Randomized phase II study of MK-3475 (Pembrolizumab) in combination with Docetaxel vs. Docetaxel alone in patients with Non-Small Cell Lung Cancer previously treated with platinum based chemotherapy

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SINGLE FORMAT FOR THE REGISTRATION OF RESEARCH PROTOCOLS

RESEARCH AND ETHICS COMMITTEE

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2. PROJECT

Name of the project

Randomized phase II study of MK-3475 (Pembrolizumab) in combination with Docetaxel vs. Docetaxel alone in patients with Non-Small Cell Lung Cancer previously treated with platinum based chemotherapy.

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Type of research
(Mark with an "X")

	Basic		Exploratory
X	Clínic		Experimental
			Comparative

Protocol origin ((Mark with a "X")

x	Internal
	External
	Thesis

Project timeline

Start:		Ending:	
Month	Year	Month	Year
10	15	10	17

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(A letter of support signed by the director of each participating institute must be attached)

Name Institution I	Does not apply
Institution Name II	Does not apply
Name Institution III	Does not apply
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Type of support
(Mark the type of help provided with an X)

	Type of help			
	Infrastructure	Personal	Material	Team
International Agency for Research on Cancer	X		X	X
Institution Name II				
Name Institution III				
Name Institution IV				
Name Institution V				

II. SYNTHESIS OF THE PROJECT

BACKGROUND:

MK-3475 (Pembrolizumab) is an IgG4 monoclonal antibody directed against PD1 which was originally used as an advanced melanoma therapy approved by the FDA in January 2013. Preliminary results of a phase I cohort study in Non-Small Cell Lung Cancer (NSCLC) using MK-3475 (Pembrolizumab) were presented at the World Conference on the Lung Cancer Meeting of 2013, where compound MK-3475 (Pembrolizumab) was administered intravenously every three weeks and continued until the progression of the disease based on immunological response criteria (IRC) or unacceptable toxicity.

Of the 38 patients evaluated, who were previously treated for advanced NSCLC, 9 (24 %) achieved an at least partial response by IRC. Through evaluation with standard oncological response criteria (Response evaluation criteria in solid tumours such as RECIST were available for 33 of these patients, presenting partial response in seven patients (21%). With a median overall survival of 51 weeks
The therapy was well tolerated; a case of pneumonitis (grade 2) and a case of pulmonary oedema (grade 3) were reported.

Based on these results, a randomized phase II trial comparing MK-3475 (Pembrolizumab) to docetaxel in patients with advanced NSCLC has been launched (NCT01905657), however, there is no study in which they were evaluated Docetaxel + MK-3475 (Pembrolizumab) to evaluate synergistic activity, this could open the possibility of using this medication simultaneously with docetaxel as a standard therapy in patients with disease progression to a double platinum-based regimen.

Primary Objective
Compare the overall response rate (ORR) of MK-3475 (Pembrolizumab) in combination with docetaxel versus docetaxel only in patients with NSCLC previously treated with platinum-based chemotherapy.

Hypothesis

In patients with metastatic NSCLC previously treated with double platinum-based chemotherapy, the co-administration of MK-3475 (Pembrolizumab) / Docetaxel will increase the overall response rate (ORR) compared with the administration of docetaxel alone in patients with previously treated NSCLC.

METHODOLOGY

Study design: This is a randomized, open-label phase 2 study in adult patients (≥18 years of age) in men and women with NSCLC after failure at the first line of platinum-based chemotherapy. Patients included will receive MK-3475 (Pembrolizumab) in combination with Docetaxel vs. Docetaxel only in a 1: 1 ratio with the possibility of crossing to the combination arm in case of progression. Patients will undergo screening evaluations to determine eligibility within 28 days prior to randomization. Subjects will be assigned to one of two treatment groups. The randomization will be carried out with a random numbers table.

Obtaining the sample, plasma and immunophenotyping: A sample of peripheral venous blood (8 ml) will be obtained from each subject included in the study. An aliquot of whole blood will be taken for staining with a combination of monoclonal antibodies for the development of the Immunophenotype panel. The samples will be acquired in an Attune NxT Acoustic Focusing Flow cytometer and analyzed with the FlowJo vX Software. The rest of the sample will be processed to obtain the plasma, stored at -70 ° C until further analysis. Nuclear polymorph cells will be separated by a density gradient, Ficoll Polymorphprep and cryopreserved.

Multiple quantification assay of soluble analytes: For quantification commercial kits of pearl-coupled immunoassays (CBA) will be used in plasma of the study subjects.

Study evaluations and primary assessment criteria: Compare the overall response rate (ORR) of MK-3475 (Pembrolizumab) in combination with docetaxel versus docetaxel alone in patients with previously treated NSCLC. Evaluated by RECIST 1.1.

III. PROJECT BACKGROUND

Lung cancer is the leading cause of cancer-related death worldwide. (1) It is estimated that 221,130 new cases of lung cancer were diagnosed in 2011. (2) Between 1999 and 2006, according to the SEER database, the overall 5-year survival rate was only 15.8%. The majority of subjects (approximately 78%) were diagnosed with advanced or metastatic disease. Progression occurred after first-line treatment in almost all of these subjects, and the 5-year survival rate is only 3.6%. There is a particular unmet need in subjects with non-squamous cell NSCLC (representing up to 75% of all NSCLC) since there are few treatment options after first-line treatment in most patients with cancer that It is not induced by mutations. According to the NCCN guidelines, the use of chemotherapy with a single agent is the standard care in subjects with recurrent and metastatic NSCLC after the platinum-based treatment (2) has failed. The historical value of the median Progression-Free Survival (PFS) rates in second-line NSCLC average approximately 2.6 to 3.2 months, and the median OS is approximately 6.7 to 8.3 months (3-6) more in the most recent ZODIAC study (10+ months). (7) Current second-line treatment includes docetaxel, erlotinib and pemetrexed. No agent has demonstrated superiority in OS when compared to docetaxel. Additional studies showed that gefitinib is non-inferior to docetaxel in previously treated NSCLC, except for study V-15-32. (8-20) Regimens other than docetaxel (other than the 3-week standard), double chemotherapies using docetaxel, and other comparative agents, have not

shown improvement compared to docetaxel in this treatment line. (11-15) Among the different histologies of NSCLC, non-squamous cell carcinoma of the lung typically accounts for up to 75% of all cases of lung cancer. (16) The majority of studies involving first-line and second-line treatment do not specifically separate subjects by histology, although this was recorded in all pivot studies. (4-6,17) The first study that demonstrated a difference in histology involved the comparison of gemcitabine and cisplatin with pemetrexed and cisplatin. In this study, subjects with non-squamous cell NSCLC presented a median composite survival time of 10.3 months with the combination of gemcitabine, and 10.3 months with pemetrexed. This later changed when studying based on specific non-squamous histologies, which showed a median survival of 10.9 months with gemcitabine versus 12.6 months with pemetrexed in adenocarcinoma, and 6.7 months with gemcitabine versus 10.4 months with pemetrexed in large cell lung cáncer. (18) A sub-analysis of the non-inferiority study with pemetrexed in second-line treatment [19] showed a statistically significant improvement in the combined non-squamous histologies when docetaxel (9.3 months vs. 8.0 months (HR 0.778)) was compared, but not in the squamous ones (6.2 months vs. 7.4 months (HR 1,563)). (19) Additional data have shown that the risk of recurrence of the disease after initial treatment is equal between adenocarcinoma and squamous cell lung cancer, despite a worse prognosis in the squamous cell subgroup. (20)

The treatment of NSCLC has also been defined by developing an understanding of the somatic mutations that drive tumour growth and development. Higher responses were observed in female, non-smoking and adenocarcinoma subjects, compared to male smoking subjects with squamous cell lung carcinoma treated with erlotinib. (21) For example, a significant clinical benefit was observed in subjects with EGFR mutations treated with EGFR TKI (representing 5 to 26% of all subjects with non-squamous NSCLC). (22-24) This was subsequently evaluated in the EURTAC study, which analyzed virgin chemotherapy subjects who presented EGFR mutations by exon 19 deletion, or L858R mutation in exon 21. The median PFS was 9.7 months in the erlotinib group and 5.2 months in the chemotherapy group (cisplatin/docetaxel or cisplatin/gemcitabine), with an HR of 0.37. (1) The use of the docetaxel-based combination, although not frequently used in first-line treatment, showed equivalent efficacy when compared to combinations based on pemetrexed and paclitaxel. (25) An additional mutation that is aberrantly activated in the non-squamous NSCLC is the EML4-ALK translocation found in approximately 4% of the subjects. Better tumour responses were observed with the use of ALK TKI crizotinib, while the median overall survival has been reached so far. (26)

The current unmet need in non-squamous NSCLC continues to be that, the majority of subjects who do not have known mutations or who have mutations, do not have a targeted treatment. In addition, once the subjects have developed resistance to several TKIs, there are few treatment options and the disease progresses rapidly. Docetaxel continues to be the preferred treatment (27), in this line of treatment, as there are few additional options.

Rationale for MK-3475

MK-3475 (Pembrolizumab) is a highly selective humanized monoclonal antibody of the IgG4 kappa isotype against PD-1 that is designed to block the negative immune regulatory signalling of the PD-1 receptor expressed by T cells. Very high variable region sequences affinity to the PD-1 anti-human mouse PD-1 (dissociation constant, 28 pM) mouse were grafted onto a human IgG4 immunoglobulin with an Fc stabilization alteration S228P. The IgG4 immunoglobulin subtype does not bind to Fc receptors, nor does it activate complement, thus avoiding the cytotoxic effects of the antibody when it binds to the T cells it is intended to activate. In the T cell activation assays using blood cells from human donors, the 50% effective concentration was in the range of 0.1 to 0.3 nM (unpublished

data). The first phase of dose escalation in a phase I study with patients with solid tumours showed that MK-3475 (Pembrolizumab) was safe at the dose levels tested (1 mg per kilogram of body weight, 3 mg per kilogram, and 10 mg per kilogram, administered every 3 weeks) without reaching a maximum tolerated dose. In addition, clinical responses were observed at all dose levels. (27-28)

Of the 135 patients who received at least one dose of MK-3475 (Pembrolizumab), 79% reported the presence of adverse events related to the drug of any grade and 13% reported grade 3 or 4 events related to the drug. However, general symptoms, such as fatigue and fatigue, fever and chills, myalgia and headache, were reported frequently but were low grade in more than 95% of cases. Eruptions and pruritus were reported in 21% of patients; Grade 3 or 4 pruritus was reported in 1% of patients, and rash grade 3 or 4 in 2%. Vitiligo was attributed to MK-3475 (Pembrolizumab) in 9% of patients. The highest incidence of overall adverse events related to treatment was observed among patients who received 10 mg of MK-3475 per kilogram every 3 weeks, compared to patients who received 3 mg per kilogram every 3 weeks and those who received 1 mg per kilogram every 3 weeks (23%, versus 4% and 9%, respectively) Treatment-related pneumonitis was reported in 4% of patients; none of the cases was grade 3 or 4. One patient, a 96-year-old man, died during the study. Initial asymptomatic pneumonitis was identified in CT, and MK-3475 (Pembrolizumab) was discontinued. Subsequently, I present dyspnea and the patient received glucocorticoids. Grade 3 or 4 elevations in aminotransferase levels were reported in 1% of patients. Two cases of grade 3 renal insufficiency were recorded, both cases were potentially mediated by autoimmunity presented improvement of renal function with glucocorticoid treatment at the same time as the interruption of MK-3475. (29,30)

Based on these and other preclinical and clinical data, the blockade of PD-1 induced by MK-3475 has been studied as a promising therapeutic strategy to reverse immune tolerance and enhance the effector function of T cells in various types of tumours, including CPCNP.

Justification for the use of docetaxel as a comparator

Docetaxel is one of the many agents that are approved for use after progression with the first-line treatment for NSCLC based on PFS and OS, compared to the best supportive care (BSC) [17] or active chemotherapies (4) It has been used as a reference comparator vs. pemetrexed in a non-inferiority study in which the PFS and OS in the docetaxel group were 2.9 months and approximately 8 months, respectively. (5) Erlotinib is another agent that was studied in the second line. In the BR.21 study, erlotinib demonstrated a PFS of 2.2 months and an OS of 6.7 months. placebo with BSC. (6) Docetaxel was chosen in this study because its activity continues to be the frame of reference for the evaluation of other agents. In addition, double treatments based on pemetrexed have been used more frequently in the first-line scenario, reducing the number of options for this subgroup of patients. Docetaxel can also be used in subjects presenting with conductive mutations and who had previously been treated with EGFR TKI or ALK TKI (including crizotinib) and double platinum-based chemotherapy.
This study will stratify and balance the groups in terms of previous use of maintenance treatment vs. no use of maintenance treatment, and second-line treatment vs. third-line treatment. The reason for maintenance treatment as a stratification factor, involves improvement in progression-free survival (PFS) and in OS observed in patients who received a change in maintenance treatment with pemetrexed after a double platinum-based régimen. (29) This is still being evaluated in the continuation of maintenance treatment with pemetrexed. (30) The maintenance change using erlotinib showed a statistically significant improvement in OS, but not as large as in the pemetrexed study. (31) The stratification and balance of second-line studies vs. the Third line, it was also chosen due to the

differences observed in the OS between these two groups, as demonstrated in the studies using afatinib. (32)

Rationale for the dose and schedule of MK-3475 (Pembrolizumab)

A phase II study by Hamid *et al.* showed that among 135 patients who received at least one dose of the MK-3475, 79% reported the presence of any grade adverse events related to drug and 13% reported grade 3 or 4 drug-related events. However, general symptoms, such as fatigue and fatigue, fever and chills, myalgia and headache, were reported frequently but were low grade in more than 95% of cases. Eruptions and pruritus were reported in 21% of patients; Grade 3 or 4 pruritus was reported in 1% of patients, and rash grade 3 or 4 in 2%. The vitiligo was attributed to the MK-3475 in 9% of patients. The highest incidence of overall adverse events related to treatment was observed among patients who received 10 mg of MK-3475 per kilogram every 3 weeks, compared to patients who received 3 mg per kilogram every 3 weeks and those who received 1 mg per kilogram every 3 weeks (23%, versus 4% and 9%, respectively) Treatment-related pneumonitis was reported in 4% of patients; none of the cases was grade 3 or 4. One patient, a 96-year-old man, died during the study. Initial asymptomatic pneumonitis was identified in CT, and MK-3475 was discontinued. Subsequently, I present dyspnea and the patient received glucocorticoids. Grade 3 or 4 elevations in aminotransferase levels were reported in 1% of patients. Two cases of grade 3 renal insufficiency were recorded, both cases were potentially mediated by autoimmunity presented improvement of renal function with glucocorticoid treatment at the same time as the interruption of MK-3475. (27-28) The adverse events of special interest were autoimmune or inflammatory nature. Hypothyroidism was reported in 8% of patients and was treated effectively by administering thyroid hormone replacement therapy. Grade 3 hyperthyroidism and grade 2 adrenal insufficiency developed in a patient; these were handled with standard measures, and the patient continued in the study with a lasting response. (33-34)

Justification for the Crossing-over

Preliminary data suggest that nivolumab has clinical activity both in patients with previously treated NSCLC and in the first line (45-46). Similar preliminary results have also been reported in clinical studies of other immuno-oncological agents whose therapeutic target is the PD-1 pathway in patients with NSCLC. According to these data, the clinical activity of MK-3475 in patients with NSCLC who have progressed after the second line of chemotherapy may be similar or potentially greater than another third-line chemotherapy. Therefore, this study will give patients randomized in Arm B the option of receiving MK-3475 as monotherapy when documented progression exists and such crossover treatment is discussed with and approved by the MSD Medical Monitor. It is recognized that this cross-treatment with MK-3475 may decrease any potential benefit in OS (General Survival), but it will not affect the PFS criteria.

Justification for the initial evaluation of the tumour

The accumulation of clinical evidence indicates that some patients treated with agents that stimulate the immune system may develop disease progression (using conventional response criteria) before demonstrating clinical objective responses and/or stable disease. This phenomenon was observed in the CA209003 phase 1 study of Nivolumab (another anti-PD-1). Two hypotheses have been proposed to explain this phenomenon. First, elevated inflammation within tumours can lead to an increase in

tumour size appearing as enlarged index lesions and as newly visible small non-index lesions. Over time, both the malignant and inflammatory portions may decrease leading to obvious signs of clinical improvement. Another hypothesis is that the tumour growth kinetics may initially overcome the antitumor immune activity in some individuals. With enough time, it will dominate the antitumor activity and will become clinically evident. For these reasons, the initial evaluation of the tumour in CA209003 was carried out at 8 weeks and it is unknown if an earlier assessment would demonstrate similar activity due to the premature termination of the treatment under study. (34-35)

To mitigate the risk of detecting false progression at an early stage within the period of treatment with MK-3475, the initial evaluation of the tumour for both arms in this study will take place at Week 9 (±5 days). Thereafter, all subsequent tumour assessments every 6 weeks (will regularly place ±5 days) until documented disease progression or discontinuation of treatment, whichever comes later.

Justification for the collection of tumour tissue and evaluation of the PD-L1 expression of the tumour as a potential predictive biomarker

Aberrant expression of PD-L1 protein has been reported by tumour cells (retrospectively detected by IHC) in several human malignancies, especially in relation to poor prognosis in various types of tumours, including squamous and non-squamous NSCLC. (33-41) These findings can be explained by the fact that the high expression of PD-L1 causes immune evasion. This hypothesis is supported by several studies that demonstrate that PD-L1 expressed by tumour cells increases apoptosis of tumour-specific activated cells in vitro, (40) and that PD-L1 expression protects tumour cells from induction of Apoptosis by effector T cells. (42) In NSCLC, blocking PD-L1 to increase allows the number of CD8 + T cells infiltrating the tumour, and cause increased production of IFN- γ, but no differences were observed in CD8 + peripheral blood cells when subjects with NSCLC were compared with healthy controls. (43) These high levels of PD - L1 protein expression in NSCLC have also been significantly associated with poor prognosis and with the presence of tumour infiltration by immature dendritic cells. (44)

Interestingly, preliminary data indicate that PD-L1 protein expression in tumours can be correlated with the clinical activity of MK-3475. Archived tumour samples from a limited subgroup (N=30) of subjects in CA209003 were evaluated for the expression of PD-L1 protein measured by immunohistochemistry (IHC). In this subgroup, 100% of the subjects whose tumors lacked detectable expression of the PD-L1 protein (N=13), did not present evidence of clinical benefit (response, stable disease, or mixed response) with Nivolumab, while the subjects whose tumours were positive for PD-L1 (based on the expression of PD-L1 protein in a pre-defined threshold of tumour cells), were more likely to demonstrate clinical benefit. Despite the limited number of subjects evaluated in this initial study, our findings indicate that the expression status of the PD-L1 protein may have a profound impact on the likelihood of the patient responding to treatment with Anti PD-1. Because the clinical benefit seemed to correlate with the PD-L1 status measured in baseline pretreatment samples, these data also suggest that PD-L1 expression could serve as a predictive biomarker to select patients. As such, the analysis of a larger number of samples merits, and the evaluation of additional patients (and their tumours) recruited in the CA209003 study is ongoing. (33-41)

In this Phase II study, basal tumour tissue will be collected prospectively from randomized patients, and a retrospective efficacy analysis will be performed based on PD-L1 protein expression. The sponsor is in the process of developing a simple IHC assay, adjusted for what is proposed, which can be used to reproduce the expression of PD-L1 in tumour tissues reproducibly, and that could one day serve as a diagnostic aid for Select patients for treatment. Compulsory collection of tumour tissue in this phase II

scenario ensures that the number of subjects and samples needed to optimize the IHC assay is achieved, and by generating data on PD-L1 in a larger group of subjects, it will help to achieve analysis with statistical power. Contingently with the development of an optimized trial and the continuous indication that the expression status of the PD-L1 protein is predictive of clinical benefit (patients with a partial response as well as patients with complete response).

Justification for the evaluation of blood cells and soluble protein parameters of patients

The composition and characteristics of the cellular populations of the immune system as well as the soluble factors that mediate the different responses (cytokines, chemokines and growth factors) vary widely according to the location of the tumour and are important in determining the anti-immune response. -tumoral. For example, certain immune system cells, including natural killer cells (NK), dendritic cells (DC) and CD8 + T cells, are capable of conducting potent antitumor responses. However, tumour cells often induce an immunosuppressive microenvironment, which favours the development of immunosuppressive populations of immune cells, such as myeloid suppressor cells and regulatory T cells. Being able to understand the complex network of interactions of the various cell and protein types in peripheral blood, which are involved in the regulation of the immune processes involved in lung cancer. The development of a model that allows generating groups of patients or clusters characterized by the patterns generated that integrate the values of markers of evasion of the immune response simultaneously in the cells of the immune system, together with plasma protein levels. Associated with the clinical-pathological characteristics of the patients and the feasibility that may be potential biomarkers associated with prognosis and/or survival of clinical utility.

Justification for the evaluation of the results reported by the patient

Due to the proposed increase in ORR, OS and PFS of treatment with MK-3475 / Docetaxel in relation to docetaxel, it is hypothesized that the time for significant symptoms related to the disease according to the measurements of the EORTC QLQ C30 Questionnaire and LC-13 will also increase in relation to the combination MK-3475 / Docetaxel on docetaxel. EORTC QLQ-C30 questionnaire will be used to assess the general state of health and the data will be used to calculate the utilities of its use in economic models.

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LIST OF ABBREVIATIONS

ADA	Anti Drug Antibody
AE	Adverse event
AIDS	Acquired immunodeficiency syndrome
ALK	Anaplastic lymphoma kinase (CD246)
ALT	Alanine Aminotransferase
APC	Antigen-presenting cells
AST	Aminotransferase Aspartate
Bcl- x_L	Extra-large B cell lymphoma
BID	Twice daily
B7-DC	B7 human dendritic cells
B7-H1	Homologue 1 of human B7
BSC	Better supportive care
BTLA	B and T cell attenuator
CD28	A cluster of differentiation 28
CD273	A cluster of differentiation 273
CD274	A cluster of differentiation 274
C57BL/6	C57 black inbred mice 6
CI	Confidence interval
CMV	Cytomegalovirus
CNS	Central Nervous System
COX2	Cyclooxygenase 2
CR	Complete answer
NSCLC	Non-Small Cell Lung Cancer
CRF	Case Report Form
CT	CT scan
CTA	Clinical Study Agreement
CTCAE	Common Terminology Criteria for Adverse Events
CTL	Cytotoxic T lymphocyte
CTLA-4	Antigen 4 associated with Cytotoxic T lymphocyte
CYP	Cytochrome P450

D	Day
DCF	Data clarification form
LANGUAGE	Drug-induced liver injury
DLT	Dose-limiting toxicity
DMC	Data Monitoring Committee
DOOR	Duration of objective response
ECL	Electrochemiluminescence
ECOG	Eastern Cooperative Cancer Group
eCRF	Electronic form of case report
EDC	Electronic data capture
EGFR	Epidermal growth factor receptor
NO	Equivalence interval
ELISA	Immunoabsorbent Assay Linked to Enzymes
EOI	End of the infusion
ESOI	Special Interest Events
I	European Union
FLIP	Caspase 8-like inhibitory protein (FLICE)
FSH	Follicle Stimulating Hormone
FU	Tracing
GCP	Good clinical practices
GMP	Good manufacturing practices
HCG	Human Chorionic Gonadotropin
HIPAA	Portability and Social Security Responsibility Act
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
HR	Risk ratio
HTA	Sanitary Authority
ICF	Informed consent form
I	International Conference on Harmonization
ICOS	With the inducible T cell stimulator (CD278)
GONE	With the inducible stimulator
IFN	Interferon
IFNGR1	Interferon Gamma 1 receiver
IFN-γ	Interferon Gamma
IgG4	G4 immunoglobulin
IHC	Immunohistochemistry
THE	Interleukin
ITIM	Reason for immuno receptor tyrosine inhibitor
ITSM	Reason changed based on tyrosine of the immuno receptor
IRB/IEC	Institutional review board / independent ethics committee

IV	Intravenous
IVRS	Interactive voice response system
KM	Curve the Kaplan Meier
LMP	Low molecular mass protein
mAb	Monoclonal antibody
mCRPC	Castration resistant metastatic prostate cancer
MedDRA	Medical Dictionary for Regulatory Activities
MEL	Metastatic melanoma
mg	Milligram
mL	Milliliter
MLR	Mixed Lymphocyte Reaction
MRI	Magnetic Resonance Imaging
MTD	Maximum tolerated dose
M^2	Square meter
NCI	National Cancer Institute
NK	Natural killer
NSAID	Nonsteroidal anti-inflammatory drugs
CPCNP	Non-small cell lung cancer
WE	Not specified
NOS2	Nitric Oxide Syntase 2
ORR	Objective Response Rate
THE	Overall survival
PBMC	Peripheral blood mononuclear cell
PD	Progressive disease
PD-1	Scheduled Death-1
PD-L1	Ligand 1 of programmed death
PD-L2	Ligand 2 of programmed death
PFS	Progression free survival
PGE2	Prostaglandin E2
PK	Pharmacokinetics
PO	Orally
P19	Serine protease inhibitor
PR	Partial response
PRO	Results reported by the subject
PSA	Prostate Specific Antigen
PVG	Pharmacovigilance
q	Every
PRO	Results reported by the patient
RAG	Recombination activator gene
RCC	Renal cell carcinoma

RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ácido ribonucleico
RT	Radiation treatment
SAE	Serious adverse event
SD	Stable disease
SLD	Sum of the larger diameters
SNP	Single nucleotide polymorphism
SOC	Organic System Class
SOP	Standard Operating Procedures
Src	Sarcoma
STAT	Signal Transducers and Transcription Activators
TAP1	Conveyor associated with antigen processing 1
TCR	T cell receptor
teaer	Emerging adverse event with treatment
TGF	Transforming growth factor
TO	Tumor infiltrating lymphocytes
TKI	Tyrosine kinase inhibitor
TNF	Tumor necrosis factor
TRAIL	Inductor Ligand Treatment Related to Tumor Necrosis Factor Apoptosis
Tregs	Regulatory T cells
TTOR	Time to objective response
ULN	Upper limit than normal
WBC	Leukocytes
WOCBP	Women of reproductive age

V. CONTRIBUTION OF THE PROJECT IN THE ADVANCE OF THE KNOWLEDGE IN YOUR OWN THEME AND IN YOUR KNOWLEDGE AREA

The current unmet need in NSCLC continues to be the majority of subjects who do not have known mutations, or who present mutations for which there is no targeted treatment. In addition, once the subjects have developed resistance to TKI, there are few treatment options and the disease progresses rapidly. Docetaxel continues to be the reference treatment in this line of treatment since there are few additional options

Based on the background, a randomized phase II clinical trial comparing MK-3475 (Pembrolizumab) against docetaxel as a standard second-line therapy in patients with advanced NSCLC has been launched (NCT01905657), However, there is no study in which the synergistic activity of Docetaxel + MK-3475 (Pembrolizumab) was evaluated , this could open the possibility of using this medication simultaneously with docetaxel as a standard therapy in patients with disease progression despite a double regimen based on platinum .

OBJECTIVES

Primary objective

- To compare the objective response rate (ORR) of MK-3475 / Docetaxel compared to Docetaxel alone in patients with previously treated NSCLC.

Secondary objectives: Secondary objectives include the following:

- To compare the OS of MK-3475 (Pembrolizumab) / Docetaxel compared to docetaxel alone in patients with previously treated NSCLC.
- To compare progression-free survival (PFS) of MK-34 75 / Docetaxel compared to Docetaxel alone.
- To evaluate the clinical benefit of MK-3475 / Docetaxel versus docetaxel, in the PD-L1 + protein expression subgroups versus PD-L1 negative.
- To assess the proportion of subjects showing a progression of disease-related symptoms, measured by LCSS, with MK-3475 / Docetaxel and docetaxel.
- To evaluate the overall safety and tolerability of MK-3475 / Docetaxel versus docetaxel.
- To evaluate the general health status of the subject using the EORTC QLQ C30 and LC-13 questionnaire.
- To evaluate the percentage of expression and the average intensity of fluorescence CD279 (PD-1), CD274 (PD-L1), CD47 and CD172a / b (SIRP α / β) in the populations of immune cells by multiparametric blood flow cytometry peripheral of patients before the start of treatment and at the end of the 4 cycle.

  - Virgin CD4 T lymphocytes, central memory, effectors and effector memory
  - Virgin CD8 lymphocytes, central memory, effectors and effector memory
  - Double negative lymphocytes
  - Memory and Virgin Regulatory T lymphocytes
  - Th1, Th2 and Th17 lymphocytes
  - B lymphocytes in transition, plasma, Memory and Virgins
  - Classic and non-classic monocytes
  - Myeloid and Plasmacytoid dendritic cells
  - Mature and immature neutrophils
  - Natural Killer immunoregulatory and cytotoxic cells
  - NKT cells

  * To quantify plasma levels of soluble mediators of the immune response in peripheral blood in the patients before the initiation of treatment and at the end of the four-cycle.
  - Cytokines: IL-1 β, IL-2, IL-4, IL-6, IL-10, IL-12p70, IL-17A.
  - Growth Factors: TNF- α, TGF- β, VEGF, IFN- γ.
  - Chemokines: CXCL8 / IL-8, CXCL9 / MIG, CXCL10 / IP-10, CCL2 / MCP-1, CCL5 / RANTES.

VII. HYPOTHESIS

In patients with metastatic NSCLC previously treated with double platinum-based chemotherapy, administration MK-3475 / Docetaxel increases the overall response rate (ORR) compared with the administration of docetaxel alone.

VIII. GOALS PER YEAR

Approximately 70 patients will be randomized in the two treatment arms in a 1: 1 ratio. The study requires at least 45 deaths. It will take approximately 24 months to obtain the required number of deaths for the final OS analysis (12 months for accumulation and 12 months for survival monitoring). It is projected that an observed risk ratio of 0.74 or less, corresponding to 2.5 months or more of improvement in the median OS (7 vs. 9.5 months) would result in a statistically significant improvement in the final OS analysis.

The team of researchers will conduct eligibility assessments for the study during the patient selection phase for approximately 6 months, subsequently safety assessments at each visit, which will include physical examination, vital signs and laboratory tests, as well as Continuous monitoring of the survival and clinical and radiological response of the subjects who are taking the study drug, and every 3 months through personal or telephone contact after the subjects suspend the study drug, these activities are outlined in the tables contained in the Procedures section per visit.

IX. RESEARCH STRATEGIES OR METHODOLOGIES

UNIVERSE OF STUDY AND DESIGN

This is an open, randomized Phase 2 study in adult subjects (≥□18 years of age) men and women with NSCLC who progressed to the first line of platinum-based chemotherapy. Subjects will be randomized to MK-3475 (Pembrolizumab) / Docetaxel vs. Docetaxel only in a 1: 1 ratio.

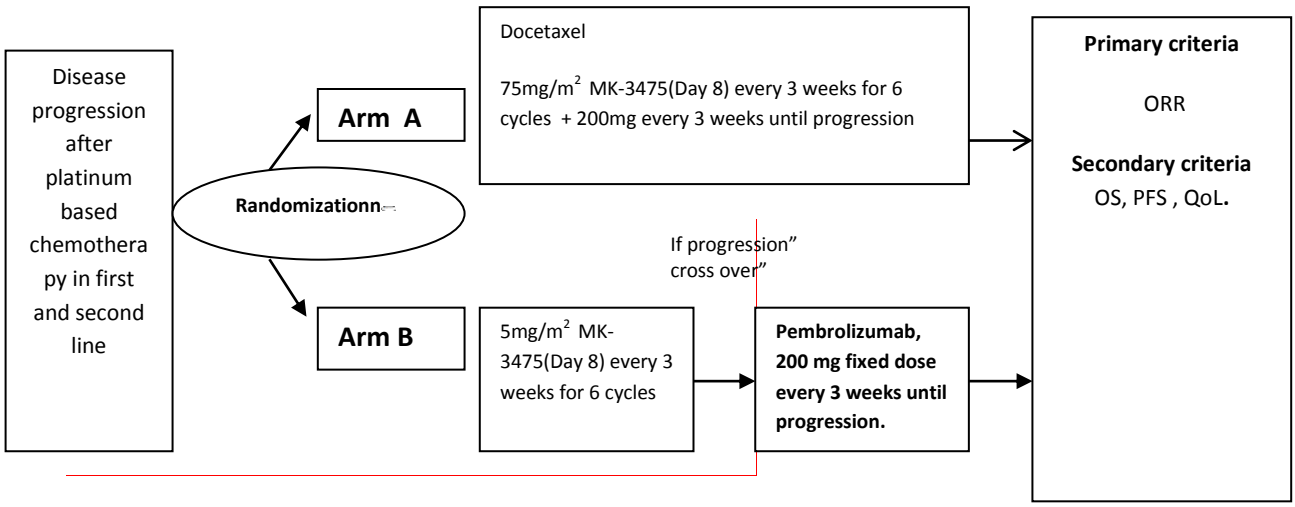
Initial Cohort
To ensure that the concomitant administration of docetaxel and MK-3475 is safe, a cohort of ten patients who will receive a fixed dose of 200mg will be followed.

Dose Increase
Since we will only use a fixed dose of 200 mg, a dose increase study is not required.

Safety Assessment
The safety assessment will be determined by concomitant review of laboratory tests (blood and urine samples to assess clinical parameters), pregnancy test (if warranted), ECOG, physical examination including measurement of vital signs, electrocardiogram (ECG), and adverse events. Safety will also include immunological safety assessments (serum autoimmunity tests, inflammation events regardless of causation and immunogenicity).

DESIGN AND SAMPLE SIZE:

Study design



Sample size:

The sample size was calculated to estimate a two-sample proportion with a difference of 25%. The null hypothesis stated that the proportion between groups would be equal (Ho:P2=P1), whereas the alternative hypothesis stated that the proportion between groups would not be equal (Ha:p2 (7%)!=p1(32%)). The alpha value was set at 0.05, and power was set at 0.80. Therefore, the sample size estimate resulted in 78 patients (39 patients per group).

Inclusion criteria

1) Signed written informed consent

a) Patients must have signed and dated a written informed consent form approved by the IRB / IEC in accordance with regulatory and institutional guidelines. This must be obtained before performing any procedure related to the protocol that is not part of the patient's normal care.

b) Patients must be willing and able to comply with scheduled visits, the treatment program, laboratory tests including filling in the questionnaires of the results reported by the patient and other study requirements.

2) Target population

a) Subjects with locally advanced non-squamous cell NSCLC, histologically or cytologically documented, who present with Stage IIIB / Stage IV or recurrent disease after receiving radiation treatment or surgical resection.

b) Men and women ≥ 18 years of age.

c) Performance status of the Eastern Cooperative Cancer Group (ECOG) ≤ 1.

d) Subjects must have measurable disease by CT or MRI according to RECIST 1.1 criteria; Radiographic Evaluation of Tumor performed within 28 days before randomization.

e) Target lesions may be located in a previously irradiated field if there is a progression of documented (radiographic) disease at that site.

Subjects must have experienced progression or recurrence of the disease during or after a previous chemotherapy regimen containing platinum for metastatic disease. This includes subjects who meet the following criteria:

(1) Subjects who received pemetrexed, bevacizumab, or erlotinib as maintenance treatment (non-progressors with double platinum-based chemotherapy) and progressed are eligible. However, patients with wild-type EGFR who received a tyrosine kinase inhibitor after the failure of previous platinum-based treatment are excluded.

(2) Patients who received double chemotherapy based on adjuvant or neo-adjuvant platinum (after surgery and/or radiation) and developed recurrent or metastatic disease within 6 months after finishing treatment are eligible

(3) Subjects with recurrent disease> 6 months after receiving platinum-based adjuvant or neoadjuvant chemotherapy are eligible, who also subsequently progressed during or after a double platinum-based regimen to treat recurrences

(4) Subjects with a known *EGFR* mutation and who received a TKI EGFR (erlotinib, gefitinib or experimental) and double platinum-based chemotherapy (regardless of the order of administration).

(5) Subjects with a known translocation of ALK who received double platinum-based chemotherapy and an ALK inhibitor (crizotinib or experimental)

(6) Patients who have received> 30Gy to the chest should have waited a minimum of 6 months from the end of the radiation scheme at the beginning of pembrolizumab.

f) A blood sample must be available for the evaluation of biomarkers.

g) All baseline laboratory requirements will be evaluated and must be obtained -14 days from randomization. The scrutiny laboratory values must meet the following criteria:

i) WBC ≥2000 / µL

ii) Neutrophils ≥1500 / µL

iii) Platelets ≥100 x 10^3 / µL

iv) Hemoglobin ≥9.0 g / dL

v) Serum creatinine ≤ 1.5 X ULN or creatinine clearance> 40 mL / minute (using the Cockcroft / Gault formula)

Women: $CrCl = \frac{(140 - \text{age in years}) \times \text{weight in kg} \times 0.85}{72 \times \text{serum creatinine in mg / dL}}$

Men: $CrCl = \frac{(140 - \text{age in years}) \times \text{weight in kg} \times 1.00}{72 \times \text{serum creatinine in mg / dL}}$

vi) AST ≤1.5 X ULN

vii) ALT ≤1.5 X ULN

viii) Total bilirubin ≤ 1.5x ULN (except in subjects with Gilbert's syndrome, who must have total bilirubin <3.0 mg / dL)

h) The previous treatment with radiotherapy or radiosurgery must have been completed at least 2 weeks before randomization.

i) Patients with a history of previously treated brain metastases may participate if they are stable (without evidence of progression verified by image for at least four weeks with neurological symptoms that have recovered at baseline), without evidence of new metastases or growth of the same , without the use of steroids for at least 7 days prior to the start of the study treatment or under a stable dose ≤ 10mg daily . The fulfilment of all the previously mentioned requirements makes them eligible to participate in the understanding that they are asymptomatic. This exception does not include carcinomatous meningitis that is excluded despite presenting clinical stability.

3) Age and Reproductive Status

a) Women with reproductive potential (WOCBP) should use contraception methods based on the tables found in Appendix 2. When a teratogenic study drug is used, and/or a drug for which there is insufficient information available to assess its teratogenicity (no pre-clinical studies have been conducted), it is required to use a highly effective method of contraception (failure rate less than 1% per year). Individual methods of contraception should be determined by consulting the investigator.

b) WOCBP must have a negative serum or urine pregnancy test (minimum sensitivity of 25 IU / L or equivalent units of HCG) 24 hours before starting the product under investigation.

c) Women should not be breastfeeding.

d) Sexually active men with WOCBP should use any contraceptive method with a failure rate of less than 1% per year. The researcher should review the contraceptive methods and the period of time during which contraception should be used. Men who are sexually active with WOCBP must follow the birth control instructions for a period of 90 days, plus the time required for the investigational drug to undergo five half-lives.

Exclusion criteria

1. Exceptions for Target Disease

a) Subjects with carcinomatous meningitis.

b) Subjects with active CNS metastases are excluded. Subjects are eligible if CNS metastases are treated appropriately and if the subjects return neurologically to the baseline (except for symptoms or residual signs related to CNS treatment), at least for 2 weeks before recruitment. In addition, subjects should not be taking corticosteroids, or they should be taking a stable dose or that is decreasing ≤ 10 mg daily of prednisone (or equivalent).

2. Clinical History and Concurrent Diseases

a) Any serious or uncontrolled medical disorder or active infection with hepatitis or HIV that could be reactivated.

b) Other malignancies that require concurrent intervention.

c) Subjects with previous malignancies (except skin cancers other than melanoma, and the following cancers in situ: bladder, gastric, colon, cervical / dysplasia, endometrial, melanoma, or

breast) are excluded unless remission has been achieved Complete at least 2 years before entering the study and do not require additional treatment or anticipate that additional treatment will be required during the study period.

d) Subjects with a condition that requires systemic treatment with corticosteroids (> 10 mg daily of prednisone or equivalent), or other immunosuppressive medications within 14 days before randomization. Inhaled or topical corticosteroids and doses of adrenal replacement steroids> 10 mg daily or equivalent is allowed in the absence of active autoimmune disease.

e) Subjects with known or suspected active autoimmune disease. Subjects with vitiligo, type I diabetes mellitus, residual hypothyroidism requiring hormonal replacement, or conditions that are not expected to recur in the absence of an external trigger may be recruited.

f) All toxicities attributed to a previous treatment against cancer other than alopecia and fatigue must have been resolved to grade 1 (NCI CTCAE version 4) or to baseline, before administration of the study drug.

g) Previous treatment with vaccines against the tumour or other immuno-stimulating anti-tumour agents.

h) Previous treatment with anti-PD-1, anti-PD-L1, anti-PD-L-2, anti-CD-137, or anti-CTLA-4 antibodies (including ipilimumab or any other antibody or drug specifically directed to co-stimulate T cells or the checkpoint pathways).

i) Prior treatment with docetaxel.

j) Subjects with a history of interstitial lung disease.

k) Subjects must be recovered from the effects of major surgery, or significant traumatic injury at least 14 days before the first dose of study treatment.

3. Physical Findings and Laboratory Tests

a) Positive tests for the Hepatitis B virus surface antigen (HBV sAg) or Hepatitis C ribonucleic acid (HCV RNA) indicating acute or chronic infection

b) Known history of positive test for Human Immunodeficiency Virus (HIV) or Acquired Immunodeficiency Syndrome (AIDS).

4. Allergies and Adverse Drug Reactions

a) History of severe hypersensitivity to other monoclonal antibodies.

b) Previous history of severe hypersensitivity reaction to paclitaxel.

c) History of allergy or intolerance (unacceptable adverse event) to the components of the study drug, or to infusions containing Polysorbate 80.

5. Sexual and Reproductive State

a) WOCBP pregnant or nursing.

b) Women with a positive pregnancy test at recruitment or before administration of the study medication.

6. Prohibited Treatments and / or Restricted Treatments

a) Ongoing or planned administration of cancer treatments other than those specified in this study.

b) Use of corticosteroids or other immunosuppressive medications according to the exclusion criteria contained in 2d.

c) Strong CYP3A4 inhibitors (See Section 3.4.1).

d) Treatment with any investigational drug 28 days before the first administration of the study treatment.

7. Other Exclusion Criteria

a) Any other serious or uncontrolled medical disorder, active infection, physical examination finding, laboratory finding, altered mental status, or psychiatric condition that, in the opinion of the investigator, would limit a subject's ability to meet the requirements of the study, which significantly increases the risk to the subject, or affects the interpretability of the study results.

The eligibility criteria of this study have been carefully considered to ensure the safety of the study subjects, and to ensure that the study results can be used.

Elimination criteria:

Patients withdrawing informed consent, patients with disease progression according to RECIST 1.1, or patients presenting unacceptable toxicity.

Dose of the Groups

Medicine	Dose / Potency	Dose frequency	Route of Administration	Treatment Scheme / Period	Use
Pembrolizumab	**200 mg**	**Every 3 weeks**	**IV infusion**	**2 years or until progression**	**Experimental**
Docetaxel	**75 mg / m ^{2}**	**Every 3 weeks**	**IV infusion**	**6 cycles**	**Experimental / Control**
The dosage range of pembrolizumab can be modified if toxicity occurs, it is mentioned in the section on Modification and Selection of the Dose.					

Criteria

For subjects previously assigned to the Docetaxel arm and who experienced disease progression by RECIST 1.1 criteria.

- They must continue to meet all the inclusion criteria specified above and all exclusion criteria with the exception of criterion 2 (i).

- Any toxicity from previous therapy must be resolved to the baseline or Grade 1 (except for alopecia, fatigue, and neuropathy, which may be grade 2) before beginning the crossing to Pembrolizumab.

The clinical activity of Pembrolizumab in patients with advanced NSCLC who have progressed after second-line chemotherapy may be similar to or potentially greater than that of third-line chemotherapy. Therefore, this study will provide subjects who were randomly assigned to arm B the option of receiving monotherapy with Pembrolizumab in those with documented progression, conditioned on the progression being confirmed after review and said treatment being evaluated by the principal investigator. It is recognized that this crossing of treatment to Pembrolizumab could reduce any possible benefit in the OS, but it will not affect the PFS.

Drug allocation process (randomization)

After the subject's eligibility is established and informed consent has been obtained, the subject will be recruited and assigned a number to be randomized. Each subject that signs the informed consent must have an assigned subject number. Once recruited, recruited subjects who have signed in informed consent and who meet all eligibility criteria will be ready to be randomized. Subjects who meet all eligibility criteria and who are randomized will be assigned to one of two treatment groups.

Patient Safety Procedures

The safety assessment will be determined by examinations of clinical laboratory tests (blood and urine sampling for clinical laboratory parameters), pregnancy tests, ECOG functional status, physical examination that includes measurements of vital signs and Adverse events.

Patients will be treated with docetaxel at 75 mg / m 2 every 3 weeks on day 1 of the cycle, on day 8 of the cycle (1 week later) MK-3475 (Pembrolizumab) will be applied intravenously at a fixed dose of 200 mg every 3 weeks until disease progression compared with docetaxel only intravenously administered at two is 75 mg / m 2 on day 1 of the first cycle, with subsequent toxicity assessment on day 8 (1 week after) of the first cycle Then, the D1 of each cycle will only be evaluated for treatment (every 3 weeks) until 6 cycles are completed , because of unacceptable toxicity and / or investigator criteria, docetaxel can be suspended and continue only with MK-3475 or close monitoring.

For patients experiencing limiting toxicities, the dose modification criteria of MK-3475 and Docetaxel will be any grade 4 toxicity such as hypothyroidism, diarrhoea, increased level of aminotransferase, renal failure, dyspnea, pneumonitis that lasted more than 1 week.

Patients will be treated with MK-3475 until disease progression, unacceptable toxicity or revocation of consent, and Docetaxel until completing 6 cycles will be treated at the discretion of the principal investigator.

Modification and Selection of the Dose.

Adverse events (both severe and non-severe) associated with exposure to Pembrolizumab may present an immunological aetiology. These adverse events may occur just after the start of the first dose or different months after the last dose of treatment. Adverse events probably caused by Pembrolizumab should be classified as drug-related or serious or life-threatening toxicities, according to Table 1, presented below.

Table 1. Dose Change Guidelines for Adverse Drug-Related Events

Toxicity	Stop treatment for Grade	Treatment re-start time	Suspend in the Patient
Diarrhea / Colitis	2-3	Toxicity resolves or becomes Grade 0-1.	The toxicity is not resolved within 12 weeks of the last dose or inability to reduce the steroid to 10 mg or less of prednisone or its equivalent per day within 12 weeks.
	4	Suspend permanently.	Suspend permanently.
Increase in AST, ALT, or Bilirubin to	2	Toxicity resolves or becomes Grade 0-1.	Toxicity does not resolve within 12 weeks of the last dose

Toxicity	Stop treatment for Grade	Treatment re-start time	Suspend in the Patient
	3-4	Suspend permanently. (see exception [1])	Suspend permanently.
Type 1 diabetes (recently diagnosed) or Hyperglycemia	DM T1 or 3-4	Suspend Pembrolizumab in case of newly diagnosed type 1 DM or Grade 3-4 hyperglycemia associated with evidence of beta-cell failure.	Restart Pembrolizumab when patients are clinically and metabolically stable.
Hypophysitis	2-3	Toxicity resolves or becomes Grade 0-1.	The toxicity is not resolved within 12 weeks of the last dose or inability to reduce the steroid to 10 mg or less of prednisone or its equivalent per day within 12 weeks.
	4	Suspend permanently.	Suspend permanently.
Hyperthyroidism	3	Toxicity resolves or becomes Grade 0-1.	The toxicity is not resolved within 12 weeks of the last dose or inability to reduce the steroid to 10 mg or less of prednisone or its equivalent per day within 12 weeks.
	4	Suspend permanently.	Suspend permanently.
Hypothyroidism	2-4	Treatment with Pembrolizumab can be continued while on treatment for dysfunction thyroid On.	Pembrolizumab treatment can be continued while in treatment for dysfunction thyroid On.
Infusion Reaction	3-4	Suspend permanently.	Suspend permanently.
Pneumonitis	2	Toxicity resolves or becomes Grade 0-1.	The toxicity is not resolved within 12 weeks of the last dose or inability to reduce the steroid to 10 mg or less of prednisone or its equivalent per day within 12 weeks.
	3-4	Suspend permanently.	Suspend permanently.
Kidney Failure or Nephritis	2	Toxicity resolves or becomes Grade 0-1.	The toxicity is not resolved within 12 weeks of the last dose or inability to reduce the steroid to 10 mg or less of prednisone or its equivalent per day within 12 weeks.
	3-4	Suspend permanently.	Suspend permanently.
Any other toxicity related to Medication [2]	3 or Grave	Toxicity resolves or becomes Grade 0-1.	The toxicity is not resolved within 12 weeks of the last dose or inability to reduce the steroid to 10 mg or less of prednisone or its equivalent per day within 12 weeks.
	4	Suspend permanently.	Suspend permanently.

Note: Suspend permanently in case of any serious EA or Grad or 3 related to the medication that is recurring or a life-threatening event.

[1] In the event that patients present with metastases and begin treatment with AST or Grade 2 ALT, if AST or ALT increases greater than or equal to 50% relative to baseline and for at least one week then it should be suspended in patients.

[2] Patients with persistent grade 2 AD may be temporarily suspended according to the doctor's opinion. It should be discontinued permanently if Grade 2 adverse AE persists for which treatment with the study medication has been temporarily suspended, and those who do not recover from Grade 0-1 within 12 weeks of the last dose.

Dose Modification

The application of MK-3475 will be stopped in case of haematological or grade 3 toxicities for drug-related non-haematological, including laboratory, serious or life-threatening abnormalities as in Table 2 below.

Dose modification rules for adverse events related to the drug.

Table 2 : Dose modification rules for adverse events related to the drug and experimental.

Toxicity	Grade	Maintain Treatment (Y / N)	Time to restart treatment	Dose and scheme to restart treatment	Treatment Suspension
Haematological Toxicity	1, 2	Do not	N / A	N / A	N / A
	3* * Excluding neutropenia, anaemia, and grade 3 thrombocytopenia	Yes	Toxicity Resolved or grade 1	The application interval can be increased by 1 week	Toxicity does not resolve after 12 weeks of infusion *The permanent interruption must be considered for any serious or life-threatening event*
	4	Yes	Toxicity Resolved or grade 1	The application interval can be increased by 1 week	
Non- Hematological Toxicity Note: Exception to be treated similar to grade 1 toxicity • 2 grade alopecia • 2 degree fatigue	one	Do not	N / A	N / A	N / A
	2	Consider retention for persistent symptoms	Toxicity Resolved or grade 1	*EA Clinically resolves in 4 weeks: The same dose and schedule* *Clinically EA does not resolve in 4 weeks: You can increase the dosage interval by 1 week for each case*	Toxicity does not resolve after 12 weeks of infusion
	3. 4	Yes	Toxicity Resolved or grade 1	The application interval can be increased by 1 week	Toxicity does not resolve after 12 weeks of infusion *Permanent interruption must be considered for any serious or life-threatening event*

In case the toxicity is not resolved to grade 0-1 within 12 weeks after the last infusion, the treatment should be discontinued. Subjects with an adverse laboratory event still in grade 2 after 12 weeks may continue treatment if, in the opinion of the investigator, it is an asymptomatic and controlled reaction.

Subjects who experience a recurrence of the same serious or life-threatening event in the same or greater degree, with MK-3475 (Pembrolizumab) should be discontinued trial treatment.

The dose of Docetaxel can be modified in patients presenting with febrile neutropenia, neutropenia <500 cells / mm ^{3} for more than a week despite support with granulocyte stimulating factor, severe skin

reactions or other non-hematological grade 3/4 toxicity according to CTCAE criteria during treatment with Docetaxel, if required it will be carried out according to the following table :

Table 3: Dose modification standards for adverse events related to Docetaxel.

Docetaxel dose reduction	
Dose level	**Docetaxel**
Initial dose	75 mg / m ^{2}
First reduction	55 mg / m ^{2}
Second reduction	37.5 mg / m ^{2}
Third reduction	Discontinue Docetaxel

Rescue Medications and Supportive Care

Supportive Care Guidelines

Subjects should receive therapeutic support measures when deemed necessary by the investigator that includes but is not limited to the elements described below:

- Diarrhoea: Subjects should be carefully monitored for signs and symptoms of enterocolitis (such as diarrhoea, abdominal pain, blood or mucus in the stool, with or without fever) and intestinal perforation (such as peritoneal signs and ileus). In symptomatic subjects, infectious etiologies should be ruled out, and if the symptoms are persistent and/or severe, endoscopic evaluation should be considered.

- In subjects with severe enterocolitis (grade 3), MK-3475 should be permanently discontinued and treatment with systemic corticosteroids should be initiated with a dose of 1 to 2 mg/kg/ day of prednisone or equivalent. When symptoms improve to grade 1 or less, the decrease in corticosteroids should be initiated and continued for at least 1 month.

- In subjects with moderate enterocolitis (grade 2), MK-3475 should be suspended and anti-diarrheal treatment should be initiated. If the symptoms are persistent for more than a week, systemic corticosteroids should be initiated (for example, 0.5 mg /kg/day of prednisone or equivalent). When symptoms improve to grade 1 or less, the decrease in corticosteroids should be initiated and continued for at least 1 month.

- All subjects experiencing diarrhoea should advise drinking plenty of clear liquids. If there is sufficient fluid intake by mouth, it is not necessary to replace fluids and electrolytes by IV infusion.

- Nausea / Vomiting: Nausea and vomiting should be treated aggressively, and should be considered in the cycles following the administration of prophylactic antiemetic

treatment according to medical practice. Subjects should be strongly encouraged to keep the intake free of oral fluids.

o Anti-infectives: Subjects with a documented infectious complication should receive oral or intravenous antibiotics or other anti-infectious agents as deemed appropriate by the investigator.

o Management of infusion reactions: acute infusion reactions (which may include cytokine release syndrome, angioedema or anaphylaxis) are different from allergic reactions/hypersensitivity, although some of the manifestations are common to both entities. Signs and symptoms usually develop during or shortly after the infusion of the drug and usually resolve completely within 24 hours of the end of the infusion. Signs / symptoms may include: Allergic reaction / hypersensitivity (such as drug fever); Arthralgia (joint pain); Bronchospasm; Cough; Dizziness; Shortness of breath (trouble breathing); Fatigue (asthenia, lethargy, malaise); Headache; Hypertension; Hypotension; Myalgia (muscle pain); Sickness; Itching / itching; Rash / peeling; Rigors / chills; Sweating (diaphoresis); tachycardia; Tumor pain (onset or exacerbation of pain due to tumor treatment); Hives (rash, hives, hives); Vomiting

o Table 4 shows the treatment guidelines for subjects experiencing an infusion reaction associated with the administration of MK-3475.

o The use of palliative radiotherapy to bone lesions that remain symptomatic will be allowed, treatment will be suspended one week before, during and after treatment for patient safety

Table 4 Infusion Reaction Treatment Guidelines

NCI CTCAE grade	Treatment	ubsequent dose medication
Grade 1 Mild reaction; infusion interruption is not indicated; intervention not indicated	Increased control of vital signs as medically indicated until the subject is considered medically stable in the opinion of the investigator.	Any
Grade 2 It requires infusion interruption but responds quickly to symptomatic treatment (for example, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for <= 24 hrs	Stop infusion and monitor symptoms. Appropriate additional medical therapy may include but is not limited to: IV liquids antihistamines NSAID Paracetamol narcotics Increased control of vital signs as medically indicated until the subject is considered medically stable in the opinion of the investigator. If the symptoms resolve within an hour of stopping the infusion of the drug, the infusion can be restarted at 50% of the	The subject can be premedicated 1.5 hours (± 30 minutes) before infusion of MK-3475 with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Paracetamol 500-1000 mg po (or equivalent dose of antipyretic).

NCI CTCAE grade	Treatment	ubsequent dose medication
	initial infusion rate (for example, from 100 ml / hr to 50 ml / h). Otherwise, the dosage will be carried out until the symptoms resolve and the issue should be premedication for the next dose. Subjects who develop grade 2 toxicity despite adequate premedication should be permanently interrupted from the subsequent administration of the trial treatment.	
Grades 3 or 4 3rd grade: Prolonged (ie, does not respond quickly to symptomatic medication and / or brief interruption of the infusion); recurrence of symptoms after initial improvement; hospitalization indicated for other clinical sequelae (eg renal failure, pulmonary infiltrates) Grade 4: Life threatening; vasopressor or ventilatory support indicated	Stop Infusion Appropriate additional medical therapy may include but is not limited to: IV liquids antihistamines NSAID Paracetamol narcotics oxygen pressors Corticosteroids Epinephrine Increased control of vital signs as medically indicated until the subject is considered medically stable in the opinion of the investigator. Hospitalization may be indicated. The subject is permanently interrupted from the subsequent administration treatment trial.	No subsequent dose

Supportive Care Guide for Pneumonitis

Subjects with symptomatic pneumonitis should stop receiving MK-3475 and have an evaluation. The evaluation may include imaging studies (Chest Tomography, X-rays) and lung function tests to rule out other causes, such as an infection. If the subject is determined pneumonitis associated drug study, the suggested treatment plan is detailed in Table 5.

Table 5 Recommended approach for Pneumonitis Management

Drug-associated pneumonitis	Maintain / Discontinue MK-3475?	Support Treatment
Grade 1 (asymptomatic)	No action	No intervention
Grade 2	Maintain the MK-3475, you can return to your treatment if it improves to grade 1 or resolves in 12 weeks	Systemic corticosteroids are indicated.
Grade 3 and Grade 4	**Suspend MK-3475**	Systemic corticosteroids are indicated. The use of infliximab may be indicated, as appropriate.

For Grade 2 pneumonitis that improves to ≤ Grade 1 in the 12 weeks, the following rules will apply:

• In the first episode of pneumonitis, the dosage interval can be increased by one week in subsequent cycles

• The second episode of pneumonitis - permanently discontinue MK-3475 if subject to reexposure develops pneumonitis ≥ Grade 2

MK-3475

Prior medications are not recommended for the start of dosing.

Docetaxel

Dexamethasone should be administered with a dose of 8mg.

Treatment arms :

Arm A: Will include treatment with Docetaxel at 75 mg / m2 every 3 weeks with MK-3475, 200 mg every 3 weeks until progression.

Arm B: Will include treatment with Docetaxel at 75 mg / m2 every 3 weeks, where there will be the possibility of crossing to start treatment with MK-3475, 200 mg every 3 weeks until progression.

Methods and techniques that will be used for the analysis and interpretation of the data

Primary Efficacy Assessment

All subjects will be monitored by a radiological evaluation on a calendar, first evaluation at 9 weeks later every 6 weeks, to determine changes in tumour size. The RECIST 1.1 criteria will be used for the evaluation (*see Appendix 1*). To determine the overall response rate (ORR), patients with partial response and complete response evaluated according to RECIST 1.1 criteria will be taken into account.

Secondary and exploratory efficacy evaluations

Every effort will be made to collect the survival data of all subjects, including subjects withdrawn from treatment for any reason, who are eligible to participate in the study and who have not withdrawn their consent for the collection of data from survival. If the death of the subject is not reported, all dates in this study that represent a date of contact with the subject will be used to determine the last date on which it was known that the subject was alive.

Additional data will be collected to determine the change in the proportion of disease-related symptoms in subjects with NSCLC, using the EORTC QLQ-LC13 questionnaire.

Evaluation of the modification of symptoms.

The results reported by the patients (PRO) will be measured using the following two self-applied questionnaires and validated: EORTC QLQ-C30 and EORTC QLQ-LC13.

Subjects will be asked to fill out the questionnaires before performing any clinical activity during the study clinic visits in the scrutiny, on the days of the start of the cycle every 9 weeks, at the end of the treatment or when withdrawing from the study.

Questionnaires will be provided in the language preferred by the subject.

Procedures per visit (Annex protocol diagram)

Flowchart / Calendar of Times and Events

Table 6 .1A: Screening Assessments and Procedures for GROUPS A and B		
Process	**Scrutiny Visit**	**Notes**
Eligibility Assessments		
Informed consent	X	
Inclusion / Exclusion Criteria	X	Assessed before randomization
Clinic history	X	
Security Assessments		
Vital Signs and Oxygen Saturation	X	Vital signs include: Temperature, BP, HR, RR O_2 saturation by pulse oximetry (obtained at rest, also monitor the amount of supplemental oxygen, if applicable) Obtain vital signs at the screening visit and within 72 hours after the first dose
Physical Measurements (including Performance Status)	X	Height and Weight and ECOG status
Lab tests	X	Done locally 14 days before randomization CBC with differential, Blood chemistry in serum (BUN or serum urea level, serum creatinine, albumin, sodium, potassium, calcium, magnesium, phosphate, chlorine and bicarbonate), AST, ALT, total bilirubin, alkaline phosphatase, glucose, LDH, and endocrine panel (including free TSH, T3 and T4), Hep B and C- (HBV sAg, HCV RNA),
Pregnancy test	X	Performed **24** hours before randomization (in serum or urine only for women of reproductive age)
Evaluation of Adverse Events (AE) and Serious Adverse Events (SAE) (of signs and symptoms)	X	After obtaining the Informed Consent, all the signs and symptoms will be evaluated 14 days before randomization and beginning the study treatment.
Concomitant Drug Collection	X	14 days before randomization
Efficacy Assessments		
Radiographic Evaluation of Tumor (Thorax and abdomen)	X	It must be done 28 days before randomization.
Electrocardiogram	X	Only on this visit will it take place

Protocol version #1 amendment 3. Date: July 21 of 2017.

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Table 6 .1B: Evaluations During the Study for GROUP A (Docetaxel / MK 3475 Pembrolizumab)				
Process	**C1D1**	**C1D8**	**Every 3 cycles (6 weeks ±□5 days)**	**Notes (add notes on the cycles)**
Security Assessments				
Vital Signs and Oxygen Saturation	X	X		Vital signs include: Temperature, BP, HR, RR O_2 saturation by pulse oximetry should be at rest without supplemental oxygen (also monitor the amount of supplemental oxygen, if applicable); Oximetry should be performed before dosing and at any time when the subject has new or worsening respiratory symptoms.
Evaluation of Adverse Events (AE) and Serious Adverse Events (SAE)	Related to the treatment. Evaluated using the NCA CTCAE v. 4.0			
Physical measurements (including Performance Status)	X	X		Including Weight and ECOG status
Complete blood counts (CBC) (Results obtained before dosing on infusion days)	X	X		Includes differential WBC count, ANC, lymphocyte count, haemoglobin, hematocrit, and platelet count
Blood Chemistry Tests	X	X		Blood chemistry (BUN or serum urea level, serum creatinine, sodium, potassium, calcium, magnesium, phosphate, chlorine), LDH, glucose
Liver Function Tests (Results obtained **72** hours before dosing on infusion days)	X	X		It includes aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, alkaline phosphatase, albumin.
Endocrine Tests	X		X	TSH (see free T3 and T4 if the result is abnormal) every 6 weeks (+/- 5 days) throughout the study from C1D1
Concomitant Meds Review	X	X		It must be checked at each visit
Pregnancy test			X	The serum or urine test should be performed **every 6 weeks.**
Efficacy Assessments				

Table 6 .1B: Evaluations During the Study for GROUP A (Docetaxel / MK 3475 Pembrolizumab)					
Process	**C1D1**	**C1D8**	**Every 3 cycles (6 weeks ±□5 days)**	**Notes (add notes on the cycles)**	
Radiographic Tumor Evaluation			X	Evaluations should include thorax and abdomen (with contrast). It must be done ±□5 days from the date of the visit. According to RECIST criteria 1.1. The **tumour assessments** should continue every 6 weeks (±□5 days), starting at week 9 (±□5 days) from randomization until it is documented disease progression or suspension of treatment, whichever comes later.	
Evaluation of Patient-Reported Results (PRO)	X			**For C1D1** - performed after randomization, but BEFORE the first dose (day -3 to +1). **For visits during the study**: Evaluations (EORTC QLQ-C30 and EORTC QLQ-LC13) will be carried out BEFORE any procedure and treatment of the study. They will be carried out every 9 weeks.	
Clinical Drug Supplies					
MK -3475 Pembrolizumab (10mg / Kg) on day 8 of the cycle Docetaxel 75 mg / m2 on day 1 of the cycle	X	X			Every 21 days Record the start and end times of the Study Drug Infusion. Premedication with Dexamethasone 8mg.

Table 6 .1C: Evaluations During the Study for GROUP B (Docetaxel)					
Process	**C1D1**	**C1D8 ±□5 days**	**Every Cycle every 3 weeks on Day 1 (±□5 days)**	**Every 2 cycles (6 weeks ±□5 days)**	**Notes**
Security Assessments					
Vital Signs and Oxygen Saturation	X	X	X		Temperature, BP, HR, RR, O2 saturation by pulse oximetry (obtained at rest without supplemental O2, before dosing and at any time when a subject has new or worsening respiratory symptoms)
Physical	X	X	X		Includes Weight (calculated BSA)

Table 6 .1C: Evaluations During the Study for GROUP B (Docetaxel)					
Process	**C1D1**	**C1D8 ±□5 days**	**Every Cycle every 3 weeks on Day 1 (±□5 days)**	**Every 2 cycles (6 weeks ±□5 days)**	**Notes**
measurements (including Performance Status)					and ECOG status
Evaluation of Adverse Events (AE) and Serious Adverse Events (SAE)	----------continually----------			Evaluated using the NCA CTCAE v. 4.0	
Complete blood counts (CBC) (Results obtained before dosing on infusion days)	X	X	X		Includes differential WBC count, ANC, lymphocyte count d, hemoglobin, hematocrit, and platelet count
Blood Chemistry Tests	X	X	X		It includes serum creatinine, blood urea nitrogen, or blood urea level, sodium, calcium, magnesium, phosphate, potassium, chlorine, glucose, LDH,
Liver Function Tests (Results obtained 72 hours before dosing on infusion days)	X	X	X		It includes aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, alkaline phosphatase, albumin.
Thyroid Function Tests	X			X	TSH (see free T3 and T4 if the result is abnormal)
Concomitant Meds Review	X	X	X		Revised at each visit
Pregnancy test				X	The serum or urine test should be performed every 6 weeks.
Efficacy Assessments					

Table 6 .1C: Evaluations During the Study for GROUP B (Docetaxel)					
Process	**C1D1**	**C1D8 ±□5 days**	**Every Cycle every 3 weeks on Day 1 (±□5 days)**	**Every 2 cycles (6 weeks ±□5 days)**	**Notes**
Radiographic Tumor Evaluation				X	Evaluations should include thorax and abdomen (with contrast. It should be done ±□5 days from the date of the visit. According to RECIST 1.1 criteria. The First Tumor Evaluation should be carried out in Week 9, and then every 6 weeks (±□5 days) from week 9 (±□5 days) from randomization, until disease progression or treatment discontinuation is documented, whichever occurs most late.
Evaluation of Patient Reported Results (PRO)	X				**For C1D1** - performed after randomization, but BEFORE the first dose (day -3 to +1). **For visits during the study** : Evaluations (EORTC QLQ-C30 and EORTC QLQ-LC13) will be performed BEFORE any procedure and treatment of the study. They will be held every 9 weeks.
Clinical Drug Supplies					
Docetaxel (75 mg / M^2)	X		X		Every 21 days . Record the start and end times of the Study Drug Infusion. Premedication with Dexamethasone 8mg.

STATISTIC ANALYSIS

Data collection will be done through the electronic file and by a direct interview in the lung cancer clinic's office. The information that will be collected will be variables such as age, gender, symptoms, date of diagnosis, factors associated with lung cancer such as; smoking, smoking rate, exposure to asbestos, wood smoke, hours-years exposed to wood smoke, type and histological subtype, response to chemotherapy, among others.

For descriptive purposes, continuous variables will be measured as arithmetic means, medians and standard deviations, categorical variables will be understood in proportions with 95% confidence intervals. Differential comparisons will be made using the Student t-test or the Mann-Whitney U test, according to the data (Normal and abnormal) determined from the Kolmogorov-Smirnov test. The Chi-square test will be used to determine significant differences between categorical variables. The probability value less than or equal to 0.05 ($p < 0.05$) is determined statistically significant, with a two-tailed design. Statistically significant and marginally significant variables ($p < 0.1$) will be included in the multivariate logistic regression analysis. Progression-free and overall survival will be calculated using the Kaplan-Meier survival tables, while comparisons between subgroups will be analyzed with the Log Rank tests or the Breslow tests.

All statistical analyses will be carried out with the SPSS version 21 software program (SPSS, Inc. Chicago, IL, USA).

ETHICAL CONSIDERATIONS

Good Clinical Practices

This study will be conducted in accordance with Good Clinical Practices (GCP), defined by the International Conference on Harmonization (ICH) and complying with the ethical principles of the European Union Directive 2001/20 / EC and the Code of Federal Regulations of United States, Title 21, Part 50 (21CFR50).The study will be conducted in compliance with the protocol. The protocol and any of its amendments, as well as the subject's informed consent, will receive approval /favourable opinion from the Institutional Review Board / Independent Ethics Committee (IRB / IEC) before beginning the study. All potential violations must be reported to MSD immediately. A serious violation is a violation of the conditions and principles of the CPGs related to the study or the protocol, which probably affect, to a significant degree, the safety or physical or mental integrity of the subjects of the study or the scientific value of the study. The personnel involved in conducting this study will be qualified by their level of education, training and experience to perform their respective task (s). This study will not use the services of the study staff when sanctions have been appealed. or when there has been scientific misconduct or fraud (eg, cancellation of medical license, suspension).

Institutional Review Board / Independent Ethics Committee

Before the start of the study, the researcher must have written and dated the approval / favorable opinion of the IRB / IEC for the protocol, consent form, patient recruitment, materials/processes (for example, commercials) and any other written information that It will be provided to patients. The

researcher or sponsor must also provide the IRC / IEC with a copy of the Researcher's Manual or product data sheet, the information provided to the patients and any updates.

The researcher or sponsor must provide the IRB / IEC with reports, updates and other information (for example, urgent safety reports, amendments and administrative letters) in accordance with regulatory requirements or institutional procedures.

Informed consent

Researchers must ensure that patients are clearly and fully informed about the purpose, potential risks and other critical issues related to clinical studies in which patients voluntarily participate. In situations where consent cannot be granted by patients, their legally acceptable representatives must be clearly and fully informed about the purpose, potential risks and other critical issues related to clinical studies in which patients voluntarily participate.

Researchers must:

1) Provide a copy of the consent form and written information about the study in the language in which the patient is most skilled before participating in the clinical study. The language must be non-technical and easily understandable.

2) Give the necessary time for the patient or the legally acceptable representative of the patient to ask about the details of the study

3) Obtain an informed consent signed and dated personally by the patient or the legally acceptable representative of the patient and by the person who carried out the discussion of the informed consent.

4) Obtain the approval /favourable opinion of the written informed consent form of the IRB / IEC and any other information that will be provided to the patients, before the start of the study, and after all the reviews are completed in relation to the new information.

5) If the informed consent is initially granted by the legally acceptable representative or legal guardian of a patient, and the patient subsequently becomes able to perform and communicate their informed consent during the study, then the consent must be additionally obtained from the patient.

6) Review the informed consent whenever new important information that is relevant to the patient's consent is available. The investigator, or a person designated by the investigator, must fully inform the patient or the legally acceptable representative or legal guardian, of all relevant aspects of the study and of any new relevant information for the patient to voluntarily continue with his participation in the study. This communication must be documented.

Researchers should ensure that the subjects, or, in those situations where the subjects cannot provide consent, their legally acceptable representatives are clearly and fully informed about the purpose, potential risks and other critical aspects related to clinical studies in They participate voluntarily.

Researchers must:

2) Provide a copy of the consent form and written information about the study in the language in which the subject is most competent before the clinical study participates. The language should not be technical and should be easily understood.

Allow the time necessary for the subject or the legally acceptable representative of the subject to ask questions about the details of the study.

Obtain a signed and dated consent form personally by the subject or the legally acceptable representative of the subject and by the person who addressed the informed consent talk.

Obtain the favourable approval/opinion of the IRB / IEC in the form of informed written consent and any other information that will be provided to the subjects before the start of the study and after any review has been completed for new information.

If the informed consent is initially granted by the legally acceptable representative or legal guardian and subsequently the subject becomes able to make and communicate their informed consent during the study, then the consent must also be obtained from the subject.

Review informed consent whenever important new information that is relevant to the subject's consent is available. The investigator, or a person designated by the investigator, must fully inform the subject or the legally acceptable representative of the subject or legal guardian of all relevant aspects of the study and any relevant new information so that the subject wishes to continue their participation in the study. This communication must be documented.

The consent form must also include a statement that MSD and regulatory authorities have direct access to the subject's records.

The rights, security and welfare of the subjects of the study are the most important considerations and should be imposed on the interests of science and society. According to the General Law of Health in Research Matters, the format will be signed by 2 witnesses.

3. AGREEMENTS FOR INDEMNIFICATION TO PARTICIPATING PATIENTS BY POTENTIAL DAMAGES DERIVED FROM THE STUDY

4. INCOME FOR RESEARCHERS:

a) The income will be distributed according to the regulations in force in the Institute. [X]

b) There is no income, it is a protocol of researchers initiative. [ ]

RESEARCH PROTOCOL

5. THE STUDY WILL BE CONDUCTED IN ACCORDANCE WITH WHAT IS SIGNED IN:

	YES	NO	N/A
- **Declaration of Helsinki**	x		
- **Good Clinical Practice**	x		
- **Norms established in the General Health Law in Mexico**	x		

6. APPENDIX THE LETTER OF INFORMED CONSENT

SEE DOCUMENT SEPARATELY