Official Title: "Survival, quality of life and self-reported outcomes of elderly patients with advanced non-small cell lung cancer (NSCLC), treated with pembrolizumab (MK-3475) in the first line setting" PEBEL

NCT Number: NCT03293680

Document Dates: Summary of Protocol Amendment Version 2.1: 28 December 2018

SURVIVAL, QUALITY OF LIFE AND SELF-REPORTED OUTCOMES OF ELDERLY PATIENTS WITH ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC), TREATED WITH PEMBROLIZUMAB (MK-3475) IN THE FIRST LINE SETTING

PEBEL: **Pembrolizumab in Elderly patients with Advanced Lung Cancer**

Study Sponsor: Fundación GECP

EudraCT Number: 2016-004353-32

Sponsor code: GECP 16/06

Version 2.1

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Protocol Signature Page

SURVIVAL, QUALITY OF LIFE AND SELF-REPORTED OUTCOMES OF ELDERLY PATIENTS WITH ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC), TREATED WITH PEMBROLIZUMAB (MK-3475) IN THE FIRST LINE SETTING

PEBEL: Pembrolizumab in Elderly patients with Advanced Lung Cancer

Sponsor code: GECP 16/06

Approved by:

Signature

[redacted]

Signature

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Fundación GECP President

Principal Investigator Protocol Signature Page

Study Title: "Survival, quality of life and self-reported outcomes of elderly patients with advanced non-small cell lung cancer (NSCLC), treated with pembrolizumab (MK-3475) in the first line setting" PEBEL

Sponsor protocol code: GECP 16/06

EudraCT Number: 2016-004353-32

Protocol version: v 2.1, 28th December 2018

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

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1.0 TRIAL SUMMARY

Abbreviated Title	Pembrolizumab (MK-3475) in elderly patients with non-small cell lung cancer
Trial Phase and Type	Phase II, Interventional
Clinical Indication	First line treatment in PD-L1 positive advanced non-small cell lung cancer patients
Trial Identification	Sponsor Code: GECP 16/06; Short name: PEBEL
Type of control	Not applicable
Route of administration	Intravenous
Trial Blinding	Open label
Treatment Groups	1 group, Pembrolizumab (MK-3475) 200 mg, every 3 weeks
Number of trial subjects	82
Estimated enrollment period	12 months
Estimated duration of trial	The sponsor estimates that the trial will require approximately 4 years (1 year recruiting patients, 2 years of treatment and at least 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. After a screening phase of up to 28 days (see Section 6.0), eligible subjects will receive assigned treatment on Day 1 of each 3-week (Q3W) dosing cycle. Treatment with MK-3475 will continue until two years of therapy have been administered, 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. MK-3475 treated subjects who attain a complete response may consider stopping trial treatment. These subjects will be eligible for re-treatment for up to one year with MK-3475 after experiencing disease progression at the discretion of the investigator if they meet the criteria for re-treatment; this will be designated the Second Course phase. 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). 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.
Estimated average length of treatment per patient	According to previous data of patients treated with Pembrolizumab, the estimated average length of the treatment is approximately 7 months

2.0 GENERAL INFORMATION

2.1 Trial Identification

Sponsor code: GECP 16/06

Eudract: 2016-004353-32

Protocol title: "Survival, quality of life and self-reported outcomes of elderly patients with advanced non-small cell lung cancer (NSCLC), treated with pembrolizumab (MK-3475) in the first line setting" PEBEL

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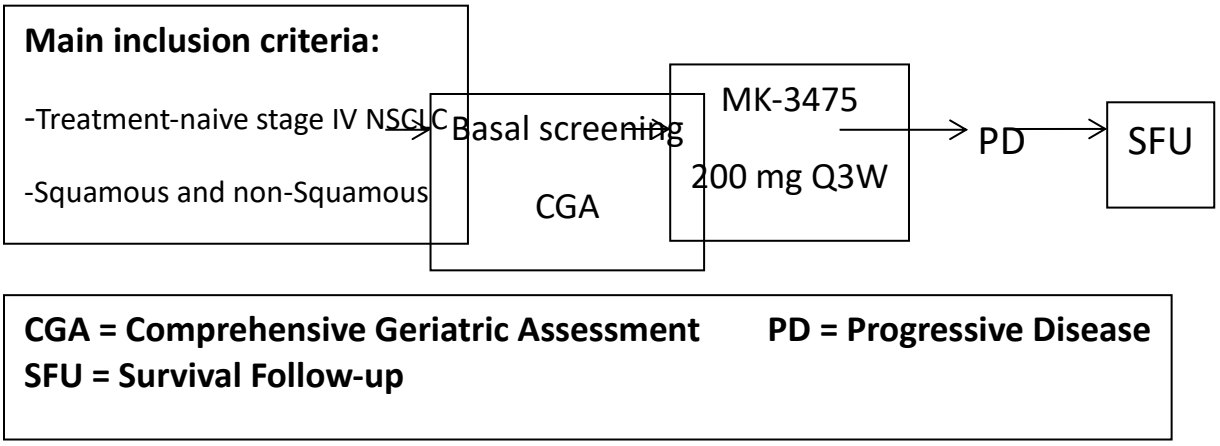
2.3 Trial Diagram

Figure 1



2.4 Primary Objective(s) & Hypothesis(es)

- To determine the efficacy, in terms of overall survival at one year, of first-line treatment with Pembrolizumab (MK-3475) in elderly patients with advanced NSCLC expressing PD-L1.

Hypothesis: Patients older than 70 years with advanced Non-small cell Lung Cancer (NSCLC) expressing PD-L1, can be treated with Pembrolizumab (MK-3475) in the first line setting, with an overall survival at one year of 50% at least. This result supposes an improvement of 4 months in the median respect of historical data.

2.5 Secondary Objective(s) & Hypothesis(es)

- To evaluate changes in health-related quality of life in responder and non-responder patients older than 70 years with advanced non-small cell lung cancer (NSCLC) expressing PD-L1, treated with pembrolizumab (MK-3475) in the first line setting, according to the QLQ-C30, the LCSS and the QLQ-ELD14 questionnaires.

- To evaluate the impact on functional, cognitive and nutritional geriatric assessments of patients older than 70 years with advanced non-small cell lung cancer (NSCLC), expressing PD-L1, treated with pembrolizumab (MK-3475) in the first line setting

- To describe the Objective Response Rate (ORR), and the Progression-free Survival (PFS), according to RECIST criteria v. 1.1 of the first-line treatment with pembrolizumab (MK-3475) in elderly patients with advanced NSCLC expressing PD-L1.

- To assess the median disease-specific survival (DSS) and the Overall Survival rate at 2 years.

- To describe the safety and tolerability profile of first-line pembrolizumab (MK-3475) in previously untreated elderly patients with advanced NSCLC expressing PD-L1.

Hypothesis: Treatment with Pembrolizumab (MK-3475) in the first line setting of patients older than 70 years with advanced non-small cell lung cancer (NSCLC) expressing PD-L1 can maintain or improve health-related quality of life, according to the QLQ-C30, the LCSS and the QLQ-ELD14 questionnaires. Also, the treatment can maintain or improve functional, cognitive, and nutritional geriatric assessments.

2.6 Exploratory Objective

- Description of PD-L1 expression in previously untreated elderly patients with advanced NSCLC.

Approximately 60% of the patients evaluated for being included in this trial will express PD-L1.

2.7 Trial Study centers

This trial will be carried out in around 10 participant study sites in Spain.

2.8 Trial duration

Approximately 4 years (1 year recruiting patients, 2 years of treatment and at least 1 year of follow up)

2.9 Sponsor details and monitor identification

Sponsor

Fundación GECPAvenida Meridiana 358, 6ªplanta

08027 Barcelona

Monitor

[redacted]

Fundación GECPAvenida Meridiana 358, 6ªplanta

08027 Barcelona

[redacted]

3.0 BACKGROUND & RATIONALE

3.1 Background

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

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3.3 Preclinical and Clinical Trial Data

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

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4.0 METHODOLOGY

4.1 Eligibility Criteria

4.1.1 Subject Inclusion Criteria

1. Patients with histological or cytological documented stage IIIB or IV squamous and non-squamous non-small-cell lung cancer previously untreated.

2. EGFR and ALK have to be wild-type.

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

4. Patients must be aged ≥70 years, on day of signing informed consent.

5. Measurable disease (at least 1 lesion) based on RECIST criteria v1.1. Patients will not be eligible if this lesion was irradiated before inclusion.

6. Be willing to provide tissue from a newly obtained core or excision biopsy of a tumor lesion. 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.

7. PD-L1 expression ≥ 1%

8. Have a performance status of 0 or 1 on the ECOG Performance Scale.

9. Screening laboratory values must meet the following criteria (Table 1), all screening labs should be performed within 8 days of treatment initiation.

Table 1 Adequate Organ Function Laboratory Values

SYSTEM	Laboratory value
Hematological	
Absolute neutrophil count (ANC)	≥1,500 / µL
Platelets	≥100,000 / µL
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 creatinine clearance (Cockcroft–Gault formula) (GFR can also be used in place of creatinine or CrCl)	≤1.5 X upper limit of normal (ULN) **OR** ≥50 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)	≤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
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

10. Male subjects of childbearing potential must agree to use an adequate method of 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.

4.1.2 Subject Exclusion Criteria

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

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 at a dose over 10 mg of prednisone or equivalent, 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 any prior anti-cancer therapy for his or her metastatic NSCLC. In the case of patients who have progressed to a metastatic stage after having been treated for early stage NSCLC, chemotherapy or radiation therapy as part of this previous treatment is allowed, provided they have been completed more than three months ago. Patients who received adjuvant or neoadjuvant treatment or both for early stages will be

eligible for this trial. All adverse events related to these previous treatments must have recovered (i.e., ≤ Grade 1 or at baseline).

6. Has had any previous malignancy (except non melanoma skin cancer, and cancer in situ of: bladder, gastric, colon, cervical/dysplasia, melanoma, breast), unless a complete remission was achieved at least 2 years prior to study entry and no additional therapy is required or anticipated to be required during the study period.

7. Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate if 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.

8. 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., thyroxin, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.

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

10. Has an active infection requiring systemic therapy.

11. 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.

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

13. Has any geriatric exclusion criteria:

    - advanced dementia (GDS ranking $\geq$6)

    - moderate or severe functional dependence (Barthel Index $\leq$ 35)

    - Life expectancy less than one year, due to co-morbidities other than lung cancer.

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

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

16. 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.

17. Evidence of interstitial lung disease.

4.2 Trial Treatments

The treatment to be used in this trial is outlined below:

Table 2. Trial Treatment

Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen/Treatment Period
Pembrolizumab (MK-3475)	200 mg	Q3W	IV, infusion	Day 1 of each 3 week cycle

The treatment must start as soon as possible after receiving PD-L1 positive results and no more than 7 days. The treatment will continue until disease progression, unacceptable toxicity, consent withdrawal, or until the treatment is administered during two years, whichever occurs first.

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

4.2.1 Dose Selection/Modification

Dose Selection

The rationale for selection of the dose to be used in this trial is provided in Section 3.5 – Background and Rationale.

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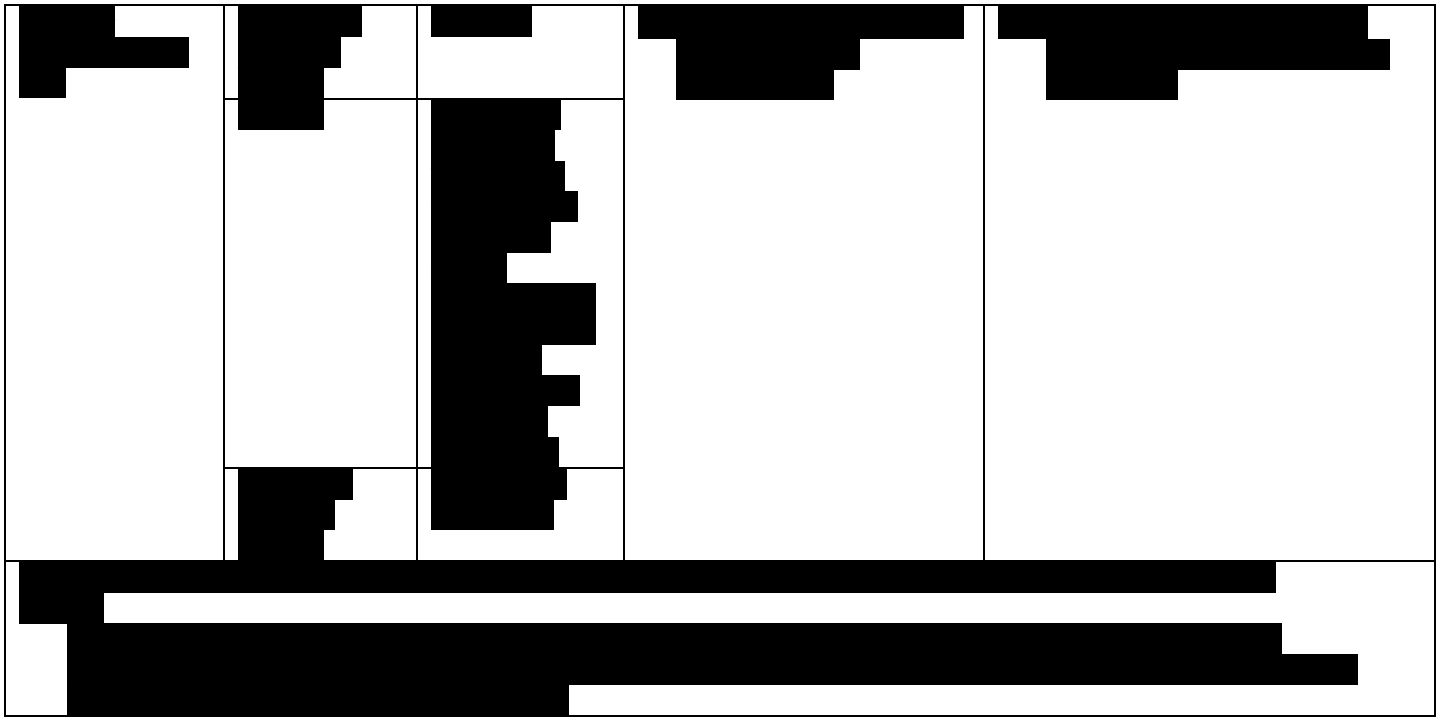

4.2.2 Timing of Dose Administration

Trial treatment should be administered on Day 1 of each cycle (QW3) after all procedures/assessments have been completed as detailed on the Trial Flow Chart (Section 5.0). Trial treatment may be administered up to ±3 days the scheduled Day 1 of each cycle due to administrative or personal reasons.

All trial treatments will be administered on an outpatient basis.

Pembrolizumab (MK-3475) 200 mg will be administered as a 30 minute IV infusion every 3 weeks. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes: -5 min/+10 min).

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

[redacted]

4.2.4 Trial Blinding/Masking

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

4.3 Concomitant Medications/Vaccinations (allowed & prohibited)

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial.

If there is a clinical indication for one of these or other medications or vaccinations specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required.

The investigator should discuss any questions regarding this with the sponsor of the study. The final decision on any supportive therapy or vaccination rests with the investigator and/or the subject's primary physician.

4.3.1 Acceptable Concomitant Medications

All treatments that the investigator considers necessary for a subject's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care.

All concomitant medication will be recorded on the case report form (CRF) including all prescription, over-the-counter (OTC), herbal supplements, and intravenous medications and

fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date may also be included on the CRF.

All concomitant medications received within 28 days before the first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded.

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4.6 Subject Withdrawal/Discontinuation Criteria

4.6.1 Subject Withdrawal

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 6.10.

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.
- Unacceptable adverse experiences
- Intercurrent illness that prevents further administration of treatment
- Investigator's decision to withdraw the subject
- 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. Subjects who stop pembrolizumab after 24 months may be eligible for up to one year of additional study treatment if they progress after stopping study treatment provided they meet the requirements detailed in Section 6.12.

- Administrative reasons

The End of Treatment and Follow-up visit procedures are listed in Section 5 (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 7.6). 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.

4.6.2 Discontinuation of Study Therapy after Complete Response (CR)

Discontinuation of treatment may be considered for subjects who have attained a confirmed CR that have been treated for at least 24 weeks with Pembrolizumab and had at least two treatments with Pembrolizumab beyond the date when the initial CR was declared.

Subjects who then experience radiographic disease progression may be eligible for up to one year of additional treatment with Pembrolizumab via the Second Course Phase at the discretion of the investigator if no cancer treatment was administered since the last dose of Pembrolizumab, the subject meets the safety parameters listed in the Inclusion/Exclusion criteria, and the trial is open. Subjects will resume therapy at the same dose and schedule at the time of initial discontinuation.

4.7 Clinical Criteria for Early Trial Termination

Early trial termination will be the result of the criteria specified below:

1. Quality or quantity of data recording is inaccurate or incomplete

2. Poor adherence to protocol and regulatory requirements

3. Incidence or severity of adverse drug reaction in this or other studies indicates a potential health hazard to subjects

4. Plans to modify or discontinue the development of the study drug

In the event of the Marketing Authorization Holder of the drug (MSD) decides to no longer supply study drug, ample notification will be provided so that appropriate adjustments to subject treatment can be made.

5.0 [redacted]

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6.0 TRIAL PROCEDURES

The Trial Flow Chart - Section 5.0 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.

Furthermore, additional evaluations/testing may be deemed necessary by the Sponsor for reasons related to subject safety. In some cases, such evaluation/testing may be potentially sensitive in nature (e.g., HIV, Hepatitis C, etc.), and thus local regulations may require that additional informed consent be obtained from the subject. In these cases, such evaluations/testing will be performed in accordance with those regulations.

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7.0 ASSESSING AND RECORDING ADVERSE EVENTS

7.1 Definition of Adverse Event

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 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.

Adverse events may occur during the course of the use of the medical product in clinical trials, or as prescribed in clinical practice, from overdose (whether accidental or intentional), from abuse and from withdrawal.

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 90 days following cessation of treatment, all events must be reported by the investigator, regardless of whether it is considered related to the trial treatment. Such events will be recorded at each examination on Adverse Event case report forms. The reporting timeframe for adverse events meeting any serious criteria will be described in the 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.4. The CTCAE is available for downloading on the internet, see Appendix III.

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

7.2 Main adverse events related to Pembrolizumab

According to the last version of the Investigator's Brochure of the investigational drug, in the prembrolizumab monotherapy trials, in general, the most commonly reported adverse events included: fatigue, diarrhea, decreased appetite, nausea, dyspnoea and anaemia. Also, constipation, nausea and alopecia were found.

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7.4 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

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Reporting SAE and targeted adverse events to the Sponsor (Fundación GECP)

Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures. All SAEs must be collected that occur within 90 days of discontinuation of dosing.

All SAEs must be collected that occur during the screening period. If applicable, SAEs must be collected that relate to any protocol-specified procedure (eg, a follow-up skin biopsy). The investigator should report any SAE that occurs after these time periods that is believed to be related to study drug or protocol-specified procedure.

Any SAE, whether related or not related to study drug, and pregnancies, must be reported by sending the completed SAE Form through the ECRF (electronic data capture form) or the SAE Pregnancy Form by fax (+ 34 93 419 17 68) (see Appendix V) within 24 hours of awareness to the Fundación GECP (SLCG/GECP) pharmacovigilance office [redacted]

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If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports should include the same investigator term(s) initially reported.)

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Any Suspected Unexpected Serious Adverse Reaction (SUSAR) occurred during the trial will be notified under Spanish clinical regulation to the Health Authorities via Eudravigilance within the timelines specified in GCP. Also, the principal investigators must be informed.

8.0 STATISTICAL ANALYSIS PLAN

This will be a multicenter, phase II, single-arm trial.

Historical data show that median overall survival of elderly patients with advanced NSCLC is approximately 8 months in the first-line setting. Our statistical design stipulates that 74 patients accrued over 12 months with 12 months of additional follow-up will be sufficient to test with an alpha and beta errors of 0.05 and 0.10 respectively whether the new treatment can improve median survival to 12 months (SWOG One Sample Survival). Accepting a 10% loss to follow up, we plan to recruit 82 patients in the study.

Data for response rate, safety, and PD-L1 expression will be described. We will summarize objective response rates with binomial responses and their corresponding two-sided exact 95% CI by the Clopper-Pearson method. We will assess duration of response, progression-free survival, and overall survival by the Kaplan-Meier product-limit method.

We will perform the safety and activity analyses, as well as the geriatric follow-up, in all treated patients, defined as those who receive at least one dose of Pembrolizumab. The safety analysis will be based on adverse events reported within 90 days of the last dose of Pembrolizumab.

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.

Clinical Supplies will be provided by MSD as summarized in Table 5.

Table 5. Product Descriptions

Product Name & Potency	Dosage Form
Pembrolizumab 100 mg/ 4mL	Solution for Injection

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

The investigator is responsible for keeping accurate records of the clinical supplies received from Merck or designee, the amount dispensed to and returned by the subjects and the amount remaining at the conclusion of the trial.

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

10.0 ETHICAL ASPECTS

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 the Ethics Committee for Clinical Investigation (ECCI)

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 Organic Law of protection of data 15/1999.

10.4 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.

10.5 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.

11.0 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.

APPENDICES

Appendix I. 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 ClinOncol 5:649-655, 1982.* The Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.	

Appendix II. 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)

Appendix III. Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 and irRC Criteria

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.

irRC Criteria: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4679210/table/table1/

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