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Official Title: "Neo-adjuvant chemo/immunotherapy for the treatment of resectable stage IIIA non small cell lung cancer (NSCLC): a phase II multicenter exploratory study" **NADIM**

NCT Number: NCT03081689

Document Dates: Summary of Protocol Amendment Version 7.0:

08 June 2022

Confidential

NEO -ADJUVANT CHEMO/IMMUNOTHERAPY FOR THE TREATMENT OF RESECTABLE STAGE IIIA NON SMALL CELL LUNG CANCER (NSCLC): A PHASE II MULTICENTER EXPLORATORY STUDY

NADIM: Neo-Adjuvant Immunotherapy

Study Sponsor: Fundación GECP

EudraCT Number: 2016-003732-20
Sponsor code: GECP 16/03
[redacted]

Version 7.0
08 June 2022

Contacts

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Protocol Signature Page

NEO -ADJUVANT CHEMO/IMMUNOTHERAPY FOR THE TREATMENT OF RESECTABLE STAGE IIIA NON SMALL CELL LUNG CANCER (NSCLC): A PHASE II MULTICENTER EXPLORATORY STUDY

NADIM: Neo-Adjuvant Immunotherapy

Sponsor code: GECP 16/03

Approved by:

Signature

_____
Dr. Mariano Provencio
Trial Chair

Signature

_____
[redacted]

Signature

_____
Dr. Mariano Provencio
Fundación GECP President

Principal Investigator Protocol Signature Page

Study Title: "Neo-adjuvant chemo/immunotherapy for the treatment of resectable stage IIIA non small cell lung cancer (NSCLC): a phase II multicenter exploratory study" NADIM

Sponsor protocol code: GECP 16/03

EudraCT Number: 2016-003732-20

Protocol version: v 7.0_08 June 2022

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

1. SUMMARY

1.0. StudyType:

Clinical trial

1.1. Sponsor Identification:

Fundación GECP
Avda. Meridiana 358, 6ª planta
08027 Barcelona

1.2. Title:

Neo-adjuvant chemo/immunotherapy for the treatment of resectable stage IIIA non small cell lung cancer (NSCLC): a phase II multicenter exploratory study"

NADIM: **Neo-Adjuvant Immunotherapy**

1.3. Sponsor Protocol Code:

GECP 16/03

1.4. Principal investigator:

Dr. Mariano Provencio, MD, PhD

1.5. Participating centers:

25 hospitals in Spain

1.6. Experimental drug: doses, type, route of administration

- Neoadjuvant treatment: Nivolumab 360 mg IV Q3W + Paclitaxel 200mg/m2 + Carboplatin AUC 6 IV Q3W, 3 cycles
- Surgery
- Adjuvant treatment: Nivolumab 240 mg Q2W for 4 months and Nivolumab 480 mg Q4W for 8 months (1 year) after surgical resection

1.7. Clinical trial type

Phase II, single-arm, open-label study

1.8. Primary and secondary objectives

Primary objective:

- Estimate progression-free survival (PFS) at 24 months from diagnosis. The PFS is defined as the time from diagnosis to relapse, progression or death, whichever occurred first.

The tumor assessment schedule after surgery will be:

- Every 3 months (Q3 month) CT for 1 year

During the follow up phase the tumor assessments will be done as follows:

- Every 3 months (+/- 7 days) (Q3 month) CT for 1 year (from day 1 of adjuvant treatment)
- Every 4 months (+/- 7 days) (Q4 month) CT during the second year
- Every 6 months (+/- 7 days) (Q6 month) CT thereafterduring the third year
- Every 6 months (+/- 28 days) (Q6 month) CT therafter

RECIST criteria v 1.1 will be used for the tumor assessment.

Secondary objectives:

- Assess the toxicity profile of the combination, the down-staging rate, complete resection rate, time to progression and overall survival at 5 years (follow up visits after adjuvant treatment, every 3 months for 1 year, every 4 monts the second year and every 6 months the following 3 years). Also, surgical outcome and operative and post-operative complications will be assessed.
- Perform correlatives studies with the objectives of exploring the expression of other biomarkers, such as PD-L1, in tumor tissue: at screening and after surgery (resected tumor sample), free DNA and circulating tumor cells in liquid biopsy
- To describe whether PD-L1 expression is a predictive biomarker for ORR
- To describe Progression Free Survival (PFS) in PD-L1+ (>=1%) population
- Report imaging response vs pathological response rate
- To describe the tumoral microenvironment and to identify response biomarkers and resistance mechanisms to neoadjuvant chemo-inmune treatment and which of them are accessible by liquid biopsy:

  In Tumor tissue:

  - To characterize the immune microenvironment in pre- and post-treatment tumoral biopsies by Multiplexed immunofluorescence.
  - To analyze mRNA levels of immune-oncology and metabolism related genes.

- To characterize TCR locus clonality using next generation sequencing (NGS) on tissue.
  In Blood:
- To characterize the different populations, proportions, metabolism and activation levels of T cells, B cells and NK cells from patients treated with chemo-immunotherapy and on healthy adults as a control.
- To characterize TCR locus clonality using next generation sequencing (NGS) on PBMCs.
- To analyze the levels of 160 cytokines secreted by the tumor microenvironment on patient plasma and healthy controls.
- To analyse mutations in cfDNA from patients' blood

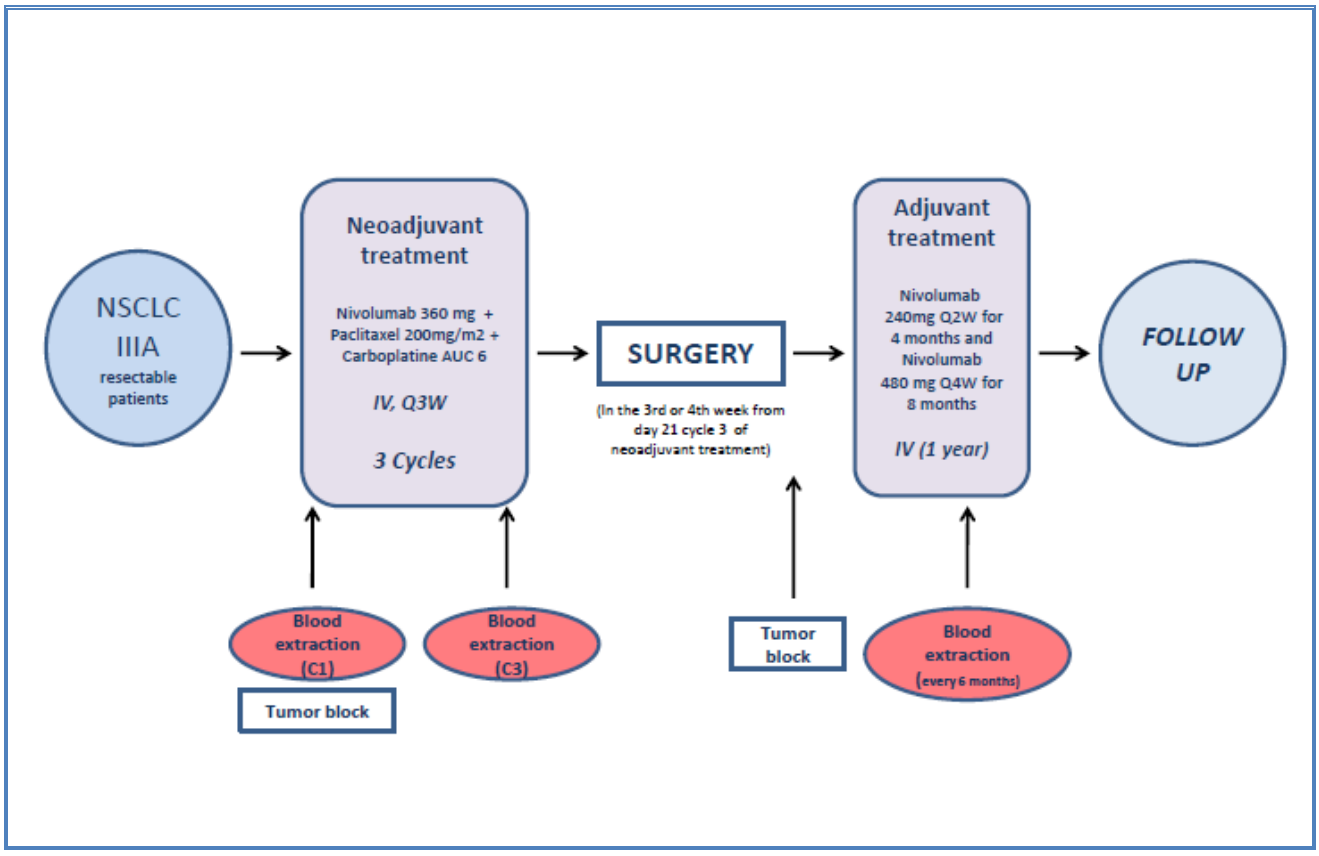
1.09. Design

Phase II, single-arm, open-label multicenter study that assesses feasibility, safety and efficacy of combined neoadjuvant chemotherapy and immunotherapy with Nivolumab 360 mg IV Q3W + Paclitaxel 200mg/m2 + Carboplatin AUC 6 IV Q3W in resectable stage IIIA NSCLC adult patients followed by adjuvant treatment for 1 year with Nivolumab 240 mg IV Q2W for 4 months and Nivolumab 480mg Q4W for 8 months.

Three cycles of neoadjuvant chemotherapy in combination with nivolumab will be administered.

After completion of neoadjuvant therapy (3 cycles) and before surgery, a tumor assessment will be done. Patients have to leave the study if there is evidence of progression. Patients with instable disease or partial response may be considered for surgery.

The report imaging response vs pathological response rate will be evaluated.



1.10. Disease or Disorder to be investigated

Operable and resectable, non-small-cell lung cancer, stage IIIA

1.11. Primary and secondary endpoints

The primary endpoint will be PFS at 24 months. The secondary endopoints will be overall survival at 5 years, response rate (RR), toxicity profile of the combination, the down-staging rate and complete resection rate. Also, surgical outcome and complications will be assessed.

1.12 Trial population and sample size

Patients eligible for the trial are those with a histological diagnosis or cytologically proven operable and resectable non-small-cell lung cancer. The total number of patients to be included will be 46 from 25 participating sites in Spain.

It is expected that approximately the 10% of the patients initially enrolled should be discarded because they do not meet the inclusion criteria; so that in order to reach the proposed sample size, if a patient initially enrolled in the study does not fulfil the inclusion criteria, they will be replaced by a new one subject that fulfil them, this replacement will ensure that the sample

size will be the one calculated initially.

1.13. Study Duration

Accrual period of 1.5 years or until the inclusion of the last patient necessary to achieve the sample set in the protocol of 46 patients. After that, all patients will be treated for 1 year with adjuvant immunotherapy and they will be followed during 5 years after adjuvant treatment.

2. INDEX

3. GENERAL INFORMATION

A. Trial Identification

Sponsor code: GECP 16/03
[redacted]
Eudract: 2016-003732-20

Protocol title: Neo-adjuvant chemo/immunotherapy for the treatment of resectable stage IIIA non small cell lung cancer (NSCLC): a phase II multicenter exploratory study.

B. Type of clinical trial: Open-label, multicenter, Phase II single-arm clinical trial.

C. Trial products description

Nivolumab (also referred to as BMS-936558 or MDX1106) is a human monoclonal antibody (HuMAb; immunoglobulin G4 [IgG4]-S228P) that targets the programmed death-1 (PD-1) cluster of differentiation 279 (CD279) cell surface membrane receptor. PD-1 is a negative regulatory molecule expressed by activated T and B lymphocytes.1 Binding of PD-1 to its ligands, programmed death–ligands 1 (PD-L1) and 2 (PD-L2), results in the down-regulation of lymphocyte activation. Inhibition of the interaction between PD-1 and its ligands promotes immune responses and antigen-specific T-cell responses to both foreign antigens as well as self-antigens. Nivolumab is expressed in Chinese hamster ovary (CHO) cells and is produced using standard mammalian cell cultivation and chromatographic purification technologies. The clinical study product is a sterile solution for parenteral administration.

D. Sponsor details

Fundación GECP
Avda.Meridiana 358, 6ª planta
08027 Barcelona

E. Technical director responsible for sample production/control

Not applicable since the product is commercially available

F. Monitor identification

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G. Trial investigators and participant study centers

This trial will be carried out in 25 participant study sites in Spain.

H. Proposed trial duration

7.5 years (1.5 years recruiting patients, 1 year of adjuvant treatment of the last patient included and 5 years of follow up)

4. RATIONALE AND OBJECTIVES

4.1 BACKGROUND AND INTRODUCTION

Lung cancer is the primary cause of cancer mortality in western countries. Approximately 80% of lung cancers are non-small-cell lung cancer (NSCLC).

In Spain occur about 18,800 new cases per year[1] and has been responsible for 19,513 deaths in 2006, twice the mortality of colon cancer (the most common tumor in absolute terms in Spain) [2] and NSCLC accounts for 85% of newly diagnosed cases. Most patients are diagnosed with unresectable disease and around 40% advanced[3] disease. The cure is unlikely in patients with NSCLC and locally advanced stage who are not surgical candidates, with a 3-year survival rate of 27% in those patients receiving chemotherapy and concomitant radiotherapy[4]. On the contrary, in localized stages (stage I, II, IIIA) with surgical resection and cytostatic therapy, a survival of 5 years of 51% [5] is achieved and those with an absolute benefit in survival at 5 years of 5.4%, especially in patients with good performance status (PS) [6].

At diagnosis, at least 40% of patients are diagnosed at an advanced stage and a third locally advanced disease (stage III). We understand as locally advanced disease when the tumor exceeds the lung structures, but without clinical evidence of distant spread, and are a very heterogeneous group of patients with a controversial treatment based on a combination of surgery, chemotherapy and radiotherapy.

In the past, radiation therapy was considered standard therapy for patients with stage IIIA and IIIB, but presented poor survival with poor local control and early development of distant disease. Patients with inoperable stage III treated with chest radiation therapy alone, had a median survival of 11.9 months, survival at 2 years of 10-20% and 3 years 5-10% [7].

Currently, there is no consensus on the best standard treatment and it has been demonstrated that the experience of the therapeutic team plays an important role in the decisions to take.

Only 25-30% of the NSCLC are candidates for curative-intent surgery. The rest are advanced local tumors or widespread metastases. Survival at 5 years depends, among other factors, on the size of the tumor and lymph node involvement. But even without mediastinal involvement, less than half of the patients survive more than 5 years and the majority dies of disseminated metastases.

Patients with stage IIIA disease with clinically evident N2 nodal spread have an overall 5-year survival rate of only 10%-15%, although this falls to 2%-5% in those with bulky mediastinal N2 involvement. The surgical management of stage IIIA NSCLC remains highly controversial and most patients with stage IIIB disease are generally considered inoperable. The aims of therapy in stage III NSCLC are to increase both locoregional and systemic control of the disease. As a matter of fact, it is reported that at least 80% of patients treated with local modalities alone will have micrometastases and will relapse. These

aims could in some way be in conflict and may require different combined modality therapy sequencing strategies. Success in achieving them is measured in time of progression, survival and cure rate. Strategies that have been investigated include induction chemotherapy, concomitant chemoradiotherapy, intensified radiotherapy and adjuvant treatment. Since distant metastases remain the major site of failure, it is likely that more effective cytotoxic or other anti-tumor agents will be required further to improve current levels of response and survival[8]. Meta-analysis has suggested that cisplatin-based induction chemotherapy prior to surgery reduces risk of death by 13 % and increased absolute 5 year survival rates by 5%[9]. Neoadjuvant therapy has theoretical advantages: in vivo assessment of response to chemotherapy helps identify patients who will potentially benefit from adjuvant chemotherapy, early treatment of micrometastatic disease, reduction in drug resistance by early exposure to treatment and downstaging with improved resectability. Potential disadvantages include: delay in local therapy secondary to toxicity, risk progression in chemoresistant patients and pre-operative complications.

Several newly available chemotherapeutic agents are both highly active against NSCLC and potent radiosensitizers.

The results of stage IIIA with induction treatment of clinical practice outside the clinical trial show a median survival of 22 months and a 3-year survival rate of 34%[10]. An EORTC study[11] with carboplatin and paclitaxel used as induction regimen in patients with biopsy-proven stage N2 non-small cell lung cancer of the 52 eligible patients, 33 patients responded, one CR and 32 PR, for an overall response rate of 64% (95% CI, 48%- 76%). In addition, there were 10 patients with no changes (10%) and 9 with progressive disease (17%). The median duration of survival was 20.5 months (95% CI, 16.1-31.2 months) with an estimated 1-year survival rate of 68.5% (95% CI, 55.2-81.7). Furthermore, phase II neoadjuvant studies of docetaxel alone, in combination with cisplatin or carboplatin, or in combination with platinum and gemcitabine have produced promising results, with more recently reported RRs ranging from 44 to 82% and rates of complete resection raging from 67 to 79%[12]

Prognostic factors after neoadjuvant therapy

Complete surgical resection[13, 14], tumor downstaging and pathologic complete response are predictors of long term survival following neoadjuvant therapy.

Pathologic complete response after induction chemotherapy generally ranges from 0% to 9.5%others higher complete response: one Martini[15]with 16.7% and one Kumar with 15%[16] are rare.

Andre analyzed a cohort of 702 patients with resected N2 disease and identified four negative factors: preoperative clinical N2 status, involvement of multiple lymph node levels, pathological T3 or T4 disease, and absence of preoperative chemotherapy[17] . Choi et al[18], reviewed cases of pathologic proven N2 disease, complete resection rate was 83,2% and overall 5-year was 23,3%. Five-year recurrence –free survival was 19,6%. Among 19 clinicopathological prognostic factors, incomplete resection and non-downstaging after neoadjuvant therapy were unfavorable prognostic factors in univariate analyses. Clinical N2 status, multiple N2 nodes, and cell type of adenocarcinoma showed

poor prognosis but were not statistically significant. Postoperative chemotherapy showed good prognosis but was not statistically significant. Multivariate analysis showed that significant favorable prognostic factors were complete resection and adjuvant chemotherapy[19]. Experience of Memorial Sloan-Kettering Cancer Center confirms survival is significantly influenced by patient age, the median survival for complete resection 27.8 months compared with 11.4 months for incomplete resection, pathologic stage with 3-year survival for N0/N1 was 43.3% and 25.5% for N2 patients[20].
An emerging hallmark of cancer is immunoevasion—the cancer cell's ability to avoid destruction by the immune system. The three general categories of immunoevasive mechanisms include: (A) an insufficient number of T cells generated within the lymphoid compartment; (B) an insufficient number of T cells extravasating into the tumor; and (C) inhibition of T cells in the tumor microenvironment. The tumor microenvironment, in turn, offers three main immunoevasive tools: (1) surface membrane proteins that function as immune checkpoints, including PD-1, CTLA-4, lymphocyte-activation gene 3 (LAG-3) protein, T-cell immunoglobulin and mucin domain–containing protein 3 (TIM-3), B- and T-lymphocyte attenuator (BTLA), and the adenosine A2a receptor (A2aR); (2) the relationship between selected soluble factors and metabolic alterations, such as IL-10, transforming growth factor beta, adenosine, indoleamine 2,3-dioxygenase (IDO), and arginase; and (3) inhibitory cells, including cancer-associated fibroblasts (CAFs), regulatory T cells, myeloid-derived suppressor cells (MDSCs), and tumor-associated macrophages.

The immune response and the use of strategies to upregulate surface proteins, including programmed death 1 (PD-1), is a new approach for the treatment of tumors. PD-L1 overexpression has been observed in 40% - 50% of all NSCLC tumours, on the set of all stages and histologies[21]. Targeted therapy to PD-1 receptor and to PD-L1 ligands is intended to inhibit their intervention and is an attractive therapeutic option in the locally advanced NSCLC stage, which can reactivate the host immune responses and allow good long term control of the tumor[22].
In lung cancer, inhibition of the Check Point PD-1 pathway with antibodies directed against PD-1 or against its ligand, PD-L1, has showed preliminary and encouraged results that suggest a "class effect" and validate this pathway as a therapeutic target in NSCLC.
Results from cohorts of heavily pretreated NSCLC patients in phase I studies showed objective responses dose dependent, ranging from 10% to 32%[23].
Inhibition of the Checkpoint PD-1 pathway with antibodies against PD-1 or PD-L1 produces long lasting tumor response and stable disease as well, for more than 6 months.
Exploratory analysis of PD-L1 tumor expression and treatment response have confirmed the prevalence of > 40% of PD-L1 expression in NSCLC. Some studies suggest an association between treatment response and PD-L1 tumor expression before treatment.
However, PD-L1 expression role as a biomarker for response has not yet been validated. Immunotherapy with antibodies anti-PD-1 and anti-PD-L1 in many different tumors types has been, in general, well tolerated. Frequent adverse events related to the drug are limited episodes of grade 1 or 2 fatigue, diarrhea, rash, pruritus, nausea and decreased appetite.

In clinical trials, grade 3 or 4 adverse events related to the treatment occur in < 15% of patients. Inmune related adverse events treatment related are infrequent (<2%) and include pneumonitis, vitiligo, colitis, hepatitis, thyroiditis and hypophysitis[24]

Numerous ongoing trials are evaluating the combination of chemotherapy and checkpoint blockade in solid tumors, including melanoma, NSCLC, and SCLC. In untreated metastatic melanoma, a phase III study showed that ipilimumab (at 10 mg/kg) plus dacarbazine improved OS compared with dacarbazine alone (11.2 vs 9.1 months, respectively), but this was at the expense of higher toxicity and there was no ipilimumab-alone comparator arm A phase II study showed that phased but not simultaneous ipilimumab plus platinum doublet chemotherapy (carboplatin/paclitaxel) improved immune-related PFS in patients with stage IIIB or IV NSCLC and extensive-stage SCLC, when compared with chemotherapy alone[25, 26]. The choice of chemotherapy and dosing schedule are thus critical to optimizing outcomes of checkpoint blockade and chemotherapy combinations. With this in mind, a phase I four-cohort study evaluated first-line nivolumab at 10 mg/kg (N10) vs 5 mg/kg (N5) in combination with gemcitabine/cisplatin (N10) in advanced squamous-cell NSCLC, pemetrexed/cisplatin (N10) in advanced nonsquamous NSCLC, and paclitaxel/carboplatin (N5 vs N10) in combined cohorts of squamous and nonsquamous NSCLC[27] .The toxicity profile was additive, representing effects of both nivolumab and chemotherapy. The ORR, PFS, and 1-year OS outcomes were acceptable. In particular, the 1-year OS rate was 85% for the N5 paclitaxel/carboplatin group and 87% for the N10 pemetrexed/cisplatin group, which may reflect a positive signal.

A phase Ib study enrolled untreated patients with locally advanced or metastatic NSCLC to three treatment arms of atezolizumab plus chemotherapy, including carboplatin/pemetrexed, carboplatin/paclitaxel, and carboplatin/nab-paclitaxel[28]. Atezolizumab at 15 mg/kg every 3 weeks was administered with standard chemotherapy for 4 to 6 cycles followed by atezolizumab maintenance or atezolizumab/pemetrexed maintenance in the carboplatin/pemetrexed arm. A preliminary analysis on 41 patients showed that the ORR was 64% (95% CI, 46.9–77.9) by RECIST, with the carboplatin/pemetrexed arm having the highest response rate at 75% (95% CI, 45–93). The four complete responses occurred in the carboplatin/nab-paclitaxel arm. The toxicity profile was as expected for chemotherapy, and no pneumonitis was observed. There was one grade 5 adverse event in a patient in the carboplatin/nab-paclitaxel arm who developed candidemia after prolonged neutropenia. Overall, the combination therapy response rates exceeded the 30% traditionally expected with platinum doublet chemotherapy; more mature data are forthcoming.

In this study, prospective tissue and blood samples will be obtained from all patients to increase our knowledge of the predictive value of molecular variables. Determining mutational profiles is crucial in NSCLC. The relationship between known promoters or other mutations and PD-L1 status and clinical outcomes will be studied[29].

Other markers, such as IFN-γ, TNF-α (tumor necrosis factor), and IL-2, IL-6, IL-10, IL-8 and IL-12 may have a correlation with clinical outcomes and response to treatment. In addition to these correlation studies that are planned prospectively, it will be preserved in tissue banks.

Rationale for Nivolumab 360 mg Flat Dose

Nivolumab monotherapy has been extensively studied in NSCLC patient population in studies CA209003, CA209063, CA209017, and CA209057 with body weight normalized dosing (mg/kg). Nivolumab pharmacokinetics (PK) and exposures of subjects in these studies have been characterized by population pharmacokinetic (PPK) analysis of data collected from these studies, together with PK data from several Phase 1, 2, and 3 clinical studies of nivolumab monotherapy in solid tumors. Nivolumab PK was determined to be linear, with dose proportional exposures over a dose range of 0.1 to 10 mg/kg. Nivolumab clearance and volume of distribution was found to increase with increasing body weight, but the increase was less than proportional, indicating that mg/kg dose represents an over-adjustment for the effect of body weight on nivolumab PK.

Flat dosing offers several advantages over body weight normalized dosing, including reduced potential for dosing errors and shortened dosage preparation time. A flat dose of 360 mg every 3 weeks is expected to produce the equivalent average exposure to 3 mg/kg every 2 weeks at the median body weight of ~80 kg in nivolumab-treated subjects.
A PPK model predicted overall nivolumab exposures across subjects with a wide range of body weight (35-160 kg) for a 360 mg every 3 weeks flat dose to be similar to that from 3 mg/kg every 2 weeks. Although the flat dose is expected to lead to higher exposure in lighter patients, relative to the exposure in heavier patients given the relationship between nivolumab PK and body weight, the predicted median and 95th percentile of exposures from these regimens are maintained well below those in 10 mg/kg every 2 weeks, which was established as a safe and well-tolerable dose.

In addition, data from the Japanese Phase 1 study ONO-4538-01 did not demonstrate doselimitingtoxicity at nivolumab up to 20 mg/kg every 2 weeks in Japanese subjects and showed similarity in PK properties between Global and Japanese population. Therefore, the proposed 360 mg flat dose is expected to be safe and tolerable in an Asian population.
Nivolumab 5 or 10 mg every 3 weeks plus platinum-based chemotherapy was evaluated in CA209012 and deemed to be tolerable. In addition, nivolumab 360 mg every 3 weeks plus platinum-based chemotherapy is further being evaluated in the global randomized Phase 3 trial (CA209227).

Rationale for Nivolumab 240 mg Q2W and 480 mg Q4W as adjuvant treatment

The every 4-week schedule (Q4W) will be more convenient for subjects.
Based on pharmacokinetic modeling, the 480 mg Q4W (after steady state is reached with 3 mg/kg or 240 mg every 2 weeks for 4 months) will provide steady-state average concentrations similar to 3 mg/kg or 240 mg Q2W, which has been shown to provide longer survival in NSCLC patients.
However, 480 mg Q4W is expected to result in higher (approximately 20%) steady-state maximum concentration (peaks), and lower (approximately 10%) steady-state trough concentrations compared to steady state of 3 mg/kg Q2W. Nivolumab was adequately tolerated up to 10 mg/kg, the highest dose level tested, and no maximum tolerated dose was identified. In addition, the exposure-response relationship for safety is flat. Thus, a slight increase in the steady-state maximum concentration is not

expected to increase the safety risk of nivolumab. However, a marginal decrease in steady-state trough concentration is not expected to reduce the efficacy as high trough concentrations and > 90% intra-tumoral receptor occupancy are still maintained at 480 mg Q4W dose. Nivolumab 480 mg Q4W is expected to have similar efficacy and safety profile to 3 mg/kg Q2W.

Rationale for the correlative's studies regarding tumoral microenvironment and response biomarkers

Immunotherapy is the routine treatment for advanced non-small cell lung cancer (NSCLC), a cancer with a high incidence and mortality rate. The next step is the locally advanced stage, in this field the Fundación GECP has sponsored the study NADIM, which is testing the benefit of using immunotherapy together with chemotherapy as a neoadjuvant treatment in patients with stage IIIA NSCLC. Currently, the preliminary data for this new setting is encouraging, showing a rate of complete pathological responses never seen before for in these patients.

However, due to its novelty, there are currently no good biomarkers available to identify which patients will benefit most from this type of treatment.

Combining patients' clinical data and their tumor microenvironment molecular information, this study will identify new predictive biomarkers of response to chemo-immunotherapy. For this purpose, biopsies of tumor tissue before and after treatment will be analyzed, as well as liquid biopsies from 5 time points (before and after neoadjuvant treatment, 6 and 12 months of adjuvant treatment, and after a relapse).

Different lymphocyte populations (NK, T and B cells), their activation levels and the TCR repertoire will be studied. On the other hand, levels of gene expression related to inflammatory signature and immune evasion in the tumor, as well as the levels of different modulating factors such as cytokines and metabolic changes will be analysed. In addition, cfDNA will be collected from blood samples to analyse tumor mutations through ddPCR at diferent timepoints.

The knowledge derived from this study could improve the selection of patients, reducing unnecessary patient treatment and reducing costs for the NHS. It can also identify relevant new pathways and resistance mechanisms for the development of new personalized therapies to rescue non-responders.

4.2. WORKING HYPOTHESIS

Chemotherapy stimulates an immune response against tumors, which may facilitate immunotherapy´s anticancer activity. Evidence of synergy between chemotherapy and immunotherapy was shown in several studies. The feasibility of combining both targeted agents and immunotherapy is also being studied in the CheckMate 012 trial and more recently in CheckMate 227 phase III study.

This approach can be used in N2, the combination of chemotherapy based on platine doublets +

immunotherapy with anti PD1 (nivolumab) could be feasible achieving good responses and tumor donwstaging; in addition, the possibility to study in vivo the presence of tumor biomarkers and analyze the expression of different immune markers and TILs/ frequency and functional activity of Tregs within the tissue.

4.3. OBJECTIVES

Primary objective:

- To assess the efficacy of the combination of chemotherapy with immnutherapy in NSCLC, PFS at 24 months from diagnosis.

Secondary objectives:

- Assess the toxicity profile of the combination, the down-staging rate, complete resection rate, time to progression and overall survival at 5 years (follow up visits after adjuvant treatment, every 3 months for 1 year, every 4 monts the second year and every 6 months the following 5 years). Also, surgical outcome and surgical complications will be assessed.
- Perform correlatives studies with the objectives of exploring the expression of other biomarkers, such as PD-L1, in tumor tissue: at screening and after surgery (resected tumor sample), free DNA and circulating tumor cells in liquid biopsy
- To describe whether PD-L1 expression is a predictive biomarker for ORR
- To describe Progression Free Survival (PFS) in PD-L1+ (>=1%) population
- Report imaging response vs pathological response rate
- To describe the tumoral microenvironment and to identify response biomarkers and resistance mechanisms to neoadjuvant chemo-inmune treatment and which of them are accessible by liquid biopsy:
    In Tumor tissue:
    - To characterize the immune microenvironment in pre- and post-treatment tumoral biopsies by Multiplexed immunofluorescence.
    - To analyze mRNA levels of immune-oncology and metabolism related genes.
    - To characterize TCR locus clonality using next generation sequencing (NGS) on tissue.

    In Blood:
    - To characterize the different populations, proportions, metabolism and activation levels of T cells, B cells and NK cells from patients treated with chemo-immunotherapy and on healthy adults as a control.
    - To characterize TCR locus clonality using next generation sequencing (NGS) on PBMCs.
    - To analyze the levels of 160 cytokines secreted by the tumor microenvironment on patient plasma and healthy controls.
    - To analyse mutations in cfDNA from patients' blood

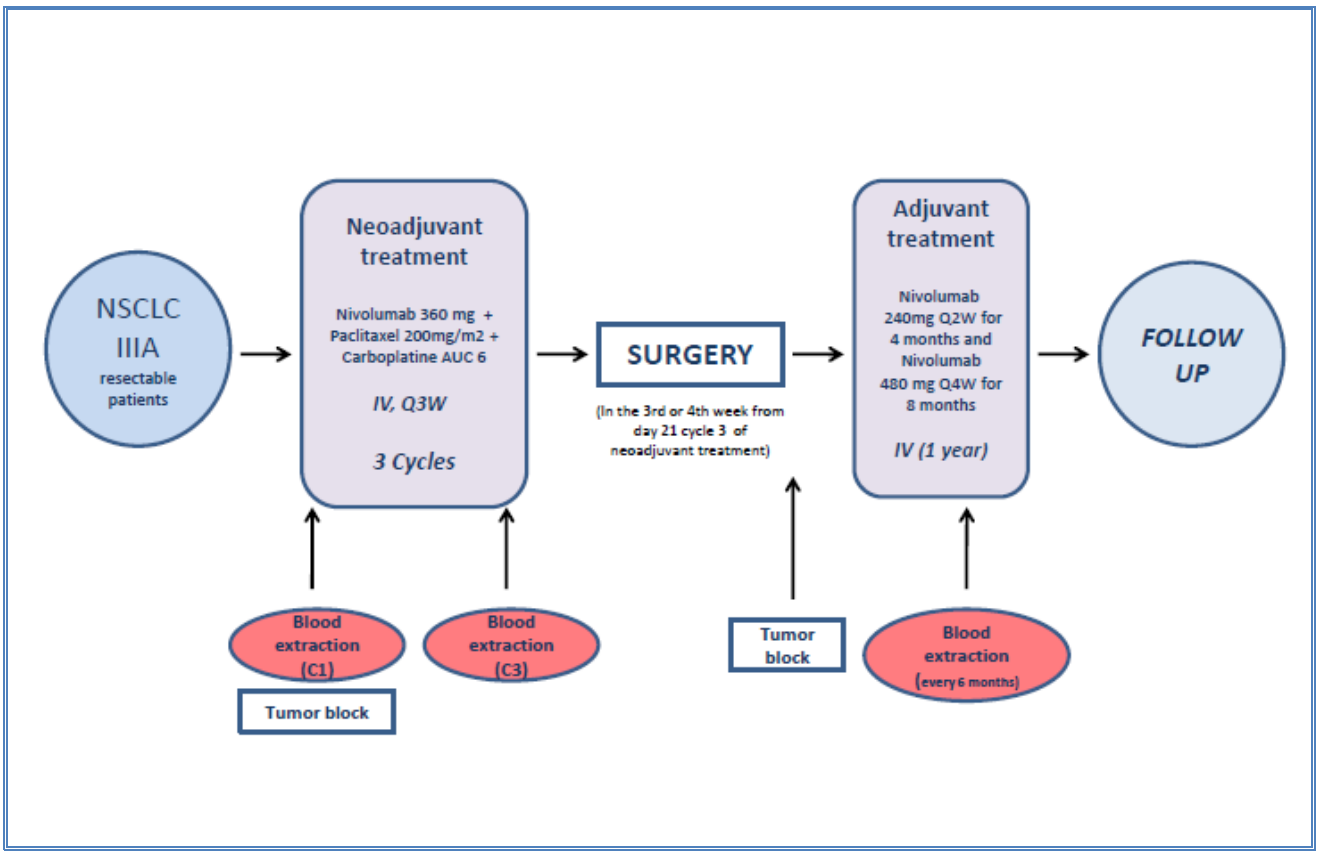
5. CLINICAL TRIAL TYPE AND DESIGN

5.1. CLINICAL TRIAL TYPE

Open-label, multicenter, phase II, single-arm clinical trial

5.2. DESIGN OF THE STUDY

Prospective, phase II, single-arm, open-label, and multicenter study that assesses feasibility, safety and potential efficacy of combined neo-adjuvant chemotherapy and immunotherapy with Nivolumab 360 mg IV + Paclitaxel 200mg/m2 + Carboplatin AUC 6 IV Q3W as neoadjuvant treatment followed by Nivolumab 240 mg IV Q2W for 4 months and Nivolumab 480 mg IV Q4W for 8 months as adjuvant treatment during 1 year in resectable stage IIIA NSCLC patients.



6. PATIENT SELECTION CRITERIA

There will be NO EXCEPTIONS to eligibility requirements at the time of registration. Questions about eligibility criteria should be addressed prior to registration or randomization.

The eligibility criteria for this study have been carefully considered. Eligibility criteria are standards used to ensure that patients who enter this study are medically appropriate candidates for this therapy. For the safety of the patients, as well as to ensure that the results of this study can be useful for making treatment decisions regarding other patients with similar diseases, it is important that no exceptions be made to these criteria for admission to the study.

Patients must fulfill all of the following criteria to be eligible for admission to the study.

6.1. INCLUSION CRITERIA

Target Population

1. The subjects eligible for the study are those with histologically- or cytologically- documented NSCLC who present stage IIIA disease (according to version 8th of the International Association for the Study of Lung Cancer Staging Manual in Thoracic Oncology) and previously untreated. Locally advanced patients who present stage IIIA by the previous version can be included if are considered potencially resectable. In case of N2 disease suspicion, pathological assessment by EBUS, mediastinoscopy or thoracotomy has to be carried out for N2 confirmation.

2. Tumor should be considered resectable before study entry by a multidisciplinary team.

3. Performance Status of 0 or 1 if using ECOG/Zubrod.

4. Screening laboratory values must meet the following criteria and should be obtained within 14 days prior to registration/inclusion.

    i. WBC ≥ 2000/µL

    ii. Neutrophils ≥ 1500/µL

    iii. Platelets ≥ 100 x103/µL

    iv. Hemoglobin > 9.0 g/dL

    v. Serum creatinine ≤ 1.5 x ULN or creatinine clearance (CrCl) ≥ 40 mL/min (if using the Cockcroft-Gault formula below):

a. Female CrCl = (140 - age in years) x weight in kg x 0.85
   1. 72 x serum creatinine in mg/dL

b. Male CrCl = (140 - age in years) x weight in kg x 1.00
   a. 72 x serum creatinine in mg/dL

vi. AST/ALT ≤ 3 x ULN

vii. Total Bilirubin ≤ 1.5 x ULN (except subjects with Gilbert Syndrome, who can have total bilirubin < 3.0 mg/dL)

viii. INR/APTT within normal limits

5. The patients need to have a forced expiratory volume (FEV1) ≥ 1.2 liters
6. All patients are notified of the investigational nature of this study and signed a written informed consent in accordance with institutional and national guidelines, including the Declaration of Helsinki prior to any trial-related intervention

Age and Reproductive Status

7. Patients aged > 18 years

8. Women of childbearing potential (WOCBP) must use appropriate method(s) of contraception. WOCBP should use an adequate method to avoid pregnancy for 23 weeks (30 days plus the time required for nivolumab to undergo five half-lives) after the last dose of investigational drug

   Women of childbearing potential must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 72 hours prior to the start of nivolumab

9. Women must not be breastfeeding
10. Men who are sexually active with WOCBP must use any contraceptive method with a failure rate of less than 1% per year. Men receiving nivolumab and who are sexually active with WOCBP will be instructed to adhere to contraception for a period of 31 weeks after the last dose of investigational product. Women who are not of childbearing potential (ie, who are postmenopausal or surgically sterile as well as azoospermic men do not require contraception)

Women of childbearing potential are defined as any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) or who is not postmenopausal. Menopause is defined clinically as 12 months of amenorrhea in a woman over 45 in the absence of other biological or physiological causes. In addition, women under the

age of 62 must have a documented serum follicle stimulating hormone (FSH) level less than 40mIU/mL.

Women of childbearing potential receiving nivolumab will be instructed to adhere to contraception for a period of 23 weeks after the last dose of investigational product. Men receiving nivolumab and who are sexually active with WOCBP will be instructed to adhere to contraception for a period of 31 weeks after the last dose of investigational product. These durations have been calculated using the upper limit of the half-life for nivolumab (25 days) and are based on the protocol requirement that WOCBP use contraception for 5 half-lives plus 30 days and men who are sexually active with WOCBP use contraception for 5 half-lives plus 90 days.

Highly effective methods of contraception

Male condoms with spermicide

Hormonal methods of contraception including combined oral contraceptive pills, vaginal ring, injectables, implants and intrauterine devices (IUDs) such as Mirena® by WOCBP subject or male subject's WOCBP partner Female partners of male subjects participating in the study may use hormone based contraceptives as one of the acceptable methods of contraception since they will not be receiving study drug

Nonhormonal IUDs, such as ParaGard®
Tubal ligation
Vasectomy
Complete Abstinence*

*Complete abstinence is defined as complete avoidance of heterosexual intercourse and is an acceptable form of contraception for all study drugs. Subjects who choose complete abstinence are not required to use a second method of contraception, but female subjects must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence.

Less effective methods of contraception

Diaphragm with spermicide
Cervical cap with spermicide
Vaginal sponge
Male Condom without spermicide
Progestin only pills by WOCBP subject or male subject's WOCBP partner
Female Condom
A male and female condom must not be used together

6.2. EXCLUSION CRITERIA

1. All patients carrying activating mutations in the TK domain of EGFR or any variety of alterations in the ALK gene.

2. Patients with active, known or suspected autoimmune disease. Subjects with vitiligo, type I diabetes mellitus, residual hypothyroidism due to autoimmune thyroiditis only requiring hormone replacement or unexpected conditions of recurrence in the absence of an external trigger are allowed to be included.

3. Patients with a condition requiring systemic treatment with either corticosteroids (>10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of enrollment. Inhaled or topical steroids, and adrenal replacement steroid doses > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.

4. Patients with a history of interstitial lung disease cannot be included if they have sympthomatic ILD (Grade 3-4) and/or poor lung function. In case of doubt please contact trial team.

5. Patients with other active malignancy requiring concurrent intervention and/or concurrent treatment with other investigational drugs or anti-cancer therapy

6. Patients with previous malignancies (except non-melanoma skin cancers, and the following in situ cancers: bladder, gastric, colon, endometrial, cervical/dysplasia, melanoma, or breast) are excluded unless a complete remission was achieved at least 2 years prior to study entry AND no additional therapy is required during the study period.

7. Any medical, mental or psychological condition which in the opinion of the investigator would not permit the patient to complete the study or understand the patient information

8. Patients who have had prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell costimulation or immune checkpoint pathways

9. Patients with positive test for hepatitis B virus surface antigen (HBV sAg) or hepatitis C virus ribonucleic acid (HCV antibody) indicating acute or chronic infection

10. Patients with known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS)

11. Patients with history of allergy to study drug components excipients

6.3 PROPOSED NUMBER OF SUBJECTS AND SAMPLE SIZE

The sample size is 46 patients recruited from 25 hospitals in Spain.

6.4. WITHDRAWAL CRITERIA

Patients may be withdrawn from the protocol under the following circumstances:

a) Intercurrent illnesses or other reasons that, in the opinion of the investigator, would significantly affect the patient´s safety or render trial results for this patient unacceptable and those that require interruption of treatment.

b) Unacceptable toxicity (defined in Section 7.5).

c) Patient's request to withdraw from the study.

d) Protocol non-compliance or study termination by Sponsor

Specific reasons for trial discontinuation include (further collection of data is not allowed):

- Withdrawal of consent
- Patient lost to follow-up
- Death

All possible measures will be undertaken to maintain the investigation program and to continue the follow-up even if the treatment was prematurely concluded and/or if the patient did not attend the follow-up visits at the participating institution.

6.5 RECRUITMENT PERIOD DURATION AND FOLLOW UP

Recruitment period: 1.5 years. Follow up: 5 years

7. TREATMENT DESCRIPTION

7.1 CARBOPLATIN

Structure: The cis-diamino (cyclobutan-1, 1 dicarboxilate) platin.

Stability: 24 hours at ambient temperature in 5% glucose, glucosaline or physiologic saline. It is recommended not to dilute with chlorinated solutions since this could affect the cisplatin.

Route of administration: Intravenous infusion.

7.2 PACLITAXEL

Structure: A diterpene whose composition is: 5β, 20-epoxi-1, 2α, 4,7β, 10β, 13α-hexahidroxytax-11-en 9 one 4,10-diacetato 2-benzoate 13-ester with (2R,3S)- N-benzoyl-3-phenylisoserine.

Stability: Concentrations of 0.3-1.2 mg/ml in 5% dextrose or normal saline have demonstrated chemical and physical stability for more that 27 hours at ambient temperature (25ºC approximately). The intact vial must be stored between 15º and 25ºC.

Route of administration: Intravenous infusion.

7.3. NIVOLUMAB

Structure: Nivolumab is a soluble protein consisting of 4 polypeptide chains, which include 2 identical heavy chains and 2 identical light chains.

Route of administration: Intravenous infusion.

Product Description:

Product Description and Dosage Form	Potency	Primary Packaging (Volume) / Label Type	Secondary Packaging (Qty) /Label Type	Appearance	Storage Conditions (per label)
Nivolumab (BMS-936558-01)* Injection drug product is a sterile, non-pyrogenic, single-use, isotonic aqueous solution formulated at 10 mg/mL	100 mg/Vial (10 mg/mL).	Carton of 5 or 10 vials	10-cc Type 1 flint glass vials stoppered with butyl stoppers and sealed with aluminum seals.	Clear to opalescent, colorless to pale yellow liquid. May contain particles	BMS-936558-01 Injection must be stored at 2 to 8 degrees C (36 to 46 degrees F) and protected from light and freezing

Storage Conditions & Handling:

- Store at +2°C - +8°C (36-46°F), protect from light, freezing, and shaking. If stored in a glass front refrigerator, vials should be stored in the carton.
- If any temperature excursions are encountered during storage, please report these to - Fundación GECP for assessment via the Temperature Excursion Response Form.
- As with all injectable drugs, care should be taken when handling and preparing nivolumab. Whenever possible, nivolumab should be prepared in a laminar flow hood or safety cabinet using standard precautions for the safe handling of intravenous agents applying aseptic technique. Recommended safety measures for preparation and handling of nivolumab include laboratory coats and gloves.
- Partially used vials should be disposed at the site following procedures for the disposal of anticancer drugs.

For additional details on prepared drug storage and use time of nivolumab under room temperature/light and refrigeration, please refer to the BMS-936558 (nivolumab) data sheet section for “Recommended Storage and Use Conditions”

Guidelines for Nivolumab administration

The administration of BMS-936558-01 injection prepared for dosing nivolumab infusion must be completed within 24 hours of preparation. If not used immediately, the infusion solution may be stored up to 20 hours in a refrigerator at under refrigeration conditions (+2°-+8°C; +36°-+46°F) and used within for up to 24 hours, and a maximum of 4 hours of the total 24 hours can be at room temperature (+20°-+25°C, +68°-+77°F) and under room light. The maximum 4-hour period under room temperature and room light conditions for undiluted and diluted solutions of BMS-936558-01 injection in the IV bag should be inclusive of the includes the product administration period.

After final drug reconciliation, unused nivolumab vials should be disposed at the site following procedures for the disposal of anticancer drugs.

TREATMENT SCHEDULES

1. **Neodjuvant Chemotherapy scheme:**
   Administration of 3 cycles at 21-day intervals (+/-3 days) prior to surgery
   Nivolumab 360 mg IV Q3W over 30 minutes
   Paclitaxel: 200mg/m^2 infusion over 3 hours
   Carboplatin: AUC6 at the end of the Paclitaxel infusion

2. **Surgery**
   Within the 3rd-4th week from day 21 of cycle 3 of neoadjuvant treatment (day 42-49 after first day of cycle 3)

3. **Nivolumab as adjuvant therapy**
   Within the 3rd to 8th week from surgery and for 1 year in patients that had response by surgical pathology evaluation
   Nivolumab 240 mg IV Q2W(+/-3days) over 30 minutes for 4 months followed by nivolumab 480 mg Q4W(+/-3 days) over 60 minutes for 8 months

Radiotherapy is not allowed at any time.

7.4. SPECIAL REQUIREMENTS FOR THE HANDLING OF THE STUDY DRUGS

7.4.1. Dosage and Administration of Nivolumab

[redacted]

Dose Modifications

[redacted]

7.4.2. Administration of Carboplatin

Carboplatin must be administered by intravenous infusion, according to the standards of each center.

7.4.3. Administration of Paclitaxel

[redacted]

Guidelines for Paclitaxel administration

[redacted]

7.5. DOSE DELAY/REDUCTION CRITERIA

7.5.1. NIVOLUMAB

[redacted]

[redacted]

[redacted]

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

[redacted]

Management Algorithms

[redacted]

[redacted]

[redacted]

Discontinuation Criteria

[redacted]

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

[redacted]

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

Treatment of Nivolumab Related Infusion Reactions

[redacted]

[redacted]

7.5.2. PACLITAXEL AND CARBOPLATIN

[redacted]

Dose modification based on Hematological toxicity criteria

Decrease Paclitaxel, Carboplatin one dose level in case of:

- [redacted]

[redacted]

[redacted]

[redacted]

Suspension of treatment until hematological recovery:

[redacted]

[redacted]

[redacted]

[redacted]

Dose modification based on non-hematological toxicity criteria

The toxicity effects are graded using the new toxicity criteria (CTC) of the NCI (National Cancer Institute) (Appendix B). If for a given symptom the NCI system does not describe a grade, the toxicity will be described as:

1= slight; 2= moderate; 3= severe; 4= life threatening; 5=fatal

[redacted]

[redacted]

[redacted] [redacted] TOXICITIES

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

- [redacted]
- [redacted]

[redacted]

[redacted]

Guidelines for the re-initiation of treatment following hypersensitivity reactions

[redacted]

[redacted]

[redacted]

7.6. TREATMENT DURATION

Patients will receive 3 cycles every 21 days (+/-3 days) of Paclitaxel, Carboplatin and Nivolumab prior to surgery. Adjuvant therapy with Nivolumab will be given for 1 year.

7.7 PROHIBITED AND PERMITTED CONCOMITANT TREATMENTS

[redacted]

[redacted]

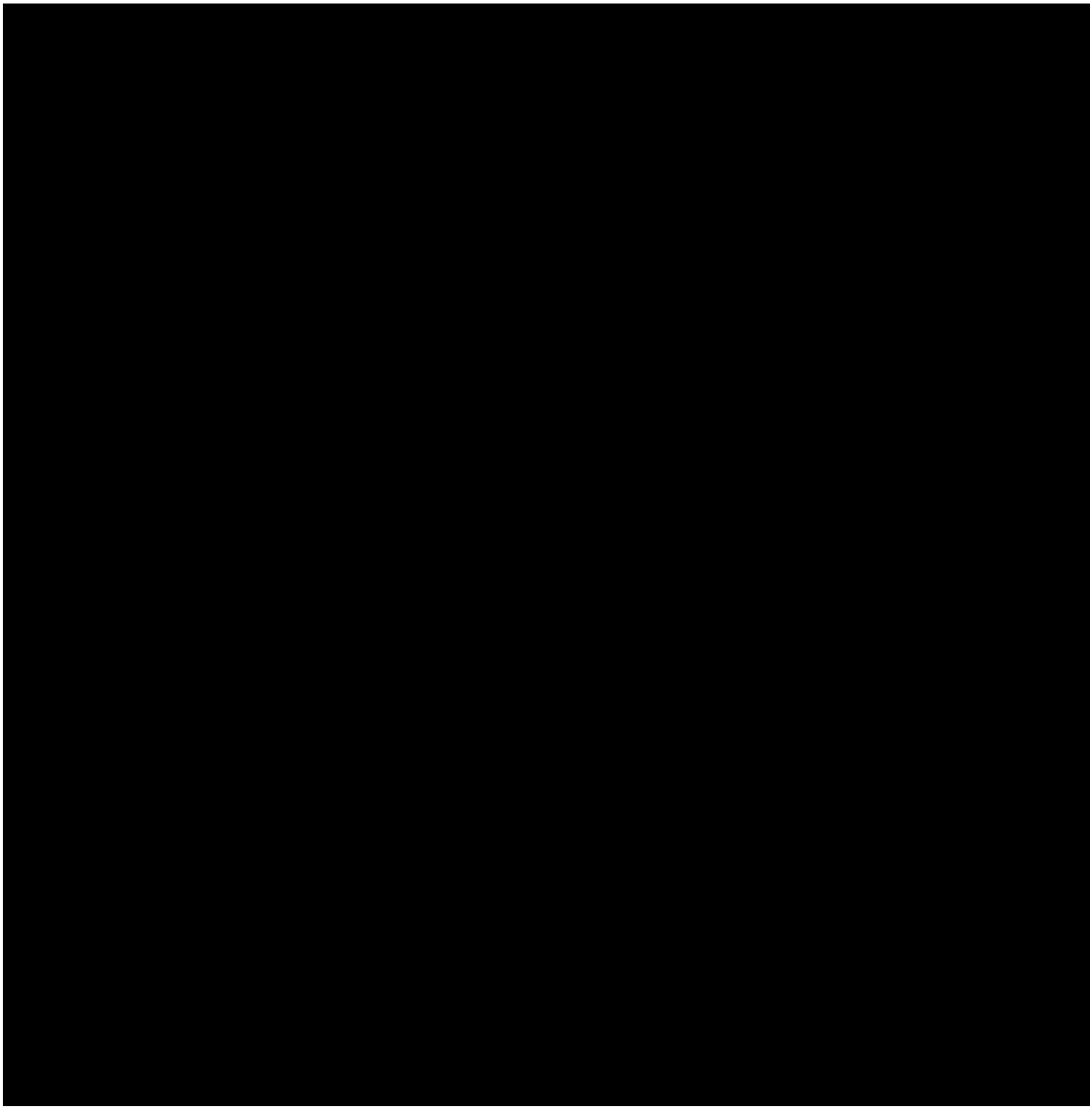
Permitted Concomitant Therapy

[redacted]

8. TRIAL PROGRESS AND PATIENT EVALUATION

The investigation team of each center will be responsible for all treatment administration and evaluations throughout the study.

8.1 TRIAL PROGRESS



[redacted]

[redacted]

8.2 PATIENT EVALUATION

8.2.1. Pre treatment and Neoadjuvant treatment patient evaluation

A complete history, physical examination, complete blood cell count with differential serum biochemistry, spirometry, bronchoscopy, computed tomography (CT) scan of chest and upper abdomen and PET-CT and an electrocardiogram are obtained at baseline.

[redacted]

[redacted]

Patients are monitored every 3 weeks with complete blood cell counts and recording of toxic events according the CTCAE v. 4.0.

[redacted]

[redacted]

[redacted].

[redacted]

[redacted]

[redacted]

8.2.2. Surgery

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

8.2.3. Adjuvant treatment patient evaluation

[redacted]

A complete history, physical examination, complete blood cell count with differential serum biochemistry has to be done during adjuvant treatment

[redacted]

Adverse events have to be followed for 1 year and until 100 days from the last dose of Nivolumab.

[redacted]

8.2.4 Follow up

A complete history, physical examination, complete blood cell count with differential and serum biochemistry has to be done.

[redacted]

8.2.5 Analysis of CT-SCANs performed on patients during the study

Analysis the CT SCANs images for the NADIM included and valid patients will be analysed over time for patient outcome prediction.

[redacted]

[redacted].

9. ADVERSE EVENTS

9.1. GENERAL INFORMATION

Adverse events (AE): Defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation subject administered an investigational (medicinal) product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory finding), symptom, or disease temporally associated with the use of investigational product, whether or not considered related to the investigational product.

The medical occurrence is considered as an AE when it occurs from the day of enrolment in the study until **100** days after the final dose of IMP, regardless of whether it is considered related to the trial treatment.

The relationship of the adverse event with the administered trial treatment is determined by a physician and should be used to assess all adverse events (AE). The casual relationship can be one of the following:

- **Related**: There is a reasonable causal relationship between study drug administration and the AE.
- **Not related**: There is not a reasonable causal relationship between study drug administration and the AE.

The term "reasonable causal relationship" means there is evidence to suggest a causal relationship.

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 B.

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

Serious Adverse Event (SAE): Defined as any untoward medical occurrence that at any dose:

- results in death (fatal due to any cause)
- is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- requires inpatient hospitalization or causes prolongation of existing hospitalization
- 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.)
- Potential drug induced liver injury (DILI) is also considered an important medical event.
- 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.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

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

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 (data sheet)

Expected adverse event: An event described in the basic product information (data sheet).

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

9.2 ADVERSE EVENTS ASSOCIATED WITH NIVOLUMAB

[redacted]

Target Adverse Events

[redacted]

[redacted]

9.2.1. *Pulmonary Adverse Events*

[redacted]

9.2.2. *Gastrointestinal Adverse Events*

[redacted]

9.2.3. *Hepatic Adverse Events*

[redacted]

9.2.4. *Endocrinopathies*

[redacted]

9.2.5. *Skin Adverse Events*

[redacted]

9.2.6. *Renal Adverse Events*

[redacted]

9.2.7. *Neurologic Adverse Events*

[redacted]

[redacted]

9.2.8. *Lipase/Amylase Elevations*

[redacted]

9.2.9. *Uveitis and Visual Complaints*

[redacted]

9.2.10. *Infusion Reactions*

[redacted]

9.2.11. Overdose, Warnings, and Precautions

[redacted].

9.2.12. Precautions for Women of Childbearing Potential

The nonclinical findings of increased late-stage pregnancy loss and early infant deaths/euthanasia in nivolumab-exposed pregnant monkeys suggest a potential risk to human pregnancy if there is continued treatment with nivolumab during pregnancy. Given the potential risk suggested by preliminary data from nonclinical and clinical data, dosing during pregnancy will continue to be prohibited. In addition, women of childbearing potential (WOCBP) receiving nivolumab will be instructed to adhere to contraception [redacted]

9.3. ADVERSE EVENTS ASSOCIATED WITH PACLITAXEL

The Paclitaxel data sheet provides detailed information on adverse events observed during Phase I/Phase II trials with Paclitaxel

[redacted]

[redacted]

9.4. ADVERSE EVENTS ASSOCIATED WITH CARBOPLATIN

[redacted]

[redacted]

1. Hematological toxicity

[redacted]

2. Gastrointestinal toxicity

[redacted]

3. Neurotoxicity

[redacted]

[redacted]

4. Nephrotoxicity

[redacted]

5. Hepatotoxicity

[redacted]

6. Allergy

[redacted]

7. Others

[redacted]

9.5. CAUSALITY CRITERIA

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.

9.6. COMMUNICATION OF ADVERSE EVENTS

An AE classified as SEVERE must conform to the legal requirements. When a severe AE occurs, based on the classification described above, the investigator must not only record it in the appropriate page in the CRF but must notify it IMMEDIATELY to the health authorities and to the Ethical Committee; as must all adverse events that are severe, unexpected and possibly related to the study treatment.

Similarly, severe AE possibly related to the treatments in the study must be communicated by the study sponsor to the respective owners of the authorization of commercialization of the drugs used in the trial.

9.6.1. Reporting SAE and targeted adverse events

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 that occur within 100 days of discontinuation of dosing must be reported.

All SAEs that occur during the screening period must be reported. If applicable, SAEs that relate to any protocol-specified procedure (eg, a follow-up skin biopsy) must be reported. 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.

[redacted]

[redacted]

Fundación GECP (SLCG/GECP) Pharmacovigilance office will record the SAE and prepare a summary report of all SAEs received. Listings of SAEs will be prepared as required.

Any 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.

9.6.2. Nonserious Adverse Event Collection and Reporting

The collection of nonserious AE information should begin at initiation of study drug. All nonserious adverse events (not only those deemed to be treatment-related) should be collected continuously during the treatment period and for a minimum of 100 days following the last dose of study treatment.

Nonserious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious. Follow-up is also required for nonserious AEs that cause interruption or discontinuation of study drug and for those present at the end of study treatment as appropriate.

9.6.3. Laboratory Test Abnormalities

All laboratory test results captured as part of the study should be recorded following institutional procedures. Test results that constitute SAEs should be documented and reported as such.

[redacted]

9.6.4. Pregnancy

If, following the initiation of the investigational product, it is subsequently discovered that a study subject is pregnant or may have been pregnant at the time of investigational product exposure, [redacted]

Any pregnancy that occurs in a female partner of a male study participant should be reported to Fundación GECP (SLCG/GECP) Pharmacovigilance office via Pregnancy Form.

Overdose

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as an SAE.

Other Safety Considerations

Any significant worsening noted during interim or final physical examinations, electrocardiograms, x-rays, and any other potential safety assessments, whether or not these procedures are required by the protocol, should also be recorded as a nonserious or serious AE, as appropriate, and reported accordingly.

10. 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.

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 amendmed, this amendment will be submitted for approval to the Ethic Committees and Health Authorities (if applicable).

10.2 INFORMED CONSENT

Before recruitment and entry into the study, a complete explanation will be given to each patient eligible for participation in this study. The formula for informed consent will be submitted to the Ethical Committee responsible for assessment and approval.

Once this essential information has been provided to the patient and the investigator has ensured that the individual candidate has understood the implications of participating in the study, the consent will be requested for participation in the study. In case that the subject is not able to give informed consent (for example, minors, mentally deficient, or physically incapacitated such as those who are comatose) this informed consent of the patient may be given by a legal guardian. Nevertheless, the consent of the patient must be obtained as well when he/she is capable of understanding the nature, importance and level of risk associated with the clinical trial. It is preferable that the person who gives the consent signs the form. If this is not possible, the verbally testified consent with the signature of the witness will be sufficient. In whichever of these two cases, the informed consent form will carry an additional note to the effect that it was obtained with informed consent.

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 confidenciality 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.

11. PRACTICAL CONSIDERATIONS

11.1 RESPONSIBILITIES OF THE INVESTIGATOR

- Provide guarantee of sufficient time for the completion of the study, with a competent team and appropriate equipment for the conduct of the study and to give assurance that no other study is being conducted that may divert patients away from the present study.
- To efficiently record and maintain up-to-date data notes and other documents of the study.

11.2 RESPONSIBILITY FOR THE PRODUCT

The investigation teams in the study centers will be responsible for all treatment administration and evaluation throughout the period of the study.

Report on product inventory

The investigator, or the responsible person designated, must ensure that the drug is not used incorrectly by maintaining inventories of prescription of the medication in the study.

11.3 RECORDS AND REPORTS

The investigator takes responsibility for the recording of drug prescription, data acquisition records and documentation (Note: documentation includes: patient's clinical history, hospital communications, office notes, patient's notes and all original documents that contain information for the completion of the data acquisition forms).

The investigator, for a minimum period of 25 years after the conclusion or interruption of the study, must keep the investigator file where it will be filed a copy of the patient's identity code. The investigator must ensure that the initials and ID number of the patient corresponds to the patient's real identity.

11.4 PROTOCOL ADHERENCE

Except in situations of emergency in which the person responsible for the protection, security and well being of the subject of the study elects an alternative treatment, the study will conclude as and how described in the approved protocol.
All deviations from the protocol must be documented and justified by the principal investigator of the center.

11.5 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 contact person will be:

[redacted]
Fundación GECP CRA
Meridiana 358, 6ª planta
08027 Barcelona
Tel. 93 430 20 06
[redacted]

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11.6 PUBLICATION POLICY

[redacted]

12. STATISTICAL ANALYSES

Intention to treat population will be described using clinical and biological characteristics of all the patients included in the clinical trial.

For this analysis, descriptive methods will be used and expressing the results as means, medians, standard deviations and distribution descriptions for continuous variables while the results for discrete variables will be expressed as percentages and frequency distributions. The estimates will be accompanied by confidence intervals (95%). These statistics will be repeated using the patient values according to the protocol.

Progression-Free survival (PFS) is defined as the time from diagnosis until objective tumor

progression or death. Censoring dates are defined in patients with no documented progression before data cutoff or dropout. In these patients, the censoring date is defined as the last date on with progression status was adequately assessed. The PFS curve will be estimated using Kaplan-Meier method, obtaining an estimate for PFS at 24 months (and its associated CI95%) and for median PFS time.
Overall Survival (OS) is defined as the time from diagnosis until death from any cause. Censoring dates are defined in patients with no death before date cutoff or dropout. The OS curve will be estimated using Kaplan-Meier method.

Safety and the tolerability of the therapy will be described by tabulation of the CTCAE Version 4 grade. The safety cohort will encompass all patients who have received at least 1 dose of IMP treatment.

[redacted]

Calculation of sample size

The sample size estimation was completed using a one sample test based on exponential distribution. A sample size of 46 patients provided at least 80% power to detect an inprovement of 15% for PFS at 24 months [redacted] with on-sided type I error of 5%. [redacted] This follow-up time [redacted] allows us to achieve secondary objectives established in the protocol [redacted].

It is expected that approximately the 10% of the patients initially enrolled should be discarded because they do not meet the inclusion criteria; so that in order to reach the proposed sample size, if a patient initially enrolled in the study does not fulfil the inclusion criteria, it will be replaced by a new subject that fulfil them, this replacement will ensure that the sample size is the one calculated initially.

13. REFERENCES

1. Mountain CF: Revisions in the international system for staging lung cancer. Chest 1997; 111:1710-1717

2. López-Abente G, Pollán M, Aragonés N et al. Situación del cáncer en España: incidencia. An Sist Sanit Navar 2004; 27 (2): 165-173.

3. 7Ramalingam S, Belani C. Systemic chemotherapy for advanced non-small cell lung cancer: recent advances and future directions. The Oncologist 2008;1: 5-13

4. Hanna N, Neubauer M, Yiannoutsos et al. Phase III study of cisplatin, etoposide and concurrent chest radiation with or without consolidation with docetaxel in patients with inoperable stage III NSCLC: The Hoosier Oncology Group and U.S. Oncology. J Clin Oncol 2008; 26: 5755-60

5. Douillard JY, Rosell R, De Lena M et al. Adjuvant vinorelbine plus cisplatin versus observation in patients with completely resected satge IB-IIIA NSCLC (Adjuvant Navelbine International Trialist Association (ANITA): A randomised controlled trial. Lancet Oncol 2006 ; 7 : 719-27.

6. Pignon JP, Tribodet H, Scagliotti GV et al. Lung adjuvant cisplatin evaluation: A pooled analysis by LACE Collaborative Group. J Clin Oncol 2008; 26: 3552-9

7. Perez CA, Pajak TF, Rubin P, et al. Long-term observations of the patterns of failure in patients with unresectable non oat cell carcinoma of the lung treated with definitive radiotherapy. Report by the Radiation Therapy Oncology Group. Cancer 1987; 59:1874–81.

8. Langer CJ, Leighton JC, Comis RL, O'Dwyer PJ, McAleer CA, Bonjo CA, Engstrom PF, Litwin S, Ozols RF. Paclitaxel and carboplatin in combination in the treatment of advanced non-small-cell lung cancer (NSCLC): A phase II toxicity, response, and survival analysis (FCCC 93-024). J Clin Oncol 1995; 13: 1860-1870.

9. Non-Small Cell Lung Cancer Co-operative Group. Chemotherapy in non-small cell lung cancer: a meta-analysis using updated data on individual patients from 52 randomized clinical trials. Br Med J 1995;311:899-909.

10. Martin J, Ginsberg RJ, Ennapadam S, et al. Long-term results of combined-modality therapy in resectable non-small cell lung cancer. J Clin Oncol 2002;20:1989-1995.

11. O´Brien MER, Splinter T, Smit EF, et al. Carboplatin and paclitaxel (Taxol) as an induction regimen for patients with biopsy-proven stage IIIA N2 non-small cell lung cancer : an EORTC phase II study (EORTC 08958). Eur J Cancer 2003; 39:1416-1422.

12. Zaragoulidis K, Kontakiotis T, Hatziapostolou P, et al. A phase II study of docetaxel and carboplatin in the treatment of non-small cell lung cancer. Lung Cancer 2001;32:281-287.

13. Sugarbaker DJ, Herdon J, Kohman LJ, et al. Results of cancer and leukemia group B protocol 8935: A multi-institutional phase II trimodality trial for stage IIIA (N2) non-small-cell lung cancer-Cancer and Leukemia Group B Thoracic Surgery Group. J Thorc Cardiovasc Surg 1995; 109:473-485.

14. Kirn DH, Lynch TJ, Mentzer SJ, et al. Multimodality therapy of patients with satge IIIA, N2 non-small –cell lung cancer: Impact of preoperative chemotherapy on resectability and downstaging,. J Thorac Cardiovasc Surg 1993; 106: 696-702.

15. Martini N, Kris MG, Flehinger BJ, eta al. Preoperative chemotherapy for stage IIIa (N2) lung cancer: The Sloan-Kettering experience with 136 patients. Ann Thorc Surg 1993; 55:1365-1374.

16. Martín N. Mediatinal lymph node dissection for lung cancer: The Memorial experience. Chest Surg Clin N Am 1995; 5: 189-203.

17. Kumar P, Herdon J, Elias D, et al. Comparison of pre-operative thoracic radiation therapy to pre-opetative chemotherapy on surgically staged IIIA (N2) non-small cell lung cancer: initial results of Cancer and Leucemia Group B Phase III Protocol 9134. Int J Radiat Oncol Biol Phys 1997; 39: 195.

18. Choi Y S, shim Y M, Kim J, Kim K. Recurrence-free survival and prognostic factors in resected pN2 non-small cell lung cancer. European Journal of Cardiothoracic Surgery 2002; 22: 695-700.

19. Miller AB, Hoogstraten B, Staquet M, et al. Reporting results of cancer treatment.Cancer 1981; 47: 207-214.

20. Martín N. Mediatinal lymph node dissection for lung cancer: The Memorial experience. Chest Surg Clin N Am 1995; 5: 189-203.

21. Johnson DH, Paul DM, Hande KR, Shyr Y, Bianke C, Murphy B, Lewis M, DeVore RF. Paclitaxel plus carboplatin in advanced non-small-cell lung cancer - a phase II trial. J Clin Oncol 1996; 14: 2054-2060.

22. Rowinsky EK, Flood WA, Sartorius SE, Bowling MK, Wagner J, Ettinger DS. Phase I study of paclitaxel as a 3-hour infusion followed by carboplatin in untreated patients with stage IV non-small-cell lung cancer. Semin Oncol 1995; 22 (Suppl 9): 48-54.

23. Vafai D, Israel V, Zaretsky S, Natale RB. Phase III trial of combination carboplatin and taxol in non-small-cell lung cancer (NSCLC). ProcAm Soc Clin Oncol 1995; 14: A352.

24. Klastersky J, Sculier JP, Lacroix H, Dabouis G, Bureau G, Libert P, Richez M, Ravez P, Vandermoten G, Thiriaux J, et al. A randomized study comparing cisplatin or carboplatin with etoposide in patients with advanced non-small-cell lung cancer:EORTC Protocol 07861. J. Clin. Oncol. 1990 Sep; 8(9): 1556-1562.

25. Bonomi P, Finkelstein D, Ruckdeschel J, et al. Combination Chemotherapy versus single agents followed by combination in stage IV non-small-cell lung cancer: astudy of the ECOG. J. Clin. Oncol. 1989; 7: 1602.

26. Greco FA y Hainsworth JD. Paclitaxel (1-hour infusion) plus carboplatin in the treatment of advanced NSCLC. Semin Oncol 1997; 24: S12-17.

27. DeVore RF, Jagasia M y Johnson D. Paclitaxel by either 1-hour or 24h infusion in combination with carboplatin in advanced NSCLC. Semin Oncol 1997;24: S27-29.

28. Palackdharry CS, Durham SJ, Durzinsky DS, et al: Preliminary results of neoadjuvant paclitaxel and carboplatin in the treatment of early stage NSCLC. Semin Oncol 1997; 24:S12-34-S12-36.

29. Stroun M et al. Neoplastic characateristics of the DNA found in the plasma of cancer patients. Oncology 1989; 46:318-322.

APPENDIX A Performance status evaluation scales

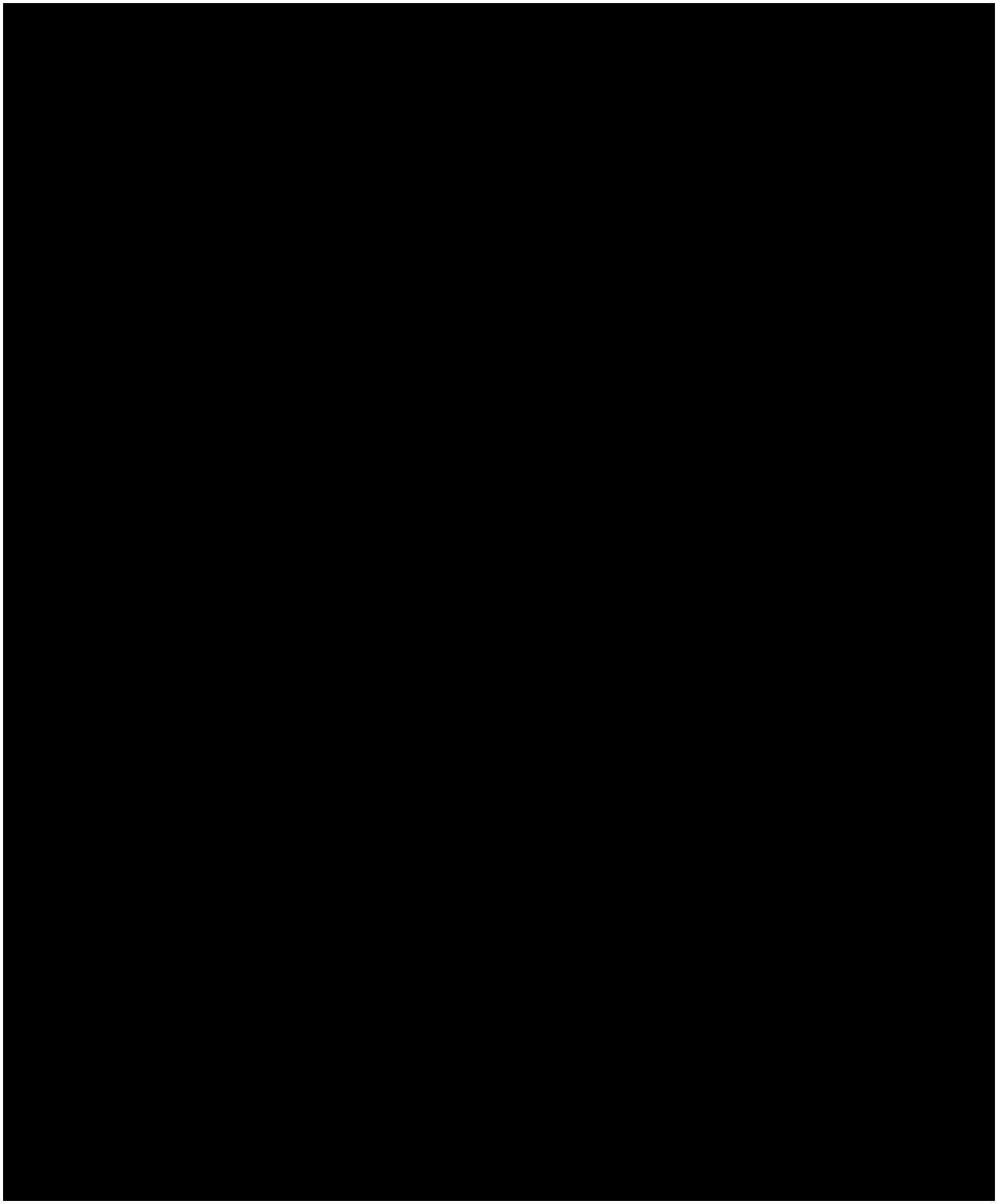
STATUS	SCALES		STATUS
	KARNOFSKY	**ZUBROD-ECOG-WHO**	
Normal, without disease	100	0	Normal activity
Capacity to continue habitual activity. Slight signs and symptoms of disease	90	1	Symptomatic, but completely ambulatory
Normal activity with difficulty	80		
Incapacity for normal activities or for active work	70	2	Symptomatic, but in bed <50% of the day
Requires occasional help but is capable of attending to almost all necessities			
Requires considerable help and frequent medical attention	60		Although not prostrate, needs to stay in bed >50% of the day
	50	3	
Incapacitated. Requires attention and special help			
Severely incapacitated. Hospitalisation indicated but death not imminent	40	4	Incapacity to rise from bed
Very ill. Hospitalisation necessary. Active assistance-treatment necessary	30		
Moribund	20		
Death	10	5	Death
	0		

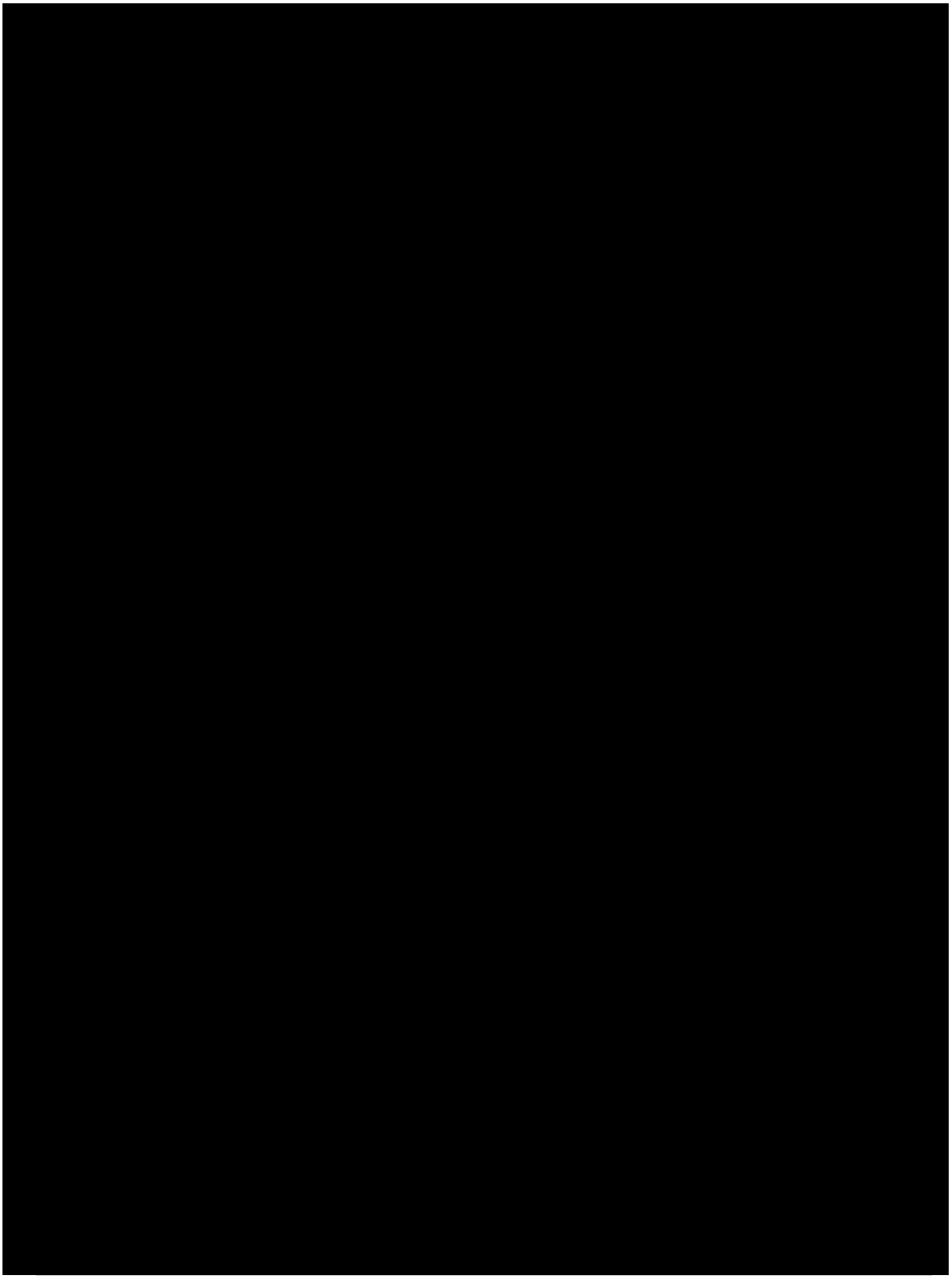
APPENDIX B Common Toxicity Criteria (CTC-NCIC)

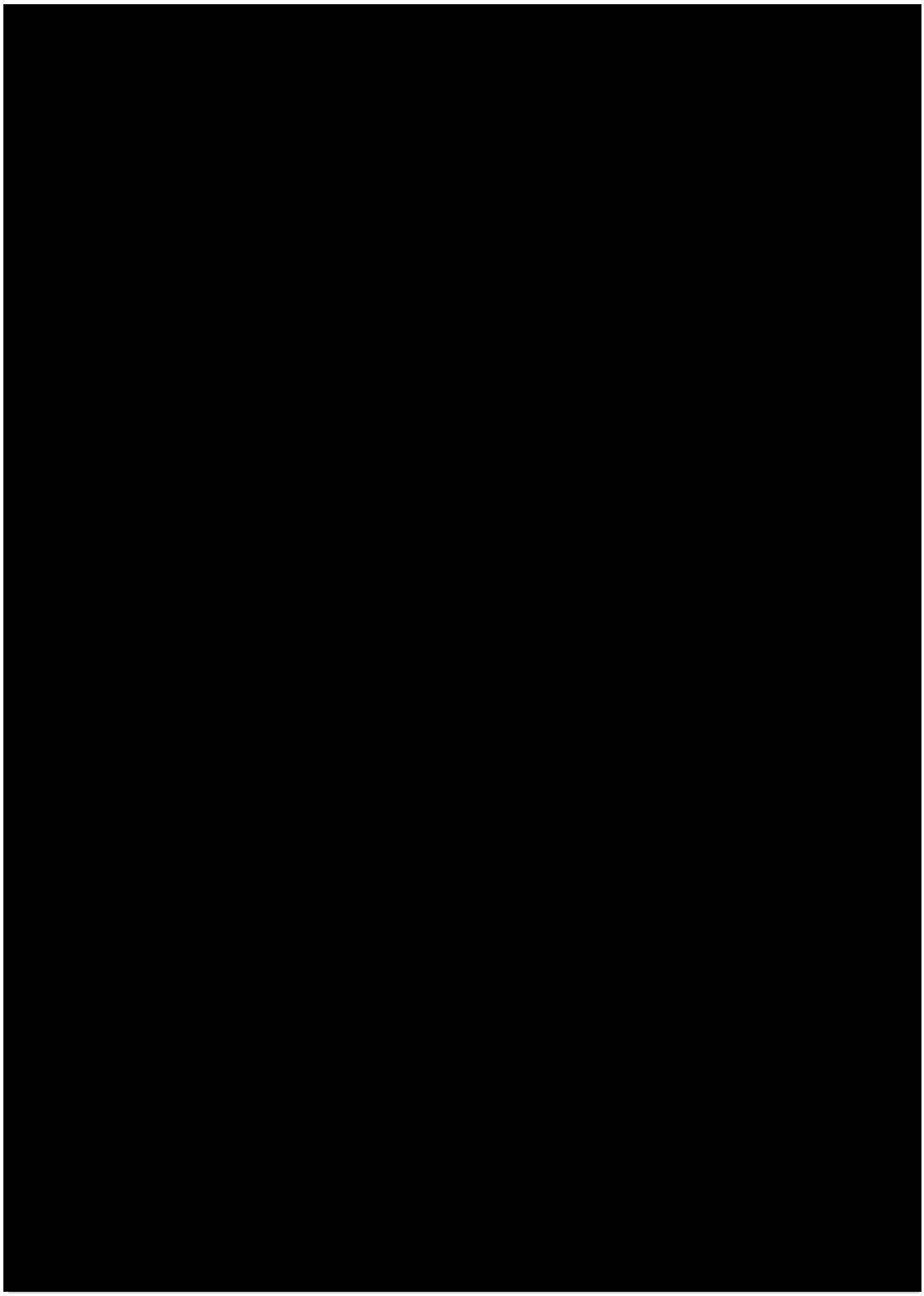
Version 4.03: June 14, 2010 is available from the internet at:

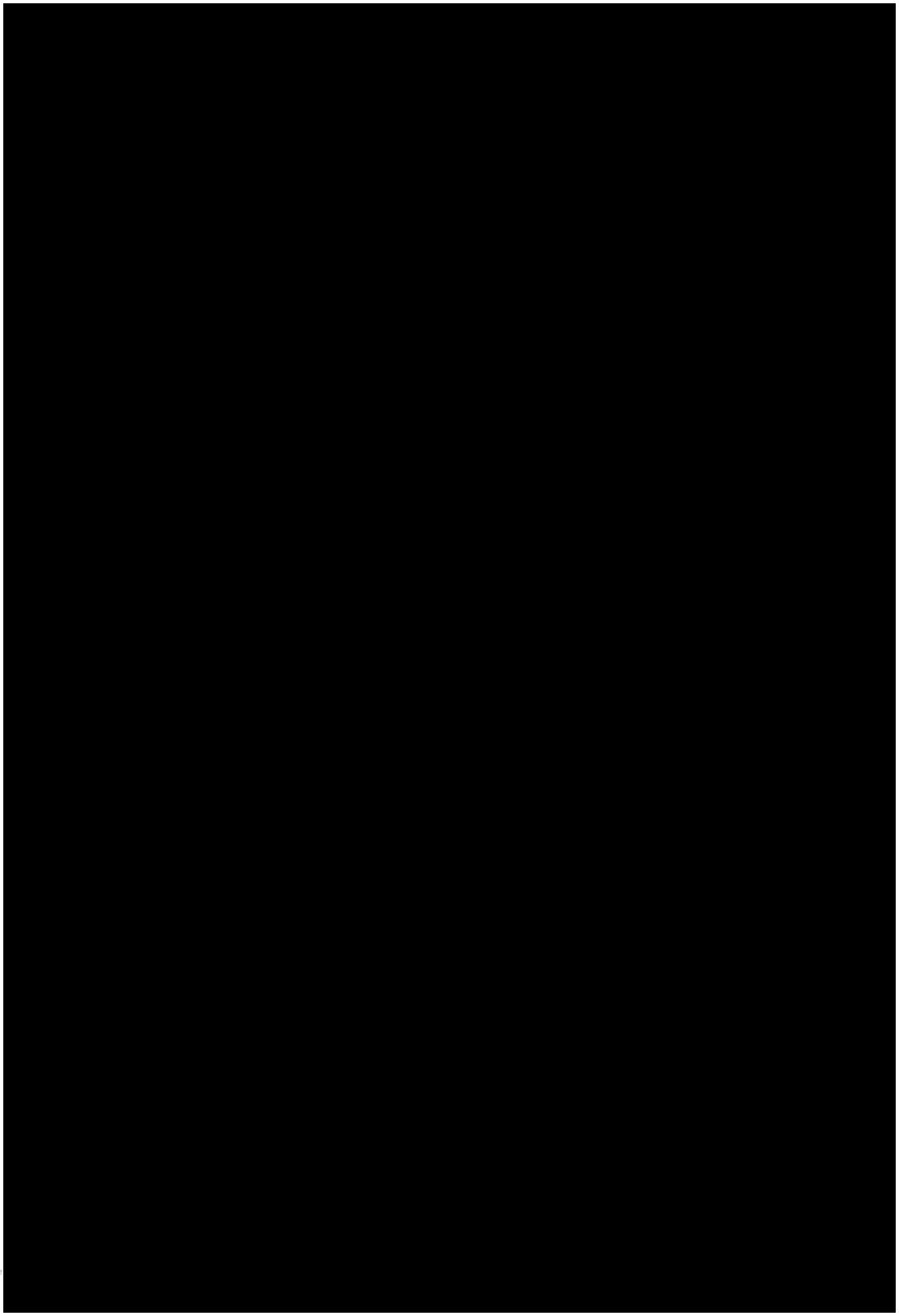
http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

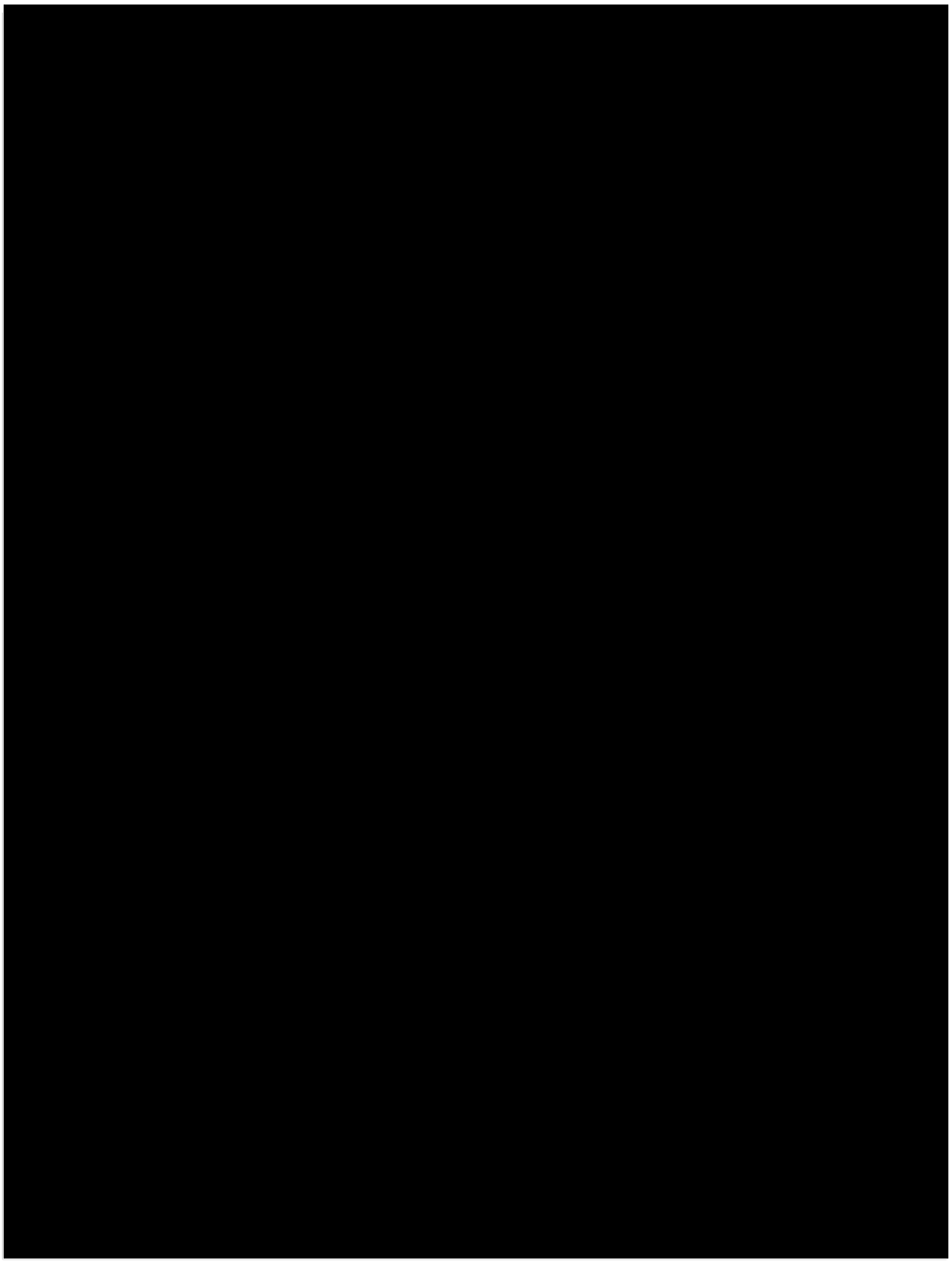
APPENDIX C SAE FORM AND PREGNANCY FORM











APPENDIX D Carboplatin dose calculation

To calculate the creatinine clearance (CrCl) of serum creatinine:

CrCl= (140 - age) x weight in kg x 0.85 (females) or 1.0 (males)
72 x serum creatinine in mg/100 ml

umol/l x 0.0113 = mg/100 ml

CALCULATION OF CARBOPLATIN DOSE ACCORDING TO THE FORMULAR OF CALVERT:

USING: **THE CALCULATED CREATININE CLEARANCE (see above) TO CALCULATE GLOMERULAR FILTRATION RATE (GFR)**

(6)*(GFR + 25) = CARBOPLATIN DOSE (in mg) PER CYCLE
(6)*(____ +25) = _____ mg of carboplatin

This is the **TOTAL DOSE** of carboplatin in mg (NOT in mg/m2)

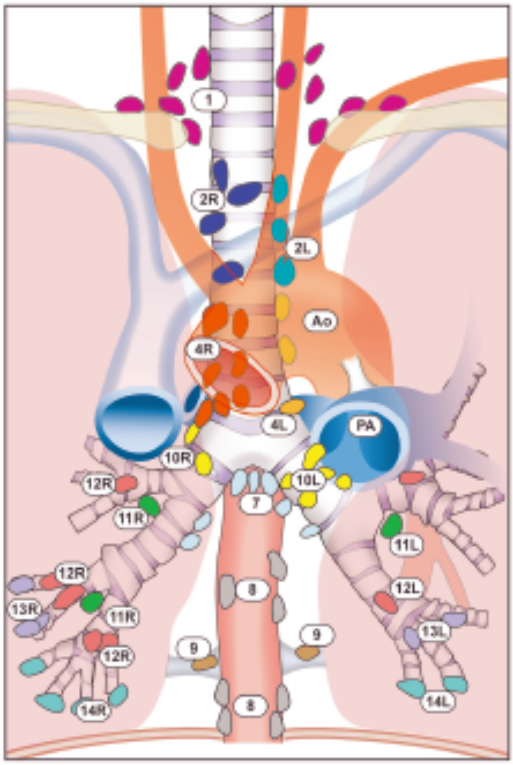
*The carboplatin dose must be calculated before each cycle

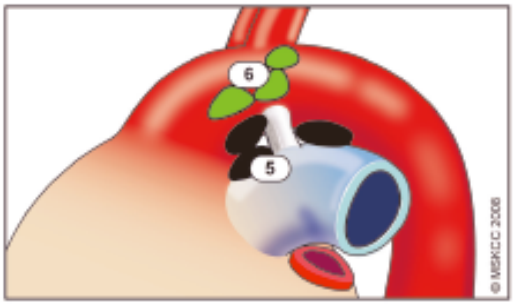
**Use current weight

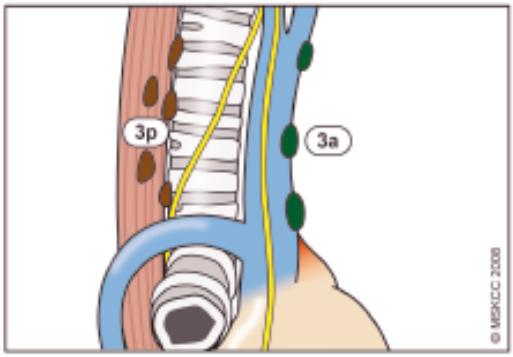
APPENDIX E: System of classification for non-microcytic lung cancer (NSCLC) and definition of lymph-nodes maps, 8th Edition

T: Primary tumor	
Tx	Primary tumor cannot be assessed or tumor proven by presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor ≤3 cm in greatest dimension surrounded by lung or visceral pleura without bronchoscopic evidence of invasion more proximal than the lobar bronchus (i.e., not in the main bronchus)[a]
T1a(mi)	**Minimally invasive adenocarcinoma**[b]
T1a	**Tumor ≤1 cm in greatest dimension**[a]
T1b	**Tumor >1 cm but ≤2 cm in greatest dimension**[a]
T1c	**Tumor >2 cm but ≤3 cm in greatest dimension**[a]
T2	Tumor >3 cm **but ≤5 cm** or tumor with any of the following features[c]: - **Involves main bronchus regardless of distance from the carina but without involvement of the carina** - Invades visceral pleura - **Associated with atelectasis or obstructive pneumonitis that extends to the hilar region, involving part or all of the lung**
T2a	**Tumor >3 cm but ≤4 cm in greatest dimension**
T2b	**Tumor >4 cm but ≤5 cm in greatest dimension**
T3	**Tumor >5 cm but ≤7 cm in greatest dimension** or associated with separate tumor nodule(s) in the same lobe as the primary tumor or directly invades any of the following structures: chest wall (including the parietal pleura and superior sulcus tumors), phrenic nerve, parietal pericardium
T4	**Tumor >7 cm in greatest dimension** or associated with separate tumor nodule(s) in a different ipsilateral lobe than that of the primary tumor or invades any of the following structures: **diaphragm**, mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, and carina
N: Regional lymph node involvement	
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension
N2	Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)
N3	Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)
M: Distant metastasis	
M0	No distant metastasis
M1	Distant metastasis present
M1a	Separate tumor nodule(s) in a contralateral lobe; tumor with pleural or pericardial nodule(s) or malignant pleural or pericardial effusion[d]
M1b	**Single extrathoracic metastasis**[e]
M1c	**Multiple extrathoracic metastases in one or more organs**

Note: Changes to the seventh edition are in bold.
[a]The uncommon superficial spreading tumor of any size with its invasive component limited to the bronchial wall, which may extend proximal to the main bronchus, is also classified as T1a.
[b]Solitary adenocarcinoma, ≤ 3cm with a predominately lepidic pattern and ≤ 5mm invasion in any one focus.
[c]T2 tumors with these features are classified as T2a if ≤4 cm in greatest dimension or if size cannot be determined, and T2b if >4 cm but ≤5 cm in greatest dimension.
[d]Most pleural (pericardial) effusions with lung cancer are due to tumor. In a few patients, however, multiple microscopic examinations of pleural (pericardial) fluid are negative for tumor and the fluid is nonbloody and not an exudate. When these elements and clinical judgment dictate that the effusion is not related to the tumor, the effusion should be excluded as a staging descriptor.
[e]This includes involvement of a single distant (nonregional) lymph node.







Supraclavicular zone

- **1** Low cervical, supraclavicular, and sternal notch nodes

Superior Mediastinal Nodes

Upper zone

- **2R** Upper Paratracheal (right)
- **2L** Upper Paratracheal (left)
- **3a** Pre-vascular
- **3p** Retrotracheal
- **4R** Lower Paratracheal (right)
- **4L** Lower Paratracheal (left)

Aortic Nodes

AP zone

- **5** Subaortic
- **6** Para-aortic (ascending aorta or phrenic)

Inferior Mediastinal Nodes

Subcarinal zone

- **7** Subcarinal

Lower zone

- **8** Paraesophageal (below carina)
- **9** Pulmonary ligament

N_1 Nodes

Hilar/Interlobar zone

- **10** Hilar
- **11** Interlobar

Peripheral zone

- **12** Lobar
- **13** Segmental
- **14** Subsegmental

PROPOSED STAGE GROUPINGS FOR 8TH EDITION TNM FOR LUNG CANCER (CHANGES TO THE 7TH EDITION ARE HIGHLIGHTED IN BOLD AND UNDERLINED)

Occult carcinoma	TX	N0	M0
Stage 0	Tis	N0	M0
Stage IA1	**T1(mi)**	**N0**	**M0**
	T1a	**N0**	**M0**
Stage IA2	**T1b**	**N0**	**M0**
Stage IA3	**T1c**	**N0**	**M0**
Stage IB	T2a	N0	M0
Stage IIA	T2b	N0	M0
Stage IIB	**T1a-c**	**N1**	**M0**
	T2a	**N1**	**M0**
	T2b	N1	M0
	T3	N0	M0
Stage IIIA	**T1a-c**	**N2**	**M0**
	T2a-b	N2	M0
	T3	N1	M0
	T4	N0	M0
	T4	N1	M0
Stage IIIB	**T1a-c**	**N3**	**M0**
	T2a-b	N3	M0
	T3	**N2**	**M0**
	T4	N2	M0
Stage IIIC	**T3**	**N3**	**M0**
	T4	**N3**	**M0**
Stage IVA	**Any T**	**Any N**	**M1a**
	Any T	**Any N**	**M1b**
Stage IVB	**Any T**	**Any N**	**M1c**