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Official Title: "A phase II trial of neoadjuvant treatment with carboplatin-pemetrexed-bevacizumab plus atezolizumab for the treatment of locally advanced and potentially resectable NSCLC patients with EGFR mutations" Neo-DIANA

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A PHASE II TRIAL OF NEOADJUVANT TREATMENT CARBOPLATIN-PEMETREXED-BEVACIZUMAB PLUS ATEZOLIZUMAB FOR THE TREATMENT OF LOCALLY ADVANCED AND POTENTIALLY RESECTABLE NSCLC PATIENTS WITH EGFR MUTATIONS

Neo-DIANA: Neoadjuvant treatment for EGFR mutated patients

Sponsor: Fundación GECP

EudraCT Number: 2020-000642-33

Sponsor code: GECP 20/01

[redacted]

Version 3.0

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Protocol Signature Page

A PHASE II TRIAL OF NEOADJUVANT TREATMENT CARBOPLATIN-PEMETREXED-BEVACIZUMAB PLUS ATEZOLIZUMAB FOR THE TREATMENT OF LOCALLY ADVANCED AND POTENTIALLY RESECTABLE NSCLC PATIENTS WITH EGFR MUTATIONS

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Approved by:

Signature

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Trial Chair

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Fundación GECP President

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Principal Investigator's protocol signature page

Study Title: "A phase II trial of neoadjuvant treatment with carboplatin-pemetrexed-bevacizumab plus atezolizumab for the treatment of locally advanced and potentially resectable NSCLC patients with EGFR mutations"

Sponsor protocol code: GECP 20/01

EudraCT Number: 2020-000642-33

Protocol version: v.3.0, 16th February 2022

Name of Principal Investigator: Dr. _____

Institution's name: Hospital _____

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.

Signed in _____ (place),

_____ _____

Signature Date

[redacted]

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1. Protocol summary

A PHASE II TRIAL OF NEOADJUVANT TREATMENT CARBOPLATIN-PEMETREXED-BEVACIZUMAB PLUS ATEZOLIZUMAB FOR THE TREATMENT OF LOCALLY ADVANCED AND POTENTIALLY RESECTABLE NSCLC PATIENTS WITH EGFR MUTATIONS

Neo-DIANA: Neoadjuvant treatment for EGFR mutated patients

Sponsor: Fundación GECP

Trial Chair: Mariano Provencio Pulla (MD, PhD)

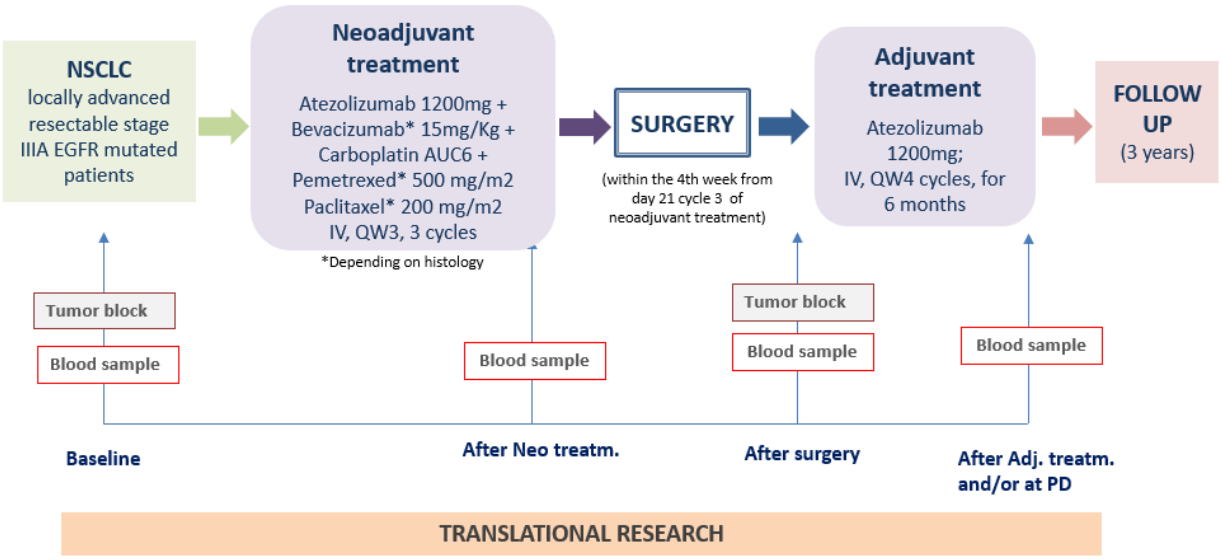
Pharma Partner: Roche Farma S.A

Protocol code: GECP 20/01 (Neo-DIANA).[redacted]

Population: stage IIIA or IIIB with T3N2 disease potentially resectable EGFR mutated non-small cell lung cancer patients

Design: Open-label, non-randomised, phase II, multi-centre clinical trial

Figure 1. Study schema



[redacted]

Sample size: 26 patients

Rationale:

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.

At diagnosis, at least 40% of patients are diagnosed at an advanced stage and a third locally advanced disease (stage III). Only 25-30% of the NSCLC are candidates for curative-intent surgery. 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%.

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

Locally advanced NSCLC is one of the most heterogeneous conditions, with multidimensional treatments involved.

Neoadjuvant therapy had been commonly considered an optimal management strategy for patients with operable locally advanced. Pre-operative therapy in early stage in has many advantages: better treatment delivery, early treatment of micro-metastatic disease, ability to study biological impact treatment intervention and identify sensitive vs resistant disease.

However, as targeted therapy has been widely applied in advanced NSCLC, neoadjuvant targeted therapy has remained poorly explored in locally advanced disease.

Patients with stage IIIA-N2 NSCLC have a poor prognosis, especially those with EGFR mutations[35].

EGFR TKI therapy has shown good efficacy and favorable tolerability in patients with EGFR mutation-positive NSCLC in stage IV. The efficacy and tolerability of preoperative EGFR TKI therapy, although promising[36], requires further research.

There is a clinical trial recently published[37] with erlotinib in 19 patients, radical resection was 68%, with 21% rate of pathologic downstaging. The objective response rate was 42% and 89% of patients achieved disease control.

CTONG 1103 is an ongoing trial comparing erlotinib vs gemcitabine plus cisplatin as neoadjuvant treatment for stage IIIA EGFR mutation (EMERGING trial)[38] with 72 patients included, PFS favored erlotinib (HR: 0.42), nodal downstaging 11% erlotinib vs 3% in chemotherapy arm, safety results are consistent with prior studies, but no pathological complete response was observed with erlotinib.

Neoadjuvant studies are difficult to execute because requires multidisciplinary setting, need for additional biopsy, patient inclination to undergo surgery right away and competing priorities and surgical considerations.

Previously, IMpower150 showed significant improvements in PFS and OS with atezolizumab plus bevacizumab plus carboplatin plus paclitaxel (ABCP) vs the standard-of-care bevacizumab plus carboplatin plus paclitaxel (BCP) in chemotherapy-naive patients with non-squamous NSCLC. The addition of atezolizumab to standard-of-care bevacizumab and carboplatin-paclitaxel chemotherapy

appears to improve survival outcomes in an all-comer population of chemotherapy-naive patients with metastatic non-squamous NSCLC.

This randomized phase 3 study is the first to show promising results with the combination of atezolizumab plus bevacizumab and chemotherapy in patients with *EGFR* mutations. PFS at 12 months= 22.2% chemotherapy arm vs 42% in mutated arm. HR= 0.61 (0.36-1.03).

The ABCP regimen represents a new therapy option for these key patient subgroups, especially those with sensitizing *EGFR* mutations and it could useful in neoadjuvant setting.

NADIM Study (CA209-547) is a Phase II, single-arm, open-label multicentre study aimed to assess the 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 locally advanced resectable stage IIIA NSCLC adult patients followed by adjuvant treatment during 1 year (4 months with Nivolumab 240mg IV Q2W and 8 months with Nivolumab 480 mg IV Q4W). The primary endpoint is the progression-free survival (PFS) at 24 months from diagnosis. The PFS was defined as the time from diagnosis to relapse, progression or death, whichever occurred first. Secondary endpoints include overall survival at 3 years, response rate (RR), toxicity profile of the combination, the down-staging rate and complete resection rate. A total of 46 patients were to be included from 25 participating sites in Spain.
NADIM Study results: (cut-off date 30th June 2018), 80% are N2 IIIA. Available efficacy results for this subset of 30 out of 46 patients: Tumor responses after neoadjuvant therapy (100% compliance rate), according to RECIST criteria v1.1 assessed per CT-SCAN: ORR= 21/30 (70%), including 3 CR (10%) and 18 PR (60%), SD was reported for the remaining 9/30 (30%) patients. Pathological responses after surgery: The high total MPR defined as <10% of tumor viable cells in the resection specimen (pCR+ MPR) = 24/30 (80%), including 18 pCR (60%) and 6 MPR (20%). Pathological response <90%= 6 (20%). pCR rates observed are unprecedented and highly promising in the context of neoadjuvant therapy of NSCLC.

Current study results are considered an acceptable evidence to support the hypothesis of efficacy of the proposed Chemo Immunotherapy (Ch-IO) combination in the setting of neoadjuvant treatment in NSCLC.

We can use the screening that is going to be performed for the NADIM II stage IIIA clinical trial to identify all patients EGFR mutated for the Neo-DIANA trial.

Objectives and endpoints:

Primary objective:

- To evaluate the major pathologic response (MPR) defined as 10 percent or fewer viable cancer cells detectable in the resected tumor and in lymph nodes in stage IIIA EGFR mutated patients treated in neoadjuvant setting with atezolizumab- bevacizumab- carboplatin and pemetrexed

[redacted]

Secondary objectives:

- Overall survival
- Progression-free survival at 12 months
- Complete response rate
- Downstaging
- Major pathological response
- Safety and tolerability: Adverse events graded according to CTCAE v5.0
- Biomarker endpoints

Eligibility criteria:

Inclusion criteria:

1. Previously untreated patients with histologically- or cytologically- documented NSCLC who present stage IIIA disease (according to 8th version of the International Association for the Study of Lung Cancer Staging Manual in Thoracic Oncology) and also, potentially resectable locally advanced NSCLC patients' stage IIIB with T3N2 disease according to 8th edition can be included.
    - PET/CT including IV contrast (CT of diagnostic quality) will be performed at baseline (28 days +10 before inclusion)
2. Tumor should be considered resectable before study entry by a multidisciplinary team
3. Sensitizing EGFR mutation (Del Exon 19 and mut Exon 21)
4. ECOG (Performance status) 0-1
5. Screening laboratory values must meet the following criteria and should be obtained within 14 days prior to inclusion
    i. Neutrophils ≥ 1500×109/L
    ii. Platelets ≥ 100 ×109/L
    iii. Hemoglobin > 9.0 g/dL
    iv. 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/ 72 x serum creatinine in mg/dL
        b. Male CrCl = (140 - age in years) x weight in kg x 1.00/ 72 x serum creatinine in mg/dL
    v. AST/ALT ≤ 3 x ULN
    vi. Total Bilirubin ≤ 1.5 x ULN (except subjects with Gilbert Syndrome, who can have total bilirubin < 3.0 mg/dL)
    vii. PT/APTT/INR within normal limits
6. Measurable or evaluable disease according to RECIST v1.1
7. The patients need to have a forced expiratory volume (FEV1)≥ 1.2 liters or >40% predicted value
8. 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

9. Patients aged > 18 years
10. Patient capable of proper therapeutic compliance and accessible for correct follow-up
11. For female patients of childbearing potential, agreement (by patient and/or partner) to use a highly effective form(s) of contraception that results in a low failure rate (< 1% per year) when used consistently and correctly, and to continue its use for 5 months after the last dose of Atezolizumab and/or 6 months after the last dose of Bevacizumab, whichever is later. Such methods include: combined (estrogen and progestogen containing) hormonal contraception, progestogen-only hormonal contraception associated with inhibition of ovulation together with another additional barrier method always containing a spermicide, intrauterine device (IUD): intrauterine hormone-releasing system (IUS), bilateral tubal occlusion, vasectomized partner (on the understanding that this is the only one partner during the whole study duration), and sexual abstinence.
12. For male patients with female partners of childbearing potential, agreement (by patient and/or partner) to use a highly effective form(s) of contraception that results in a low failure rate [< 1% per year] when used consistently and correctly, and to continue its use for 6 months after the last dose of Bevacizumab. Male patients should not donate sperm during this study and for at least 6 months after the last dose of Bevacizumab.
13. Oral contraception should always be combined with an additional contraceptive method because of a potential interaction with the study drugs. The same rules are valid for male patients involved in this clinical study if they have a partner of childbirth potential. Male patients must always use a condom.
14. Women who are not postmenopausal (≥ 12 months of non−therapy-induced amenorrhea) or surgically sterile must have a negative serum pregnancy test result within 14 days prior to initiation of study drug

Exclusion criteria:

1. All patients carrying other EGFR mutations.
2. Patients with known anaplastic lymphoma kinase (ALK) fusion oncogene, STK11 ligand alteration or ROS1 translocations.
3. Clinically significant comorbidities that impaired administration of platinum-based chemotherapy
4. Patients with a condition requiring systemic treatment with either corticosteroids (>10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of inclusion. Inhaled or topical steroids, and adrenal replacement steroid doses > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.
5. Patients with a history of interstitial lung disease cannot be included if they have symptomatic ILD (Grade 3-4) and/or poor lung function. In case of doubt please contact trial team.
6. Patients with other active malignancy requiring concurrent intervention and/or concurrent treatment with other investigational drugs or anti-cancer therapy.
7. 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.

8. 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
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. Active tuberculosis
12. Severe infections within 4 weeks prior to be included in the study, including but not limited to hospitalization for complications of infection, bacteremia, or severe pneumonia
13. Patients with history of allergy to study drug components excipients
14. History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins
15. Women who are pregnant or in the period of breastfeeding
16. Sexually active men and women of childbearing potential who are not willing to use an effective contraceptive method during the study
17. Patients with active, known or suspected autoimmune disease, including but not limited to myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with antiphospholipid syndrome, Wegener's granulomatosis, Sjögren's syndrome, Guillain-Barré syndrome, multiple sclerosis, vasculitis, or glomerulonephritis.
    Patients with a history of autoimmune-related hypothyroidism on a stable dose of thyroid replacement hormone are eligible for this study.

    Patients with controlled Type 1 diabetes mellitus on a stable dose of insulin regimen are eligible for this study.

    Patients with eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (e.g., patients with psoriatic arthritis would be excluded) are permitted provided that they meet the following conditions:

    - Rash must cover less than 10% of body surface area (BSA).
    - Disease is well controlled at baseline and only requiring low-potency topical steroids.
    - No acute exacerbations of underlying condition within the previous 12 months (not requiring PUVA [psoralen plus ultraviolet A radiation], methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, high-potency or oral steroids).
18. Patients with any contraindication for bevacizumab administration:
    - Inadequately controlled hypertension (defined as systolic blood pressure > 150 mmHg and/or diastolic blood pressure > 100 mmHg).

Anti-hypertensive therapy to achieve these parameters is allowable.

- Prior history of hypertensive crisis or hypertensive encephalopathy.
- Significant vascular disease (e.g., aortic aneurysm requiring surgical repair or recent peripheral arterial thrombosis) within 6 months prior to inclusion.
- History of hemoptysis (≥ one-half teaspoon of bright red blood per episode) within 1 month prior to inclusion.
- Evidence of bleeding diathesis or coagulopathy (in the absence of therapeutic anticoagulation).
- Current or recent (within 10 days of inclusion) use of aspirin (> 325 mg/day) or treatment with dipyramidole, ticlopidine, clopidogrel, and clostazol.
- Current use of full-dose oral or parenteral anticoagulants or thrombolytic agents for therapeutic purposes that has not been stable for > 2 weeks prior to inclusion.
  The use of full-dose oral or parenteral anticoagulants is permitted as long as the INR or aPTT is within therapeutic limits (according to the medical standard of the enrolling institution) and the patient has been on a stable dose of anticoagulants for at least 2 weeks prior to inclusion.
  Prophylactic anticoagulation for the patency of venous access devices is allowed, provided the activity of the agent results in an INR < 1.5 × ULN and aPTT is within normal limits within 14 days prior to inclusion.
  Prophylactic use of low-molecular-weight heparin (i.e., enoxaparin 40 mg/day) is permitted.
- Core biopsy or other minor surgical procedure, excluding placement of a vascular access device, within 7 days prior to the first dose of Bevacizumab.
- History of abdominal or tracheoesophageal fistula or gastrointestinal perforation within 6 months prior to inclusion.
- Clinical signs of gastrointestinal obstruction or requirement for routine parenteral hydration, parenteral nutrition, or tube feeding.
- Evidence of abdominal free air not explained by paracentesis or recent surgical procedure.
- Serious, non-healing wound, active ulcer, or untreated bone fracture.
- Proteinuria, as demonstrated by urine dipstick or > 1.0 g of protein in a 24-hour urine collection.
  All patients with ≥ 2+ protein on dipstick urinalysis at baseline must undergo a 24-hour urine collection and must demonstrate ≤ 1 g of protein in 24 hours.
- Known sensitivity to any component of Bevacizumab.

[redacted]

Treatment:

Neoadjuvant treatment:

Atezolizumab: 1200 mg, IV infusion

Bevacizumab: 15mg/Kg mg, IV infusion

Carboplatin: AUC6, IV infusion

Pemetrexed: 500 mg/m^2, IV infusion

Treatment sequence:

Atezolizumab → Bevacizumab → Carboplatin → Pemetrexed

[redacted]

[redacted]

NOTE:

for squamous or adenosquamous patients, neodjuvant treatment must switch to:

Atezolizumab: 1200 mg, IV infusion

Carboplatin: AUC6, IV infusion

Paclitaxel: 200 mg/m^2, IV infusion

Treatment sequence:

Atezolizumab → Paclitaxel → Carboplatin

Surgery: [redacted]

Adjuvant treatment

Atezolizumab: 1200 mg, IV infusion Q4W (+/- 3 days) *for 6 months (6 cycles)*

[redacted]

[redacted]

Statistical considerations:

To find a 40% of MPR vs a theorical reference equals to 10.7% in patients with EGFR mutation NSCLC stage IIIA, with a 80% of power and alpha level of 0.05, 22 patients are needed. If we expect a 15% of losses of follow-up, 26 patients with EGFR mutation and NSCLC stage IIIA will be necessary. Thus, considering a prevalence of EGFR mutation of 15% in patients with NSCLC stage IIIA, 174 patients NSCLC stage IIIA should perform the test to check the presence of EGFR mutation.

It is expected that approximately the 15% 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 the 15% is exceeded because 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 will be the one calculated initially.

The analysis will be conducted according to the intention-to-treat (ITT) principle. Descriptive analysis will be performed by means of absolute and relative frequencies for categorical variables and mean and standard deviation, or median and percentiles 25 and 75 for numerical variables.

The main analysis asses the response rate after the neoadjuvant therapy plus surgery. Response rates will be estimated along with their corresponding 95% confidence interval and then compared with other variables through a chi-square test or Fisher exact test if expected frequencies are less than or equal to 5. Effect size will be estimated by means of logistic regression analysis through the Odds Ratio (OR) as well as their corresponding confidence interval (95%CI).

Progression free survival (PFS) is set as a secondary outcome. Survival function will be estimated by the Kaplan-Meier method. Cox proportional hazards model, will be used to estimate potential risk factors, along with the Hazard Ratios (HR) and 95% confidence intervals.

Reported p values will be two-sided, and the significance level will be set at 5% (0.05) for all analyses unless otherwise noted. Stata v15.1 software (StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC) will be used for statistical analyses.

Total trial duration:

6 years: 2 years of recruitment, 1 year of treatment and 3 years of follow up (excluding a run-in period of 3-6 months and a close out period of at least 4 months)

Translational research:

[redacted]

[redacted]

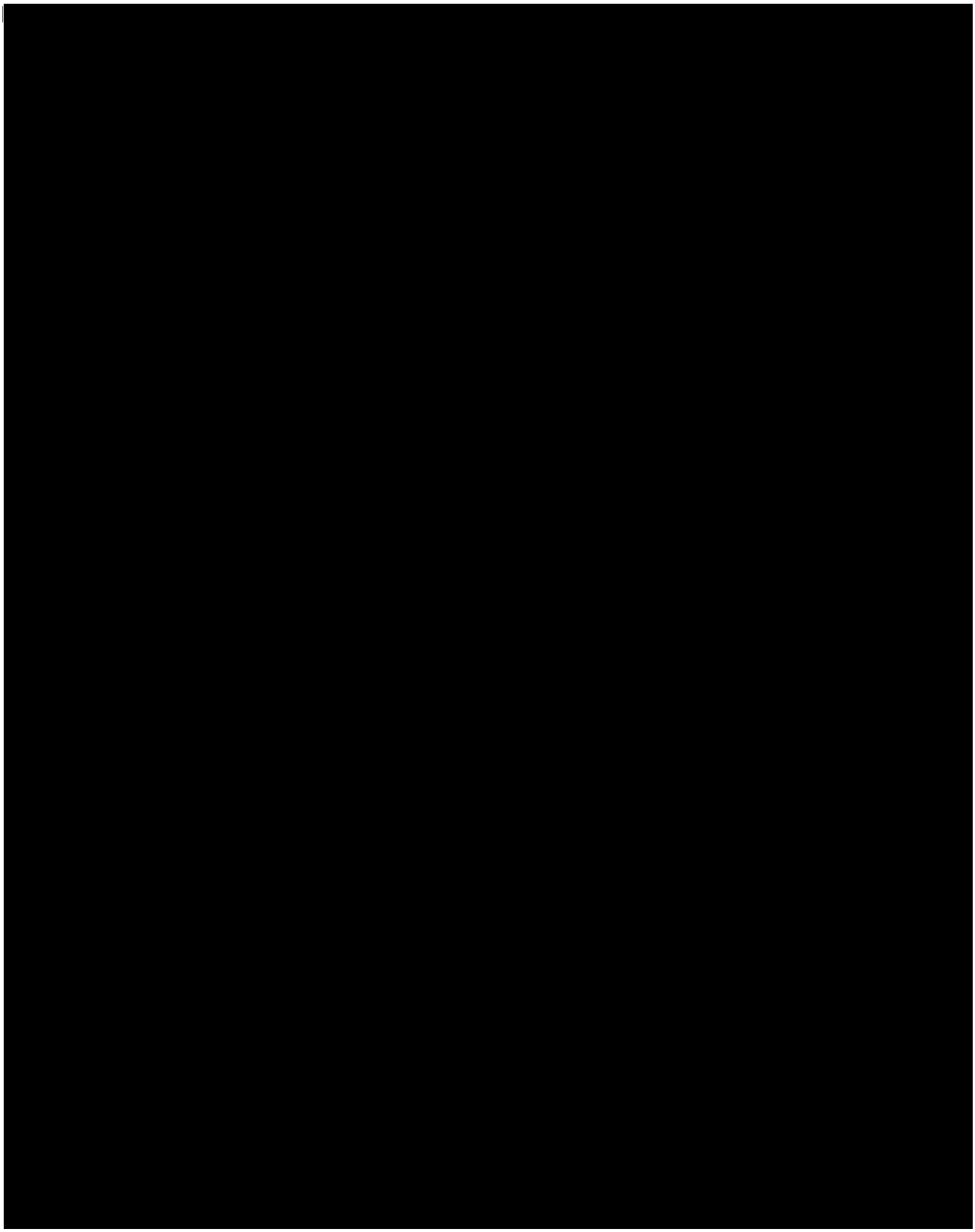
[redacted]

2. Trial schedule

	Baseline *(-28 days before inclusion)*	**Neoadjuvant treatment**	**Surgery**[15]	**Adjuvant treatment**[16] *(Atezolizumab)*	**End of Treatment**[17]	**Follow up**[18]
[redacted]						

[redacted]

	Baseline *(-28 days before inclusion)*	**Neoadjuvant treatment**	**Surgery**[15]	**Adjuvant treatment**[16] *(Atezolizumab)*	**End of Treatment**[17]	**Follow up**[18]
[redacted]						



[redacted]

3. Background and rationale

3.1. Disease background

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 fall 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 chemo-resistant 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 ranging from 67 to 79%[12]

3.2. Prognostic factors after neoadjuvant treatment

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].

[redacted]

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 tumors, 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. Immune-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

[redacted]

[redacted]

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 non-squamous NSCLC, and paclitaxel/carboplatin (N5 vs N10) in combined cohorts of squamous and non-squamous 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.

3.3. Immunotherapy

Several studies in patients with NSCLC suggested an association of increased immune cell infiltration into tumours with improved survival. In recent years, improved identification of antigenic targets, the addition of immunoadjuvants, and the production of more efficient delivery systems have resulted in more efficient vaccines, able to elicit a potent immune response, leading to the development of immunotherapy for the treatment of NSCLC[30].

3.4. Immune checkpoint receptors

[redacted]

[redacted]

3.5. Rationale for trial design

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted].

4. Objectives and endpoints

4.1. Primary objective and endpoint

- To evaluate the major pathologic response (MPR)

  MPR defined as 10 percent or fewer viable cancer cells detectable in the resected tumor and in lymph nodes in stage IIIA EGFR mutated patients treated in neoadjuvant setting with atezolizumab- bevacizumab- carboplatin and pemetrexed.

4.2. Secondary objectives and endpoint

- To evaluate the PFS rate at 1 year of treatment

  PFS defined as the length of time from the date of diagnosis to the date of the first documented progression of disease

- To evaluate the Overall Survival (OS) rate at 1 year, 2 and 3 years

  OS defined as the length of time from either the date of diagnosis or the start of the treatment that patients diagnosed with the disease are still alive.

[redacted]

- To assess the complete response rate and major pathological response
- To evaluate the downstaging after surgery
- To evaluate the safety and tolerability of the combination.

  Occurrence and severity of adverse events, with severity determined by NCI CTCAE v5.0 criteria.

5. Trial design, duration and termination

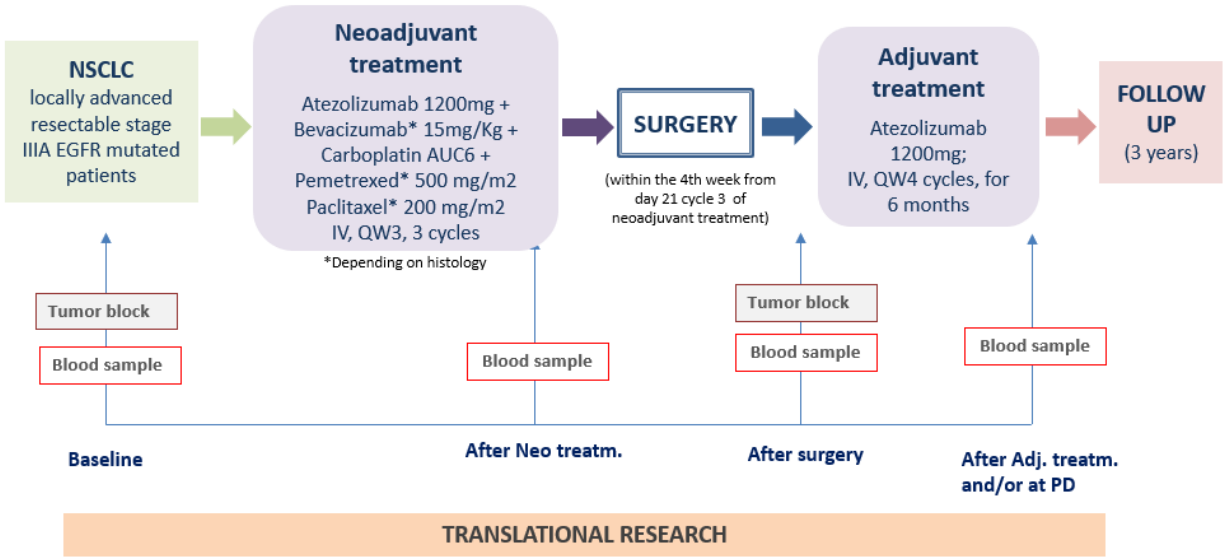
This is an open-label, non-randomised, phase II, multi-centre clinical trial.

Patients enrolled will receive Atezolizumab 1200mg + Bevacizumab 15mg/Kg + Carboplatin AUC6 + Pemetrexed 500mg/m2 for 3 cycles every 21 days (+/- 3 days) as neoadjuvant treatment followed by surgery and 6 months of adjuvant treatment with Atezolizumab 1200 mg Q4W (+/- 3 days). Note: squamous or adenosquamous patients neodjuvant treatment must switch to Atezolizumab 1200mg + Carboplatin AUC6 + Paclitaxel 200mg/m2.

Patient accrual is expected to be completed within 2 years excluding a run-in-period of 3-6 months. Treatment and follow-up are expected to extend the study duration to a total of 6 years. Patients will be followed 3 years after adjuvant treatment. The study will end once survival follow-up has concluded. This will be followed by a close out period of 4 months.

The trial will end with the preparation of the final report, scheduled for 7 years after the inclusion of the first patient approximately.

Figure 1. Study schema



[redacted]

6. Patient selection

Written Informed Consent (IC) must be signed and dated by the patient and the investigator prior to any trial-related intervention for trial treatment and biomaterial submission to the central laboratory.

Patients should only be selected and consented for enrolment if they fulfil the following criteria:

6.1. Inclusion criteria

1. Previously untreated patients with histologically- or cytologically- documented NSCLC who present stage IIIA disease (according to 8th version of the International Association for the Study of Lung Cancer Staging Manual in Thoracic Oncology) and also, potentially resectable locally advanced NSCLC patients' stage IIIB with T3N2 disease according to 8th edition can be included.
   - PET/CT including IV contrast (CT of diagnostic quality) will be performed at baseline (28 days +10 before inclusion)
2. Tumor should be considered resectable before study entry by a multidisciplinary team
3. Sensitizing EGFR mutation (Del Exon 19 and mut Exon 21)
4. ECOG (Performance status) 0-1
5. Screening laboratory values must meet the following criteria and should be obtained within 14 days prior to inclusion
   i. Neutrophils ≥ 1500×109/L
   ii. Platelets ≥ 100 ×109/L
   iii. Hemoglobin > 9.0 g/dL
   iv. 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/ 72 x serum creatinine in mg/dL
      b. Male CrCl = (140 - age in years) x weight in kg x 1.00/ 72 x serum creatinine in mg/dL
   v. AST/ALT ≤ 3 x ULN
   vi. Total Bilirubin ≤ 1.5 x ULN (except subjects with Gilbert Syndrome, who can have total bilirubin < 3.0 mg/dL)
   vii. PT/APTT/INR within normal limits
6. Measurable or evaluable disease according to RECIST v1.1
7. The patients need to have a forced expiratory volume (FEV1) ≥ 1.2 liters or >40% predicted value
8. 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
9. Patients aged > 18 years
10. Patient capable of proper therapeutic compliance and accessible for correct follow-up

[redacted]

11. For female patients of childbearing potential, agreement (by patient and/or partner) to use a highly effective form(s) of contraception that results in a low failure rate (< 1% per year) when used consistently and correctly, and to continue its use for 5 months after the last dose of Atezolizumab and/or 6 months after the last dose of Bevacizumab, whichever is later. Such methods include: combined (estrogen and progestogen containing) hormonal contraception, progestogen-only hormonal contraception associated with inhibition of ovulation together with another additional barrier method always containing a spermicide, intrauterine device (IUD): intrauterine hormone-releasing system (IUS), bilateral tubal occlusion, vasectomized partner (on the understanding that this is the only one partner during the whole study duration), and sexual abstinence.
12. For male patients with female partners of childbearing potential, agreement (by patient and/or partner) to use a highly effective form(s) of contraception that results in a low failure rate [< 1% per year] when used consistently and correctly, and to continue its use for 6 months after the last dose of Bevacizumab. Male patients should not donate sperm during this study and for at least 6 months after the last dose of Bevacizumab.
13. Oral contraception should always be combined with an additional contraceptive method because of a potential interaction with the study drugs. The same rules are valid for male patients involved in this clinical study if they have a partner of childbirth potential. Male patients must always use a condom.
14. Women who are not postmenopausal (≥ 12 months of non−therapy-induced amenorrhea) or surgically sterile must have a negative serum pregnancy test result within 14 days prior to initiation of study drug

6.2. Exclusion criteria

1. All patients carrying other EGFR mutations.
2. Patients with known anaplastic lymphoma kinase (ALK) fusion oncogene, STK11 ligand alteration or ROS1 translocations.
3. Clinically significant comorbidities that impaired administration of platinum-based chemotherapy
4. Patients with a condition requiring systemic treatment with either corticosteroids (>10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of inclusion. Inhaled or topical steroids, and adrenal replacement steroid doses > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.
5. Patients with a history of interstitial lung disease cannot be included if they have symptomatic ILD (Grade 3-4) and/or poor lung function. In case of doubt please contact trial team.
6. Patients with other active malignancy requiring concurrent intervention and/or concurrent treatment with other investigational drugs or anti-cancer therapy.
7. 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.
8. 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

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. Active tuberculosis
12. Severe infections within 4 weeks prior to be included in the study, including but not limited to hospitalization for complications of infection, bacteremia, or severe pneumonia
13. Patients with history of allergy to study drug components excipients
14. History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins
15. Women who are pregnant or in the period of breastfeeding
16. Sexually active men and women of childbearing potential who are not willing to use an effective contraceptive method during the study
17. Patients with active, known or suspected autoimmune disease, including but not limited to myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with antiphospholipid syndrome, Wegener's granulomatosis, Sjögren's syndrome, Guillain-Barré syndrome, multiple sclerosis, vasculitis, or glomerulonephritis.
    Patients with a history of autoimmune-related hypothyroidism on a stable dose of thyroid replacement hormone are eligible for this study.

    Patients with controlled Type 1 diabetes mellitus on a stable dose of insulin regimen are eligible for this study.

    Patients with eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (e.g., patients with psoriatic arthritis would be excluded) are permitted provided that they meet the following conditions:

    - Rash must cover less than 10% of body surface area (BSA).
    - Disease is well controlled at baseline and only requiring low-potency topical steroids.
    - No acute exacerbations of underlying condition within the previous 12 months (not requiring PUVA [psoralen plus ultraviolet A radiation], methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, high-potency or oral steroids).
18. Patients with any contraindication for bevacizumab administration:
    - Inadequately controlled hypertension (defined as systolic blood pressure > 150 mmHg and/or diastolic blood pressure > 100 mmHg).
      Anti-hypertensive therapy to achieve these parameters is allowable.
    - Prior history of hypertensive crisis or hypertensive encephalopathy.

- Significant vascular disease (e.g., aortic aneurysm requiring surgical repair or recent peripheral arterial thrombosis) within 6 months prior to inclusion.
- History of hemoptysis (≥ one-half teaspoon of bright red blood per episode) within 1 month prior to inclusion.
- Evidence of bleeding diathesis or coagulopathy (in the absence of therapeutic anticoagulation).
- Current or recent (within 10 days of inclusion) use of aspirin (> 325 mg/day) or treatment with dipyramidole, ticlopidine, clopidogrel, and clostazol.
- Current use of full-dose oral or parenteral anticoagulants or thrombolytic agents for therapeutic purposes that has not been stable for > 2 weeks prior to inclusion.
  The use of full-dose oral or parenteral anticoagulants is permitted as long as the INR or aPTT is within therapeutic limits (according to the medical standard of the enrolling institution) and the patient has been on a stable dose of anticoagulants for at least 2 weeks prior to inclusion.
  Prophylactic anticoagulation for the patency of venous access devices is allowed, provided the activity of the agent results in an INR < 1.5 × ULN and aPTT is within normal limits within 14 days prior to inclusion.
  Prophylactic use of low-molecular-weight heparin (i.e., enoxaparin 40 mg/day) is permitted.
- Core biopsy or other minor surgical procedure, excluding placement of a vascular access device, within 7 days prior to the first dose of Bevacizumab.
- History of abdominal or tracheoesophageal fistula or gastrointestinal perforation within 6 months prior to inclusion.
- Clinical signs of gastrointestinal obstruction or requirement for routine parenteral hydration, parenteral nutrition, or tube feeding.
- Evidence of abdominal free air not explained by paracentesis or recent surgical procedure.
- Serious, non-healing wound, active ulcer, or untreated bone fracture.
- Proteinuria, as demonstrated by urine dipstick or > 1.0 g of protein in a 24-hour urine collection.
  All patients with ≥ 2+ protein on dipstick urinalysis at baseline must undergo a 24-hour urine collection and must demonstrate ≤ 1 g of protein in 24 hours.
- Known sensitivity to any component of Bevacizumab

7. Patient enrolment

This trial will use a web-based registration and enrolment system (eCRF-Electronic Case Report Form). Each participating centre will access the system directly to enrol patients.

Note that written informed consent has to be obtained from the patient prior to any trial-specific intervention.

Patient eligibility needs to be checked before enrolment of the patient in the Fundación GECP web-based system (eCRF). The dates of the patient signature of the Informed Consent Form and the consent

[redacted]

to pathology material submission section are required to be filled in the eligibility checklist of the eCRF. Neoadjuvant treatment has to start within 1-3 days from inclusion.

8. Trial procedures

8.1. Overview of treatment sequence

8.1.1. Screening/Baseline visit:

[redacted]

8.1.2. Neoadjuvant treatment

Neoadjuvant treatment:

Atezolizumab: 1200 mg, IV infusion

Bevacizumab: 15mg/Kg mg, IV infusion

[redacted]

Carboplatin: AUC6, IV infusion

Pemetrexed: 500 mg/m^2, IV infusion

Treatment sequence:

Atezolizumab ⟹ Bevacizumab ⟹ Carboplatin ⟹ Pemetrexed

[redacted]

NOTE: for squamous or adenosquamous patients, neodjuvant treatment must switch to:

Atezolizumab: 1200 mg, IV infusion

Carboplatin: AUC6, IV infusion

Paclitaxel: 200 mg/m^2, IV infusion

Treatment sequence:

Atezolizumab ⟹ Paclitaxel ⟹ Carboplatin

[redacted]

[redacted]

8.1.3. Surgery

[redacted]

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

[redacted]

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

[redacted]

[redacted]

8.1.4. Adjuvant treatment

[redacted]

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

[redacted]

8.1.5. End of treatment

[redacted]

8.1.6. Follow up visits

[redacted]

9. Investigational Medicinal Product

Atezolizumab and Bevacizumab are the Investigational Medicinal Products (IMP) used in this trial. Roche will provide the IMP at no cost for this trial.

Complete details of the trial drug logistics, distribution, packaging, labelling, storage and handling as well as accountability are described in the ***Neo-DIANA drug supply manual*** that will be provided in the Pharmacy site file to all the participant sites.

[redacted]

Description of the Investigational Medicinal Products

[redacted]

9.1. Packaging and labelling

[redacted]

9.2. Receipt and storage of the IMP

[redacted]

9.3. Unused trial drug supplies

[redacted]

[redacted]

10.Trial treatments description

10.1. ATEZOLIZUMAB

[redacted]

[redacted]

10.2. BEVACIZUMAB

[redacted]

10.3. 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 carboplatin.

Route of administration: Intravenous infusion

[redacted]

Guidelines of Carboplatin administration: According to the standard of each center

10.4. PEMETREXED

[redacted]

Pemetrexed disodium (ALIMTA®, pemetrexed) is a novel pyrrolo[2,3 d]pyrimidine–based folic acid analogue.

Route of administration: Intravenous infusion.

Guidelines of Pemetrexed administration: According to the standard of each center

[redacted]

[redacted]

10.5. PACLITAXEL

Patients will receive Paclitaxel 200mg/m2 administered by IV infusion every 21 days, for 3 cycles during neoadjuvant phase.

Structure: A diterpene whose composition is: 5b, 20-epoxi-1, 2a, 4,7b, 10b, 13a-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.

Guidelines of Paclitaxel administration: Paclitaxel must be administered by infusion over 3 hours in dextrose (D5W) or normal saline (NS). The concentration must not exceed 1.2 mg/ml.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

11.Dose modifications criteria

Reasons for dose modifications (delays/reductions), the supportive measures taken, and the outcomes will be documented in the patient's chart and recorded on the eCRF.

11.1. General Notes Regarding Dose Modification

When several toxicities with different grades of severity occur at the same time, the dose modifications should be according to the highest grade observed.

The investigator may use discretion in modifying or accelerating the dose modification guidelines described below depending on the severity of toxicity and an assessment of the risk versus benefit for the patient, with the goal of maximizing patient compliance and access to supportive care.

Treatment should not be delayed or interrupted for more than 2 weeks during neoadjuvant treatment or more than 6 weeks during the adjuvant treatment. In the event that longer interruptions or delays are required, please contact trial team for assessment of the case.

11.2. ATEZOLIZUMAB dose modifications

[redacted]

[redacted]

[redacted].

11.3. BEVACIZUMAB dose modifications

[redacted]

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

[redacted]

[redacted]

[redacted]

Management of bevacizumab related toxicities

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Surgery and wound healing complications

[redacted]

11.4. CARBOPLATIN and PACLITAXEL dose modifications

[redacted]

[redacted]

DOSE MODIFICATION BASED ON NON-HEMATOLOGICAL TOXICITY CRITERIA

[redacted]

[redacted]

- [redacted]

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

- [redacted]

[redacted]	[redacted]

- [redacted]

[redacted]	[redacted]
Bilirubin Grade 4 (≥10.0 x UNL)	Withdraw the patient from the protocol

OTHER TOXICITIES

[redacted]

HYPERSENSITIVITY REACTIONS

[redacted]

[redacted]

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

[redacted]

[redacted]

- [redacted]
- [redacted]

[redacted]

If [redacted]

[redacted]

[redacted]

Guidelines for the re-initiation of treatment following hypersensitivity reactions

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

[redacted]

[redacted]

[redacted]

[redacted].

11.5. PEMETREXED dose modification

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Non-Hematologic Toxicity

[redacted]

Treatment Delays Caused by Insufficient Folic Acid or Vitamin B12 Supplementation

[redacted]

12.Prohibited and permitted concomitant treatments

[redacted]

[redacted]

Prohibited Concomitant Therapy

[redacted]

Permitted Concomitant Therapy

[redacted]

[redacted]

Cautionary Concomitant Therapy

[redacted]

13.Adverse events and reporting

13.1. Definition of an Adverse Event (AE) and AE's reporting

The main criterion for tolerability is the occurrence of toxicities and Adverse Events (AEs). [redacted]

An adverse event can therefore be any of the following:

Any unfavorable and unintended sign (including an abnormal laboratory finding) (see **NOTE 1** below), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition), except events that are clearly consistent with the expected pattern of the disease progression. These data will be captured as efficacy assessment data

only. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an adverse event.

Recurrence of an intermittent medical condition (e.g., headache) not present at baseline.

Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug.

Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies).

Adverse events that occur during or within 24 hours after study drug administration and are judged to be related to study drug infusion should be captured as a diagnosis (e.g., "infusion-related reaction" or "anaphylactic reaction") on the Adverse Event eCRF. If a patient experiences both a local and systemic reaction to the same dose of study drug, each reaction should be recorded separately on the Adverse Event eCRF. Associated signs and symptoms should be recorded on the dedicated Infusion-Related Reaction eCRF.

A pre-existing medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study (e.g., “more frequent headaches”).

NOTE 1: Abnormal laboratory and vital signs values:

A laboratory test result must be reported as an adverse event if it is a change from baseline and meets any of the following criteria:

Is accompanied by clinical symptoms,

Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation),

Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy,

Is clinically significant in the investigator’s judgment.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating if the test result is above or below the normal range (e.g., "elevated potassium").

A vital sign result must be reported as an adverse event if it is a change from baseline and meets any of the following criteria:

Is accompanied by clinical symptoms,

Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation),

Results in a medical intervention or a change in concomitant therapy,

Is clinically significant in the investigator’s judgment.

[redacted]

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded on the Adverse Event eCRF.

The finding of an elevated ALT or AST ($> 3 \times$ baseline value) in combination with either an elevated total bilirubin ($> 2 \times$ ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury. Therefore, investigators must report as an adverse event the occurrence of either of the following:

Treatment-emergent ALT or AST $> 3 \times$ baseline value in combination with total bilirubin $> 2 \times$ ULN (of which $\geq 35\%$ is direct bilirubin),

Treatment-emergent ALT or AST $> 3 \times$ baseline value in combination with clinical jaundice.

This abnormal laboratory values related to the liver function should be recorded on the Adverse Event eCRF and reported immediately as a SAE (AESI).

The severity will be classified according to the NCI CTCAE Version 5.0. The CTCAE is available for downloading on the internet (see appendix 1).
The AE severity grade provides a qualitative assessment of the extent or intensity of an AE, 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

However, depending on the SAE term, there is some AE that do not have all the grades (e.g., the SAE term Alopecia only has the Grade 1 and 2).

The causal relationship to study drug is determined by the physician and should be used to assess all 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.

About the AEs that have to be recorded in the eCRF note that:

- Baseline symptoms will be recorded on the eCRF and changes and updates in grade as well as resolution of an AE during treatment have to be reported,
- An AE has to be reported for each SAE notified,
- AEs should not be reported in a narrative description.

AEs 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).

Any AE must be reported by an entry in the eCRF within 5 days of awareness, even if they do not meet the whole information. The diagnosis of the event should be recorded as AE term. If there is a secondary AE separated in time from the initiating event, it should be recorded as an independent event (e.g., if vomiting results in severe dehydration, both events should be reported separately).

13.2. Definition of Serious Adverse Event (SAE) and Suspected Unexpected Serious Adverse Reaction (SUSAR)

A Serious Adverse Event (SAE) is defined in general as any undesirable medical occurrence/adverse drug experience that occurs from the subject's written consent to participate in the study through **100** days after the final administration of the IMP, regardless of whether it is considered related or not to the study drug and that, or immediately before initiation of any other anticancer therapy, whichever comes first, and results in any of the following:

- results in death (fatal),
- is life-threatening (defined as an event in which the participant 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 was more severe),
- requires inpatient hospitalization or causes prolongation of existing hospitalization (see **NOTE 2** below),
- 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 (e.g., medical, surgical, laboratory abnormal parameters…) to prevent one of the other serious outcomes listed in the definition above (see **NOTE 3** below),

After informed consent has been obtained, but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies, discontinuation of medications) should be reported.

Seriousness is based on patient/event outcome or action criteria usually associated with events that pose a threat to a patient's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations

NOTE 2: The following hospitalizations are not considered SAEs:

- A visit to the emergency room or other hospital department < 24 hours, that does not result in admission, except if it is considered as an important medical event or life- threatening,
- elective surgery, planned prior to signing consent,
- routine health assessment requiring admission for baseline/trending of health status (e.g., routine colonoscopy),
- admissions as per protocol for a planned medical/surgical procedure,
- admission for administration of anticancer therapy in the absence of any other SAEs,
- admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g., lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason),
- progression of disease. By convention, clinical events related to the primary cancer being studied or to the primary cancer progression are not to be reported as SAEs, even if they meet any of the seriousness criteria from the standard SAE definition, unless the event is more severe than expected and therefore the investigator considers that their clinical significance deserves reporting.

NOTE 3: Any laboratory abnormalities should be documented as a SAE if:

- Intensive treatment in an emergency room or at home for allergic bronchospasm is needed,
- Blood dyscrasias or convulsions that do not result in hospitalization,
- Any untoward event related, and unexpected, to the protocol procedures,
- The laboratory test result is clinically significant or meets the definition of a SAE,
- The laboratory abnormality required the participant to have study drug discontinued or interrupted,
- The laboratory abnormality required the subject to receive specific corrective therapy.

A SAE report should be completed for any event where doubt exists regarding its seriousness. Although overdose, pregnancy, AESI (e.g., potential drug-induced liver injury (DILI)), important medical event, and cancer (secondary malignancy) are not always serious by regulatory definition, these events must be handled as SAEs. If applicable, SAEs must be collected that relate to any later protocol-specified procedure (e.g., a follow-up skin biopsy).

[redacted]

If the investigator believes that a SAE is not related to study drug but is potentially related to the conditions of the study (such as withdrawal of previous therapy or a complication of a study procedure), the relationship should be specified in the narrative section of the SAE Report Form and an important medical event would be the seriousness.

All deaths that occur during the reporting period that are clearly the result of disease progression should not be reported as a SAE, but they should be collected as an AE. All deaths where it is not due to disease progression and deaths with an unknown cause should always be reported as a SAE.

Death should be considered as an outcome and not the event, the AE causing the death must be reported as the SAE term. The term "sudden death" should be used only for the occurrence of an abrupt and unexpected death due to presumed cardiac causes in a patient with or without preexisting heart disease, within 1 hour after the onset of acute symptoms or, in the case of an unwitnessed death, within 24 hours after the patient was last seen alive and stable. If the cause of death is unknown and cannot be ascertained at the time of reporting, "Death due to Unknown Cause" should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), the event should be replaced by the established cause of death.

If the SAE is considered as related to the study drug by the Principal Investigator, it is a Serious Adverse Reaction. The SAR is assessed by the Fundación GECP (SLCG/GECP) to know if it is expected. A SAR that is not listed as a known toxicity of the investigational drug in the summary of product characteristics (Investigator Brochure or Data Sheet) will be considered as a Suspected Unexpected Serious Adverse Reaction (SUSAR). The sponsor will inform to the Principal Investigator that this SAE has been considered as a SUSAR. In Spain, Health authority (AEMPS: Agencia Española del Medicamento y Productos Sanitarios) will also be informed about all SUSARs via EudraVigilance.

13.3. Adverse events of Special Interest for Atezolizumab (Immediately reportable to the Sponsor)

[redacted]

[redacted]

13.4. Overdose and secondary malignancies

[redacted]

13.5. SAEs and SUSARs reporting

[redacted] Any SAE must be reported by submitting the completed Initial SAE Form in the online eCRF within 24 hours of awareness, even if they do not meet any of the seriousness criteria.

In case of the eCRF is unavailability, the submission could be done by sending the SAE form preferably by email to [redacted] An appropriate SAE form (see appendix 3) should be used to report SAEs to Fundación GECP (SLCG/GECP). The paper SAE form has to be sent within the timeline period for reporting of 24 hours of awareness. **Once the eCRF system is available again, the SAE has to be completed and submitted by the site into the eCRF**.

[redacted]

If only limited information is initially available, a follow-up report is required to complete the information as soon as possible. (Note: Follow-up SAE reports should include the same SAE term(s) initially reported.)

The SAE outcome must be reported within 14 days after initial reporting by submitting the Follow up SAE Form in the online eCRF. In case the SAE is reported as ongoing after 14 days, a follow-up report has to be submitted again with the final outcome.

If an ongoing SAE changes in its grade, relationship to study drug, seriousness, SAE term or if new information becomes available, a new follow-up SAE report should be sent within 24 hours to the Fundación GECP (SLCG/GECP) using the same procedure after described.

Any SUSAR occurred during the trial will be notified under Spanish clinical regulation to the principal investigators, to the Health Authority (AEMPS) via Eudravigilance within the timelines specified in the Royal Decree 1090/2015 on clinical trials regarding the recording, evaluation and reporting of adverse events. Also, the autonomous regions will be informed about all SUSARs according to the current Spanish clinical trial regulation.

[redacted]

[redacted]

[redacted]

13.6. Pregnancy

If, following initiation of the investigational product, it is subsequently discovered that a study participant is pregnant or may have been pregnant at the time of investigational product exposure, within 5 months after the last dose of atezolizumab and/or bevacizumab, or within 6 months after the last dose of atezolizumab and/or bevacizumab, the investigational product will be permanently discontinued in an appropriate manner (e.g., dose tapering if necessary for participant).

Any pregnancy that occurs in a female partner of a male study participant should also be reported to the Fundación GECP (SLCG/GECP). Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if his partner becomes pregnant during the chemotherapy treatment period or within 6 months after the last dose of chemotherapy. In order for Fundación GECP (SLCG/GECP) or designee to collect any pregnancy surveillance information from the female partner, the female partner must sign an informed consent form for disclosure of this information.

[redacted]

[redacted]

[redacted]

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information, study discontinuation must be reported following the before procedure described during at least 1 year after child-bearing.

Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) or abortion should be reported as a SAE.

13.7. 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 non-serious or serious AE, as appropriate, and reported accordingly.

Reference Safety information:

- Atezolizumab: Investigator Brochure
- Bevacizumab: Investigator Brochure
- Carboplatin: SmPC
- Pemetrexed: SmPC
- Paclitaxel: SmPC

13.8. Adverse events related to the treatment and associated risks

ATEZOLIZUMAB

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

BEVACIZUMAB

[redacted]

[redacted]

CARBOPLATIN

[redacted]

PEMETREXED

[redacted]

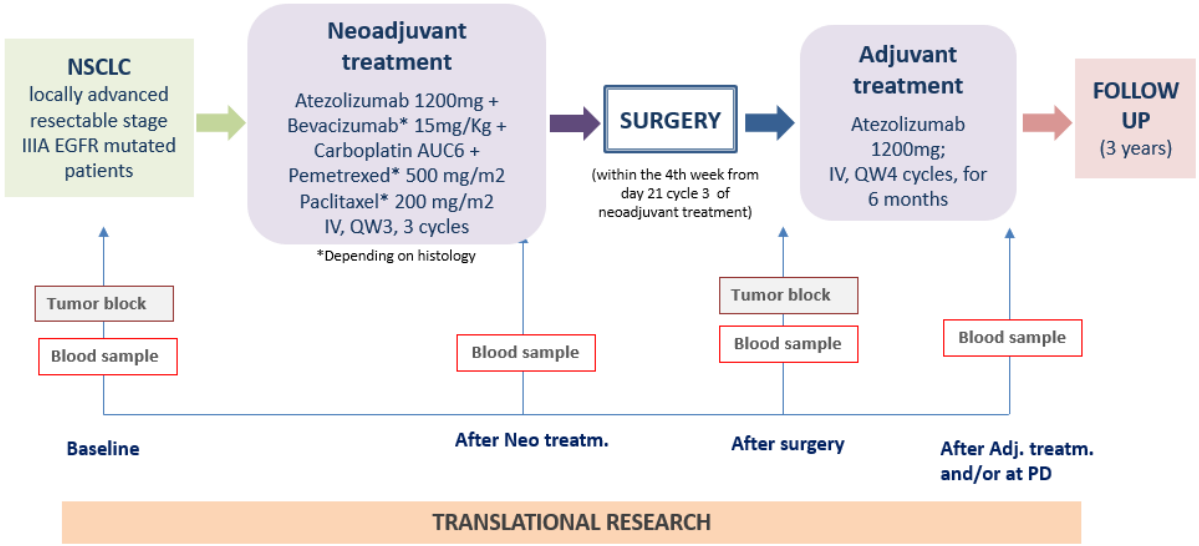
[redacted]

PACLITAXEL

[redacted]

14.Biological material and translational research

Figure 1. Study schema



[redacted]

- [redacted]
- [redacted]

[redacted]

15.Case report forms and documentation

eCRFs will only be available on-line at the Remote Data Entry (RDE) facility of Fundación GECP for patient enrolment.

Also, another exception will be a paper SAE form and pregnancy form that will be used only in case of eCRF system unavailability.

16.Statistical considerations

To find a 40% of MPR vs a theorical reference equals to 10.7% in patients with EGFR mutation NSCLC stage IIIA, with an 80% of power and alpha level of 0.05, 22 patients are needed. If we expect a 15% of losses of follow-up, 26 patients with EGFR mutation and NSCLC stage IIIA will be necessary. Thus, considering a prevalence of EGFR mutation of 15% in patients with NSCLC stage IIIA, 174 patients NSCLC stage IIIA should perform the test to check the presence of EGFR mutation.

It is expected that approximately the 15% 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 the 15% is exceeded because 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 will be the one calculated initially.

The analysis will be conducted according to the intention-to-treat (ITT) principle. Descriptive analysis will be performed by means of absolute and relative frequencies for categorical variables and mean and standard deviation, or median and percentiles 25 and 75 for numerical variables.

The main analysis asses the response rate after the neoadjuvant therapy plus surgery. Response rates will be estimated along with their corresponding 95% confidence interval and then compared with other variables through a chi-square test or Fisher exact test if expected frequencies are less than or equal to 5. Effect size will be estimated by means of logistic regression analysis through the Odds Ratio (OR) as well as their corresponding confidence interval (95%CI).

Progression free survival (PFS) is set as a secondary outcome. Survival function will be estimated by the Kaplan-Meier method. Cox proportional hazards model, will be used to estimate potential risk factors, along with the Hazard Ratios (HR) and 95% confidence intervals.

Reported p values will be two-sided, and the significance level will be set at 5% (0.05) for all analyses unless otherwise noted. Stata v15.1 software (StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC) will be used for statistical analyses.

17.Criteria for termination of the trial

17.1. General criteria for termination of the trial

The trial may be discontinued early in parts or completely if the information on the product leads to doubt as to the benefit/risk ratio, by decision Trial Steering Committee of Fundación GECP, or at the suggestion of the IDMC/DSMB.

The trial can be terminated at any time if the authorization and approval to conduct the study is withdrawn by ethics committee or regulatory authority decision, insufficient accrual, emerging new data impacting the scientific value of the trial or on ethical grounds.

17.2. Discontinuation of protocol treatment and from the study for individual patients

Patients may be withdrawn from the protocol treatment and from the study in the following situations:

- Occurrence of unacceptable toxicities. Stopping protocol treatment is determined by medical judgment of the treating physician.
- Disease progression per investigator assessment according to RECIST v1.1
- Inter-current severe illnesses which would in the judgment of the investigator affect assessments of the clinical status to a significant degree and require discontinuation of protocol therapy
- Request by the patient. Patients have the right to refuse further trial treatment at any time during the trial. Such patients will remain in the trial and will be transferred to the follow-up phase.
- If a patient refuses to have follow-up examinations and tests needed to determine whether the treatment is safe and effective
- Protocol non-compliance or study termination by sponsor or site closure by the sponsor (poor protocol adherence, inaccurate or incomplete data recording…)
- Pregnancy
- Patient non-compliance, defined as a failure to comply with the protocol requirements as determined by the protocol

The decision for discontinuation of protocol treatment and the study of individual patients is taken by the treating physician based on his medical evaluation and taking into account the patient's individual situation.

Specific reasons for trial discontinuation where further collection of data is not allowed are: 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.

The primary reason for the treatment and study discontinuation should be documented on the appropriate form of the eCRF.

18.Ethics aspects, regulatory approval, and Patient Informed Consent

The Investigator will ensure that this study is conducted in full conformance with the principles of the "Declaration of Helsinki" or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study must fully adhere to the principles outlined in "Guideline for Good Clinical Practice" ICH6 Tripartite Guideline (January 1997) or local Spanish law. For studies conducted in the EU/EEA countries, the Investigator will ensure compliance with the EU Clinical Trial Directive (2001/20/EC).

18.1. Ethical Review Board/Ethics Committee/Health Authority

All protocols and the patient informed consent form must have the approval of a properly constituted committee or committees responsible for approving clinical trials. The Ethic Committee decision must contain approval of the designated investigator, the protocol (identifying protocol title and version number), and of the patient informed consent.

The Ethic Committee written, signed approval letter/form must contain approval of the designated investigator, the protocol (identifying protocol title and version number), and of the patient informed consent.

Any modifications made to the protocol must be submitted to the appropriate Ethic Committee for information or approval in accordance with local procedures and regulatory requirements and to Health Authorities if required.

Once approved or acknowledged by the appropriate ERB/IRB and by the Health Authorities (if required), the investigator shall implement the protocol modifications.

If applicable, in addition to the approval of the Ethics Committee according to national legislation, the protocol, other protocol related documents including patient information and informed consent and other documents as required locally must be submitted to and be approved by the health authority.

18.2. Informed consent

The Informed consent will be obtained prior to initiating any trial procedures in each patient. Once signed and dated, a copy of the informed consent must be given to the patient and the original copy

must be retained in the investigator's site file. The informed consent form must be available in case of audits.

The "Declaration of Helsinki" recommends that consent be obtained from each potential patient in biomedical research trials after the aims, methods, anticipated benefits, and potential hazards of the trial, and discomfort it may entail, are explained to the individual by the physician. The potential patient should also be informed of her/his right to not participate or to withdraw from the trial at any time. The patient should be told that material from her/his tumor and blood samples will be stored and potentially used for additional studies not described in this protocol.

If the patient is in a dependent relationship to the physician or gives consent under duress, the informed consent should be obtained by an independent physician. It is preferable that the patient who gives the consent signs the form but if it is not possible or if the patient is legally incompetent (i.e., a minor, or mentally incompetent), informed consent must be obtained from the parent, legal guardian, or legal representative in accordance with the law of the country in which the trial is to take place.

By signing this protocol, the investigator agrees to conduct the trial in accordance with Good Clinical Practice and the "Declaration of Helsinki".

The template Patient Information Sheet and Informed Consent has been written according to ICH guidelines which state the Informed Consent should adhere to GCP and to the ethical principles that have origin in the "Declaration of Helsinki" and also, according to the Spanish Health Authority recommendations.

19.Governance and administrative issues

19.1. Study documentation

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including, but not limited to, the protocol, protocol amendments, Patient Information Sheet and Informed Consent Forms, and documentation of IRB/EC and Health Authority approval.

19.2. Protocol non-compliances/deviations

The investigator should document and explain any protocol non-compliances/deviations. [redacted]

[redacted]

19.3. Protocol amendment

Any protocol amendments will be prepared by the Sponsor. Protocol amendments will be submitted to the IRB/EC and to regulatory authorities in accordance with local regulatory requirements. Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (e.g., change in Medical Monitor or contact information).

19.4. Final report

A final clinical trial report will be written and distributed to the Ethic committees and Health Authorities as required by applicable regulatory requirements.

19.5. Independent Data Monitoring Committee

The trial will be presented periodically for review to the Fundación GECP Independent Data Monitoring Committee (IDMC/DSMB).

19.6. Publication

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

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

19.7. Financial disclosure

Investigators will provide the sponsor with enough, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

19.8. Clinical trial insurance

A civil responsibility policy for subjects participating in a clinical trial has to be contracted. Fundación GECP will contract the appropriate liability insurance for this trial. Patients who suffer injuries due to the trial should report them immediately to their physician.

[redacted]

19.9. Quality assurance

Fundación GECP conducts trials according to the ICH Good Clinical Practice (GCP) guidelines. The Trial Data Manager and the monitors (CRA) review each eCRF as per monitoring plan schedule.

Fundación GECP will conduct periodic triggered visits to the participating sites to ensure proper trial conduct, verify compliance with GCP, and perform source data verification.

The Investigator should ensure that source documents are made available to appropriately qualified personnel from Fundación GECP, or to ethics committee and health authority inspectors if needed, after appropriate notification.

At regular intervals during the clinical trial, the centre will be contacted, through monitoring visits, letters or telephone calls, by a representative of the Monitoring Team to review study progress, investigator and patient compliance with clinical trial protocol requirements and any emergent problems. These monitoring visits will include but not be limited to review of the following aspects: patient informed consent, patient recruitment and follow-up, SAE documentation and reporting, AEs with pre-specified monitoring documentation and reporting, AE documentation, dispensing IMP, compliance with protocol, drug accountability, concomitant therapy use, quality of data and storage of blood samples.

19.10. Data protection

The samples and data collected will be coded to protect patient confidentiality. Each patient will have a pre-screening number at the pre-screening phase to identify the biological material and a unique identifier assigned by the eCRF of the study once enrolled. Sites are responsible to keep a patient log locally in order to be able to link the pre-screening number and the unique identifier to the record of the patient.

No identifiable / personal data will be stored in the trial database or the tissue and blood repositories in the central laboratory.

Regulatory authorities and pertinent Ethics Committees (IRB/ERB) may have access to patient data on-site. Fundación GECP audit or monitoring personnel will also have access to such data on-site.

To ensure the patient confidentiality of data applies from the 25th of May 2018 the Reglamento (UE) 2016/679 del Parlamento europeo y del Consejo de 27 de abril de 2016 de Protección de Datos (RGPD) and in Spain it is regulated by the Organic Law 3/2018, 5th of December, on Personal data protection and digital rights guarantee.

19.11. Study monitoring team

The Fundación GECP will be responsible for monitoring the trial at all the participant sites.

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 persons will be:

[redacted]
Fundación GECP CRA
Meridiana 358, 6ª planta
08027 Barcelona
[redacted]

[redacted]

[redacted]

19.12. Record retention

The centre must retain all essential documents according to ICH GCP. This includes copies of the patient trial records, which are considered as source data, patient informed consent statement, laboratory printouts, drug inventory and destruction logs, and all other information collected during the trial. These documents are to be stored until at least 25 years after the termination of the trial.

In the event that the Principal Investigator retires or changes employment, custody of the records may be transferred to another competent person who will accept responsibility for those records. Written notice of such transfer must be given to the Fundación GECP and the local Ethics Committee at least 1 month in advance.

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Appendices:

1. Common Terminology criteria for Adverse Events (CTCAE)
2. RECIST criteria v1.1
3. SAE Form
4. Pregnancy Form
5. System of classification for non-microcytic lung cancer (NSCLC) and definition of lymph node maps, 8th edition
6. Risks associated with Atezolizumab and guidelines for management of adverse events associated with Atezolizumab

[redacted]

APPENDIX 1. Common Terminology criteria for Adverse Events (CTCAE)

Version 5.0: November 27, 2017 is available from the internet at:

https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf

APPENDIX 2. RECIST criteria v1.1

1. Introduction

All included patients will be evaluated for response according to the revised Response Evaluation Criteria In Solid Tumors (RECIST version 1.1) [1]. This appendix defines all criteria applied in this trial.

2. Methods of assessment

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.

CT is the best currently available and reproducible method to measure lesions selected for response assessment. CT should generally be performed using a ≤ 5 mm contiguous reconstruction algorithm. **MRI** is acceptable for certain situations, e.g. body scans.

Clinical lesions will only be considered measurable when they are superficial (e.g. skin nodules) and ≥10 mm. In the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is recommended.

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

Ultrasound is not useful in assessment of lesion size and is not accepted as method of assessment.

FDG-PET is not foreseen for regular response assessments. It may, however, be used to detect or confirm the appearance of new lesions. Attenuation correction CT scans performed as part of a **PET/CT** scan frequently show lower resolution; therefore, dedicated CT scans are preferred. However, if the site can demonstrate that the CT performed as part of a PET/CT is of the same diagnostic quality as a diagnostic CT (with IV and oral contrast), then the CT portion of the PET/CT can be used for RECIST measurements.

3. Measurability of tumor at baseline

Measurable disease is defined as the presence of at least one measurable lesion.

Measurable lesions:

- **Tumor lesions** must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of
    - 10 mm by CT scan (CT scan slice thickness no greater than 5mm)
    - 10mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable)
    - 20 mm by chest X-ray
- **Malignant lymph nodes:** to be considered pathologically enlarged and measurable, a lymph node must be ≥ 15mm in *short* axis when assessed by CT scan, assuming the slice thickness is ≤ 5 mm. At baseline and in follow-up, only the *short* axis will be measured.

Non-measurable lesions: all other lesions, i.e.:

- Small non-nodal lesions (longest diameter < 10 mm in CT scan)
- Small lymph nodes (short axis ≥ 10 and < 15 mm). Lymph nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followedBone lesions. Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above. Blastic bone lesions are non-measurable.
- Leptomeningeal disease
- Ascites
- Pleural or pericardial effusion
- Inflammatory breast disease
- Lymphangitic involvement of skin or lung
- Cystic lesions. Cystic lesions thought to represent cystic metastases may be considered as measurable lesions. However, if non-cystic lesions are present, these are preferred as target lesions
- Tumor lesions situated in a previously irradiated area, or subjected to other locoregional therapy. Such lesions may be considered measurable if there has been demonstrated progression in the lesion
- abdominal masses/abdominal organomegaly identified by physical exam that are not measurable by reproducible imaging techniques

4. Selection of lesions

4.1. Selection of target lesions

At baseline, measurable lesions up to a maximum of 5 lesions representative of all involved organs, and up to 2 per organ, should be identified as target lesions and measured and recorded. Target lesions (TL) should be selected on the basis of their size and their suitability for accurate repetitive measurements. A sum of diameters for all target lesions will be calculated and reported as the baseline sum of diameters. Lymph nodes selected as TL should always have the short axis recorded. All other lesions should always have their longest diameters recorded. The sum of diameters will be used as

reference to further characterize the objective tumor response of the measurable dimension of the disease.

4.2. Selection of non-target lesions

All other lesions (or sites of disease) should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required, but the presence or absence of each should be noted throughout follow-up. It is possible to record multiple non-target lesions as a single item on the CRF (e.g. "multiple liver metastases").

5. Evaluation of Lesions

5.1. Evaluation of Target Lesions

All target lesions will be measured at each tumor assessment, and the sum of their diameters will be compared to previous assessments in order to assign the response status as specified below.

- Complete Response (CR): Disappearance of all target lesions. Lymph nodes selected as target lesions must each have reduction in the short axis to < 10 mm in order for the response to be considered complete. In this case, the sum of diameters may be > 0.
- Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions taking as reference the baseline sum of diameters.
- Progression (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum recorded on study. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.
- Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as reference the smallest sum of diameters recorded on study.
- Inevaluable for response: specify reasons (for example: early death due to malignant disease or toxicity; tumor assessment not repeated/incomplete; other, specify).

Note: All target lesions, including lymph nodes, should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g. 2 mm). If the radiologist does not feel comfortable assigning an exact measure and reports a lesion as "too small to measure", a default value of 5 mm should be recorded. If a TL is thought likely to have disappeared, "0 mm" is noted.

5.2. Evaluation of Non-Target Lesions

- Complete Response (CR): Disappearance of all non-target lesions; lymph nodes selected as non-target lesions must be non-pathological in size (< 10 mm).
- Non-CR/non-PD: Persistence of one or more non-target lesions (non-CR).
- Progression (PD): unequivocal progression of existing non-target lesions. Unequivocal means: comparable in magnitude to the increase that would be required to declare PD for measurable disease, or an overall substantial increase in tumor burden that merits treatment discontinuation.

[redacted]

5.3. Determination of new lesions

The appearance of any new malignant lesions denotes disease progression. The finding of a new lesion should be unequivocal, i.e. not attributable to differences in scanning technique or findings thought to represent something other than tumor. If a new lesion is equivocal, e.g. because of its small size, the patient will stay on treatment (if the decision on PD is based on this lesion only). If the repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the previous scan.

Lesions found in a new location not included in the baseline scan (e.g. brain metastases) are considered new lesions.

Note: the "re-appearance" of a previously "disappeared" target or non-target lesion does not in itself necessarily qualify as PD; this is the case only if the overall evaluation meets the PD criteria, or if the patient was previously in CR.

5.4. Additional considerations

In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends upon this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before confirming the complete response status.

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

6. Determination of time point response

Based on the responses of Target Lesions, Non-Target Lesions, and the presence or absence of new lesions, the overall response will be determined at each tumor assessment time point, according to the table below:

Target lesions	**Non-target lesions**	**New lesions**	**Overall response**
CR	CR	No	CR
CR	Non-CR / non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD

Not all evaluated	Non-PD	No	NE (unless the sum of diam. Of evaluated lesions indicates PD[1])
PD	Any	Yes or no	PD
Any	PD	Yes or no	PD
Any	Any	Yes	PD

[1] From ref. 1 p.234: When no imaging/measurement is done at all at a particular time point, the patient is not evaluable (NE) at that time point. If only a subset of lesion measurements are made at an assessment, usually the case is also considered NE at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would be most likely to happen in the case of PD. For example, if a patient had a baseline sum of 50mm with three measured lesions and at follow-up only two lesions were assessed, but those gave a sum of 80 mm, the patient will have achieved PD status, regardless of the contribution of the missing lesion.

7. Determination of best overall response

Best overall response is defined as best response across all time points. Confirmation of partial or complete response by an additional scan is not requested in this trial. Best overall response will be determined by central review.

8. References

1. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D, Verweij J. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). EurJ Cancer 2009;45(2):228-47.

[redacted]

APPENDIX 3. SAE Form

SAEs will be reported in the eCRF. Only in the case that it is not working the paper form will be used.

See the form attached

APPENDIX 4. Pregnancy Form

Pregnancies will be reported in the eCRF. Only in the case that it is not working the paper form will be used.

See the form attached

[redacted]

APPENDIX 5. System of classification for non-microcytic lung cancer (NSCLC) and definition of lymph node 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.

[redacted]

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**

APPENDIX 6. Risks associated with Atezolizumab and guidelines for management of adverse events associated with Atezolizumab

Please see current version of the Atezolizumab's IB.