>Treatment</b>																	
Durvalumab (Arms A and B)	X			X	X	X		X	X								
Tremelimumab (Arm B)																	
BI 1361849 - 6 components (Arms A and B)		X			X		X		X								
<b>Tumor and Disease Assessments</b>																	
Disease Staging (date/stage at 1st diagnosis and at study entry)																	
Disease Assessment by iRECIST/RECIST <sup>a</sup>	X				X			X						Q8W starting 8 weeks after last disease assessment			
<b>Study Procedures and Examinations</b>																	
Eligibility Assessment and Informed Consent (IC) <sup>h</sup>																	
Demographics (incl. DoB; sex; height; race; ethnicity)																	
Medical history																	
Physical Exam (incl. weight and ECOG Perf Status) <sup>b</sup>	X	X		X	X	X	X	X	X		X	X	X	X	X	X	
12-Lead ECG <sup>a</sup>				X		X			X			X		X			
Vital Signs (T, HR, BP, RR) <sup>e</sup>	X	X		X	X	X	X	X	X		X	X	X	X	X	X	
Concomitant Medication(s)/ Procedure(s)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse Events (starting or worsening after IC) <sup>f</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
<b>Specimens for Routine Laboratory Procedures</b>																	
Blood Hematology (complete blood count, differential, platelets) <sup>a</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Chemistry (glucose, BUN, creat., Na, K, Cl, CO <sub>2</sub> , Ca, Mg, protein, albumin, Tbili., AST, ALT, ALP, LDH) <sup>a</sup>	X	X		X	X	X	X	X	X	X				X	X	X	
Chemistry cont. (Free T3, Free T4, TSH) <sup>a</sup>	X	X		X	X	X	X	X	X	X				X	X	X	
Chemistry cont. (Amylase and lipase) <sup>a</sup>	X	X		X	X	X	X	X	X	X				X	X	X	
Urinalysis <sup>a,c</sup>	X			X	X	X		X	X					X			
Coagulation parameters <sup>a,d</sup>														X			
Serum pregnancy test (Urine test only on Day 1) <sup>a</sup>	X				X			X						X		X	
<b>Specimens for Other Peripheral Blood Assays</b>																	
Blood for exosomal profiling <sup>a</sup>													X	X			
Blood for PaxGene RNA and DNA <sup>a,k</sup> Note: Discontinued per Amendment 9.1			X <sup>l</sup>									X <sup>l</sup>	X				
Blood (PBMC and plasma) for flow cytometry and biological assays <sup>a,k</sup> Note: Discontinued per Amendment 9.1																	
Blood for humoral responses and other biomarkers <sup>a,k</sup> Note: Discontinued per Amendment 9.1			X <sup>l</sup>									X <sup>l</sup>	X				
<b>Tumor Biopsy</b>																	
Biopsy or FFPE slides for tumor microenvironment <sup>6</sup>														optional post-treatment			
<b>Long Term Follow-up</b>																	
Overall Survival																	X
Progression Free Survival																	X

**Flowchart Footnotes**

a - pre-dose, when applicable. Note: Review of results for hematology, chemistry and pregnancy test (when applicable) is required prior to dosing.

b - Full physical examination at baseline; targeted physical examination at other time points

c - Urinalysis performed at Screening, Day 1, every 4 weeks and as clinically indicated.

d - Coagulation tests: prothrombin time, APTT and INR – only performed at Screening, first On Study Follow-up, and as clinically indicated.

e - See Section 6.5 for assessment of vital signs on drug admin days. Note: when durvalumab vital assessments do not precede the BI 1361849 dose, pre-dose vital assessments must be done for BI 1361849.

f - See section 7.1.5 for details regarding collection of AEs for 90 days after last study drug administration

g - Biopsy Samples:

1. A fresh core pre-treatment biopsy (minimum 3 cores from lung tissue or 4 cores from another site) obtained within 60 days of study start will be requested prior to study entry; archival sample may be used if a pre-treatment fresh biopsy is not feasible.

NOTE: Per Amendment 9.1, biopsies should not be taken from a target lesion unless that is the only suitable lesion, in which case it should be of reasonable size (refer to Section 4.3.1.1).

2. If a fresh core pre-treatment biopsy was obtained, an on-treatment biopsy will be collected 1 week after the 3rd or 5th BI 1361849 treatment, if feasible; this on-treatment biopsy should only be collected if a pre-treatment fresh biopsy was obtained (so that paired biopsies may be examined).

3. Optional post-treatment core biopsies (minimum 3 cores from lung or 4 cores from another site) will be obtained at the time of tumor progression or at the completion of treatment from subjects who consent to this procedure, and if clinically feasible. See Section 4.3.1.1 for details

4. If possible and as determined by Investigator, a minimum of 8 subjects in each arm will have fresh tissue sampling from which fine needle aspiration (FNA) can be also obtained for immune profiling

h - Standard of Care procedures may be used for eligibility assessments provided they meet the criteria specified in either the inclusion criteria or flowchart

i - See Section 3.3 for instructions for blood draws for PBMC collection. Note: PBMC collection is discontinued per Amendment 9.1.

J - Sampling at 7(±2) days after preceding vaccine administration. If vaccine administration time points are delayed, the PBMC & biological specimen collection time points should also be delayed to maintain the 5-9 day time frame after preceding vaccination. If the vaccination is omitted, blood sampling should occur after the next subsequent vaccine administration.

Sample for WBC (hematology) must be available for the day of the blood samples for immunomonitoring.

Note: Sample collection for PaxGene, PBMC, and humoral response is discontinued per Amendment 9.1 (See Section 4.3.1.2)

Visits 6, 14, and 28 are no longer required per Amendment 9.1.

k - If treatment is discontinued after <14 weeks of treatment, samples for PBMC, PaxGene and humoral response should be collected within 5-9 days after the last preceding vaccination or as close as possible to this time frame if the 5-9 day window is not feasible.

Note: Sample collection for PaxGene, PBMC, and humoral response is discontinued per Amendment 9.1 (See Section 4.3.1.2)

## 17.2 Appendix B: Drug Administrative Schedules per Cycle

Cycle (28d)	Cycle Day	Arm A Dosing Schedule		Arm B Dosing Schedule		
		BI 1361849 (12 x i.d. each)	<del>Durvalumab</del> (i.v.)	BI 1361849 (12 x i.d. each)	<del>Durvalumab</del> (i.v.)	<del>Tremelimumab*</del> (i.v.)
1	1	X	X	X	X	X
	8	X		X		
	15	X		X		
2	1	X	X	X	X	X
	15	X		X		
3	1	X	X	X	X	X
	15	X		X		
4	1	X	X	X	X	X
5	1	X	X	X	X	
6	1	X	X	X	X	
7	1		X		X	
	15	X		X		
8	1		X		X	
9	1	X	X	X	X	
10	1		X		X	
	15	X		X		
11	1		X		X	
12	1	X	X	X	X	

i.d. = intradermal; i.v. = intravenous

Note: the dosing intervals for BI 1361849 intervals increase over time