

LUDWIG CANCER RESEARCH	<b>Study Protocol</b>	<b>LUD2014-012-VAC NCT03164772</b>	<b>US-IND# 17480</b>
	<b>Amendment 10.0</b>	<b>Final</b>	<b>30-JUL-2021</b>

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

**Objectives and Synopsis**

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. 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. 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).

Dose Level Table for Evaluation Phase						
Dose Level	Arm A		Dose Level	Arm B*		
	BI 1361849	Durvalumab		BI 1361849	Durvalumab	Tremelimumab
-1	12 x 80 µg**	750 mg				
<b>Starting</b>	<b>12 x 80 µg**</b>	<b>1500 mg</b>	<b>Starting</b>	<b>12 x 80 µg**</b>	<b>Arm A RCD</b>	<b>75 mg</b>

\*If there is unacceptable toxicity in Arm B, dosing will continue at RCD from Arm A, without tremelimumab.

\*\*See Note 2 below.

**NOTE 1:** See Section 3.1.7.1 for durvalumab and tremelimumab doses for instances when a subject's body weight drops to ≤ 30 kg while on the study.

**NOTE 2:** The BI 1361849 drug product is a vaccine comprising six drug product components (F2408, F2409, F2410, F2624, F2625, and F2626), which are provided and administered separately; each component is administered twice, thus there are 12 administrations of 100 µL (80 µg) each.

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<b>Primary Objective [Endpoints]</b>	<b>Dose Evaluation Phase:</b> <i>Safety and Tolerability</i> [CTCAE 4.03, including DLTs and RCD] <b>Expansion Phase:</b> <i>Safety and Tolerability</i> [CTCAE 4.03]
<b>Secondary Objectives [Endpoints]</b>	<b>Dose Evaluation and Expansion Phases (all subjects):</b> <i>Clinical Efficacy by irRECIST and RECIST 1.1</i> [PFS rate and ORR at 8 and 24 weeks, best overall response, DCR, DoR, OS]
<b>Exploratory Objectives [Endpoints]</b>	<b>Dose Evaluation and Expansion Phases (all subjects):</b> <i>Biologic Activity</i> [Effects on Tumor Microenvironment, Immune Response]
DLT=Dose-limiting Toxicity; RCD=Recommended Combination Dose; ORR=Objective Response Rate; DCR=Disease Control Rate; DoR=Duration of Response; PFS=Progression-free Survival; OS=Overall Survival; CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events; RECIST = Response Evaluation Criteria in Solid Tumors; irRECIST=immune-related RECIST.	

<b>Sponsor:</b> Ludwig Institute for Cancer Research, New York, NY	
<b>Sponsor Representative Signature and Date</b>	

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# 1 Background

## 1.1 Checkpoint Inhibitors in the Treatment of Non-Small Cell Lung Cancer

Lung cancer is responsible for nearly 1 in 5 cancer-related deaths, or an estimated 1.6 million people, worldwide. In the U.S., lung cancer is the leading cause of cancer-related death among both men and women.(1) For patients who are diagnosed with advanced disease, conventional treatment options including surgery, chemotherapy, and radiation are unlikely to result in cure.

Lung cancer has also emerged as an exciting target of immune-based therapies, specifically checkpoint inhibitors.(2) In non-small cell lung cancer (NSCLC), marked single-agent activity has been observed with inhibition of programmed death receptor 1 (PD-1) on immune cells or inhibition of programmed death receptor ligand 1 (PD-L1).(3-5) Notably, PD-L1 appears to be expressed in 25% to 50% of NSCLC tumors, with expression both on tumor cells and within the tumor microenvironment (TME) on tumor-associated macrophages.(6) While the relationship of expression to therapeutic response is still being defined, early studies indicate there may be some activity of such inhibitors in NSCLC.(7-9)

Checkpoint inhibitors, particularly PD-1/PD-L1 antibodies, have been shown to be effective in the treatment of NSCLC(10-12), and in 2015, nivolumab and pembrolizumab were approved by FDA for the treatment of lung cancer after progression on or after platinum-based chemotherapy.

In March 2015, FDA approved the PD-1 checkpoint inhibitor nivolumab for the treatment of advanced squamous NSCLC that has stopped responding to chemotherapy. This approval was based on results of a Phase 3 trial in which subjects receiving nivolumab had median overall survival of 9.2 months versus 6.0 months with docetaxel.(11) In October 2015, FDA expanded its approval of nivolumab to include non-squamous NSCLC that has stopped responding to chemotherapy. This approval was based on the results of a Phase 3 trial that showed that subjects who received nivolumab had a median overall survival of 12.2 months compared to 9.4 months for those receiving docetaxel.(10)

Also in October 2015, pembrolizumab, a PD-1 checkpoint inhibitor was approved for patients with NSCLC (both squamous and non-squamous) with tumors that test positive for PD-L1. In a Phase 1 clinical trial, PD-L1 expression level of 50% was associated with the likelihood of clinical benefit. Among subjects with a proportion score of at least 50%, the response rate was 45.2%.(12)

For both of these immunotherapies, it is recommended that patients with epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) genomic tumor aberrations should have disease progression on FDA-approved therapy prior to receiving nivolumab or pembrolizumab.

Both nivolumab and pembrolizumab are being studied in multiple indications in randomized Phase 3 trials compared to standard of care chemotherapy as first-line treatment, and several other PD-1/PD-L1 checkpoint inhibitors are also in late stage clinical testing.

An alternate checkpoint inhibitor strategy, inhibition of cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) on regulatory T-cells (Tregs) which are often increased in the TME, has also demonstrated single-agent activity in certain tumor types. Although single-agent anti-CTLA-4 antibodies have not shown responses in NSCLC or improvement in overall survival, there has been prolongation of progression-free survival observed with phased ipilimumab in a randomized Phase 2 trial.(13) Furthermore, there is significant synergy seen with combining anti-CTLA-4 antibodies with anti-PD-1 antibodies in melanoma, as the two immunotherapies target complementary checkpoints in immune activation.(14) In EGFR-driven models of lung adenocarcinoma, PD-1 inhibition did not alter the numbers of Tregs expressing high levels of CTLA-4, and EGFR signaling itself results in increased Treg infiltration, which may provide synergistic efficacy with anti-CTLA-4 in NSCLC as well.(15)

## **1.2 Study Drugs**

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.

### **1.2.1 Durvalumab (MEDI4736) - PD-L1 Antibody**

Durvalumab is briefly described in the section below using excerpts that have been extracted from the Investigator's Brochure (IB). Please refer to the current IB for complete and current information.

Durvalumab is a human monoclonal antibody (mAb) of the immunoglobulin G (IgG) 1 kappa subclass that inhibits binding of PD-L1. Durvalumab is selective for recombinant PD-L1 and blocks the binding of recombinant PD-L1 to the PD-1 and cluster of differentiation (CD) 80 receptors.

As of the data cutoff dates in the IB (15Apr2015 to 18Sep2015), a total of 1,910 subjects have been enrolled and treated in 30 ongoing durvalumab clinical studies, including 20 sponsored and 10 collaborative studies. Of the 1,910 subjects, 1,279 received durvalumab monotherapy, 454 received durvalumab in combination with tremelimumab or other anticancer agents, 14 received other agents (1 gefitinib, 13 MEDI6383), and 163 have been treated with blinded investigational product. No studies have been completed or terminated prematurely due to toxicity.

The safety profile of durvalumab as monotherapy and combined with other anticancer agents was consistent with the pharmacology of the target and other agents in the immune checkpoint inhibitor class. No tumor types appeared to be associated with unique adverse events (AEs). Immune-related AEs (irAEs), which are important risks of immune checkpoint inhibitors, have been observed with durvalumab and include colitis, pneumonitis, hepatitis/hepatotoxicity, neuropathy / neuromuscular toxicity, endocrinopathy, dermatitis, and nephritis. In addition, pancreatitis is an important potential risk particularly with durvalumab and tremelimumab combination therapy. These events are manageable by available/established treatment guidelines as described in Section 8.3.

Partial efficacy data are available for 2 monotherapy studies (CD-ON-MEDI4736-1108 and D4190C00007) and 2 combination therapy studies (CD-ON-MEDI4736-1161 and D4190C00006).



Clinical activity has been observed across the 4 studies, and two of the studies have data for NSCLC as detailed below.

**Study CD-ON-MEDI4736-1108:** Overall, 456 of 694 subjects treated with durvalumab 10 mg/kg Q2W were evaluable for response (defined as having  $\geq$  24 weeks follow-up, measurable disease at baseline, and  $\geq$  1 follow-up scan, or discontinued due to disease progression or death without any follow-up scan). In PD-L1 unselected subjects, the objective response rate (ORR), based on investigator assessment per RECIST v1.1, ranged from 0% in uveal melanoma (n = 23) to 20.0% in bladder cancer (n = 15), and disease control rate at 24 weeks ranged from 4.2% in triple-negative breast cancer (n = 24) to 39.1% in advanced cutaneous melanoma (n = 23). PD-L1 status was known for 383 of the 456 response evaluable subjects. Across the PD-L1 positive tumors, ORR was highest for bladder cancer, advanced cutaneous melanoma, hepatocellular carcinoma (HCC) (n = 3 each, 33.3% each), NSCLC (n = 86; 26.7%), and squamous cell carcinoma of the head and neck squamous cell carcinoma of the head and neck (SCCHN) (n = 22; 18.2%). In the PD-L1 positive subset, disease control rate at 24 weeks was highest in advanced cutaneous melanoma (n = 3; 66.7%), NSCLC (n = 86; 36.0%), HCC and bladder cancer (n = 3 each; 33.3% each), and SCCHN (n = 22; 18.2%).

**Study D4190C00006:** Of the 102 subjects with advanced NSCLC treated with durvalumab in combination with tremelimumab, 63 subjects with at least 16 weeks of follow-up were evaluable for response (defined as measurable disease at baseline and at least 1 follow-up scan; this included discontinuations due to disease progression or death without follow-up scan). Of the 63 evaluable subjects, 17 (27%) had a best overall response of partial response (PR), 14 (22%) had stable disease (SD), 22 (35%) had progressive disease (PD), and 10 (16%) were not evaluable. The ORR (confirmed and unconfirmed complete response (CR) or PR) was 27% and the disease control rate ([DCR], CR, PR, or SD) was 49% as assessed by RECIST v1.1.

Durvalumab, like other drugs in the anti PD-L1 class, has shown early evidence of activity against solid tumors as a single agent and is currently being evaluated in combination with tremelimumab and other therapies in NSCLC. (16, 17)

### 1.2.2 Tremelimumab - CTLA-4 Antibody

Tremelimumab is briefly described in the section below using excerpts that have been extracted from the Investigator's Brochure (IB). Please refer to the current IB for complete and current information.

Tremelimumab (formerly CP-675,206) is a human immunoglobulin G2 (IgG2) mAb being investigated as a cancer immunotherapeutic agent. Tremelimumab is specific for human CTLA-4, with no cross-reactivity to related human proteins.

As of the data cutoff dates (1 November 2015 for monotherapy studies and 15 April 2015 to 12 July 2015 for combination therapy studies), 34 sponsored clinical studies have been conducted as part of the tremelimumab clinical development program. Of these, 13 studies have completed and 21 are ongoing. Eight tremelimumab monotherapy studies have been completed and 3 are ongoing. As of the data cutoff date of 1 November 2015, 973 subjects received tremelimumab in completed monotherapy studies and the ongoing Study D4881C00024 and 569 subjects have been treated in the ongoing blinded Phase 2b monotherapy Study D4880C00003 [DETERMINE]). In the third ongoing monotherapy study (D4884C00001), no subjects have been treated as of the data cutoff. In addition, approximately 59 subjects have

been treated with tremelimumab in monotherapy arms of combination studies. Five studies of tremelimumab in combination with other anticancer agents have been completed and 18 are ongoing. In total, 250 subjects with a variety of tumor types have received tremelimumab in combination with other anticancer agents in these studies.

In clinical patients, tremelimumab exhibits linear (dose-proportional) PK following IV infusion. The estimate of clearance (CL), volume of distribution at steady state (V<sub>ss</sub>), and terminal-phase half-life is 0.132 mL/h/kg, 81.2 mL/kg and 22.1 days, respectively. These values are consistent with those of natural IgG2.

Across the clinical development program for tremelimumab, a pattern of efficacy has emerged that is similar to that of the related anti-CTLA-4 antibody, ipilimumab. Response rates to anti-CTLA-4 antibodies are generally low, approximately 10%. However, in patients who respond, the responses are generally durable, lasting several months even in patients with aggressive tumors such as refractory metastatic melanoma. Some patients may have what is perceived to be progression of their disease in advance of developing disease stabilization or a tumor response. Overall, the impact on conventionally-defined progression-free survival (PFS) can be small; however, the durable response or stable disease seen in a proportion of patients can lead to significant prolongation of overall survival (OS). For example, ipilimumab was shown to significantly improve OS in both first- and second-line treatment of patients with metastatic melanoma. The melanoma data with ipilimumab clearly demonstrate that a small proportion of patients with an objective response and a small impact on PFS rates can lead to significant prolongation of OS. In a large, single-arm Phase II tremelimumab study (A3671008) in subjects with advanced refractory and/or relapsed melanoma, objective responses (primary endpoint) following tremelimumab 15 mg/kg administered once every 90 days (Q90D) were observed in 7% of subjects. In each case, the response was durable (present at ≥6 months from enrolment). A Phase III, open-label, randomized study (A3671009) comparing tremelimumab 15 mg/kg Q90D (Arm A) to either dacarbazine (DTIC) or temozolomide (Arm B) in subjects with advanced melanoma was terminated following a pre-specified interim futility analysis. Based on the final analysis, the median OS (primary endpoint) was 12.6 months in Arm A and 10.7 months in Arm B.(18) Although Phase II and Phase III studies (A3671002, A3671008, and A3671009) of tremelimumab in metastatic melanoma did not meet the primary endpoints of response rate and OS, respectively, the data suggest activity of tremelimumab in melanoma.(18, 19) Preliminary activity of single-agent tremelimumab observed in studies of malignant mesothelioma (20, 21) provided a sound scientific rationale for further investigation of single-agent tremelimumab in this patient population.

Clinical studies of tremelimumab are ongoing in several solid tumor types, including malignant mesothelioma, and have been completed in solid tumor types including melanoma, adenocarcinoma of the colon or rectum, non-small cell lung cancer (NSCLC), prostate cancer, breast cancer, pancreatic cancer, and renal cell carcinoma. In a Phase II maintenance study in NSCLC, PFS at 3 months was 22.7% in the tremelimumab arm compared with 11.9% in the best supportive care arm (Study A3671015).

The profile of adverse events (AEs) and the spectrum of event severity have remained stable across the tremelimumab clinical program and are consistent with the pharmacology of the target. To date, no tumor type or stage appears to be associated with unique AEs (except for vitiligo that appears to be confined to patients with melanoma).

### 1.2.3 BI 1361849

BI 1361849 (previously known as CV9202) is briefly described in this section below using excerpts that have been extracted from the Investigator's Brochure (IB). Please refer to the current IB for complete and current information.

Vaccination with mRNA molecules represents a novel approach in cancer immunotherapy. RNAActive® cancer vaccines are based on a proprietary technology platform (CureVac), aiming to enhance stability and efficiency of in vivo translation for RNA encoding for selected tumor-associated antigens (TAA). BI 1361849 comprises 6 different mRNAs, encoding for the TAAs MUC1, survivin, NY-ESO-1, 5T4, MAGE-C2 and MAGE-C1. The vaccine is intended for the treatment of patients with histologically or cytologically confirmed NSCLC.

RNAActive® vaccines, and in particular the antigen components of BI 1361849, have been shown to be effectively translated into the encoded proteins. Systemic effects of RNAActive® vaccination occur via priming of immune effectors via dendritic cells that have locally taken up the RNA-based vaccine and present the encoded antigens to the immune system in the lymph nodes draining the injection site, and via systemic recirculation of these effectors (immune cells, antibodies). Dendritic cell migration, increased activation of lymph node immune cells and increased proliferation of antigen-specific lymphocytes have been shown to occur after RNAActive® vaccination. RNAActive® vaccination induces a balanced systemic antigen-specific immune response, comprising humoral and cellular responses, including multifunctional cytotoxic CD8+ T lymphocytes.

Anti-tumor efficacy has been shown in a syngeneic murine animal model, using tumor cells stably expressing the well accepted model antigen ovalbumin as a surrogate tumor-associated antigen. In this model, vaccination with ovalbumin-encoding RNAActive® vaccine led to effective reduction of tumor growth, which was dependent to a large extent on the presence of CD8+ T-cells. Intra-tumoral changes of gene expression reflecting increased cytotoxicity were demonstrated. Also, synergy between radiotherapy and the added vaccine could be shown, and similarly for checkpoint inhibition and the added vaccine. Pre-clinical studies were not suggestive of relevant toxicities aside from commonly mild alterations at the site of injection. The RNAActive® was degraded locally with an average half-life of 2 days. There was no detectable systemic exposure to the administered RNA. Systemic effects of the vaccine are based on the systemically recirculating immune effectors rather than systemic exposure to the RNA.

For each of the individual RNAActive® cancer vaccines, data from one trial are currently available. The trials for CV9201 (Trial CV-9201-003) and CV9103 (Trial CV-9103-001) have been completed, the respective trials for BI 1361849 (Trial CV-9202-006) and CV9104 (Trial CV-9104-004) are currently ongoing.

As of March 2017, an estimated >250 subjects have to date been exposed to four RNAActive® cancer vaccines. The majority of the subjects were enrolled in a placebo-controlled, double-blind ongoing trial of the hexavalent prostate cancer vaccine CV9104. CV9104 shares one of its six constituents with BI 1361849, namely the RNAActive® vaccine encoding for MUC1. Forty-six subjects have been treated with vaccine CV9201 (comprising 5 of the six antigen constituents of BI 1361849 lacking the MUC1 constituent).

Data from all RNAActive® cancer vaccines are considered of interest for the development of BI 1361849, as many general aspects, in particular regarding feasibility and safety of multiple

and reiterated intradermal RActive® administrations, are shared by the vaccines. The pertinence of data especially from the development of the pentavalent vaccine CV9201 for BI 1361849, sharing five of the six antigen constituents comprised in BI 1361849, is ascertained by the confirmed comparability of the shared antigen components between the two vaccines.

To date, 26 subjects have been exposed to BI 1361849 (see details for Study CV-9202-006 below).

Based on the initial dose escalation trials and preliminary Phase 2 data, RActive® vaccines appear well tolerated and safe, with all 4 clinical vaccines sharing a very similar safety profile.

Adverse events frequently reported as vaccine related were very similar for all RActive® cancer vaccines tested in clinical trials and consisted of mild injection site reactions as well as flu-like symptoms such as pyrexia and occasionally chills. Grade 3 transient pyrexia was reported for one subject of 26 for BI 1361849; none was reported in trial CV9201-003. No signs or symptoms of a clinically manifest autoimmune disorder were observed for any of the RActive® cancer vaccines. Also, no anaphylactic or hypersensitivity reactions to the vaccines have been reported, except for one AE of non-serious asthma that occurred in a subject with known chronic obstructive pulmonary disease, and was considered probably related to study treatment with CV9201 by the investigator.

The recommended dose for each constituent of RActive® vaccines, encoding for a specific tumor antigen, is identical across all RActive® cancer vaccines. All individual antigen constituents of a multivalent RActive® cancer vaccine are to be administered individually and in duplicate, based on data showing enhanced efficiency of vaccination. The recommended dose per antigen constituent is 320 µg, split into two administrations of 160 µg each, and the two administrations are to occur in two different defined regions (upper arm, thigh) drained by separate lymph nodes. In particular, the recommended dose of BI 1361849, based on trial CV-9201-003 and trial CV-9202-006, has been confirmed as 320 µg/antigen component and administration time point, which is identical to the dose of the antigen components of the other RActive® cancer vaccines.

The BI 1361849 components may also be administered by a needle-free device, the PharmaJet Tropis® device. Due to the fill volume of 100 µL, the device allows for administration of half the previously established doses. Instead of 320 µg per antigen, 160 µg per antigen is dosed when using the same manner of administration of two inoculations per antigen and vaccination time point. Preclinical data, demonstrating a more even intradermal distribution of the applied volume, increased protein production even at reduced doses (e.g. 25% of dose), and clinical data (trial CV-9104-007 of RActive® vaccine CV9104), showing at least similar immunogenicity, support the use of this device. Device-related AEs were qualitatively and quantitatively similar to conventional needle administration.

#### **Summary for Trial CV-9202-006 (See IB for details)**

The Phase 1b trial with BI 1361849, CV-9202-006, was an exploratory, open label study of BI 1361849 combined with local radiation as consolidation/maintenance treatment in subjects with stage IV NSCLC and a response or stable disease after standard first-line therapy. Radiation was to be started one week after the first vaccination. The population was stratified by histological subtype (non-squamous cell carcinoma [non-EGFR mutated], squamous cell carcinoma, non-squamous carcinoma with activating EGFR mutations) and subjects were to

receive indicated standard maintenance treatments in combination with BI 1363849. All subjects were to receive 1920 µg per administration time point, and treatment was to continue until disease progression requiring subsequent anticancer therapy. All subjects were to receive also 20 Gy of radiotherapy, fractionated in daily doses of 5 Gy over a course of 4 days, to be administered in week two of vaccine treatment.

The trial, which was closed in July 2016, confirmed feasibility and tolerability of the recommended dosing (320 µg per antigen constituent and administration time point) and for long-term therapy up to 806 days (>2 years). In total, about 225 vaccinations (on average ~8.6 vaccinations per subject) were administered. Exploratory efficacy results showed a median PFS of about 2.9 months after initiation of study treatment, i.e. maintenance therapy, and a median OS of about 14 months. One subject in stratum 1, who was treated with BI 1361849, pemetrexed and experimental low-dose radiotherapy, achieved a partial response; otherwise, best response was SD or PD. Two subjects in stratum 1 achieved long-term disease control (20 months and 27 months, respectively); one subject in stratum 3, treated with BI 1361849 added to erlotinib therapy received vaccination therapy for >25 months despite having experienced a new pulmonary lesion after 14 months (treatment beyond progression was allowed per protocol if clinical benefit was maintained).

Many of the subjects showed a pre-existing immune response to target antigens at baseline (baseline immune response to the respective TAA). Overall, 21 (84%) of 25 evaluable subjects fulfilled the criteria for humoral and / or cellular immune responders. Ten (40%) subjects fulfilled criteria for cellular immune responders to any of the CV9202 encoded antigens at any post-baseline assessments based on either IFN-γ ELISpot or flow cytometry-based intracellular cytokine staining (ICS). The frequency of CD4 (measured by ICS) immune responders to any CV9202 encoded antigen was slightly higher compared to that of CD8 responders (measured by ICS) at any post-baseline assessment time-point (28.0% / 7 subjects vs. 16.0% / 4 subjects, respectively). All 25 subjects in the evaluable population were positive for IgM and IgG against any of the CV9202 encoded antigens at baseline. Twenty (80%) subjects had a humoral immune response post-baseline (i.e. IgG or IgM against any of the CV9202 encoded antigens at any post-baseline time point) and were rated as humoral immune responder after applying responder criteria. The majority of subjects (19 [76.0%]) were responders for IgG at any post-baseline time point, whereas only few subjects (7 [28.0%]) were positive for IgM at post-baseline time points. A total of 13 (52%) subjects were multiple responders, i.e. 9 subjects in stratum 1 and 4 subjects in stratum 2. Overall, only a limited number of the performed post-baseline cellular immunomonitoring assays fulfilled “immune responder” criteria for the individual assay outcome, and among those, persistence over both post-baseline time points was not common.

The tolerability profile of BI 1361849 appeared very similar to that of other RActive® vaccines. All subjects reported at least one AE and 25 (96.2%) subjects reported BI 1361849 related AEs. Eleven (42.3%) subjects reported serious adverse events (SAEs), none of which were considered BI 1361849 related. Treatment-emergent AEs by maximum CTCAE grade were Grade 1 (4 [15.4%] subjects), Grade 2 (7 [26.8%] subjects), Grade 3 (13 [50.0%] subjects), and Grade 4 (2 [7.7%] subjects). The two Grade 4 events, neutrophil count decreased, were not considered related to BI 1361849. With very few exceptions, BI 1361849-related AEs were of Grade 1 and Grade 2. Three of the Grade 3 AEs (one subject with pyrexia and 2 subjects with fatigue) were considered related to BI 1361849. No drug-related SAE has been reported in the trial. A low number of subjects experienced nausea/emesis considered related to BI 1361849 in the trial.

The most frequent AEs reported were erythema at the injection site and pyrexia, mostly being reported as vaccine-related but of grade 1 only. Flu-like symptoms potentially represent a pharmacodynamic effect (mimicking of a viral infection, stimulation of the innate immune system via TLRs 7 and 8 due to the RNA-related properties). None of the findings, including e.g. cardiorespiratory or vascular AEs, suggest the occurrence of an uncontrolled release of cytokines or the emergence of autoimmune disorders. This is in line with experience with other vaccines directed against BI 1361849 encoded antigens, which suggests that autoimmune disorders are not commonly observed with such treatment.

## 2 Study Rationale

As described in Section 1.1, checkpoint inhibitors, particularly PD-1/PD-L1 antibodies, have been shown to be effective in the treatment of NSCLC. Checkpoint inhibitors are also associated with minimal toxicities compared with chemotherapy or targeted therapies and function quite distinctly from other therapies. Therefore, the potential for effective and safe combination with existing therapies is significant.

Vaccine therapies stimulate the immune system to attack cancer cells (“active immunotherapy”), as opposed to blocking immune inhibition in the TME by checkpoint inhibitors (“passive immunotherapy”). Randomized vaccine studies in NSCLC have shown benefit in some subgroups. Tecemotide (Stimuvax®) demonstrated overall survival (OS) benefit over placebo in a subgroup of stage III subjects who received concurrent chemotherapy and radiation prior to vaccine, and belagenpumatucel-L (Lucanix®) demonstrated OS benefit in squamous cell carcinoma subjects who were randomized within 12 weeks of completion of prior treatment and in those who had received prior radiation.(22, 23) However, checkpoint mechanisms limit the effectiveness of vaccines at the TME, which may explain why more global long-term benefit from vaccines has not been realized. Therefore, combining “passive immunotherapy” with “active immunotherapy” may overcome some of limitations of vaccine therapy alone. In an animal model of RNActive® vaccination using ovalbumin (OVA) as model cancer antigen stably transfected into E.G7 tumor cells, the combination of the vaccine and a PD-1 inhibitor was more effective than either medication alone. Similar results were also obtained for the combination of the RNActive® vaccine and a CTLA-4 inhibitor. Combination of the PD-1 inhibitor and OVA-RNActive® resulted in complete tumor responses in a part of the treated mice, who were also protected against subsequent rechallenge with the OVA-negative parent tumor cell line.(24)

### 2.1 BI 1361849 Dose

The BI 1361849 drug product is a vaccine comprising six drug product components (F2408, F2409, F2410, F2624, F2625, and F2626), which are provided and administered separately. The recommended dose per antigen constituent is 320 µg (160 µg x 2), for a total of 1920 µg (320 µg x 6 constituents).

BI 1361849 may also be administered by a needle-free device, the PharmaJet Tropis® device. See Section 1.2.3 for additional details.

Due to the filling volume of 100 µL, the device allows for administration of half the previously established doses, i.e., 160 µg instead of 320 µg per antigen when using the same manner of administration of two inoculations per antigen and vaccination time point. Advantages include improved patient convenience, handling safety, ease, and reliability of intradermal administration. Preclinical data showed that using a needle-free device such as the PharmaJet Tropis® device, the efficiency of delivery increases and protein production is higher even at half or a quarter of the administered dose, hence lower doses can be used. Clinical data from a Phase 2 trial, CV-9104-007, suggests that administration of half the dose by the PharmaJet Tropis® device results in at least similar immunogenicity compared to needle administration of the full dose.

For this study, the Pharmajet Tropis® device will be used for the administration of the BI 1361849 components. Allowing for a filling volume of 100 µL (80 µg) and 2 administrations per component, the recommended dose per each of the 6 antigen components will be 160 µg (2 x 80 µg), for a total of 960 µg (12 administrations).

## 2.2 Durvalumab and Tremelimumab Dose

Currently, fixed dosing is recommended for durvalumab and tremelimumab with the dose and schedule of 1500 mg durvalumab Q4W and 75 mg tremelimumab Q4W for subjects > 30 kg.

A population PK model was developed for durvalumab using monotherapy data from a Phase 1 study (*Study 1108; N=292; doses= 0.1 to 10 mg/kg Q2W or 15 mg/kg Q3W; solid tumors*).<sup>(25)</sup> Population PK analysis indicated only minor impact of body weight on PK of durvalumab (coefficient of  $\leq 0.5$ ). The impact of body weight-based (10 mg/kg Q2W) and fixed dosing (750 mg Q2W) of durvalumab was evaluated by comparing predicted steady state PK concentrations (5<sup>th</sup>, median and 95<sup>th</sup> percentiles) using the population PK model. A fixed dose of 750 mg was selected to approximate 10 mg/kg (based on median body weight of approximately 75 kg). A total of 1000 patients were simulated using body weight distribution of 40–120 kg. Simulation results demonstrate that body weight-based and fixed dosing regimens yield similar median steady state PK concentrations with slightly less overall between-subject variability with fixed dosing regimen.

Similarly, a population PK model was developed for tremelimumab using data from Phase 1 through Phase 3 (*N=654; doses= 0.01 to 15 mg/kg Q4W or Q90D; metastatic melanoma*).<sup>(26)</sup> Population PK model indicated minor impact of body weight on PK of tremelimumab (coefficient of  $\leq 0.5$ ). The weight-based (1 mg/kg Q4W) and fixed dosing (75 mg/kg Q4W; based on median body weight of approximately 75 kg) regimens were compared using predicted PK concentrations (5<sup>th</sup>, median and 95<sup>th</sup> percentiles) using population PK model in a simulated population of 1000 patients with body weight distribution of 40 to 120 kg. Similar to durvalumab, simulations indicated that both body weight-based and fixed dosing regimens of tremelimumab yield similar median steady state PK concentrations with slightly less between-subject variability with fixed dosing regimen.

Similar findings have been reported by others.<sup>(27-30)</sup> Wang and colleagues investigated 12 monoclonal antibodies and found that fixed and body size-based dosing perform similarly, with fixed dosing being better for 7 of 12 antibodies. In addition, Zhang et al. investigated 18 therapeutic proteins and peptides and showed that fixed dosing performed better for 12 of 18 in terms of reducing the between-subject variability in pharmacokinetic/pharmacodynamics parameters.<sup>(29)</sup>

A fixed dosing approach is preferred by the prescribing community due to ease of use and reduced dosing errors. Given expectations of similar pharmacokinetic exposure and variability, we considered it feasible to switch to fixed dosing regimens. Based on average body weight of 75 kg, a fixed dose of 1500 mg Q4W durvalumab (equivalent to 20 mg/kg Q4W) and a fixed dose of 75 mg Q4W tremelimumab (equivalent to 1 mg/kg Q4W) are included in the current study.

The 1500 mg Q4W dosing of durvalumab is recommended only for subjects with > 30kg body weight in order to limit endotoxin exposure. Subjects with a body weight  $\leq 30$  kg are not eligible for enrollment in the current study. See Section 3.1.7.1 for additional details regarding the dose



de-escalation cohort for durvalumab and for durvalumab and tremelimumab dose requirements for instances when a subject's body weight drops to  $\leq 30$  kg while on the study.

### 3 Experimental Plan

#### 3.1 Study Design

This is an open-label multicenter Phase 1/2 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] + 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. 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).

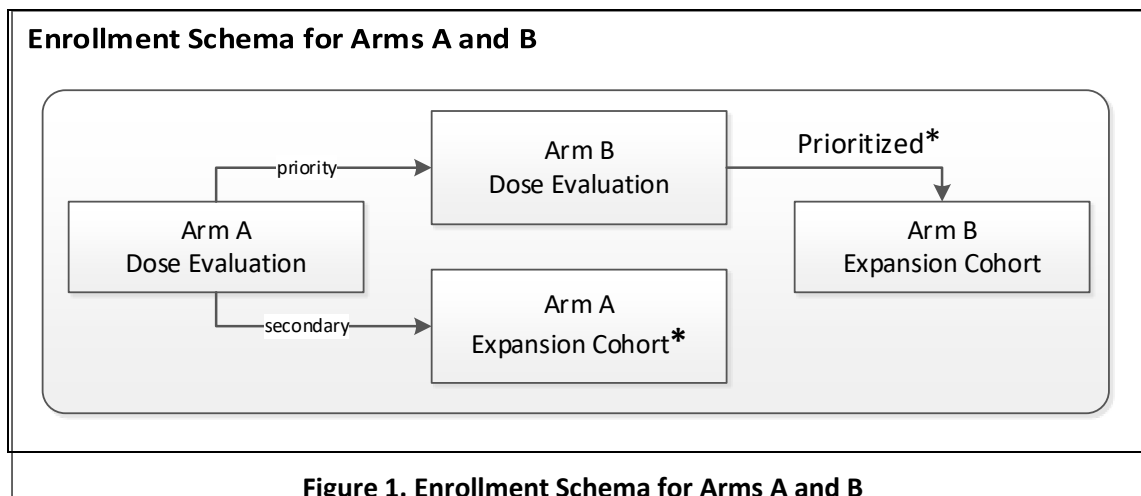
NOTE: The BI 1361849 drug product is a vaccine comprising six drug product components (F2408, F2409, F2410, F2624, F2625, and F2626), which are provided and administered separately. See Section 6.3 for additional details.

##### 3.1.1 Study Phase

Phase 1/2

##### 3.1.2 Enrollment/Randomization

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 (see Section 3.1.7.1) and for the Arm A Expansion Cohort (see Figure 1), 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 will be prioritized over Arm A (see Figure 1).



**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.

### 3.1.3 Blinding/Unblinding

This is an open-label study.

### 3.1.4 Subject Population

Subjects with histologically confirmed metastatic NSCLC. For subjects with known EGFR or ALK/ROS-1 mutations, prior therapy must have included an EGFR tyrosine kinase inhibitor or ALK/ROS-1 inhibitor, respectively. Subjects may have had 1 prior line of anti-PD-1/PD-L1 therapy and must not have had progression at or before 12 weeks after start of treatment. Details on subject eligibility are found in Section 5.

### 3.1.5 Number of Sites/Subjects

Up to 8 sites in the US, with a total of up to 56 subjects.

### 3.1.6 Sample Size Considerations

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. The Clopper Pearson confidence intervals (CI) for incidence of adverse events based on a sample size of 20 subjects are provided below:

Number of Subjects with Event	Incidence	95% Confidence Interval (Clopper Pearson)
1/20	0.05	(0.00127, 0.24873)
2/20	0.10	(0.01235, 0.31698)
3/20	0.15	(0.03207, 0.37893)
4/20	0.20	(0.05733, 0.43661)
5/20	0.25	(0.08657, 0.49105)
6/20	0.30	(0.11893, 0.54279)
7/20	0.35	(0.15391, 0.59219)
8/20	0.40	(0.19119, 0.63946)
9/20	0.45	(0.23058, 0.68472)
10/20	0.50	(0.27196, 0.72804)
11/20	0.55	(0.31528, 0.76942)
12/20	0.60	(0.36054, 0.80881)
13/20	0.65	(0.40781, 0.84609)
14/20	0.70	(0.45721, 0.88107)
15/20	0.75	(0.50895, 0.91343)
16/20	0.80	(0.56339, 0.94267)
17/20	0.85	(0.62107, 0.96793)
18/20	0.90	(0.68302, 0.98765)

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<b>Number of Subjects with Event</b> 19/20	<b>Incidence</b> 0.95	<b>95% Confidence Interval (Clopper Pearson)</b> (0.75127, 0.99873)
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### 3.1.7 Treatment Arms and Treatment Schema

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 below:

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

Cycle (28d)	Cycle Day	Arm A Dosing Schedule		Arm B Dosing Schedule		
		BI 1361849 (12 x i.d. each)	Durvalumab (i.v.)	BI 1361849 (12 x i.d. each)	Durvalumab (i.v.)	Tremelimumab* (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	X

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

#### 3.1.7.1 Dose Evaluation Phase

Each subject enrolled in the dose evaluation cohorts of the study will be evaluated for dose-limiting toxicities (DLTs), as defined in Section 3.1.9. Dose de-escalation and evaluation of RCD will be performed based on the available dose levels (see table below) and the respective rules for a standard 3 + 3 study design (see Schema below).

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. 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.

Dose Level Table for Evaluation Phase						
Dose Level	Arm A		Dose Level	Arm B*		
	BI 1361849	Durvalumab		BI 1361849	Durvalumab	Tremelimumab
-1	12 x 80 µg**	750 mg				
<b>Starting</b>	<b>12 x 80 µg**</b>	<b>1500 mg</b>	<b>Starting</b>	<b>12 x 80 µg**</b>	<b>RCD from Arm A</b>	<b>75 mg</b>

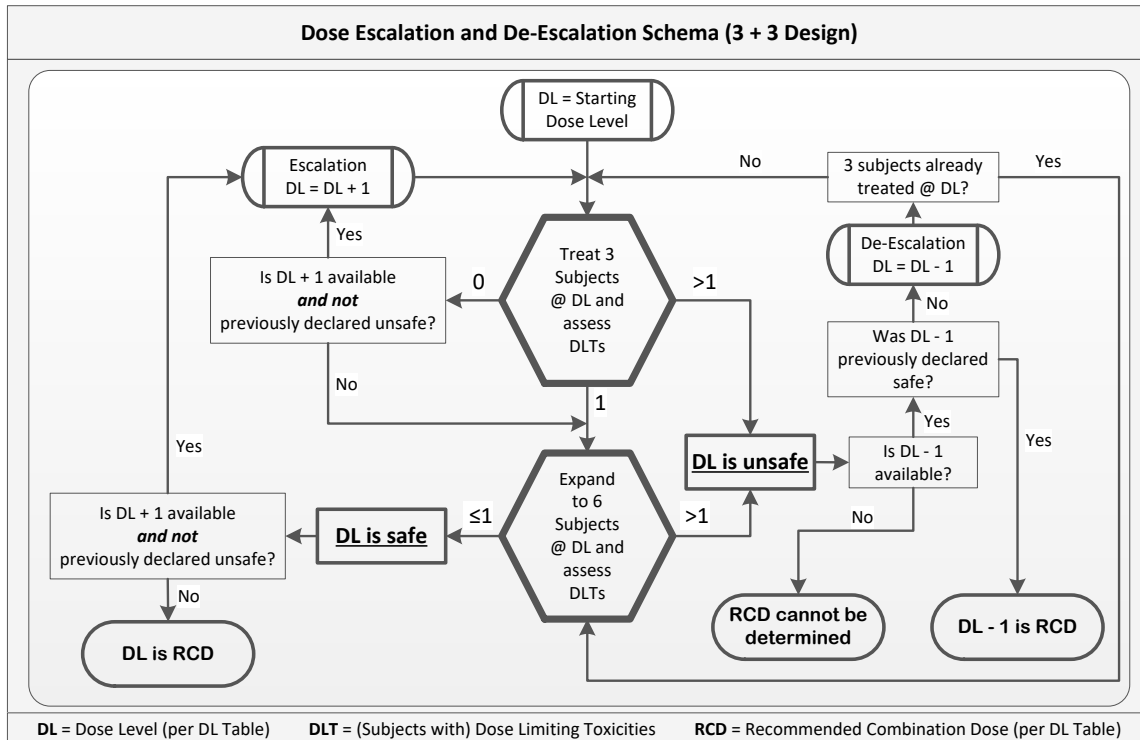
\*If there is unacceptable toxicity in Arm B, dosing will continue at RCD from Arm A, without tremelimumab.

\*\*BI 1361849 is a vaccine comprising six drug product components (F2408, F2409, F2410, F2624, F2625, and F2626), which are provided and administered separately; each component is administered twice, thus there are 12 administrations of 100 µL (80 µg) each.

**NOTE 1:** The Pharmajet Tropis® device will be used for the administration of the BI 1361849 components. Allowing for a filling volume of 100 µL (80 µg) and 2 administrations per component, the recommended dose per each of the 6 antigen components will be 160 µg (2 x 80 µg), for a total of 960 µg (12 administrations). See Section 6.3.3 for details on the administration of BI 1361849.

**NOTE 2:**

- **The durvalumab dose of 1500 mg Q4W is for subjects > 30 kg.** If a subject's body weight drops to ≤ 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 ≤ 30 kg (e.g., a 30 kg subject would receive a 600 mg dose; a 25 kg subject would receive a 500 mg dose; etc.). When the weight improves to >30 kg, the subject may return to fixed dosing of durvalumab 1500 mg.
- **When tremelimumab 75 mg Q4W (x4) is given with durvalumab 1500 mg Q4W,** if a subject's body weight drops to ≤ 30 kg while on the study, the subject will receive weight-based dosing for both drugs. For durvalumab, the weight-based dosing is described above; for tremelimumab, weight-based dosing equivalent to 1 mg/kg tremelimumab will be given as long as the body weight remains ≤ 30 kg (e.g., a 30 kg subject would receive a 30 mg dose; a 25 kg subject would receive a 25 mg dose; etc.). When the weight improves to >30 kg, the subject may return to fixed dosing of tremelimumab 75 mg and durvalumab 1500 mg.



**Figure 2. Dose Escalation and De-Escalation Schema**

Per Figure 2, the RCD for Arm A and Arm B is defined as the highest dose level at which no more than 1 of 6 subjects (i.e., < 33%) experience DLTs. The RCD cannot be determined if none of the predefined dose level cohorts fulfill that criterion. In such case, the arm will be discontinued without an expansion phase.

### 3.1.7.2 Dose Expansion Phase

In each arm for which an RCD is declared in the dose evaluation phase, the RCD dose level cohort will be expanded to 20 subjects (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)).

### 3.1.8 Dosing Adjustments, Delays, and Discontinuations

Individual subject dosing adjustments due to toxicity will be allowed/may be required in accordance with the “Dose Adjustment and Management Guidelines” for toxicity related to durvalumab / tremelimumab and BI 1361849, outlined in Section 8.3 and Section 8.4, respectively.

If a toxicity occurs that requires toxicity management in accordance with Sections 8.3 or 8.4, and the toxicity causing drug can be clearly identified, then the respective guideline should be followed. If the toxicity causing drug cannot be identified, then the more conservative guideline should be followed.

### 3.1.9 DLT and MTD/RCD for the Combination Therapy

MTDs will not be determined in this study. Instead, RCDs will be determined in the context of the predefined dose levels used during the dose evaluation phase as per Section 3.1.7.1.

DLTs will be observed over a period of the first 2 cycles of the combination therapy, including the pre-dose assessment for Cycle 3, defined as the **DLT Evaluation Period**. The decisions for dose evaluations, de-escalations and RCD, as described in Section 3.1.7.1 will primarily be based on the number of subjects with DLTs occurring during the DLT Evaluation Period. DLTs occurring outside the DLT Evaluation Period will also be evaluated and may impact such decisions.

DLTs are defined as any adverse events that are possibly, probably, or definitely related to the administration of durvalumab, tremelimumab, or BI 1361849 components, and fulfill any of the following criteria:

1. Any Grade  $\geq 3$  colitis, pneumonitis, neurological event or uveitis.
2. Any Grade 2 pneumonitis, neurological event or uveitis, with the following exception:
  - Grade 2 pneumonitis, neurological event or uveitis that downgrade to Grade  $\leq 1$  within 3 days after onset, whereby maximal supportive care, including systemic corticosteroids, is permitted.
3. Any *other* Grade  $\geq 3$  toxicity, with the following exceptions:
  - Grade 3 irAEs that downgrade to Grade  $\leq 2$  within 3 days, or to Grade  $\leq 1$  or baseline within 14 days after onset, whereby maximal supportive care, including systemic corticosteroids, is permitted.
  - Grade 3 endocrinopathy that becomes asymptomatic when managed with or without systemic corticosteroid therapy and/or hormone replacement therapy.
  - Grade 3 inflammatory reaction attributed to a local antitumor response (e.g., inflammatory reaction at sites of metastatic disease, lymph nodes, etc.).
  - Grade 3 fatigue for  $\leq 7$  days.
  - Grade 3 infusion-related reaction (first occurrence and in the absence of steroid prophylaxis) that resolves within 6 hours with appropriate clinical management.
  - Liver transaminase elevation  $\leq 8$  times ULN that downgrades to Grade  $\leq 2$  ( $\leq 5$  times ULN) within 7 days after onset, whereby maximal supportive care, including systemic corticosteroids, is permitted.
  - Total bilirubin  $\leq 5$  times ULN that downgrades to Grade  $\leq 2$  ( $\leq 3$  times ULN) within 7 days after onset, whereby maximal supportive care, including systemic corticosteroids, is permitted.
  - Grade  $\geq 3$  neutropenia that (1) is not associated with fever or systemic infection, (2) does not require medical intervention, and (3) improves to Grade 2 within 7 days.
  - Grade 3 and 4 lymphopenia.
  - Grade 3 thrombocytopenia that (1) is not associated with clinically significant bleeding, (2) does not require medical intervention, and (3) improves to Grade 2 within 7 days.
  - Isolated Grade 3 electrolyte abnormalities that are not associated with clinical signs or symptoms and are reversed with appropriate maximal medical intervention within 3 days.
  - Any pre-existing laboratory abnormality that deteriorates to Grade 3/4, but where the increment of deterioration is considered not clinically significant by both investigator and sponsor.
  - Grade 3 or 4 asymptomatic increases in amylase or lipase levels for which appropriate evaluation shows no clinical evidence of pancreatitis.

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

While rules for adjudicating DLTs are specified above, an AE that is Grade < 3 or listed as exempt above may also be defined as DLT after consultation with the sponsor and Investigators, based on the emerging safety profiles of durvalumab, tremelimumab, and BI 1361849. Likewise, subjects who become not evaluable for DLT, because they discontinued or interrupted treatment due to toxicities other than DLTs, may be counted as DLT subjects, if the toxicities cannot be managed in accordance with the dosing modifications described in Section 3.1.8.

Subjects who experience a DLT will be discontinued from study treatment and will enter the On Study and Post Study Follow-up (see Section 3.1.16). However, if it is in the best interest of the subject, the Investigator, subject and Sponsor may agree to continue treatment with BI 1361849.

### 3.1.10 Subject Withdrawal from Treatment or from Study

A subject will be **withdrawn from study treatment** for any of the following reasons:

1. Withdrawal of consent for further treatment
2. Pregnancy or intent to become pregnant
3. DLT at any time (see Section 3.1.9)
4. Progressive disease requiring alternative systemic treatment
5. Significant protocol violation or noncompliance that, in the opinion of the Investigator or Sponsor, warrants withdrawal
6. Development of intercurrent, non-cancer-related illnesses or complications that prevent either continuation of therapy or regular follow-up
7. Best medical interest of the subject (at the discretion of the Investigator)

Discontinuation from receiving study treatment does not mean that the subject is withdrawn from the study. If applicable, subjects who are withdrawn from study treatment should undergo the planned On Study Follow-up procedures (see Study Flowchart, Section 3.2), followed by the Post Study follow-up period (see Section 3.1.16).

A subject will be **withdrawn from the study** for the following reasons:

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

Section 7.2.6 provides additional details regarding documentation for early subject withdrawal from study treatment and early withdrawal from study.

See also Sections 8.3 and 8.4 for subject withdrawal from treatment due to necessary dosing interruptions or discontinuations.



### **3.1.10.1 Treatment beyond Progression**

Subjects meeting criteria for progression by irRECIST (Section 8.5) will be allowed to continue on therapy until confirmation of progression by irRECIST if the subject agrees and signs an appropriate informed consent form regarding continuation of treatment and as long as the following criteria are met at the discretion of the Investigator:

- a. Absence of symptoms and signs (including worsening of laboratory values) indicating disease progression;
- b. No significant decline in ECOG performance status;
- c. Absence of rapid progression of disease or of progressive tumor at critical anatomical sites (e.g., cord compression) requiring urgent alternative medical intervention.

See Section 8.5 for additional information regarding RECIST 1.1 and irRECIST.

### **3.1.11 Subject Evaluability and Subject Replacements**

In the *dose evaluation phase*, subjects are fully evaluable for DLT if they fulfill the criteria for the Per-Protocol Population for DLT Assessment (as defined in Section 4.1.2).

Subjects who are not fully evaluable for DLT per Section 4.1.2 will be replaced.

Subjects are fully evaluable for secondary endpoints of PFS rate and ORR, if they fulfill the criteria for the Per-Protocol Population for Clinical Efficacy (as defined in Section 4.2.2).

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

### **3.1.12 Optional Study Treatment Extension**

Treatment extension beyond 12 cycles is not planned at this time.

### **3.1.13 Interim Analysis**

Interim Safety Reviews will be performed to assess DLTs in the dose evaluation cohorts for determination of RCD (see Section 3.1.7.1). Interim analyses may be performed to analyze the 8- and 24-week endpoints.

### **3.1.14 Safety Monitoring and Study Stopping Rules**

In accordance with the Administrative, Legal, and Ethical Requirements section of the protocol (see Section 7), Safety Monitoring will be performed by an internal data safety monitoring panel, consisting of the Principal Investigators (and co-investigators as needed), the Sponsor's Medical Monitor/Clinical Advisor, and drug safety personnel from Medimmune/AstraZeneca and CureVac/Boehringer Ingelheim, providers of the study drugs. Additional investigators and staff, or additional Sponsor personnel and consultants, shall participate in reviews, if indicated. The safety monitoring panel will communicate by phone and/or email on a regular basis, and in particular, to review the safety of individual cohorts for the purpose of dose evaluation or de-escalation as per Section 3.1.7.1.

An Independent Data Monitoring Board will not be utilized for this open-label study.

The study will be suspended or possibly stopped prematurely for any of the following reasons:

1. A death that is unexpected and at least probably related to any of the study drugs.

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2. Severe anaphylactic reaction (i.e., with respiratory and cardiovascular failure) to any of the study drugs.
3. Any events that, in the judgment of the Medical Monitor, are deemed serious enough to warrant immediate review by the internal data safety monitoring panel. This may include any symptomatic and/or irreversible treatment-related Grade 4 pneumonitis, colitis, dermatitis, or hepatitis or any symptomatic treatment-related Grade  $\geq 3$  neurological toxicity or uveitis.
4. Any other safety finding assessed as related to study drug that, in the opinion of the internal data safety monitoring panel, contraindicates further dosing of study subjects.
5. Any interim findings that, in the opinion of the Investigators and the Sponsor, suggest that the study treatment has no clinical benefit for the subjects.

Study stopping rules may be applied to individual study arms, if the internal data safety monitoring panel concludes that the identified risk to one study arm does not carry over to another.

General criteria for premature trial termination are outlined in Section 7.2.7.

### 3.1.15 Duration of Study

Length of Study per subject:	Up to 15 months; 12 months for treatment and 3 months for On Study Follow-up.
Enrollment Period:	24 months
Length of Study:	39 months
Length of Survival Post Study Follow-up	5 years from initiation of treatment
	NOTE: Per Amendment 10.0, all post study follow-up will be discontinued as of 31 October 2021

### 3.1.16 On Study and Post Study Follow-up

All subjects, whether they complete the study as planned, discontinue treatment, or prematurely withdraw from the study as per Section 3.1.10, will be followed as per institutional guidelines in accordance with the usual standard of care principles.

Subjects who complete study treatment or discontinue treatment prematurely will enter an On Study Follow up, which will be conducted for 90 days (over 3 visits) after the last administration of study drug according to the flowchart in Section 3.2. Refer to Section 7.1.5 for information on recording AEs during the On Study Follow-up.

If the determination is made to remove a subject from treatment at a visit that coincides with the first visit of the On Study Follow-up Period, any assessments required in the first On Study Follow-up visit that are not covered as part of the last on-treatment visit (usually correlative labs) should be done as soon as possible. If these assessments cannot be done on the same day, the subject should be brought back in at the earliest opportunity. Any assessments or correlative samples required by both the last on-treatment visit and the first On Study Follow-up visit should not be repeated.

In addition to the On Study Follow-up, there will be a Post Study Follow-up, during which clinical outcomes data (dates of progression/relapse and survival) will be collected at least every 6 months for 5 years from initiation of treatment. If after 5 years there are a significant number of subjects who are still alive, there will be an option to extend this period.

The Post Study Follow-up will include a query to determine if there were any immune-related adverse events (irAEs) during the 90 days since the last administration of study drug.

NOTE: Per Amendment 10.0, all post study follow-up will be discontinued as of 31 October 2021.

For subjects who do not continue Post Study Follow-up at one of the study sites after the end of study, the Principal Investigators or the clinical team, under the supervision of the Principal Investigator, will obtain this data through review of outside records or communication with the subject or his/her physician.

### **3.1.16.1 End of Study Visit**

If a subject is **withdrawn from study** according to the criteria defined in Section 3.1.10, an End of Study visit must be conducted at the time of withdrawal. For subjects not yet in On Study Follow-up, this End of Study visit will be the first planned visit of the On Study Follow-up. For subjects already in On Study Follow-up, this End of Study visit will be the next planned visit of the On Study Follow-up. However, any procedures/assessments that were done within 7 days of the End of Study visit need not be repeated. 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.

After the End of Study Visit, the subject will proceed into Post Study Follow-up as described above, unless otherwise unable to do so (e.g., subject withdraws consent for all follow-up).

### 3.2 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 T <sub>3</sub> , Free T <sub>4</sub> , 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<sup>L</sup></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<sup>L</sup></b>													
Biopsy or FFPE slides for tumor microenvironment <sup>g</sup>	X					X							
						(one week after 3rd or 5th BI 1361849 injection)							
<b>Long Term Follow-up<sup>L</sup></b>													
Overall Survival													
Progression Free Survival													

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LUD2014-012-VAC Study Flowchart (cont.)	Treatment (each cycle = 4 weeks)										On Study Follow-up <sup>f,K</sup>			Post Study Follow-up <sup>L</sup>
	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	Every 6 months until 5 years post initiation of treatment
Study Week	25	27	28 <sup>J</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 irRECIST/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	
12-Lead ECG <sup>a</sup>				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 T <sub>3</sub> , Free T <sub>4</sub> , 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>	X				X			X			X		X	
<b>Specimens for Other Peripheral Blood Assays<sup>L</sup></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>J</sup>							X <sup>J</sup>	X			
Blood (PBMC and plasma) for flow cytometry and biological assays <sup>a,i,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>J</sup>							X <sup>J</sup>	X			
<b>Tumor Biopsy<sup>L</sup></b>														
Biopsy or FFPE slides for tumor microenvironment <sup>g</sup>											optional post- treatment			
<b>Long Term Follow-up<sup>L</sup></b>														
Overall Survival														X
Progression Free Survival														X

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### 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)
L- Per Amendment 10, Post Study Follow-up will be discontinued as of 31 October 2021; and all correlative testing will be discontinued, with the possible exception of PD-L1 expression and whole exome sequencing.

### 3.3 Additional Instructions for Blood Draws for PBMC Collection

NOTE: Per Amendment 9.1, this section will no longer be applicable. See Note in Section 4.3.1.2 regarding discontinuation of blood sample collection for immune monitoring.

Blood for PBMC collection (for correlative testing) is drawn on Cycle 1/Day 1, Cycle 2/Day 8, and Cycle 4/Day 8. Please refer to the Laboratory Manual for details regarding the higher volume (a maximum of 130 mL for PBMCs only) of blood that is required for these blood draws.

For subjects who weigh ≤ 55 kg at any of the above mentioned visits, please refer to the Laboratory Manual for specific details regarding the lower limits for the allowable volume of blood to be drawn.

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## 4 Study Objectives and Endpoints

<b>Primary Objective [Endpoints]</b>	<b>Dose Evaluation Phase:</b> <i>Safety and Tolerability</i> [CTCAE 4.03, including DLTs and RCD] <b>Expansion Phase:</b> <i>Safety and Tolerability</i> [CTCAE 4.03]
<b>Secondary Objectives [Endpoints]</b>	<b>Dose Evaluation and Expansion Phases (all subjects):</b> <i>Clinical Efficacy by irRECIST and RECIST 1.1</i> [PFS rate and ORR at 8 and 24 weeks, best overall response, DCR, DoR, OS]
<b>Exploratory Objectives [Endpoints]</b>	<b>Dose Evaluation and Expansion Phases (all subjects):</b> <i>Biologic Activity</i> [Effects on Tumor Microenvironment, Immune Responses]
DLT=Dose-limiting Toxicity; RCD=Recommended Combination Dose; ORR=Objective Response Rate; DCR=Disease Control Rate; DoR=Duration of Response; PFS=Progression-free Survival; OS=Overall Survival; CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events; RECIST = Response Evaluation Criteria in Solid Tumors; irRECIST=immune-related RECIST	

### 4.1 Safety and Tolerability

Assessment of safety and tolerability will be performed by the internal data safety monitoring panel on an ongoing basis, based on data review and regular conference calls.

#### 4.1.1 Endpoints and Assessment Methods

Clinical laboratory tests, vital signs and weight measurements, physical exams, ECG, ECOG performance status evaluation, imaging scans and any other medically indicated assessments, including subject interviews, will be performed (as detailed in Section 3.2) to detect new abnormalities and deteriorations of any pre-existing conditions. The investigator will evaluate any laboratory abnormalities for clinical significance, and clinically significant abnormalities will be recorded as adverse events. All treatment-emergent clinically significant abnormalities and deteriorations from time of signing the informed consent to the end of study visit will be recorded in the Case Report Forms as adverse events and graded according to the CTCAE Version 4.03. See further adverse event documentation and reporting requirements in Section 7.1.

For the dose evaluation phase, DLTs and RCDs will be assessed as per Sections 3.1.9 and 3.1.7.1, respectively.

#### 4.1.2 Subject Evaluation and Statistics

The **Per-Protocol (PP) Population for DLT Assessment** includes:

- All subjects who experience a DLT at any time during the DLT Evaluation Period (as defined in Section 3.1.9)
- 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 as well as respective safety assessments without major protocol violations during the DLT Evaluation Period (as defined in Section 3.1.9)

Refer to Section 3.1.11 for subject replacement.

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The **Safety Population** is defined as all subjects who receive at least one dose of any of the study drugs.

In the dose evaluation phase, for the primary endpoint of determining DLTs and the RCD, the analysis of safety and tolerability will be based on the **PP Population for DLT Assessment**.

In both phases (evaluation and expansion), the overall analysis of safety and tolerability will be based on the **Safety Population**.

Appropriate summaries of AEs, SAEs, laboratory data and vital signs data will be presented for the Safety Population overall and by cohort. Adverse events will be coded using the MedDRA dictionary. Incidences of treatment-emergent adverse events (TEAE, those events that started after dosing or worsened in severity after dosing) will be presented overall and by maximum severity and relationship to study drugs.

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 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. Additionally, for each continuous hematology and chemistry parameter, descriptive statistics will be presented for the changes from baseline to each post-treatment assessment time point. Descriptive statistics will be presented for the changes in vital signs from baseline to each post-treatment assessment time point.

## **4.2 Clinical Efficacy**

### **4.2.1 Endpoints and Assessment Methods**

Clinical efficacy will be assessed by irRECIST and RECIST 1.1 (see Section 8.5), measuring progression free survival (PFS) rate and objective response rate (ORR) at 8 and 24 weeks based on disease assessments at the scheduled Weeks 9 and 25 visits, as well as best overall response, disease control rate (DCR), duration of response (DoR), and overall survival (OS). Tumor disease assessments will be made at a minimum of every 8 weeks on study. See the sections below for additional details.

For the primary analysis, all efficacy endpoints will be assessed at the completion of the On Study Follow-up or completion of 12 cycles of therapy for the last subject.

PFS and OS will be updated at yearly intervals during the Post Study Follow-up and can be provided as addendums to the final report.

NOTE: Per Amendment 10.0, all post study follow-up will be discontinued as of 31 October 2021.

#### **4.2.1.1 Objective Response Rate (ORR)**

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. Subjects who drop out prior to meeting the responder criteria for ORR will be considered as non-responders.



#### **4.2.1.2 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. Subjects who drop out prior to meeting the responder criteria for DCR will be considered as non-responders.

#### **4.2.1.3 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.

#### **4.2.1.4 Progression-free Survival (PFS)**

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. 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 or death will be censored at the date of last response assessment prior to discontinuation or withdrawal.

#### **4.2.1.5 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. 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.

### **4.2.2 Subject Evaluation and Statistics**

The Intent-To-Treat (ITT) Population is defined as all subjects who receive at least one dose of any of the study drugs.

The **Per-Protocol (PP) Population for 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, without major protocol violations.

All efficacy analyses will be based on both ITT and PP populations for each cohort.

Tumor Response will be summarized and analyzed descriptively for each arm and analysis population. A 95% Confidence Interval based on 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.

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PFS and 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.

## 4.3 Biological Activity

### 4.3.1 Endpoints and Assessment Methods

Samples for exploratory assessment of correlative immunologic response will be collected according to the Study Flowchart in Section 3.2. Correlative data will be obtained to assess the effects of the regimen on the tumor microenvironment and biological activity in blood. The exploratory assessments will help to determine whether protein expression, mutational burden, gene expression, soluble PD-L1 or immune cell profiling can be associated with clinical benefit or resistance to combination therapy.

For BI 1361849, cellular and humoral immune response to vaccine target antigens and additional antigens can be assessed to detect signs of antigen spreading (e.g. based on a panel of selected additional NSCLC antigens). NOTE: Per Amendment 9.1, some assessments will no longer be applicable. See Note in Section 4.3.1.2 regarding discontinuation of blood sample collection for immune monitoring.

NOTE: Per Amendment 10.0, all correlative testing will be discontinued, with the possible exception of PD-L1 expression and whole exome sequencing.

#### 4.3.1.1 Tumor Microenvironment

##### 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 5.1, #2).
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 tissue 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.
4. If possible and as determined by the 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.

A minimum of 25 slides (5 µm formalin-fixed, paraffin embedded (FFPE)) will be requested from the biopsy specimens to evaluate PD-L1 expression as assessed by immunohistochemistry, neoantigen signature and immune biomarker expression in tissue, and to assess the correlation

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of these evaluations with clinical response as well as changes in profiling associated with resistance. Analyses may include the following:

- Mutational burden, gene expression profiling, and immune profiling from before therapy
- Immune markers of response and resistance.

Remaining core biopsies will be formalin-fixed and paraffin-embedded as per institutional standards for further evaluation with immunohistochemistry (IHC) or tumor DNA/RNA extraction for microarrays sequencing or nanostring.

#### **4.3.1.1.1 Immunohistochemistry**

Quantitative immunofluorescence will be used to evaluate multiple immune biomarkers simultaneously in FFPE archival tissue or in biopsy samples, as available.

PD-L1 has been examined in studies of PD-1/PD-L1 inhibitors with mixed results in terms of prevalence and impact on clinical benefit from anti-PD-1/PD-L1 therapy, although this has been attributed to variability in different assays and in different definitions of positivity. It is unknown how the introduction of the vaccine may alter PD-L1 expression and the immune microenvironment and whether that may influence outcomes to combination therapy.

In this study, a pre-treatment biopsy will allow the evaluation of PD-L1 and other immune biomarkers to determine correlation with response to combination therapy. In addition to PD-L1 immunohistochemistry, CD3, CD4 and CD8 immunostaining will be performed to evaluate the degree of immune infiltrate in tumor specimens, as available. Finally, other markers of immune suppression (FoxP3 to stain T regulatory cells, TIM-3, Lag-3 and others) will be evaluated, as feasible.

#### **4.3.1.1.2 DNA sequencing**

Whole-exome sequencing (WES) targeted next-gen sequencing will be performed, as feasible. The targeted sequencing (Oncopanel) is a cancer genomic assay, which is used to detect somatic mutations, copy number variations, and structural variants in tumor DNA that surveys exonic DNA sequences of 275 cancer genes and 91 introns across 30 genes for rearrangement detection.

#### **4.3.1.1.3 Gene expression**

Inflammatory or immune-related gene expression signatures may serve as predictors of clinical benefit and will be evaluated in biopsy samples, as available.

#### **4.3.1.1.4 Immune profiling**

Immune profiling in tumor biopsies will be done to evaluate correlates of response and resistance. FNA samples will also be used, if available.

#### **4.3.1.1.5 Cytokines & Chemokines**

Cytokine and chemokine environment will be determined on protein level in biopsy samples, as available.

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#### 4.3.1.2 Biological Activity in Blood Samples

Blood samples will be collected according to Section 3.2 and may be used for the evaluation of PBMC profile by flow cytometry, cytokine profile, soluble PD-L1 analysis, and exosomal profiling.

**NOTE: Per Amendment 9.1, the following sample collections will be discontinued:**

1. Blood for PaxGene RNA and DNA
2. Blood (PBMC and plasma) for flow cytometry and biological assays
3. Blood for humoral responses and other biomarkers

Blood collection for exosomal profiling will continue as indicated in Section 3.2. Refer to Section 8.1, Amendment 9.1, for rationale.

##### 4.3.1.2.1 Immune Monitoring for Responses to BI 1361849 Vaccine

NOTE: Per Amendment 9.1, these assessments will no longer be applicable. See Note in Section 4.3.1.2 regarding discontinuation of blood sample collection for immune monitoring.

There is a great potential for mutual benefits by combining passive and active cancer vaccine strategies to improve clinical efficiency.

Assays for antigen-specific immune responses encompass, for example, intracellular cytokine staining (ICS) and ELISpot for detection of antigen-specific T-cells by their functional capacity to produce various effector cytokines in response to the vaccine (NY-ESO-1, MageC1, MageC2, 5T4, Survivin, Muc-1) and/or non-vaccine tumor antigens (e.g. MAGE-A3). Humoral responses against vaccine antigens are routinely analyzed by immunoassay techniques such as ELISA and can easily be extended to non-vaccine antigens (antigen arrays). If possible, the immune analyses will also include a detailed phenotypic characterization of, e.g., circulating T-cell subsets, activation and differentiation states of immune cells, and checkpoint marker expression. Furthermore, B cells, NK cells, DCs, monocytes and the peripheral immune-suppressive environment mediated by myeloid derived suppressor cells (MDSCs) and regulatory T-cells are evaluated. Measurements of systemic lymphoid repertoire, e.g., T-cell receptor sequencing and immune-related transcriptional changes, cytokine and chemokine profiling are additional approaches of interest suitable to identify potential blood-derived biomarkers.

Blood samples will be collected according to Section 3.2 for the assessment of humoral and cellular immune responses and additional biomarker screenings. A sample for white blood cell (WBC) count must also be available for the day of the blood samples for immunomonitoring.

Immunomonitoring blood sampling is scheduled at  $7 \pm 2$  days after preceding vaccine administration. In the event that, prior to a planned blood sampling time point, the immediately preceding vaccination has to be delayed or omitted, the blood sampling has to be delayed in the same fashion to ensure that the blood sample has been obtained within  $7 \pm 2$  days (5-9 day time frame) after the immediately preceding vaccination. In the event that the vaccination had to be omitted, blood sampling should occur after the next subsequent vaccine administration.

See Section 8.4 for maximum allowable delays for vaccine administrations.

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The primary aim of these specific immunomonitoring assessments is to trace the immunological effects of the vaccine in regard to *antigen-specific immune responses*, which may be more pronounced under conditions of simultaneous checkpoint inhibition.

Specifically, the aims are:

- to compare vaccine-induced antigen-specific responses, under conditions of simultaneous checkpoint inhibition, with immune-reactivity under checkpoint-blockade alone (cellular and humoral immune responses against vaccine encoded antigens may increase to some extent in context of a general, non-specific immune activation by checkpoint inhibition).
- to generate hypotheses with regards to combination therapy-related biomarker candidates based on comparative immune analysis within a comprehensive data set.

#### 4.3.2 Subject Evaluation and Statistics

NOTE: Per Amendment 9.1, some assessments will no longer be applicable. See Note in Section 4.3.1.2 regarding discontinuation of blood sample collection for immune monitoring.

NOTE: Per Amendment 10.0, all correlative testing will be discontinued, with the possible exception of PD-L1 expression and whole exome sequencing.

For each arm of the study, only subjects who receive at least 1 dose of the respective drugs and who provide the baseline and at least 1 on-treatment sample (if applicable) will be evaluated. As these analyses represent exploratory evaluations of potential biomarkers of response or resistance to therapy, descriptive statistics will be used to describe findings and potential relationships to outcomes to therapy. Criteria for assay positivity (changes compared to baseline) of individual assays will be described in the statistical analysis plan (SAP).

The exploratory pharmacodynamic assessment of the immunologic changes in the tumor microenvironment will include the correlation between clinical activity and the expression level of PD-L1 and tumor-infiltrating lymphocyte (TILs) changes in biopsy samples, as available. The association between response and PD-L1 expression within each arm will be assessed descriptively. Confidence intervals for the overall odds ratio and the odds ratio within each arm will be presented. The association between response and TILs changes (increase, decrease, or no change) will be evaluated similarly.

Subjects are considered fully evaluable for immune response if the following criteria are met:

- Subjects have received at least 4 treatments with BI 1361849 including all vaccine antigens according to protocol
- Samples from baseline and both post-baseline sample 7 days ( $\pm 2$  days) after treatment are available
- Subjects have not received any prohibited concomitant treatments (see Section 5.3.1) within 21 days before on-treatment blood sampling. Immunosuppressive medication that has been taken by subjects 2 to 3 weeks prior to randomization will be documented so that any potential influence on baseline values may be evaluated.
- Sufficient amount and quality of blood sample and isolated PBMCs is available to fully perform and analyze, in accordance with respective assay SOPs, at least the ICS assay, as a measure for antigen-specific cellular immune response

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- The analysis of antigen-specific cell-mediated immune response by ICS is required to include all BI 1361849 antigens including baseline values to be fully evaluable.

All other exploratory results will be summarized descriptively.

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## 5 Subject Eligibility

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

### 5.1 Inclusion Criteria

Eligible subjects ***must fulfill*** all of the following criteria:

1.	<p>Histologic confirmation of metastatic NSCLC.            For subjects with known EGFR or ALK/ROS-1 mutations, prior therapy must have included an EGFR tyrosine kinase inhibitor or ALK/ROS-1 inhibitor, respectively.            Subjects may have had 1 prior line of anti-PD-1/PD-L1 therapy. Subjects who received prior anti-PD-1/PD-L1 therapy must have progressed during or after treatment, but not prior to Week 12 of treatment.</p>																
2.	<p>Measurable disease according to RECIST 1.1, defined as <math>\geq 1</math> lesion that can be accurately measured in at least 1 dimension (longest diameter to be recorded for non-lymph node lesions, shortest diameter to be recorded for lymph node lesions). Each lesion must be <math>\geq 10</math> mm when measured by CT, MRI, or caliper measurement by clinical examination or <math>\geq 20</math> mm when measured by chest x-ray.             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).</p>																
3.	<p>Willing to undergo a pre-treatment biopsy, or if not feasible, availability of archival (diagnostic) specimens.</p>																
4.	<p>Subjects with treated brain metastases must have been treated with surgery and/or radiation therapy <math>\geq 21</math> days pre-study and must be clinically stable with no requirement for steroids.</p>																
5.	<p>Laboratory parameters for vital functions should be in the normal range. Laboratory abnormalities that are not clinically significant are generally permitted, except for the following laboratory parameters, which must be within the ranges specified, regardless of clinical significance:</p> <table border="1" data-bbox="394 1367 1279 1766"> <tr> <td data-bbox="394 1367 683 1402">Hemoglobin</td> <td data-bbox="683 1367 1279 1402"><math>\geq 9</math> g/dL</td> </tr> <tr> <td data-bbox="394 1402 683 1438">Neutrophil count</td> <td data-bbox="683 1402 1279 1438"><math>\geq 1.5 \times 10^9/L</math></td> </tr> <tr> <td data-bbox="394 1438 683 1507">Lymphocyte count</td> <td data-bbox="683 1438 1279 1507"><math>\geq 400</math> cells/<math>\mu L</math>. (See Section 3.3 for instructions for blood draws for PBMC collection.)</td> </tr> <tr> <td data-bbox="394 1507 683 1543">Platelet count</td> <td data-bbox="683 1507 1279 1543"><math>\geq 100,000/mm^3</math></td> </tr> <tr> <td data-bbox="394 1543 683 1612">Serum creatinine, or Creatinine Clearance</td> <td data-bbox="683 1543 1279 1612"><math>\leq 1.5 \times</math> Institutional Upper Limit of Normal (ULN), or <math>&gt; 40</math> mL/min (by Cockcroft-Gault formula)</td> </tr> <tr> <td data-bbox="394 1612 683 1703">Serum bilirubin</td> <td data-bbox="683 1612 1279 1703"><math>\leq 1.5 \times</math> ULN (except for subjects with Gilbert's syndrome who will be allowed after consultation with their physician)</td> </tr> <tr> <td data-bbox="394 1703 683 1738">AST/ALT</td> <td data-bbox="683 1703 1279 1738"><math>\leq 2.5 \times</math> ULN</td> </tr> <tr> <td data-bbox="394 1738 683 1766">Alkaline phosphatase</td> <td data-bbox="683 1738 1279 1766"><math>\leq 2.5 \times</math> ULN</td> </tr> </table>	Hemoglobin	$\geq 9$ g/dL	Neutrophil count	$\geq 1.5 \times 10^9/L$	Lymphocyte count	$\geq 400$ cells/ $\mu L$ . (See Section 3.3 for instructions for blood draws for PBMC collection.)	Platelet count	$\geq 100,000/mm^3$	Serum creatinine, or Creatinine Clearance	$\leq 1.5 \times$ Institutional Upper Limit of Normal (ULN), or $> 40$ mL/min (by Cockcroft-Gault formula)	Serum bilirubin	$\leq 1.5 \times$ ULN (except for subjects with Gilbert's syndrome who will be allowed after consultation with their physician)	AST/ALT	$\leq 2.5 \times$ ULN	Alkaline phosphatase	$\leq 2.5 \times$ ULN
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Alkaline phosphatase	$\leq 2.5 \times$ ULN																
6.	<p>ECOG Performance Status <math>\leq 2</math>.</p>																

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7.	Age ≥ 18 years.
8.	Able and willing to provide valid written informed consent.
9.	Subject is willing and able to comply with the protocol for the duration of the study including undergoing treatment and scheduled visits and examinations including follow up.
10.	Body weight > 30 kg.

## 5.2 Exclusion Criteria

Subjects **may not** enter the study if they fulfill any of the following criteria:

1.	Treatment with an investigational agent within 4 weeks of starting treatment, and any prior drug-related toxicity (except alopecia) should have recovered to Grade 1 or less.
2.	Prior treatment with anti-CTLA-4 therapy.
3.	Active, suspected or prior documented autoimmune disease or inflammatory disorders (including but not restricted to inflammatory bowel disease [e.g., colitis or Crohn's disease], celiac disease, diverticulitis [with the exception of diverticulosis], Sarcoidosis syndrome, Wegner's granulomatosis with polyangiitis, Hashimoto's thyroiditis, rheumatoid arthritis, systemic lupus, Graves' disease, rheumatoid arthritis, hypophysitis, uveitis, scleroderma and its variants, multiple sclerosis, myasthenia gravis, etc. ). Vitiligo, alopecia, residual hypothyroidism (e.g., following Hashimoto syndrome) due to autoimmune condition only requiring hormone replacement, psoriasis or any chronic skin condition not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted. Subjects without active disease in the last 5 years may be included but only after consultation with the study physician. Subjects with celiac disease controlled by diet alone may also be included.
4.	Subjects with clinically significant cardiovascular disease, including: <ul style="list-style-type: none"> <li>a. New York Heart Association (NYHA) Class II or higher congestive heart failure.</li> <li>b. Myocardial infarction, unstable angina, cerebrovascular accident or transient ischemic attack within 6 months of Day 1.</li> <li>c. Clinically significant supraventricular or ventricular arrhythmia.</li> <li>d. QTcF ≥ 450 ms (male) or QTcF ≥ 470 ms (female).</li> <li>e. Clinically uncontrolled hypertension.</li> </ul>
5.	History of pneumonitis or interstitial lung disease, or any unresolved immune-related adverse events following prior therapy.
6.	Major surgery within 4 weeks of starting treatment (or scheduled for surgery during the projected course of the study).
7.	Women of child bearing potential who are pregnant as evidenced by positive serum pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) or nursing.
8.	<b>Female subjects of childbearing potential</b> who are sexually active with a non-sterilized male partner must use at least one <u>highly effective</u> method of contraception (see table below) from the time of screening and must agree to continue using such precautions for 90 days after the last dose of durvalumab or for 6 months after the last dose of tremelimumab (whichever is longer). Non-sterilized male partners of a female subject

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must use male condoms plus spermicide throughout this period. Cessation of birth control after this point should be discussed with a responsible physician. Not engaging in sexual activity for the total duration of the drug treatment and the drug washout period is an acceptable practice; however, periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception.

Female subjects should refrain from breastfeeding throughout the period described above.

Females of childbearing potential are defined as those who are not surgically sterile (i.e., bilateral tubal ligation, bilateral oophorectomy, or complete hysterectomy) or post-menopausal.

Females will be considered post-menopausal if they have been amenorrheic for 12 months without an alternative medical cause. The following age-specific requirements apply:

- Females <50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatments and if they have luteinizing hormone and follicle-stimulating hormone levels in the post-menopausal range for the institution or underwent surgical sterilization (bilateral oophorectomy or hysterectomy).
- Females ≥50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of all exogenous hormonal treatments, had radiation-induced menopause with last menses >1 year ago, had chemotherapy-induced menopause with last menses >1 year ago, or underwent surgical sterilization (bilateral oophorectomy, bilateral salpingectomy or hysterectomy).

**Non-sterilized male subjects** who are sexually active with a female partner of childbearing potential must use male condoms plus spermicide from screening through 90 days after last dose of durvalumab or through 6 months after the last dose of tremelimumab (whichever is longer). Female partners of childbearing potential of a male subject must use a highly effective method of contraception (see table below) throughout this period. Cessation of birth control after this point should be discussed with a responsible physician. Not engaging in sexual activity for the total duration of the trial and the drug washout period is an acceptable practice; however, periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception.

Male subjects should refrain from sperm donation throughout the period described above.

Highly effective methods of contraception are described in the table below. A highly effective method of contraception is defined as one that results in a low failure rate (i.e. less than 1% per year) when used consistently and correctly. Note that some contraception methods are not considered highly effective (e.g. male or female condom with or without spermicide; female cap, diaphragm, or sponge with or without spermicide; non-copper containing intrauterine device; progestogen-only oral hormonal

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	<p>contraceptive pills where inhibition of ovulation is not the primary mode of action [excluding Cerazette/desogestrel which is considered highly effective]; and triphasic combined oral contraceptive pills).</p> <p>Acceptable highly effective methods of contraception are described in the following table:</p> <table border="1"> <thead> <tr> <th colspan="2">Highly Effective<sup>a</sup> Methods of Contraception</th> </tr> <tr> <th>Barrier/Intrauterine Methods</th> <th>Hormonal Methods</th> </tr> </thead> <tbody> <tr> <td> <ul style="list-style-type: none"> <li>Copper T intrauterine device</li> <li>Levonorgestrel-releasing intrauterine system (e.g., Mirena<sup>®</sup>)<sup>b</sup></li> </ul> </td> <td> <ul style="list-style-type: none"> <li>“Implants”: Etonogestrel-releasing implants: e.g., Implanon<sup>®</sup> or Norplan<sup>®</sup></li> <li>“Intravaginal Devices”: Ethinylestradiol/etonogestrel-releasing intravaginal devices: e.g., NuvaRing<sup>®</sup></li> <li>“Injection”: Medroxyprogesterone injection: e.g., Depo-Provera<sup>®</sup></li> <li>“Combined Pill”: Normal and low dose combined oral contraceptive pill</li> <li>“Patch”: Norelgestromin/ethinylestradiol-releasing transdermal system: e.g., Ortho Evra<sup>®</sup></li> <li>“Minipill<sup>c</sup>”: Progesterone based oral contraceptive pill using desogestrel: e.g., Cerazette<sup>®</sup></li> </ul> </td> </tr> <tr> <td colspan="2"> <p>a - Highly effective (i.e. failure rate of &lt;1% per year)</p> <p>b - This is also considered a hormonal method</p> <p>c - Cerazette<sup>®</sup> is currently the only highly effective progesterone based pill.</p> </td> </tr> </tbody> </table>	Highly Effective <sup>a</sup> Methods of Contraception		Barrier/Intrauterine Methods	Hormonal Methods	<ul style="list-style-type: none"> <li>Copper T intrauterine device</li> <li>Levonorgestrel-releasing intrauterine system (e.g., Mirena<sup>®</sup>)<sup>b</sup></li> </ul>	<ul style="list-style-type: none"> <li>“Implants”: Etonogestrel-releasing implants: e.g., Implanon<sup>®</sup> or Norplan<sup>®</sup></li> <li>“Intravaginal Devices”: Ethinylestradiol/etonogestrel-releasing intravaginal devices: e.g., NuvaRing<sup>®</sup></li> <li>“Injection”: Medroxyprogesterone injection: e.g., Depo-Provera<sup>®</sup></li> <li>“Combined Pill”: Normal and low dose combined oral contraceptive pill</li> <li>“Patch”: Norelgestromin/ethinylestradiol-releasing transdermal system: e.g., Ortho Evra<sup>®</sup></li> <li>“Minipill<sup>c</sup>”: Progesterone based oral contraceptive pill using desogestrel: e.g., Cerazette<sup>®</sup></li> </ul>	<p>a - Highly effective (i.e. failure rate of &lt;1% per year)</p> <p>b - This is also considered a hormonal method</p> <p>c - Cerazette<sup>®</sup> is currently the only highly effective progesterone based pill.</p>	
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9.	Subjects who are immunosuppressed, including those with known immunodeficiency.								
10.	Active infection including tuberculosis (clinical evaluation that includes clinical history, physical examination and radiographic findings, and TB testing in line with local practice), hepatitis B (known positive HBV surface antigen (HBsAg) result and/ or HBV DNA), hepatitis C (defined as presence of HCV RNA), or human immunodeficiency virus (positive HIV 1/2 antibodies) and/or known HIV carrier. Subjects with a past or resolved HBV infection (defined as the presence of hepatitis B core antibody [anti-HBc] and absence of HBsAg) are eligible. Subjects positive for hepatitis C (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV RNA.								
11.	History of severe allergic reactions to any unknown allergens or components of the study drugs (see specific exclusions for BI 1361849 below).								
12.	Uncontrolled intercurrent illness, including but not limited to, ongoing or active infection, bleeding disorders, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, interstitial lung disease, or serious chronic gastrointestinal conditions associated with diarrhea.								
13.	Mental impairment or social situations that may compromise compliance with the requirements of the study or compromise the ability of the subject to give written informed consent.								
14.	Lack of availability for immunological and clinical follow-up assessment.								
15.	<ul style="list-style-type: none"> <li>Allergy to any components of BI 1361849 protamine sulfate (e.g. allergy to protamine-containing insulins), or fish allergy, or prior vasectomy (as it may</li> </ul>								

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	<p>increase the risk of protamine allergy), or known Type I allergy to beta-lactam antibiotics.</p> <ul style="list-style-type: none"> <li>• Skin disease (e.g., psoriasis) that may prevent intradermal administration of the vaccine into the target areas.</li> <li>• Prior cancer vaccine treatment or allogeneic bone marrow transplantation.</li> <li>• Any previous vaccination or immunotherapy (including any treatments that have immunostimulatory properties such as mistletoe extract) within 2 weeks prior to Day 1</li> <li>• History of splenectomy.</li> <li>• Requirement for chronic immunosuppressive treatment including daily systemic steroid doses of <math>\geq 10</math> mg prednisone equivalent per day.</li> <li>• Any severe systemic infection which continued until 2 weeks prior to Day 1.</li> </ul>
16.	Any condition that, in the clinical judgment of the treating physician, is likely to interfere with the interpretability of the data or prevent the subject from complying with any aspect of the protocol or that may put the subject at unacceptable risk.
17.	Subjects must not donate blood while on study and for at least 90 days following the last durvalumab treatment or for 6 months after the last dose of tremelimumab (whichever is longer).
18.	History of allogeneic organ transplant.
19.	History of leptomeningeal carcinomatosis.
20.	Active or prior malignancy except for history of other prior malignancy treated with curative intent which, in the opinion of the treating investigator and the Sponsor, has minimal risk of interfering with safety or efficacy endpoints of the study.

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## 5.3 Restrictions on Concomitant Therapies

### 5.3.1 Non-Permitted Concomitant Therapies

Subject **may not** receive the following concomitant therapies during the study:

1.	Systemic treatment with corticosteroids (greater than Prednisone 10 mg daily or equivalent) or other immunosuppressive treatments (e.g., methotrexate, chloroquine, azathioprine). See Section 5.3.2 for exceptions. [Wash-out period: 2 weeks prior to Day 1.]
2.	Other cancer therapy (e.g., drug, non-palliative radiation, or immunotherapy). [Wash-out period: 4 weeks or 5 half-lives (whichever is shorter) prior to Day 1 (6 weeks for nitrosoureas)].
3.	Live/attenuated vaccines 1 month prior to Day 1 and for at least 6 months after the last dose of treatment.
4.	Sunitinib within 3 months after the last dose of tremelimumab.
5.	Drugs with laxative properties and herbal or natural remedies for constipation should generally be avoided through 90 days post last dose of tremelimumab because of the potential for exacerbation of diarrhea, but, for example, opiate-induced constipation may be treated with laxatives at the Investigator's discretion.
6.	<ul style="list-style-type: none"><li>• Systemic immunosuppressive drugs including systemic steroid doses of <math>\geq 10</math> mg prednisone equivalent per day are prohibited. In case immunosuppressive therapy, or treatment with steroids <math>\geq 10</math> mg prednisone equivalent per day <math>&gt;3</math> days, is clinically mandated due to an intercurrent illness, it should be agreed upon with the Sponsor whether continuation of BI 1361849 can be allowed, and the possible risks to continue the vaccine treatment during the intercurrent illness should be judiciously weighed against the potential benefit of continued treatment.</li><li>• Any treatments that have immunostimulatory properties including mistletoe extract are prohibited and should be discontinued at least 2 weeks prior to Day 1.</li><li>• No local anesthetics for the vaccination procedure are allowed.</li></ul>
The wash-out period prior to Day 1 of the study for all non-permitted drugs should be at least 1 week, unless stated otherwise above.	

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### 5.3.2 Permitted Concomitant Therapies

Subject **may** receive the following concomitant therapies during the study:

1.	Inhaled or oral steroids for treating mild to moderate asthma or allergies, or topical steroids for localized (< 5% of body surface area) dermatitis, not to exceed 10 mg/day prednisone or bioequivalent corticosteroid.
2.	Physiologic replacement of glucocorticoids as maintenance therapy for adrenal insufficiency. Standard doses of hydrocortisone for maintenance therapy are up to 10–20 mg/m <sup>2</sup> /day divided 2–4 times per day. For a subject with a body surface area (BSA) of 1.73 m <sup>2</sup> , this translates to a total dose of up to 34.6 mg of hydrocortisone per day. The equivalent dose of dexamethasone is up to 1.2 mg per day. Some subjects may additionally receive mineralocorticoid-replacement maintenance therapy with fludrocortisone. The maintenance dose of fludrocortisone for this indication is 0.05–0.1 mg/day.
3.	NSAIDs, acetylsalicylic acid, and specific COX-2 inhibitors.
4.	Antihistamines and other non-steroidal anti-allergy medication.
5.	Hormone or hormone-related anti-cancer therapy.
6.	At the discretion of the Investigator, any drug or non-drug therapy necessary to treat any condition arising during the study, including high-dose corticosteroids to treat immune-mediated adverse reactions. Subjects should receive full supportive care, including transfusions of blood and blood products, and treatment with antibiotics, anti-emetics, anti-diarrheal, and analgesics, and other care as deemed appropriate, and in accordance with their institutional guidelines. Use of anticoagulants such as warfarin is permitted; however, caution should be exercised and additional international normalized ratio (INR) monitoring is recommended.
All prescription and nonprescription drugs and herbal supplements must be recorded in the concomitant medications section of the case report form, listing generic (preferably) or brand name, indication, dose, route, and dates of administration. All non-drug therapies must be recorded in the respective sections of the case report form.	

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## 6 Study Drug Preparation and Administration

All study drugs are supplied by the Sponsor (see Section 7.2.8). Commercially available 0.9% (w/v) saline or 5% (w/v) dextrose will be supplied by each site. BI 1361849 requires reconstitution with Ringer's lactate solution (see Section 6.3.2).

On the days when both tremelimumab and durvalumab are to be administered, the durvalumab infusion will start at least 60 minutes after the end of the tremelimumab infusion. The BI 1361849 injections will start at least 60 minutes after the end of the durvalumab infusion is completed when injections and infusions occur on the same day.

See Section 6.5 for monitoring of subjects during tremelimumab, durvalumab and BI 1361849 dose administrations.

### 6.1 Durvalumab (MEDI 4736)

#### 6.1.1 Study Drug Information

Manufacturer	MedImmune		
Expiration/Retest Date	<i>Expiration/retest dates are documented in the QA Disposition of Investigational Medicinal Product (IMP) Report.</i>		
Container Description	<i>Type:</i> Single use vial	<i>Material:</i> clear glass	<i>Size:</i> 10 mL
Formulation	Liquid solution containing 500 mg durvalumab per vial. The solution contains 50 mg/mL durvalumab, 26 mM histidine/histidine-HCl, 275 mM trehalose dihydrate, 0.02% (weight/volume [w/v]) polysorbate 80, at pH 6.0.		
Active Ingredient Content	<i>Mass/Weight:</i> 500 mg	<i>Volume:</i> 10mL	<i>Concentration:</i> 50 mg/mL
Storage Conditions	2°C to 8°C (36°F to 46°F) Do not freeze		
Labeling	Product name, lot number, and storage conditions		

#### 6.1.2 Durvalumab Investigational Product Inspection

Each vial of durvalumab selected for dose preparation should be inspected. If there are any defects noted with the investigational product (IP), the Investigator and Sponsor should be notified immediately. See Section 7.2.8 for additional details.

#### 6.1.3 Durvalumab Preparation

The dose of durvalumab for administration must be prepared by the IP manager or designated personnel using aseptic technique. No incompatibilities between durvalumab and polyvinylchloride or polyolefin copolymers have been observed.

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Dose Calculation:

Subjects will receive a fixed dose of durvalumab:

- **Starting dose:1500 mg Q4W**

NOTE: the durvalumab dose of 1500 mg Q4W is for subjects > 30 kg. If a subject's body weight drops to ≤ 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 ≤ 30 kg (e.g., a 30 kg subject would receive a 600 mg dose; a 25 kg subject would receive a 500 mg dose; etc.). When the weight improves to >30 kg, the subject may return to fixed dosing of durvalumab 1500 mg.

- **Dose de-escalation: 750 mg Q4W**

The volume of durvalumab (in mL) to be added to the IV bag is calculated as follows:

Volume of Durvalumab (mL)	=	Dose level (mg)	÷	Durvalumab Concentration (nominal 50 mg/mL)
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Dose Preparation:

Durvalumab will be administered using an IV bag containing 0.9% (w/v) saline or 5% (w/v) dextrose and delivered through an IV administration set with a 0.2 or 0.22 µm in-line filter. The final durvalumab concentration after dilution in the bag must be 1 mg/mL to 15 mg/mL. The calculated volume of durvalumab is added to the IV bag, and the bag is mixed by gentle inversion to ensure homogeneity of the dose in the bag.

*Example:* For a 1500 mg dose (for subjects > 30 kg in weight), 30 mL of durvalumab may be diluted in a 250 mL IV bag, and the bag is mixed by gentle inversion.

Durvalumab does not contain preservatives; any unused portion must be discarded.

### 6.1.4 Durvalumab Administration

Following preparation of the dose, durvalumab will be administered according to the following guidelines:

- A physician must be present at the site or immediately available to respond to emergencies during all administrations of investigational products. Fully functional resuscitation facilities should be available.
- Prior to the start of the infusion, the IV bag contents must be at room temperature to avoid an infusion reaction due to the administration of the solution at low temperatures.
- Durvalumab must not be administered via IV push or bolus, but as an IV infusion.
- Durvalumab solution should not be infused with other solutions or medications.
- Durvalumab must be administered at room temperature by controlled infusion into a peripheral vein or central line.
- The entire contents of the IV bag should be administered as an IV infusion over approximately 60 (± 5) minutes (a 0.2- or 0.22-µm in-line filter is required). **An infusion of less than 55 minutes is considered a deviation.**

- After the contents of the IV bag are fully administered, the IV line will be flushed with a volume of IV diluent equal to the priming volume of the infusion set used. Alternatively, the infusion will be completed according to institutional policy to ensure the full dose is administered; documentation is required if the line was not flushed.
- The total time between needle puncture of the durvalumab vial to start of administration should not exceed 4 hours at room temperature or 24 hours at 2°C to 8°C (36°F to 46°F). Standard infusion time is 60 ± 5 minutes (an infusion of less than 55 minutes is considered a deviation). However, if there are interruptions during infusion, the total allowed infusion time should not exceed 8 hours. In the event that either preparation time or infusion time exceeds the time limits, a new dose must be prepared from new vials.
- The date, start time, interruption, and completion time of durvalumab administration must be recorded in the source documents.
- Subjects will be monitored before, during and after infusion with assessment of vital signs according to Section 6.5.
- See Section 8.3.1 for guidelines for infusion-related reactions.

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## 6.2 Tremelimumab

### 6.2.1 Study Drug Information

Manufacturer	MedImmune		
Expiration/Retest Date	<i>Expiration/retest dates are documented in the QA Disposition of IMP Report.</i>		
Container Description	<i>Type:</i> Single use vial	<i>Material:</i> Clear glass	<i>Size:</i> 20 mL
Formulation	Liquid solution containing 400 mg tremelimumab per vial. The solution contains 20 mg/mL tremelimumab, 20 mM histidine/histidine hydrochloride, 222 mM trehalose dihydrate, 0.27 mM disodium edetate dihydrate, and 0.02% weight/volume (w/v) polysorbate 80; it has a pH of 5.5.		
Active Ingredient Content	<i>Mass/Weight:</i> 400 mg	<i>Volume:</i> 20 mL	<i>Concentration:</i> 20 mg/mL
Storage Conditions	2°C to 8°C (36°F to 46°F) Do not freeze		
Labeling	Product name, lot number, and storage conditions		

Tremelimumab is also available in a 25 mg/vial format; the concentration remains 20 mg/mL.

Manufacturer	MedImmune		
Expiration/Retest Date	<i>Expiration/retest dates are documented on the QA Disposition of Investigational Medicinal Product (IMP) Report.</i>		
Container Description	<i>Type:</i> Single-use vial	<i>Material:</i> Clear glass	<i>Size:</i> 2 mL
Formulation	Liquid solution containing 25 mg tremelimumab per vial. The solution contains 20 mg/mL tremelimumab, 20 mM histidine/histidine hydrochloride, 222 mM trehalose dihydrate, 0.27 mM disodium edetate dihydrate, and 0.02% weight/volume (w/v) polysorbate 80; it has a pH of 5.5.		
Active Ingredient Content	<i>Mass/Weight:</i> 25 mg/vial	<i>Volume:</i> 1.25 mL/vial	<i>Concentration:</i> 20 mg/mL
Storage Conditions	+2°C to +8°C (36°F to 46°F). Do not freeze.		
Labeling	Product name, lot number, and storage conditions		

### 6.2.2 Tremelimumab Investigational Product Inspection

Each vial of tremelimumab selected for dose preparation should be inspected. If there are any defects noted with the investigational product (IP), the Investigator and Sponsor should be notified immediately. See Section 7.2.8 for additional details.

### 6.2.3 Tremelimumab Preparation

The dose of tremelimumab for administration must be prepared by the IP manager or designated personnel using aseptic technique. No incompatibilities between tremelimumab and polyvinylchloride or polyolefin have been observed.

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Dose Calculation:

Subjects will receive a fixed dose of tremelimumab: 75 mg Q4W (x4). When tremelimumab is given with durvalumab 1500 mg Q4W, if a subject’s body weight drops to ≤ 30 kg while on the study, the subject will receive weight-based dosing for both drugs. For durvalumab, the weight-based dosing is described in Section 6.1.3; for tremelimumab, weight-based dosing equivalent to 1 mg/kg tremelimumab will be given as long as the body weight remains ≤ 30 kg (e.g., a 30 kg subject would receive a 30 mg dose; a 25 kg subject would receive a 25 mg dose; etc.). When the weight improves to >30 kg, the subject may return to fixed dosing of tremelimumab 75 mg and durvalumab 1500 mg.

The volume of tremelimumab (in mL) to be added to the IV bag is calculated as follows:

Tremelimumab Dose (mL)	=	dose level (mg)	÷	Tremelimumab concentration (20 mg/mL)
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Dose Preparation:

Tremelimumab will be administered using an IV bag containing 0.9% (w/v) saline or 5% (w/v) dextrose and delivered through an IV administration set with a 0.2- or 0.22-µm in-line filter. The final concentration of tremelimumab after dilution in the bag must be between 0.10 mg/mL and 10 mg/mL. The calculated volume of tremelimumab is added to the IV bag, and the bag is mixed by gentle inversion to ensure homogeneity of the dose in the bag.

*Example:* The volume of tremelimumab required for 75 mg dose is 3.75 mL and may be administered using a 250 ml bag.

The corresponding volume of investigational product should be rounded according to institutional practice. For example, (for a 75 mg dose of tremelimumab), if the institutional practice is to round the volume to the nearest tenth mL, 3.75 mL would be rounded to 3.8 mL, which would be the volume of tremelimumab added to the bag; the bag is then mixed by gentle inversion.

Tremelimumab does not contain preservatives; any unused portion must be discarded.

**6.2.4 Tremelimumab Administration**

Following preparation of the dose, tremelimumab will be administered according to the following guidelines:

- A physician must be present at the site or immediately available to respond to emergencies during all administrations of investigational product. Fully functional resuscitation facilities should be available.
- Prior to the start of the infusion, the IV bag contents must be at room temperature to avoid an infusion reaction due to the administration of the solution at low temperatures.
- Tremelimumab must not be administered via IV push or bolus, but as an IV infusion.
- Tremelimumab solution should not be infused with other solutions or medications.

- Tremelimumab must be administered at room temperature by controlled infusion into a peripheral vein or central line.
- The entire contents of the IV bag should be administered as an IV infusion over approximately 60 ( $\pm$  5) minutes (a 0.2- or 0.22- $\mu$ m in-line filter is required).
- After the contents of the IV bag are fully administered, the IV line will be flushed with a volume of IV diluent equal to the priming volume of the infusion set used. Alternatively, the infusion will be completed according to institutional policy to ensure the full dose is administered; documentation is required if the line was not flushed.
- The total time from needle puncture of the tremelimumab vial to the start of administration should not exceed 4 hours at room temperature or 24 hours at 2 to 8°C (36°F to 46°F). Standard infusion time is 60  $\pm$  5 minutes (an infusion of less than 55 minutes is considered a deviation). However, if there are interruptions during infusion, the total allowed infusion time should not exceed 8 hours. In the event that either preparation time or infusion time exceeds the time limits, a new dose must be prepared from new vials.
- The date, start time, interruption, and completion time of tremelimumab administration must be recorded in the source documents.
- Subjects' vital signs will be monitored before, during and after infusion as indicated in Section 6.5.
- See Section 8.3.1 for guidelines for infusion-related reactions.

## 6.3 BI 1361849

### 6.3.1 Study Drug Information

The BI 1361849 drug product is a vaccine comprising six drug product components. The drug products are derived from drug substances which are antigen-encoding mRNAs (R1857, R1861, R1863, R1859, R1855, R2312). The drug substance components are formulated individually to produce the drug product components of BI 1361849 (F2408, F2409, F2410, F2624, F2625, F2626). These are subsequently lyophilized for the purpose of storage and prior to intradermal injection reconstituted in a specific Ringer's Lactate injection solution (see note in Section 6.3.2). Throughout the process, individual components are kept separate. The various names and abbreviations used to refer to the BI 1361849 components are summarized in the table below.

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Names and abbreviations of the six drug product components comprising BI 1361849					
Drug Product Component	Drug Substance Component	mRNA Sequence Length	Name	Official abbreviation	Common abbreviation
F2408	R2312	1885 bases	Mucin 1, cell surface associated	MUC1	MUC1
F2409	R1859	646 bases	BIRC5 baculoviral IAP repeat-containing 5	BIRC5	survivin
F2410	R1857	760 bases	Cancer/testis antigen 1B	CTAG1B	NY-ESO-1
F2624	R1855	1480 bases	Trophoblast glycoprotein	TPBG	5T4
F2625	R1861	1339 bases	Melanoma antigen family C, 2	MAGEC2	MAGE-C2
F2626	R1863	1813 bases	Melanoma antigen family C, 1	MAGEC1	MAGE-C1

### 6.3.2 Preparation of Components of BI 1361849

BI 1361849 comprises 6 drug product components. Each box of BI 1361849 contains one vial of each of the components, which are formulated as a sterile lyophilizate in a 2 mL glass vial with rubber stopper closure. Each vial will be reconstituted with 600 µL (0.6 mL) of Ringer's Lactate solution to provide a solution containing the drug substance at a concentration of 0.8 g/L (equivalent to 0.48 mg per vial and 0.16 mg (80 µg) per injection of 100 µL).

NOTE: The Ringer's Lactate solution (from Fresenius Kabi) used for reconstitution will be provided to the sites; the solution contains the following ingredients in the respective concentrations: Sodium Chloride 103 mM, Potassium Chloride 5.5 mM, Calcium Chloride dehydrate 1.8 mM, Sodium lactate 28 mM. Other Ringer's Lactate solutions may contain Mg, which may seriously impair the vaccine, according to CureVac.

Based on results of stability studies of drug product components F2408, F2409, F2410, F2624, F2625, and F2626, the product is stable at room temperature for the shelf life indicated on the product labeling.

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The drug product should be administered as soon as possible after reconstitution. Based on in-house data and for reasons of sterility it is recommended to use reconstituted product within 4 hours.

NOTE (per Amendment 7):

The first lot for this study (Lot E142087-008L002) expired at the end of May 2019. During testing of the replacement lots, one of the components (F2409) precipitated at 3 hours after reconstitution in Ringer Lactate Solution (the precipitate was identified as protamine and RNA). Therefore, F2409 must be used within 2 hours of reconstitution. It is recommended that all of the components should be administered within the 2-hour timeframe, if possible. If this is not feasible, the 4-hour in use period is still applicable to the other 5 components.

### 6.3.3 BI 1361849 Administration

The Pharmajet Tropis® device will be used for the administration of the BI 1361849 components. Allowing for a filling volume of 100 µL (80 µg) and 2 administrations per component, the recommended dose per each of the 6 antigen components will be 160 µg (2 x 80 µg), for a total of 960 µg (12 administrations). Directions for use of the Pharmajet Tropis® device will be provided separately.

Each of the 6 components of BI 1361849 will be administered on the same day as 2 intradermal injections of 100 µL each, for a total of 12 administrations distributed across 4 different lymph node targeting areas (i.e., the inner parts of the right and left upper arm and the right and left thigh). The 2 administrations of each of the 6 components are applied into the thigh and the upper arm, respectively, of the same side of the body, alternating body sides for the first 5 vaccinations. Thereafter the components will be injected at the same sites for the rest of the trial period. See detailed application scheme below:

Drug product component			F2408 A	F2409 B	F2410 C	F2624 D	F2625 E	F2626 F
Day 1/Week 1 and Day 1 / Week 3	Upper arm	left	x	x	x			
		right				x	x	x
	Thigh	left	x	x	x			
		right				x	x	x
Day 1 / Week 2 and Day 1 / Week 5	Upper arm	left				x	x	x
		right	x	x	x			
	Thigh	left				x	x	x
		right	x	x	x			
all subsequent vaccinations	Upper arm	left	x	x	x			
		right				x	x	x
	Thigh	left	x	x	x			
		right				x	x	x

A single dose of BI 1361849 represents a total dose of 960 µg mRNA at each vaccination time point, as follows:

- 2 administrations of F2624 coding for 5T4;
- 2 administrations of F2410 coding for NY-ESO-1;
- 2 administrations of F2409 coding for survivin;

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- 2 administrations of F2626 coding for MAGE-C1;
- 2 administrations of F2625 coding for MAGE-C2;
- 2 administrations of F2408 coding for MUC1.

There are no specific requirements concerning the day or time when the vaccine is to be administered. Injections should occur after any blood drawings on the day of the visits, and injections will start at least 60 minutes after the infusion of durvalumab is completed when injections and infusions occur on the same day.

See Section 6.5.2 for monitoring of subjects post vaccinations.

There are defined maximal time windows in case a vaccine cannot be given within the scheduled administrative time window (e.g. due to AEs; see Section 8.4). If the vaccine cannot be given within this maximal time frame, it is to be omitted.

## 6.4 Estimated Study Requirements

<i>Drug</i>	<i>Required Quantity (vials)</i>
<b>Durvalumab</b> (500 mg / 10 ml vials)	2400
<b>Tremelimumab</b> (400 mg / 20 ml vials)	128
<b>BI 1361849</b> (2 X 100 µL from 1 vial each of: F2408, F2409, F2410, F2624, F2625, and F2626); the 6 components will be provided in a box containing 1 vial of each component. Ringer's lactate solution will also be provided (one bottle per subject per dosing day).	1000 boxes containing 6 vials (1 vial for each of the 6 components)

## 6.5 Monitoring of Tremelimumab, Durvalumab, and BI 1361849 Dose Administration

### 6.5.1 Monitoring for Tremelimumab and Durvalumab Administration

Subjects will be monitored before, during and after tremelimumab and durvalumab infusion with assessment of vital signs according to the table below:

Vital Signs Assessment on Study Drug Administration Days					
Drug	Pre Dose	During Infusion	End of Infusion (± 5 minutes)	30 (± 5) Minutes Post Infusion	60 (± 5) Minutes Post Infusion
<b>Tremelimumab</b>	X	Every 30 (± 5) minutes	X		
<b>Durvalumab</b>	X	Every 15 (± 5) minutes	X	X	x

Note: When durvalumab and tremelimumab are to be administered on the same day, durvalumab infusion will start at least 60 minutes after the end of tremelimumab infusion even

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though vital signs assessment is not required during the entire 60 minute period post tremelimumab.

If a subject tolerates treatment well for the first 4 doses of durvalumab (i.e., no infusion reactions), subsequent infusions in that subject can be monitored according to the table below. A longer duration of observation after the end of infusion can be used if the Investigator deems it clinically necessary.

Vital Signs Assessment on Study Drug Administration Days (after first 4 doses)				
Drug	Pre Dose	During Infusion	End of Infusion ( $\pm 5$ minutes)	15 ( $\pm 5$ ) Minutes Post Infusion
Durvalumab	X	Every 30 ( $\pm 5$ ) minutes	X	X

### 6.5.2 Monitoring for BI 1361849 Administration

For the first and second vaccination visits, subjects will be monitored for 2 hours with assessment of vital signs at 30 ( $\pm 5$ ), 60 ( $\pm 5$ ) and 120 ( $\pm 5$ ) minutes post completion of injections. For all subsequent vaccinations, subjects will be monitored for 1 hour with assessment of vital signs at 30 ( $\pm 5$ ) and 60 ( $\pm 5$ ) minutes post completion of injections, provided no undue occurrences were observed during the initial vaccinations. Note: on dosing days when durvalumab vital assessments do not precede the BI 1361849 dose, pre-dose vital assessments must be done for BI 1361849.

## 6.6 Drug Overdose Management

There are no known antidotes available for durvalumab, tremelimumab, or BI 1361849. Any overdoses with these drugs should be managed symptomatically. An overdose is defined as a subject receiving any dose in excess of that specified in this protocol by  $> 10\%$ . All such overdoses must be reported, with or without associated AEs/SAEs, according to Section 7.1.2.2.

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## 7 Administrative, Legal and Ethical Requirements

### 7.1 Documentation and Reporting of Adverse Events

#### 7.1.1 Definitions

An **Adverse Event (AE)** is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

N.B.: The definition above, provided for in the GCP-ICH Guideline E6, is being extended for the purpose of LICR studies to include any events, intercurrent diseases and accidents observed while the patient/subject is on study, i.e., during the actual treatment period, as well as during drug-free, pre- and post-treatment periods, under placebo or in a reference group receiving drug or non-drug therapy or no treatment.

A **Serious Adverse Event (SAE)** is any untoward medical occurrence that:

1. Results in death,
2. Is life-threatening<sup>A</sup>,
3. Requires inpatient hospitalization or prolongation of existing hospitalization,
4. Results in persistent or significant disability or incapacity,
5. Is a congenital anomaly / birth defect or
6. Is another medically important condition<sup>B</sup>.

A The term “life-threatening” in the definition of “serious” refers to an event in which the patient/subject is at risk of death at the time of the event; it does not refer to an event, which hypothetically might have caused death if it were more severe.

B Medically important conditions that may not result in death, be immediately life-threatening or require hospitalization may be considered as SAE when, based upon appropriate medical judgment, they may jeopardize the patient/subject or may require intervention to prevent one of the outcomes listed in the definition above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

N.B.: The term “severe” is often used to describe the intensity (severity) of an event (such as: mild, moderate, or severe, e.g., pain). The event itself may be of relatively minor medical significance (such as severe headache). This is not the same as “serious”, which is based on patient/event outcome or action criteria usually associated with events that pose a threat to patient’s life or vital functions. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

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## 7.1.2 Additional Expedited Reporting Requirements for this Study

For the purpose of this study, the following events must be reported by phone or email to the Sponsor within 24 hours of knowledge of the event (see Section 7.1.6 for Sponsor contact information) **and may result in submission of an SAE based on certain criteria outlined below:**

- Pregnancy
- Overdose (as defined in Section 6.6)
- Hepatic Function Abnormality (as defined in Section 7.1.8)
- New Cancers
- Deaths

### 7.1.2.1 Pregnancy

#### 7.1.2.1.1 Maternal Exposure

Female subjects should avoid becoming pregnant and breastfeeding during the study and for 90 days after the last dose of durvalumab or for 6 months after the last dose of tremelimumab, whichever is longer (see Section 5.2, #8).

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

Pregnancy itself is not regarded as an AE unless there is a suspicion that the drug under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities or birth defects and spontaneous miscarriages should be reported and handled as SAEs (see Section 7.1.6). Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) should be followed up and documented even if the subject was discontinued from the study.

If any pregnancy occurs in the course of the study, the Investigator or other site personnel should inform the Sponsor within 1 day, i.e., immediately, but **no later than 24 hours** of when he or she becomes aware of it.

The Sponsor will work with the Investigator to ensure that all relevant information is provided within 1 to 5 calendar days for SAEs and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

#### 7.1.2.1.2 Paternal Exposure

Male subjects should refrain from fathering a child or donating sperm during the study and for 90 days after the last dose of durvalumab or for 6 months after the last dose of tremelimumab, whichever is longer (see Section 5.2, #8).

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

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Where a report of pregnancy is received, prior to obtaining information about the pregnancy, the Investigator must obtain the consent of the subject's partner. Therefore, the local study team should adopt the generic ICF template in line with local procedures and submit it to the relevant Ethics Committees (ECs)/Institutional Review Boards (IRBs) prior to use.

#### **7.1.2.2 Overdose**

Any overdose (as defined in Section 6.6) of a study subject, with or without associated AEs/SAEs, is required to be reported within **24 hours of knowledge of the event to the Sponsor**. If the overdose results in an AE, the AE must also be recorded as an AE according to Section 7.1.5. Overdose does not automatically make an AE serious, but if the consequences of the overdose are serious, for example death or hospitalization, the event is serious and must be recorded and reported as an SAE according to Section 7.1.6. There is currently no specific treatment in the event of an overdose of the study drugs. The Investigator will use clinical judgment to treat any overdose. See Section 6.6 for additional details.

#### **7.1.2.3 Hepatic Function Abnormality**

Hepatic function abnormality (as defined in Section 7.1.8 in a study subject, with or without associated clinical manifestations, is required to be reported as "hepatic function abnormal" **within 24 hours of knowledge of the event** to the Sponsor, unless a definitive underlying diagnosis for the abnormality (e.g., cholelithiasis or bile duct obstruction) that is unrelated to investigational product has been confirmed.

- If the definitive underlying diagnosis for the abnormality has been established and is unrelated to investigational product, the decision to continue dosing of the study subject will be based on the clinical judgment of the investigator.
- If no definitive underlying diagnosis for the abnormality is established, dosing of the study subject must be interrupted immediately. Follow-up investigations and inquiries must be initiated by the investigational site without delay.

Each reported event of hepatic function abnormality will be followed by the Investigator and evaluated by the Sponsor and MedImmune/AstraZeneca.

#### **7.1.2.4 New Cancers**

The development of a new cancer should be regarded as an SAE. New primary cancers are those that are not the primary reason for the administration of the IP and have been identified after the subject's inclusion in this study.

#### **7.1.2.5 Deaths**

All deaths that occur during the study treatment period, or within the protocol-defined follow-up period (On Study Follow-up) after the administration of the last dose of study drug, must be reported as follows:

- Death clearly resulting from disease progression should be reported to the Study Monitor/Physician at the next monitoring visit and should be documented in the eCRF. It should be reported as an SAE if it meets SAE reporting criteria per Section 7.1.6.

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- Where death is not due (or not clearly due) to progression of the disease under study, the AE causing the death must be reported to the Study Monitor/Physician as an SAE within 24 hours. It should also be documented in the eCRF.
- The report should contain a comment regarding the co involvement of PD, if appropriate, and should assign main and contributory causes of death.
- Deaths with an unknown cause should always be reported as an SAE. It should also be documented in the eCRF.
- A post mortem may be helpful in the assessment of the cause of death, and if performed, a copy of the post-mortem results should be forwarded to LICR within the usual timeframes.

Deaths occurring after the protocol-defined safety follow-up period after the administration of the last dose of study drug should be documented only in the Post Study Follow-up eCRF form. If the death occurred as a result of an event that started after the defined safety follow-up period and the event is considered to be due to a late onset toxicity to study drug, then it should also be reported as an SAE.

LICR and AstraZeneca retain the right to request additional information for any subject with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

### **7.1.3 Severity of an Adverse Event**

The severity of all serious and non-serious adverse events should be assessed according to the National Cancer Institute CTCAE Scale (Version 4.03).

### **7.1.4 Relationship of Adverse Events to Study Drug**

The relationship of all serious and non-serious adverse events to the investigational agent(s) will be determined by the Investigator on the basis of their clinical judgment, using one of the following terms (in accordance with NCI Guideline “Expedited Adverse Event Reporting Requirements for NCI Investigational Agents”, NCI Cancer Therapy Evaluation Program, January 2001):

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)

**N.B.:** When making the assessment on causality, it should be taken into consideration that immune-therapeutic agents have the potential to cause very late and/or permanent effects on the immune system, i.e., a causal relationship could exist despite a lack of apparent temporal relationship. Information provided in the IB and/or in “Background” of this protocol may support these evaluations.

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### 7.1.5 General Reporting Requirements

All serious and non-serious adverse events must be documented in the source records and on the respective section of the CRF, regardless of severity or the assumption of a causal relationship. The documentation includes: dates of onset and resolution, severity, seriousness, study drug intervention, treatment and outcome, as well as, the causal relationship between the event and the study drug in accordance with Section 7.1.4. This documentation is required for all AEs that occur:

- a. from the date of signing the informed consent, and
- b. until the off-study date or 90 days after the last administration of study drug, whichever is longer, or until a new treatment is initiated (see Section 3.1.10 for subjects who begin other anti-cancer treatment).

Immune Related Adverse Events (irAEs) will be collected from the time of informed consent through 90 days after the last dose of the last study treatment (regardless of initiation of another therapy).

### 7.1.6 Expedited Serious Adverse Event (SAE) Reporting Requirements

**In addition to the General Reporting Requirements specified in Section 7.1.5, all events meeting the criteria for an SAE per Section 7.1.1, irrespective of suspected causation, must be reported by the Investigator to the Sponsor’s Drug Safety Contact (primarily) or, alternatively, to the Primary Sponsor Contact, within 24 hours of becoming aware of the event (see contact information below). SAEs should be reported via the Medidata RAVE data capture system (which utilizes “Safety Gateway”), using the respective Adverse Event and Safety Case Summary eCRFs. This includes any deaths that occur after the off-study date, but within 30 days of last study drug administration. In the event that the SAE cannot be reported via Medidata RAVE, the SAE should be reported using the “Initial Serious Adverse Event Report Form,” provided by the Sponsor.**

**Note: If an SAE cannot be reported via Medidata RAVE or the “Initial Serious Adverse Event Report Form” within 24 hours of becoming aware of the event, the Sponsor’s Drug Safety Contact (primarily) or, alternatively, the Primary Sponsor Contact, must be contacted by phone or email within 24 hours of becoming aware of the event. In this case, the phone or email notification can then be followed up through Medidata RAVE or an “Initial Serious Adverse Event Report Form” within one working day of the event.**

If the “Initial Serious Adverse Event Report Form” is being used, the expedited reports should be directed by fax or e-mail to the Drug Safety Contact (primarily) or, alternatively, the Primary Sponsor Contact. Studies utilizing Medidata RAVE (and the “Safety Gateway”), built into the eCRF, and respective SAE reporting procedures, do not require reporting by fax or email. Questions related to Medidata RAVE and “Safety Gateway” procedures should be directed to the Drug Safety Contact or Primary Sponsor Contact (see table below for contact information).

**In urgent cases, pre-notification via phone or informal e-mail should be considered.**

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<p><i>Drug Safety Contact:</i>  ██████████  Senior Manager, Drug Safety  Clinical Trials Management  Ludwig Institute for Cancer Research  666 3rd Ave, 28th Floor  New York, New York 10017  ██████████</p>	<p><i>Primary Sponsor Contact:</i>  ██████████  Director  Clinical Trials Management  Ludwig Institute for Cancer Research  666 3rd Ave, 28th Floor  New York, New York 10017  ██████████</p>
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Serious adverse events must also be reported by the Principal Investigator to the respective Institutional Review Board after being assigned a serious adverse event tracking number by the Sponsor. Institutional Review Boards may have specific rules on which Adverse Events need to be reported expeditiously, as well as, the time frames for such reporting.

SAE Reports will be evaluated by the Sponsor’s Medical Monitor. Regulatory authorities and other investigators, as well as institutional and corporate partners, will be informed by the Sponsor as required by ICH guidelines, laws and regulations in the countries where the investigational agent is being administered. In particular, SAEs that are unexpected and for which a causal relationship with the study drug cannot be ruled out, will be reported by the Sponsor within 15 calendar days; if they are life-threatening or fatal, they will be reported within 7 calendar days.

Serious adverse event reporting to AstraZeneca/Medimmune and to Boehringer Ingelheim is described in separate respective agreements.

**7.1.7 Serious Adverse Event (SAE) Follow-up Requirements**

Subjects experiencing SAEs should be followed closely until the condition resolves or stabilizes, and every effort should be made to clarify the underlying cause. Follow-up information related to SAEs must be submitted to the Sponsor as soon as relevant data are available.

**7.1.8 Adverse Events of Special Interest (AESIs)**

An adverse event of special interest (AESI) is one of scientific and medical interest specific to the understanding of the investigational products and may require close monitoring and rapid communication by the Investigator to the Sponsor. An AESI may be serious or non-serious. The rapid recording of all AEs, including AESIs, allows ongoing surveillance of these events in order to characterize and understand them in association with the use of the investigational products.

AESIs for durvalumab and tremelimumab include but are not limited to events with a potential inflammatory or immune-mediated mechanism and which may require more frequent monitoring and/or interventions such as steroids, immunosuppressants and/or hormone replacement therapy. These AESIs are being closely monitored in clinical studies with durvalumab monotherapy and combination therapy. An immune-related adverse event (irAE) is defined as an adverse event that is associated with drug exposure and is consistent with an immune-mediated mechanism of action and where there is no clear alternate aetiology.

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

If the Investigator has any questions in regards to an AE being an irAE, the Investigator should promptly contact the Medical Monitor.

**If an AESI also meets SAE criteria, the event will be reported as an SAE per Section 7.1.6.**

**AESIs observed with durvalumab and tremelimumab and those considered AESIs for the purpose of this study are listed below.** Further information on these AESIs (e.g. presenting symptoms) can be found in the current versions of the durvalumab (MEDI4736) and tremelimumab Investigator's Brochures. Guidelines for the management of subjects experiencing toxicities for durvalumab and tremelimumab can be found in Section 8.3 and in the following Medimmune guideline: ***“Medimmune’s Dosing Modification and Toxicity Management Guidelines for Immune-mediated, Infusion Related, and Non Immune-mediated Reactions (MEDI4736 (durvalumab) Monotherapy or Combination therapy with Tremelimumab or Tremelimumab monotherapy).”***

- **Diarrhea/Colitis and intestinal perforation**  
Diarrhea and colitis are the most commonly observed treatment-emergent AEs following dosing with study medications. In rare cases, colon perforation may occur that requires surgery (colectomy) or can lead to a fatal outcome, if not properly managed.
- **Pneumonitis/Interstitial lung disease (ILD)**  
Adverse events of pneumonitis have been observed with anti-PD-1, and anti-PD-L1 antibodies (see IB). Initial work-up should include high-resolution CT scan, ruling out infection, and pulse oximetry. Typically, pulmonary consultation is required.
- **Hepatic Function Abnormality (Hepatitis / transaminase increases)**  
Increased transaminases have been reported during treatment with anti-PD-L1/anti-PD-1 antibodies (see IB). Inflammatory hepatitis has been reported in 3% to 9% of subjects treated with anti-CTLA-4 monoclonal antibodies (e.g., ipilimumab). The clinical manifestations of ipilimumab-treated subjects included general weakness, fatigue, nausea and/or mild fever and increased liver function tests such as AST, ALT, alkaline phosphatase, and/or total bilirubin. Hepatic function abnormality is defined as any increase in ALT or AST to greater than 3 × ULN and concurrent increase in total bilirubin to be greater than 2 × ULN. Concurrent findings are those that derive from a single blood draw or from separate blood draws taken within 8 days of each other. Follow-up investigations and inquiries will be initiated promptly by the investigational site to determine whether the findings are reproducible and/or whether there is objective evidence that clearly supports causation by a concurrent or pre-existing disease (e.g., cholelithiasis and bile duct obstruction with distended gallbladder) or an agent other than the investigational product. Cases where a subject shows an AST **or** ALT ≥ 3 x ULN **or** total bilirubin ≥ 2 x ULN may need to be reported as SAEs. These cases should be reported as SAEs if, after evaluation they meet the criteria for a Hy's Law case or if any of the individual liver test parameters fulfill any of the SAE criteria.

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C O N F I D E N T I A L

- **Neurotoxicity (Neuropathy / neuromuscular toxicity)**  
Immune-mediated nervous system events include encephalitis, peripheral motor and sensory neuropathies, Guillain-Barré, and myasthenia gravis.
- **Endocrine Disorders**  
Immune-mediated endocrinopathies include hypo- and hyper-thyroidism, adrenal insufficiency, hypophysitis/hypopituitarism, and Type 1 diabetes mellitus.  
**Type 1 diabetes mellitus:** For subjects with suspected diabetes mellitus, Investigators should obtain an endocrinology consult and institute appropriate management which may include the administration of insulin.
- **Dermatitis/Rash**  
Prompt treatment with steroids (topical or systemic based on severity) is important as per current established toxicity management guidelines.
- **Nephritis and increases in serum creatinine**  
A consult with a Nephrologist should be done as well as monitoring for signs and symptoms that may be related to changes in renal function (e.g., routine urinalysis, elevated serum BUN and creatinine, decreased creatinine clearance, electrolyte imbalance, decrease in urine output, proteinuria, etc.). Subjects should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, infections, etc.). Steroids should be considered in the absence of clear alternative etiology even for low grade events (Grade 2), in order to prevent potential progression to higher grade event.
- **Pancreatic Disorders**  
Immune-mediated pancreatitis includes autoimmune pancreatitis or labs suggestive of pancreatitis (increased serum lipase, increased serum amylase).
- **Myocarditis**  
Myocarditis, a rare, but severe immune-mediated adverse event, presents with signs/symptoms such as decreased ejection fraction, arrhythmias, in particular occurrences of atrioventricular block. For patients with suspected myocarditis, investigators should obtain a cardiology consult and institute full diagnostic work-up (that includes exclusion of other alternate causes such as infection).
- **Myositis /Polymyositis**  
Myositis or polymyositis should be suspected in patients who present with proximal muscle weakness and the evaluation should include an examination of the skin, muscle enzyme measurement, antibody testing, any systemic disease manifestations and exclusion of other diseases including drug-induced myopathy. Cases of myositis have been reported with myocarditis in which immune infiltration has been described in skeletal and cardiac muscle (see IB).
- **Other inflammatory responses** that are rare / less frequent with a potential immune-mediated aetiology include, but are not limited to, pericarditis, sarcoidosis, uveitis, and other events involving the eye, skin, haematological and rheumatological events.
- **Hypersensitivity and Infusion Reactions**

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Hypersensitivity reactions as well as infusion-related reactions have been reported with anti-PD-L1 and anti-PD-1 therapy (see IB). As with the administration of any foreign protein and/or other biologic agents, reactions following the infusion of monoclonal antibodies (MAbs) can be caused by various mechanisms, including acute anaphylactic (IgE-mediated) and anaphylactoid reactions against the MAb, and serum sickness. Acute allergic reactions may occur, may be severe, and may result in death. Acute allergic reactions may include hypotension, dyspnea, cyanosis, respiratory failure, urticaria, pruritus, angioedema, hypotonia, arthralgia, bronchospasm, wheeze, cough, dizziness, fatigue, headache, hypertension, myalgia, vomiting and unresponsiveness.

Guidelines for the management of subjects experiencing toxicities for BI 1361849 can be found in Section 8.4.

## **7.2 Administrative Sponsor Requirements**

### **7.2.1 Trial Master Files**

The Investigator must retain a Sponsor-specified comprehensive and centralized filing system (“Trial Master File” or “Study Master File”) of all trial-related documentation that is suitable for inspection by the Sponsor and regulatory authorities. Upon completion of the trial, the Investigator is required to submit a summary report to the Sponsor.

The Investigator must arrange for the retention of the Study Master File for a period of time determined by the Sponsor. No part of the Study Master File shall be destroyed or relocated without prior written agreement between the Sponsor and the Investigator.

### **7.2.2 Case Report Form Data Collection**

Electronic Case Report Forms (eCRF) will be completed in accordance with respective guidance and after training provided by the Sponsor. The use of eCRFs encompasses electronic data entry, query management and sign-off. Systems used for electronic data capture will be compliant with FDA regulations 21 CFR Part 11 and within the constraints of the applicable local regulatory agency guidelines (whichever provides the greatest protection to the integrity of the data).

All subjects who sign an informed consent form, regardless of study procedures performed, will be assigned a screening number and have their data entered into the eCRF.

The Investigator will sign and date the completed eCRF sections. The Investigator’s signature will indicate a thorough inspection of the data in the CRF and will certify its content.

### **7.2.3 Language**

The protocol is written in English. All correspondence between the study site and the Sponsor should be maintained in English. Case Report Forms must be completed in English. All written material to be used by subjects and para-clinical staff must use vocabulary that is clearly understood, and be in the language appropriate for the trial site.

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#### **7.2.4 Monitoring**

The Sponsor will oversee the conduct of the study and perform clinical monitoring visits for site qualification, site initiation, routine monitoring and site close-out. Clinical Monitors and/or other sponsor staff will meet with the investigator staff and require direct access to source data/documents. Such access may also be required for Institutional Review Board review, and regulatory inspection/audits. Direct access is defined as permission to examine, analyze, verify, and reproduce any records and reports that are important to the evaluation of the study. All reasonable precautions within the constraints of the applicable regulatory requirement(s) to maintain the confidentiality of subjects' identities and sponsor's proprietary information will be exercised.

It is the Clinical Monitor's responsibility to inspect the case report forms at regular intervals throughout the trial to verify adherence to the protocol, the completeness, accuracy and consistency of the data, and adherence to Good Clinical Practice guidelines. The Clinical Monitor should have access to patient charts, laboratory reports and other subject records needed to verify the entries on the case report forms ("source data verification").

#### **7.2.5 Protocol Amendments**

Protocol amendments may be implemented only after approval by the Investigator, Sponsor, Institutional Review Board and, if required, the regulatory authorities. Amendments that are intended to eliminate an apparent immediate hazard to subjects may be implemented prior to such approvals. However, in this case, approval must be obtained as soon as possible after implementation. Implementation of administrative amendments that do not affect the safety of the subjects usually do not require prior Institutional Review Board approval, just notification.

When immediate deviation from the protocol is required to eliminate an immediate hazard(s) to subjects, the Investigator will contact the Sponsor if circumstances permit, to discuss the planned course of action. Any departures from the protocol must be fully documented in the source documentation.

#### **7.2.6 Premature Subject Withdrawal from Treatment or from Study**

A subject may withdraw from study treatment or from the study at any time for any reason without prejudice to his/her future medical care by the physician or at the study site. Likewise, the Investigator and/or Sponsor have the right to withdraw subjects from treatment or from the study. Specific subject withdrawal criteria are listed in Section 3.1.10. Should a subject (or a subject's legally authorized representative) decide to withdraw from study treatment or from the study, all efforts will be made to complete the required study procedures and report the treatment observations as thoroughly as possible.

For all subject withdrawals, a complete final evaluation should be made at the time of withdrawal. The appropriate form in the Case Report Form should be completed with an explanation of why the subject is withdrawing, and an attempt should be made to perform a follow-up evaluation.

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### **7.2.7 Early Trial Termination**

Sponsor and Investigator have the right to terminate the study early. Specific study stopping rules are listed in Section 3.1.14. In such case, one party must notify the other in advance in writing about the intent of and the reasons for the termination. The investigator must also notify the appropriate Institutional Review Board accordingly.

### **7.2.8 Study Drug Shipments and Accountability**

Study drug shipments will be addressed to the Principal Investigator's authorized designee, preferably, the site's pharmacy. The recipient will verify the amount and condition of the drug and will return a signed Acknowledgment of Receipt to the shipper.

A drug dispensing log (inventory) will be kept by the study site, containing at least the following:

- the subject's identification (subject number and code)
- date and quantity of drug dispensed
- date and quantity of drug returned to the investigator/pharmacy (if applicable)
- date and quantity of accidental loss of drug (if any)

These inventories must be made available for inspection by the Clinical Monitor. The Investigator is responsible for seeing to it that all used and unused trial supplies are accounted for. At the end of the study, the Clinical Monitor will also collect the original study drug dispensing records.

At the end of the study or as directed by the Sponsor, all used and unused supplies, including partially used or empty containers, will be disposed of or transferred as instructed by the Sponsor, and in accordance with local written procedures, if applicable. Any disposal or transfer of investigational agent shall be noted on the investigational drug disposition log and signed-off by a second person. At the end of the study, the Clinical Monitor will collect the original drug disposition logs.

## **7.3 Regulatory, Legal and Ethical Requirements**

### **7.3.1 Good Clinical Practice (GCP), Laws and Regulations**

The Investigator must ensure that he/she and all authorized personnel for the study are familiar with the principles of Good Clinical Practice (GCP) and that the study is conducted in full conformity with the current revision of the Declaration of Helsinki, ICH Guidelines and applicable local laws and regulations, with the understanding that local laws and regulations take precedence over respective sections in the Declaration of Helsinki and/or the ICH Guidelines.

### **7.3.2 Informed Consent**

The investigator must obtain witnessed (if applicable) written informed consent from the subject or the subject's legally authorized representative after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any study procedures are performed. The subject should be given a copy of the informed consent documentation. The original signed and dated informed consent form must be retained in the

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study records at the study site, and is subject to inspection by representatives of the Sponsor, or representatives from regulatory agencies.

### **7.3.3 Institutional Review Board**

The investigator must obtain written approval from the appropriate Institutional Review Board for the protocol and informed consent, and all amendments thereof, prior to recruitment of subjects and prior to shipment of investigational agents.

The investigator must report Serious Adverse Events (SAEs) to the appropriate Institutional Review Board in accordance with the Institutional Review Board's rules and guidelines (see also Section 7.1).

The Investigator must assure that continuing review (at least once per year) of the study is performed by the Institutional Review Board throughout the duration of the study. If so required by the Institutional Review Board, the investigator must provide study reports on an annual basis and upon completion of the study.

All correspondence with, and reports to, the Institutional Review Board must be maintained in the study files at the study site and copies must be sent to the Sponsor.

### **7.3.4 Subject Confidentiality**

The Investigator must ensure that the subject's privacy is maintained. A subject should only be identified by their initials, date of birth and subject number on the case report forms or other documents submitted to the Sponsor. Documents that are not submitted to the Sponsor (e.g., signed informed consent form) should be kept in a strictly confidential section of the study file by the Investigator.

The Investigator shall permit the Sponsor and authorized representatives of regulatory agencies to review the portion of the subject's medical record that is directly related to the study. As part of the informed consent process, the subject must have given written consent that his/her records will be reviewed in this manner.

## 8 Appendices

### 8.1 Protocol Version History

<p><b>Original Issue</b>  <b>Issue date: 14-DEC-2016</b>  <b>Summary of Changes:</b> not applicable</p>																																							
<p><b>Amendment 1</b>  <b>Issue date: 12-APR-2017</b>  <b>Summary of Changes:</b></p> <p>1. Synopsis: Control Group B was added, Control Group A was modified, and total dose for BI 1361849 was changed from 1920 µg to 12 x 80 µg due to introduction of needle-free device. These change were made throughout based on updated information from Boehringer Ingelheim.</p> <p>a. Paragraph 3 was updated as follows (changes in bold): “For each arm of the study, there is a <i>dose escalation phase</i> in which the Recommended Combination Dose (RCD) is determined according to a standard 3 + 3 design. The <i>dose escalation phase</i> is followed by an <i>expansion phase</i>, in which the cohort at the RCD is expanded to 20 subjects (inclusive of the subjects from the dose escalation cohort). <del>For Arm A, there will be an additional Control group (n = 10) added to the expansion phase in which the subjects will receive only durvalumab every 4 weeks.</del> During expansion, there will be an additional Control Group (n = 10) added to expansion for Arm B, where the subjects in the Control Group will receive only durvalumab + tremelimumab. If Arm B is not expanded, the Control Group will be added to the expansion for Arm A, where the subjects in the Control Group will receive only durvalumab.”</p> <p>b. Table was changed <b>FROM:</b></p>																																							
<table border="1"> <thead> <tr> <th colspan="7">Dose Level Table</th> </tr> <tr> <th rowspan="2">Dose Level</th> <th colspan="2">Arm A Escalation</th> <th rowspan="2">Dose Level</th> <th colspan="3">Arm B*</th> </tr> <tr> <th>BI 1361849</th> <th>Durvalumab</th> <th>BI 1361849</th> <th>Durvalumab</th> <th>Tremelimumab</th> </tr> </thead> <tbody> <tr> <td>-1</td> <td>1920 µg</td> <td>750 mg</td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td><b>Starting</b></td> <td><b>1920 µg</b></td> <td><b>1500 mg</b></td> <td><b>Starting</b></td> <td><b>1920 µg</b></td> <td><b>Arm A RCD</b></td> <td><b>75 mg</b></td> </tr> </tbody> </table>							Dose Level Table							Dose Level	Arm A Escalation		Dose Level	Arm B*			BI 1361849	Durvalumab	BI 1361849	Durvalumab	Tremelimumab	-1	1920 µg	750 mg					<b>Starting</b>	<b>1920 µg</b>	<b>1500 mg</b>	<b>Starting</b>	<b>1920 µg</b>	<b>Arm A RCD</b>	<b>75 mg</b>
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<p>*Dose in Arm B is based on RCD determined in Arm B. If there is unacceptable toxicity, dosing will continue at RCD from Arm A, without tremelimumab.</p> <p>NOTE 1: See Section 3.1.7.1 for durvalumab and tremelimumab doses for instances when a subject’s body weight drops to ≤ 30 kg while on the study.</p> <p>NOTE 2: The BI 1361849 drug product is a vaccine comprising six drug product components (F2408, F2409, F2410, F2624, F2625, and F2626), which are provided and administered separately.</p>																																							
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\*If there is unacceptable toxicity in Arm B, dosing will continue at RCD from Arm A, without tremelimumab. \*\*See Note 2 below.

**NOTE 1:** See Section 3.1.7.1 for durvalumab and tremelimumab doses for instances when a subject's body weight drops to  $\leq 30$  kg while on the study.

**NOTE 2:** The BI 1361849 drug product is a vaccine comprising six drug product components (F2408, F2409, F2410, F2624, F2625, and F2626), which are provided and administered separately; each component is administered twice, thus there are 12 administrations of 100  $\mu$ L (80  $\mu$ g) each.

2. Section 1.2.3 (BI 1361849): section was updated according to data available as of March 2017 from Boehringer Ingelheim:
  - a. Data supporting a needle-free device, the PharmaJet Tropis<sup>®</sup>, were provided
  - b. Summary for Trial CV-9202-006 was updated
3. Section 2.1 (BI 1361849 dose), the following paragraphs were added for the needle-free device and dosing: "BI 1361849 may also be administered by a needle-free device, the PharmaJet Tropis<sup>®</sup> device. See Section 1.2.3 for additional details. Due to the filling volume of 100  $\mu$ L, the device allows for administration of half the previously established doses, i.e., 160  $\mu$ g instead of 320  $\mu$ g per antigen when using the same manner of administration of two inoculations per antigen and vaccination time point. Advantages include improved patient convenience, handling safety, ease, and reliability of intradermal administration. Preclinical data showed that using a needle-free device such as the PharmaJet Tropis<sup>®</sup> device, the efficiency of delivery increases and protein production is higher even at half or a quarter of the administered dose, hence lower doses can be used. Clinical data from a Phase 2 trial, CV-9104-007, suggests that administration of half the dose by the PharmaJet Tropis<sup>®</sup> device results in at least similar immunogenicity compared to needle administration of the full dose. For this study, the PharmaJet Tropis<sup>®</sup> device will be used for the administration of the BI 1361849 components. Allowing for a filling volume of 100  $\mu$ L (80  $\mu$ g) and 2 administrations per component, the recommended dose per each of the 6 antigen components will be 160  $\mu$ g (2 x 80  $\mu$ g), for a total of 960  $\mu$ g (12 administrations)."
4. Section 2.2 (Durvalumab and tremelimumab dose): The last paragraph was changed because weight based dosing was added for subjects whose weight drops to  $\leq 30$  kg during the study. The paragraph was changed **FROM:** This dosing of durvalumab and tremelimumab is recommended only for subjects with  $> 30$ kg body weight due to endotoxin exposure. 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 be dosed at 600 mg Q4W for durvalumab and 30 mg Q4W for tremelimumab as long as the body weight remains  $\leq 30$  kg. See Section 3.1.7.1 for additional details regarding the dose de-escalation cohort for durvalumab. **TO:** "This dosing of durvalumab and tremelimumab is recommended only for subjects with  $> 30$ kg body weight due to endotoxin exposure. Subjects with a body weight  $\leq 30$  kg are not eligible for enrollment in the current study. See Section 3.1.7.1 for additional details regarding the dose de-escalation cohort for durvalumab and for dose requirements for instances when a subject's body weight drops to  $\leq 30$  kg while on the study.
5. Section 3.1 (Study Design), Control Group B was added and Control Group A was modified. The language was changed **FROM:**  
"For Arm A, there will be an additional **Control Group** (n = 10) added to the expansion phase in which the subjects will receive only durvalumab every 4 weeks:
  - **Arm A1 (Expansion group):** BI 1361849 + durvalumab (n=20)
  - **Arm A2 (Control Group):** durvalumab (n=10)"

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**TO:** “During expansion, there will be an additional Control Group (n = 10) added to the expansion for Arm B, where the subjects in the Control Group will receive only durvalumab + tremelimumab (no BI 1361849 components):

- **Arm B Expansion Cohort:** BI 1361849 + durvalumab + tremelimumab (n=20)
- **Arm B Control Group:** durvalumab + tremelimumab (n=10)

If Arm B is not expanded due to toxicities, the Control Group will be added after the completion of expansion for Arm A, where the subjects in the Control Group will receive only durvalumab (no BI 1361849):

- **Arm A Expansion Cohort:** BI 1361849 + durvalumab (n=20)
- **Arm A Control Group:** durvalumab (n=10)”

6. Section 3.1.2 (Enrollment/Randomization): Control Group B was added and Control Group A was modified.
- a. The language was changed **FROM:** “Enrollment will start in the Arm A dose escalation cohorts in a sequential fashion. After the RCD is determined for Arm A, enrollment will start for the dose evaluation of Arm B (see Section 3.1.7.1) and for the Arm A expansion phase (Arm A1 Expansion + Arm A2 Control; see Figure 1), 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 in Arm B is complete and enrollment is completed in the Arm A (A1 and A2) expansion cohorts, enrollment will begin in the Arm B expansion cohort.” **TO:** “Enrollment will start in the Arm A dose escalation cohorts in a sequential fashion. After the RCD is determined for Arm A, enrollment will start for the dose evaluation of Arm B (see Section 3.1.7.1) and for the Arm A Expansion Cohort (see Figure 1), 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 in Arm B is complete and enrollment is complete in Arm A Expansion Cohort, enrollment will begin in the Arm B Expansion Cohort and Arm B Control Group in an alternating fashion (see Figure 1 and description below). If Arm B is not expanded due to toxicities, the Control Group will be added to the expansion for Arm A. The Arm A Control Group, will then start enrolling after the completion of Arm A Expansion Cohort, in a non-alternating fashion.”
- b. Figure 1 was updated to add Control Group B and modify Control Group A. The following footnote was added: “\*If Arm B Expansion Cohort and Arm B Control Group are not initiated due to toxicities, an Arm A Control Group (n=10 subjects; durvalumab only) will be added, which will start enrollment (in a non-alternating fashion) after Arm A Expansion Cohort has completed.”
- c. Language in the last paragraph was changed **FROM:**  
***“For the expansion phase for Arm A,*** subjects will be enrolled in an alternating fashion so that there are a total of 20 subjects (inclusive of the subjects from the dose escalation cohort that is being expanded) for the expansion cohort (Arm A1) and 10 subjects for the Control Group (Arm A2). In order to have only 14 additional subjects in Arm A1, enrollment will start with the 6<sup>th</sup> subject of the Arm A dose escalation cohort. Thus, 3 subjects will be enrolled in Arm A1, followed by 2 subjects in Arm A2, and so forth, as depicted below:

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Subj. No.	Arm A1	Arm A2	Subj. No.	Arm A1	Arm A2	Subj. No.	Arm A1	Arm A2	Subj. No.	Arm A1	Arm A2	Subj. No.	Arm A1	Arm A2
6	X		11	X		16	X		21	X		26	X	
7	X		12	X		17	X		22	X		27	X	
8	X		13	X		18	X		23	X		28	X	
9		X	14		X	19		X	24		X	29		X
10		X	15		X	20		X	25		X	30		X

Enrolling subjects in this fashion will result in the following:

- A total of 20 subjects in Arm A1 expansion cohort (6 subjects from the Arm A dose escalation cohort + 14 additional subjects)
- 10 subjects in Arm A2 Control Group.”

**TO: “For the expansion phase for Arm B,** subjects will be enrolled in an alternating fashion into the Expansion Cohort and the Control Group. This is done so that there is a total of 20 subjects (inclusive of the subjects from the dose evaluation cohort that is being expanded) for the Arm B Expansion Cohort and 10 subjects for the Arm B Control Group. In order to have only 14 additional subjects in the Arm B Expansion Cohort, enrollment will start with the 6<sup>th</sup> subject of the Arm B dose evaluation cohort. Thus, 3 subjects will be enrolled in Arm B Expansion Cohort, followed by 2 subjects in Arm B Control Group, and so forth, as depicted below:

Subj. No.	Arm B Exp	Arm B Con	Subj. No.	Arm B Exp	Arm B Con	Subj. No.	Arm B Exp	Arm B Con	Subj. No.	Arm B Exp	Arm B Con	Subj. No.	Arm B Exp	Arm B Con
6	X		11	X		16	X		21	X		26	X	
7	X		12	X		17	X		22	X		27	X	
8	X		13	X		18	X		23	X		28	X	
9		X	14		X	19		X	24		X	29		X
10		X	15		X	20		X	25		X	30		X

Exp = Expansion Cohort; Con = Control Group

Enrolling subjects in this fashion will result in the following:

- A total of 20 subjects in Arm B Expansion Cohort (6 subjects from the Arm B dose evaluation cohort + 14 additional subjects)
- 10 subjects in Arm B Control Group.

NOTE: If Arm B is not expanded due to toxicities, an Arm A Control Group (n = 10 subjects; durvalumab only) will be added after the completion of Arm A Expansion Cohort. The subjects the Arm A Control Group will be enrolled in a non-alternating fashion. “

7. Section 3.1.6 (Sample Size Considerations). Paragraph 2 was updated to reflect the changes in the control groups (changes in bold): “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). **For Arm A, an additional 10 subjects will be added to expansion phase for Arm A2 (Control Group). The control group is added primarily for the analysis of the immune response in this group (see Section 3.1.7.2).** For Arm B, an additional 10 subjects will be added to expansion phase for the Control Group. The control group is added primarily for the analysis of the immune response in this group (see Section 3.1.7.2). If Arm B is not expanded, the Arm A Control Group will open for enrollment (in a non-alternating fashion) after completion of Arm A Expansion Cohort.”

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8. Section 3.1.7 (Treatment Arms and Treatment Schema). The table footnote was changed  
**FROM:** “Note: For Arm A, there will be an additional **Control Group** (n = 10) added to the expansion phase in which the subjects will receive only durvalumab every 4 weeks (see Section 3.1.7.2).” **TO:** “Note: During expansion, there will be an additional **Control Group** (n = 10) added to the expansion phase for Arm B, where the subjects in the Control Group will receive only durvalumab + tremelimumab. If Arm B is not expanded, the Control Group will be added to the expansion for Arm A, where the subjects in the Control Group will receive only durvalumab. See Section 3.1.2 for details.”
9. Section 3.1.7.1 (Dose Escalation Phase). Pharmajet Tropis® device was added and doses for BI 1361849 were updated. Weight based dosing was added for subjects whose weight drops to ≤ 30 kg during the study. The language was changed as follows:

**FROM:**

Dose Level Table						
Dose Level	Arm A Escalation		Dose Level	Arm B*		
	BI 1361849	Durvalumab		BI 1361849	Durvalumab	Tremelimumab
-1	1920 µg	750 mg				
<b>Starting</b>	<b>1920 µg</b>	<b>1500 mg</b>	<b>Starting</b>	<b>1920 µg</b>	<b>RCD from Arm A</b>	<b>75 mg</b>

\*If there is unacceptable toxicity, dosing will continue at RCD from Arm A, without tremelimumab.

**Note: The durvalumab and tremelimumab doses are for subjects > 30 kg.**

- **Durvalumab starting dose:1500 mg Q4W for subjects > 30 kg.** If a subject’s body weight drops to ≤ 30 kg while on the study, the subject will be dosed at **600 mg Q4W** for durvalumab as long as the body weight remains ≤ 30 kg.
- **Durvalumab dose de-escalation: 750 mg Q4W for subjects > 30 kg.** If a subject’s body weight drops to ≤ 30 kg while on the study, the subject will be dosed at **300 mg Q4W** for durvalumab as long as the body weight remains ≤ 30 kg.
- **Tremelimumab dose: 75 mg Q4W for subjects > 30 kg.** If a subject’s body weight drops to ≤ 30 kg while on the study, the subject will be dosed at **30 mg Q4W** for tremelimumab as long as the body weight remains ≤ 30 kg.

**TO:**

Dose Level Table						
Dose Level	Arm A Escalation		Dose Level	Arm B*		
	BI 1361849	Durvalumab		BI 1361849	Durvalumab	Tremelimumab
-1	12 x 80 µg**	750 mg				
<b>Starting</b>	<b>12 x 80 µg**</b>	<b>1500 mg</b>	<b>Starting</b>	<b>12 x 80 µg**</b>	<b>RCD from Arm A</b>	<b>75 mg</b>

\*If there is unacceptable toxicity in Arm B, dosing will continue at RCD from Arm A, without tremelimumab.

\*\*BI 1361849 is a vaccine comprising six drug product components (F2408, F2409, F2410, F2624, F2625, and F2626), which are provided and administered separately; each component is administered twice, thus there are 12 administrations of 100 µL (80 µg) each.

**NOTE:** The Pharmajet Tropis® device will be used for the administration of the BI 1361849 components. Allowing for a filling volume of 100 µL (80 µg) and 2 administrations per component, the recommended dose per each of the 6 antigen components will be 160 µg (2 x 80 µg), for a total of 960 µg (12 administrations).

**Note: The durvalumab and tremelimumab doses are for subjects > 30 kg.**

- **Durvalumab starting dose:1500 mg Q4W for subjects > 30 kg.** If a subject’s body weight drops to ≤ 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 (e.g., a 30 kg subject would receive a 600 mg dose; a 25 kg subject would receive a 500 mg dose; etc.). When the weight improves to  $>$ 30 kg, the subject may return to fixed dosing of durvalumab 1500 mg.

- **Durvalumab dose de-escalation: 750 mg Q4W for subjects  $>$  30 kg.** If a subject's body weight drops to  $\leq$  30 kg while on the study, the subject will receive weight-based dosing equivalent to 10 mg/kg of durvalumab as long as the body weight remains  $\leq$  30 kg (e.g., a 30 kg subject would receive a 300 mg dose; a 25 kg subject would receive a 250 mg dose; etc.). When the weight improves to  $>$ 30 kg, the subject may return to fixed dosing of durvalumab 750 mg.
- **Tremelimumab dose: 75 mg Q4W (x4) for subjects  $>$  30 kg.** If a subject's body weight drops to  $\leq$  30 kg while on the study, the subject will receive weight-based dosing equivalent to 1mg/kg tremelimumab as long as the body weight remains  $\leq$  30 kg (e.g., a 30 kg subject would receive a 30 mg dose; a 25 kg subject would receive a 25 mg dose; etc.). When the weight improves to  $>$ 30 kg, the subject may return to fixed dosing of tremelimumab 75 mg

10. Section 3.1.7.2 (Dose Expansion Phase), Paragraph 2 was changed **FROM:** "There will be an additional Control Group (Arm A2, n = 10) added to the expansion phase for Arm A in which the subjects receive only durvalumab. The control group is added primarily for the analysis of the immune response in this group." **TO:** "During expansion, there will be an additional **Control Group** (n = 10) added to the expansion phase for Arm B, where the subjects in the Control Group will receive only durvalumab + tremelimumab. If Arm B is not expanded, the Control Group will be added to the expansion for Arm A, where the subjects in the Control Group will receive only durvalumab. See Section 3.1.2 for details. The control group is added primarily for the analysis of the immune response in this group."
11. Section 3.2 (flowchart):
  - a. Treatment section was updated to reflect changes for Control Groups
  - b. Footnote i was updated to reflect changes to Arms A and B Control Groups
  - c. Added Concom meds and AEs to Week 46
  - d. Footnote g was updated to clarify timing of optional tumor progressions (see changes to Section 4.1.3.1.
  - e. Optional tumor biopsy was removed from Cycle 12 per change to Section 4.3.1.1
12. Section 4.3.1.1 (Tumor Microenvironment): Paragraph 5 was updated to clarify timing of optional tumor progressions (changes in bold): Optional core biopsies will be obtained at the time of tumor progression or at the ~~end of the study~~ **completion of treatment** from subjects who consent to this procedure. A minimum of 3 cores will be required.
13. Section 4.3.1.2.1 (Immune Monitoring for Responses to BI 1361849 Vaccine), Paragraph 2 was updated per updated information from Boehringer Ingelheim (Changes in bold): "Assays for antigen-specific immune responses encompass **e.g, for example**, intracellular cytokine staining (ICS) **and** ELISpot ~~and/or CFSE-based proliferation~~, for detection of antigen-specific T-cells by their functional capacity to produce various effector cytokines ~~or proliferate~~ in response to the vaccine (NY-ESO-1, MageC1, MageC2, 5T4, Survivin, Muc-1) and/or non-vaccine tumor antigens (e.g. MAGE-A3). Humoral responses against vaccine antigens are routinely analyzed by **immunoassay techniques such as** ELISA and can easily be extended to non-vaccine antigens (~~antibody chips~~ **antigen arrays**). **If possible, the immune analyses will**

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also include a detailed phenotypic characterization of, e.g., circulating T-cells **subsets, including follicular helper T cells, T memory stem cells, Th1 and Th2 lineages**, activation and differentiation states of **immune cells**, and checkpoint marker expression. Furthermore, B cells, NK cells, DCs, monocytes and the peripheral immune-suppressive environment mediated by myeloid derived suppressor cells (MDSCs) and regulatory T-cells are evaluated. Measurements of systemic **immunological lymphoid repertoire, e.g., T-cell receptor sequencing**, and **immune-related** transcriptional changes, **e.g., T-cell receptor sequencing**, cytokine and chemokine profiling **and genome-wide transcriptional profiling** are additional approaches **of interest suitable** to identify potential blood-derived biomarkers.”

14. Section 4.3.2 (Subject Evaluation and Statistics) was updated, per updated information from Boehringer Ingelheim (changes in bold): “For each arm of the study, only subjects who receive at least 1 dose of the respective drugs and who provide the baseline and at least 1 on-treatment sample (if applicable) will be evaluated. As these analyses represent exploratory evaluations of potential biomarkers of response or resistance to therapy, descriptive statistics will be used to describe findings and potential relationships to outcomes to therapy. **Criteria for assay positivity (changes compared to baseline) of individual assays will be described in the statistical analysis plan (SAP).** The exploratory pharmacodynamic assessment of the immunologic changes in the tumor microenvironment will include the correlation between clinical activity and the expression level of PD-L1 and tumor-infiltrating lymphocyte (TILs) changes in biopsies pre and post treatment. The association between response and PD-L1 expression within each arm will be assessed descriptively. Confidence intervals for the overall odds ratio and the odds ratio within each arm will be presented. The association between response and TILs changes (increase, decrease, or no change) will be evaluated similarly. ~~Subjects are considered to show an immune response against BI 1361849 if at least one of the two post-baseline time points show assay positivity for at least one of the assessments by ICS, ELISpot or ELISA for at least one of the six antigens (see table below).~~ **Criteria for assay positivity (changes compared to baseline) of individual assays will be described in the statistical analysis plan (SAP).**”

	PBMCs									Serum	
	ICS								ELISpot	ELISA	
	CD8				CD4				PBMCs		
	IFN-γ	TNF-α	IL-2	CD107a	IFN-γ	TNF-α	IL-2	CD107a	IFN-γ	IgM	IgG
<b>MUC-1</b>	x	x	x	x	x	x	x	x	x	x	x
<b>Survivin</b>	x	x	x	x	x	x	x	x	x	x	x
<b>MAGE-C1</b>	x	x	x	x	x	x	x	x	x	x	x
<b>MAGE-C2</b>	x	x	x	x	x	x	x	x	x	x	x
<b>ST4</b>	x	x	x	x	x	x	x	x	x	x	x
<b>NY-ESO</b>	x	x	x	x	x	x	x	x	x	x	x

Subjects are considered fully evaluable for immune response if the following criteria are met:

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- Subjects have received at least 4 treatments with BI 1361849 including all vaccine antigens according to protocol
- Samples from baseline and both post-baseline sample 7 days ( $\pm 2$  days) after treatment are available
- Subjects have not received any prohibited concomitant treatments (see Section 5.3.1) within 21 days before on-treatment blood sampling. Immunosuppressive medication that has been taken by subjects 2 to 3 weeks prior to randomization will be documented so that any potential influence on baseline values may be evaluated.
- Sufficient amount and quality of blood sample and isolated PBMCs is available to fully perform and analyze, in accordance with respective assay SOPs, at least **the ICS assay, as a measure for antigen-specific cellular immune response** ~~one of the two antigen-specific cellular immune assay according to assay priority (ICS is prioritized over ELISpot)~~
- **The analysis of antigen-specific cell-mediated immune assays response by ICS** ~~are~~ is required to include all BI 1361849 antigens and negative controls to be fully evaluable
- ~~Amount and quality of serum samples need to be sufficient to perform and analyze serum antibody ELISA according to assay SOP~~
- ~~Measurement of serum antibody ELISAs against all available BI 1361849 antigens and negative controls could be performed~~

All other exploratory results will be summarized descriptively.”

15. Section 5.1 (Inclusion Criteria): Criterion # 5 was updated per Medimmune guidelines; creatinine clearance “ $\geq 50$  mL/min” was changed to “ $> 40$  mL/min” (by Cockcroft-Gault formula)
16. Section 5.2 (Exclusion Criteria) was updated per current Medimmune guidelines
  - a. #3 was changed **FROM:** “Active, suspected or prior documented autoimmune disease (including but not restricted to inflammatory bowel disease, celiac disease, irritable bowel syndrome, Wegner’s granulomatosis, Hashimoto’s thyroiditis, rheumatoid arthritis, systemic lupus, scleroderma and its variants, multiple sclerosis, myasthenia gravis). Vitiligo, residual hypothyroidism due to autoimmune condition only requiring hormone replacement, psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted.”  
**TO:** “Active, suspected or prior documented autoimmune disease or inflammatory disorders (including but not restricted to inflammatory bowel disease [e.g., colitis or Crohn's disease], celiac disease, diverticulitis [with the exception of diverticulosis], Sarcoidosis syndrome, Wegner’s granulomatosis with polyangiitis, Hashimoto’s thyroiditis, rheumatoid arthritis, systemic lupus, Graves' disease, rheumatoid arthritis, hypophysitis, uveitis, scleroderma and its variants, multiple sclerosis, myasthenia gravis, etc. ). Vitiligo, alopecia, residual hypothyroidism (e.g., following Hashimoto syndrome) due to autoimmune condition only requiring hormone replacement, psoriasis or any chronic skin condition not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted. Subjects without active disease in the last 5 years may be included but only after consultation with the study physician. Subjects with celiac disease controlled by diet alone may also be included.”

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- b. #12 was changed **FROM:** "Other serious illnesses (e.g., serious infections requiring antibiotics, bleeding disorders)." **TO:** "Uncontrolled intercurrent illness, including but not limited to, ongoing or active infection, bleeding disorders, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, interstitial lung disease, or serious chronic gastrointestinal conditions associated with diarrhea."
  - c. #13 was changed **FROM:** "Mental impairment that may compromise compliance with the requirements of the study."  
**TO:** "Mental impairment or social situations that may compromise compliance with the requirements of the study or compromise the ability of the subject to give written informed consent."
  - d. # 19 and # 20 were added.
17. Section 6.1.3 (Durvalumab Prep) and 6.2.3 (Tremelimumab Prep): Weight based dosing was added for subjects whose weight drops to  $\leq 30$  kg during the study. See changes made to Section 3.1.7.1.
18. Section 6.1.4 (Durvalumab administration) was updated per current Medimmune guidelines:
- a. Bullet 8 was changed **FROM:** "The total time between needle puncture of the durvalumab vial to start of administration should not exceed 4 hours at room temperature or 24 hours at 2°C to 8°C (36°F to 46°F). Standard infusion time is 60 ± 5 minutes. However, if there are interruptions during infusion (total infusion time not to exceed 4 hours), the total allowed time for preparation and administration should not exceed 8 hours at room temperature. In the event that either preparation time or infusion time exceeds the time limits, a new dose must be prepared from new vials." **TO:** "The total time between needle puncture of the durvalumab vial to start of administration should not exceed 4 hours at room temperature or 24 hours at 2°C to 8°C (36°F to 46°F). Standard infusion time is 60 ± 5 minutes (an infusion of less than 55 minutes is considered a deviation). However, if there are interruptions during infusion, the total allowed infusion time should not exceed 8 hours at room temperature. In the event that either preparation time or infusion time exceeds the time limits, a new dose must be prepared from new vials."
  - b. The last bullet was summarized as "See Section 8.3.1 for guidelines for infusion-related reactions."
19. Section 6.2.4 (Tremelimumab Administration) was updated per current Medimmune guidelines:
- a. Bullet 8 was changed **FROM:** "The total time between needle puncture of the tremelimumab vial to start of administration should not exceed 4 hours at room temperature or 24 hours at 2°C to 8°C (36°F to 46°F). Standard infusion time is 60 ± 5 minutes. However, if there are interruptions during infusion (total infusion time not to exceed 4 hours), the total allowed time for preparation and administration should not exceed 8 hours at room temperature. In the event that either preparation time or infusion time exceeds the time limits, a new dose must be prepared from new vials." **TO:** "The total time between needle puncture of the tremelimumab vial to start of administration should not exceed 4 hours at room temperature or 24 hours at 2°C to 8°C (36°F to 46°F). Standard infusion time is 60 ± 5 minutes (an infusion of less than 55 minutes is considered a deviation). However, if there are interruptions during infusion, the total allowed infusion time should not exceed 8 hours at room temperature. In the

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event that either preparation time or infusion time exceeds the time limits, a new dose must be prepared from new vials.”

20. Section 6.3.2 (Preparation of Components of BI 1361849): Language was updated per Boehringer Ingelheim; changed **FROM**: “BI 1361849 comprises 6 drug product components, each of which is provided separately as a sterile lyophilizate in a 2 mL glass vial with rubber stopper closure that will be reconstituted with 600 µL (0.6 mL) of Ringer-Lactate solution to provide an extractable volume for intradermal injection of 400 µL (0.40 mL) of solution containing the drug substance at a concentration of 0.8 g/L (equivalent to 0.48 mg per vial and 0.32 mg per injection of 400 µL). NOTE: The Ringer-Lactate solution used for reconstitution must be obtained from Fresenius Kabi (or alternatively, it will be provided by Boehringer Ingelheim), and must include the following ingredients in the respective concentrations: Sodium Chloride 103 mM, Potassium Chloride 5.5 mM, Calcium Chloride dehydrate 1.8 mM, Sodium lactate 28 mM. Other Ringer-Lactate solutions may contain Mg, which may seriously impair the vaccine according to CureVac.” **TO**: “BI 1361849 comprises 6 drug product components. Each box of BI 1361849 contains one vial of each of the components, which are formulated as a sterile lyophilizate in a 2 mL glass vial with rubber stopper closure. Each vial will be reconstituted with 600 µL (0.6 mL) of Ringer’s Lactate solution to provide a solution containing the drug substance at a concentration of 0.8 g/L (equivalent to 0.48 mg per vial and 0.16 mg (80 µg) per injection of 100 µL). NOTE: The Ringer’s Lactate solution (from Fresenius Kabi) used for reconstitution will be provided to the sites; the solution contains the following ingredients in the respective concentrations: Sodium Chloride 103 mM, Potassium Chloride 5.5 mM, Calcium Chloride dehydrate 1.8 mM, Sodium lactate 28 mM. Other Ringer’s Lactate solutions may contain Mg, which may seriously impair the vaccine according to CureVac.”
21. Section 6.3.3 (Administration):
- the following language was added regarding the needle-free device, Pharmajet Tropis®: “The Pharmajet Tropis® device will be used for the administration of the BI 1361849 components. Allowing for a filling volume of 100 µL (80 µg) and 2 administrations per component, the recommended dose per each of the 6 antigen components will be 160 µg (2 x 80 µg), for a total of 960 µg (12 administrations). Directions for use of the Pharmajet Tropis® device will be provided separately.”
  - “injections” was changed to “administrations” (this was changed throughout)
  - Filling volume was changed from 200 to 100 µL (80 µg); total for all 12 administrations changed from 1920 to 960 µg.
  - Paragraph regarding use of 30 gauge needle was deleted.
22. Section 6.4 (Estimated Study Requirements): Table was changed to clarify supply of BI 1361849 components and Ringer’s lactate solution; it was changed **FROM**:

<i><b>Drug</b></i>	<i><b>Required Quantity (vials)</b></i>
<b>Durvalumab</b> (500 mg / 10 ml vials)	2400
<b>Tremelimumab</b> (400 mg / 20 ml vials)	128
<b>BI 1361849</b> (2 X 200 µL from 1 vial each of: F2408, F2409, F2410, F2624, F2625, and F2626)	1000 for each of the 6 components

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**TO:**

<b>Drug</b>	<b>Required Quantity (vials)</b>
<b>Durvalumab</b> (500 mg / 10 ml vials)	2400
<b>Tremelimumab</b> (400 mg / 20 ml vials)	128
<b>BI 1361849</b> (2 X 100 µL from 1 vial each of: F2408, F2409, F2410, F2624, F2625, and F2626); this will be provided in a box containing 1 vial of each component. Ringer's lactate solution will also be provided (one bottle per subject per dosing day).	1000 boxes containing 6 vials (1 vial for each of the 6 components)

23. Section 7.1.6 (Expedited SAE Reporting Requirements): the last paragraph was updated to include Boehringer Ingelheim (changes in bold): "Serious adverse event reporting to AstraZeneca/Medimmune **and to Boehringer Ingelheim** is described in a separate **respective** agreements.
24. Section 7.18 (AEsIs): additional detail was provided for each of the listed AEsIs per current Medimmune guidelines. The last paragraph was also updated (changes in bold): "Guidelines **for the management of subjects experiencing toxicities** for BI 1361849 can be found in Section 8.4."
25. Section 8.3.1 (Durvalumab and tremelimumab Dose Modifications due to Toxicity): For Infusion related reactions Grades 1 and 2, the phrase "total infusion time not to exceed 4 hours." was deleted per Medimmune current guidelines.
26. Administrative:
  - a. Spelling, grammar and typographical errors were corrected; formatting changes were implemented, as applicable.
  - b. List of abbreviations was updated

**Amendment 2****Issue date: 10-AUG-2017****Summary of Changes:**

1. IND # was added.
2. For clarification, dose escalation phase was renamed as dose evaluation phase in the Synopsis, Figure 1, and Sections 3.1, 3.1.2, 3.1.6, 3.1.7.1, 3.1.7.2, 3.1.9, 3.1.11, 3.1.13, 3.1.14, 4.0, 4.1.1, and 4.1.2. The following clarification was added in the Synopsis and Section 3.1.7.1: "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. 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."
3. The administration method for BI 1361849 was changed from the Pharmajet Tropis® device to standard needle.
  - a. Section 2.1 (BI 1361849): deleted: "Due to the filling volume of 100 µL, the device allows for administration of half the previously established doses, i.e., 160 µg instead of 320 µg per antigen when using the same manner of administration of two inoculations per

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antigen and vaccination time point. Advantages include improved patient convenience, handling safety, ease, and reliability of intradermal administration. Preclinical data showed that using a needle-free device such as the PharmaJet Tropis® device, the efficiency of delivery increases and protein production is higher even at half or a quarter of the administered dose, hence lower doses can be used. Clinical data from a Phase 2 trial, CV-9104-007, suggests that administration of half the dose by the PharmaJet Tropis® device results in at least similar immunogenicity compared to needle administration of the full dose.”

- b. Section 2.1 (BI 1361849): Last paragraph was changed **FROM** “For this study, the Pharmajet Tropis® device will be used for the administration of the BI 1361849 components. Allowing for a filling volume of 100 µL (80 µg) and 2 administrations per component, the recommended dose per each of the 6 antigen components will be 160 µg (2 x 80 µg), for a total of 960 µg (12 administrations).” **TO** “For this study, the Pharmajet Tropis® device will not be used for the administration of the BI 1361849 components. Instead, standard intradermal injections using needles will be performed (see Section 6.3.3 for details).”
- c. The change from Tropis® device to needle administration resulted in different volume requirements for each of the BI 1361849 components. Thus 80 µg was changed to 160 µg and 100 µL was changed to 200 µL in the Synopsis and Sections 3.1.7.1, 6.3.3, and 6.4.
- d. The following clarification was added to the first paragraph in Section 2.1 (changes in bold) “The BI 1361849 drug product is a vaccine comprising six drug product components (F2408, F2409, F2410, F2624, F2625, and F2626), which are provided and administered separately. The recommended dose per antigen constituent is 320 µg (**160 µg x 2**), for a total of 1920 µg (**320 µg x 6 constituents**).
- e. Section 3.1.7.1: The first NOTE was changed **FROM** “The Pharmajet Tropis® device will be used for the administration of the BI 1361849 components. Allowing for a filling volume of 100 µL (80 µg) and 2 administrations per component, the recommended dose per each of the 6 antigen components will be 160 µg (2 x 80 µg), for a total of 960 µg (12 administrations).” **TO**: “See Section 6.3.3 for details on the administration of BI 1361849.”
- f. Section 6.3.3 (BI 1361849 Administration):
  - i. The following paragraph was deleted “The Pharmajet Tropis® device will be used for the administration of the BI 1361849 components. Allowing for a filling volume of 100 µL (80 µg) and 2 administrations per component, the recommended dose per each of the 6 antigen components will be 160 µg (2 x 80 µg), for a total of 960 µg (12 administrations). Directions for use of the Pharmajet Tropis® device will be provided separately.”
  - ii. The following paragraph was added: “A 30-gauge needle will be used for the injection. The needle should penetrate the skin at an angle of about 15 degrees and the injection should be administered slowly until a bubble appears underneath the skin surface. Subcutaneous injection (characterized by a missing bubble after the injection) must be avoided as it may result in reduced efficacy of the vaccine. However, if an injection is administered subcutaneously by error, the injection must not be repeated for this vaccination time point. Incorrect injections will be documented.”

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4. Section 3.2 (Flowchart): Per FDA recommendation, Footnote “a” was changed **FROM** “pre-dose, when applicable. Note: It is strongly recommended that hematology, chemistry and pregnancy test (when applicable) results are reviewed before dosing.” **TO** “pre-dose, when applicable. Note: Review of results for hematology, chemistry and pregnancy test (when applicable) is **required** prior to dosing.”
5. Sections 6.1.4 (Durvalumab Administration) and 6.2.4 (Tremelimumab Administration): In bullet 8, the following sentence was modified to provide clarification (changes in bold): “However, if there are interruptions during infusion, the total allowed infusion time should not exceed 8 hours **at room temperature.**”
6. Section 7.1.8 (AESI):
  - a. Bullet 2 (changes in bold): **Pneumonitis/Interstitial lung disease (ILD)**
  - b. Bullet 5 (Endocrine disorders): diabetes insipidus was added per current MedImmune recommendations.
  - c. Last bullet was added, per current MedImmune recommendations: “**Other inflammatory responses** that are rare with a potential immune-mediated aetiology include, but are not limited to, myocarditis, pericarditis, and uveitis.”
7. Section 8.3.1 (Durva and Treme Dose Modification due to toxicity): per FDA recommendations, added myocarditis to Pneumonitis/ILD bullet In Grades 1, 2, and 3.
8. Administrative: Spelling, grammar and typographical errors were corrected; formatting changes were implemented, as applicable.

### Amendment 3

Issue date: 23-OCT-2017

#### Summary of Changes:

1. The administration method for BI 1361849 was changed from the standard needle to the Pharmajet Tropis® device.
  - a. The change from needle administration to Tropis® device resulted in different volume requirements for each of the BI 1361849 components. Thus 160 µg was changed to 80 µg and 200 µL was changed to 100 µL in the Synopsis and Sections 3.1.7.1, 6.3.3, and 6.4.
  - b. Section 2.1 (BI 1361849 dose): the following additions/changes were made (changes in bold):
 

“**Due to the filling volume of 100 µL, the device allows for administration of half the previously established doses, i.e., 160 µg instead of 320 µg per antigen when using the same manner of administration of two inoculations per antigen and vaccination time point. Advantages include improved patient convenience, handling safety, ease, and reliability of intradermal administration. Preclinical data showed that using a needle-free device such as the PharmaJet Tropis® device, the efficiency of delivery increases and protein production is higher even at half or a quarter of the administered dose, hence lower doses can be used. Clinical data from a Phase 2 trial, CV-9104-007, suggests that administration of half the dose by the PharmaJet Tropis® device results in at least similar immunogenicity compared to needle administration of the full dose. For this study, the Pharmajet Tropis® device will ~~not~~ be used for the administration of the BI 1361849 components. ~~Instead, standard intradermal injections using needles will be performed (see Section 6.3.3 for details).~~ Allowing for a filling volume of 100 µL (80 µg) and 2 administrations per component, the recommended dose per each of the 6**

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**antigen components will be 160 µg (2 x 80 µg), for a total of 960 µg (12 administrations).**

- c. Section 3.1.7.1 (Dose Evaluation Phase): the following note was added:  
“The Pharmajet Tropis® device will be used for the administration of the BI 1361849 components. Allowing for a filling volume of 100 µL (80 µg) and 2 administrations per component, the recommended dose per each of the 6 antigen components will be 160 µg (2 x 80 µg), for a total of 960 µg (12 administrations).”
  - d. Section 6.3.3 (BI 1361849 Administration): the following paragraph was added:  
“The Pharmajet Tropis® device will be used for the administration of the BI 1361849 components. Allowing for a filling volume of 100 µL (80 µg) and 2 administrations per component, the recommended dose per each of the 6 antigen components will be 160 µg (2 x 80 µg), for a total of 960 µg (12 administrations). Directions for use of the Pharmajet Tropis® device will be provided separately.”
  - f. Section 6.3.3(BI 1361849 Administration): the following paragraph was deleted:  
“A 30-gauge needle will be used for the injection. The needle should penetrate the skin at an angle of about 15 degrees and the injection should be administered slowly until a bubble appears underneath the skin surface. Subcutaneous injection (characterized by a missing bubble after the injection) must be avoided as it may result in reduced efficacy of the vaccine. However, if an injection is administered subcutaneously by error, the injection must not be repeated for this vaccination time point. Incorrect injections will be documented.”
2. Section 3.1.9 (DLT and MTD/RCD for the Combination Therapy): The following exception bullet was added to Point #3: “Grade 3 or 4 asymptomatic increases in amylase or lipase levels for which appropriate evaluation shows no clinical evidence of pancreatitis.” This was done to align with the amylase/lipase information in Section 8.3.1 dose modifications.
  3. Administrative: Spelling, grammar and typographical errors were corrected; formatting changes were implemented, as applicable.

#### **Amendment 4**

**Issue date: 19-MAY-2018**

#### **Summary of Changes:**

1. Synopsis: The following clarification was added (changes in bold: 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).
2. Section 3.2 (Flowchart)
  - a. Vital sign assessments were deleted from Cycle 2/Day 8, Cycle 4/Day 8, and Cycle 7/Day 22, as these visits require blood collection only, and no drug is being administered; vital sign assessments are not required.
  - b. Footnote e: the following note was added “Note: when durva vital assessments do not precede the BI 1361849 dose, pre-dose vital assessments must be done for BI 1361849.” This was added for clarification.
  - c. Footnote g was updated for clarification of biopsy sample collections and to align with the details and updates in Section 4.3.1.1.
3. Section 4.3.1.1 (Tumor Microenvironment) was re-organized and clarification was provided regarding the biopsy samples. It was clarified that on-treatment biopsy samples will only be

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collected if pre-treatment fresh biopsy samples were provided (so that paired biopsies may be examined); other clarifications were also provided. The text was changed

**FROM:**

“A minimum of 25 slides (5-µm, formalin-fixed, paraffin embedded (FFPE)) will be requested from archival (diagnostic) or pre-treatment biopsy specimens and post-treatment (end of study, if clinically feasible) biopsy specimens to evaluate PD-L1 expression as assessed by immunohistochemistry, neoantigen signature and immune biomarker expression in tissue, and to assess the correlation of these evaluations with clinical response as well as changes in profiling associated with resistance. Analyses may include the following:

- Mutational burden, gene expression profiling, and immune profiling from before therapy
- Immune markers of response and resistance in pre-treatment and post-treatment tumor biopsies.

A fresh core biopsy (minimum 3 cores from lung tissue or 4 cores from another site) obtained within 60 days of study start will be required prior to study entry; archival sample may be used if pre-treatment biopsy is not feasible. If possible, a post treatment biopsy will be collected 1 week after the 3rd or 5th BI 1361849 treatment.

If possible and as determined by the 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.

Remaining core biopsies will be formalin-fixed and paraffin-embedded as per institutional standards for further evaluation with immunohistochemistry (IHC) or tumor DNA/RNA extraction for microarrays sequencing or nanostring.

Optional core biopsies will be obtained at the time of tumor progression or at the completion of treatment from subjects who consent to this procedure. A minimum of 3 cores will be required.”

**TO:**

Samples:

- 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.
- 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.
- Optional post-treatment core biopsies (minimum 3 cores from lung tissue 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.
- If possible and as determined by the 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.

A minimum of 25 slides (5 µm formalin-fixed, paraffin embedded (FFPE)) will be requested from the biopsy specimens to evaluate PD-L1 expression as assessed by immunohistochemistry, neoantigen signature and immune biomarker expression in tissue, and to assess the correlation of these evaluations with clinical response as well as changes in profiling associated with resistance. Analyses may include the following:

- Mutational burden, gene expression profiling, and immune profiling from before therapy
- Immune markers of response and resistance.

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Remaining core biopsies will be formalin-fixed and paraffin-embedded as per institutional standards for further evaluation with immunohistochemistry (IHC) or tumor DNA/RNA extraction for microarrays sequencing or nanostring.

4. Section 4.3.1.1.1 (Immunohistochemistry). Language was clarified (changes in bold):
  - a. Paragraph 1: “Quantitative immunofluorescence will be used to evaluate multiple immune biomarkers simultaneously in FFPE archival tissue or in ~~pre and post treatment~~ biopsy samples, as available.”
  - b. Paragraph 3: “In this study, a pre-treatment biopsy will allow the evaluation of PD-L1 and other immune biomarkers to determine correlation with response to combination therapy. In addition to PD-L1 immunohistochemistry, CD3, CD4 and CD8 immunostaining will be performed to evaluate the degree of immune infiltrate in tumor specimens ~~pre and post therapy, as available~~. Finally, other markers of immune suppression (FoxP3 to stain T regulatory cells, TIM-3, Lag-3 and others) will be evaluated, **as feasible**.”
5. Section 4.3.1.1.3 (Gene Expression). Language was clarified (changes in bold): “Inflammatory or immune-related gene expression signatures may serve as predictors of clinical benefit and will be evaluated in ~~pre treatment and post treatment biopsies~~ **biopsy samples, as available**.”
6. Section 4.3.1.1.5 (Cytokines & Chemokines). Language was clarified (changes in bold): “Cytokine and chemokine environment will be determined on protein level in ~~pre and post-treatment biopsies~~ **biopsy samples, as available**.”
7. Section 4.3.2 (Subject Evaluation and Statistics), Paragraph 2, Sentence 1. Language was clarified (changes in bold): “The exploratory pharmacodynamic assessment of the immunologic changes in the tumor microenvironment will include the correlation between clinical activity and the expression level of PD-L1 and tumor-infiltrating lymphocyte (TILs) changes in ~~biopsy samples, as available. biopsies pre and post treatment~~.”
8. Section 5.1 (Inclusion Criteria) #3 was modified for clarification (changes in bold): “~~Availability of archival (diagnostic) specimens or willing~~ **Willing** to undergo a pre-treatment biopsy, **or if not feasible, availability of archival (diagnostic) specimens**.”
9. Section 5.2 (Exclusion Criteria), #16 was clarified as follows (changes in bold): “Any condition that, in the clinical judgment of the treating physician, is likely to **interfere with the interpretability of the data** or prevent the subject from complying with any aspect of the protocol or that may put the subject at unacceptable risk.” This was updated to reflect current protocol language.
10. Section 5.2 (Exclusion Criteria), #20 was changed **FROM**: “History of another primary malignancy except for: Malignancy treated with curative intent and with no known active disease  $\geq$ 5 years before the first dose of study drug and of low potential risk for recurrence; Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease; Adequately treated carcinoma in situ without evidence of disease.” **TO**: “Active or prior malignancy except for history of other prior malignancy treated with curative intent which, in the opinion of the treating investigator and the Sponsor, has minimal risk of interfering with safety or efficacy endpoints of the study.”  
Rationale: The language was updated to be consistent with current standards.
11. Section 6.5.2 (Monitoring for BI 1361849): the following Note was added for clarification: “Note: on dosing days when durvalumab vital assessments do not precede the BI 1361849 dose, pre-dose vital assessments must be done for BI 1361849.”

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12. Section 7.1.8 (AEIs): The section was updated and reorganized based on updated recommendations from Medimmune in the updated IB. Specifically:
  - a. Endocrine disorders-deleted diabetes insipidus.
  - b. Myocarditis and myositis/polymyositis were added
  - c. Other inflammatory responses section was updated (changes in bold):  
 “Other inflammatory responses that are rare / **less frequent** with a potential immune-mediated aetiology include, but are not limited to, **myocarditis**, pericarditis, **sarcoidosis**, uveitis, **and other events involving the eye, skin, hematological and rheumatological events**.”
13. Section 8.3.1 (Durvalumab and tremelimumab dose modification due to toxicity): Immune-related AEs were updated based on updated Toxicity Mgt Guidelines from Medimmune (Dated 01Nov2017). Specifically, myocarditis, myositis/polymyositis were added; Diarrhea/colitis and endocrinopathies were updated.
14. Administrative: Spelling, grammar and typographical errors were corrected; formatting changes were implemented, as applicable.

## Amendment 5

Issue date: 06-AUG-2018

### Summary of Changes:

1. The signature page was updated:
  - a. [REDACTED] was removed
  - b. Local Sponsor in EU was added
  - c. Coordinating Investigator in Germany was added
2. Section 2.2 (Durvalumab and Tremelimumab Dose). Last paragraph was clarified (changes in bold): “The **1500 mg Q4W** dosing of durvalumab ~~and tremelimumab~~ is recommended only for subjects with > 30kg body weight **due to in order to limit** endotoxin exposure. Subjects with a body weight ≤ 30 kg are not eligible for enrollment in the current study. See Section 3.1.7.1 for additional details regarding the dose de-escalation cohort for durvalumab and for **durvalumab and tremelimumab** dose requirements for instances when a subject’s body weight drops to ≤ 30 kg while on the study.”
3. Section 3.1.2 (Enrollment/Randomization).
  - a. First paragraph was updated to reflect change in prioritization from Cohort A Expansion to Cohort B Expansion, based on discussion with BI:

~~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 (see Section 3.1.7.1) and for the Arm A Expansion Cohort (see Figure 1), 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 in for Arm B is complete, and enrollment is complete in Arm A Expansion Cohort, enrollment will begin in into the Arm B Expansion Cohort and Arm B Control Group will be prioritized over Arm A (see Figure 1). Enrollment into Arm B Expansion Cohort and Arm B Control Group will be done in an alternating fashion (see Figure 1 and description below). If Arm B is not expanded due to toxicities, the Control Group will be added to the expansion for Arm A. The Arm A Control Group, will then start enrolling after the completion of Arm A Expansion Cohort, in a non-alternating fashion.¶~~

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b. Figure 1 was updated FROM:

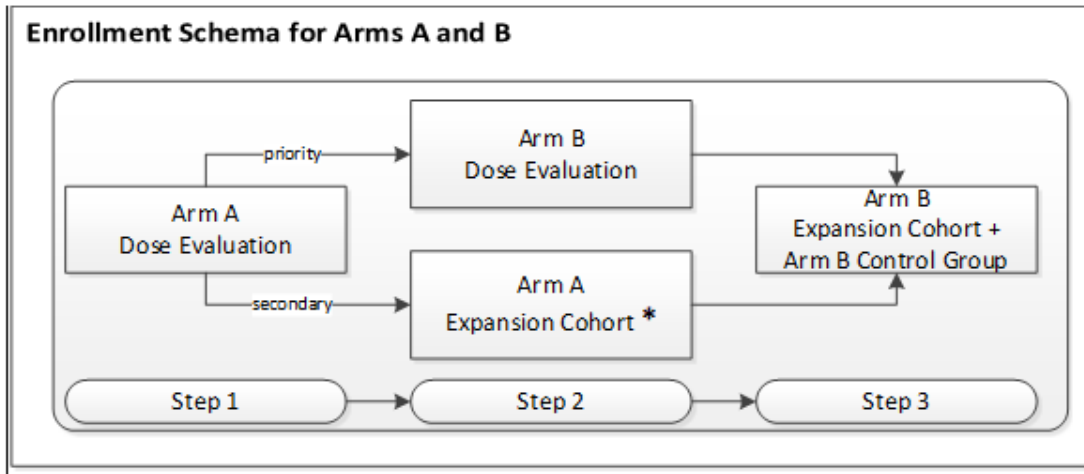


Figure-1. Enrollment Schema for Arms A and B¶

\*If Arm B Expansion Cohort and Arm B Control Group are not initiated due to toxicities, an Arm A Control Group (n=10 subjects; durvalumab only) will be added, which will start enrollment (in a non-alternating fashion) after Arm A Expansion Cohort has completed. ¶

TO:

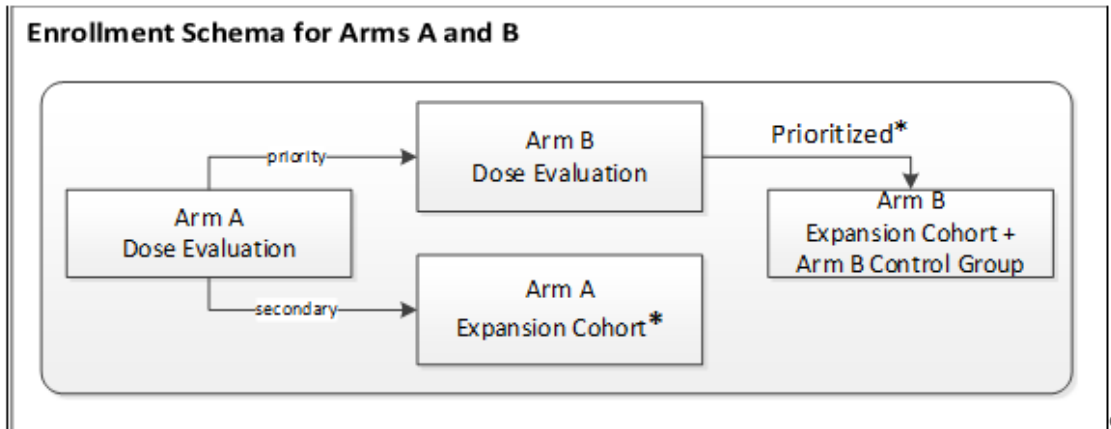


Figure-1. Enrollment Schema for Arms A and B¶

~~\*After the dose evaluation and safety review for Arm B is complete, enrollment into the Arm B Expansion Cohort and Arm B Control Group will be prioritized over Arm A. Enrollment into Arm B Expansion Cohort and Arm B Control Group will be done in an alternating fashion (as described below). ¶~~

~~If Arm B Expansion Cohort and Arm B Control Group are not initiated due to toxicities, an Arm A Control Group (n=10 subjects; durvalumab only) will be added, which will start enrollment (in a non-alternating fashion) after Arm A Expansion Cohort has completed. ¶~~

4. Section 3.1.7.1 (Dose Evaluation Phase).

- a. Numbers 1 and 2 were added to the notes
- b. Clarification was provided to indicate that weight-based dosing for subjects whose body weight drops to  $\leq 30$  kg while on study only applies to durvalumab 1500 mg Q4W and tremelimumab when it is given with durvalumab 1500 mg Q4W.

5. Section 4.3.1.1.2 (DNA Sequencing). Information was updated to remove Dana Farber Cancer Institute as the assay facility.
6. Section 6.1.3 (Durvalumab Preparation). Clarification was provided to indicate that weight-based dosing for subjects whose body weight drops to  $\leq 30$  kg while on study only applies to durvalumab 1500 mg Q4W.
7. Section 6.1.4 (Durvalumab Administration). Clarification was provided to indicate that a 0.2- or 0.22- $\mu$ m in-line filter is required for durvalumab infusion.
8. Section 6.2.3 (Tremelimumab Preparation). Clarification was provided to indicate that weight-based dosing for subjects whose body weight drops to  $\leq 30$  kg while on study applies to tremelimumab only when it is given along with durvalumab 1500 mg Q4W.
9. Section 6.2.4 (Tremelimumab Administration). Clarification was provided to indicate that a 0.2- or 0.22- $\mu$ m in-line filter is required for tremelimumab infusion.
10. Administrative: Spelling, grammar and typographical errors were corrected; formatting changes were implemented, as applicable.
11. Added EudraCT# to cover page.

#### Amendment 6

Issue date: 18-SEP-2018

#### Summary of Changes:

1. The signature page was updated because German sites will not be included in the study:
  - a. Deleted Signature lines for Local Sponsor in EU and Coordinating Investigator in Germany.
  - b. Deleted EudraCT# on cover page.
2. Section 3.1.4 (Subject Population) and Section 5.1 (Inclusion Criterion #1).  
 Changes in bold: "Subjects with histologically confirmed metastatic NSCLC. For subjects with **known EGFR or ALK/ROS-1** mutations, prior therapy must have included an EGFR tyrosine kinase inhibitor **or ALK/ROS-1 inhibitor, respectively. Subjects must not have ALK rearrangement. Subjects may have had 1 prior line of anti-PD-1/PD-L1 therapy and must not have had progression at or before 12 weeks after start of treatment.**"  
 Rationale: The reason for the change is that the number of patients who have not received anti-PD-1/PD-L1 antibody therapy is low due to the approval of pembrolizumab for first line in combination with chemotherapy as well as a single agent first line or after failure of platinum-based therapy as well as the approved indication for nivolumab and atezolizumab. Patients who received one of these therapies would now be eligible for this study.
3. Section 5.2 (Exclusion Criterion #2). Language was updated based on changes in Inclusion Criterion 1 (changes in bold): "Prior treatment with anti-~~PD-1, PD-L1, or~~ **CTLA4 therapy or other immunotherapy.**"

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4. Sections 6.1.1 and 6.2.1 (Study Drug Information). The following correction was made:

Labeling	Product name, lot number, <del>route of administration,</del> and storage conditions
----------	--

5. Section 6.1.3 (Durvalumab Preparation). The following changes were made to align with current Medimmune recommendations:

▪ Dose Preparation:

Durvalumab will be administered using an 250 mL IV bag containing 0.9% (w/v) saline or 5% (w/v) dextrose and delivered through an IV administration set with a 0.2- or 0.22- $\mu$ m in-line filter. ~~The final durvalumab concentration after dilution in the bag must be 1 mg/mL to 15 mg/mL. A volume of diluent equal to the calculated volume of durvalumab to be added to the IV bag must be removed from the bag prior to addition of durvalumab.~~ The calculated volume of durvalumab is ~~then~~ added to the IV bag, and the bag is mixed by gentle inversion to ensure homogeneity of the dose in the bag.

*Example:* For a 1500-mg dose (for subjects > 30 kg in weight), 30 mL of durvalumab ~~is to~~ may be diluted in a 250-mL IV bag, ~~and First, 30.0 mL of diluent is removed from the IV bag, and then 30 mL of durvalumab is added to the bag,~~ the bag is mixed by gentle inversion.

6. Section 6.2.3 (Tremelimumab Preparation). The following changes were made to align with current Medimmune recommendations:

a.

The dose of tremelimumab for administration must be prepared by the IP manager or designated personnel using aseptic technique. No incompatibilities between tremelimumab and polyvinylchloride or polyolefin have been observed. ~~However, administration sets containing cellulose based filters should not be used with tremelimumab.~~

b.

Dose Preparation:

Tremelimumab will be administered using an 250 mL IV bag containing 0.9% (w/v) saline or 5% (w/v) dextrose and delivered through an IV administration set with a 0.2- or 0.22- $\mu$ m in-line filter. ~~The final concentration of tremelimumab after dilution in the bag must be between 0.10 mg/mL and 10 mg/mL.~~ The calculated volume of tremelimumab is added to the IV bag, and the bag is mixed by gentle inversion to ensure homogeneity of the dose in the bag.

*Example:* The volume of tremelimumab required for 75-mg dose is 3.75 mL ~~and may be administered using a 250-mL bag.~~

7. Section 6.2.4 (Tremelimumab Administration). The following changes were made to align with current Medimmune recommendations:

The entire contents of the IV bag should be administered as an IV infusion over approximately 60 ( $\pm$  5) minutes (a 0.2- or 0.22- $\mu$ m in-line filter is required). ~~An infusion of less than 55 minutes is considered a deviation.~~

8. Administrative: Spelling, grammar and typographical errors were corrected; formatting changes were implemented, as applicable.

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**Amendment 6.1****Issue date: 01-NOV-2018****Summary of Changes:**Section 5.1, (Inclusion Criterion #1): last sentence was changed to provide clarification.**Changed FROM:** "Subjects may have had 1 prior line of anti-PD-1/PD-L1 therapy and must not have had progression at or before 12 weeks after start of treatment."**Changed TO:** "Subjects may have had 1 prior line of anti-PD-1/PD-L1 therapy. Subjects who received prior anti-PD-1/PD-L1 therapy must have progressed during or after treatment, but not prior to Week 12 of treatment."**Amendment 7****Issue date: 21-MAY-2019****Summary of Changes:**

- Section 3.1.10.1 (Treatment Beyond Progression). The first paragraph was changed (changes in bold), as irRECIST is the primary method for determining response and progression in this study.

"Subjects meeting criteria for radiographic progression by **irRECIST** ~~RECIST 1.1~~ (Section 8.5) will be allowed to continue on therapy until confirmation of progression **by irRECIST** if the subject agrees and signs an appropriate informed consent form regarding continuation of treatment and as long as the following criteria are met at the discretion of the Investigator:"

- Section 5.3.1 (Non-permitted concomitant therapies). Criterion # 5 was updated as follows (changes in bold):

"Drugs with laxative properties and herbal or natural remedies for constipation should **generally** be avoided through 90 days post last dose of tremelimumab because of the potential for exacerbation of diarrhea, **but, for example, opiate-induced constipation may be treated with laxatives at the Investigator's discretion.**"

- Section 6.2.1 (Tremelimumab Study Drug Information). The following was added: Tremelimumab is also available in a 25 mg/vial format; the concentration remains 20 mg/mL.

Manufacturer	MedImmune		
Expiration/Retest Date	<i>Expiration/retest dates are documented on the QA Disposition of Investigational Medicinal Product (IMP) Report.</i>		
Container Description	<i>Type:</i> Single-use vial	<i>Material:</i> Clear glass	<i>Size:</i> 2 mL
Formulation	Liquid solution containing 25 mg tremelimumab per vial. The solution contains 20 mg/mL tremelimumab, 20 mM histidine/histidine hydrochloride, 222 mM trehalose dihydrate, 0.27 mM disodium edetate dihydrate, and 0.02% weight/volume (w/v) polysorbate 80; it has a pH of 5.5.		
Active Ingredient Content	<i>Mass/Weight:</i> 25 mg/vial	<i>Volume:</i> 1.25 mL/vial	<i>Concentration:</i> 20 mg/mL
Storage Conditions	+2°C to +8°C (36°F to 46°F). Do not freeze.		
Labeling	Product name, lot number, and storage conditions		

- Section 6.3.2 (Preparation of Components of BI 1361849). The following paragraph was added: "NOTE (per Amendment 7):  
The first lot for this study (Lot E142087-008L002) expired at the end of May 2019.  
During testing of the replacement lots, one of the components (F2409) precipitated at 3

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hours after reconstitution in Ringer Lactate Solution (the precipitate was identified as protamine and RNA). Therefore, F2409 must be used within 2 hours of reconstitution. It is recommended that all of the components should be administered within the 2-hour timeframe, if possible. If this is not feasible, the 4-hour in use period is still applicable to the other 5 components.”

5. Formatting/administrative changes were implemented, as applicable.

#### **Amendment 8**

**Issue date: 24-JUL-2019**

##### **Summary of Changes:**

1. Section 5.1 Inclusion criteria 5. The following change was made (changes in bold):

Lymphocyte count	<b>&gt;800 ≥ 400 cells/μL. (See Section 3.3 for instructions for blood draws for PBMC collection.)</b>
------------------	--

2. Section 3.2 (Study Flowchart). Footnote L was added.
3. Section 3.3 (Additional Instructions for Blood Draws for PBMC Collection) was added.

##### **Rationale for the changes:**

The original lymphocyte requirement of 800 cells/μL was intended to allow for enough PBMCs to be collected for correlative analyses. However, the requirement was not allowing otherwise qualified subjects to enroll in the study. As the restriction was intended only to optimize the PBMC collection, it was decided to lower the lymphocyte requirement to 400 cells/μL with adjustment to blood volume collection for PBMCs when appropriate for the particular subject (See Laboratory Manual for additional details on blood volume and weight restriction).

#### **Amendment 8.1**

**Issue date: 17-SEP-2019**

##### **Rationale for the changes:**

The decision was made not to enroll any subjects into the Control Group for Arms A and B. As the protocol was previously amended to allow subjects pretreated with PD-1/PD-L1 inhibitors, baseline correlative sample testing can serve the purposes of the Control Group. In addition, reported results of the Phase III MYSTIC, ARCTIC and NEPTUNE studies of durvalumab plus tremelimumab in NSCLC did not find the combination to be superior to standard of care chemotherapy making it inappropriate to recruit subjects to the control treatment arm with tremelimumab and/or durvalumab without vaccine.

##### **Summary of Changes:**

All references to the Control Group for Arms A and B were removed. The following sections were affected:

- Synopsis
- Section 3.1 (Study Design)
- Section 3.1.2 (Enrollment Randomization), including Figure 1 (Enrollment Schema)
- Section 3.1.6 (Sample Size Considerations)
- Section 3.1.7 (Treatment Arms and Treatment Schema)
- Section 3.1.7.2 (Dose Expansion Phase)

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- Section 3.2 (Study Flowchart).
  - Removed footnote “I” which referenced the Control Group for Arm A/Arm B.
  - Footnote “L” (“See Section 3.3 for instructions for blood draws for PBMC collection”) was repositioned as Footnote “i”. Note: Footnote L was added per Amendment 8.
- Section 4.3.1.2.1 (Immune Monitoring for Responses to BI 1361849 Vaccine). The last 2 sentences in the first paragraph were deleted as they referred to the Control Group.
- Section 4.3.2 (Subject Evaluation and Statistics). The last bullet was changed as follows:  
~~The analysis of antigen-specific cell-mediated immune response by ICS is required to include all BI<sup>®</sup>1361849 antigens and including negative controls baseline values to be fully evaluable.~~ ¶

#### **Amendment 9 (27-AUG-2020)**

**NOTE: Amendment 9 was not released. Further clarifications were added and all changes were incorporated into Amendment 9.1.**

#### **Amendment 9.1**

**Issue date: 01-SEP-2020.**

1. Section 4.3.1.2 (Biological Activity in Blood Samples): Based on the decision of CureVac/Boehringer Ingelheim to discontinue immune monitoring testing, the collection of blood samples for this purpose was also discontinued. A note was added to Section 4.3.1.2 to indicate that the following sample collections were discontinued:
  - Blood for PaxGene RNA and DNA
  - Blood (PBMC and plasma) for flow cytometry and biological assays
  - Blood for humoral responses and other biomarkers
 Blood collections for exosomal profiling and tumor biopsy collections were continued.
2. ctDNA testing was removed from Section 4.3.1.2 .
3. Section 3.2 (Study Flowchart).
  - Notes were added to indicate discontinued blood collection for PaxGene RNA/DNA, PBMC, and humoral responses
  - Notes were added to footnotes i, J, and k to indicate the discontinuation of blood collection for PaxGene RNA/DNA, PBMC, and humoral responses
  - Note was added to footnote J to indicate that Visits 6, 14, and 28 would no longer be required per Amendment 9.1
  - ctDNA was deleted from the blood for exosomal profiling collection
4. References to the Note in Section 4.3.1.2 were also added to Section 3.3 (Additional Instructions for Blood Draws for PBMC Collection), Section 4.3.1 (Endpoints and Assessment Methods); Section 4.3.1.2.1 (Immune Monitoring for Responses to BI 1361849 Vaccine), and Section 4.3.2 (Subject Evaluation and Statistics).
5. Section 5.1 (Inclusion Criteria): The following note was added to criterion #2 for clarification:  
 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.

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The same note was added to Section 4.3.1.1 (Tumor Microenvironment) for item #1 and to Section 3.2 (Flowchart), footnote g, item #1.

**Amendment 10.0**

**Issue date: 30-JUL-2021.**



the following changes were made to the protocol:

1. All post study follow-up will be discontinued as of 31 October 2021. The following note was added to Sections 3.1.15 (Duration of Study), 3.1.16 (On Study and Post Study Follow-up), and 4.2.1 (Efficacy Endpoints and Assessment Methods):  
“NOTE: Per Amendment 10.0, all post study follow-up will be discontinued as of 31 October 2021.”
2. Section 4.3.1 (Biological Activity Endpoints and Assessment Methods) and Section 4.3.2 (Subject Evaluation and Statistics). The following note was added: “NOTE: Per Amendment 10.0, all correlative testing will be discontinued, with the possible exception of PD-L1 expression and whole exome sequencing.”
3. Section 3.2 (Flowchart). Footnote “L” was added: “Per Amendment 10, Post Study Follow-up will be discontinued as of 31 October 2021; and all correlative testing will be discontinued, with the possible exception of PD-L1 expression and whole exome sequencing.”
4. In addition to the above changes, AstraZeneca provided updated language for Section 7.1.2 (Additional reporting requirements for this study). Section 7.1.2.4 (New Cancers) and Section 7.1.2.5 (Deaths) were added.

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## **8.2 Participating Study Sites, Investigators and Staff, Laboratories, and Sponsor Information**

This information is provided in the Clinical Study File.

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### 8.3 Dose Adjustments and Delays for Durvalumab and Tremelimumab

If a toxicity occurs that requires toxicity management in accordance with Sections 8.3 or 8.4, and the toxicity causing drug can be clearly identified, then the respective guideline should be followed. If the toxicity causing drug cannot be identified, then the more conservative guideline should be followed.

#### 8.3.1 Durvalumab and Tremelimumab Dose Modification Due to Toxicity

Durvalumab (MEDI4736) and tremelimumab administration may be modified or discontinued as a result of toxicities as described in the table below.

Additional information and guidance regarding dose modification due to toxicity are provided from Medimmune in the following guidelines:

***“Medimmune’s Dosing Modification and Toxicity Management Guidelines for Immune-mediated, Infusion Related, and Non Immune-mediated Reactions (MEDI4736 (durvalumab) Monotherapy or Combination therapy with Tremelimumab or Tremelimumab monotherapy).”***

Dose modifications will not be required for AEs that are clearly not attributed to durvalumab or tremelimumab (such as an accident) or for laboratory abnormalities that are not deemed to be clinically significant.

MEDI4736 (M) and Tremelimumab (T) Dose Modification Due to Toxicity
<b>Note: If M and T dosing is held temporarily until resolution of the event as per instructions below, treatment should resume at the next <u>scheduled</u> treatment date.</b>
<b><i>Immune-related Adverse Events (irAEs)</i></b> Immune-related adverse events are defined as AEs of immune nature (i.e., inflammatory) in the absence of a clear alternative etiology. Maximum supportive care, including immunosuppressive medications, such as high dose steroids, is allowed to induce resolution of the event. <b>However, infliximab should not be used for management of immune-related hepatitis.</b> In addition to the criteria for permanent discontinuation of M and T depicted below, <b><u>permanently discontinue M and T</u></b> also for: <ul style="list-style-type: none"><li>• Any Grade rash with bullous skin formations.</li><li>• Inability to reduce corticosteroid to a dose of <math>\leq 10</math> mg of prednisone per day (or equivalent) within 12 weeks after last dose of study drug/regimen.</li><li>• Recurrence of a previously experienced Grade 3 treatment-related AE following resumption of dosing.</li><li>• <b>Any Grade biopsy-proven immune-mediated myocarditis.</b></li></ul> <b>Grade 1</b> <ul style="list-style-type: none"><li>• In general, no dose modification required.</li><li>• For <i>pneumonitis/interstitial lung disease and myocarditis</i>, consider holding M and T dosing as clinically appropriate and during diagnostic work-up for other etiologies.</li></ul>

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## Grade 2

- In general, hold M and T until resolution to  $\leq$  Grade 1 and after the end of any steroid taper, and discontinue M and T permanently if such resolution does not occur within 60 days (30 days for neurotoxicities). Criteria for temporary hold or permanent discontinuation of M and T may differ by event as detailed below.
- For *myositis/polymyositis*, hold M and T until resolution to  $\leq$  Grade 1; permanently discontinue M and T if it does not resolve to  $\leq$  Grade 1 within 30 days or if there are signs of respiratory insufficiency.
- For *pneumonitis/interstitial lung disease and myocarditis*, the decision to reinitiate M and T upon resolution shall be based upon treating physician's clinical judgment (as long as the event does not meet DLT criteria).
- For *peripheral neuromotor syndromes*, such as *Guillain-Barre* and *Myasthenia Gravis*, follow general instructions above, but always discontinue M and T permanently if there are signs of respiratory insufficiency or autonomic instability.
- For *endocrinopathies, other than isolated hypothyroidism and isolated Type 1 diabetes mellitus*, follow general instructions above, but subjects may be retreated if the endocrinopathy is controlled and the subject is clinically stable while requiring steroid doses of  $\leq$  10 mg/day prednisone equivalent.
- For *isolated hypothyroidism* managed with hormone replacement therapy, *isolated Type 1 diabetes mellitus* treated with appropriate diabetic therapy, and for *sensory neuropathy/neuropathic pain*, holding M and T is at the discretion of the Investigator.
- For *elevated creatinine* or *rash*, M and T should be held until resolution to  $\leq$  Grade 1 or baseline and after completion of steroid taper.
- For *vitiligo*, no dose modification required.

## Grade 3

- In general, hold M and T until resolution to  $\leq$  Grade 1, and after the end of any steroid taper, and discontinue M and T permanently if such resolution does not occur within 60 days (30 days for neurotoxicities and rash). Criteria for permanent discontinuation of M and T may differ by event as detailed below.
- For *myositis/polymyositis*, follow Grade 2 instructions above.
- For *peripheral neuromotor syndromes* (such as *Guillain-Barre* and *Myasthenia Gravis*), apply respective Grade 2 rules.
- For *endocrinopathies*, follow Grade 2 instructions above.
- For *diarrhea/colitis*, permanently discontinue M and T if toxicity does not improve to  $\leq$  Grade 1 within 14 days.
- For *pneumonitis/interstitial lung disease, myocarditis, and elevated serum creatinine (e.g., nephritis or renal dysfunction)*, always discontinue M and T permanently.
- For *asymptomatic increases of amylase or lipase* levels, hold M and T, and if complete work up shows no evidence of pancreatitis, M and T may be continued.
- For *hepatitis*, discontinue M and T permanently for (1) transaminases or bilirubin not resolving to  $\leq$  Grade 1 or baseline within 14 days, (2) transaminases  $> 8 \times$  the upper limit of normal (ULN) or bilirubin  $> 5 \times$  ULN, or (3) any case meeting Hy's law criteria (as defined in FDA Guidance Document "Drug-Induced Liver Injury").
- For *rash*, M and T should be held until resolution to  $\leq$  Grade 1 or baseline.

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<b>MEDI4736 (M) and Tremelimumab (T) Dose Modification Due to Toxicity</b>
<p><b>Grade 4</b></p> <ul style="list-style-type: none"> <li>• In general, discontinue M and T permanently.</li> <li>• For <i>endocrinopathies</i>, follow Grade 2 instructions above.</li> <li>• For <i>asymptomatic increases of amylase or lipase</i> levels, hold M and T, and if complete work up shows no evidence of pancreatitis, M and T may be continued.</li> </ul>
<p><b><u>Infusion-related Reactions</u></b></p> <p><b>Grade 1</b></p> <ul style="list-style-type: none"> <li>• The infusion rate of M and T may be decreased 50% or temporarily interrupted until resolution of the event.</li> <li>• Acetaminophen and/or antihistamines may be administered per institutional standards at the discretion of the Investigator.</li> <li>• Premedication for subsequent doses should be considered.</li> <li>• Steroids should not be used for routine premedication of <math>\leq</math>Grade 2 infusion reactions</li> </ul> <p><b>Grade 2:</b></p> <ul style="list-style-type: none"> <li>• <b>Same as Grade 1</b>, but consider giving subsequent infusions at 50% of the initial infusion rate.</li> </ul> <p><b>Grade 3 and 4:</b></p> <ul style="list-style-type: none"> <li>• <b>The infusion must be stopped</b> immediately and treatment permanently discontinued.</li> <li>• Manage severe infusion-related reactions per institutional standards (e.g., IM epinephrine, followed by IV diphenhydramine and ranitidine, and IV glucocorticoid).</li> </ul>
<p><b><u>All other Adverse Events</u></b></p> <p><b>Grade 1</b></p> <ul style="list-style-type: none"> <li>• No dose modification required.</li> </ul> <p><b>Grade 2</b></p> <ul style="list-style-type: none"> <li>• Hold M and T until resolution to <math>\leq</math> Grade 1 or baseline, and discontinue M and T permanently if such resolution does not occur within 60 days.</li> </ul> <p><b>Grade 3</b></p> <ul style="list-style-type: none"> <li>• Hold M and T. If AEs downgrade to <math>\leq</math> Grade 2 within 7 days or resolve to <math>\leq</math> Grade 1 or baseline within 14 days, resume M and T administration at next scheduled dose. Otherwise, discontinue M and T permanently.</li> </ul> <p><b>Grade 4</b></p> <ul style="list-style-type: none"> <li>• In general, discontinue M and T permanently.</li> <li>• For isolated lab results, decision to discontinue should be based on accompanying clinical signs/symptoms and per Investigator's clinical judgment and in consultation with the Sponsor.</li> </ul>

### **8.3.2 Durvalumab and Tremelimumab Dose Modification Not Due to Treatment-related Toxicities**

Durvalumab and tremelimumab administration may be modified or discontinued as a result of events other than toxicity, e.g., intercurrent illness or logistical/administrative reasons, whereby the following rules should apply:

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1. The originally planned visit/treatment schedule should be maintained in general, i.e., dosing interruptions should not reset the original treatment schedule. Exceptions may be made only for individual dosing days, whereby the interval between any two doses shall be no less than 21 days. All resulting protocol deviations should be documented.
2. If the dosing interruption causes 2 consecutive planned doses to be missed, the treatment should be discontinued.
3. If the dosing interruption is  $\leq$  half the planned dosing interval, the originally planned dose should be given and the next dose(s) should be adjusted in accordance with #1, if necessary.
4. If the dosing interruption is greater than half the planned dosing interval, the dose should be skipped and the next dose(s) should be adjusted in accordance with #1, if necessary.

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## 8.4 BI 1361849 Toxicity Management and Dose Modification

If a toxicity occurs that requires toxicity management in accordance with Sections 8.3 or 8.4, and the toxicity causing drug can be clearly identified, then the respective guideline should be followed. If the toxicity causing drug cannot be identified, then the more conservative guideline should be followed.

In case of adverse events considered related to BI 1361849 or to the combination of BI 1361849 with durvalumab or with durvalumab and tremelimumab, treatment with the vaccine (or with the vaccine as well as durvalumab and/or tremelimumab) may have to be withheld. If a subject experiences any  $\geq$  CTCAE Grade 3 treatment-related AE not fulfilling the criteria for permanent discontinuation, study drug treatment may be resumed after the toxicity has returned to baseline or Grade  $\leq$  1 within a time period  $\leq$  4 weeks for vaccination. No dose reduction of the vaccine dose is foreseen.

Administration of BI 1361849 must be withheld in the following cases and may be postponed to later time points within the allowance windows defined in the table below:

- Subject has fever  $\geq$  38.5 °C or other signs of an acute systemic infection on the day of administration.
- Subject has a suspected autoimmune disease - in this case BI 1361849 should be omitted until the diagnosis is confirmed or excluded. In case of a confirmed autoimmune disease the Sponsor should be contacted to decide whether BI 1361849 should be permanently discontinued.
- Subject has ongoing BI 1361849 related systemic toxicity of initially CTCAE grade 3 or higher that has not yet resolved to at least grade 1 or baseline.
- Subject has a suspected pneumonitis or other interstitial lung disease (ILD). In this case BI 1361849 should be omitted until the diagnosis is confirmed or excluded. In case of confirmed pneumonitis or other ILD, BI 1361849 should be discontinued.
- Subject has an important medical event that in the investigators opinion might be worsened by the administration of BI 1361849 (e.g. acute cardiac events that may deteriorate in case of fever induced by BI 1361849).

Vaccinations should always be administered within the planned time windows given in Section 3.2. However, vaccinations may have to be delayed to allow for recovery of AEs prior to continuation of vaccine treatment. For these circumstances, maximal allowance windows have been specified below. After the delayed vaccination all subsequent vaccinations must be continued within the schedule relative to the first vaccination presented in the flow chart. If a vaccination cannot be administered within the maximal allowance windows for an administration time point, the vaccine administration for this time point has to be omitted, and further vaccinations should be given at subsequent planned time points according to the flowchart in Section 3.2.

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<b>Maximal allowance windows due to AEs:</b>		
<b>Vaccination</b>	<b>Scheduled Week (Day 1 of)</b>	<b>Total extended visit window from originally scheduled vaccination (days)</b>
2 <sup>nd</sup>	2	3
3 <sup>rd</sup> , 4 <sup>th</sup> , 5 <sup>th</sup> , 6 <sup>th</sup> , 7 <sup>th</sup>	3, 5, 7, 9, 11	7
8 <sup>th</sup> , 9 <sup>th</sup>	13, 17	10
10 <sup>th</sup> and continuing	21, 27 and every 6 weeks	28

In the event that prior to a planned blood sampling time point for immunomonitoring, the immediately preceding vaccination has to be delayed or omitted, the blood sampling has to be delayed in the same fashion to ensure that the blood sample has been obtained within 7 ± 2 days after the immediately preceding vaccination. In the event that the vaccination had to be omitted, blood sampling should occur after the next subsequent vaccine administration.

The following toxicities prohibit continuation of study treatment:

- Grade ≥ 3 study treatment-related anaphylactic reactions.
- Study treatment related AEs that are potentially life threatening or may result in permanent disability.
- Grade ≥ 3 pneumonitis/inflammatory lung disease, or other ILD
- Grade ≥ 3 study treatment-related AEs not recovering to baseline or grade 1 within 4 weeks in case of vaccination. The Sponsor should be contacted in case it is considered justifiable to continue treatment at a later time point, to approve continuation of treatment of BI 1361849, which in any case must not occur before the AE finally has resolved or recovered to baseline or grade 1.
- Grade ≥ 3 study treatment-related AEs that reoccur after re-exposure to BI 1361849 (with the exception of local reactions at individual injections sites if they are considered tolerable by the investigator and the patient).

Note: After occurrence of related grade 1 or 2 anaphylactic reactions, a re-exposure may be considered, at the investigator's discretion, if anti-allergic premedication will be added (antihistaminergic agents and/or a steroid). A minimal acceptable allergy prophylaxis regimen will be 50 mg oral prednisone, to be taken at 13 hours, 7 hours and 1 hour prior to vaccination (or other equivalent) and/or 50 mg diphenhydramine i.v. 1 hour prior to vaccination (or other equivalent).

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## 8.5 RECIST 1.1 and irRECIST Guidelines

The Response Evaluation Criteria in Solid Tumors (RECIST) guidelines were revised in 2009 as RECIST 1.1.(31) These guidelines have been the widely accepted criteria to assess response and progression in solid tumors; however, limitations have been noted in the use of RECIST 1.1 for immunotherapy trials. With immunotherapeutic agents, clinical trials have shown that complete response, partial response, or stable disease status can still be achieved after an initial increase in overall tumor burden, and regression of initial lesions may occur despite development of new lesions. The Immune-related Response Criteria (irRC) were developed to address the need for response criteria in an immunotherapy setting.(32) The main difference with irRC was that it considered the subject's total tumor burden at each subsequent assessment and required confirmation of suspected disease progression with subsequent imaging, approximately four weeks later. In addition, a greater number of lesions (10 vs. 5) were measured in a bidimensional manner instead of unidimensionally as in RECIST 1.1. In 2013, Nishino et al. demonstrated that immune-related response criteria using unidimensional measurements were highly concordant with the bidimensional results of irRC, but with less measurement variability.(33) Based on these findings and in order to utilize both the established criteria of irRC and RECIST 1.1, the two systems have been adapted, modified, and combined into the Immune-related Response Evaluation Criteria in Solid Tumors (irRECIST).(34) The adapted irRECIST criteria are modifications to the irRC, incorporating the findings of Nishino et al. and the advantages of RECIST 1.1 while overcoming the shortcomings of each of the other guidelines.

The guidelines for RECIST 1.1 are summarized below, followed by a summary for irRECIST.

### RECIST 1.1

The following section outlines the RECIST 1.1 guidelines as published (31) and as summarized by National Cancer Institute for CTEP-involved clinical trials.

#### I. Disease Parameters for RECIST 1.1

Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST 1.1 criteria.

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as  $\geq 20$  mm by chest x-ray, as  $\geq 10$  mm with CT scan, or  $\geq 10$  mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable. *If the investigator thinks it appropriate to include them, the conditions under which such lesions should be considered must be defined in the protocol.*

**NOTE for irRECIST: During target lesion selection the radiologist will consider information on the anatomical sites of previous intervention (e.g. previous irradiation, RF-ablation, TACE, surgery, etc.). Lesions undergoing prior intervention will not be selected as target lesions unless there has been a demonstration of progress in the lesion.**

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Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be  $\geq 15$  mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter  $< 10$  mm or pathological lymph nodes with  $\geq 10$  to  $< 15$  mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts. 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same subject, these are preferred for selection as target lesions.

**NOTE for irRECIST:**

**Lesions that are partially cystic or necrotic can be selected as target lesions. The longest diameter of such a lesion will be added to the Total Measured Tumor Burden (TMTB) of all target lesions at baseline. If other lesions with a non-liquid/non-necrotic component are present, those should be preferred.**

**Brain lesions detected on brain scans can be considered as both target or non-target lesions depending on the protocol definition.**

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions. All other lesions (or sites of disease) including any non-measurable as well as measurable lesions over and above the 5 target lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

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## II. Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and  $\geq 10$  mm diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest x-ray: Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

PET-CT: At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to

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the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, Laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

Tumor markers: Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a subject to be considered in complete clinical response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published.(35-37) In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer.(38)

Cytology, Histology: These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (e.g., residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

FDG-PET: While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

- a) Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
- b) No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
- c) FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

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Note: A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

### III. Response Criteria for RECIST 1.1

#### A. Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study

#### B. Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis)

Note: If tumor markers are initially above the upper normal limit, they must normalize for a subject to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits

Progressive Disease (PD): Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

#### C. Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The subject's best response assignment will depend on the achievement of both measurement and confirmation criteria.

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**1. For Subjects with Measurable Disease (i.e., Target Disease)**

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	documented at least once ≥4 wks. from baseline**
SD	Non-CR/Non-PD/not evaluated	No	SD	
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

\* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.  
 \*\* Only for non-randomized trials with response as primary endpoint.  
 \*\*\* In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.  
 Note: Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as “*symptomatic deterioration.*” Every effort should be made to document the objective progression even after discontinuation of treatment.

**2. For Subjects with Non-Measurable Disease (i.e., Non-Target Disease)**

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

\* ‘Non-CR/non-PD’ is preferred over ‘stable disease’ for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

**D. Duration of Response**

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

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## irRECIST

Immune-related RECIST (irRECIST) guidelines according to Bohnsack et al. (34) are presented below.

### I. Baseline Assessments in irRECIST

In irRECIST, baseline assessment and measurement of measurable/non-measurable and target/non-target lesions and lymph nodes are in line with RECIST 1.1. One new definition is added: If a subject has no measurable and no non-measurable disease at baseline the radiologist will assign 'No Disease' (irND) as the overall tumor assessment for any available follow-up time points unless new measurable lesions are identified and contribute to the total measured tumor burden (TMTB). irND is a valid assessment in studies with adjuvant setting where the protocol and study design allow the inclusion of subjects with no visible disease.

### II Follow-up Assessments in irRECIST

#### *A. Follow-up recording of target and new measurable lesions*

**A key difference in irRECIST is that the appearance new lesions does not automatically indicate progression. Instead, all measured lesions (baseline-selected target lesions and new measurable lesions) are combined into the total measured tumor burden (TMTB) at follow up. Baseline-selected target lesions and new measurable lesions are NOT assessed separately. Measurements of those lesions are combined into the TMTB, and one combined assessment provided.**

In order to be selected as new measurable lesions ( $\leq 2$  lesions per organ,  $\leq 5$  lesions total, per time point), new lesions must meet criteria as defined for baseline target lesion selection and meet the same minimum size requirements of 10 mm in long diameter and minimum 15 mm in short axis for new measurable lymph nodes. New measurable lesions should be prioritized according to size, and the largest lesions elected as new measured lesions.

#### *B. Follow-up non-target assessment*

RECIST 1.1 definitions for assessment of non-target lesions apply. The response of non-target lesions primarily contributes to the overall response assessments of irCR and irNon-CR/Non-PD (irNN). Non-target lesions do not affect irPR and irSD assessments. Only a massive and unequivocal worsening of non-target lesions alone, even without progress in the TMTB is indicative of irPD. In alignment with RECIST 1.1, baseline selected non-target lesions can never convert to measurable lesions, not even if they increase in size at subsequent time points and become measurable. Only true new lesions can be measured and contribute to the TMTB.

#### *C. Follow-up for New Non-Measurable Lesions*

All new lesions not selected as new measurable lesions are considered new non-measurable lesions and are followed qualitatively. Only a massive and unequivocal progression of new non-measurable lesions leads to an overall assessment of irPD for the time point. Persisting new non-measurable lesions prevent irCR.

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### III Overall Assessments for irRECIST

The irRECIST overall tumor assessment is based on TMTB of measured target and new lesions, non-target lesion assessment and new non-measurable lesions.

At baseline, the sum of the longest diameters (SumD) of all target lesions (up to 2 lesions per organ, up to total 5 lesions) is measured. At each subsequent tumor assessment, the SumD of the target lesions and of new, measurable lesions (up to 2 new lesions per organ, total 5 new lesions) are added together to provide the total measurable tumor burden (TMTB).

Overall Assessments by irRECIST	
<b>Complete Response (irCR)</b>	Complete disappearance of all measurable and non-measurable lesions. Lymph nodes must decrease to < 10 mm in short axis.
<b>Partial Response (irPR)</b>	<p>Decrease of <math>\geq 30\%</math> in TMTB relative to baseline, non-target lesions are irNN, and no unequivocal progression of new non-measurable lesions</p> <ul style="list-style-type: none"> <li>If new measurable lesions appear in subjects with <b>no target lesions at baseline</b>, irPD will be assessed. That irPD time point will be considered a new baseline, and all subsequent time points will be compared to it for response assessment. irPR is possible if the TMTB of new measurable lesions decreases by <math>\geq 30\%</math> compared to the first irPD documentation</li> <li>irRECIST can be used in the <b>adjuvant setting</b>, in subjects with no visible disease on CT/MRI scans. The appearance of new measurable lesion(s) automatically leads to an increase in TMTB by 100% and leads to irPD. These subjects can achieve a response if the TMTB decreases at follow-up, as a sign of delayed response.</li> <li>Based on the above, sponsors may consider enrolling subjects with no measurable disease and/or no visible disease in studies with response related endpoints.</li> </ul>
<b>Stable Disease (irSD)</b>	Failure to meet criteria for irCR or irPR in the absence of irPD
<b>Progressive Disease (irPD)</b>	<p>Minimum 20% increase and minimum 5 mm absolute increase in TMTB compared to nadir, or irPD for non-target or new non-measurable lesions. Confirmation of progression is recommended minimum 4 weeks after the first irPD assessment. An irPD confirmation scan may be recommended for subjects with a minimal TMTB %-increase over 20% and especially during the flare time-window of the first 12 weeks of treatment, depending on the compound efficacy expectations, to account for expected delayed response.</p> <ul style="list-style-type: none"> <li>In irRECIST a substantial and unequivocal increase of <b>non-target lesions</b> is indicative of progression.</li> <li>IrPD may be assigned for a subject with multiple <b>new non-measurable lesions</b> if they are considered to be a sign of unequivocal massive worsening</li> </ul>
<b>Other</b>	<p><b>irNE:</b> used in exceptional cases where insufficient data exist.</p> <p><b>irND:</b> in adjuvant setting when no disease is detected</p> <p><b>irNN:</b> no target disease was identified at baseline, and at follow-up the subject fails to meet criteria for irCR or irPD</p>

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## **8.6 Exploratory Assessment of Correlative Immunologic Research**

Please refer to the Study Laboratory Manual for information on testing to be done and instructions on specimen handling and logistics.

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## 8.7 ECOG Performance Status

### Eastern Cooperative Oncology Group Performance Status

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

Reference: (39)

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## 8.8 List of Abbreviations

AE	adverse event
AESI	adverse event of special interest
ALK	Anaplastic lymphoma kinase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
CD	Cluster of differentiation
CI	confidence intervals
CR	Complete response
CRF	Case report form
CTC	Circulating tumor cell
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	Cytotoxic T lymphocyte-associated antigen 4
DC	Dendritic cell
DCR	Disease Control Rate
DLT	Dose limiting toxicity
DoR	Duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EGFR	epidermal growth factor receptor
FDA	Food and Drug Administration
FDG-PET	fluorodeoxyglucose (FDG)-positron emission tomography (PET)
FNA	Fine needle aspiration
FFPE	Formalin-fixed paraffin-embedded
GCP	Good Clinical Practice
GMP	Good manufacturing practice
HCC	hepatocellular carcinoma
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IHC	Immunohistochemistry
ICS	intracellular cytokine staining
IL	interleukin
ILD	Interstitial lung disease
IND	Investigational new drug
IMP	Investigational medicinal product
IP	Investigational product
irAE	Immune-related adverse event
irRC	immune-related response criteria

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irRECIST	Immune-related Response Evaluation Criteria in Solid Tumors
IV	intravenous
IRB	Institutional Review Board
LICR	Ludwig Institute for Cancer Research
mAb	Monoclonal antibody
MDSC	myeloid derived suppressor cells
MedDRA	Medical Dictionary for Regulatory Activities
MTD	maximum tolerated dose
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NSCLC	Non-small cell lung cancer
NK	Natural killer
ORR	Objective Response Rate
OS	Overall survival
OVA	ovalbumin
PBMC	Peripheral blood mononuclear cell
PD	Progressive disease
PD-1	Programmed death-1
PD-L1	Programmed death ligand 1
PFS	Progression free survival
PK	Pharmacokinetics
PR	Partial response
Q4W	Every 4 weeks
QTc	corrected QT interval
RECIST	Response Evaluation Criteria in Solid Tumors
RCC	Renal cell carcinoma
RCD	Recommended combination dose
SAE	Serious Adverse Event
SCCHN	squamous cell carcinoma of the head and neck
SD	Stable disease
TAA	Tumor-associated antigens
TIL	tumor-infiltrating lymphocyte
TME	Tumor microenvironment
TMTB	Total Measured Tumor Burden
Tregs	regulatory T-cells
ULN	Upper limit of normal
WFI	Water for Injection

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