# NIVOTAX Statistical Analysis Plan

## Phase II multicenter randomized trial to assess the efficacy and safety of first line nivolumab in combination with paclitaxel in subjects with R/M HNSCC unable for cisplatin-based chemotherapy (NIVOTAX)"

**NCT: NCT04282109**

**Date: 21-Oct-2022**

# "Phase II multicenter randomized trial to assess the efficacy and safety of first line nivolumab in combination with paclitaxel in subjects with R/M HNSCC unable for cisplatin-based chemotherapy (NIVOTAX)"

## NIVOTAX Study

## APICES Project No. TTC277007

## Statistical Analysis Plan

**Version 1.0**
**October 21st, 2022**

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Clinical Research Support in Europe

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# 1. HISTORY OF REVISION (Documentation of changes)

| SECTIONS | VERSION | DATE REVISED | REVISED BY | DESCRIPTION OF CHANGES |
|---|---|---|---|---|
| 5.3 | 0.1 | 19-Sep-2022 | Carmen Montalbán | Figure 1 modified |
| 6.2 | 0.1 | 19-Sep-2022 | Carmen Montalbán | Variable analysis G8 added. ECOG-PS calculation added, definition variables modified |
| 7.1; 7.2; 7.3 | 0.1 | 19-Sep-2022 | Carmen Montalbán | Definitions added/ modified |
| 7.4 | 0.1 | 19-Sep-2022 | Carmen Montalbán | Section added |
| 9.4 | 0.1 | 19-Sep-2022 | Carmen Montalbán | New variable added to listing |
| 9.5 | 0.1 | 19-Sep-2022 | Carmen Montalbán | Abbreviatures meaning added (SOC & PT) |
| 9.6 | 0.1 | 19-Sep-2022 | Carmen Montalbán | Section suppressed |

# INDEX

# 2. INTRODUCTION

This statistical analysis plan (SAP) describes the final statistical analysis for NIVOTAX study.

# 3. SYNOPSIS

## 3.1. Study title

Phase II multicenter randomized trial to assess the efficacy and safety of first line nivolumab in combination with paclitaxel in subjects with R/M HNSCC unable for cisplatin-based chemotherapy (NIVOTAX).

## 3.2. Study Code

TTCC-2019-01 / CA209-7HE

## 3.3. Protocol

Previous protocol versions / amendments (number and date):

- 1.0 dated on November 18th, 2019.
- 2.0 dated on March 3rd, 2020.
- 3.0 dated on July 10th, 2020.

Current version (number and date):

- 4.0 dated on November 4th, 2021.

## 3.4. Sponsor

Grupo Español de Tratamiento de Tumores de Cabeza y Cuello (TTCC).

## 3.5. Design and study treatment

This is a randomized, open-label, controlled, multicenter, phase II trial to assess the efficacy of nivolumab plus paclitaxel for first-line treatment of recurrent or metastatic HNSCC in the platinum ineligible and platinum refractory settings.

Approximately 141 subjects will be randomized to the two treatment arms in a 2:1 ratio (94 in experimental arm and 47 in control arm) and stratified by the following factors:

1. Karnofsky performance status (70% vs 80-100%).
2. CPS ≥1 vs < 1 (DAKO PD-L1 IHC 22C3) (see annex 12 of protocol v4.0). PD-L1 determination (CPS, before patient inclusion) will be performed by a central lab (Pathological Anatomy Service, Hospital 12 de Octubre, Madrid, Spain).

3. Oropharyngeal cancer: oropharyngeal cancer HPV+ (p16 IHC & HPV DNA) vs oropharyngeal cancer HPV–(p16 IHC/ HPV DNA) / non-oropharyngeal cancer).

HPV status of tumor tissue has to be locally determined at screening by any of the following methods: p16 IHC, in situ hybridization or polymerase chain reaction-based assay. If HPV status by p16 IHC is positive, result confirmation by PCR is mandatory.

HPV p16 status (OPC), PD-L1 status (CPS) and Karnofsky performance status will be needed prior to randomization. Subjects will undergo screening evaluations to determine eligibility prior to randomization.

Once enrolled in the study, patients will be randomized in a 2:1 ratio to receive:

- **Arm 1 (experimental)**: **NIVOTAX** (Combination of nivolumab + paclitaxel, follow by maintenance with nivolumab).

Combination treatment: Nivolumab 240 mg will be administered via IV infusion every 2 weeks. Paclitaxel 80mg/m$^2$ will be administered via IV infusion weekly. After 12 weeks from the start of the combined treatment paclitaxel will be stopped.

Maintenance treatment with nivolumab 480 mg every 4 weeks will start two weeks after the last administration of nivolumab 240 mg. Once nivolumab is administered at 480 mg, paclitaxel can no longer be administered.

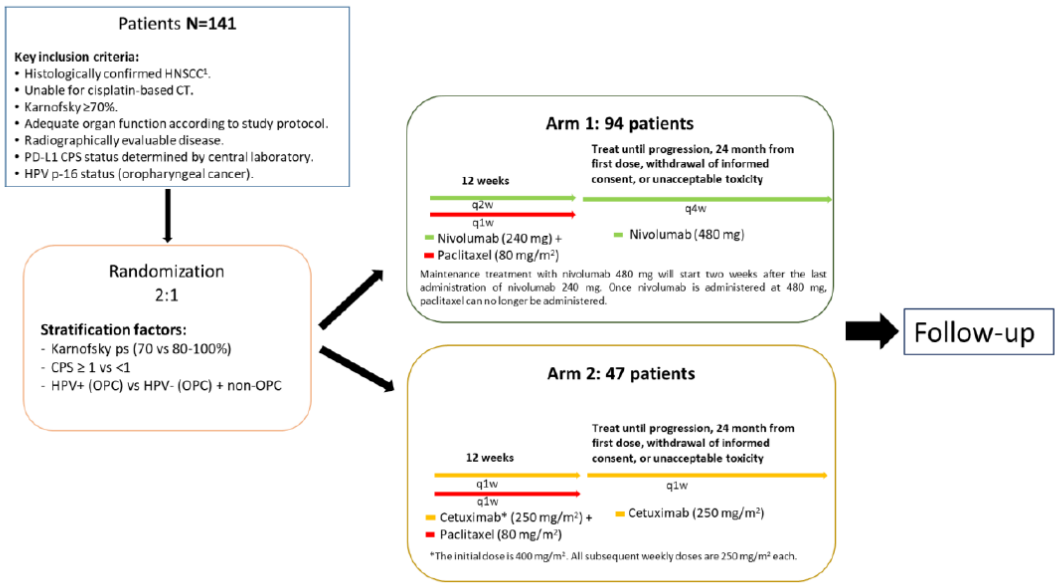
Nivolumab will be continued alone until disease progression, unacceptable toxicity, or withdrawal of consent up to a maximum of 24 months.

- **- Arm 2 (standard): ERBITAX** (Combination of cetuximab + paclitaxel follows by maintenance with cetuximab).

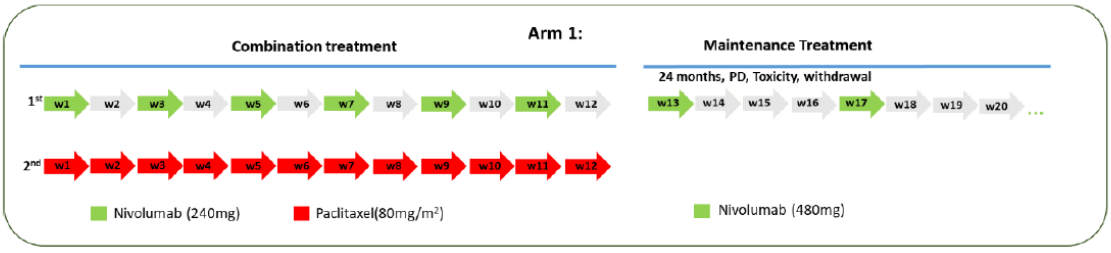
Combination treatment: Cetuximab 250 mg/m$^2$ (first dose of 400 mg/m$^2$) administered via IV infusion weekly plus weekly paclitaxel (80 mg/m$^2$) administered via IV infusion.

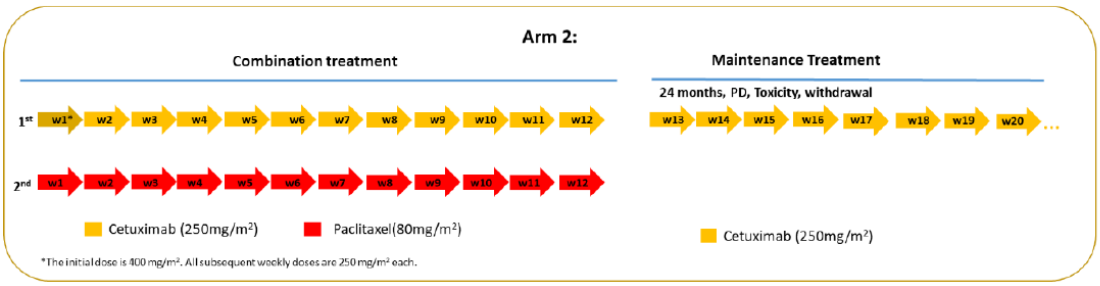
After 12 weeks from the start of the combined treatment paclitaxel will be stopped and weekly cetuximab will be continued alone until disease progression, unacceptable toxicity, or withdrawal of consent up to a maximum of 24 months.

## Study Scheme




## Study Treatment



## 3.6. Objectives

Primary objective:

- Primary objective of this study is to assess the efficacy of nivolumab plus paclitaxel, in terms of two years overall survival (OS), for first-line treatment of recurrent or metastatic HNSCC in the platinum ineligible and platinum refractory settings.
  OS is defined as the time between the date of randomization and the date of death. For subjects without documentation of death, OS will be censored on the last date the subject was known to be alive.

Secondary objectives:

- To evaluate the efficacy of Nivolumab with paclitaxel in patients with recurrent or metastatic HNSCC in the platinum ineligible and platinum refractory settings by:
  - Progression free survival (PFS).
  - Overall response rate (ORR) using Response Evaluation Criteria In Solid Tumors (RECIST 1.1) as determined by investigator criteria.
  - Disease control rate (DCR).
  - Duration of response (DoR).
  - Rate of progressive disease at 6 months.
  - Five years Overall Survival (5y-OS).
- To evaluate the efficacy of study treatment in patients ≥ 70 years and according to G8 result.
- To evaluate efficacy (ORR, PFS, OS) based on: PDL1 expression measured by Combined Positive Score (CPS), Presence of Human Papilomavirus (HPV) in Oropharynx Carcinoma (OPC), cisplatin refractory, cisplatin ineligibility and Karnofsky Performance Status Scale.
- To evaluate safety profile of Nivolumab with paclitaxel by:
  - Percentage of patients with AEs.
  - Percentage of patients with Grade 3 and Grade 4 AEs.
  - Percentage of patients with SAEs.
  - Percentage of patients who discontinued due to AEs.
  - Percentage of patients with each AE by grade.

## 3.7. Inclusion Criteria

Each patient must meet all the following inclusion criteria to be enrolled in the study:

1. Voluntary written consent must be given before performance of any study-related procedure not part of standard medical care.
2. Histologically confirmed HNSCC (oral cavity, oropharynx, hypopharynx, larynx) not amenable to therapy with curative intent (surgery or radiation therapy with or without chemotherapy).
3. Patients not previously treated for recurrent/metastatic disease.
4. Radiographically measurable disease as defined by RECIST version 1.1. Previously irradiated lesions can only be considered as measurable disease if disease progression according to RECIST version 1.1.
5. Patients unable for cisplatin-based chemotherapy, defined "unable" by:
    a. Karnofsky 70% or
    b. Karnofsky 80-100% and amenable to chemotherapy, but:
        1) Impaired renal function, creatinine clearance >30 mL/min and <80 mL/min GFR could be assessed by direct measurement (EDTA or creatinine clearance) if available or by calculation from serum or plasma creatinine (see annex 5), or
        2) grade ≥2 hearing loss, according to the NCI CTCAE v 5.0, or
        3) Class III heart failure according to the New York Heart Association (annex 9), or
        4) History of allergic reactions to cisplatin, carboplatin, or other platinum-containing compounds or
        5) Prior dose of cisplatin ≥225 mg/m² for locally advanced disease (a patient who received prior RT + 3 cycles of cisplatin 100 mg/m2 or 3 cycles induction TPF (with cisplatin ≥75/m2) for locally advanced primary HN cancer can be included), or
        6) Disease progression or relapse during or within 6 months of receiving platinum-based therapy administered as neoadjuvant, adjuvant therapy or as concomitant chemotherapy with radiotherapy and have received at least 200 mg/m2 of cisplatin.
6. Male or female patients aged ≥18 years.

    Patients aged ≥70 years old can only be included with a G8 (Geriatric 8) (see protocol annex 10) health status screening score ≥ 14.

    **a. Female patients:**

    i. Are postmenopausal for at least 1 year before the Screening visit, or
    ii. Are surgically sterile, or
    iii. If they are of childbearing potential, agree to practice one highly effective method of contraception and one additional effective (barrier) method, at the same time, from the time of signing the informed consent through 180 days after the last dose of study drug, or

iv. Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods] withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together).

v. Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test within 72 hours prior to the start of study drug.

vi. Women must not be breastfeeding.

**b. Male patients,** even if surgically sterilized (ie, status postvasectomy), who:

i. Agree to practice effective barrier contraception during the entire study treatment period and through 6 months after the last dose of study drug, OR

ii. Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods] withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together). Investigators shall counsel WOCBP and male subjects who are sexually active with WOCBP on the importance of pregnancy prevention and the implications of an unexpected pregnancy.

7. Clinical laboratory values as specified below within 28 days before the first dose of study drug:
   a. Total bilirubin must be ≤2 × the upper limit of normal (ULN).
   b. Magnesium ≥ lower limit of normal.
   c. Calcium ≥ lower limit of normal.
   d. ALT and AST must be ≤3 × ULN unless liver metastases are present, in which case they must be ≤5x ULN.
   e. Hemoglobin must be ≥9 g/dL, absolute neutrophil count (ANC) must be ≥1.500/µL, WBC must be ≥2.000/µL and platelet count must be ≥100.000/µL.
8. Subjects who have received radiation as primary therapy are eligible if radiation therapy treatment was completed > 4 weeks prior to inclusion.
9. Documentation of PD-L1 status by IHC performed by the central lab at randomization. A pre-treatment tumor tissue sample should be sent.

   A representative formalin-fixed paraffin-embedded (FFPE) tumor specimen (at least 5mm3 in which more than 60% of the sample is tumor) in paraffin block or unstained, freshly cut, serial sections (preferably at least 5) from an FFPE tumor specimen, are preferred. A newly obtained biopsy (within 6 months prior to start of study treatment) is preferred but an archival sample is acceptable, if several tumor samples are available, testing should be performed on the most recently obtained tumor sample

This specimen should be accompanied by the associated pathology report anonymized. Freshly cut, serial sections must have been cut no more than 14 days prior to analysis by central lab. Slides that have been cut more than 14 days prior to analysis by central lab should not be used and new slides should be made.

PD-L1 expression determined by using Combined Positive Score (CPS) (see annex 12) before patient randomization (DAKO PD-L1 IHC 22C3) will be performed by a central lab (Anatomic Pathology Department, Hospital 12 de Octubre, Madrid, Spain).

10. Documentation of HPV p16 status (OPC) is required for HNSCC tumor of the oropharynx. For subjects with oropharyngeal cancer, sites are defined in annex 8. HPV status of tumor tissue has to be locally determined at screening by any of the following methods: p16 IHC, in situ hybridization, or polymerase chain reaction-based assay. If HPV status by p16 IHC is positive result confirmation by PCR is mandatory.

## 3.8. Exclusion Criteria

Patients meeting any of the following exclusion criteria will not to be enrolled in the study:

1. Male or female patients aged <18 years. Patients aged ≥70 years old should not be included with a G8 (Geriatric 8) health status screening score < 14.
2. Karnofsky <70%.
3. Patients that meet more than one of the following criteria:
    a. Karnofsky 70%,
    b. Impaired renal function, creatinine clearance >30 mL/min and <80 mL/min GFR could be assessed by direct measurement (EDTA or creatinine clearance) if available or by calculation from serum or plasma creatinine,
    c. Class III heart failure according to the New York Heart Association.
4. Any unresolved toxicity NCI CTCAE Grade ≥2 from previous anticancer therapy except for alopecia, vitiligo, hear loss and the laboratory values defined in the inclusion criteria.
5. Histologically confirmed squamous cell carcinoma of unknown primary, of the nasopharynx or non-squamous histologies (eg, mucosal melanoma).
6. Active brain metastases or leptomeningeal metastases.
7. Carcinomatous meningitis.
8. Active, known, or suspected autoimmune disease. Subjects with vitiligo, type I diabetes mellitus, residual hypothyroidism due to autoimmune thyroiditis only requiring hormone replacement, or unexpected conditions of recurrence in the absence of an external trigger are allowed to be included.
9. Diagnosis of immunodeficiency or any condition requiring systemic treatment with either corticosteroids (>10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days of treatment.

10. History of pneumonitis requiring treatment with steroids; history of idiopathic pulmonary fibrosis, drug-induced pneumonitis, organizing pneumonia, or evidence of active pneumonitis on screening chest CT scan; history of radiation pneumonitis in the radiation field (fibrosis) is permitted.
11. Patients with a history of interstitial lung disease cannot be included if they have symptomatic ILD (Grade 3-4) and/or poor lung function.
12. Prior therapy with experimental antitumor vaccines; any T-cell co-stimulation agents or inhibitors of checkpoint pathways, such as anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody; or other agents specifically targeting T cells are prohibited.
13. Any serious medical or psychiatric illness, including drug or alcohol abuse, that could, in the investigator's opinion, potentially interfere with the completion of treatment according to this protocol.
14. Life-threatening illness unrelated to cancer.
15. Female patients who are lactating and breast-feeding or a positive serum pregnancy test during the screening period.
16. Systemic anticancer treatment or radiotherapy less than 4 weeks or 5 half-lives, whichever is longer, before the first dose of study treatment or not recovered from acute toxic effects from prior chemotherapy and radiotherapy.
17. Prior treatment with investigational agents ≤21 days (≤4 weeks for monoclonal antibodies with evidence of PD) or ≤5 their half-lives (whichever is shorter) before the first dose of study treatment. A minimum of 10 days should elapse from prior therapy to initiating protocol therapy.
18. Major surgery within 14 days before the first dose of study drug and not recovered fully from any complications from surgery.
19. Systemic infection requiring IV antibiotic therapy or other serious infection within 14 days before the first dose of study drug.
20. Known human immunodeficiency virus (HIV) positive (testing not required) or known acquired immunodeficiency syndrome (AIDS).
21. Patients with positive test for hepatitis B virus or hepatitis C virus indicating presence of virus, eg, Hepatitis B surface antigen (HBsAg) positive, or Hepatitis C antibody (anti-HCV) positive (except if HCV-RNA negative).
22. Active secondary malignancy that requires treatment. 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
23. Any clinically significant co-morbidities, such as uncontrolled pulmonary disease, known impaired cardiac function or clinically significant cardiac disease (specified below), active central nervous system disease, active infection, or any other condition that could compromise the patient's participation in the study.

    Patients with any of the following cardiovascular conditions are excluded:

    a. Acute myocardial infarction within 6 months before starting study drug.

b. Evidence of current uncontrolled cardiovascular conditions including cardiac arrhythmias, angina, pulmonary hypertension, or electrocardiographic evidence of acute ischemia or active conduction system abnormalities.
c. Friderichia corrected QT interval (QTcF) >450 milliseconds (msec) (men) or >475 msec (women) on a 12-lead ECG during the screening period.
d. Abnormalities on 12-lead ECG including, but not limited to, changes in rhythm and intervals that in the opinion of the investigator are considered to be clinically significant.

24. Patients with history of hypersensitivity reactions to study drugs (nivolumab, cetuximab or paclitaxel) or any of their excipients.
25. Symptomatic peripheral neuropathy of Grade ≥ 2 based on the CTCAE v5.0
26. Pulmonary embolism, deep vein thrombosis, or other significant thromboembolic event ≤ 8 weeks prior to starting the study treatment.
27. History of severe skin disorder that in the opinion of the investigator may interfere with study conduct.

## 3.9. Total number of subjects

Sample size has been calculated based on the primary objective of this clinical trial, to evaluate 2-year overall survival.

Previous studies shown that the two-year OS in patients with recurrent or metastatic head and neck squamous cell carcinoma was about 16%. To accept the treatment efficacy, we will assume that the 2-year OS with nivolumab in combination with weekly paclitaxel will be at least 26%. A sample size of 94 evaluable patients achieves 80% power at a 0.05 significance level (alpha) to accept the efficacy of nivolumab in combination with weekly paclitaxel. An accrual time of 18 months and follow-up time of 24 months (treatment and follow-up time) have been considered in the sample size calculation. Sample size was calculated for the experimental arm. 94 patients will be included in the experimental arm and 47 in the control arm. Total sample size is 141 patients. Patients will be randomized in a 2:1 ratio.

Sample size has been calculated with one-sample survival method. The test statistic for survival probability is assumed to be based on the non-parametric estimate of the survival distribution. For median survival, a Brookmeyer-Crowley like test assumed*.

A control group has been included to have a contemporary reference with a profile of patients equal to that of the experimental arm.

** Brookmeyer R and Crowley, JJ. A confidence interval for the median survival time. Biometrics, 38, 29-41, 1982.*

# 4. GENERAL CONSIDERATIONS

The planned analysis specified in this document will be carried out after the database lock approved by the Sponsor.

The statistical analysis will be performed using SPSS software.

Data will be generally provided with one decimal. In those cases that a greater accuracy is required, as much decimals as needed will be provided.

Adverse events will be codified using MedDRA dictionary (last version available).

Continuous variables will be described by mean, median, standard deviation, minimum, maximum, Q1 and Q3. Categorical variables will be shown as distribution of frequencies and percentage. In case of missing data, to calculate percentages, missing values will not be considered for the analysis. In the frequency tables, missing data will not be included. The number of missing data will be detailed. No use of any method or imputation of data for the handling of missing data is foreseen.

All results will be provided by treatment arm and global.

# 5. STUDY POPULATIONS

## 5.1. Definition of study populations to analyse

The populations used for analysis will include the following:

**Intention-to-treat (ITT) efficacy population:** consists of all patients who are randomized will analyse for efficacy endpoints. This will be the primary dataset for analysis of study conduct, study population and efficacy.

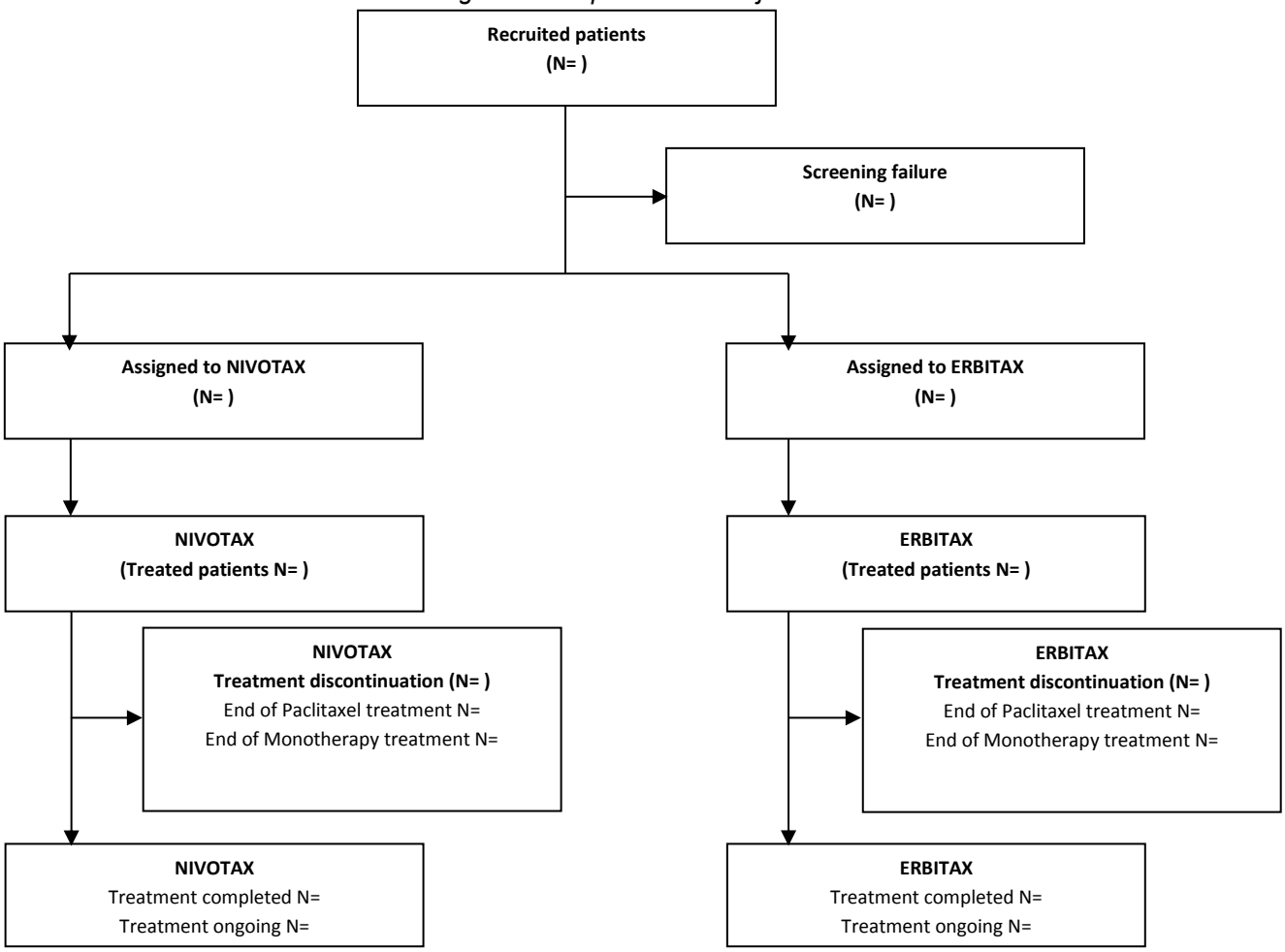
**Safety population**: consists of all patients who received at least one dose of the study treatment and had at least one valid post baseline safety assessment.

## 5.2. Study recruitment period

The date of inclusion of the first and last subject in the study will be provided.

## 5.3. Disposition of subjects

*Figure 1: Disposition of subjects*




Discrepancies between the number of analysed patients and number of recruited patients into the database will be described. A list reporting the screening failures per patient and arm will be included.

The frequency distribution and percentage of patients analysed will be provided by site.

## 5.4. Early withdrawal

Number and percentage of patients who discontinued the study and their reasons will be described (End of treatment form from the clinical database information).

A listing will be provided with the following information: Subject ID, arm, site, date, reason, relationship with the study drug, description, AE grade (if applicable), last time administered and comments (if applicable).

## 5.5. Deaths

Number and percentage of patients who died during the study and their reasons will be provided. Patients who have died due to adverse events or adverse reactions will be described in detail.

# 6. SUBJECT DESCRIPTION

## 6.1. Demographic and baseline description. General considerations

The demographic and baseline description will be performed into the ITT population defined in section 5.1.

## 6.2. Subject Characteristics

The following variables will be described:

**a) Baseline characteristics:**

- Age (Continuous).
- G8 score (only patients ≥ 70 years).
- Gender (Male, Female).
- Race (Caucasian, Black, Arab, Latin, Asian, Other and specify).
- Weight (Kg) (Continuous).
- Height (cm) (Continuous).
- Serology:
  - HBsAg (Negative, Positive, or Not done and the reason)
  - HC Ab (Negative, Positive, or Not done and the reason)
  - HCV RNA (negative, positive, or not done and the reason)
- Toxic habits:
  - Smoking history:
    - Has the patient ever smoked? (Yes, No, Unknown); if yes:
      - Average number of cigarettes smoked per day (Continuous).
      - Number of years (Continuous)
    - Does the patient currently smoke? (Yes, No, Unknown); if yes:
      - Average number of cigarettes smoked per day (Continuous).
  - Alcohol consumption:

- Has the patient ever abused alcohol? (Yes, No, Unknown); if yes:
  - Current, Former, or never.

**b) Cancer history:**

- Time from initial diagnosis (Continuous): defined as time elapsed between the initial diagnosis date and randomization date (months).
- Time from initial diagnosis to metastatic diagnosis (Continuous): defined as time elapsed between the initial diagnosis date and the metastatic diagnosis date (months).
- Time from metastatic diagnosis (Continuous): Defined as time elapsed between metastatic diagnosis date and randomization date (months).
- Number and percentage of patients whose initial diagnosis was metastatic disease.
- Stage will be described for initial diagnosis:
  - Stage (0, I, II, III, IVA, IVB, IVC)
- Karnofsky* (Categorical; 0, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100).
  - Karfnosky will be classified as Karnofsky performance status (70% vs 80-100%) and will be described (Categorical).
- The equivalence between Karnofsky and ECOG will be calculated, and the variable will be described, the following table describes the relation:

| Karnofsky Status | Karnofsky Grade | ECOG Grade | ECOG Status |
|---|---|---|---|
| Normal, no complaints | 100 | 0 | Fully active, able to carry on all pre-disease performance without restriction |
| Able to carry on normal activities. Minor signs or symptoms of disease | 90 | 1 | Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work |
| Normal activity with effort | 80 | 1 | Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work |
| Care for self. Unable to carry on normal activity or to do active work | 70 | 2 | Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours |
| Requires occasional assistance, but able to care for most of his needs | 60 | 2 | Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours |
| Requires considerable assistance and frequent medical care | 50 | 3 | Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours |
| Disabled. Requires special care and assistance | 40 | 3 | Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours |
| Severely disabled. Hospitalisation indicated though death non-imminent | 30 | 4 | Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair |
| Very sick. Hospitalisation necessary. Active supportive treatment necessary | 20 | 4 | Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair |
| Moribund | 10 | 4 | Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair |

| Karnofsky Status | Karnofsky Grade | ECOG Grade | ECOG Status |
|---|---|---|---|
| Dead | 0 | 5 | Dead |

- Tumor tissue sample collected prior to study treatment (Yes/No).
  - PD-L1 CPS (Continuous).
  - PD-L1 CPS will be classified as CPS score ≥1 / <1 and will be described (Categorical)*.
- HNSCC type (Oral cavity, Oropharynx (related or not related HPV), Larynx, Hypopharynx).
- Histology (squamous, other, if other specify).
- Differentiation grade (G1, G2, G3, G4, GX, Not available)
- Type of disease (loco-regional disease, loco-regional disease + M1, Metastatic disease).
- Oropharyngeal cancer** (Yes, No). If affirmative,
  - Oropharyngeal cancer HPV – (p16 IHC/HPV DNA)
  - Oropharyngeal cancer HPV + (p16 IHC & HPV DNA).
- Unable platinum treatment group***: Group 1 (Platinum-refractory); Group 2 (Platinum-sensitive but unable to receive cisplatin); Group 3 (Platinum-sensitive but cumulative cisplatin dose≥225mg/m²given for locally-advanced disease) (Categorical).

Note*: Screening visit Karnofsky and PD-L1 variables will be analysed since the information collected on the randomization screen is not correct.

Note**: The information of oropharyngeal and HPV+ and HPV- for the analysis will be provided by the study CRA (protocol deviations) since the information collected on the randomization screen is not correct.

Definition (randomization screen information) ***:

**Group 1:** Platinum resistant population: Patients who have experienced disease progression or relapse during or within 6 months of receiving platinum-based therapy administered as neoadjuvant, adjuvant therapy or as concomitant chemotherapy with radiotherapy and have received at least 200 mg/m2 of cisplatin.

**Group 2**: Platinum sensitive but unable for cisplatin-based therapy according to one of these criteria:

1. Karnofsky grade 70% or
2. Impaired renal function, creatinine clearance >30 Ml/min and <80 Ml/min GFR could be assessed by direct measurement (EDTA or creatinine clearance) if available or by calculation from serum or plasma creatinine, or
3. Class III heart failure according to the New York Heart Association (see annex 9 of protocol v4.0), or
4. Grade ≥2 hearing loss, according to the NCI CTCAE v 5.0, or
5. History of allergic reactions to cisplatin, carboplatin, or other platinum-containing compounds.

If the patient meets more than one of the first three criteria, the patient cannot be included in the study. (Criteria 1, 2 and 3 cannot coincide in the same patient; criteria 4 and 5 can go alone or in combination with any other).

**Group 3:** Platinum sensitive but prior dose of cisplatin ≥225 mg/m² for locally advanced disease (a patient who received prior RT + 3 cycles of cisplatin 100 mg/m2 or 3 cycles induction TPF (with cisplatin ≥75/m2) for locally advanced primary HN cancer). The interval from the last cycle of cisplatin and the start of first line treatment for R/M disease is >6 months.

**c) Locations:**

The analysis of target and non-target baseline lesions will be performed together.
It will be considered affected location when the patient presents at least one lesion in one organ or system, regardless of the number of lesions in the organ or system. It will be provided:

- The number and percentage of patients with each affected location (Categorical).
- The number and percentage of patients by number of affected locations (Categorical).

# 7. TREATMENT ADMINISTRATION

## 7.1. Treatment description. General considerations

Treatment description will be performed for ITT efficacy population defined in section 5.1.

It will be described the number of administrations received by study drug in each study phase (combination and monotherapy) and considering both phases together.

## 7.2. Combination treatment administration

It will be described the number of patients who received the complete pattern of 12 administrations of combination treatment phase in each study drug by the number and percentage by treatment arm.

### 7.2.1. NIVOTAX arm

The following data will be described for **nivolumab**:

- Delay administration (Yes, No): If yes:
  - Number and percentage of patients by the no. of delayed doses (Categorical).
  - Reasons for dose delay (Categorical).
  - Total number of weeks with dose delay and percentage regarding total weeks with administration (Categorical).

- No administered treatment (Yes, No): If dose no administered:
  - Number and percentage of patients by the no. of no administered doses (Categorical).

- Reasons for no administration (Categorical).
- Total number of weeks no administered and percentage regarding total weeks with administration (Categorical).

The following data will be described for **paclitaxel**:

- Dose reductions (Yes, No): If yes:
  - Number and percentage of patients by the no. of reductions (Categorical).
  - Reasons for dose reduction (Categorical).
  - Total number of weeks with dose reduction and percentage regarding total weeks with administration (Categorical).

- Delay administration (Yes, No): If yes:
  - Number and percentage of patients by the no. of delayed doses (Categorical).
  - Reasons for dose delay (Categorical).
  - Total number of weeks with dose delay and percentage regarding total weeks with administration (Categorical).

- No administered treatment (Yes, No): If dose no administered:
  - Number and percentage of patients by the no. of no administered doses (Categorical).
  - Reasons for no administration (Categorical).
  - Total number of weeks no administered and percentage regarding total weeks total weeks with administration (Categorical).

The NIVOTAX treatment time will be defined as the elapsed time, in weeks, between the date of first administered week and the end of combination treatment date. The NIVOTAX treatment will be described as continuous variable.

It will be described the number of administrations received by study drug separately and additionally the combination: nivolumab, paclitaxel and nivolumab + paclitaxel.

#### 7.2.1.1. NIVOTAX dose intensity

Dose intensity will be defined as the total dose of nivolumab or paclitaxel (separately) received by the patient with respect to the NIVOTAX treatment time.

The relative dose intensity will be defined as the total dose of nivolumab or paclitaxel received by the patient in relation to the theoretical total dose that patient should had received per protocol during Nivotax treatment time.

The dose intensity and relative dose intensity will be described as continuous variables.

### 7.2.2. ERBITAX arm

The following data will be described for **cetuximab**:

- Dose reductions (Yes, No): If yes:
  - Number and percentage of patients by the no. of reductions (Categorical).
  - Reasons for dose reduction (Categorical).
  - Total number of weeks with dose reduction and regarding total weeks with administration (Categorical).
- Delay administration (Yes, No): If yes:
  - Number and percentage of patients by the no. of delayed doses (Categorical).
  - Reasons for dose delay (Categorical).
  - Total number of weeks with dose delay and percentage regarding total weeks with administration (Categorical).
- No administered treatment (Yes, No): If dose no administered:
  - Number and percentage of patients by the no. of no administered doses (Categorical).
  - Reasons for no administration (Categorical).
  - Total number of weeks no administered and percentage regarding total weeks with administration (Categorical).

The following data will be described for **paclitaxel**:

- Dose reductions (Yes, No): If yes:
  - Number and percentage of patients by the no. of reductions (Categorical).
  - Reasons for dose reduction (Categorical).
  - Total number of weeks with dose reduction and percentage regarding total weeks with administration (Categorical).

- Delay administration (Yes, No): If yes:
  - Number and percentage of patients by the no. of delayed doses (Categorical).
  - Reasons for dose delay (Categorical).
  - Total number of weeks with dose delay and percentage regarding total weeks with administration (Categorical).

- No administered treatment (Yes, No): If dose no administered:
  - Number and percentage of patients by the no. no of administered dose (Categorical).
  - Reasons for no administration (Categorical).
  - Total number of weeks no administered and percentage regarding total weeks with administration (Categorical).

The ERBITAX treatment time will be defined as the elapsed time, in weeks, between the date of first administered week and the end of combination treatment date. The ERBITAX treatment will be described as continuous variable.

It will be described the number of administrations received by study drug separately and additionally the combination: cetuximab, paclitaxel and cetuximab + paclitaxel.

#### 7.2.2.1. ERBITAX dose intensity

Dose intensity will be defined as the total dose of cetuximab, or paclitaxel (separately) received by the patient with respect to the Erbitax treatment time.

The relative dose intensity will be defined as the total dose of cetuximab, or paclitaxel received by the patient in relation to the theoretical total dose that patient should had received per protocol during treatment time.

The dose intensity and relative dose intensity will be described as continuous variables.

### 7.2.3. End of paclitaxel treatment (combination treatment administration)

Number and percentage of patients who discontinued paclitaxel treatment and their reasons will be described by treatment arm.

A listing will be provided with the following information: subject ID, arm, site, date, reason, relationship with the study drug, description, AE grade (if applicable), last time administered and comments (if applicable).

## 7.3. Monotherapy treatment administration

The number and percentage of patients who continued study treatment will be provided by treatment arm.

### 7.3.1. NIVOTAX arm

The following data will be described for **nivolumab**:

- Delay administration (Yes, No): If yes:
  - Number and percentage of patients by the no. of delayed doses (Categorical).
  - Reasons for dose delay (Categorical).
  - Total number of administrations with dose delay and percentage regarding total administrations (Categorical).

- No administered treatment (Yes, No): If no administered:
  - Number and percentage of patients by the no. of no administered dose (Categorical).
  - Reasons for no administration (Categorical).
  - Total number of no administrations and percentage regarding total administrations (Categorical).

The monotherapy Nivolumab treatment time will be defined as the elapsed time, in weeks, between the date of first monotherapy administration and the end of monotherapy treatment date (end of treatment form). The monotherapy nivolumab treatment will be described as continuous variable.

It will be described the number of nivolumab administrations received during monotherapy phase.

#### 7.3.1.1. NIVOTAX dose intensity

Dose intensity will be defined as the total dose of Nivolumab received by the patient with respect to the nivolumab monotherapy treatment time.

The relative dose intensity will be defined as the total dose of Nivolumab received by the patient in relation to the theoretical total dose that patient should had received per protocol during treatment time.

The dose intensity and relative dose intensity will be described as continuous variables.

### 7.3.2. ERBITAX arm

The following data will be described for **cetuximab**:

- Dose reductions (Yes, No): If yes:
  - Number and percentage of patients by the no. of reductions (Categorical).
  - Reasons for dose reduction (Categorical).
  - Total number of administrations with dose reduction and percentage regarding total administrations (Categorical).

- Delay administration (Yes, No): If yes:
  - Number and percentage of patients by the no. of delayed doses (Categorical).
  - Reasons for dose delay (Categorical).
  - Total number of administrations with dose delay and percentage regarding total administrations (Categorical).

- No administered treatment (Yes, No): If no administered:
  - Number and percentage of patients by the no. of no administered dose (Categorical).
  - Reasons for no administration (Categorical).
  - Total number of no administrations and percentage regarding total administrations (Categorical).

The monotherapy cetuximab treatment time will be defined as the elapsed time, in weeks, between the date of first monotherapy administered week and the end of monotherapy treatment date (end of treatment form). The monotherapy cetuximab treatment will be described as continuous variable.

It will be described the number of cetuximab administrations received during monotherapy phase.

#### 7.3.2.1. ERBITAX dose intensity

Dose intensity will be defined as the total dose of cetuximab received by the patient with respect to the cetuximab monotherapy treatment time.

The relative dose intensity will be defined as the total dose of cetuximab received by the patient in relation to the theoretical total dose that patient should had received per protocol during treatment time.

The dose intensity and relative dose intensity will be described as continuous variables.

### 7.4. Post-study anticancer treatments

It will be described the number and percentage of patients who received post-study treatments by treatment arm.

All post-study anticancer treatments will be classified in immunotherapies (alone or combination), cetuximab-based and chemotherapy-based. The description on classified post-study treatments will be provided by treatment arm.

Additionally, the subgroup of patients who withdrawn study treatment due to progression (described in section 5.4 Early withdrawal) will be describe the post-study treatment by treatment arm.

## 8. EFFICACY ASSESSMENT

Efficacy assessment will be performed for ITT efficacy population defined in section 5.1.

Time-to-event variables will be analyzed according to the Kaplan-Meier method. Kaplan-Meier survival curves, median, 95% CI, number of events and censored and number of patients at risk will be presented.

ORR and DCR will be provided by treatment arm using RECIST criteria v1.1.

### 8.1. Primary endpoint

Primary objective of this study is to assess the efficacy of nivolumab plus paclitaxel, in terms of **two years Overall Survival (OS)**, for first-line treatment of recurrent or metastatic HNSCC in the platinum ineligible and platinum refractory settings.

OS is defined as the time (in months) between the date of randomization and the date of death. For subjects without documentation of death, OS will be censored on the last date in which the subject was known to be alive.

OS in each treatment arm will be estimated using KM method. Kaplan-Meier survival curves, median, 95% CI, number of events and censored and number of patients at risk will be presented. OS rates at 2 and 5 years and 95%CI will be estimated for each treatment arm.

OS in each treatment arm will be evaluated in the following groups:

- CPS score ≥1 vs <1.
- Oropharyngeal cancer HPV - (p16 IHC/HPV DNA) vs Oropharyngeal cancer HPV + (p16 IHC & HPV DNA).
- Karnofsky performance status (70% vs 80-100%).
- Group 1 vs Group 2 vs Group 3 (Unable platinum treatment group).
- Patients < 70 years vs ≥ 70 years.

Cox regression models will be used to calculate the risk reduction. Hazard ratio (HR) with 95% CIs will be reported to evaluate the impact of treatment arm and stratification variables: CPS (≥1vs <1), HPV (positive vs negative) and Karnofsky PS (70% vs 80-100%). Individual and general Cox regression models will be calculated.

## 8.2. Secondary endpoints

**Progression free survival (PFS):** PFS will be defined as the time (in months) from randomization to the date of first documented disease progression, as assessed by the investigator using RECIST 1.1 criteria, or death due to any cause, whichever occurs first. Subjects who died without a reported progression will be considered to have progressed on the date of their death. Subjects who did not progress or die will be censored on the date of their last evaluable tumor assessment. Subjects who did not have any on study tumor assessments and did not die will be censored on the date they were randomized. Subjects who started any subsequent anti-cancer therapy without a prior reported progression will be censored at the last evaluable tumor assessment prior to/on initiation of the subsequent anti-cancer therapy.

PFS in each treatment arm will be estimated using KM method. Kaplan-Meier survival curves, median, 95% CI, number of events and censored and number of patients at risk will be presented. PFS rates at 6 months and 2 years and 95%CI will be estimated for each treatment arm.

PFS in each treatment arm will be evaluated in the following groups:

- CPS score ≥1 vs <1.
- Oropharyngeal cancer HPV - (p16 IHC/HPV DNA) vs Oropharyngeal cancer HPV + (p16 IHC & HPV DNA).
- Karnofsky performance status (70% vs 80-100%).
- Group 1 vs Group 2 vs Group 3 (Unable platinum treatment group).
- Patients < 70 years vs ≥ 70 years.

Cox regression models will be used to calculate the risk reduction. Hazard ratio (HR) with 95% CIs will be reported to evaluate the impact of treatment arm and stratification variables: CPS (≥1vs <1), HPV (positive vs negative) and Karnofsky PS (70% vs 80-100%). Individual and general Cox regression models will be calculated.

**Overall Response Rate (ORR):** ORR is defined as the number of subjects with a best overall response (BOR) of a complete response (CR) or partial response (PR) divided by the number of randomized subjects for each treatment group. The BOR is defined as the best response designation, as determined investigator assessment, recorded between the date of randomization and the date of progression, as assessed by investigator per RECIST 1.1, or the date of subsequent anticancer therapy, whichever occurs first. For subjects without evidence of RECIST 1.1 progression or subsequent anticancer therapy, all available response designations will contribute to the BOR assessment. For subjects who continue treatment beyond progression, the BOR will be determined based on response designations up to the time of initial RECIST 1.1 progression.

Number and percentage of ORR will be provided by treatment arm, along with associated 95% confident interval.

ORR in each treatment arm will be evaluated in the following groups:

- CPS score ≥1 vs <1.
- Oropharyngeal cancer HPV - (p16 IHC/HPV DNA) vs Oropharyngeal cancer HPV + (p16 IHC & HPV DNA).
- Karnofsky performance status (70% vs 80-100%).
- Group 1 vs Group 2 vs Group 3 (Unable platinum treatment group).
- Patients < 70 years vs ≥ 70 years.

**Disease control rate (DCR):** DCR is defined as the number of subjects with a best overall response (BOR) of a complete response (CR), partial response (PR) or stable disease (SD) divided by the number of randomized subjects for each treatment group.

Description of DCR will be provided by treatment arm, along with associated 95 % confident interval.

**Duration of Response (DoR):** DoR is defined as the time between the date of first confirmed response to the date of the first documented tumor progression (per RECIST 1.1), or death due to any cause, whichever occurs first. Subjects who neither progress nor die will be censored on the date of their last evaluable tumor assessment. Subjects who started any subsequent anti-cancer therapy without a prior reported progression will be censored at the last evaluable tumor assessment prior to or on initiation of the subsequent anti-cancer therapy. DoR will be evaluated for responders (confirmed CR or PR) only.

DoR in each treatment arm will be estimated using KM method for all randomized subjects. Kaplan-Meier survival curves, median, 95% CI, number of events and censored and number of patients at risk will be presented.

**Rate of progressive disease (PD) at 6 months**: Rate of PD is defined as the number of subjects with PD at 6 months divided by the number of randomized subjects for each treatment group.

Description of rate of PD will be provided by treatment arm, along with associated 95% confident interval.

# 9. SAFETY ASSESSMENT

## 9.1. Safety assessment. General considerations

The assessment will be performed for safety population defined in section 5.1. Adverse events will be evaluated according to NCI CTCAE vs 5.0 criteria. Adverse events will be coded by the latest available version of MedDRA dictionary. AEs will be evaluated with the MedDRA code by system organ class (SOC) and preferred term (PT).

The analysis will be performed with the information completed into the adverse event eCRF section.

The analysis of adverse events will be performed per patient, for that the maximum grade for each adverse event completed of each patient will be calculated.

All safety sections detailed below (9.1.1 and 9.1.2) will be analyzed for the following subgroups separately:

- Combination treatment:
  - NIVOTAX
  - ERBITAX
- Monotherapy treatment:
  - NIVOTAX
  - ERBITAX
- Complete treatment (combination + monotherapy):
  - NIVOTAX
  - ERBITAX

## 9.2. Adverse Events

All adverse events evaluated will be described. The analysis of AEs will be described the following:

- The number and percentage of patients with at least one adverse event.

- The number and percentage of patients with each adverse event by grade, grades 3+4 and grades 3+4+5 aggrupation.
- The number and percentage of patients who discontinued due to AEs.

## 9.3. Adverse Reactions (toxicities)

All adverse event indicated as related with any study treatment drug in the eCRF adverse event section will be considered. The analysis of toxicities will be provided:

- The number and percentage of patients with at least one toxicity.
- The number and percentage of patients with each toxicity by grade, grades 3+4 and grades 3+4+5 aggrupation.

These analyses will be performed separately for each study drug and according to section 9.1.

## 9.4. Adverse Events of Special Interest (AESI)

The AESIs were defined as Nivolumab Immune-mediated AEs (IMAE) and is only applicable in NIVOTAX arm defined in protocol section *11.3.6 Immune-mediated adverse events*. the analysis of AESIs will be performed with the information collected into the Pharmacovigilance database. AESIs listing will be provided the following information:

- Site.
- Subject ID.
- AE description.
- Grade (1-5) NCI CTC AE v5.0.
- Start date.
- End date.
- Action taken

Additionally, the analysis of AESIs will be provided:

- The number and percentage of patients with at least one AESI.
- The number and percentage of patients with each AESI by grade, grades 3+4 and grades 3+4+5 aggrupation.

## 9.5. Serious Adverse Events

Serious adverse events listing will be provided the following information:

- Site.
- Subject ID.
- Arm.
- SOC (System Organ Class).
- PT (Preferred Term).
- AE description.
- Grade (1-5) NCI CTC AE v5.0.
- Seriousness criteria.
- Resolution.
- Relation.

Serious adverse events analysis includes the following:

- The number and percentage of patients with at least one serious adverse event by arm.
- The number and percentage of patients with each serious adverse event by grade and arm.

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## Certificado de finalización

Identificador del sobre: C471B839966E4B95B04962A32C47B15E
Estado: Completado
Asunto: Complete with DocuSign: TTC277007(NIVOTAX)_StatisticalAnalysisPlan_VF1.0_20221021.docx
Sobre de origen:
Páginas del documento: 28
Firmas: 3
Páginas del certificado: 2
Iniciales: 0
Firma guiada: Activado
Sello del identificador del sobre: Activado
Zona horaria: (UTC+01:00) Bruselas, Copenhague, Madrid, París

Autor del sobre:
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susana.vara@apices.es
Dirección IP: 83.33.49.201

## Seguimiento de registro

Estado: Original
14 de noviembre de 2022 | 13:16
Titular: Susana Vara
susana.vara@apices.es
Ubicación: DocuSign

| Eventos de firmante | Firma | Fecha y hora |
|---|---|---|
| Santiago Martín<br>santiago.martin@apices.es<br>DM<br>APICES<br>Nivel de seguridad: Correo electrónico, Autenticación de cuenta (ninguna) | DocuSigned by:<br>Santiago Martín<br>D71B317F831444B...<br>Adopción de firma: Estilo preseleccionado<br>Utilizando dirección IP: 46.25.253.163 | Enviado: 14 de noviembre de 2022 \| 13:19<br>Visto: 14 de noviembre de 2022 \| 13:20<br>Firmado: 14 de noviembre de 2022 \| 13:20 |
| **Información sobre confidencialidad de registros y firmas electrónicos:**<br>No ofrecido a través de DocuSign | | |
| Laura Fuentes<br>laura.fuentes@apices.es<br>PROJECT MANAGER<br>APICES<br>Nivel de seguridad: Correo electrónico, Autenticación de cuenta (ninguna) | DocuSigned by:<br>Laura Fuentes<br>9E0AEDBCC83A473...<br>Adopción de firma: Estilo preseleccionado<br>Utilizando dirección IP: 77.211.4.234 | Enviado: 14 de noviembre de 2022 \| 13:21<br>Visto: 14 de noviembre de 2022 \| 13:22<br>Firmado: 14 de noviembre de 2022 \| 13:22 |
| **Información sobre confidencialidad de registros y firmas electrónicos:**<br>No ofrecido a través de DocuSign | | |
| Marisa Durán<br>mduran@ttccgrupo.com<br>TTCC<br>Nivel de seguridad: Correo electrónico, Autenticación de cuenta (ninguna) | DocuSigned by:<br>Marisa Durán<br>2A1A3646513847C...<br>Adopción de firma: Estilo preseleccionado<br>Utilizando dirección IP: 2.138.93.30 | Enviado: 14 de noviembre de 2022 \| 13:22<br>Reenviado: 15 de noviembre de 2022 \| 09:27<br>Visto: 15 de noviembre de 2022 \| 09:28<br>Firmado: 15 de noviembre de 2022 \| 09:28 |
| **Información sobre confidencialidad de registros y firmas electrónicos:**<br>No ofrecido a través de DocuSign | | |

| Eventos de firmante en persona | Firma | Fecha y hora |
|---|---|---|

| Eventos de entrega al editor | Estado | Fecha y hora |
|---|---|---|

| Eventos de entrega al agente | Estado | Fecha y hora |
|---|---|---|

| Eventos de entrega al intermediario | Estado | Fecha y hora |
|---|---|---|

| Eventos de entrega certificada | Estado | Fecha y hora |
|---|---|---|

| Eventos de copia de carbón | Estado | Fecha y hora |
|---|---|---|

| Eventos del testigo | Firma | Fecha y hora |
|---|---|---|

| Eventos de notario | Firma | Fecha y hora |
|---|---|---|

| Eventos de resumen de sobre | Estado | Marcas de tiempo |
|---|---|---|
| Sobre enviado | Con hash/cifrado | 14 de noviembre de 2022 \| 13:19 |
| Certificado entregado | Seguridad comprobada | 15 de noviembre de 2022 \| 09:28 |
| Firma completada | Seguridad comprobada | 15 de noviembre de 2022 \| 09:28 |
| Completado | Seguridad comprobada | 15 de noviembre de 2022 \| 09:28 |

| Eventos del pago | Estado | Marcas de tiempo |
|---|---|---|