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Official Title: "A Phase II open-label multicenter exploratory study to assess efficacy of Pembrolizumab re-challange as second or further line in patients with advanced non - small cell lung cancer" **REPLAY**

NCT Number: NCT03526887

Document Dates: Summary of Protocol Amendment Version 3.0: 14th January 2019

A PHASE II OPEN-LABEL MULTICENTER EXPLORATORY STUDY TO ASSESS EFFICACY OF PEMBROLIZUMAB RE-CHALLENGE AS SECOND OR FURTHER LINE IN PATIENTS WITH ADVANCED NON-SMALL CELL LUNG CANCER

REPLAY: Re-challenge Pembrolizumab study

Study Sponsor: Fundación GECP

EudraCT Number: 2017-003947-39

Sponsor code: GECP 17/02

[redacted]

Version 3.0

Contacts

[redacted]

Confidential

Trial Chairs **Principal Investigator** **Coordinator**	[redacted]	Oncology Service Hospital 12 de Octubre Avda. de Córdoba s/n [redacted]
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Protocol Signature Page

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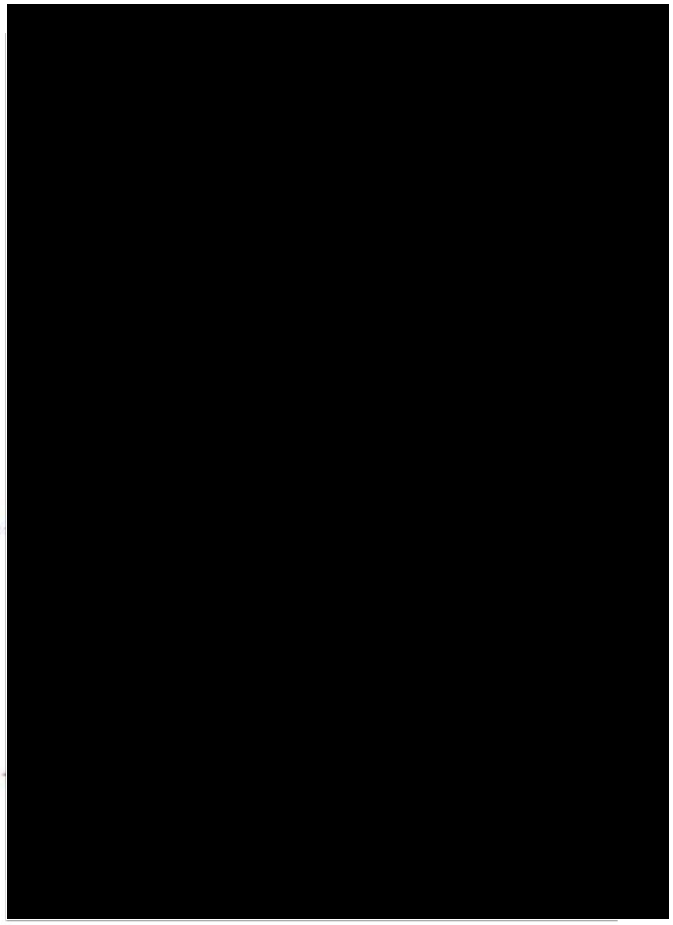
Sponsor code: GECP 17/02

Approved by:



Principal Investigator Protocol Signature Page

Study Title: "A Phase II open-label multicenter exploratory study to assess efficacy of Pembrolizumab re-challange as second or further line in patients with advanced non - small cell lung cancer" REPLAY

Sponsor protocol code: GECP 17/02

EudraCT Number: 2017-003947-39

Protocol version: v 3.0, 14th January 2019

As principal investigator of this site, I hereby confirm that:

I have read the protocol and agree that it contains all necessary details for conducting this trial. I will conduct the trial as outlined in the following protocol and in compliance with GCP, and will apply due diligence to avoid protocol deviations.

I will provide copies of the protocol and all drug information relating to pre-clinical and prior clinical experience furnished to me by the Fundación GECP, to all physicians responsible to me who participate in this trial. I will discuss this material with them to assure that they are fully informed regarding the drug and the conduct of the trial.

I agree to keep accurate records on all patient information including patient's informed consent statement, drug shipment and return forms, and all other information collected during the trial for a minimum period of 25 years according to the new Royal Decree 1090/2015 approved in Spain.

Name of Principal Investigator:_____

Institution's name and place:_____ _____

Signature Date

INDEX

1.0 TRIAL SUMMARY

Abbreviated Title	**Pembrolizumab(MK-3475) re-challenge as second or further line in patients with advanced non - small cell lung cancer**
Trial Phase	Phase II
Clinical Indication	Second or further line treatment in advanced NSCLC patients
Trial Type	Exploratory study
Trial Identification	Sponsor Code: GECP 17/02; Short name: REPLAY; MSD code: 345-726
Type of control	Not Applicable
Route of administration	Intravenous
Trial Blinding	Open label
Treatment Groups	2 groups depending on when the progression disease is diagnosed but the treatment after progression will be the same: Pembrolizumab
Number of trial subjects	110
Number of participant sites	19 sites in Spain
Estimated enrollment period	2 years
Estimated duration of trial	The sponsor estimates that the trial will require approximately 4 years (2 years of inclusion period + 1 year to achieve (FPLV) + 1 year of follow up)
Duration of Participation	Each subject will participate in the trial from the time the subject signs the Informed Consent Form (ICF) through the final protocol-specified contact. Estimated period of time of two years per patient.
Estimated average length of treatment per patient	According to previous data of patient treated with Pembrolizumab, the estimated average length of the treatment is approximately 7 to 10 months.
Sponsor details	Fundación GECP Avenida Meridiana 358, 6ª planta, 08027 Barcelona (Spain) [redacted]

2.0 TRIAL DESIGN

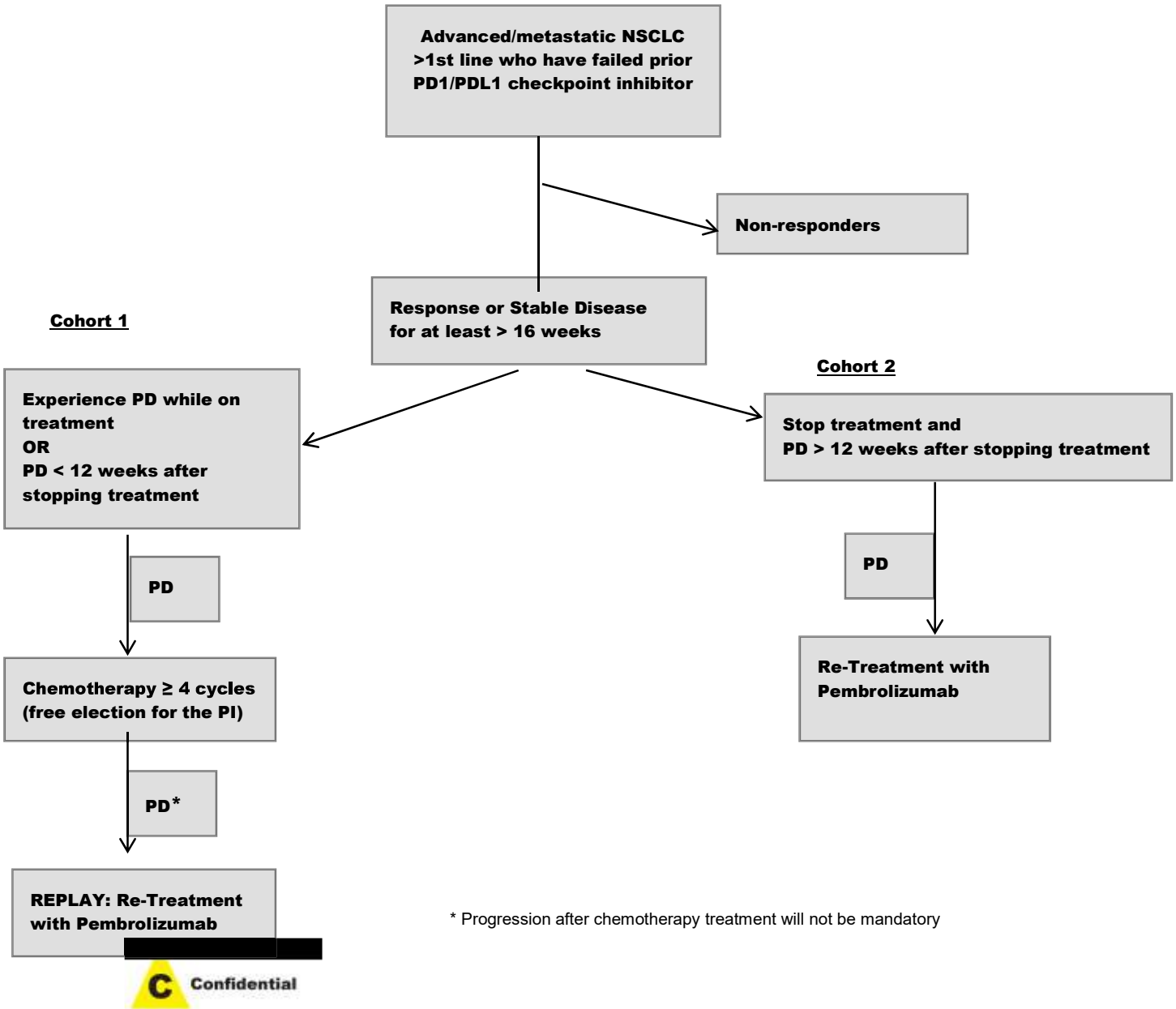
2.1 Trial Identification

Sponsor code: GECP 17/02

Eudract: 2017-003947-39

Protocol title: "**A Phase II open-label multicenter exploratory study to assess efficacy of Pembrolizumab re-challenge as second or further line in patients with advanced non - small cell lung cancer**" REPLAY

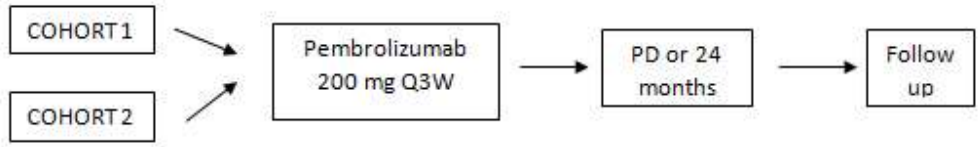
2.2 Patient selection diagram



* Progression after chemotherapy treatment will not be mandatory

[redacted]

2.3 Trial diagram design



This is a multi-center exploratory phase II trial of intravenous (IV) Pembrolizumab MK-3475 as second or further line with advanced Non-small cell Lung Cancer (NSCLC) who have failed to a prior treatment with anti-PDL1 drug. 110 patients will be enrolled in this trial to examine the efficacy and outcomes of these patients.

Specific procedures to be performed during the trial, as well as their prescribed times and associated visit windows, are outlined in the Trial Flow Chart. - Section 5.0. Details of each procedure are provided in Section 6.0 – Trial Procedures. In addition to the usual procedures in a phase II study (evaluation of response, toxicity, etc.) special attention will be paid in this trial to the molecular assessment in biological samples.

Subjects will receive Pembrolizumab at a fixed dose of 200 mg every 3 weeks (Q3W) Subjects will be evaluated with radiographic imaging to assess response to treatment. Investigators will make all treatment-based decisions using the Immune-Related Response Criteria (irRC). However, for determination of overall response rate (ORR) and progression-free survival (PFS), the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 will be used. Adverse events will be monitored throughout the trial and graded in severity according to the guidelines outlined in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Treatment with Pembrolizumab will continue until documented disease progression, unacceptable adverse event(s), intercurrent illness that prevents further administration of treatment, investigator's decision to withdraw the subject, subject withdraws consent, noncompliance with trial treatment or procedure requirements, or administrative reasons. After the end of treatment, each subject will be followed for a minimum of 30 days for adverse event monitoring (serious adverse events will be collected for up to 90 days after the end of treatment unless the subject starts a new anticancer therapy between days 31 and 90). Subjects will have post-treatment follow-up for disease status, including initiating a non-study cancer treatment and experiencing disease progression, until death, withdrawing consent, or becoming lost to follow-up.

Participation in this trial will be dependent upon supplying tumor tissue from a newly obtained formalin-fixed specimen from locations not radiated prior to biopsy. The specimen will be evaluated at a central laboratory facility for expression status of PD-L1 in a prospective manner. Only subjects whose tumors express PD-L1 as determined by the central laboratory facility will be eligible for inclusion in this study. Also, it is highly recommended to send archival tumor tissue from the patient.

3.1 3.0 OBJECTIVE(S) & HYPOTHESIS(ES)Primary Objective(s) & Hypothesis(es)

- To evaluate the efficacy of Pembrolizumab re-challenge administered 200 mg iv every 21 days in second or further line for advanced NSCLC after progression tocheck point PD1 / PDL1 inhibitors measured by Overall Response Rate (ORR) per RECIST v1.1 and per modified RECIST(irRC).

Hypothesis: Patients that have exhibit benefit to check point PD1 / PDL1 inhibitors may benefit from further Pembrolizumab therapy at the time of progression. The degree of benefit may depend on the initial response to previous check point PD1 /PDL1 inhibitors and its duration, and to the intercalation (or not) of any additional treatments such as chemotherapy among those patients without benefit to check point PD1/PDL1 inhibitors.

3.2 Secondary Objective(s) &Hypothesis(es)

- To evaluate the efficacy of Pembrolizumab re-challenge administered 200 mg iv every 21 days in second or further line for advanced NSCLC after progression to check point PD1 / PDL1 inhibitors measured by Progression Free Survival (PFS) per RECIST v1.1 and per modified RECIST. and Overall Survival (OS).

- To evaluate the safety and tolerability profile of Pembrolizumab re-challange administered 200 mg iv every 21 days in second or further line for advanced NSCLC after progression to check point PD1 / PDL1 inhibitors measured by Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 (U.S. Department of Health and Human Services - National Cancer Institute - National Institutes of Health)

3.3 Exploratory Objective

- To evaluate predictive and prognostic exploratory biomarkers in archival or newly obtained formalin-fixed specimen and blood and their association with disease status and/or response to treatment.

3.4 Trial Study centers

This trial will be carried out in 19 participant study sites in Spain.

3.5 Trial duration

Approximately 4 years (2 years of inclusion period + 1 year to achieve (FPLV) + 1 year of follow up).

3.6 Sponsor details and monitor identification

Sponsor

Fundación GECP

Avenida Meridiana 358, 6ª planta

08027 Barcelona

Monitors

[redacted]

Fundación GECP

Avenida Meridiana 358, 6ª planta

08027 Barcelona

4.0 BACKGROUND & RATIONALE

4.1 Background and rationale

Lung cancer is the leading cause of cancer related deaths among men and women worldwide, with 1.2 million new cases diagnosed each year. Non-small cell lung cancer (NSCLC) is the most common type of lung cancer, accounting for 80% of all new cases. There are an estimated 1.1 million lives lost per year (approximately 500,000 in the United States and European Union alone) due to NSCLC.

The majority of patients are not diagnosed until the tumor has progressed beyond the primary site. Despite step-wise advances in patient selection, targeted agents and optimizing chemotherapy regimens, patients with advanced NSCLC continue to have an unmet medical need (1).

Platinum containing chemotherapy regimens remain the standard first line treatment in the majority of patients in the US and Japan. For first line therapy in patients with Stage IV NSCLC and good performance status, the American Society of Clinical Oncology (ASCO) clinical practice guideline recommends treatment with a platinum based two drug combination of cytotoxic drugs (2). For patients without disease progression, the option of maintenance monotherapy pemetrexed or erlotinib could also be considered (3). A trend that is becoming more prevalent is personalized NSCLC treatment based on tumor histology (squamous versus non squamous), on molecular characteristics of the tumor, and on the patient's clinical status using agents targeting specific receptors and kinases and pathways (ie, epidermal growth factor receptor [EGFR], echinoderm microtubule associated protein like 4 [EML4] and anaplastic lymphoma kinase [ALK] fusion protein).

In second-line NSCLC, single agent chemotherapy (pemetrexed, EGFR-inhibitors and taxanes) are standards of care for treatment of patients with locally advanced or metastatic NSCLC after failure of prior platinum-based chemotherapy. Docetaxel has been widely evaluated in this setting and is currently approved by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) as a single agent for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of prior platinum-based chemotherapy. For patients with a good performance status at the time of disease progression following first-line chemotherapy, docetaxel, despite a low response rate, is associated with a 10% to 20% prolongation of 1-year survival and an improved quality of life when compared with ifosfamide, vinorelbine, or BSC alone (4). Erlotinib is indicated for the treatment of patients with locally advanced or metastatic NSCLC after failure of at least one prior chemotherapy regimen. Pemetrexed is indicated as a single-agent for the treatment of patients with locally advanced or metastatic nonsquamous NSCLC after prior chemotherapy.

The programmed death receptor 1 (PD-1) is a key immune checkpoint receptor expressed by activated T cells that modulates a late stage of the immune response by negatively regulating the activation of T cells in peripheral tissues. The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. PD-1 is an immunoglobulin (Ig) superfamily member related to CD28 and CTLA-4 which has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands PD-L1 and/or PD-L2 (5,6). PD-1 and family members are type I transmembrane glycoproteins containing an Ig Variable-type (V-type) domain responsible for ligand binding and a cytoplasmic tail responsible for the binding of signaling molecules. Following T cell stimulation, PD-1 recruits the tyrosine phosphatases, SHP-1 and SHP-2, to the ITSM motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules which are

involved in the CD3 T cell signaling cascade (6, 7, 8). The mechanism by which PD-1 down modulates T cell responses is similar to, but distinct from, that of CTLA-4, as both molecules regulate an overlapping set of signaling proteins (9). PD-1 was shown to be expressed on activated lymphocytes including peripheral CD4+ and CD8+ T cells, B cells, T regs, and natural killer cells (10). Expression has also been shown during thymic development on CD4-CD8- (double negative) T cells, as well as subsets of macrophages and dendritic cells (11). The ligands for PD-1 (PD-L1 (B7-H1) and PD-L2 (B7-DC)) are constitutively expressed or can be induced in a variety of cell types including non-hematopoietic tissues and in various tumors (9,12, 13,14). Binding of either PD-L1 or PD-L2 to PD-1 inhibits T cell activation triggered through the T cell receptor. PD-L1 is expressed at low levels on various non-hematopoietic tissues, most notably on vascular endothelium; whereas PD-L2 is only detectably-expressed on antigen-presenting cells found in lymphoid tissue or chronic inflammatory environments. PD-L2 is thought to control immune T cell activation in lymphoid organs, whereas PDL1 serves to dampen T cell function in peripheral tissues (9). Although healthy organs express little PD-L1, a variety of cancers were demonstrated to express abundant levels of this T cell inhibitor. High expression of PD-L1 on tumor cells has been found to correlate with poor prognosis and survival in various cancer types (15, 16). PD-L1 expression was described in many cancer types and in particular in lung cancer where up to 50% of NSCLCs are reported to express PD-L1 (17, 18, 19). High expressers of PD-L1 on IHC of tumor samples appear to get the best benefit from PD-1 or PD-L1 inhibitors although the benefit is not exclusive to this group (20, 21, 22, 23)

Antibody directed therapies against check point PD1/PDL1 have demonstrated efficacy in some malignancies, and now are true options in management of metastatic lung cancer. Two monoclonal antibodies directed to PD-1 (Nivolumab, Pembrolizumab) have reach the clinical practice as second line options for NSCLC. Also, monoclonal antibodies directed to PDL1 /PD1 (Atezolizumab, Durvalumab, Avelumab, Pidilizumab) are under investigational exploration. Three anti-PD-1 (Nivolumab, Pidilizumab, Pembrolizumab) and four anti-PD-L1 (BMS-936559, Durvalumab, Atezolizumab, Avelumab) antibodies have been investigated in phase I studies and are under further development in NSCLC (24). In all phase I trials, the maximum-tolerated dose was not reached, and all doses were found to be safe. The frequency of immune-related toxicities from anti–PD-1/anti–PD-L1 treatments appears less than that from anti-CTLA4 treatment. The common drug-related AEs were decreased appetite, anemia, diarrhea, nausea, pruritus, fatigue, pneumonitis, and elevated transaminase (25, 26, 27, 28, 29, 30).

The clinical efficacy of check point PD1/PDL1 inhibitors has been tested and confirmed in four randomized clinical trials. Two phase III trial to compare Nivolumab versus docetaxel in patients that have progression to doublet platinum-based chemotherapy, both squamous or non-squamous NSCLC (20, 21). In the squamous trial Nivolumab resulted in improved overall survival (HR, 0.59, p< 0.001; median 9.2 vs 6 months), PFS (HR: 0.62, p<0.001; median 3.5 vs 2.8 months) and RR (20% vs 9%; p<0.008). The preplanned analysis for

efficacy and survival for PDL1 positive or negative resulted in global benefit for both groups (20). In the non-squamous trial Nivolumab resulted in improved OS (HR, 0.73. p<0.002; median 12.2 vs 9.4 months) and RR (19% vs 12%, p<0.02) but not PFS benefit was shown in global population. The preplanned analysis for efficacy and survival for PDL1 status emerged as a significant biomarker to determine Nivolumab benefit; patients with PDL1 positive doubled median OS when treated in the experimental arm versus docetaxel. On the other group of PDL negative there was a trend in PFS benefit and RR but there was no difference in OS between Nivolumab or Docetaxel (21). Another PD1 check point inhibitor also confirmed in a phase III randomized trial – Keynote 010 - comparing Pembrolizumab (two doses levels) versus docetaxel in patients that have progression to doublet platinum-based chemotherapy but limited to patients that expressed PDL1 (at least >1% of cells). OS was longer for Pembrolizumab versus Docetaxel (for 2 mg/kg dose HR, 0.71 p<0.0008; median 10.4 vs 8.5 months and for 10 mg/kg dose HR, 0.61 p<0.0001; median 12.7 vs 8.5 months). Similar to Nivolumab there was no significant PFS benefit. Among patients with at least 50% of tumor cells expressing PD-L1, OS was significantly longer with Pembrolizumab (HR, 0.54 p=0.0002; median 14.9 vs 8.2 months and HR, 0.50 p<0.0001; median 17.3 vs 8.2 months) (22). Based on previous data Nivolumab and Pembrolizumab have been approved for the treatment of patients with advanced disease that have progressed to first line chemotherapy. Atezolizumab, an anti PDL1 check point inhibitor showed consistent benefit over docetaxel in a phase II randomized trial in patients that have progressed to first or second-line chemotherapy (31)

Refer to the Investigator's Brochure (IB)/approved labeling for detailed background information on MK-3475.

4.2 Pharmaceutical and Therapeutic Background

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes (TILs) in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T-cells / FoxP3+ regulatory T-cells seems to correlate with improved prognosis and long-term survival in many solid tumors.

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an Ig superfamily member related to CD28 and CTLA-4 which has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PDL2). The structure of murine PD-1 has been resolved. PD-1 and family members are type I transmembrane glycoproteins containing an Ig Variable-type (V-type) domain responsible for ligand binding and a cytoplasmic tail which is responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an

immunoreceptor tyrosine-based inhibition motif (ITIM) and an immunoreceptor tyrosine-based switch motif (ITSM). Following T-cell stimulation, PD1 recruits the tyrosine phosphatases SHP-1 and SHP-2 to the ITSM motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3ζ, PKCθ and ZAP70 which are involved in the CD3 T-cell signaling cascade. The mechanism by which PD-1 down modulates T-cell responses is similar to, but distinct from that of CTLA-4 as both molecules regulate an overlapping set of signaling proteins. PD-1 was shown to be expressed on activated lymphocytes including peripheral CD4+ and CD8+ T-cells, B-cells, T regs and Natural Killer cells. Expression has also been shown during thymic development on CD4-CD8- (double negative) T-cells as well as subsets of macrophages and dendritic cells. The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types, including non-hematopoietic tissues as well as in various tumors . Both ligands are type I transmembrane receptors containing both IgV- and IgC-like domains in the extracellular region and contain short cytoplasmic regions with no known signaling motifs. Binding of either PD-1 ligand to PD-1 inhibits T-cell activation triggered through the T-cell receptor. PD-L1 is expressed at low levels on various non-hematopoietic tissues, most notably on vascular endothelium, whereas PD-L2 protein is only detectably expressed on antigen-presenting cells found in lymphoid tissue or chronic inflammatory environments. PD-L2 is thought to control immune T-cell activation in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T-cell function in peripheral tissues. Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T-cell inhibitor. PD-1 has been suggested to regulate tumor-specific T-cell expansion in subjects with melanoma (MEL). This suggests that the PD-1/PD-L1 pathway plays a critical role in tumor immune evasion and should be considered as an attractive target for therapeutic intervention.

Pembrolizumab is a potent and highly selective humanized monoclonal antibody (mAb) of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Keytruda™ (pembrolizumab) has been approved in the United Stated and by EMA for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilumumab and, if BRAF V600 mutation positive, a BRAF inhibitor. Also, it was approved for first and second-line lung cancer, head and neck cancer, and relapsed/refractory Hodgkin's disease..

4.3 Preclinical and Clinical Trial Data

Refer to the Investigator's Brochure for Preclinical and Clinical data.

4.4 Rationale for the Trial and Selected Subject Population

Lung cancer remains the most common cause of cancer related death in US and second one of the majors causes of cancer related death in EU. Despite latest progress with check point PD1/PDL1 inhibitors many patients still experience progression, recurrence disease or primary resistance being a challenge the treatment options of these patients. As previously explained PDL1 has been correlated with prognosis fueling the hypothesis that PDL1

expression is a mechanism for tumor immune evasion. Additionally PD1 is highly expressed on infiltrating human and circulating tumor specific T cells, a phenotype correlated with impaired T cell function (32, 33) These findings suggest that interrupting PD1-PDL1 interaction after progression could be an effective anticancer therapy in the context of immuno-editing: a)PD1 blockade, similar to CTL4 inhibition has the potential to establish a favorable equilibrium between adequate T cell response against the tumor and immune evasion by the tumor; b) tumor recurrence after successful treatment with PD1 blockade indicates disruption of this equilibrium; c) re-treatment with PD-1 inhibition after recurrence can reset this balance (34). Based on this rational Lipson reported a melanoma stage IV patient with good partial response to Nivolumab and after discontinuation of the drug the patient experienced progression; re induction with the same anti PD1 could swing immunological pendulum back in favor of the patient redirecting the immune system, after re treatment with Nivolumab again partial response was observed.

Moreover, the mechanism of governing homeostasis of the memory T cells remain undefined. Charlton published the crucial role of the negative co-stimulator PD1 in regulating developmental fates of memory phenotype cells. Thus, in lymphoid organs and tissues of PD1 knockout mice a marked accumulation of functional effector memory phenotype CD8 T cells was observed. CD8 T effector memory cells from PD1 knockout mice exhibit decreased proliferation but increased survival potential. In a elegant way is shown that the ablation of the PD1 pathway drives CD8 memory phenotype to CD8 T effector memory cells. That implies that increased duration of signal, in the absence of PD1, favors CD8 T effector memory cells differentiation through a T cell central memory (35)

For those tumors that experience primary resistant to check point PD1/PDL1 inhibitors as pancreatic cancer Winograd and colleagues reported their experience using a genetically engineered mouse model of pancreatic ductal adenocarcinoma, showing that PDL1 is prominent in the tumor microenvironment, a phenotype confirmed in patients. But treatment with check point PD1 monoclonal antibodies failed in well-established tumors, recapitulating clinical results. The combination of anti CD40 antibody and chemotherapy (especially gemcitabine) plus check point PD monoclonal antibody induced regression of subcutaneous tumors and improved OS. This finding suggests that in those patients with primary resistant to check point PD1/PDL1 inhibitors can be rescued by the priming of a T cell response with chemotherapy (36).

4.5 Rationale for Dose Selection/Regimen/Modification

An open-label Phase I trial (Protocol 001) was conducted to evaluate the safety and clinical activity of single agent MK-3475. The dose escalation portion of this trial evaluated three dose levels, 1 mg/kg, 3 mg/kg, and 10 mg/kg, administered every 2 weeks (Q2W) in subjects with advanced solid tumors. All three dose levels were well tolerated and no dose-limiting toxicities were observed. This first in human study of MK-3475 showed evidence of target

engagement and objective evidence of tumor size reduction at all dose levels (1 mg/kg, 3 mg/kg and 10 mg/kg Q2W). No MTD has been identified to date. 10.0 mg/kg Q2W, the highest dose tested in PN001, was the dose and schedule utilized in Cohorts A, B, C and D of this protocol to test for initial tumor activity. Recent data from other clinical studies within the MK-3475 program has shown that a lower dose of MK-3475 and a less frequent schedule may be sufficient for target engagement and clinical activity.

PK data analysis of MK-3475 administered Q2W and Q3W showed slow systemic clearance, limited volume of distribution, and a long half-life (refer to IB). Pharmacodynamic data (IL-2 release assay) suggested that peripheral target engagement is durable (>21 days). This early PK and pharmacodynamic data provides scientific rationale for testing a Q2W and Q3W dosing schedule.

A population pharmacokinetic analysis has been performed using serum concentration time data from 476 patients. Within the resulting population PK model, clearance and volume parameters of MK-3475 were found to be dependent on body weight. The relationship between clearance and body weight, with an allometric exponent of 0.59, is within the range observed for other antibodies and would support both body weight normalized dosing or a fixed dose across all body weights. MK-3475 has been found to have a wide therapeutic range based on the melanoma indication. The differences in exposure for a 200 mg fixed dose regimen relative to a 2 mg/kg Q3W body weight based regimen are anticipated to remain well within the established exposure margins of 0.5 – 5.0 for MK-3475 in the melanoma indication. The exposure margins are based on the notion of similar efficacy and safety in melanoma at 10 mg/kg Q3W vs. the proposed dose regimen of 2 mg/kg Q3W (i.e. 5-fold higher dose and exposure). The population PK evaluation revealed that there was no significant impact of tumor burden on exposure. In addition, exposure was similar between the NSCLC and melanoma indications. Therefore, there are no anticipated changes in exposure between different indication settings.

The rationale for further exploration of 2 mg/kg and comparable doses of pembrolizumab in solid tumors is based on: 1) similar efficacy and safety of pembrolizumab when dosed at either 2 mg/kg or 10 mg/kg Q3W in melanoma patients, 2) the flat exposure-response relationships of pembrolizumab for both efficacy and safety in the dose ranges of 2 mg/kg Q3W to 10 mg/kg Q3W, 3) the lack of effect of tumor burden or indication on distribution behavior of pembrolizumab (as assessed by the population PK model) and 4) the assumption that the dynamics of pembrolizumab target engagement will not vary meaningfully with tumor type.

The choice of the 200 mg Q3W as an appropriate dose for the switch to fixed dosing is based on simulations performed using the population PK model of pembrolizumab showing that the fixed dose of 200 mg every 3 weeks will provide exposures that 1) are optimally consistent with those obtained with the 2 mg/kg dose every 3 weeks, 2) will maintain

individual patient exposures in the exposure range established in melanoma as associated with maximal efficacy response and 3) will maintain individual patients exposure in the exposure range established in melanoma that are well tolerated and safe.

A fixed dose regimen will simplify the dosing regimen to be more convenient for physicians and to reduce potential for dosing errors. A fixed dosing scheme will also reduce complexity in the logistical chain at treatment facilities and reduce wastage.

4.6 Rationale for Endpoints

Current experience with immunomodulatory treatments shows that the objective response rate ant the progression-free survival may not correlate with the final clinical benefit for the patients, in terms of overall survival.

[redacted]

4.7 Efficacy Endpoints

ORR is the portion of patients with a tumor size reduction of a predefined amount for a minimum time period. Response duration is measured from the time of initial response until documented tumor progression. The FDA has generally defined RR as the sum of partial responses (PRs) and CRs. When defined in this manner, ORR is a direct measure of the drug's antitumor activity. Stable disease is not included in the ORR. Stable disease is optimally evaluated in randomized trials examining TTP or PFS. The selected response criteria to be used in registration trials should be prospectively discussed with the FDA. When comparing ORRs in different arms, the number of PRs and CRs, response durations, locations of responses, and associations between responses and symptom improvement should be examined. The clinical significance of the ORR should be assessed by the magnitude and duration in a risk-benefit analysis.

The progression-free survival (PFS) duration is defined as the time from randomization to objective tumor progression or death. Compared with TTP, PFS may be a preferred regulatory endpoint because it includes death and may correlate better with OS. In TTP analysis, deaths are censored either at the time of death or at an earlier visit. Assessment of either PFS or TTP needs to be conducted in randomized trials. Because of the subjectivity that may be introduced in endpoint assessment, blinding of trials or the use of an external blinded review committee is recommended. In assessing TTP or PFS, patients must be evaluated on a regular basis in all treatment arms, and an assessment of all disease sites should be performed. To reduce bias, the same assessment technique should be used at each follow-up, and the same evaluation schedule should be consistently used.

OS is the gold standard for demonstrating clinical benefit. Defined as the time from randomization to death, this endpoint is unambiguous and is not subject to investigator

[redacted]

interpretation. Survival is a direct clinical benefit to patients, and assessment can be calculated to the day. Patient benefit can be described as superior survival or noninferior survival after consideration of toxicity and the magnitude of benefit. Survival analysis requires a large sample size and may require long follow-up.

[redacted]

5.0 METHODOLOGY

5.1 Eligibility Criteria

5.1.1 Subject Inclusion Criteria

1. Patients with hystologically or cythologically confirmed NSCLC advanced or locally advanced disease (according to 8th version of the International Association for the Study of Lung Cancer Staging Manual in Thoracic Oncology) not amenable to radical treatment (IIIA, IIIB, IIIC, IV), squamous or non-squamous, recurrent after at least one prior line.

2. The subject must be willing and able to provide written informed consent/assent for the trial.

3. Patient must be aged ≥ 18 years of age on day of signing informed consent.

4. Measurable disease (at least 1 lesion) based on RECIST 1.1. Patients will not be eligible if this lesion was irradiated before inclusion.

5. Documented prior benefit (Stable Disease, Partial Response, Complete Response) to check point PD1/PDL1 inhibitor (Nivolumab, Pembrolizumab, Durvalumab, Atezolizumab, Avelumab or others) for at least 16 weeks (Stable Disease, Partial Response, Complete Response) and progression while on treatment (or <12 weeks after stopping) with the same PD-1/PD-L1 inhibitors. These patients should have received subsequent treatment with Chemotherapy for at least 4 courses (Cohort 1)

OR

Documented prior benefit (Stable Disease, Partial Response, Complete Response) to check point PD1/PDL1 inhibitor (Nivolumab, Pembrolizumab, Durvalumab, Atezolizumab, Avelumab or others) for at least 16 weeks (Stable Disease, Partial Response, Complete Response) and progression >12 weeks after stopping treatment (Cohort 2). No subsequent treatment before re-challenge is allowed in this cohort

6. Patient must be willing to provide tissue from a newly obtained core or excisional biopsy of a tumor lesion. PDL1 must be evaluable and at least 1% positive in tumor tissue. *Newly-obtained is defined as a specimen obtained up to 6 weeks (42 days) prior to initiation of treatment on Day 1.* Subjects for whom newly-obtained samples cannot be provided (e.g. inaccessible or subject safety concern) may submit an archived specimen only upon agreement from the Sponsor.*

NOTE: If a new sample core or excisional biopsy cannot be obtained but the patient has the PDL1 analyzed and positive in a archival tissue sample the patient can be included in the study and start the treatment and the archival tumor tissue could be sent afterwards for central laboratory confirmation

If no previous PDL1 result is available from the archival tissue, the patient cannot be included in the trial until central laboratory PDL1 result is available.

Other cases could be consulted with the trial chair.

7. Have a performance status of 0-1 on the ECOG Performance Scale.

8. Demonstrate adequate organ function as defined in Table 1, all screening labs should be performed within 7 days of treatment initiation.

Table 1Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1,500 /mcL
Platelets	≥100,000 / mcL
Hemoglobin	≥9 g/dL or ≥5.6 mmol/L without transfusion or EPO dependency (within 7 days of assessment)
Renal	
Serum creatinine **OR** Measured or calculated[a] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5 X upper limit of normal (ULN) **OR** ≥60 mL/min for subject with creatinine levels > 1.5 X institutional ULN
Hepatic	
Serum total bilirubin	≤ 1.5 X ULN **OR**
	Direct bilirubin ≤ ULN for subjects with total bilirubin levels > 1.5 ULN
AST (SGOT) and ALT (SGPT)	≤ 2.5 X ULN **OR** **≤** 5 X ULN for subjects with liver metastases
Albumin	≥2.5 mg/dL
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT) Activated Partial Thromboplastin Time (aPTT)	≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants ≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
[a]Creatinine clearance should be calculated per institutional standard.	

9. Female subject of childbearing potential should have a negative urine or serum pregnancy within 72 hours prior to receiving the first dose of study medication. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

10. Female subjects of childbearing potential (Section 5.9.2) must be willing to use an adequate method of contraception as outlined in Section 5.9.2 – Contraception, for the course of the study through 120 days after the last dose of study medication.

Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the subject.

11. Male subjects of childbearing potential (Section 5.9.2) must agree to use an adequate method of contraception as outlined in Section 5.9.2- Contraception, starting with the first dose of study therapy through 120 days after the last dose of study therapy.

Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the subject.

12. All patients will be required to submit a tumor sample for PD-L1 IHC expression. If the sample is inadequate for analysis, another sample could be provided. If a new sample cannot be obtained due to technical or clinical reasons, archival tissue can be sent. Other cases could be consulted with the trial chair.

5.1.2 Subject Exclusion Criteria

The subject must be excluded from participating in the trial if:

1. Is currently participating and receiving study therapy or has participated in a study of an investigational agent and received study therapy or used an investigational device within 4 weeks of the first dose of treatment.

2. Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment.

3. Has a known history of active TB (Bacillus Tuberculosis)

4. Hypersensitivity to pembrolizumab or any of its excipients.

5. Has had a prior anti-cancer monoclonal antibody (mAb) within 4 weeks prior to study Day 1 or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to agents administered more than 4 weeks earlier.

6. Has had prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to study Day 1 or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to a previously administered agent.

    - Note: Subjects with ≤ Grade 2 neuropathy are an exception to this criterion and may qualify for the study.

    - Note: If subject received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.

7. Has a known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin or squamous cell carcinoma of the skin that has undergone potentially curative therapy or in situ cervical cancer.

8. Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least four weeks prior to the first dose of trial treatment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids at a dose over 10 mg of prednisone or equivalent, for at least 7 days prior to trial treatment. This exception does not include carcinomatous meningitis which is excluded regardless of clinical stability.

9. Has active autoimmune disease that has required systemic treatment in the past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (eg., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.

10. Has a history of (non-infectious) pneumonitis that required steroids or current pneumonitis.

11. Has an active infection requiring systemic therapy.

12. Documented EGFR sensitizing mutation.

13. Documented ALK translocation.

14. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject's participation for the full duration of the trial, or is not in the best interest of the subject to participate, in the opinion of the treating investigator.

15. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.

16. Is pregnant or breastfeeding or expecting to conceive or father children within the projected duration of the trial, starting with the pre-screening or screening visit through 120 days after the last dose of trial treatment.

17. Has a known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies).

18. Has known active Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative] is detected).

19. Has received a live vaccine within 30 days of planned start of study therapy.

    Note: Seasonal influenza vaccines for injection are generally inactivated flu vaccines and are allowed; however intranasal influenza vaccines (e.g., Flu-Mist®) are live attenuated vaccines, and are not allowed.

20. Received radiation therapy to the lung of >30Gy within 6 months of the first dose of trial treatment.

21. Evidence of interstitial lung disease.

22. Has had previously serious adverse reactions (grade 3-4) related to previous PD1 / PDL1 inhibitors that preclude their treatment according to the principal investigator's criteria

5.2 Trial Treatments

The treatment to be used in this trial is outlined below in Table 2

Table 2 Trial Treatment

Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen/Treatment Period	Use
Pembrolizumab	200 mg	Q3W	IV infusion	Day 1 of each 3 week cycle	Experimental
Chemotherapy will be at investigators choice.					

The treatment will continue until progression, unacceptable toxicity, consent withdraw, or until the treatment is administered during 24 months, whichever occurs first.

Details on preparation and administration of pembrolizumab (MK-3475) are provided in the Drug Supply Manual.

5.3 Dose Selection/Modification

5.3.1 Dose Selection

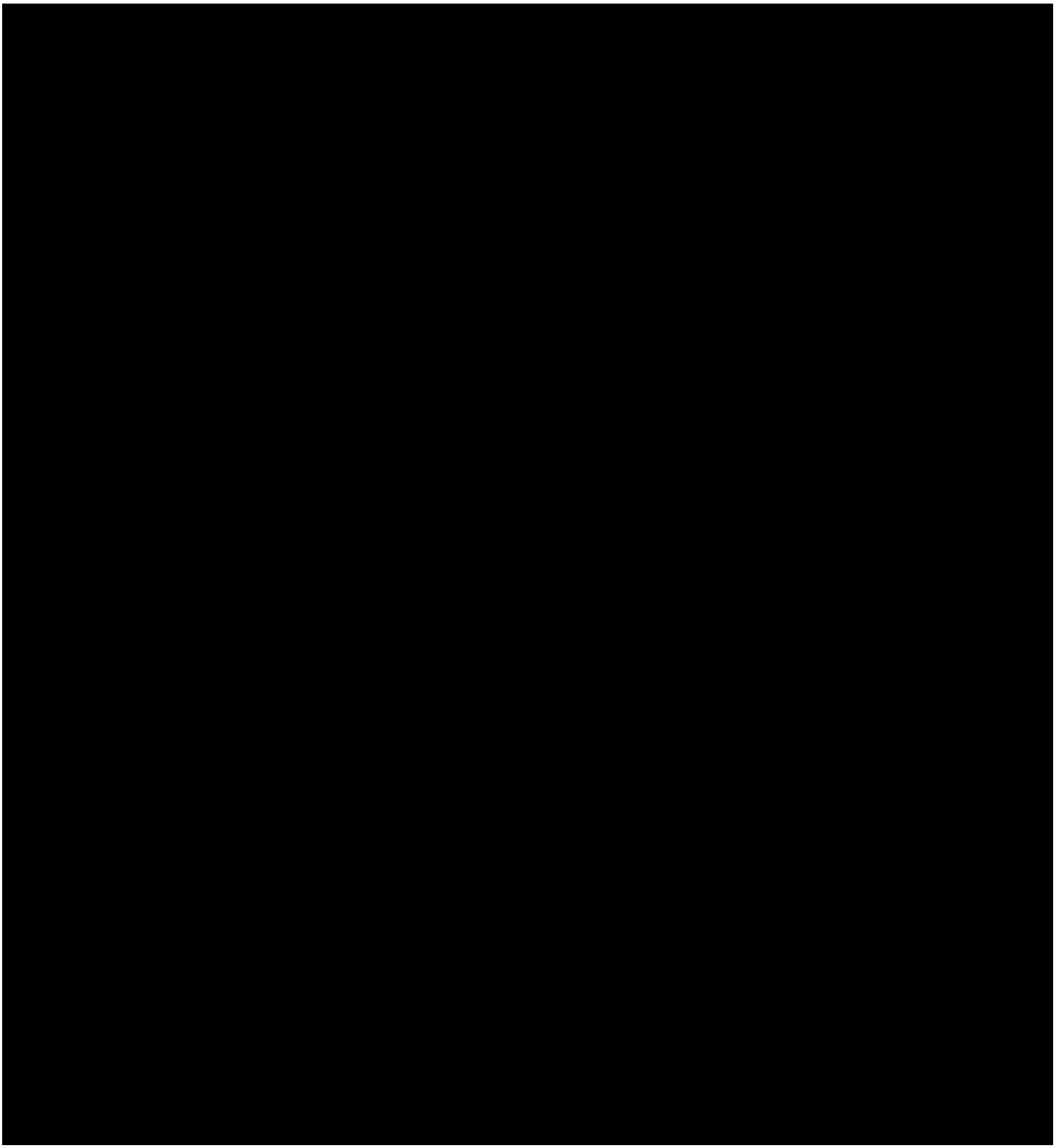
The rationale for selection of doses to be used in this trial is provided in Section 4.0 – Background and Rationale.

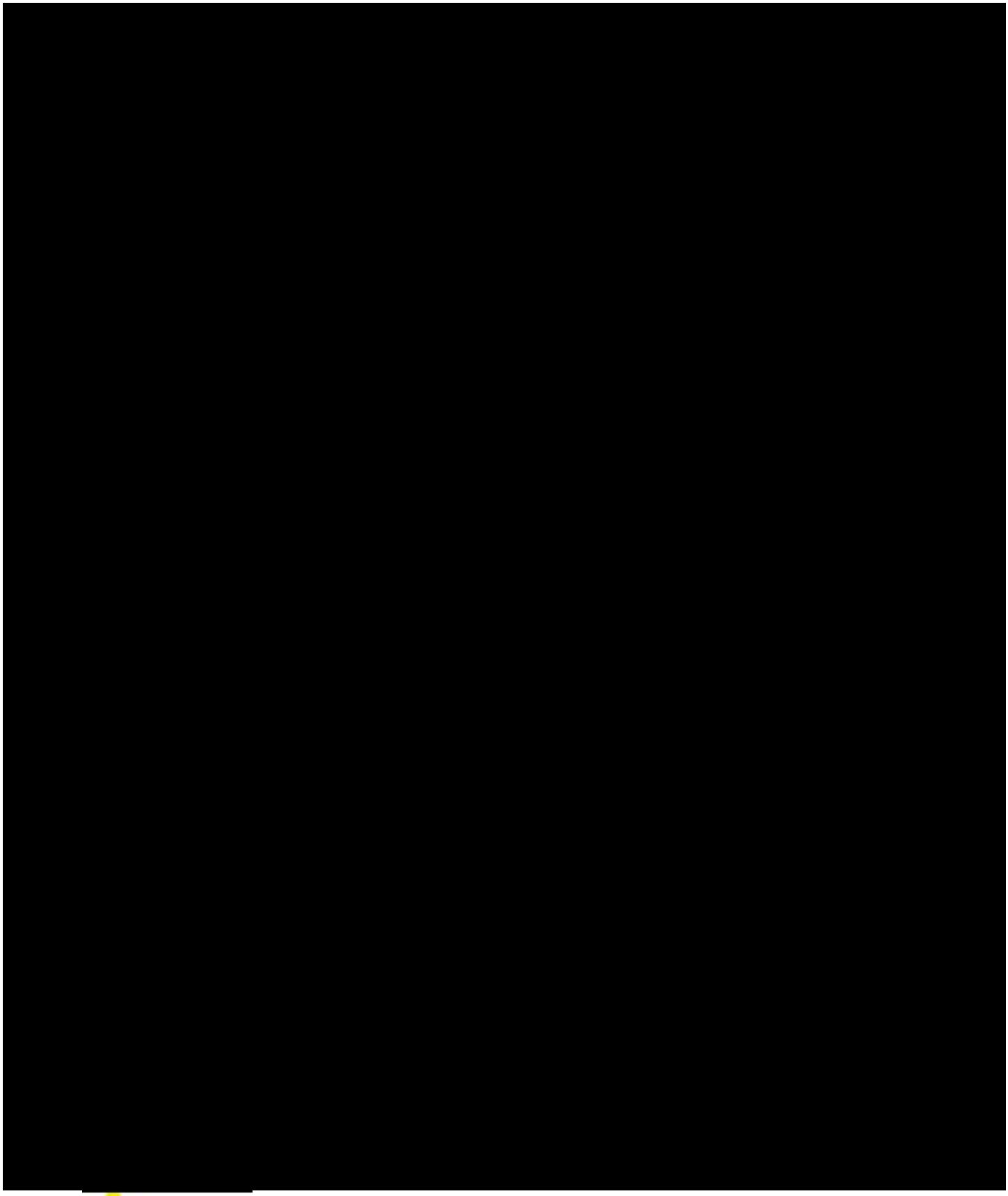
5.3.2 Dose Modification (Escalation/Titration/Other)

Adverse events (both non-serious and serious) associated with pembrolizumab exposure may represent an immunologic etiology. These adverse events may occur shortly after the first dose or several months after the last dose of treatment. Pembrolizumab must be withheld for drug-related toxicities and severe or life-threatening AEs as per 3 below. See Section 5.8.3.1 for supportive care guidelines, including use of corticosteroids.

Table 3

Dose Modification and Toxicity Management Guidelines for Immune-related AEs Associated with Pembrolizumab





[redacted]

5.4 Timing of Dose Administration and trial compliance

[redacted]

The Drug Supply Manual contains specific instructions for the preparation of the pembrolizumab infusion fluid and administration of infusion solution.

[redacted]

5.5 Trial Blinding/Masking

[redacted]

This is an open-label trial; therefore, the Sponsor, investigator and subject will know the treatment administered.

5.6 Randomization or Treatment Allocation

Step 1. Registration

Upon signing the informed consent, patients will be registered, and a sample of the tumor will be shipped and evaluated for PD-L1 expression at the central laboratory.

All patients will be required to submit a tumor sample for PD-L1 IHC expression. If the sample is inadequate for analysis, another sample could be provided. If a new sample cannot be obtained, archival tissue can be sent. Other cases could be consulted with the trial chair.

If PDL1 status cannot be assessed by the central laboratory in the archival or newly obtained sample (not enough tissue available, not concluding result, etc.) patients with previous PDL1 positive analyzed before stating the trial, can be evaluated by Trial Chair to grant the inclusion of the patient in the study.

Detailed instructions for tissue collection, processing and shipment are provided in the samples manual.

Step 2. Central Tumor Confirmation

Confirmation of PD-L1 status will be provided by the central laboratory in 7 working days (DAKO IHC 22C3) if possible.

Step 3. Treatment Allocation

The confirmation of PD-L1 (≥1%) expression must be available before proceeding with the Pembrolizumab treatment. The patient's written informed consent to undergo screening for the clinical trial must be given prior to the performance of any protocol laboratory/imaging tests that are not part of local routine guidelines.

Once patients are confirmed to be eligible they will be automatically enrolled.

A maximum of 110 eligible patients will be enrolled.

5.7 Stratification

Patients will be stratified by PDL1 expression levels (TPS 1-49% vs TPS ≥ 50%) and Performance Status (PS 0 vs1).

5.8 Concomitant Medications/Vaccinations (allowed & prohibited)

[redacted]

5.8.1 Acceptable Concomitant Medications

[redacted]

5.8.2 Prohibited Concomitant Medications

[redacted]

[redacted]

5.8.3 Rescue Medications & Supportive Care

5.8.3.1 Supportive Care Guidelines

[redacted]

[redacted]

[redacted]

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

[redacted]

[redacted]

[redacted]

[redacted]

5.9 Diet/Activity/Other Considerations

5.9.1 Diet

Subjects should maintain a normal diet unless modifications are required to manage an AE such as diarrhea, nausea or vomiting.

5.9.2 Contraception

Pembrolizumab may have adverse effects on a fetus in utero. Furthermore, it is not known that pembrolizumab has transient adverse effects on the composition of sperm.

For this trial, male subjects will be considered to be of non-reproductive potential if they have azoospermia (whether due to having had a vasectomy or due to an underlying medical condition).

Female subjects will be considered of non-reproductive potential if they are either:

(1) postmenopausal (defined as at least 12 months with no menses without an alternative medical cause; in women < 45 years of age a high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in

women not using hormonal contraception or hormonal replacement therapy. In the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.);

OR

(2) have had a hysterectomy and/or bilateral oophorectomy, bilateral salpingectomy or bilateral tubal ligation/occlusion, at least 6 weeks prior to screening;

OR

(3) has a congenital or acquired condition that prevents childbearing.

Female and male subjects of reproductive potential must agree to avoid becoming pregnant or impregnating a partner, respectively, while receiving study drug and for 120 days after the last dose of study drug by complying with one of the following:

(1) Practice abstinence[†] from heterosexual activity;

OR

(2) Use (or have their partner use) acceptable contraception during heterosexual activity.

Acceptable methods of contraception that can achieve a failure rate of less than 1% are[‡]:

Single method (one of the following is acceptable):

- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)• Bilateral tubal occlusion
- Vasectomy of a female subject's male partner
- • Sexual abstinence combined (estrogen and progesterone containing) hormonal contraception associated with inhibition of ovulation:
    - Oral
    - Intravaginal
    - Transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation
    - Oral
    - Injectable

- Implantable

†Abstinence (relative to heterosexual activity) can be used as the sole method of contraception if it is consistently employed as the subject's preferred and usual lifestyle and if considered acceptable by local regulatory agencies and ERCs/IRBs. Periodic abstinence (e.g., calendar, ovulation, sympto-thermal, post-ovulation methods, etc.) and withdrawal are not acceptable methods of contraception.

‡If a contraceptive method listed above is restricted by local regulations/guidelines, then it does not qualify as an acceptable method of contraception for subjects participating at sites in this country/region.

Acceptable methods of contraception which may not be considered as highly effective are:

- Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action
- Male or female condom with or without spermicide
- Cap, Diaphragm or sponge with spermicide

Subjects should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study subjects of childbearing potential must adhere to the contraception requirement (described above) from the day of study medication initiation (or 14 days prior to the initiation of study medication for oral contraception) throughout the study period up to 120 days after the last dose of trial therapy. If there is any question that a subject of childbearing potential will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

5.9.3 Use in Pregnancy

If a subject inadvertently becomes pregnant while on treatment with pembrolizumab, the subject will immediately be removed from the study. The site will contact the subject at least monthly and document the subject's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the Sponsor, and the sponsor will inform MSD Global Safety (GS) by fax (034 91 571 64 66) afterwards.

The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Sponsor. If a male subject impregnates his female partner the study personnel at the site must be informed immediately and the pregnancy reported to the Sponsor and to the marketing authorization holder of the drug used in this trial and followed as described above.

5.9.4 Use in Nursing Women

It is unknown whether pembrolizumab is excreted in human milk. Since many drugs are excreted in human milk, and because of the potential for serious adverse reactions in the nursing infant, subjects who are breast-feeding are not eligible for enrollment.

5.10 Subject Withdrawal/Discontinuation Criteria

Subjects may withdraw consent at any time for any reason or be dropped from the trial at the discretion of the investigator should any untoward effect occur. In addition, a subject may be withdrawn by the investigator or the Sponsor if enrollment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons.

Specific details regarding discontinuation or withdrawal are provided in section 7.6.1.

A subject must be discontinued from the trial for any of the following reasons:

- The subject or legal representative (such as a parent or legal guardian) withdraws consent.
- Confirmed radiographic disease progression

  Note: A subject may be granted an exception to continue on treatment with confirmed radiographic progression if clinically stable or clinically improved. All these cases must be approved by Trial Chair before starting the treatment beyond progression.
- Unacceptable adverse experiences
- Intercurrent illness that prevents further administration of treatment
- Investigator's decision to withdraw the subject
- The subject has a confirmed positive serum pregnancy test
- Noncompliance with trial treatment or procedure requirements

- The subject is lost to follow-up

- Completed 24 months of uninterrupted treatment with pembrolizumab or 35 administrations of study medication, whichever is later.

  Note: 24 months of study medication is calculated from the date of first dose.

- Administrative reasons

The End of Treatment and Follow-up visit procedures are listed in Section 6 (Protocol Flow Chart). After the end of treatment, each subject will be followed for 30 days for adverse event monitoring (serious adverse events will be collected for 90 days after the end of treatment as described in section 7.9.). Subjects who discontinue for reasons other than progressive disease will have post-treatment follow-up for disease status until disease progression, initiating a non-study cancer treatment, withdrawing consent or becoming lost to follow-up. After documented disease progression each subject will be followed by telephone for overall survival until death, withdrawal of consent, or the end of the study, whichever occurs first.

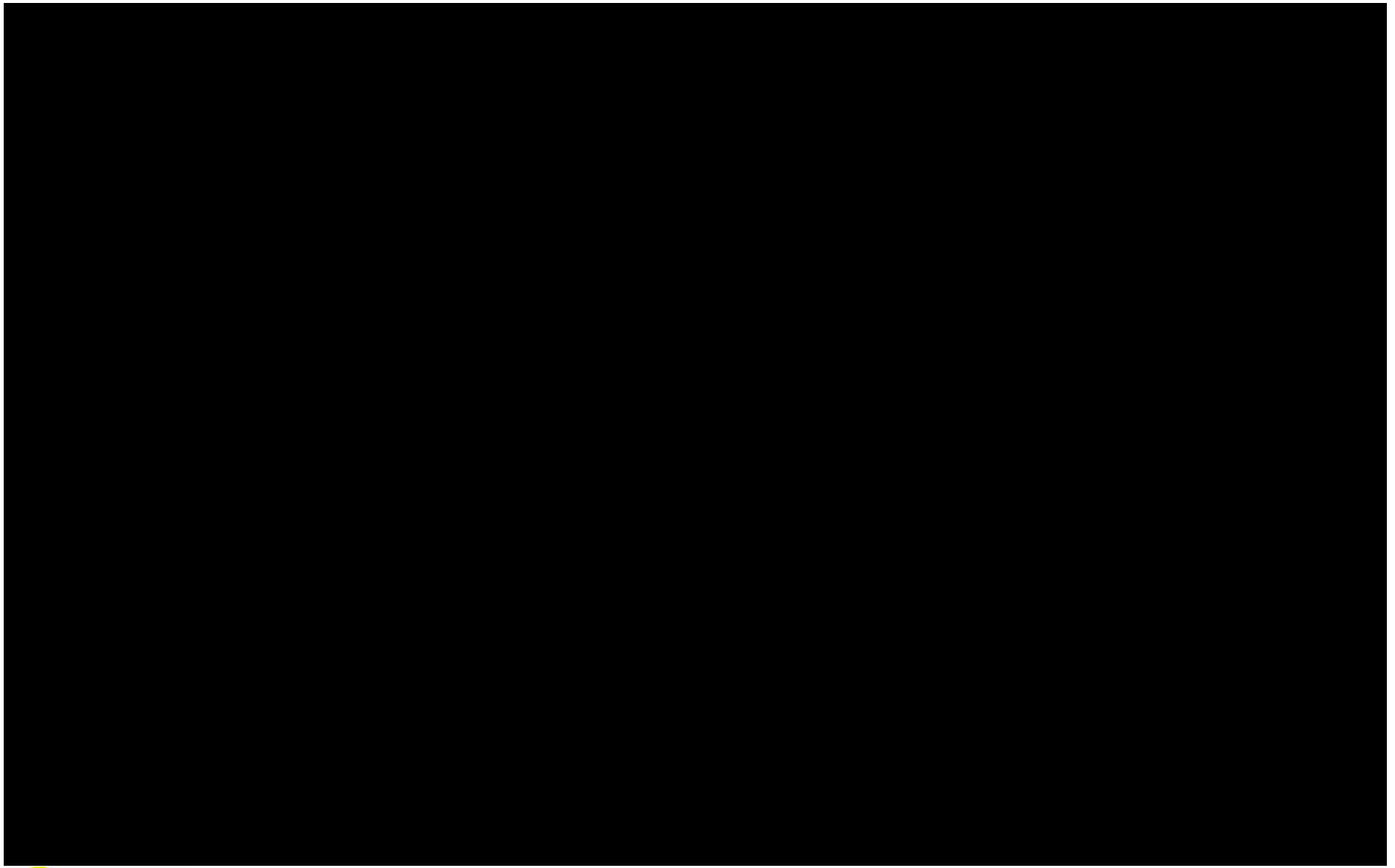
5.11 Discontinuation of Study Therapy after CR

[redacted]

5.12 Clinical Criteria for Early Trial Termination

[redacted]

6.0 TRIAL FLOW CHART



7.0 TRIAL PROCEDURES

7.1 Trial Procedures

The Trial Flow Chart- Section 6.0 summarizes the trial procedures to be performed at each visit. Individual trial procedures are described in detail below. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigator.

[redacted]

7.2 Administrative Procedures

7.2.1 Informed Consent

The Investigator must obtain documented consent from each potential subject prior to participating in a clinical trial.

Consent must be documented by the subject's dated signature or by the subject's legally acceptable representative's dated signature on a consent form along with the dated signature of the person conducting the consent discussion.

A copy of the signed and dated consent form should be given to the subject before participation in the trial.

The initial informed consent form, any subsequent revised written informed consent form and any written information provided to the subject must receive the IRB/ERC's approval/favorable opinion in advance of use. The subject or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the subject's dated signature or by the subject's legally acceptable representative's dated signature.

Specifics about a trial and the trial population will be added to the consent form template at the protocol level.

The informed consent will adhere to IRB/ERC requirements, applicable laws and regulations and Sponsor requirements.

7.2.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator or qualified designee to ensure that the subject qualifies for the trial.

7.2.3 Medical History

A medical history will be obtained by the investigator or qualified designee. Medical history will include all active conditions, and any condition diagnosed within the prior 10 years that are considered to be clinically significant by the Investigator. Details regarding the disease for which the subject has enrolled in this study will be recorded separately and not listed as medical history.

The investigator or qualified designee will obtain prior and current details regarding disease status.

In the case of patients who have progressed to a metastatic stage after having been treated for early NSCLS stage, the investigator or qualified designee will review all prior cancer treatments including systemic treatments, radiation and surgeries**.**

7.2.4 Prior Medications

[redacted].

7.2.5 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the subject during the trial. All medications related to reportable SAEs and ECIs should be recorded as defined in Section 7.2.

7.4 Assignment of Screening Number

All screened subjects will be given a unique *screening number* that will be used to identify the subject throughout the screening phase. Each subject will be assigned only one screening number. Screening numbers must not be re-used for different subjects. Any subject who is screened multiple times will retain the original screening number assigned at the initial screening visit.

After the PDL1 analysis, if positive result in the archival or newly obtained sample or previous PDL1 positive result , the subject will be included in the data base (Case report form, CRF) of the study that will assign the final *inclusion number* of the subject. Also, the screening number will be recorded in the CRF.

7.5 Clinical Procedures/Assessments

7.5.1 Adverse Event (AE) Monitoring

The investigator or qualified designee will assess each subject to evaluate for potential new or worsening AEs as specified in the Trial Flow Chart and more frequently if clinically indicated. Adverse experiences will be graded and recorded throughout the study and during the follow-up period according to NCI CTCAE Version 4.0. Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

[redacted]

The investigator or qualified designee will perform a complete physical exam during the screening period. Clinically significant abnormal findings should be recorded as medical history. A full physical exam should be performed during screening.

[redacted]

7.5.4 Vital Signs

The investigator or qualified designee will take vital signs at screening, prior to the administration of each dose of trial treatment and at treatment discontinuation as specified in the Trial Flow Chart (section 6.0). Vital signs should include temperature, pulse, respiratory rate, weight and blood pressure. Height, weight and body surface will be measured at screening only.

7.5.5 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The investigator or qualified designee will assess ECOG status at screening, prior to the administration of each dose of trial treatment and discontinuation of trial treatment as specified in the Trial Flow Chart(section 6.0).

[redacted]

7.5.6 Tumor Imaging and Assessment of Disease

[redacted]

[redacted]

[redacted].

Imaging assessment will be performed more frequently if clinically indicated.

[redacted]

[redacted]

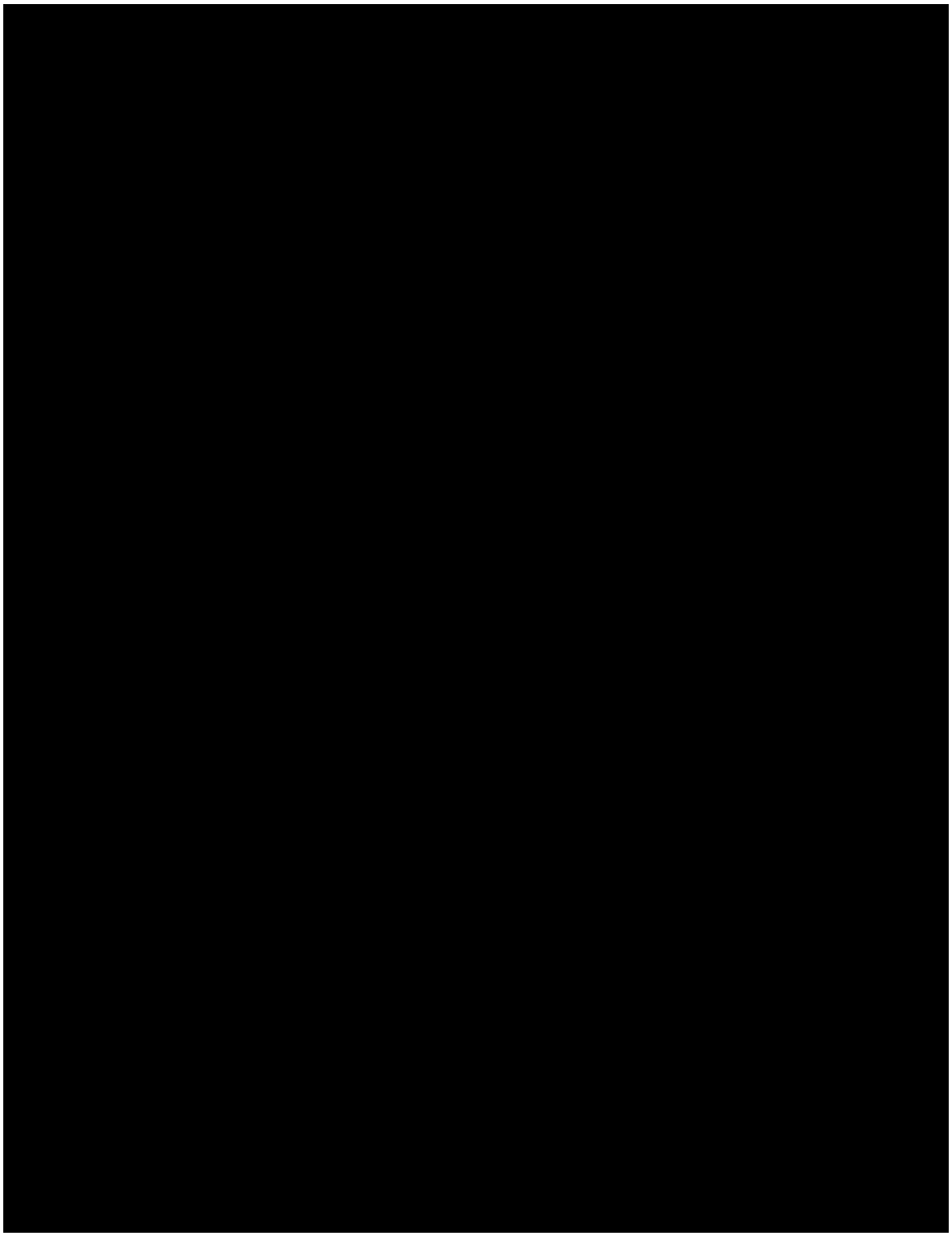
[redacted]

[redacted]

7.5.7 Tumor Tissue Collection and Correlative Studies Blood Sampling

[redacted]

[redacted]



[redacted]

7.5.9 Blood Collection for Serum Pembrolizumab
Sample collection, storage and shipment instructions for serum samples will be provided in the Blood Samples Manual.

7.6 Other Procedures

7.6.1 Withdrawal/Discontinuation
When a subject discontinues/withdraws prior to trial completion, all applicable activities scheduled for the final trial visit should be performed at the time of discontinuation.

Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements, outlined in section 7.7 Assessing and Recording Adverse Events.
Subjects who a) attain a CR or b) complete 24 months of treatment with pembrolizumab may discontinue treatment with the option of restarting treatment if they meet the criteria specified. After discontinuing treatment following assessment of CR, these subjects should return to the site for a Safety Follow-up Visit and then proceed to the Follow-Up Period of the study.

7.6.2 Visit Requirements
Visit requirements are outlined in Trial Flow Chart (section 6.0). Specific procedure-related details are provided above in Trial Procedures.

7.6.3 Screening

7.6.4 Screening Period
Screening period will be 28 days from ICF signature.

7.6.5 Treatment Period
Extension of treatment with Pembrolizumab will be up to 24 months.

7.6.6 Post-Treatment Visits
Follow up visits are outlined in Trial Flow Chart (section 6.0)

7.6.7 Safety Follow-Up Visit

[redacted]

[redacted]

[redacted]

[redacted]

7.6.8 Follow-up Visits

[redacted]

7.6.9 Survival Follow-up

[redacted]

7.6.10 Subsequent Anti-Cancer Therapy Status

[redacted]

7.7 Assessing and Recording Adverse Events

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of the MSD's product, is also an adverse event.

Changes resulting from normal growth and development that do not vary significantly in frequency or severity from expected levels are not to be considered adverse events. Examples of this may include, but are not limited to, teething, typical crying in infants and children and onset of menses or menopause occurring at a physiologically appropriate time.

[redacted]

[redacted]

Progression of the cancer under study is not considered an adverse event.

All adverse events that occur after the consent form is signed but before beginning the treatment must be reported by the investigator if they cause the subject to be excluded from the trial or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

From the time of treatment allocation/randomization through 30 days following cessation of treatment, all adverse events must be reported by the investigator. Such events will be recorded at each examination on the Adverse Event case report forms. The investigator will make every attempt to follow all subjects with non-serious adverse events for outcome. The reporting timeframe for adverse events meeting any serious criteria will be described in next sections.

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. (In order to prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more AEs.)

The severity and causality will be classified according to the NCI CTCAE v.5 The CTCAE is available for downloading on the internet, see Appendix 11.2.

The adverse event severity grade provides a qualitative assessment of the extent or intensity of an adverse event, as determined by the investigator or as reported by the patients. The severity grade does not reflect the clinical seriousness of the event, only the degree or extent of the affliction or occurrence (e.g. severe nausea, mild seizure), and does not reflect the relationship to study drug.

Severity grade for other adverse events not covered in the toxicity grading scale:

1 = Grade 1	Mild
2 = Grade 2	Moderate
3 = Grade 3	Severe
4 = Grade 4	Life-threatening
5 = Grade 5	Fatal

7.7.1 Main adverse events related to Pembrolizumab

[redacted].

7.7.2Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor and to MSD. Reporting of pregnancy

[redacted]

7.7.2.2Reporting of Pregnancy and Lactation to the Sponsor [redacted]

Although pregnancy and lactation are not considered adverse events, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a subject (spontaneously reported to them) that occurs during the trial.

Pregnancies and lactations that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if they cause the subject to be excluded from the trial or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

Pregnancies and lactations that occur from the time of treatment allocation/randomization through 120 days following cessation of Sponsor's product, or 30 days following cessation of treatment, if the subject initiates new anticancer therapy, whichever is earlier, must be reported by the investigator.

All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

[redacted]

7.8Immediate Reporting of Adverse Events to the Sponsor and to Merck

7.8.1 Definition of Serious Adverse Event (SAE)

A Serious Adverse Event is defined as any untoward medical occurrence that at any dose:

- results in death (fatal due to any cause)
- is life-threatening or places the subject, in the view of the investigator, at immediate risk of death from the event as it occurred (Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death.)Results in or prolongs an existing inpatient hospitalization (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a pre-existing condition that has not worsened is not a serious adverse event. A pre-existing condition is a clinical condition that is diagnosed prior to the use of IMP and is documented in the patient's medical history.)
- results in persistent or significant disability/incapacity

- is a congenital anomaly/birth defect
- is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [eg, medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.)
- Suspected transmission of an infectious agent (eg, pathogenic or nonpathogenic) via the study drug is an SAE.
- Although pregnancy, overdose (defined as accidental or intentional dose of a product that is considered both excessive and medically important), and cancer are not always serious by regulatory definition, these events must be handled as SAEs.

Second malignancies are always considered SAEs, no matter when they are diagnosed. These events should be reported on the Serious Adverse Event Forms.(although not serious per ICH definition, is reportable to the Sponsor within 24 hours and to MSD Global Safety (GS) by fax (+ 34 91 571 64 66) within 2 working days to meet certain local requirements)

The following hospitalizations are not considered SAEs:

- a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event)
- elective surgery, planned prior to signing consent
- admissions as per protocol for a planned medical/surgical procedure
- routine health assessment requiring admission for baseline/trending of health status (eg, routine colonoscopy)
- Medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases
- Admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (eg, lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason).

Progression of cancer under study is not considered an adverse event. All subjects with serious adverse events must be followed up for outcome.

Other definitions

Non-serious adverse event: All adverse events not classifiable as severe.

Unexpected adverse event: An event not described in nature in terms of gravity or incidence and not included in the basic product information (investigator's brochure)

Expected adverse event: An event described in the basic product information (investigator's brochure).

Adverse event associated with the use of the drug: Adverse event with a reasonable possibility of being related to the drug (adverse reaction).

The investigator will use the following definitions to evaluate the possible relationship between the adverse event and the medications of the study:

- Not related: Any event, illness or effect of other medications not related with the medication of the study (e.g. if transitory, or not having temporal relationship with the study drug, or presence of a definitive alternative etiology).

- Related: A temporal relationship with the administration of the study drug of the study, which reappears on re-instatement and in which there does not appear to be an alternative etiology

7.8.2 Events of Clinical Interest

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

- [redacted] [redacted]

7.8.3 Protocol-Specific Exceptions to Serious Adverse Event Reporting

[redacted]

[redacted]

[redacted]

[redacted]

7.9 Communication of Adverse Events

An AE classified as SEVERE must conform to the legal requirements.

When a severe AE occurs, based on the classification described above, the investigator must not only record it in the appropriate page in the CRF but must notify it IMMEDIATELY to the health authorities and to the Ethical Committee; as must notify all Suspected Unexpected Serious Adverse Reaction (SUSAR).

[redacted]

Similarly, severe AE possibly related to the treatments in the study must be communicated by the study sponsor to the respective owners of the authorization of commercialization of the drugs used in the trial (MSD Global Safety (GS) by fax + 34 91 571 64 66).

Reporting SAE and targeted adverse events to the Sponsor [redacted]

[redacted]

[redacted]

Table 6 Evaluating Adverse Events

An investigator, who is a qualified physician, will evaluate all adverse events as to:

V4.0 CTCAE Grading	**Grade 1**	**Mild; asymptomatic or mid symptoms; clinical or diagnostic observations only; intervention not indicated.**
	Grade 2	**Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.**
	Grade 3	**Severe or medically significant but not immediately life-threatening; hospitalization or prolongation or hospitalization indicated; disabling; limiting self-care ADL.**
	Grade 4	**Life threatening consequences; urgent intervention indicated.**
	Grade 5	**Death related to AE**
Seriousness	A serious adverse event is any adverse event occurring at any dose or during any use of Merck product that:	
	†**Results in death**; or	
	†**Is life threatening; or** places the subject, in the view of the investigator, at immediate risk of death from the event as it occurred (Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death.); or	
	†**Results in a persistent or significant disability/incapacity** (substantial disruption of one's ability to conduct normal life functions); or	
	†**Results in or prolongs an existing inpatient hospitalization** (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a pre-existing condition that has not worsened is not a serious adverse event. A pre-existing condition is a clinical condition that is diagnosed prior to the use of a Merck product and is documented in the patient's medical history.); or	
	†**Is a congenital anomaly/birth defect** (in offspring of subject taking the product regardless of time to diagnosis);or	
	Is a new **cancer** (that is not a condition of the study) **(**although not serious per ICH definition, is reportable to the Sponsor within 24 hours and to Merck within 2 working days to meet certain local requirements); **or**	

[redacted]

	Is an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event for collection purposes. An overdose that is not associated with an adverse event is considered a non-serious event of clinical interest and must be reported within 24 hours to the Sponsor and to Merck within 2 working days..
	Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).
Duration	Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units
Action taken	Did the adverse event cause Merck product to be discontinued?
[redacted]	[redacted]

[redacted]

The assessment of relationship will be reported on the case report forms /worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.

[redacted]

7.10Sponsor Responsibility for Reporting Adverse Events

All Adverse Events will be reported to regulatory authorities, IRB/IECs and investigators in accordance with all applicable global laws and regulations.

8.0 STATISTICAL ANALYSIS PLAN

8.1 Statistical Analysis Plan Summary

This is a non randomized phase II study designed to evaluate the ORR of Pembrolizumab rechallange after prior check point PD1/PDL1 treatment. All safety analysis will include all patients who recieved at least one dose os study drug. Primary ans secondary efficacy analysis will include all subjets

The goal of the primary analysis is to obtain an estimation of ORR. All eligible and treated patients will be included into this analysis. We hypothesize that the trial treatment with Pembrolizumab will results in an increase of the ORR. May be possible that a clinically meaningful effect may not be significant because of the low expected number of events and low power, specially for OS.

We have use a two stage design (Minimax) to estimate the trial sample size. Then we have taken into account the following statistical premises for each cohort of the study

P0: 0.05

P1: 0.15

α: 0.05

β: 0.2

First stage: needs to document at least 1 response in 24 patients to go on to second stage.

Second Stage: needs at least 5 responses out of a total of 55 patients (including those on the first stage) to consider further study of Pembrolizumab in this context. Therefore, for each stratum a maximum of 55 patients (110 in total) will be recruited.

9.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

9.1 Investigational Product

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of investigational product in accordance with the protocol and any applicable laws and regulations.

[redacted]

[redacted]

[redacted]	[redacted]
[redacted]	[redacted]

9.2 Packaging and Labeling Information

Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

9.3 Clinical Supplies Disclosure

This trial is open-label; therefore, the subject, the trial site personnel, the Sponsor and/or designee are not blinded to treatment. Drug identity (name, strength) is included in the label text; random code/disclosure envelopes or lists are not provided.

9.4 Storage and Handling Requirements

Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label.

Receipt and dispensing of trial medication must be recorded by an authorized person at the trial site.

Clinical supplies may not be used for any purpose other than that stated in the protocol.

9.5 Returns and Reconciliation

[redacted]

Upon completion or termination of the study, all unused and/or partially used investigational product will be destroyed at the site per institutional policy. It is the Investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state,

[redacted]

local and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

10.0 ETHICAL ASPECTS AND REGULATORY DETAILS

10.1 General Considerations

The study will be conducted according to the requirements of the Helsinki Declaration as amended in Tokyo, Venice, Hong Kong and South Africa and will follow the Rules of Good Clinical Practice of the European Community as well as complying with current Spanish legislation.

10.2 Protocol approval by Ethic committee and Health Authority

Before starting the study, this protocol together with the informed consents (oral and written before witnesses) and the patient information documentation will be submitted for approval by the ECCI responsible. This notification of approval by the ECCI will be submitted to the clinical monitor together with the names and responsibilities of the Committee members.

If the protocol needs to be amended, this amendment will be submitted for approval to the Ethic Committees and Health Authorities (if applicable)

10.3 Confidentiality and data protection

The data obtained from this study will be assessed and used exclusively to obtain scientific conclusions. The identity of the patient is confidential and will be known only to the investigator and his/her collaborators, the auditors, monitors and inspectors of the relevant authorities.

The samples and data collected will be coded to protect patient confidentiality. Each patient will have a unique identifier assigned by the EDC (electronic Data Capture) system. Sites are responsible to keep a patient log locally in order to be able to link the unique identifier to the record of the patient.

Biological material will be assigned the same unique identifier. No identifiable / personal data will be stored in the trial database or the tissue repositories in the central labs.
Biological material will be transferred outside the treating institution for central screening and review. Results of the assays will be coded only by the patient identifier.

Regulatory authorities and pertinent Ethics Committees (IRB/ERB) may have access to patient data on-site.

In Spain, to ensure the patient confidentiality of the data applies the Reglamento (UE) 2016/679 del Parlamento europeo y del Consejo de 27 de abril de 2016 de Protección de Datos (RGPD).

10.4 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the Sponsor of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to the Clinical Trials Data Bank, http://www.clinicaltrials.gov. Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and trial site contact information.

10.5 Insurance policy

Spanish legislation demands cover with a civil responsibility policy for subjects participating in a clinical trial. The sponsor of the study provides this in accordance with the current legal requirements.

10.6 Study monitoring

The clinical monitor is obliged to rigorously follow the study. For this, the clinical monitor will regularly visit the study centers and the investigators as well as maintain necessary written and telephone communications.

The clinical monitor will assess the data collected in the acquisition forms and compare them with the original data of the clinical history and other original documents in conjunction with the study investigator.

The monitoring tasks will be carried out by the Fundación GECP staff.

10.7 Publication policy

Authorship on the final manuscript or publications or provisional extracts will be decided in accordance with the Fundación GECP publication and authorship guidelines. (PNT GECP: Política de publicaciones y autorías).

None of the participants will present data to his center in isolation from the rest of the results of the study and will need to seek approval from the sponsor.

11.0 APPENDICES

11.1 ECOG Performance Status

Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. 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	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.
* As published in Am. J. Clin. Oncol.:*Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.* The Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.	

11.2 Common Terminology Criteria for Adverse Events V4.0 (CTCAE)

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for adverse event reporting. (http://ctep.cancer.gov/reporting/ctc.html)

11.3 Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 Criteria for Evaluating Response in Solid Tumors

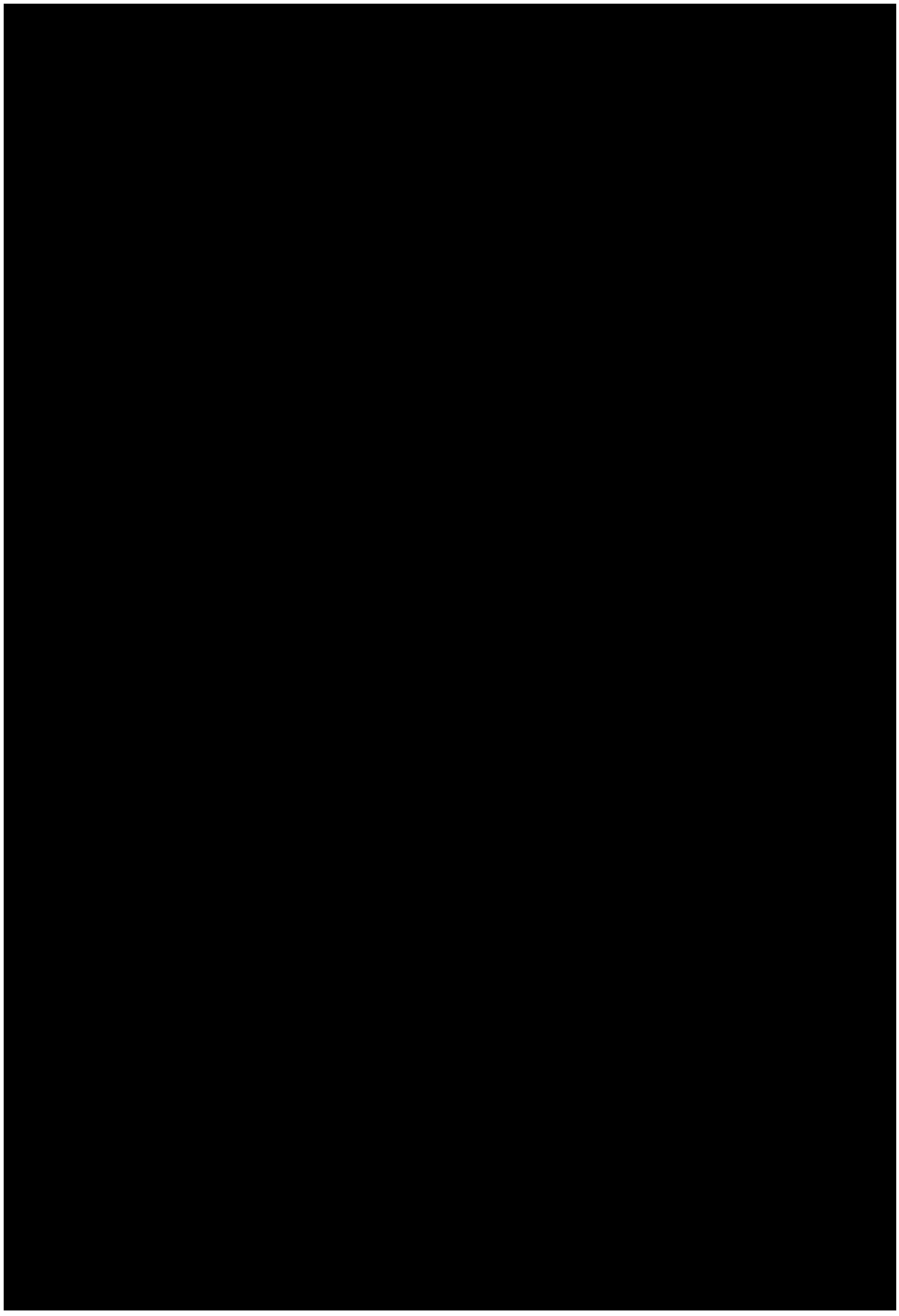
RECIST version 1.1* will be used in this study for assessment of tumor response. While either CT or MRI may be utilized, as per RECIST 1.1, CT is the preferred imaging technique in this study.

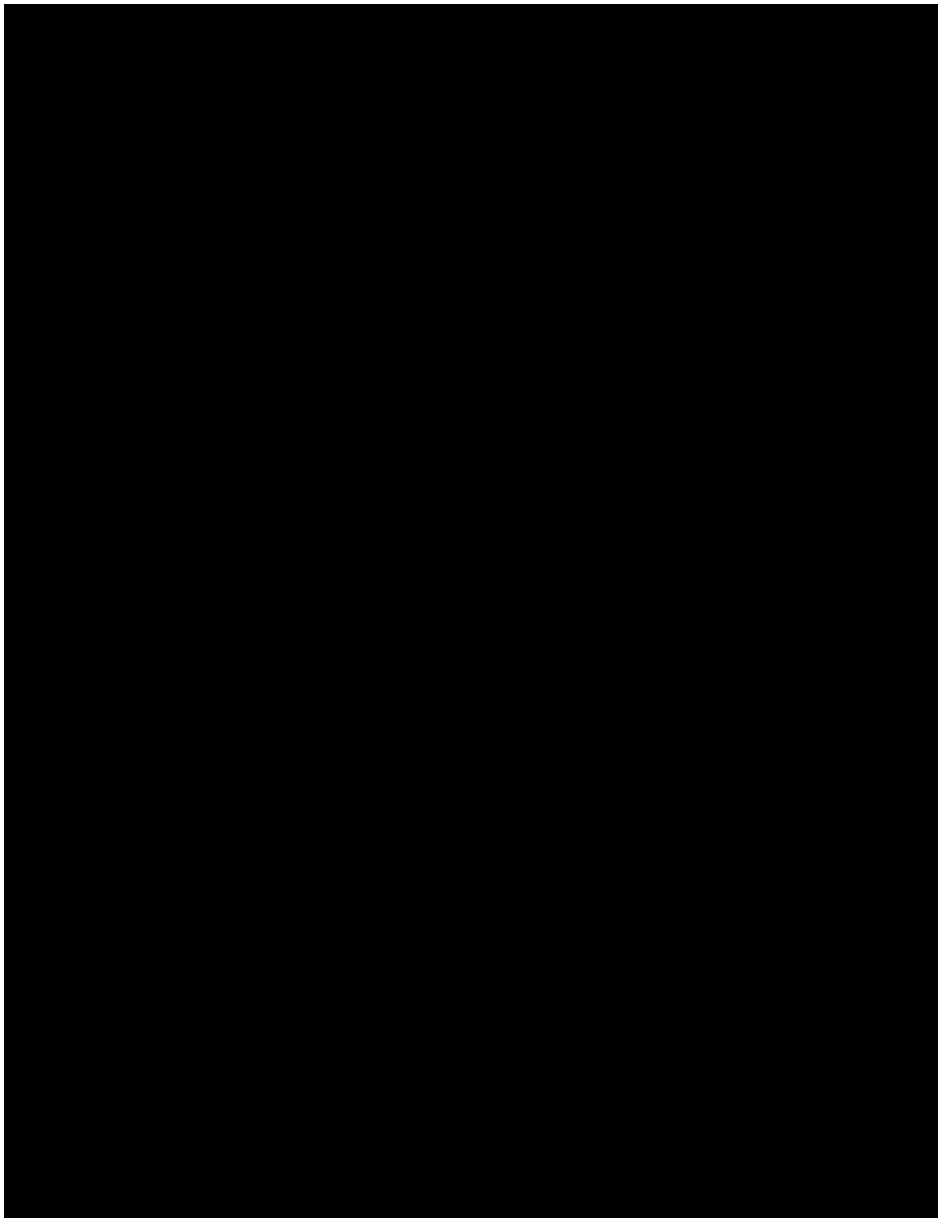
* As published in the European Journal of Cancer:

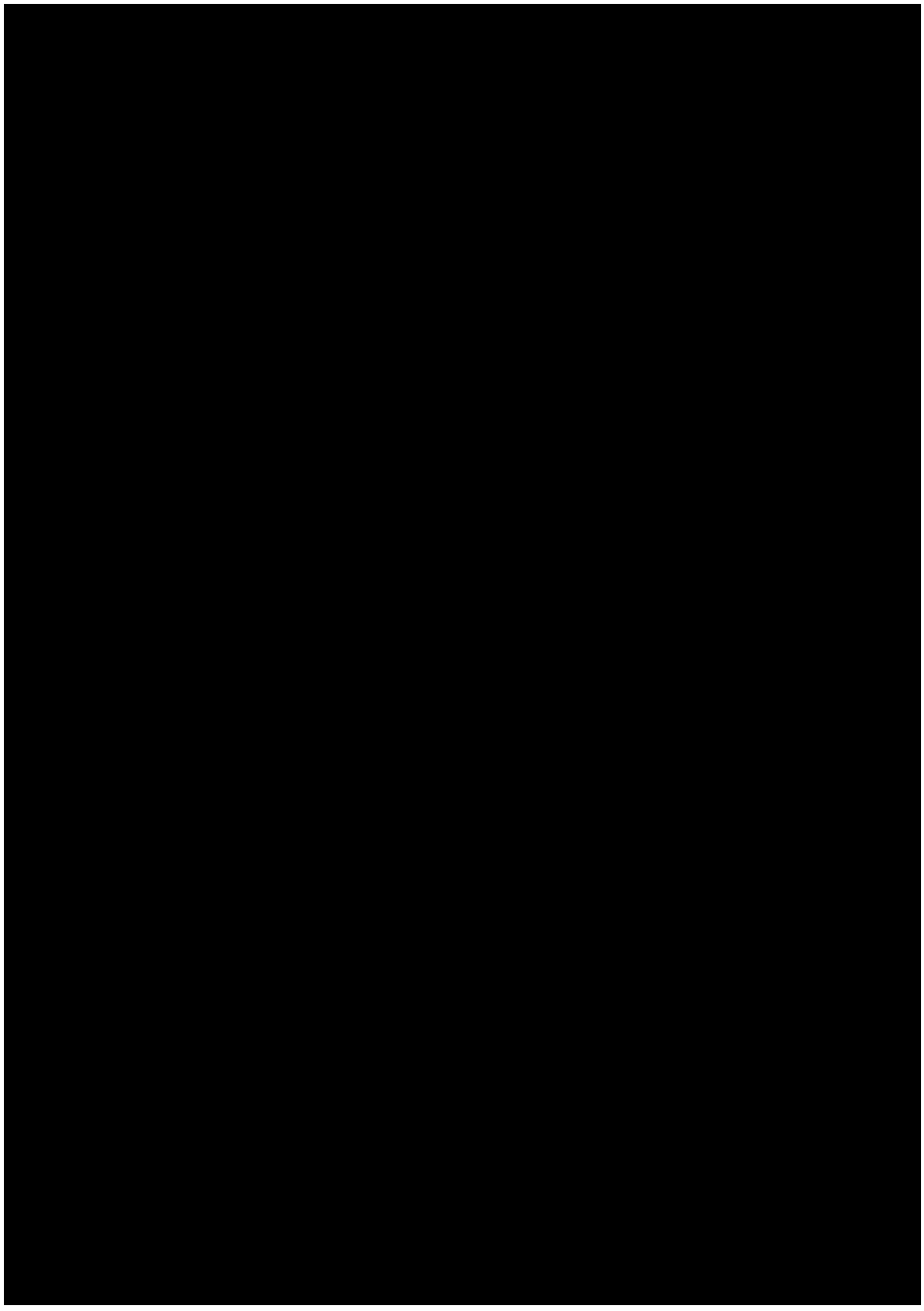
E.A. Eisenhauer, P. Therasse, J. Bogaerts, L.H. Schwartz, D. Sargent, R. Ford, J. Dancey, S. Arbuck, S. Gwyther, M. Mooney, L. Rubinstein, L. Shankar, L. Dodd, R. Kaplan, D. Lacombe, J. Verweij. New response evaluation criteria in solid tumors: Revised RECIST guideline (version 1.1). Eur J Cancer. 2009 Jan;45(2):228-47.

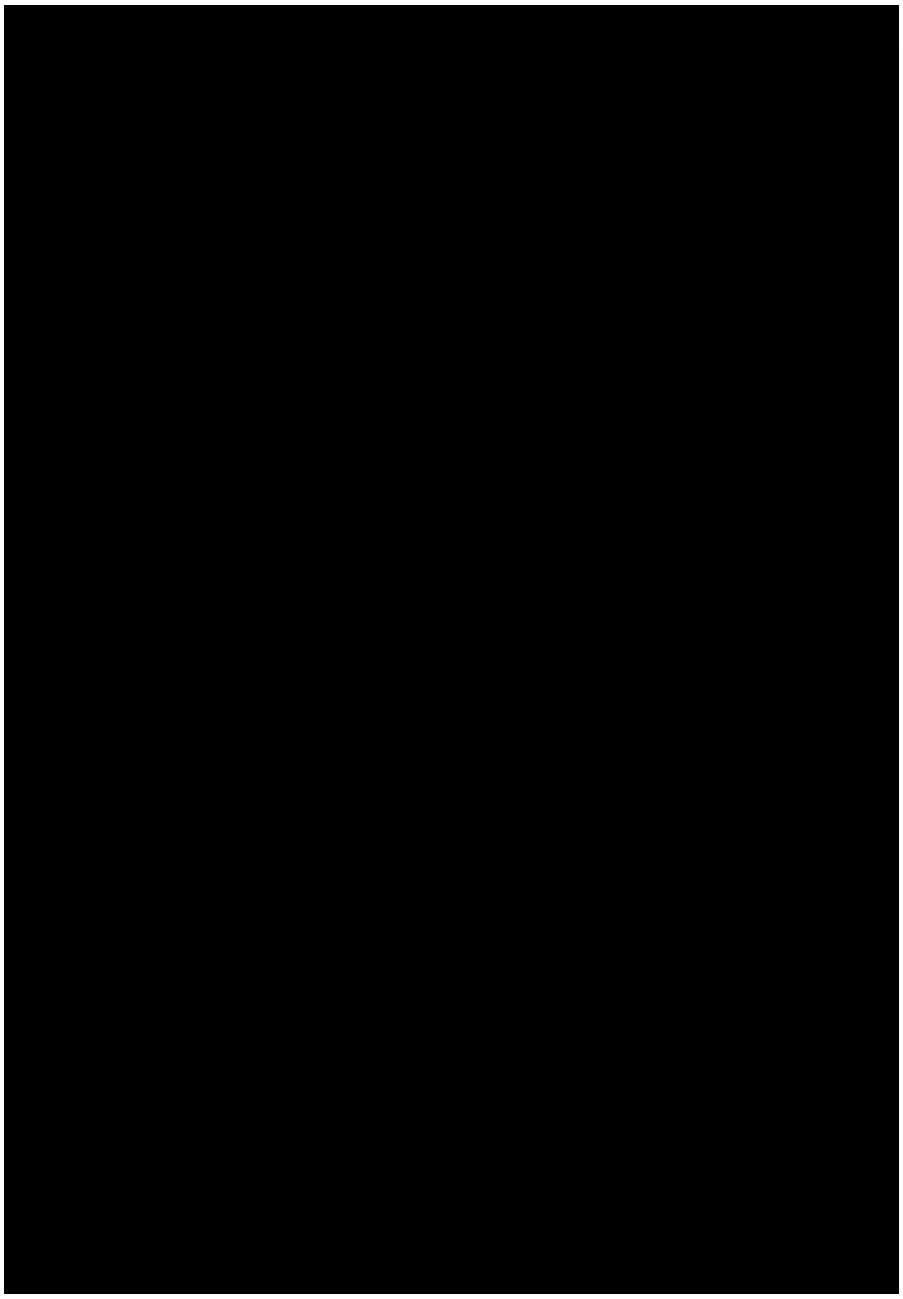
In addition, volumetric analysis will be explored by central review for response assessment.

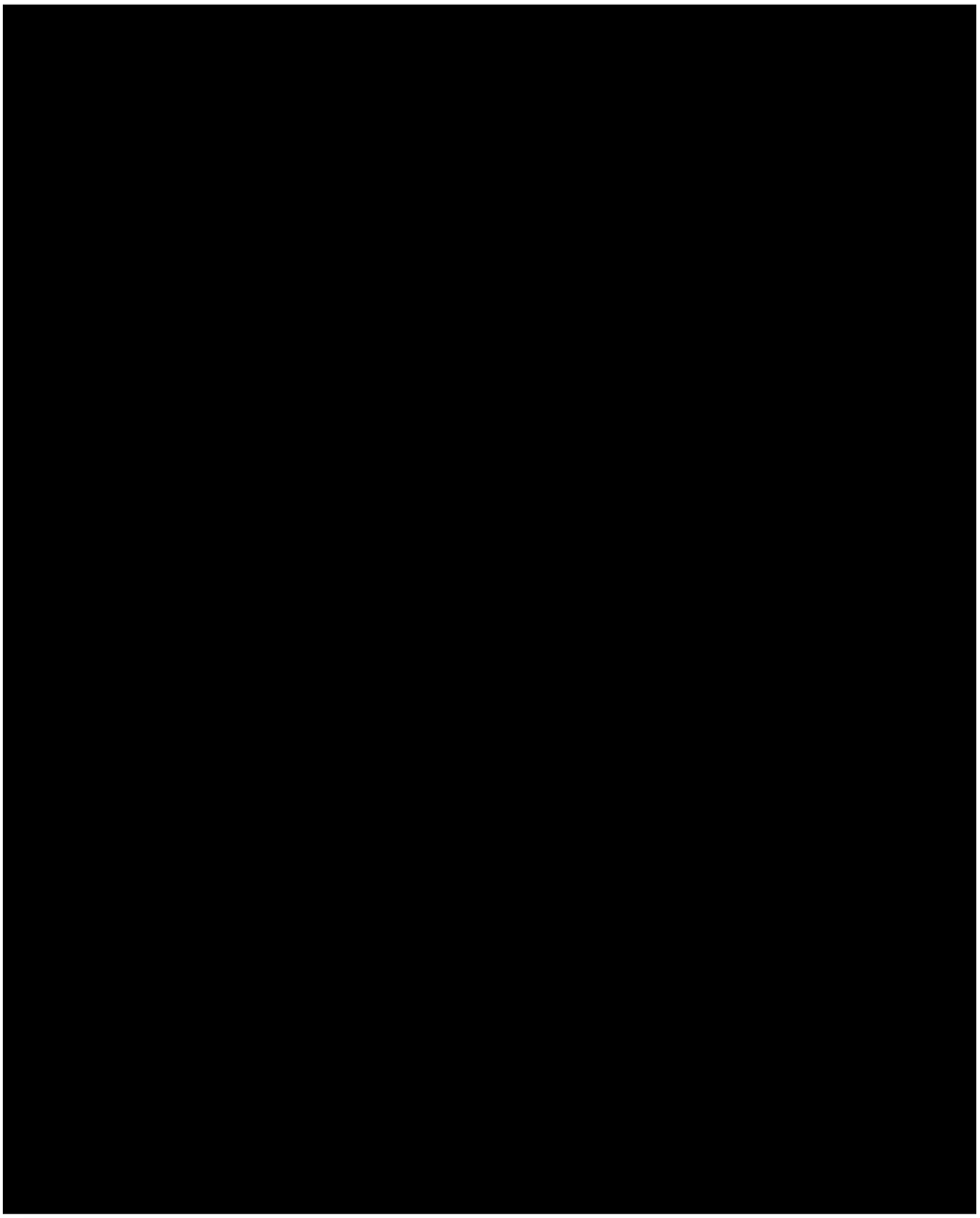
11.4 SAE form and Pregnancy form











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