NIVOTAX Clinical Study Protocol

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)

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1. PROTOCOL SUMMARY

1.1. Sponsor

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

1.2. 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)

1.3. Protocol code

TTCC-2019-01 / CA209-7HE

1.4. Ethics Committee

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1.5. Company responsible of the monitoring

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1.6. Investigational product

Nivolumab.

Nivolumab as monotherapy is indicated for the treatment of recurrent or metastatic squamous cell cancer of the head and neck in adults progressing on or after platinum-based therapy. Nivolumab is indicated also in different types of cancer as melanoma, non-small cell lung cancer, renal cell carcinoma, Hodgking lymphoma, urothelial carcinoma and gastro-oesophageal junction cancer.

Nivolumab is a human immunoglobulin G4 (IgG4) monoclonal antibody (HuMAb), which binds to the programmed death-1 (PD-1) receptor and blocks its interaction with PD-L1 and PD-L2. The PD-1 receptor is a negative regulator of T-cell activity that has been shown to be involved in the control of T-cell immune responses [1]. Engagement of PD-1 with the ligands PD-L1 and PD-L2, which are expressed in antigen presenting cells and may be expressed by tumours or other cells in the tumour microenvironment, results in

inhibition of T-cell proliferation and cytokine secretion. Nivolumab potentiates T-cell responses, including anti-tumour responses, through blockade of PD-1 binding to PD-L1 and PD-L2 ligands.

1.7. Phase

Phase II

1.8. Trial 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:

Secondary objectives of this study are:

- 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) [2] 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

1.9. Study design

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). 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). For subjects with oropharyngeal cancer, sites 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.

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.

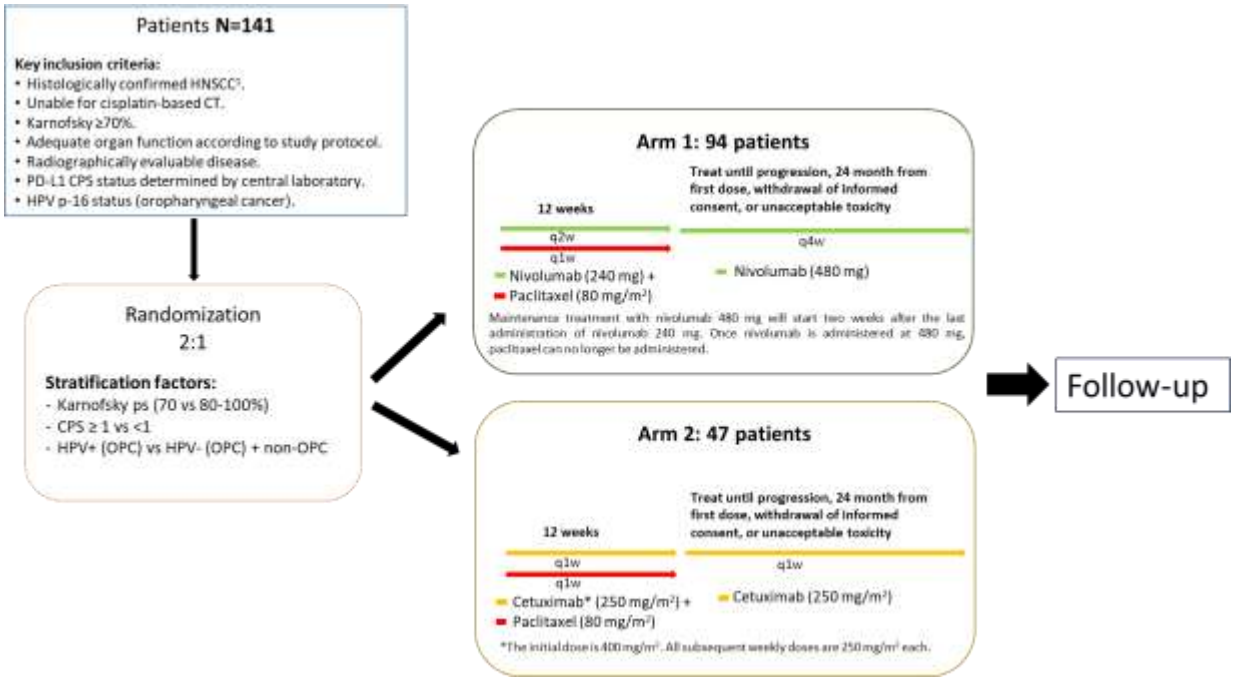
- **Arm 2** (standard): ERBITAX (Combination of cetuximab + paclitaxel follow by maintenance with cetuximab).

  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.

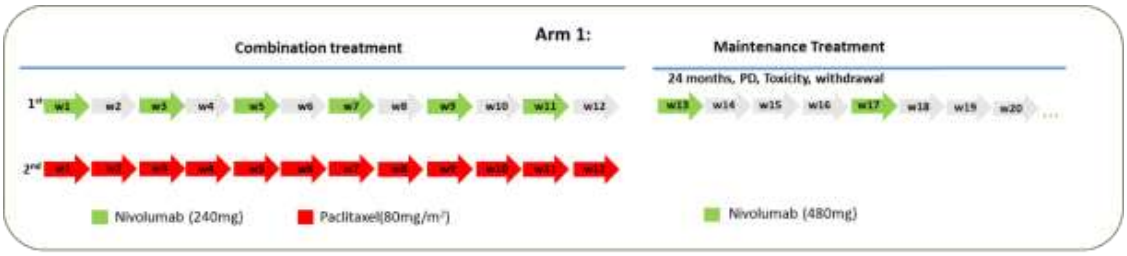
  After 12 weeks from the start of the combined treatment paclitaxel will be stopped and weekly cetuximab will be continued alone until disease progression, unacceptable toxicity or withdrawal of consent up to a maximum of 24 months.

ERBITAX has been chosen as a control group since it is the standard treatment in Spain for these patients and to have a contemporary reference with a profile of patients equal to that of the experimental arm. Guidelines for the Spanish Society of Medical Oncology (SEOM) includes for chemotherapy-naïve patients in recurrent and metastatic disease treatment this regimen. If patient cannot be treated with platinum (concomitant disease, previous treatment, etc.) or patients have PS 2, the combination ERBITAX (paclitaxel plus cetuximab) should be considered [3].

Study Scheme



Study Treatment



Patient will start study treatment within 48 hours of randomization.

Tumor progression and response endpoints will be assessed using RECIST 1.1 criteria.

Since the combination of paclitaxel and nivolumab in HNSCC has not yet been studied, the sponsor will establish a study data monitoring committee for reviewing safety data of the combination. This committee will consist of the two coordinating investigators an at least 5 of the participating investigators who will review the available safety information.

The study data monitoring committee will evaluate the safety profile of the combination once the first 10 patients included in the nivolumab arm have finished the combined treatment with paclitaxel. Additionally, the study data monitoring committee will review the available safety information every three months. It is not considered necessary to make more frequent reviews since both drugs are widely used in the participating oncology departments, there is sufficient experience in their use and the safety profile of both drugs is clearly defined.

During the periodic reviews, the study data monitoring committee together with the sponsor will review the available safety data (adverse events, serious adverse events, dropouts) and make a recommendation on whether or not to continue recruiting patients in the study, depending on the safety data from patients included. In any case, if an unexpected event related to patient safety is detected, it will be notified to the participating investigators and will be evaluated by the sponsor and the study data monitoring committee, which could increase the frequency of safety reviews if deemed appropriate.

1.10. Disease

Recurrent or metastatic head and neck squamous cell carcinoma.

1.11. Study outcome measures

Primary outcome measure:

Primary outcome measure of the study is two years overall survival. 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 outcome measures:

PFS is defined as the time 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.

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.

Disease control rate (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.

Duration of Response (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.

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.

Efficacy (ORR, PFS, OS) will be evaluated 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-PS.

All randomized subjects will be monitored by radiographic assessment at week 9 and every 12 weeks (± 7 days) thereafter. RECIST 1.1 criteria will be used for the assessment.

Subjects will be evaluated for safety if they have received any study drug. Toxicity assessments will be continuous during the treatment phase and the safety follow-up visits. Adverse events and laboratory values will be graded according to the NCI-CTCAE version 5.0.

On-study weight, Karnofsky performance status, and vital signs should be assessed at each on-study visit prior to dosing. Vital signs should also be taken as per institutional standard of care prior to, during and after infusions. The start and stop time of the study therapy infusions should be documented.

Physical examinations are to be performed as clinically indicated. If there are any new or worsening clinically significant changes since the last exam, report changes on the appropriate non-serious or serious adverse event form of the eCRF.

Laboratory toxicities (eg, suspected drug induced liver enzyme evaluations) will be monitored during the follow-up phase via on site/local labs until all study drug related toxicities resolve, return to baseline, or are deemed irreversible.

The safety analysis will be performed in all treated subjects. Descriptive statistics of safety will be presented using the NCI CTCAE version 5.0 by treatment arm. All AEs, drug-related AEs and SAEs will be tabulated using the worst grade per NCI CTCAE v 5.0 criteria by system organ class and preferred term.

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 and incidence of deaths will be provided.

1.12. Study population and number of patients

Patients with recurrent or metastatic head and neck squamous cell carcinoma unable for cisplatin-based chemotherapy will able to participate in the study.

Patients will be distributed in the following way:

- Group 1: Platinum resistant population (one third of the patients – 47 patients):
    - 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/m^2 of cisplatin.
- Group 2: Platinum sensitive but unable for cisplatin-based therapy according to one of these criteria (one third of the patients – 47 patients):
    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, 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 (one third of the patients – 47 patients) (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.

Once the planned recruitment in groups 1 or 3 is completed, sponsor will evaluate the number of patients recruited in each of the other groups as well as the remaining recruitment time to confirm whether the proportion of patients to be included in each group is maintained.

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).

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

1.13. Selection criteria

Patients diagnosed with HNSCC who are unable for first-line cisplatin-based chemotherapy and not previously treated for recurrent/metastatic disease will be include in the study.

1.13.1. 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/m^2 or 3 cycles induction TPF (with cisplatin ≥75/m^2) 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/m^2 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 annex 10) health status screening score ≥ 14.

a. <u>Female patients:</u>

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 (see annex 6), 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

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 5mm^3 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.

1.13.2. 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 meets **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 (see annex 5),

c. Class III heart failure according to the New York Heart Association (annex 9).

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.

1.14. Study calendar

First patient inclusion: Jun 2020
Last patient inclusion: Nov 2021
Subject participation duration: 5 years
Study duration: 6.5 years

2. TABLE OF CONTENTS

3. ABBREVIATIONS

Abbreviation	Full terminology
AE	Adverse event
AEMPS	Agencia Española de Medicamentos y Productos Sanitarios
ALP	alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
APC	Allophycocyanin
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
ATP	adenosine triphosphate (ATP
BMS	Bristol-Myers Squibb
BOR	Best overall response
BUN	Blood urea nitrogen
Ca	Calcium
CA	Competent authority
CBC	Complete blood count
CEIm	Comité Ético de Investigación con medicamentos
CNS	Central nervous system
CI	Confidence interval
Cl	Chloride
CPS	combined positive score
CR	Complete response
CRA	Contract research associate
CRF	Case report form
CRO	Contract research organization
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	Cytotoxic T-lymphocyte antigen 4
CT	Computed tomography

DC	Dendritic cells
DCR	Disease control rate
DILI	Drug induced liver injury
DoR	Duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDC	Electronic data capture
EGFR	Epidermal growth factor receptor
EORTC	European Organisation for the Research and Treatment of Cancer
EOT	End of treatment
ESMO	European Society of Medical Oncology
EU	European Union
FDA	Food and Drug Administration
FFPE	Formalin-Fixed Paraffin-Embedded
FU	Fluorouracil
GCP	Good clinical practice
G-CSF	granulocyte colony stimulating factor
GFR	Glomerular filtration rate
GM-CSF	granulocyte macrophage-colony stimulating factor
GORTEC	Groupe d'Oncologie Radiothérapie Tête Et Cou
HBV	Hepatitis B virus
HCB	Hepatitis C virus
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
HMGB1	High mobility group box 1
HN	Head and neck
HNC	Head and neck cancer
HNSCC	Head and neck squamous cell carcinoma
HPV	human papillomavirus
HR	Hazard Ratio
HuMAb	Human monoclonal antibody

IB	Investigator brochure
IC	Tumor-Infiltrating Immune Cells
ICD	Immunogenic cell death
ICF	Informed consent form
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IEC	Independent ethic committee
IFN	Interferon
Ig	Immunoglobulin
ILD	Interstitial lung disease
IMAE	Immune-mediated AE
Ir	Immune-related
IRR	Infusion-related reactions
ITT	Intent-to-treat
IV	Intravenous
K	Potassium
LDH	Lactate dehydrogenase
Mg	Magnesium
MoAb	Monoclonal antibody
MRI	Magnetic resonance imaging
Na	Sodium
NCI	National Cancer Institute
NK	Natural Killer
NSCLC	Non-small cell lung cancer
OPC	oropharyngeal carcinoma
OPSCC	oropharyngeal squamous cell carcinoma
ORR	Overall response rate
OS	Overall survival
PD	Progression disease
PD-L1	Programmed death-ligand 1
PET	Positron emission tomography
PFS	Progression free survival

PIL	Patient Information Leaflet
PR	Partial response
QC	Quality control
QTcF	QT interval corrected using Fridericia's formula
RBC	Red blood cells
RCC	Renal cell carcinoma
RECIST	Response Evaluation Criteria In Solid Tumors
RT	Radiotherapy
SAE	Serious adverse event
SD	Stable disease
SEOM	Sociedad Española de Oncología Médica
SJS	Stevens-Johnson syndrome
SPC/SmPC	Summary of Product Characteristics
TEN	Toxic epidermal necrolysis
TMF	Trial master file
TPF	Docetaxel, Carboplatin and Fluorouracil
TSH	Thyroid stimulating hormone
TTCC	Grupo Español de Tratamiento de Tumores de Cabeza y Cuello
ULN	Upper limit of normal
WBC	White blood cells
WOCBP	Women of childbearing potential
WWPS	Worldwide Patient Safety

4. CLINICAL TRIAL CHARACTERISTICS

4.1. Clinical trial identification

Code: TTCC-2019-01 / CA209-7HE

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)

4.2. Phase

Phase II

4.3. Investigational product

Nivolumab.

Nivolumab as monotherapy is indicated for the treatment of recurrent or metastatic squamous cell cancer of the head and neck in adults progressing on or after platinum-based therapy. Nivolumab is indicated also in different types of cancer as melanoma, non-small cell lung cancer, renal cell carcinoma, Hodgking lymphoma, urothelial carcinoma and gastro-oesophageal junction cancer

Nivolumab is a human immunoglobulin G4 (IgG4) monoclonal antibody (HuMAb), which binds to the programmed death-1 (PD-1) receptor and blocks its interaction with PD-L1 and PD-L2. The PD-1 receptor is a negative regulator of T-cell activity that has been shown to be involved in the control of T-cell immune responses [1]. Engagement of PD-1 with the ligands PD-L1 and PD-L2, which are expressed in antigen presenting cells and may be expressed by tumours or other cells in the tumour microenvironment, results in inhibition of T-cell proliferation and cytokine secretion. Nivolumab potentiates T-cell responses, including anti-tumour responses, through blockade of PD-1 binding to PD-L1 and PD-L2 ligands.

4.4. Sponsor

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

4.5. Ethics Committee

CEIC Hospital Universitari Germans Trias I Pujol

4.6. Company Responsible of the Monitoring

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4.7. Study calendar

First patient inclusion: Jun 2020

Last patient inclusion: Nov 2021

Subject participation duration: 5 years

Study duration: 6.5 years

5. STUDY RATIONALE AND OBJECTIVES

5.1. Background information

5.1.1. Head and Neck Squamous Cell Carcinoma (HNSCC)

Head and neck cancers are a heterogeneous group of neoplasms that typically originate from the mucosal lining of the lip, oral cavity, nasopharynx, larynx, and hypolarynx. Biologically, they are generally similar, with 85% of head and neck cancers being squamous cell carcinomas; they are, therefore, called head and neck squamous cell carcinoma (HNSCC) [4,5]. HNSCC is the fifth most common cancer diagnosed worldwide and the eighth most common cause of cancer death [6]. There are 500.000 new cases each year worldwide [7]. These cancers are associated with environmental and lifestyle risk factors, including smoking, alcohol consumption, exposure to ultraviolet light and certain workplace chemicals, and infection with the human papillomavirus [7].

In 2020, head and neck cancer (HNC) is expected to affect approximately 833.000 and 151.000 new patients worldwide and in Europe, respectively [8]. High risk alpha human papillomaviruses (HPV), mainly HPV type 16 (HPV16), have been recognized as causally related to a subset of oropharyngeal squamous cell carcinomas as well as to a substantial fraction of SCCs from unknown primary metastatic to the neck nodes. Both of these entities benefit from a significantly better prognosis [9-11]. According to recent estimates, worldwide 38.000–45.000 cases of HNC are yearly attributable to HPV [12-13], although the geographic prevalence of HPV-related OPSCC is extremely heterogeneous [14-15].

If detected early, HNSCC is highly curable; however, these cancers are frequently aggressive and often are first noticed only when they have spread to the lymph nodes. Radiation therapy is the most common form of treatment for HNSCC. Radiotherapy and surgery may be used in combination, and the intention of these treatment modalities is curative.

Chemotherapy is generally used to create a hostile environment for metastasis either as an additional or adjuvant treatment. Typically, the chemotherapy will combine a platinum-based therapy (carboplatin or cisplatin) with a taxane (paclitaxel, or docetaxel), sometimes including fluorouracil and cetuximab. The 5-year survival rate for patients with HNSCC is 40% to 50% [15].

Metastatic and recurrent HNSCC that is no longer amenable to local surgical/radiation therapy causes substantial morbidity and high mortality, with a median PFS of < 6 months and median overall survival of less than 12 months.

5.1.2. Recurrent or metastatic HNSCC treatment

The standard of care for recurrent/metastatic HNSCC in first-line was established in 2008 by the EXTREME study by Vermorken et al [16]. The study randomly assigned 220 of 442 eligible patients with untreated recurrent or metastatic squamous cell carcinoma of the head and neck to receive cisplatin or carboplatin plus fluorouracil every 3 weeks for a maximum of 6 cycles and 222 patients to receive the same chemotherapy plus cetuximab for a maximum of 6 cycles. Patients with stable disease who received chemotherapy plus

cetuximab continued to receive cetuximab until disease progression or unacceptable toxic effects.

Adding cetuximab to platinum-based chemotherapy with fluorouracil (platinum fluorouracil) significantly prolonged the median overall survival from 7.4 months in the chemotherapy-alone group to 10.1 months in the group that received chemotherapy plus cetuximab (hazard ratio for death, 0.80; 95% confidence interval, 0.64 to 0.99; P = 0.04). The addition of cetuximab prolonged the median progression-free survival time from 3.3 to 5.6 months (hazard ratio for progression, 0.54; P<0.001) and increased the response rate from 20% to 36% (P<0.001). The addition of cetuximab was associated with a 2.7 month increase in the median survival and a significant 20% reduction in the relative risk of death, as compared with platinum–fluorouracil chemotherapy alone. Secondary efficacy endpoints were also significantly improved in the cetuximab group, with a 2.3-month prolongation of progression-free survival (a 46% reduction in the risk of disease progression), an 83% increase in the response rate, and a 41% reduction in the risk of treatment failure.

Chemotherapy for incurable recurrent or metastatic HNSCC disease is palliative and usually platinum based, and the patients often present with poor physical condition due to alcohol and tobacco habits, malnutrition and comorbidities. Consequently, many of them are not able to withstand a platinum-based chemotherapy. The addition of taxanes to the armamentarium of drugs improve the outcome in this group. An alternative and better tolerated regimen for these patients is paclitaxel in combination with cetuximab [17].

Hitt et al. enrolled 46 patients who were unlikely to benefit from platinum-based chemotherapy in a phase II trial combining weekly paclitaxel and cetuximab [17]. Cetuximab was administered by i.v. infusion at an initial dose of 400 mg/m^2 over 2 h followed by weekly doses of 250 mg/m^2 over 1 hour. Paclitaxel (80 mg/m^2) was administered weekly over 1 hour, an hour after cetuximab infusion. The overall response rate was 54% (95% CI: 39%–69%) (complete response rate: 22%, disease control rate: 80%). Median PFS and OS were 4.2 months (95% CI: 2.9–5.5 months) and 8.1 months (95% CI: 6.6–9.6 months), respectively. Common grade 3 or 4 adverse events were acne-like rash (24%), asthenia (17%), and neutropenia (13%). The development of acne-like rash was associated with tumor response. Patients who had not previously received chemotherapy as part of a multimodal treatment of locally advanced disease had a significantly better tumor response than those who had received prior chemotherapy. However, the outcome of these patients still remains poor (P = 0.020).

Additionally, guidelines for the Spanish Society of Medical Oncology (SEOM) includes for chemotherapy-naïve patients in recurrent and metastatic disease treatment the weekly paclitaxel and cetuximab regimen. If patient cannot be treated with platinum (concomitant disease, previous treatment, etc.) or patients have PS 2, the combination ERBITAX (paclitaxel plus cetuximab) should be considered [3].

5.1.2.1. Paclitaxel

Paclitaxel is a compound extracted from the Pacific yew tree Taxus brevifolia with antineoplastic activity. Paclitaxel binds to tubulin and inhibits the disassembly of microtubules, thereby resulting in the inhibition of cell division. This agent also induces apoptosis by binding to and blocking the function of the apoptosis inhibitor protein Bcl-2 (B-cell Leukemia 2).

Taxanes are among the most active cytotoxic agents in HNSCC, and known to modulate antitumor immune responses as well. Similar to cisplatin, paclitaxel does not induce ICD. However, concurrent paclitaxel treatment was shown to significantly enhance radiation-induced ICD in breast cancer cell lines. Similarly, docetaxel treatment itself did not induce ATP or HMGB1 secretion by tumor cells. However, calreticulin exposure of tumor cells after docetaxel treatment was observed which significantly enhanced tumor cell killing by antigen-specific CD8+ cytotoxic T cells [18].

In the GORTEC 2008-3 trial [19], 54 patients with previously untreated R/M-HNSCC were treated with weekly cetuximab and four 3-week cycles of docetaxel 75 mg/m^2 and cisplatin 75 mg/m^2, followed by maintenance cetuximab until disease progression or unacceptable toxicity. Toxicity was manageable with granulocyte colony-stimulating factor support. The overall response rate was 54%. Median PFS and OS were 7.1 months and 15.3 months, respectively. These data compare favorably with the results observed with cisplatin, 5-FU, and cetuximab in the EXTREME trial.

A randomized phase III study compared cisplatin 75 mg/m^2 day 1 and paclitaxel 175 mg/m^2 over 3 hours on day 1 every 3 weeks with cisplatin 100 mg/m^2 day 1 and FU 1.000 mg/m^2 /24 hours by continuous intravenous infusion days 1 through 4 [20]. Overall survival was not different between the two groups. Median survival was 8.1 months (95% CI, 6.1 to 10.0) and 8.7 months (95% CI, 6.7 to 12.2) respectively.

In non-randomized phase II trials cetuximab was added to a taxane, either as a single agent or in combination with cisplatin. Hitt et al. [17] enrolled 46 patients who were unlikely to benefit from platinum-based chemotherapy in a phase II trial combining cetuximab administered by i.v. infusion at an initial dose of 400 mg/m^2 over 2 hour followed by weekly doses of 250 mg/m^2 over 1 hour and weekly paclitaxel 80 mg/m^2 administered weekly over 1 hour, an hour after cetuximab infusion. The overall response rate was 54% (95% CI: 39%–69%) (complete response rate: 22%, disease control rate: 80%). Median PFS and OS were 4.2 months (95% CI: 2.9–5.5 months) and 8.1 months (95% CI: 6.6–9.6 months), respectively. Common grade 3 or 4 adverse events were acne-like rash (24%), asthenia (17%), and neutropenia (13%). The development of acne-like rash was associated with tumor response. Patients who had not previously received chemotherapy as part of a multimodal treatment of locally advanced disease had a significantly better tumor response than those who had received prior chemotherapy (P = 0.020).

5.1.2.2. Cetuximab

Cetuximab is an IgG1 humanized monoclonal murine antibody targeting the epidermal growth factor receptor (EGFR). EGFR is an erbB family receptor tyrosine kinase expressed by a wide variety of tumor types. Binding of a ligand to EGFR results in receptor dimerization, autophosphorylation, and induction of signaling cascades leading to cell proliferation. Cetuximab works by inhibiting ligand binding to EGFR, thereby blocking cell growth signaling. Importantly, for colorectal cancer cetuximab is only effective for tumors expressing wild-type KRAS, as mutant KRAS provides growth signals that bypass EGFR inhibition. However, for HNSCC cetuximab appears to be effective for both KRAS-wild type and KRAS-mutant tumors. Cetuximab was approved for HNSCC in 2006 after early phase III trials demonstrated that cetuximab improved response to chemotherapy and reduced the risk of death for patients who have cetuximab-related skin toxicity.

Later studies showed that cetuximab plus platinum-based chemotherapy increases overall and progression-free survival (PFS) [16,17], and that 5-year survival is improved for patients receiving chemo-radiotherapy who developed skin rash of grade ≥2 severity in response to cetuximab. However, a more recent phase III study that included more than 800 patients found that adding cetuximab to platinum-based chemo-radiotherapy regimens did not improve PFS or OS [21], suggesting that routine cetuximab administration may not be beneficial to all patients. Therefore, further research is needed to identify patients who are most likely to benefit from cetuximab therapy.

There is accumulating data that the efficacy of cetuximab-based regimens in treatment of recurrent/metastatic HNSCC is not only based on the inhibition of EGFR signaling pathways but also on the activation of Fcγ receptor-positive NK cells leading to DC maturation and activation of cytotoxic T cells [22].

5.1.2.3. Immunotherapy in HNSCC

Immunotherapeutic approaches recently have demonstrated clinical efficacy in several cancer types, including melanoma, renal cell carcinoma, non-small cell lung cancer [23], HNSCC [24], etc. Regarding HNSCC, recently published data of pembrolizumab clinical trials showed: improvement in overall survival when compared pembrolizumab with standard of care (8.4 months vs 6.9 months ; HR 0·80, 0·65–0·98; p=0·0161) [25] in patients with R/M HNSCC that progressed during or after platinum based treatment; in an interim analysis of KEYNOTE-048 study, that included patients with R/M HNSCC with no prior systemic therapy, improvement in overall survival when compared pembrolizumab with EXTREME scheme (cisplatin or carboplatin + fluorouracil + cetuximab) in CPS ≥20 (14.9 vs 10.7 months; HR 0.61 [95% CI 0.45-0.83]; P = 0.0007) and also in CPS ≥1 (12.3 vs 10.3 months; HR 0.78 [95% CI 0.64-0.96]; P = 0.0086) [26]; and in KEYNOTE-048 final analysis, pembrolizumab + cisplatin or carboplatin + fluorouracil improved overall survival vs EXTREME scheme in the CPS ≥20 (14.7 vs 11.0 months; HR 0.60, 95% CI 0.45-0.82, P = .0004) and CPS ≥1 (13.6 vs 10.4 months; HR 0.65, 95% CI 0.53-0.80, P < .0001) [27].

Tumors may modulate and evade the host immune response through a number of mechanisms, including down regulation of tumor-specific antigen expression and presentation, secretion of anti-inflammatory cytokines, and upregulation of inhibitory ligands. In HNSCC, down-regulation of T-cell function is thought to be mediated by multiple mechanisms: i.) Reduced expression of costimulating molecules of the B7-CD28 family; ii.) Increased expression of PD L1 in tumor cells and tumor associated fibroblasts; and, iii.) Loss of HLA-class I and selective down-regulation of HLA-A,B,C locus expression resulting in defective antigen presentation [28-30]. In a subset of HPV-infected HNSCC, data shows that antigen-processing machinery components are downregulated compared to the adjacent normal squamous epithelium with incomplete activation of tumor specific T cells or suboptimal target recognition enabling tumor progression [31]. T cell checkpoint regulators such as CTLA-4 and programmed death-1 (PD-1, CD279) are cell surface molecules that, when engaged by their cognate ligands, induce signaling cascades down regulating T cell activation and proliferation.

PD-L1 expression has been associated with poor prognosis in certain tumor types such as renal, esophageal, gastric, ovarian, pancreatic, and lung cancer [32-37]. PD-1 engagement on T cells by PD-L1-positive APC or PD-L1-positive tumor cells in the tumor microenvironment may limit effective immune responses. Conversely, PD-L1 expression

may be a positive prognostic factor as it may indicate infiltration of tumor-specific T cells that secrete IFN-ɣ, which upregulates PD-L1 expression. Consistent with this hypothesis is the co-localization of lymphoid cell infiltrates and PD-L1 staining observed in human melanoma lesions [38]. PD-L1 expression in HNSCC has been reported, preliminary results from a phase 1 trial in patients with [39] recurrent or metastatic disease observed that 77.9% of patients tested (N=104) expressed PD-L1, defined as ≥ 1% of stained cells in the tumor microenvironment.

Recently published guidelines from the Society for Immunotherapy of Cancer [40] defined positivity for PD-L1 as ≥1% TPS or ≥ 1 CPS by IHC staining. However, it is important to note that expression levels may differ depending on the antibody used and whether staining includes tumor alone or tumor plus stroma. The majority of the subcommittee agreed that the best use of biomarker testing when treating patients with HNSCC with immunotherapy is by combined positive score (CPS) (see annex 12).

The role of the PD-1 blockade in squamous cell carcinoma of the lung has been established in CA209017 study [41] where nivolumab monotherapy in the second-line treatment setting demonstrated clinically meaningful survival benefit regardless of PD-L1 expression compared to standard of care docetaxel. In a similar histology, for squamous cell carcinoma of the head and neck primary, the role of PD-1 blockade is evolving. CA209141 study, is a randomized, open-label, phase 3 trial that compared nivolumab, a fully human anti-programmed death 1 (PD-1) monoclonal antibody, to investigator's choice of systemic therapy in patients with recurrent or metastatic HNSCC who progressed from a platinum containing therapy. At a preplanned interim analysis, the median OS was 7.5 months (95% confidence interval [CI], 5.5 to 9.1) with nivolumab versus 5.1 months (95% CI, 4.0 to 6.0) with investigator's choice. There is a 30% reduction in the risk of death for patients on the nivolumab arm (hazard ratio 0.70; 97.73% CI, 0.51 to 0.96; P=0.0101) over standard of care. In addition, the overall safety profile of nivolumab was favorable compared to standard of care. Clinical benefit seen in this chemotherapy pre-treated HNSCC suggests the potential clinical activity of nivolumab in the earlier treatment setting.

We expect that combination treatment of paclitaxel and immune checkpoint inhibitors would also improve the outcome of patients unable for a cisplatin-based first-line chemotherapy.

5.1.2.4. Nivolumab

Nivolumab is a human immunoglobulin G4 (IgG4) monoclonal antibody (HuMAb), which binds to the programmed death-1 (PD-1) receptor and blocks its interaction with PD-L1 and PD-L2. The PD-1 receptor is a negative regulator of T-cell activity that has been shown to be involved in the control of T-cell immune responses. Engagement of PD-1 with the ligands PD-L1 and PD-L2, which are expressed in antigen presenting cells and may be expressed by tumours or other cells in the tumour microenvironment, results in inhibition of T-cell proliferation and cytokine secretion. Nivolumab potentiates T-cell responses, including anti-tumour responses, through blockade of PD-1 binding to PD-L1 and PD-L2 ligands.

Up-regulation of PD-L1 and PD-L2 occurs in tumors. The cross-talk between tumor and T cells through the PD-1/ligand interaction in the tumor microenvironment leads to inhibition of active T-cell immune surveillance of tumors. Inhibition of PD-1, therefore, can block this negative regulatory pathway and allow T cells to regain the ability to attack tumors [42,43].

Nivolumab is currently approved by EMA in different types of cancer (refer to Nivolumab SmPC).

Melanoma: nivolumab as monotherapy or in combination with ipilimumab is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults.

Adjuvant treatment of melanoma: nivolumab as monotherapy is indicated for the adjuvant treatment of adults with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection

Non-Small Cell Lung Cancer (NSCLC): nivolumab in combination with ipilimumab and 2 cycles of platinum-based chemotherapy is indicated for the first-line treatment of metastatic non-small cell lung cancer in adults whose tumours have no sensitising EGFR mutation or ALK translocation

Non-Small Cell Lung Cancer (NSCLC): nivolumab as monotherapy is indicated for the treatment of locally advanced or metastatic non-small cell lung cancer after prior chemotherapy in adults.Malignant pleural mesothelioma (MPM): nivolumab in combination with ipilimumab is indicated for the first-line treatment of adult patients with unresectable malignant pleural mesothelioma.

Renal Cell Carcinoma (RCC): nivolumab as monotherapy is indicated for the treatment of advanced renal cell carcinoma after prior therapy in adults.

Renal Cell Carcinoma (RCC): nivolumab in combination with ipilimumab is indicated for the first-line treatment of adult patients with intermediate/poor-risk advanced renal cell carcinoma.

Renal Cell Carcinoma (RCC): nivolumab in combination with cabozantinib is indicated for the first-line treatment of adult patients with advanced renal cell carcinoma (see section 5.1).

Classical Hodgkin Lymphoma (cHL): nivolumab as monotherapy is indicated for the treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma after autologous stem cell transplant (ASCT) and treatment with brentuximab vedotin.

Squamous Cell Cancer of the Head and Neck (SCCHN): nivolumab as monotherapy is indicated for the treatment of recurrent or metastatic squamous cell cancer of the head and neck in adults progressing on or after platinum-based therapy.

Urothelial Carcinoma: nivolumab as monotherapy is indicated for the treatment of locally advanced unresectable or metastatic urothelial carcinoma in adults after failure of prior platinum-containing therapy.

Adjuvant treatment of urothelial carcinoma: nivolumab as monotherapy is indicated for the adjuvant treatment of adults with muscle invasive urothelial carcinoma

(MIUC) with tumour cell PD-L1 expression ≥1% who are at high risk of recurrence after undergoing radical resection of MIUC.

Mismatch repair deficient (dMMR) or microsatellite instability-high (MSI-H) colorectal cancer (CRC): nivolumab in combination with ipilimumab is indicated for the treatment of adult patients with mismatch repair deficient or microsatellite instability-high metastatic colorectal cancer after prior fluoropyrimidine-based combination chemotherapy (see section 5.1).

Oesophageal squamous cell carcinoma (OSCC): nivolumab in combination with ipilimumab is indicated for the first-line treatment of adult patients with unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma with tumour cell PD-L1 expression ≥ 1%.

Oesophageal squamous cell carcinoma (OSCC): nivolumab in combination with fluoropyrimidine- and platinum-based combination chemotherapy is indicated for the first-line treatment of adult patients with unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma with tumour cell PD-L1 expression ≥ 1%.

Oesophageal squamous cell carcinoma (OSCC): nivolumab as monotherapy is indicated for the treatment of adult patients with unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma after prior fluoropyrimidine- and platinum-based combination chemotherapy.

Adjuvant treatment of oesophageal or gastro-oesophageal junction cancer (OC or GEJC): nivolumab as monotherapy is indicated for the adjuvant treatment of adult patients with oseophageal or gastro-oesophageal junction cancer who have residual pathologic disease following prior neoadjuvant chemoradiotherapy.

Gastric, gastro-oesophageal junction (GEJ) or oesophageal adenocarcinoma: nivolumab in combination with fluoropyrimidine- and platinum-based combination chemotherapy is indicated for the first-line treatment of adult patients with HER2-negative advanced or metastatic gastric, gastro-oesophageal junction or oesophageal adenocarcinoma whose tumours express PD-L1 with a combined positive score (CPS) ≥ 5.

The most common adverse reactions of nivolumab as monotherapy are fatigue (30%), rash (17%), pruritus (13%), diarrhea (13%), and nausea (12%). The majority of adverse reactions were mild to moderate (Grade 1 or 2).

A variety of serious immune-mediated adverse reactions have also been observed in patients receiving nivolumab, including pneumonitis, colitis, hepatitis, nephritis, hypothyroidism and hyperthyroidism, and other immune-mediated adverse reactions.

Further details regarding the clinical experience with nivolumab may be found in the current version of the approved nivolumab investigator brochure.

Approval of nivolumab in Squamous Cell Cancer of the Head and Neck was based on data from an international, multi-center, open-label, randomized, phase III trial (CheckMate 141) [24]. Eligible patients were 18 years of age or older, had histologically confirmed, recurrent/metastatic HNSCC of the oral cavity, oropharynx, hypopharynx, or larynx, and had tumor progression on or within 6 months after the last dose of platinum-based chemotherapy administered in the locally advanced, recurrent, or metastatic disease setting. Patients (361) were randomized 2:1 to receive nivolumab (3 mg/kg every 2 weeks) (240) or standard single agent of investigator's choice (methotrexate 40–60 mg/m^2 weekly, docetaxel 30–40 mg/m^2 weekly, or cetuximab 400 mg/m^2 once, then 250 mg/m^2 weekly) and stratified by prior cetuximab treatment (121). Treatment continued until tumor progression or unacceptable toxicity. Patients in the nivolumab arm were allowed to continue nivolumab treatment beyond tumor progression if they met predefined, protocol specified criteria.

In a 2-year long-term survival update, the median overall survival was 7.7 months (95% CI, 5.7 to 8.8) in the nivolumab group versus 5.1 months (95% CI, 4.0 to 6.2) in the standard-therapy group [44]. Overall survival was significantly longer with nivolumab than with standard therapy, and nivolumab treated patients had a risk of death that was 32% lower than the risk among patients assigned to standard therapy (hazard ratio, 0.68; 95% CI, 0.54 to 0.96; P = 0.01). The estimated rate of overall survival at 2 years among patients treated with nivolumab (16.9%; 95% CI, 12.4 to 22.0) was nearly triple that of standard therapy (6.0%; 95% CI, 2.7 to 11.3). The response rate among nivolumab-treated patients was 13.3% (95% CI, 9.3 to 18.3), including 7 complete responses and 25 partial responses. In the standard-therapy group, the response rate was 5.8% (95% CI, 2.4 to 11.6), including 1 complete response and 6 partial responses.

Serious adverse reactions occurred in 49% of patients receiving nivolumab. The most frequent serious adverse reactions reported in at least 2% of patients receiving nivolumab were pneumonia, dyspnea, respiratory failure, respiratory tract infection, and sepsis. The most common adverse reactions occurring in more than 10% of nivolumab-treated patients and at a higher incidence than investigator's choice were cough and dyspnea. The most common laboratory abnormalities occurring in 10% or more nivolumab-treated patients and at a higher incidence than investigator's choice were increased alkaline phosphatase, increased amylase, hypercalcemia, hyperkalemia, and increased TSH. In the clinical trial, 13.1% of patients taking nivolumab had severe side effects related to treatment compared with 35.1% of patients in the standard therapy group. Fatigue, nausea, rash, decreased appetite, and pruritus were the most common side effects in patients treated with nivolumab.

Additional details on clinical experience with nivolumab are provided in the current version of the nivolumab Investigator's Brochure (IB).

5.2. Study rationale

While there is much excitement around the phenomenon of a chemo-induced anticancer immune response and combining biotherapy with immunotherapy, numerous questions remain to be addressed in clinical trials. A major challenge is to identify not only the optimal immune checkpoint inhibitor as partner for a given chemotherapy schedule but also the best chronological sequence for their combined application.

Chemotherapy for incurable recurrent or metastatic HNSCC disease is palliative and usually platimun based, and the patients often present with poor physical condition due to alcohol and tobacco habits, malnutrition and comorbidities. Consequently, many of them are not able to withstand a platinum-based chemotherapy. The addition of taxanes to the armamentarium of drugs improve the outcome in this group. An alternative and better tolerated regimen for these patients is paclitaxel in combination with cetuximab [17]. However, the outcome of these patients still remains poor, with a median PFS and OS of 4 and 8 months respectively.

Recently, new treatments such as immune-checkpoint inhibitors have shown promising activity and good tolerability in patients with R/M HNSCC and has been included in the recently published guidelines from the Society for Immunotherapy of Cancer [40]. Nivolumab (anti-PD1) has been approved for patients progressing on or after platinum-based therapy, as it clearly impacts on overall survival. CheckMate 141 study results showed a clear improvement in overall survival in the nivolumab group versus the standard-therapy group (7.7 months versus 5.1 months), but only patients with ECOG 0-1 were included [44], therefore it is necessary to evaluate the safety and efficacy of treatments with nivolumab in patients with a more compromised performance status than those included in that study.

Preclinical data suggests that paclitaxel may have a role as an immuno-modulator, mainly by increasing tumor infiltrating CD8+ lymphocytes. We expect that nivolumab in combination with paclitaxel would improve the outcome of patients unable for a cisplatin-based first-line chemotherapy.

For patients unable for a cisplatin-based first-line chemotherapy is important to identify an appropriate combination of therapy can represent a significant addition to the therapeutic armamentarium. The presence of severe comorbidities, age-related frailty or underlying severe psychosocial problems may be obstacles for highly intensive treatment plans. Such patients may benefit from less complicated or potentially less toxic treatment plans. The biology of the patient’s disease must also be considered in selecting or planning a combined modality approach. The goals of the addition of engineered monoclonal antibodies (MoAbs) to chemotherapy in a treatment plan, must be considered in this population to improved survival, optimization of quality of life and control of metastases.

The most common treatment toxicity grade 3/4 of paclitaxel and cetuximab published by Hitt et col. [17], were acne-like rash (24%), asthenia (17%) and neutropenia (13%), with grade 3/4 febrile neutropenia in 1 patient. Grade 3 infusion-related reactions were observed in two patients during paclitaxel infusion. These reactions were managed with medication and treatment delay and both patients then continued in the study until progression disease. Grade 3/4 gastrointestinal toxicity and renal toxicity were reported in 3% and 5% of patients, respectively. Commonly occurring lower grade treatment-related adverse events included: grade 1–2 conjunctivitis (15%) and peripheral neuropathy (4%); grade 1–3 alopecia (13%), grade 1–2 diarrhea (22%) and vomiting (22%) and grade 1–3 onycholysis (24%). Grade 1–2 hypomagnesemia was reported in seven patients (15%). Only two patients withdrew from the study due to treatment-related toxicity (conjunctivitis grade 3 and febrile neutropenia grade 4). No toxic deaths were recorded and in general treatment was well tolerated [17].

The toxicity of immunotherapy is dependent on the administered agent and dosage. In previous clinical trials, immune checkpoint blockade immunotherapy presented acceptable toxicity. Even occasional severe toxicity was manageable through treatment interruption or involvement of immunosuppressive drugs. During ipilimumab treatment approximately 60 % patients showed immune-related adverse events, of them 10–15 % being grade 3–4 [45]. The blockade of PD-1/-L1 showed less severe ir-AEs in previous phase I studies [46]. Diarrhea and skin rash were the most common immune-related adverse events after ipilimumab. Other adverse effects included enterocolitis, hypothyroidism, hypophysitis and neuropathies [46]. The most common adverse events reported for both nivolumab and pembrolizumab were mild fatigue, rash, pruritus and diarrhea, which could be usually managed without dose interruption or discontinuation [46]. In Clinical Trial CA209-141, 13.1% of patients treated with nivolumab had severe side effects related to treatment compared with 35.1% of patients in the standard therapy group [24]. Considering the different kinds and acceptable adverse events, the combination treatment of paclitaxel and immune checkpoint inhibitors seems feasible for HNSCC patients.

Adverse events (AEs) of these new regimens are described to be mild compared with those of classical chemotherapy [47]. Overall, these clinical observations provide a sound rationale for investigating immune checkpoint inhibitors with paclitaxel for primary treatment of recurrent or metastatic HNSCC unable for cisplatin-based chemotherapy.

5.3. Study 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:

Secondary objectives of this study are:

- 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) [2] 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.
- 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

6. STUDY DESIGN

6.1. Overall design

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). PD-L1 determination (CPS, before patient inclusion) will be performed by a central lab (Pathological Anatomy Service, Hospital 12 de Octubre, Madrid, Spain)
3. If oropharyngeal cancer: oropharyngeal cancer HPV+ (p16 IHC & HPV DNA) vs oropharyngeal cancer HPV– / non-oropharyngeal cancer). For subjects with oropharyngeal cancer, sites 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.

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, follow 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.

  ERBITAX has been chosen as a control group since it is the standard treatment in Spain for this patients and to have a contemporary reference with a profile of patients equal to that of the experimental arm.

Patient will start study treatment within 48 hours of randomization.

The premedication used for paclitaxel, nivolumab and cetuximab will be according to each participating site standard of care.

In Arm 1 paclitaxel premedication must be administered during or after the observation period (30 minutes following nivolumab infusion).

Tumor progression and response endpoints will be assessed using RECIST 1.1 criteria.

Tumor assessments performed as standard of care prior to obtaining informed consent and within 28 days prior to initiation of study treatment do not have to be repeated at screening. Screening assessments must include CT scans (with oral or IV contrast) of the chest and abdomen and CT scans (with oral or IV contrast) or MRI (with contrast) of the head and neck region. If a CT scan with contrast is contraindicated (e.g., in patients with contrast allergy or impaired renal clearance), a non-contrast CT scan of the chest may be performed and MRI with contrast scans of the abdomen and head and neck region must be performed. All measurable and non-measurable lesions should be assessed and documented at screening. If both a CT scan with contrast is contraindicated (e.g., in patients with impaired renal clearance or contrast allergy) and MRI is contradicted (e.g., in patients with claustrophobia), non-contrast CT scans of the chest, abdomen, and head and neck region may be performed only upon prior approval from the coordinating investigators.

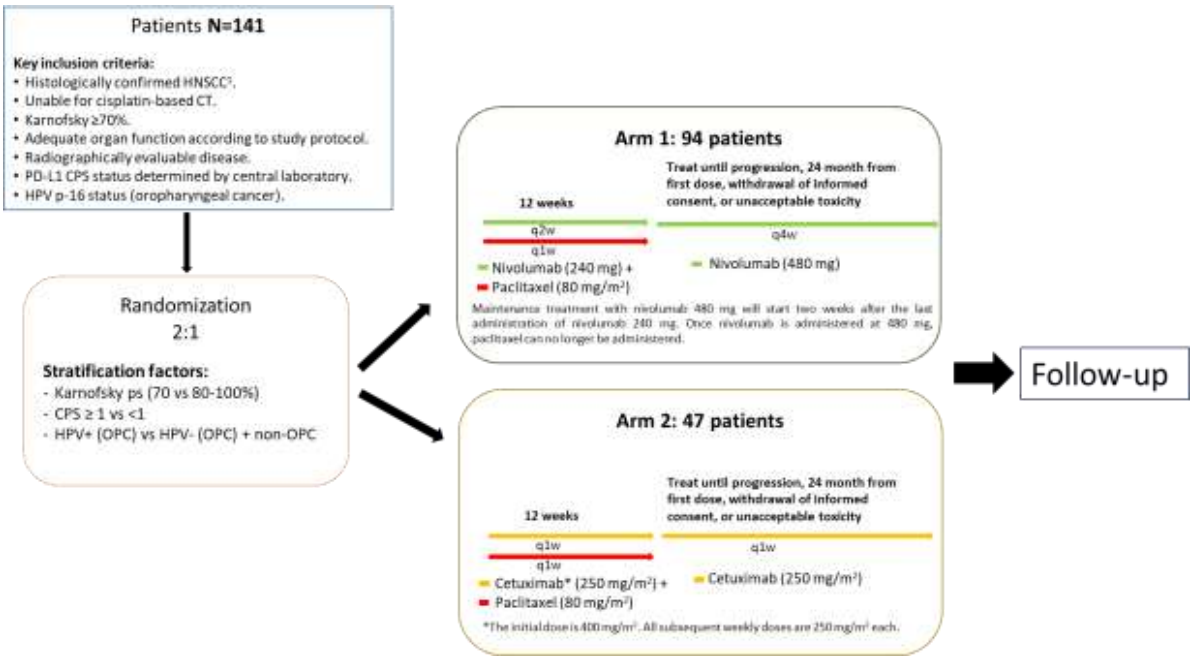
An evaluation of disease response using the RECIST version 1.1 will be performed at screening/baseline (within 28 days before the first study drug administration), at week 9 and then every 12 weeks until disease progression.

Dose modification (interruption or reduction) of cetuximab or paclitaxel should be done according to SmPC (see sections 9.4.4 and 9.4.5).

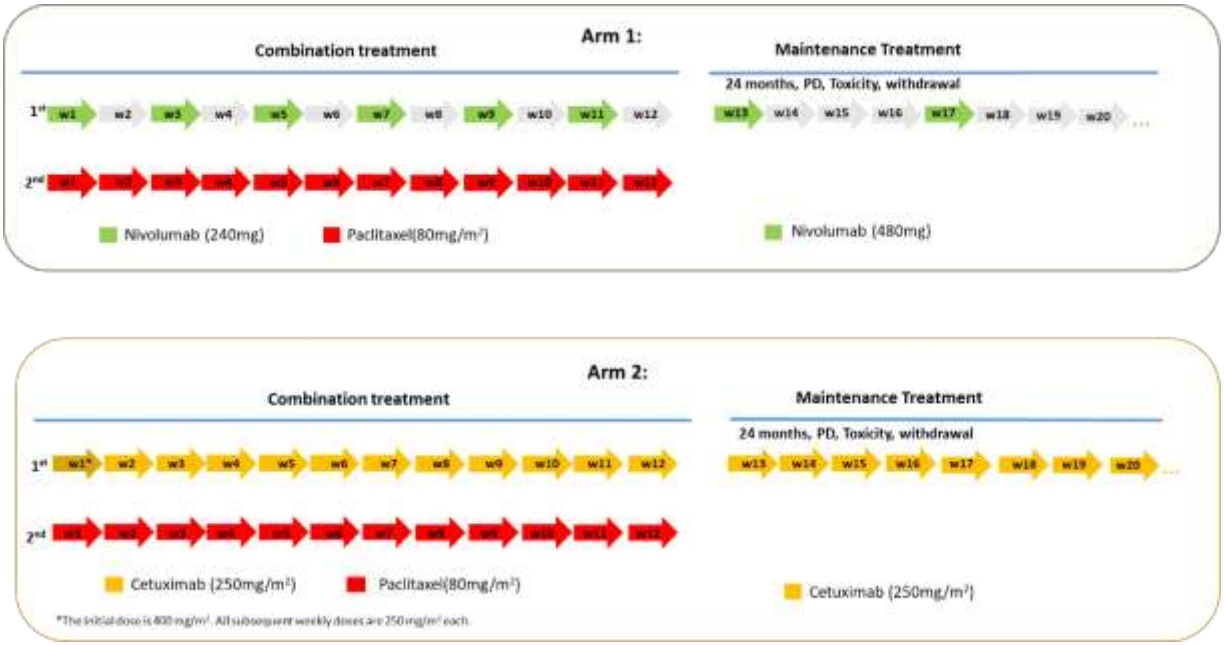
Dose reductions will be not be allowed for nivolumab. Only dose interruption **for a maximum of 6 weeks**, are allowed (see section 9.4.3.).

Cetuximab has to be permanently discontinued in case of administration interruption for 4 consecutive infusions due to any relevant circumstance. Principal investigator and study coordinators could assess the possibility of treatment reintroduction if cetuximab administration benefit is clearly documented.

Study Scheme



Study Treatment



Patient will start study treatment within 48 hours of randomization.

Tumor progression and response endpoints will be assessed using RECIST 1.1 criteria.

Since the combination of paclitaxel and nivolumab in HNSCC has not yet been studied, the sponsor will establish a study data monitoring committee for reviewing safety data of the combination. This committee will consist of the two coordinating investigators and at least 5 of the participating investigators who will review the available safety information.

The study data monitoring committee will evaluate the safety profile of the combination once the first 10 patients included in the nivolumab arm have finished the combined treatment with paclitaxel. Additionally, the study data monitoring committee will review the available safety information every three months. It is not considered necessary to make more frequent reviews since both drugs are widely used in the participating oncology departments, there is sufficient experience in their use and the safety profile of both drugs is clearly defined.

During the periodic reviews, the study data monitoring committee together with the sponsor will review the available safety data (adverse events, serious adverse events, dropouts) and make a recommendation on whether or not to continue recruiting patients in the study, depending on the safety data from patients included. In any case, if an unexpected event related to patient safety is detected, it will be notified to the participating investigators and will be evaluated by the sponsor and the study data monitoring committee, which could increase the frequency of safety reviews if deemed appropriate.

6.2. Primary endpoint

Primary endpoint of the study is two years overall survival.

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.

6.3. Secondary endpoints

PFS is defined as the time 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.

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.

Disease control rate (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.

Duration of Response (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.

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.

Efficacy (ORR, PFS, OS) will be evaluated 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-PS.

All randomized subjects will be monitored by radiographic assessment at week 9 (± 7 days) and then every 12 weeks (± 7 days). RECIST 1.1 criteria will be used for the assessment.

Subjects will be evaluated for safety if they have received any study drug. Toxicity assessments will be continuous during the treatment phase and the safety follow-up phase. Adverse events and laboratory values will be graded according to the NCI-CTCAE version 5.0. Subjects will be followed for drug-related toxicities until these toxicities resolve, return to baseline or are deemed irreversible. All adverse events will be documented for minimum of 100 days after the last dose of study medications. On-study weight, Karnofsky performance status, and vital signs should be assessed at each on-study visit prior to dosing. Vital signs should also be taken as per institutional standard of care prior to, during and after infusions. The start and stop time of the study therapy infusions should be documented.

Physical examinations are to be performed as clinically indicated. If there are any new or worsening clinically significant changes since the last exam, report changes on the appropriate non-serious or serious adverse event page.

Laboratory toxicities (eg, suspected drug induced liver enzyme evaluations) will be monitored during the follow-up phase via on site/local labs until all study drug related toxicities resolve, return to baseline, or are deemed irreversible.

The safety analysis will be performed in all treated subjects. Descriptive statistics of safety will be presented using the NCI CTCAE version 5.0 by treatment arm. All AEs, drug-related AEs and SAEs will be tabulated using the worst grade per NCI CTCAE v 5.0 criteria by system organ class and preferred term.

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, incidence of deaths and percentage of patients with each AE per grade will be provided.

7. PATIENT SELECTION

Patients diagnosed with HNSCC who are unable for first-line cisplatin-based chemotherapy and not previously treated for recurrent/metastatic disease will be include in the study.

Patients will be distributed in the following way:

- **Group 1**: Platinum resistant population (one third of the patients – 47 patients):

  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/m^2 of cisplatin.

- **Group 2**: Platinum sensitive but unable for cisplatin-based therapy according to one of these criteria (one third of the patients – 47 patients):

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), 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 (one third of the patients – 47 patients) (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.

Once the planned recruitment in groups 1 or 3 is completed, sponsor will evaluate the number of patients recruited in each of the other groups as well as the remaining recruitment time to confirm whether the proportion of patients to be included in each group is maintained.

7.1. 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 (see 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/m^2 or 3 cycles induction TPF (with cisplatin ≥75/m^2) 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/m^2 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 annex 10) health status screening score ≥ 14.

    a. <u>Female patients:</u>

        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 (see annex 6) 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

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 5 mm^3 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.

7.2. 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 can only be included with a G8 (Geriatric 8) health status screening score < 14.
2. Karnofsky <70%.
3. Patients that meets **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 (see annex 5),
    c. Class III heart failure according to the New York Heart Association (annex 9).
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.

7.3. Randomization procedures

After the subject's initial eligibility is established and informed consent has been obtained, the subject must be enrolled into the study through the e-CRF to obtain the subject number. Every subject that signs the informed consent form must be assigned a subject

number. The investigator or designee will register the subject for enrollment by following the enrollment procedures. The date that informed consent was obtained is required for enrollment.

Once enrolled in the eCRF, enrolled subjects that have met all eligibility criteria will be ready to be randomized. Karnofsky, CPS score ≥1 / <1 (PD-L1) and HPV p16 result (positive, negative or not oropharyngeal cancer) will be entered by the site directly into the eCRF for randomization.

Enrollment will stop once 141 subjects have been randomized.

Patient will start study treatment within 48 hours of randomization.

7.4. Blinding procedures

Not applicable. Open label study.

8. WITHDRAWAL CRITERIA

8.1. Reasons for Withdrawal

Subjects who request to discontinue study drug will remain in the study and must continue to be followed for protocol specified follow-up procedures except when a subject specifically withdraws consent for any further contact with him/her. The withdrawal of consent should be explained in detail in the medical records by the investigator and entered on the appropriate CRF page.

All reasonable efforts must be made to locate subjects to determine and report their ongoing status. Lost to follow-up is defined by the inability to reach the subject after a minimum of three documented phone calls or emails. All attempts should be documented in the subject's medical records. If it is determined that the subject has died, the site will try to obtain the date and cause of death.

8.2. Discontinuation of study drug

Subjects MUST discontinue study treatment for any of the following reasons:

- Subject's request to stop study treatment
- Any clinical adverse event (AE), laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the subject
- Progression disease
- Interruption of nivolumab for 6 weeks or more.
- Termination of the study by the sponsor
- Loss of ability to freely provide consent
- Pregnancy

8.3. Handling of Withdrawals

In the case of pregnancy, the investigator must immediately notify the sponsor or designee of this event. In most cases, the study drug will be permanently discontinued. Please contact the sponsor or designee within 24 hours of awareness of the pregnancy.

All subjects who discontinue study drug should comply with protocol specified follow-up procedures. The only exception is when a subject withdraws consent for all study procedures including post-treatment study follow-up.

If study drug is discontinued prior to progression disease, the reason for the discontinuation must be documented in the subject's medical records and entered on the eCRF.

8.4. Reserve and Replacement Subjects

Subjects who discontinue study drug or withdraw consent should not be replaced.

9. INVESTIGATIONAL PRODUCT

Nivolumab, cetuximab and paclitaxel are the investigational medicinal products in this clinical trial.

The sponsor, by means of manufacturer, will supply free of charge, nivolumab for the conducting of the clinical trial. Cetuximab and paclitaxel will be provided by each participant site as they are the usual treatment in Spain for these patients.

9.1. Investigational product description

9.1.1. Description

Nivolumab

Nivolumab is a clear to opalescent, colourless to pale yellow liquid that may contain few light particles. The solution has a pH of approximately 6.0 and an osmolality of approximately 340 mOsm/kg.

Nivolumab is a human immunoglobulin G4 (IgG4) monoclonal antibody (HuMAb), which binds to the programmed death-1 (PD-1) receptor and blocks its interaction with PD-L1 and PD-L2. The PD-1 receptor is a negative regulator of T-cell activity that has been shown to be involved in the control of T-cell immune responses. Engagement of PD-1 with the ligands PD-L1 and PD-L2, which are expressed in antigen presenting cells and may be expressed by tumours or other cells in the tumour microenvironment, results in inhibition of T-cell proliferation and cytokine secretion. Nivolumab potentiates T-cell responses, including anti-tumour responses, through blockade of PD-1 binding to PD-L1 and PD-L2 ligands. In syngeneic mouse models, blocking PD-1 activity resulted in decreased tumour growth.

Nivolumab as monotherapy is indicated for the treatment of recurrent or metastatic squamous cell cancer of the head and neck in adults progressing on or after platinum-based therapy. Nivolumab is indicated also in different types of cancer as melanoma, non-small cell lung cancer, renal cell carcinoma, Hodgkin lymphoma urothelial carcinoma and gastro-oesophageal junction cancer

Cetuximab

Cetuximab 5 mg/mL solution for infusion is a colourless solution supplied in vials containing 20 mL of solution.

Cetuximab is a chimeric monoclonal IgG1 antibody that is specifically directed against the epidermal growth factor receptor (EGFR).

EGFR signalling pathways are involved in the control of cell survival, cell cycle progression, angiogenesis, cell migration and cellular invasion/metastasis. Cetuximab binds to the EGFR with an affinity that is approximately 5- to 10-fold higher than that of endogenous ligands. Cetuximab blocks binding of endogenous EGFR ligands resulting in inhibition of the function of the receptor. It further induces the internalisation of EGFR, which can lead to down-regulation of EGFR. Cetuximab also targets cytotoxic immune effector cells towards EGFR-expressing tumour cells (antibody dependent cell-mediated cytotoxicity, ADCC).

The protein product of the proto-oncogene RAS (rat sarcoma) is a central down-stream signal-transducer of EGFR. In tumours, activation of RAS by EGFR contributes to EGFR-mediated increased proliferation, survival and the production of pro-angiogenic factors.

Cetuximab inhibits the proliferation and induces apoptosis of human tumour cells that express EGFR. In vitro cetuximab inhibits the production of angiogenic factors by tumour cells and blocks endothelial cell migration. In vivo cetuximab inhibits expression of angiogenic factors by tumour cells and causes a reduction in tumour neo-vascularisation and metastasis.

Paclitaxel

Paclitaxel 6 mg/ml, concentrate for solution for infusion is a clear colourless to slightly yellow solution free from visible particles with a pH in range of 3.0 – 5.5 and an osmolarity of > 4000 mOsm/l.

Paclitaxel is an antimicrotubule agent that promotes the assembly of microtubules from tubulin dimers and stabilises microtubules by preventing depolymerization. This stability results in the inhibition of the normal dynamic reorganisation of the microtubule network that is essential for vital interphase and mitotic cellular functions. In addition, paclitaxel induces abnormal arrays or bundles of microtubules throughout the cell cycle and multiple asters of microtubules during mitosis.

9.1.2. Packaging

Nivolumab

Nivolumab 10 mg/mL concentrate for solution for infusion. One vial of 10 mL contains 100 mg of nivolumab. 10 mL of concentrate in a 10 mL vial (Type I glass) with a stopper (coated butyl rubber) and a grey flip-off seal (aluminium).

Nivolumab will be labelled with the study protocol code, batch number, content, expiry date, storage conditions, investigator and sponsor name. The study medication will be labelled in accordance with annex 13 of the European Good Manufacturing Practices.

Cetuximab

Each mL of solution for infusion contains 5 mg cetuximab. Each vial of 20 mL contains 100 mg cetuximab.

Cetuximab 5 mg/mL solution for infusion is supplied in vials containing 20 mL of solution in a vial (Type I glass) with a stopper (halobutyl rubber) and a seal (aluminium/polypropylen).

Paclitaxel

Paclitaxel 6 mg/ml Concentrate for Solution for Infusion.

Paclitaxel 6 mg/ml, concentrate for solution for infusion is a clear colourless to slightly yellow solution free from visible particles with a pH in range of 3.0 – 5.5 and an osmolarity of > 4000 mOsm/l.

Paclitaxel is supplied in type I glass vials (closed with Omniflex Plus rubber stopper and sealed with aluminium flip off seal).

9.1.3. Shipping, Storage and Disposal

Nivolumab

Nivolumab must be stored in a refrigerator (2°C to 8°C). The vials must be kept in the original package in order to protect from light. Nivolumab should not be frozen.

The unopened vial can be stored at controlled room temperature up to 25°C with room light for up to 48 hours.

Nivolumab injection it is preferred to administer the drug product immediately. If not used immediately, the solution may be stored under refrigeration conditions (2°C-8°C) and protected from light for up to 7 days, including the product administration period or as described in the instructions provided to the clinical site. The infusion solution may be stored at room temperature (up to 25ºC) and room light for a maximum of 8 hours, including the product administration period.

Do not store any unused portion of the infusion solution for reuse. Any unused medicine or waste material should be disposed of in accordance with local requirements.

If the study drugs are destroyed at the hospital site, the investigator is responsible for ensuring that the appropriate procedures are followed when destroying them, as per corresponding institutional regulations, guidelines, and procedures. Satisfactory records of the destruction of the drugs should also be maintained so that these procedures can be verified. Any unused study drugs can be destroyed only once the clinical trial monitor has inspected them and carried out the drug accountability.

All unused or partially used study drugs can be destroyed on site, as long as the site has a standard operating procedure to this effect.

Cetuximab

Cetuximab must be stored in a refrigerator (2°C to 8°C). Cetuximab should not be frozen.

Chemical and physical in-use stability of cetuximab 5 mg/mL has been demonstrated for 48 hours at 25ºC.

Cetuximab does not contain any antimicrobial preservative or bacteriostatic agent. From a microbiological point of view, the product shall be used immediately after opening. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8ºC, unless opening has taken place in controlled and validated aseptic conditions.

Do not store any unused portion of the infusion solution for reuse. Any unused medicine or waste material should be disposed of in accordance with local requirements.

If the study drugs are destroyed at the hospital site, the investigator is responsible for ensuring that the appropriate procedures are followed when destroying them, as per corresponding institutional regulations, guidelines, and procedures. Satisfactory records of the destruction of the drugs should also be maintained so that these procedures can be verified. Any unused study drugs can be destroyed only once the clinical trial monitor has inspected them and carried out the drug accountability.

All unused or partially used study drugs can be destroyed on site, as long as the site has a standard operating procedure to this effect.

Paclitaxel

Do not store above 25°C. Keep the vial in the outer carton in order to protect from light. Freezing does not adversely affect the unopened vials.

After opening before dilution: Chemical and physical in-use stability has been demonstrated for 28 days at 25°C following multiple needle entries and product withdrawal. From a microbiological point of view, once opened the product may be stored for a maximum of 28 days at 25°C. Other in-use storage times and conditions are the responsibility of the user.

After dilution: Chemical and physical in-use stability of the solution prepared for infusion has been demonstrated at 5°C and at 25°C for 7 days when diluted in 5% Dextrose solution, and for 14 days when diluted in 0.9% Sodium Chloride Injection. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

9.2. Dosage and administration

Patient will start study treatment within 48 hours of randomization.

Nivolumab plus paclitaxel

Patients will receive nivolumab 240 mg via IV infusion through a 0.2-micron to 1.2-micron pore size, low-protein binding (polyethersulfone membrane) in-line filter.

Nivolumab will be administered as an intravenous infusion over 30 minutes every 2 weeks during paclitaxel treatment (first 12 weeks of treatment).

Paclitaxel IV infusion will start at least 30 minutes after completion the nivolumab infusion.

Paclitaxel premedication must be administered during or after the observation period (30 minutes following nivolumab infusion).

Paclitaxel will be administered as 60 minutes IV infusion every week at a dose of 80 mg/m² during 12 weeks.

Nivolumab

Once paclitaxel cycles are completed, nivolumab will be switch to 480 mg administered as an intravenous infusion over 60 minutes every 4 weeks until disease progression, unacceptable toxicity or withdrawal of consent up to a maximum of 24 months, which occur first.

Patient will be monitored for an observation period of at least 30 minutes after nivolumab infusion is completed.

Maintenance treatment with nivolumab 480 mg 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.

Cetuximab plus paclitaxel

Cetuximab is administered once a week. The initial dose is 400 mg/m^2 over 2 h.

A close monitoring of patients, particularly during the first administration, is required. Special attention is recommended for patients with reduced performance status and pre-existing cardio-pulmonary disease.

All subsequent weekly doses are 250 mg/m^2 each.

From second administration, cetuximab will be administered as an intravenous infusion over 60 minutes every week during paclitaxel treatment (first 12 weeks of treatment).

Cetuximab will be administered first.

Paclitaxel IV infusion will start one hour after completion the cetuximab infusion. Premedication used for paclitaxel and cetuximab will be according to each participating site standard of care.

Paclitaxel will be administered as 60 minutes IV infusion every week at a dose of 80 mg/m² during 12 weeks.

Cetuximab

Once paclitaxel cycles are completed, cetuximab treatment will be administered at same dose as an intravenous infusion over 60 minutes every week until progression disease, intolerable toxicity, patient withdrawal or during 24 months, which occur first.

After completion of the cetuximab infusion, patient will be monitored according to site standard of care.

9.3. Treatment duration

In arm 1, after 12 infusions of paclitaxel, nivolumab will be switch to 480 mg administered as an intravenous infusion over 60 minutes every 4 weeks until disease progression, unacceptable toxicity or withdrawal of consent up to a maximum of 24 months.

Maintenance treatment with nivolumab 480 mg 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.

In arm 2, after 12 infusions of paclitaxel, cetuximab will be administered via IV infusion over 60 minutes every week until disease progression, unacceptable toxicity or withdrawal of consent up to a maximum of 24 months.

Maintenance treatment with weekly cetuximab will continue after the end of the combination treatment.

During maintenance treatment nivolumab or cetuximab will be administered up to a maximum of 24 months from start of combination treatment (C1D1).

9.4. Criteria for dose adjustments

Dose reductions will not be allowed for nivolumab.

Dose modification (delay, interruption or reduction) of cetuximab or paclitaxel should be done according to SmPC (see sections 9.4.4 and 9.4.5 for dose reductions).

Patients on the study will be evaluated weekly during the first 12 weeks of study treatment and every 2 weeks thereafter. After 12 weeks of treatment, in cases in which either nivolumab, cetuximab or paclitaxel monotherapy continues following discontinuation of the other drug due to toxicities, patients will be evaluated every 4 weeks until PD or treatment discontinuation.

Toxicities are to be assessed according to the NCI CTCAE version 5.0. The causal relationship of each AE should be assessed in relation to nivolumab, paclitaxel or cetuximab so that dose modifications can be made accordingly. Administration and dose modification of nivolumab will follow prescribing information for nivolumab and also the guidance described in this section (see section 9.4.4). Dose modification guidelines for hematologic and non-hematologic toxicities will be performed based on the type and severity of AEs, causality determination by investigators, and safety and tolerability profiles of each of the study drugs. Only dose interruption and discontinuation **for a maximum of 6 weeks**, not dose reductions, are allowed for nivolumab.

Per the dose modification guidelines, patients who have the paclitaxel or cetuximab held because of treatment-related or possibly related AEs may resume study drug after resolution of the AE; they may either maintain the same dose level or have doses of study drugs reduced by dose reduction allowed only for each (paclitaxel, cetuximab) according to SmPC. When a dose reduction of paclitaxel or cetuximab occurs, dose should not be reescalated.

If one study drug is delayed because of toxicity attributed to its use, the other study drug will be administered as scheduled unless otherwise specified.

Study drug(s) can be held at the investigator's discretion for high-grade, non-drug-related toxicities if it is considered to be necessary in the clinical management of the event.

However, when study drug(s) resumes after resolution of the non-drug-related event, it should be done according SmPC. If multiple toxicities are noted, the dose adjustments and/or delays should be made according to the most severe toxicity guidelines and the causal relationship to one or both study drugs.

When the dose of study drug(s) is withheld based on toxicity, clinical and laboratory re-evaluation should be repeated at least weekly or more frequently until the toxicity resolves to ≤Grade 1 or baseline, or to an acceptable level according to the investigator's assessment. Upon recovery, study drug(s) may be reinitiated either at the same dose level or at a reduced dose level (dose reduction not allowed for nivolumab). When a dose reduction of paclitaxel or cetuximab is required, no re-escalation of dose will be permitted.

For treatment-related, Grade 4 non-hematologic toxicities, dose reduction of paclitaxel more than 2 dose levels or treatment delay for >6 weeks for nivolumab or > 4 weeks for cetuximab, in general, require that study treatment will be permanently discontinued. If, in the opinion of the investigator and the sponsor (coordinating investigator), it is in the patient's best interest to continue study treatment, then the study drug(s) can be resumed at the same dose after recovery of the toxicity or toxicities to Grade 1 or baseline. However, no exceptions should be made in the case of adverse reactions that result in nivolumab discontinuation as required per the most recent nivolumab SmPC. In particular, the study discontinuation required due to the immune-related AEs or infusion reactions associated with the use of nivolumab should not be overridden.

For transient lab value abnormalities that, based on investigator assessment, are not clinically significant or are most probably related to disease and not the study treatment, continuation of therapy without following the dose modification guidelines is permissible upon discussion with the coordinating investigator.

In general, the study drug(s) will resume only after the resolution of AEs to ≤Grade 1 or baseline or as specified in these dose modification guidelines. However, retreatment with study drug(s) could start when the AEs are resolved to a level deemed acceptable by the investigator based on consideration of the individual patient situation and discussions/agreement with the coordinating investigator.

In general, dose modification guidelines must follow the recommendations of nivolumab, paclitaxel and cetuximab SmPC. However, in individual patient cases, following discussion and agreement between the investigator and the coordinating investigator, alternative dose modifications may be recommended to maximize exposure to study treatment while protecting patient safety. However, nivolumab discontinuation should not be overridden.

9.4.1. Nausea and/or Vomiting

A patient who develops nausea and/or vomiting will be actively managed by employing optimal antiemetic treatment based on local standard practice.

Additionally, antiemetics may be used prophylactically as clinically indicated following the occurrence of a first event of study drug-related or possibly related nausea and/or vomiting. An optimal antiemetic regimen is defined as one that employs both a 5-HT3 antagonist and a corticosteroid given in standard doses and according to standard schedules.

9.4.2. Anemia, Thrombocytopenia, and/or Neutropenia

Hemoglobin and blood counts should be monitored regularly as outlined in the protocol with additional testing obtained according to standard clinical practice. Administration of nivolumab, cetuximab or paclitaxel should be modified according investigator brochure and summary of product characteristics. RBC transfusion and use of erythropoietin to manage severe anemia, platelet transfusion to prevent and minimize bleeding in case of severe thrombocytopenia, and myeloid growth factor (eg, G-CSF, GM-CSF) support to treat severe and/or febrile neutropenia are permitted per ESMO/SEOM guidelines, as necessary.

However, it should be noted that prophylactic use of myeloid growth factors is not permitted.

9.4.3. Nivolumab dose adjustments

Dose reductions will not be allowed for nivolumab. Only dose interruption **for a maximum of 6 weeks**, are allowed.

9.4.3.1. Criteria to Resume Nivolumab Treatment

Subjects may resume treatment with nivolumab when the drug-related AE(s) resolve(s) to Grade 1 or baseline, with the following exceptions:

- Subjects may resume treatment in the presence of Grade 2 fatigue.
- Subjects who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity.
- For subjects with Grade 2 AST/ALT and/or total bilirubin values, dosing may resume when laboratory values return to baseline and management with corticosteroids, if needed, is complete.
- Drug-related pulmonary toxicity, diarrhea, or colitis must have resolved to baseline before treatment is resumed. Subjects with persistent Grade 1 pneumonitis after completion of a steroid taper over at least 1 month may be eligible for retreatment if discussed with and approved by the coordinating investigator.
- Subjects with drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment after consultation with the coordinating investigator.
- Adrenal insufficiency requires discontinuation regardless of control with hormone replacement.

9.4.3.2. Immune-Mediated Adverse Reactions

Immune-mediated AEs can occur with nivolumab, both during treatment and following discontinuation. For any suspected immune-mediated AEs, other causes should be excluded. Based on the severity of the adverse reaction, nivolumab should be permanently discontinued or withheld, high-dose corticosteroids should be administered, and if appropriate, hormone-replacement therapy should be initiated. Upon improvement to Grade 1 or less, a corticosteroid taper should be initiated and continued over at least 1 month. Consideration should be given to restarting nivolumab after completion of the corticosteroid taper based on the severity of the event. For more information related to the management of immune mediated adverse reactions associated with nivolumab, see Annex 13.

9.4.3.3. Other Immune-Mediated Adverse Reactions

Nivolumab can cause other clinically significant and potentially fatal immune-mediated adverse reactions. Immune-mediated adverse reactions may occur after discontinuation of nivolumab therapy. For any suspected immune-mediated adverse reactions, exclude other causes. Based on the severity of the adverse reaction, permanently discontinue or withhold nivolumab, administer high-dose corticosteroids, and if appropriate, initiate hormone-replacement therapy. See the ***current nivolumab*** IB version for more information related to other immune-mediated adverse reactions.

9.4.3.4. Nivolumab Infusion Reactions

Since nivolumab contains only human immunoglobulin protein sequences, it is unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgia, hypotension, hypertension, bronchospasm, or other allergic-like reactions. Infusion reactions should be graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.0 guidelines.

Treatment recommendations are provided below and may be modified based on local treatment standards and guidelines, as appropriate:

For Grade 1 symptoms (mild reaction; infusion interruption not indicated; intervention not indicated):

- Remain at bedside and monitor participant until recovery from symptoms. The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg, at least 30 minutes before subsequent nivolumab/nivolumab placebo administrations.

For Grade 2 symptoms (moderate reaction required therapy or infusion interruption but responds promptly to symptomatic treatment [eg, antihistamines, non-steroidal anti-inflammatory drugs, narcotics, corticosteroids, bronchodilators, IV fluids]; prophylactic medications indicated for < 24 hours):

- Stop the study drug infusion, begin an IV infusion of normal saline, and treat the participant with diphenhydramine 50 mg IV (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg; remain at bedside and monitor participant until resolution of symptoms. Corticosteroid and/or bronchodilator therapy may also be administered, as appropriate. If the infusion is interrupted, then restart the infusion at 50%

of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor the participant closely. If symptoms recur, then no further study medication will be administered at that visit.

- For future infusions, the following prophylactic premedications are recommended: diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg should be administered at least 30 minutes before nivolumab/nivolumab placebo infusions.

If necessary, corticosteroids (up to 25 mg of hydrocortisone or equivalent) may be used.

For Grade 3 or 4 symptoms (severe reaction, Grade 3: prolonged [ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion]; recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae [eg, renal impairment, pulmonary infiltrates]; Grade 4: Life threatening; pressor or ventilatory support indicated):

- Immediately discontinue infusion of study drug. Begin an IV infusion of normal saline and treat the participant as follows: Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Participant should be monitored until the Investigator is comfortable that the symptoms will not recur. Study drug will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor the participant until recovery of the symptoms.

In the case of late-occurring hypersensitivity symptoms (eg, appearance of a localized or generalized pruritus within 1 week after treatment), symptomatic treatment may be given (eg, oral antihistamine or corticosteroids).

9.4.4. Cetuximab dose adjustments

Cetuximab has to be permanently discontinued in case of administration interruption for 4 consecutive infusions due to any relevant circumstance. Principal investigator and study coordinators could assess the possibility of treatment reintroduction if cetuximab administration benefit is clearly documented.

9.4.4.1. Skin reaction

If a patient experiences grade 3 skin toxicity (according to NCI-CTCAE v 5.0), cetuximab infusion may be delayed up to four consecutive infusions while maintaining the same dose. The investigator can establish a concomitant treatment with moisturizers and/or topical and/or oral antibiotics and/or topical corticosteroids. If skin toxicity decreases to grade ≤2 before the next cetuximab infusion, treatment can be restarted. If new episodes of grade 3 skin toxicity occur for a second or third time, treatment with cetuximab should be temporarily discontinued for up to 4 consecutive weeks by reducing the doses to 200 mg/m^2 and 150 mg/m^2, respectively. Dose reductions of cetuximab are permanent. Treatment with cetuximab should be discontinued if four consecutive infusions are suspended or if a new episode of grade 3 skin toxicity occur for the fourth time.

The patient should be monitored weekly until rash resolution. If the patient is benefiting from treatment with cetuximab, the principal investigator and/or coordinating investigator can evaluate the possibility that the patient continues receiving cetuximab.

If the patient has a grade 4 skin toxicity, treatment with cetuximab should be discontinued. If the infusion of cetuximab is suspended for 4 consecutive weeks due to toxicity to cetuximab, or for intercurrent disease (eg infection) that requires discontinuation of study treatment, treatment with cetuximab should be definitely interrupted, except when the patient is benefiting from cetuximab treatment. In that case, the principal investigator and/or coordinating investigator can evaluate the possibility that the patient continues receiving cetuximab.

9.4.4.2. Allergic reactions

If the patient has a hypersensitivity reaction, the investigator must establish the therapeutic measures corresponding to the best available medical practice. Based on previous experience with hypersensitivity reactions, the following treatment guidelines may apply:

Treatment modifications in case of allergic or hypersensitivity reaction to cetuximab

Grade 1
The infusion rate may be decreased to 50% and monitor closely monitor the patient for any worsening. The total infusion time of cetuximab should not exceed 4 hours.

Grade 2
Stop cetuximab infusion. Bronchodilators, oxygen, etc., should be administered according to the best available medical practice. Resume the infusion at 50% of the previous infusion rate once the severity of the allergic reaction has disappeared or decreased to grade 1 and closely monitor the patient for any worsening.

Grade 3 or Grade 4
Immediately stop cetuximab infusion. Adrenaline, bronchodilators, antihistamines, glucocorticoids, intravenous fluids, vasoconstrictors, oxygen, etc., should be administered when clinically indicated. Stop cetuximab treatment immediately.

9.4.4.3. Cetuximab administration after hypersensitivity reactions

Once the infusion rate of cetuximab is decreased due to the occurrence of an allergic or hypersensitivity reaction, this infusion rate should be maintained during subsequent infusions. If a patient has a second allergic or hypersensitivity reaction with the slowest infusion rate, treatment with cetuximab should be discontinued. If at any time a patient experiences a grade 3 or 4 allergic or hypersensitivity reaction, cetuximab should be definitively interrupted.

9.4.4.4. Cetuximab dose modifications or delayed administration for another reason

If a patient has a concomitant disease (eg, an infection) that, in the opinion of the investigator and/or coordinating investigator, forces the treatment interruption, this concomitant disease must be cured within a period of time less than the corresponding to four consecutive infusions of cetuximab. If treatment with cetuximab is delayed, a loading dose is not administered but the planned dose is administered. If the administration of

cetuximab is interrupted for a long period of time, the patient is withdrawn from the study except for patients who are getting benefit with cetuximab that will be evaluated by principal investigator and coordinating investigator.

9.4.5. Paclitaxel dose adjustments

Safety assessments should be performed within 24 hours prior to the administration of paclitaxel. In addition, patients should be carefully examined on the day paclitaxel is administered.

Paclitaxel should not be delayed due to toxicity related to cetuximab or nivolumab. Paclitaxel modifications are based on the observed toxicities and are graded according to NCI-CTCAE v 5.0. The dose of paclitaxel is modified according to the time at which the toxicity appears. The doses of paclitaxel should be modified according to the neutrophil and platelet count, and according to the worst grade of non-hematological toxicity.

Dose modifications are permanent and are based on the dose administered in the last infusion. Once the dose is reduced, this dose should be maintained for all following paclitaxel administrations.

9.4.5.1. Previous requirements for paclitaxel administration

The decision to administer paclitaxel is based on neutrophil and platelet counts and the severity of mucositis or other non-hematologic toxicities observed on the day the treatment has to be administered.

To administer paclitaxel, the following conditions must be met:

- Neutrophils ≥ 1,500 / mm³.
- Platelets ≥ 100,000 / mm³.
- No presence of mucositis grade ≥2 or any other non-hematological toxicity grade 3-4 (except alopecia or nausea and / or vomiting).

If a patient cannot receive paclitaxel due to toxicity, the dose is interrupted for a week. If after one week delay the patient continues unable to receive paclitaxel, the treatment is delayed another week. If patient cannot receive paclitaxel for 28 days, paclitaxel treatment will be discontinued and patient can receive cetuximab or nivolumab monotherapy according to the treatment arm.

In case of grade 2 mucositis, although neutrophils and platelets are at normal values, administration of paclitaxel is interrupted one week. In case of mucositis grade 3-4, paclitaxel is interrupted and the doses are reduced in the following administrations. In case of treatment delays, all evaluations will be performed as planned.

9.4.5.2. Paclitaxel dose reductions

Three levels of paclitaxel dose reduction have been planned: 70 mg/m²; 60 mg/m²; and 50 mg/m². If a new dose reduction is required with the administration of 50 mg/m², the administration of paclitaxel is definitely interrupted and patient can continue with cetuximab or nivloumab monotherapy.

A dose level of paclitaxel will be reduced in case of:

- Febrile neutropenia grade 3-4
- Thrombocytopenia grade 3-4
- Mucositis grade 3-4
- Neuropathy grade 2
- Any other grade 3-4 toxicity
- Interruption of paclitaxel for 2 consecutive weeks due to toxicity
- Interruption of paclitaxel one week after administration of paclitaxel, twice in a row.

Once a paclitaxel dose reduction due to toxicity is made, the dose of paclitaxel will not be increased at any time during the study.

9.4.5.3. Paclitaxel interruption

In the event of the following toxicities, paclitaxel treatment will be definitively interrupted, and patient can receive monotherapy treatment:

- Grade 3-4 neurological toxicity
- Second or third degree atrioventricular block or cardiac arrhythmia, with the exception of asymptomatic isolated extrasystoles
- Severe hypersensitivity reaction
- Paclitaxel interruption of 28 days due to toxicity
- If patient is receiving administration of 50 mg/m² of paclitaxel and a new dose reduction is required.

9.5. Accountability

Nivolumab will be provided by the sponsor. Cetuximab and paclitaxel are commercialised drugs which will be provided by the pharmacy department of the participating trial sites.

The monitor will oversee study drugs in the hospital's pharmacy. Nivolumab accountability will be documented and the quantities delivered, dispensed, returned and destroyed will be verified. Cetuximab and paclitaxel compliance will be assessed through the administration sheets available at the pharmacy department of the participating trial sites.

All inventory forms for the study medication must be available for inspection by authorised representatives of the sponsor or by inspectors from regulatory authorities. The investigator is responsible for the accountability of all used and unused study supplies at their site.

Accountability forms for study medication must be available for review by authorised representatives of the sponsor or by inspectors from regulatory authorities.

9.6. Auxiliary Medicinal Products

Not applicable.

9.7. Concomitant medication

Investigators may prescribe concomitant medications or treatments deemed necessary to provide adequate prophylactic or supportive care except for those medications identified as “prohibited”.

Premedication used for paclitaxel, nivolumab and cetuximab will be according to each participating site standard of care. In Arm 1 paclitaxel premedication must be administered during or after the observation period (30 minutes following nivolumab infusion).

Therapies that are required to manage AEs and control cancer symptoms are allowed based on standard clinical practice, unless specifically excluded. Supportive care agents, such as erythropoietin, G-CSF, blood products (red blood cell and platelet transfusions), and pain medications are permitted as needed per European Society for Medical Oncology (ESMO) guidelines, SEOM guidelines or local institutional practice. Nivolumab is associated with immune-related AEs, which may be managed per clinical judgment of the investigator in accordance with the institutional guideline and the most recent nivolumab investigator brochure.

The Investigator must be informed as soon as possible about any medication taken from the time of screening until the end of the clinical phase of the study (end of study visit). Patients must be instructed not to take any medications, including over-the-counter products, without first consulting with the Investigator.

All concomitant medications should be reported to the investigator and recorded on the appropriate eCRF.

Inhaled or topical steroids, and adrenal replacement steroid doses > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease. Subjects are permitted the use of topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption). A brief (less than 3 weeks) course of corticosteroids for prophylaxis (eg, contrast dye allergy) or for treatment of non-autoimmune conditions (eg, delayed type hypersensitivity reaction caused by a contact allergen) is permitted.

9.8. Prohibited drugs

The following medications and procedures are prohibited during the study:

- Any antineoplastic therapy other than nivolumab, paclitaxel or cetuximab.
- Chronic use of corticosteroids at daily doses greater than the equivalent of 10 mg of prednisone as part of any anticancer treatment regimens. Physiologic replacement doses of systemic corticosteroids are permitted, even if >10 mg/day prednisone or equivalents.
- Radiation therapy. Palliative radiotherapy for pain control in a pre-existing lesion may be considered after discussion with the sponsor and coordinating investigator.
- Prophylactic use of myeloid growth factors or granulocyte macrophage-colony stimulating factor. In case of neutropenia drugs administration should be stopped till recovery and subsequent dose reduction according to protocol. Supportive care agents, such as erythropoietin, G-CSF, blood products (red blood cell and platelet transfusions), and pain medications are permitted as needed per European Society

for Medical Oncology (ESMO) guidelines, SEOM guidelines or local institutional practice.

- Immunosuppressive medications within 14 days of start study treatment.

9.9. Precautions

The metabolism of paclitaxel is catalysed, in part, by cytochrome P450 isoenzymes CYP2C8 and CYP3A4. Caution should be exercised when administering paclitaxel concomitantly with medicines known to inhibit either CYP2C8 or CYP3A4 (e.g. ketoconazole and other imidazole antifungals, erythromycin, fluoxetine, gemfibrozil, clopidogrel, cimetidine, ritonavir, saquinavir, indinavir, and nelfinavir) because toxicity of paclitaxel may be increased due to higher paclitaxel exposure. Administering paclitaxel concomitantly with medicines known to induce either CYP2C8 or CYP3A4 (e.g. rifampicin, carbamazepine, phenytoin, efavirenz, nevirapine) is not recommended because efficacy may be compromised because of lower paclitaxel exposures.

Paclitaxel should be administered with caution in patients receiving protease inhibitors as concomitant therapy.

Caution should be used regarding the use of herbal medications as there may be as yet unknown interactions with study medication. Discontinuation of the use of herbal medications prior to study enrollment is encouraged.

10. STUDY SCHEDULE

Study Procedures	**Screening (Days -28 to -1)**	**Paclitaxel combination treatment (12 weeks) (±3 days)**	**Monotherapy treatment phase (±3 days)**	**EOT /withdrawal visit (±3 days)[19]**	**Safety follow-up visit (+30 days ±7 days)[20]**	**Follow-up (every 12 weeks ±7 days)**
		Every week	**Every 2 weeks**			
Informed Consent Form	X					
Eligibility criteria	X					
Medical history	X					
Vital signs[2]	X	X	X	X	X	
Demographic[3]	X					
Physical examination[4]	X	X	X	X	X	
Height	X					
Weight	X	X	X	X	X	
Karnofsky PS	X	X	X	X	X	
HPV status [5]	X					
12-lead ECG	X	If clinically indicated				
Hematology[6]	X	X[18]	X[18]	X	X	
Serum chemistry[7]	X	X[18]	X[18]	X	X	
Thyroid panel[8]	X	X[18]	X[18]	X	X	
Coagulation	X				X	
Urinalysis[9]	X	If clinically indicated			X	
Serology [10]	X					
Pregnancy test[11]	X	X	X	X	X	X[11]
Tumor Tissue Sample (PD-L1)[12]	X					
Tumor assessment[13]	X	X[13]	X[13]	X	X	
Nivolumab administration[14]		Q2w	Q4w			

Study Procedures	Screening (Days -28 to -1)	Paclitaxel combination treatment (12 weeks) (±3 days)	Monotherapy treatment phase (±3 days)	EOT /withdrawal visit (±3 days)[19]	Safety follow-up visit (+30 days ±7 days)[20]	Follow-up (every 12 weeks ±7 days)
		Every week	**Every 2 weeks**			
Cetuximab administration[15]		Q1w	Q1w			
Paclitaxel administration[16]		Q1w				
Adverse events	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	
Anticancer treatments						X
Overall survival						X[17]

1. All subjects must first read, understand, and sign the approved ICF before any study-specific screening procedures are performed.

2. Vital signs include heart rate, respiratory rate, blood pressures, and temperature. Measure vital signs before dosing (-10 minutes) and postdose (+10 minutes) of nivolumab. Blood pressure should be determined with the patient in a seated position after the patient has been sitting quietly for 5 minutes. Oxygen saturation will also be measured when vital signs are taken.

3. Sex, age, and self-reported race/ethnicity.

4. Includes evaluation of the **head, eyes, ears, nose, and throat** and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems.

5. OPC 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.

6. Include absolute red blood cell count (RBC), hemoglobin, hematocrit, platelet count, white blood cell count (WBC), with differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils). Hematology will be performed **every 4 weeks during monotherapy treatment**, except in case of a clinically significant alteration that will be performed at investigator criteria.

7. Chemistry panel including: ALT, AST, total bilirubin, creatinine or creatinine clearance, alkaline phosphatase, BUN or serum urea level, Ca, Mg, Na, K, Cl, LDH, Glucose, amylase, lipase, phosphate. Chemistry panel will be performed **every 4 weeks during monotherapy treatment**, except in the case of a clinically significant alteration (eg magnesium) that will be performed at investigator criteria.

8. Thyroid panel including: TSH, Free T4, Free T3 or Total T3, will be determined **every 8 weeks**.

9. Urinalysis: pH, protein, glucose, ketones, blood, leucocytes, nitrite and specific gravity.

10. Serology: Hepatitis B surface antigen (HBsAg), and hepatitis C antibody (HC Ab) or Hepatitis C RNA (HCV RNA). 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 positive (except if HCV-RNA negative) will not be included.

11. A serum or urine pregnancy test will be performed for women of childbearing potential at Screening (72 hours prior to start study treatment for women of childbearing potential), every 4 weeks, at the end of study treatment, in the safety follow-up visit. In arm 1 pregnancy test will be performed also every 4 weeks until 5 months (150 days) after the last dose of nivolumab.

12. A Tumor sample prior to therapy is mandatory for PD-L1 testing (to be shipped to Central Lab). If a recent tumor sample is not available at screening, a fresh biopsy will be taken at any point prior to randomization. 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. Sufficient tumor tissue should be submitted either one full block (5mm^3 and more than 60% tumor tissue) or minimum of 5 slides, obtained from core biopsy, punch biopsy, excisional biopsy or surgical specimen. 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.

13. Response assessments will be performed at screening, at week 9 and every 12 weeks (+/- 7 days). The same imaging modality and/or the same methods for disease measurement must be used throughout the study. Tumor assessments performed as standard of care prior to obtaining informed consent and within 28 days prior to initiation of study treatment do not have to be repeated at screening. Screening assessments must include CT scans (with oral or IV contrast) of the chest and abdomen and CT scans (with oral or IV contrast) or MRI (with contrast) of the head and neck region. If a CT scan with contrast is contraindicated (e.g., in patients with contrast allergy or impaired renal clearance), a non-contrast CT scan of the chest may be performed and MRI with contrast scans of the abdomen and head and neck region must be performed. All measurable and non-measurable lesions should be assessed and documented at screening. If both a CT scan with contrast is contraindicated (e.g., in patients with impaired renal clearance or contrast allergy) and MRI is contradicted (e.g., in patients with claustrophobia), non-contrast CT scans of the chest, abdomen, and head and neck region may be performed only upon prior approval from the coordinating investigators.

14. A 240 mg dose of Nivolumab will be administered as an intravenous infusion over 30 minutes every 2 weeks during paclitaxel treatment (first 12 weeks of treatment), and paclitaxel infusion will start at least 30 minutes after completion of the nivolumab infusion. Paclitaxel premedication must be administered during or after the observation period (30 minutes following nivolumab infusion). After that, a 480 mg dose over 60 minutes will be administered every 4 weeks until progression disease, intolerable toxicity, patient withdrawal or during 24 months, which occur first.

15. A 250 mg/m2 dose of cetuximab (initial dose is 400 mg/m2 as an intravenous infusion over 120 minutes) will be administered as an intravenous infusion over 60 minutes every week during paclitaxel treatment (first 12 weeks of treatment), one hour before paclitaxel infusion. Cetuximab and paclitaxel premedication will be administered according standard of care at each participating site. After that, cetuximab treatment will be administered at same dose every week until progression disease, intolerable toxicity, patient withdrawal or during 24 months, which occur first.

16. Paclitaxel will be administered IV, at least 30 minutes after completion of the nivolumab infusion (arm 1), at a dose of 80 mg/m² (infusion duration 60 minutes) until disease progression or unacceptable toxicity; and one hour after cetuximab infusion (arm 2) at a dose of 80 mg/m² (infusion duration 60 minutes) until disease progression or unacceptable toxicity.

17. Patient will be followed for at least 5 years or until he/she dies.

18. Hematology and serum chemistry can be done in the 72 hours prior to treatment administration.

19. End of treatment / withdrawal visit will be performed once the principal investigator determines patient discontinuation of study treatment (±3 days).

20. Safety follow up visit will be performed 30 days (±7 days) after the last administration of study treatment or prior to start another new therapy, whichever occurs first.

10.1. Pre-study visit (screening)

Screening procedures will be performed up to 28 days before day 1, unless otherwise specified. All subjects must first read, understand, and sign the approved ICF before any study-specific screening procedures are performed. After signing the ICF, completing all screening procedures, and being deemed eligible for entry, subjects will be enrolled in the study.

Procedures that are performed prior to the signing of the ICF and are considered standard of care may be used as screening assessments if they fall within the 28-day screening window.

The following procedures will be performed during the screening visit:

- Informed consent.
- Review of eligibility criteria.
- Medical history.
- Demographics.
- Physical exam.
- Weight and height
- Karnofsky Performance Status
- Vital signs.
- 12-lead ECG.
- Tumor tissue sample prior to therapy is mandatory for PD-L1 testing (to be shipped to Central Lab for CPS). If a recent tumor sample is not available at screening, a fresh biopsy will be taken at any point prior to randomization. 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. Sufficient tumor tissue (5 mm^3 in which more than 60% of the sample is tumor tissue) should be submitted either one full block or minimum of 5 slides, obtained from core biopsy, punch biopsy, excisional biopsy or surgical specimen. 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.
- HPV status of tumor tissue has to be locally determined at screening for subjects with oropharyngeal cancer 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.
- Review of prior/concomitant medications.
- Review of adverse events.
- Tumor assessment. Tumor assessments performed as standard of care prior to obtaining informed consent and within 28 days prior to initiation of study treatment do not have to be repeated at screening. Screening assessments must include CT scans (with oral or IV contrast) of the chest and abdomen and CT scans (with oral or IV contrast) or MRI (with contrast) of the head and neck region. If a CT scan with contrast is contraindicated (e.g., in patients with contrast allergy or impaired renal clearance), a non-contrast CT scan of the chest may be performed and MRI with contrast scans of the abdomen and head and neck region must be performed. All measurable and non-measurable lesions should be assessed and documented at screening. If both a CT scan with contrast is contraindicated (e.g., in patients with impaired renal clearance or contrast allergy) and MRI is contradicted (e.g., in patients with claustrophobia), non-contrast CT scans of the chest, abdomen, and head and neck region may be performed only upon prior approval from the coordinating investigators. Response assessments for solid tumors will be performed at screening, at week 9 and every 12 weeks (+/- 7 days). The same imaging modality and/or the same methods for disease measurement must be used throughout the study.

- Clinical laboratory tests for:
  - Hematology. CBC w/ differential.
  - Serum chemistry. ALT, AST, total bilirubin, alkaline Phosphatase, BUN or serum urea level, Ca, Mg, Na, K, Cl, LDH, Glucose, amylase, lipase, phosphate.
  - Serum creatinine or Creatinine clearance.
  - TSH, free T3 or total T3 and free T4.
  - Coagulation panel.
  - Serum or urine pregnancy test (within 72 hours prior to start study treatment for women of childbearing potential, including women who have had a tubal ligation).
  - Serology: Hepatitis B surface antigen (HBV sAg), and hepatitis C antibody (HCV Ab) or Hepatitis C RNA (HCV RNA). Subjects who test positive for hepatitis C but have undetectable HCV RNA are allowed to enroll.
  - Urinalysis: blood, glucose, ketones, PH, protein, specific gravity, leucocytes, nitrite.

Clinical laboratory tests could be done in the 72 hours prior any study treatment administration on Day 1 Cycle 1.

10.2. Paclitaxel combination treatment visits (first 12 weeks of treatment)

The following procedures will be performed during the study treatment visits until week 12:

Day 1 and every week (± 3 days)

- Physical exam. Includes evaluation of the head, eyes, ears, nose, and throat and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems.
- Weight.
- Karnofsky Performance Status
- Vital signs.
- 12-lead ECG, if clinically indicated.
- Review of concomitant medications.
- Review of adverse events.
- Clinical laboratory tests for:
  - Hematology. CBC w/ differential.
  - Serum chemistry. ALT, AST, total bilirubin, alkaline Phosphatase, BUN or serum urea level, Ca, Mg, Na, K, Cl, LDH, Glucose, amylase, lipase, phosphate.
  - Serum creatinine or Creatinine clearance.
  - TSH, Free T3 or total T3 and free T4, **every 8 weeks.**
  - Serum or urine pregnancy test every 4 weeks (+/- 7 days) for women of childbearing potential.
  - Urinalysis: blood, glucose, ketones, PH, protein, specific gravity, leucocytes, nitrite, if clinically indicated.
- Tumor assessment **at week 9** (+/- 7 days) and every 12 weeks (+/- 7 days) thereafter. The same imaging modality and/or the same methods for disease measurement must be used throughout the study.

Clinical laboratory tests could be done in the 72 hours prior to any study treatment administration.

10.3. Monotherapy treatment visits (cetuximab or nivolumab)

The following procedures will be performed during the monotherapy treatment visits every 2 weeks:

- Physical exam. Physical exam. Includes evaluation of the head, eyes, ears, nose, and throat and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems.
- Weight.
- Karnofsky Performance Status.
- Vital signs.
- 12-lead ECG, if clinically indicated.
- Review of concomitant medications.
- Review of adverse events.
- Clinical laboratory tests **(every 4 weeks [-72 hours])** for:
  - Hematology. CBC w/ differential.
  - Serum chemistry. ALT, AST, total bilirubin, alkaline Phosphatase, BUN or serum urea level, Ca, Mg, Na, K, Cl, LDH, Glucose, amylase, lipase, phosphate.
  - Serum creatinine or Creatinine clearance.
  - TSH, Free T3 or total T3 and free T4**, every 8 weeks.**
  - Serum or urine pregnancy **test every 4 weeks** (+/- 7 days) for women of childbearing potential.
  - Urinalysis: blood, glucose, ketones, PH, protein, specific gravity, leucocytes, nitrite, if clinically indicated.
- Tumor assessment **every 12 weeks** (+/- 7 days). The same imaging modality and/or the same methods for disease measurement must be used throughout the study.

Clinical laboratory tests could be done in the 72 hours prior to any study treatment administration (every 4 weeks).

10.4. End of treatment / Withdrawal visit

End of treatment / withdrawal visit will be performed once the principal investigator determines patient discontinuation of study treatment (±3 days).

The following procedures will be performed:

- Physical exam.
- Weight.
- Karnofsky Performance Status.
- Vital signs.
- 12-lead ECG, if clinically indicated.
- Review of concomitant medications.
- Review of adverse events.
- Clinical laboratory tests for:
  - Hematology. CBC w/ differential.
  - Serum chemistry. ALT, AST, total bilirubin, alkaline Phosphatase, BUN or serum urea level, Ca, Mg, Na, K, Cl, LDH, Glucose, amylase, lipase, phosphate.
  - Serum creatinine or Creatinine clearance.
  - TSH, Free T3 or total T3 and free T4.

- Serum or urine pregnancy test for women of childbearing potential.
- Tumor assessment: For study withdrawal not due to progression disease, tumor assessment will be done if clinically indicated.

10.5. Safety follow-up visit

Safety follow up visit will be performed 30 days (±7 days) after the last administration of study treatment or prior to start another new therapy, whichever occurs first.

The following procedures will be performed:

- Physical exam.
- Weight.
- Karnofsky Performance Status.
- Vital signs.
- 12-lead ECG, if clinically indicated.
- Review of concomitant medications.
- Review of adverse events.
- Clinical laboratory tests for:
  - Hematology. CBC w/ differential.
  - Serum chemistry. ALT, AST, total bilirubin, alkaline Phosphatase, BUN or serum urea level, Ca, Mg, Na, K, Cl, LDH, Glucose, amylase, lipase, phosphate.
  - Serum creatinine or Creatinine clearance.
  - TSH, Free T3 or total T3 and free T4.
  - Urinalysis: blood, glucose, ketones, PH, protein, specific gravity, leucocytes, nitrite.
  - Serum or urine pregnancy test for women of childbearing potential.
  - Coagulation panel.

10.6. Follow-up visits

Follow-up visits will be performed every 12 weeks (±7 days).

The following procedures will be performed:

- Assessments for disease progression. Tumor assessment will be performed until disease progression or until the patient receives another anticancer therapy.
- Anticancer therapy.
- Survival status.
- Review of adverse events. AEs and SAEs related to study treatment will be monitored until resolution or end of study.
- Serum or urine pregnancy test every 4 weeks (+/- 7 days) for women of childbearing potential until 5 months after the last dose of nivolumab or 4 weeks after the last dose of cetuximab.

Telephone follow-up visits may be performed if it is not necessary to do any specific study assessment.

11. ASSESSMENT OF SAFETY / ADVERSE EVENTS

Safety information should be collected in clinical studies in an efficient and consistent way. Adverse events must be identified and notified rapidly to identify possible risks to patients and satisfy regulatory requirements for notification of adverse events.

Subjects will be followed for drug-related toxicities until these toxicities resolve, return to baseline or are deemed irreversible. All adverse events will be documented for minimum of 100 days after the last dose of study medications.

11.1. Definitions

11.1.1. Adverse event (AE)

An AE is any undesired experience that occurs in a patient participating in clinical research that is associated in time with the use of a medicinal product, whether or not it is considered to be related to the investigational products. Therefore, an adverse event can be any unintentional unfavorable sign (including an anomalous laboratory result), symptom or disease that is associated in time with the use of a medicinal product, whether or not it is considered to be related to the product. Pre-existing diseases that worsen during the study shall be notified as Adverse Events.

AEs include pre- or post-treatment events that occur as a result of study procedures (e.g. invasive procedures or modification of the patient's previous medication).

11.1.2. Serious adverse event (SAE)

A SAE is an undesired medical experience that, at any dose:

- Results in death.
- Is life-threatening: (NOTE: The term "life-threatening" refers to the fact that the patient is at risk of death as a result of this event, not that death might have occurred if the SAE had been more intense).
- Results in the patient's hospitalization or prolongs a previous hospitalization (NOTE: In general, hospitalization means that the patient has remained [generally at least overnight] in the hospital or emergency room for observation or treatment that could not have been given/administered in the doctor's office or outpatient clinic. Complications that occur during a hospitalization are AEs. If a complication prolongs hospitalization or satisfies any of the other criteria for seriousness, then the event will be considered SAE. When any doubt exists as to whether a "hospitalization" has taken place or was necessary, the AE will be considered serious. The hospitalization to implement scheduled treatment of a disease present before the subject entered the study and that has not worsened with respect to baseline is not considered an AE).
- results in disability or incapacity (NOTE: Disability refers to an important alteration in a person's capacity to carry out his or her own daily living tasks, not minor clinical ailments such as headaches, nausea, vomiting, diarrhea, flu or accidental injuries (such as a sprained ankle), that can interfere with the functions of daily life, but do not alter them in an important way).
- results in a congenital anomaly or birth defect.
- is medically important (meaning important adverse events that are not immediately life-threatening or do not cause death or require patient

hospitalization but can endanger the patient or may require some type of intervention to prevent one of the results cited above).

- Suspected transmission of an infectious agent (eg, pathogenic or nonpathogenic) via the study drug is an SAE.

11.1.3. Additional considerations

Alterations in laboratory parameters (hematology, biochemistry or urine analysis), as well as anomalous results of other studies (such as ECGs, radiology, measurements of vital constants), including those that deteriorate in relation to baseline, should be recorded as AEs or SAEs if, in the medical and scientific opinion of the investigator, they are clinically relevant.

On the contrary, clinically significant alterations in safety parameters that are associated with the study disease are not characterized as AEs or SAEs unless the investigator thinks that they are more serious than would be expected considering the state of the patient.

Lack of efficacy (i.e., disease progression) is a disease-related event and should not be classified as a SAE. Death as a result of disease progression is also excluded from the definition of SAEs.

11.2. Characteristics of an adverse event

11.2.1. Causality assessment

The investigator has the obligation to establish the relation of causality between the investigational product administration and (the event) of each AE/SAE. "A reasonable possibility" is proposed to define cases in which there are facts/proof or arguments suggesting a causal relation, more than a relation that cannot be excluded. The investigator will use his or her clinical judgment to determine the relation. Alternative causes, such as the natural history of underlying diseases, concomitant treatment, other risk factors and the temporal relation between the event and the investigational drug will be considered and investigated. The investigator will also consult the investigator's brochure/summary of product characteristics in making the evaluation.

There may be situations in which a SAE occurs and the investigator has only minimal information to include in the initial report to the Sponsor. Nevertheless, it is very important that the investigator evaluate the causality of each event before the initial transmission of data to the Sponsor. The investigator can change his or her opinion about causality based on the information that appears during follow-up, which is why the SAE report may have to be modified. The evaluation of causality is one of the criteria that determine whether a case is compliant or not with the criteria of notification of the Health Authorities.

11.2.2. Expectedness

Unexpected Adverse Events: An unexpected AE is defined as any event not generally taken into consideration and not described in the approved or subsequent documents (e.g., not listed in the SPC, protocol, or the informed consent).

Expected Adverse Events: An expected AE is any adverse event side effect whose nature and intensity have been previously observed and documented for the study product (eg. in the Investigator Brochure, SPC or PIL). Expected AEs do not generally include intended effects of medications.

Expectedness of the reported Adverse Events will be classified by APICES.

11.2.3. Severity

The severity of any AEs will be graded using the CTCAE vs 5.0 (see Annex 4). If the CTCAE has no code that matches, the following guide should be used:

Grade	Description
0	No adverse event
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only
2	Moderate; minimal, local or noninvasive intervention indicated
3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated
4	Life-threatening consequences; urgent intervention indicated
5	Death related to adverse event

Grading of AEs is based on specific clinical criteria that will require evaluation by the study site Investigator. Should an AE stop and then restart, it will be considered two separate events and the severity assessed as described above.

11.3. Reporting procedures

11.3.1. Reporting of adverse events (AEs)

The investigator will try to obtain information about any adverse events that have occurred in all visits by examining or directly interrogating the patient. All serious adverse events that occur during the clinical trial, whether or not they are related to the study drug, must be communicated immediately by telephone and by e-mail to the clinical trial monitor. All information referring to adverse events must be recorded in the respective section of the CRF. All adverse events that occur during the period comprehended from the time of enrollment of the patient in the study (signing of the consent form) to 100 days after discontinuation of the investigational products will be recorded. SAEs related to disease progression or worsening of disease symptoms will not be reportable. When one or more signs or symptoms correspond to a disease, the main diagnosis or syndrome will be notified. All adverse events will be followed until resolution or stabilization, or until it is determined that the study treatment or the patient's participation in the study has not been the cause. All adverse events still present at the end of the study period will be monitored until their final outcome is determined.

11.3.2. Reporting of serious adverse events (SAEs)

The investigator will notify APICES of all serious adverse events that occur during the study within 24 h of receiving knowledge of the same.

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E-mail: safety@apices.es

The investigator will collect information about the SAE on the respective SAE form. The minimum initial information for the notification of an adverse event must include the following:

- Adverse event and date of onset of the adverse event
- Sex and age (or date (month-year) of birth) of the patient
- Information about treatment received
- Name and address of the notifying physician
- Relation of causality with the study medication.

When the SAE is notified with the minimum initial information, the complete SAE notification form with all the information will be sent in the next two working days.

Although pregnancy, overdose, cancer, and potential drug induced liver injury (DILI) are not always serious by regulatory definition, these events must be handled as SAEs.

Any component of a study endpoint that is considered related to study therapy (eg, death is an endpoint, if death occurred due to anaphylaxis, anaphylaxis must be reported) should be reported as SAE.

All SAEs must be collected that occur during the screening period and within 100 days of discontinuation of dosing. If applicable, SAEs must be collected that relate to any later protocol specified procedure (eg, a follow-up skin biopsy).

The Sponsor Institution must report all SAEs, and all follow up information to BMS on an SAE Report Form within 24 hours of becoming aware of the initial event or follow-up information.

BMS SAE, Select Adverse Event and Pregnancy Reporting Information
e-mail: mailto:worlwide.safety@bms.com Fax Number: + 1 609-818-3804

The sponsor/CRO will reconcile the clinical database AE cases (case level only) transmitted to BMS Global Pharmacovigilance (Worldwide.Safety@bms.com).

The sponsor/CRO will request from BMS Worldwide Patient Safety (WWPS), aepbusinessprocess@bms.com the SAE reconciliation report and include the BMS protocol number every 3 months and prior to data base lock or final data summary. WWPS will send the sponsor/CRO the report to verify and confirm all SAEs have been transmitted to BMS WWPS.

The data elements listed on the WWPS reconciliation report will be used for case identification purposes. If the sponsor determines a case was not transmitted to BMS WWPS, the case should be sent immediately to BMS (Worldwide.Safety@bms.com).

11.3.3. Reporting of serious adverse events (SAEs) to Health Authorities

The sponsor is responsible for notifying to the Spanish Health Authorities of all suspected serious adverse reactions and, simultaneously, unexpected, associated with investigational medicinal products of which he has knowledge, which occurred in the clinical trial. This communication shall be made within the time limits established by Spanish legislation. Additionally, suspected serious adverse reactions and, simultaneously, unexpected occurred outside the study should be notified in accordance with the criteria established in the guidelines of the European Commission.

In addition to this, the sponsor must inform without undue delay within fifteen calendar days to the Spanish Health Authorities and the IEC, any information affecting significantly the risk / benefit ratio of the trial. Such notification shall be made in accordance with the guidelines of the European Commission or, where appropriate, with the procedures set forth in the instructions for the conduct of clinical trials in Spain published by the Spanish Health Authorities.

11.3.4. Follow-up of AEs and SAEs

After the initial notification of an AE or SAE, the investigator is required to follow up each case and obtain more data on the patient's state. All the AEs and SAEs documented in previous

visits must be reviewed in subsequent visits. All AEs and SAEs must be monitored until their resolution, stabilization, explanation of the event by another cause, or until the follow-up period ends. This is applicable to all the patients, including those who withdraw early.

The investigator will include in the follow-up any additional research that may clarify the nature and/or causality of the AE or SAE. This might include additional laboratory tests or studies, histopathologic examinations, or the consultation of other healthcare professionals. Any co-investigator can ask the investigator to carry out additional evaluations to definitively clarify the nature and/or the causality of AEs or SAEs. If the patient dies while participating in the study or during a follow-up period agreed upon mutually, the investigator will provide a copy of any postmortem finding requested, including histopathology.

11.3.5. AEs or SAEs that occur after the study ends

Post-study AEs or SAEs are defined as any event that occurs outside the period of detection defined in the protocol. The investigator is not required to actively seek out AEs or SAEs in patients who have participated in the clinical trial in the past. Nevertheless, if the investigator comes to know of the existence of any AE or SAE, including the death of the patient at any time after a patient has left the study, and this AE or SAE is considered related to the study drug, the investigator must notify the sponsor promptly.

11.3.6. Immune-mediated adverse events

Selected Adverse Events (serious or non-serious) that are of scientific and medical concern specific to the nivolumab treatment require ongoing monitoring and rapid communication by the Investigator to the Sponsor Institution and BMS. Nivolumab Immune-mediated AEs (IMAE) are adverse events (that include pneumonitis, diarrhea/colitis, hepatitis, nephritis/renal dysfunction, rash, and endocrine (adrenal insufficiency, hypothyroidism/thyroiditis, hyperthyroidism, diabetes mellitus, and hypophysitis) for which subjects received immunosuppressive medication for treatment of the event, with the exception of endocrine events (hypothyroidism/thyroiditis, hyperthyroidism, hypophysitis, diabetes mellitus, adrenal insufficiency), which are included regardless of treatment since these events are often managed without immunosuppression.

IMAEs, regardless of causality, can occur within 100 days of the last dose.

A summary of the IMAEs category and their respective preferred terms (PTs) are provided below:

IMAE	**PTs included**
Pneumonitis	Pneumonitis, Interstitial lung disease
Diarrhea/Colitis	Diarrhea, Colitis, Enterocolitis
Hepatitis	Hepatotoxicity, Hepatitis, Hepatitis acute, Autoimmune hepatitis, AST increased, ALT increased, Bilirubin increased, ALP increased
Adrenal insufficiency	Adrenal insufficiency
Hypothyroidism/Thyroiditis	Hypothyroidism, Thyroiditis Thyroiditis acute (collapsed with thyroiditis for frequency), Autoimmune thyroiditis (collapsed with thyroiditis for frequency)
Hyperthyroidism	Hyperthyroidism
Hypophysitis	Hypophysitis
Diabetes mellitus	Diabetes mellitus, Diabetic ketoacidosis
Nephritis and renal dysfunction	Nephritis, Nephritis allergic, Tubulointerstitial nephritis, Acute renal

	failure, Renal failure, Increased creatinine
Rash	Rash, Rash maculopapular

11.3.7. Special Situation Reports

The following Special Situation should be collected even in the absence of an AE:

a. Data related to medicinal product usage during pregnancy or breastfeeding
b. Data related to overdose, abuse, misuse and medication error (including potential and intercepted medication errors)
c. Data related to a Suspected Transmission of Infectious Agent by Medicinal Product (STIAMP)
d. Occupational exposure
e. Lack of efficacy
f. Medication error

The investigator will notify the sponsor on the SAE form all special situations detailed above that occur during the study within 24 h of receiving knowledge of the same.

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11.3.8. Pregnancy

If, following initiation of the study treatment, it is subsequently discovered that a participant is pregnant or may have been pregnant at the time of study exposure, including during at least 6 months after product administration for WOCBP, 6 months after product administration for male participants with partners who are WOCBP, the investigator must immediately notify the APICES Monitor/designee of this event and complete and forward a Pregnancy Form to APICES Designee within 24 hours of awareness of the event and in accordance with SAE reporting procedures.

In most cases, the study treatment will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for participant safety). Please call the APICES Medical Monitor within 24 hours of awareness of the pregnancy.

Protocol-required procedures for study discontinuation and follow-up must be performed on the participant.

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported on the Pregnancy Surveillance Form.

Any pregnancy that occurs in a female partner of a male study participant should be reported to sponsor or designee. In order for Sponsor 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. Information on this pregnancy will be collected on the pregnancy form.

11.4. Study data monitoring committee

Since the combination of paclitaxel and nivolumab has not yet been studied in HNSCC, the sponsor will establish a study data monitoring committee for reviewing safety data of the combination. This committee will consist of the two coordinating investigators and at least 5 of the participating investigators who will review the available safety information.

The study data monitoring committee will evaluate the safety profile of the combination once the first 10 patients included in the nivolumab arm have finished the combined treatment with paclitaxel. Additionally, the study data monitoring committee will review the available safety information every three months. It is not considered necessary to make more frequent reviews since both drugs are widely used in the participating oncology departments, there is sufficient experience in their use and the safety profile of both drugs is clearly defined.

During the periodic reviews, the study data monitoring committee together with the sponsor will review the available safety data (adverse events, serious adverse events, dropouts) and make a recommendation on whether or not to continue recruiting patients in the study, depending on the safety data from patients included. In any case, if an unexpected event related to patient safety is detected, it will be notified to the participating investigators and will be evaluated by the sponsor and the study data monitoring committee, which could increase the frequency of safety reviews if deemed appropriate.

12. STATISTICAL CONSIDERATIONS

12.1. General considerations

A brief summary of the general statistical analysis methods is provided below; full details will be provided in a separate Statistical Analysis Plan (SAP), which will be finalized prior to database lock.

12.2. Sample size

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.*

12.3. Analytical Populations

The populations used for analysis will include the following:

- Intent-to-treat (ITT) efficacy population: all patients who are randomized will analyze for efficacy endpoints. This is the primary dataset for analyses of study conduct, study population, and efficacy.
- Safety population: all patients who received at least one dose of the study treatment and had at least one valid post baseline safety assessment.

12.4. Analysis of 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.

OS in each treatment group will be estimated using KM method for all randomized subjects. Median values along with two-sided 95% CI will be calculated. OS rates at 2 and 5 years will be estimated for each treatment arm.

12.5. Analysis of Secondary Objectives

12.5.1. Secondary Efficacy evaluations

Demographics and baseline characteristics will be summarized by treatment arm as randomized using descriptive statistics using the efficacy population.

Efficacy analyses will be performed by treatment arm and also in patients ≥ 70 years.

ORR and DCR will be performed by treatment arm using RECIST criteria v1.1. Number of responses and or stable disease, percentage and 95% CI will be calculated.

Duration of response (DoR), PFS and OS in each treatment group will be estimated using Kaplan Meier method. Median survival time along with 95% CI will be provided.

The distribution of PD-L1 expression (CPS) will be examined using descriptive statistics.

Frequency of BOR and ORR by CPS score ≥1 / <1 (PD-L1) subgroups for each treatment group will be tabulated.

Cox regression on univariate models will be used to calculate the risk reduction (OS and PFS). Hazard ratio (HR) with 95% CIs will be reported to evaluate the impact of treatment arm and stratification variables (CPS (≥1 / <1), HPV (positive vs negative) and Karnofsky PS (70% vs 80-100%)) on the time-to-event efficacy endpoints.

12.5.2. Secondary Safety evaluations

The safety analysis will be performed in all treated subjects. Descriptive statistics of safety will be presented using the NCI CTCAE version 5.0 by treatment arm. All AEs, drug-related AEs, SAEs and drug-related SAEs will be tabulated using the worst grade per NCI CTCAE v 5.0 criteria by system organ class and preferred term.

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 and incidence of deaths will be provided.

13. DATA HANDLING AND QUALITY ASSURANCE

13.1. Monitoring of the trial

The clinical monitors are employees of APICES, and representatives of the sponsor. As such, they have the obligation to follow the trial closely so that all aspects of the trial are carefully monitored for compliance with applicable government regulations and with ICH E6(R2) guidelines.

The clinical monitors will visit the study sites and Investigators at intervals as defined in the monitoring plan, in addition to maintaining necessary contact through telephone, e-mail, and letter. The clinical monitors will maintain current personal knowledge of the trial through observation, review of trial records and source documentation, and discussion of the conduct of the trial with the study site Investigators and staff.

13.2. Audits

The sponsor may choose to schedule and conduct periodic audits of ongoing clinical studies. Audits are independent of, and separate from, routine monitoring or quality control functions and are conducted to assure accuracy and compliance with the protocol, governing regulatory authorities and/or ICH E6(R2) guidelines.

13.3. Reporting of serious breaches

Serious breaches of the authorized protocol or of the Royal Decree 1090/2015 occurring in Spain must be reported by the sponsor without undue delay and no later than seven calendar days from becoming aware of the breach to the Spanish Agency of Medicines and Medical Devices (AEMPS) and the CEIm.

To this end, a serious breach shall be defined as a breach that may significantly affect the safety and rights of the trial subjects or the reliability and robustness of the data generated in the clinical trial.

Only serious breaches should be notified to the AEMPS and the CEIm, and the breaches that do not constitute a serious breach should not be notified.

Each study site Investigator must document and explain in the subject's source documentation any breaches from the approved protocol and / or the Royal Decree 1090/2015. Investigators may implement a breach to eliminate an immediate hazard to trial subjects without prior IEC informed consent approval, but the breach must be reported to the monitor/CRA within 1 working day. Such incidents will be evaluated for potential safety hazards of the ongoing study, and if deemed appropriate, a protocol amendment will be issued.

The monitor/CRA will document breaches throughout the course of monitoring visits. The monitor will notify the Investigator during a visit and a "Breach Form" will be completed and signed by the investigator and by the monitor.

13.4. Data Management

APICES will be responsible for processing and quality control of the data. Data will be handled in accordance with the Data Management Plan, Standard Operating Procedures and applicable regulatory guidelines.

Data management based on GCP refers to activities defined to achieve safe routines for efficient entry of subject information into a database, avoiding errors. The routines include procedures for handling of eCRFs, database set-up and management, data entry and verification, data validation, quality control (QC) of database, and documentation of the performed activities, including information of discrepancies in the process. The database, the data entry screens and the program, will be designed in accordance with the clinical study protocol by APICES.

13.5. Electronic Case Report Forms (eCRFs)

Data collection for this study will consist of electronic data capture for all eCRF information. APICES will supply the eCRF.

All study site Investigators agree to maintain accurate eCRFs and source documentation as part of the case histories.

All information is to be filled in the subject's eCRF. If an enroled subject is not randomized into the study (ie, fails screening), only minimum data (such as demographics and consent date) and the reason for failing screening should be reported on the eCRF. In general, no queries for missing data on these subjects will be issued for procedures indicated as 'Not done'.

For randomized subjects, information captured on the source documents will be entered into the subject's eCRF by study site personnel and monitored at the study site. If an item is not available or is not applicable, this fact should be indicated by a missing reason. Blank spaces should not be present unless otherwise directed. Any corrections should be made using the procedure outlined in the Case Report Form Completion Guide of the study manual and will be recorded in the eCRF.

Each completed eCRF must be reviewed, signed, and dated by the study site Investigator in a timely manner. The completed eCRF will be reviewed by the study Monitor as soon as practical after completion. A copy of the final, approved and signed eCRF will be provided to the site and should be stored in the appropriate files.

13.6. Web-based eCRF

Clinical data (including AEs and concomitant medications) will be entered into an Electronic Data Capture (EDC) application. The data system is password protected and includes internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete or inaccurate. Clinical data will be entered directly from the source documents. Roles and rights of the study site personnel responsible for entering the study data into the eCRF will be determined in advance. Only authorized study site personnel designated by each study site Investigator will complete data collection. Appropriate training and security measures will be completed with the Investigator and all authorized study site personnel, prior to the study initiation, and before any study data is entered into the system.

13.7. Entering of Data into the eCRF

The eCRFs should always reflect the latest observations on the subjects participating in the study. Therefore, the eCRFs should be completed as soon as possible during or after the subject's visit. Each study site Investigator must verify that all data entries in the eCRFs are accurate and correct.

If some assessments are not done, or if certain information is not available, not applicable or unknown, the Investigator or authorized designee should indicate this in the eCRF. The investigator will approve the data using an electronic signature, and this approval is used to confirm the accuracy of the data recorded.

13.8. The Query Process

Each monitor will review the eCRFs and evaluate them for completeness and consistency. Each eCRF will be compared with the respective source documents to ensure that there are no discrepancies between critical data. All entries, corrections and alterations are to be made by the Investigator or his/her authorized designee. The monitor cannot enter data in the eCRFs.

Once clinical data of the eCRF have been submitted to the central server, corrections to the data fields will be audit trailed (ie, the reason for any change, the name of the person who performed the change, and time and date will be logged). If additional corrections are needed, the responsible monitor or Data Manager will raise a query in the EDC application. The appropriate investigational staff will answer queries generated in the application. This process is audit trailed meaning that the name of investigational staff, time, and date is logged.

13.9. Source Documents

The eCRF is essentially considered a data entry form and should not constitute the original (or source) medical records unless otherwise specified. Source documents are all documents used by the Investigator or hospital that relate to the subject's medical history, that verify the existence of the subject, the inclusion and exclusion criteria, and all records covering the subject's participation in the study. They include enrolment and randomization log, investigational product accountability log, laboratory notes, memoranda, material dispensing records, subject files, etc.

Each Investigator is responsible for maintaining source documents. These will be made available for inspection by the study monitor at each monitoring visit. All supportive documentation submitted with the eCRF, such as laboratory data should be clearly identified with the study, visit and subject number. Any personal information (e.g., subject name, initials) should be removed or rendered illegible to preserve individual confidentiality.

13.10. User ID

eCRF records will be automatically appended with the identification of the creator, by means of their unique User ID. Specified records will be electronically signed by the Investigator to document his/her review of the data and acknowledgement that the data are accurate. This will be facilitated by means of the Investigator's unique User ID and password; date and time stamps will be added automatically at time of electronic signature. If an entry in an eCRF requires change, the correction should be made in accordance with the relevant software procedures.

13.11. Audit Trail

To meet regulatory requirements, the eCRF data will be electronically stored at sites. All changes will be fully recorded in a protected audit trail, and a reason for the change will be required. Once all data have been entered, verified, and validated, the database will be locked to prevent any further changes in the clinical study data.

13.12. Inspection of Records

The Investigators and institutions involved in the trial will permit trial-related monitoring, audits, IEC review, and regulatory inspection(s) by providing direct access to all trial records. In the event of an audit, the Investigator agrees to allow the sponsor, representatives of the sponsor, and the governing regulatory agency access to all trial records.

The Investigator should promptly notify the sponsor of any inspections scheduled by any regulatory authorities and promptly forward copies of any inspection reports received to the sponsor.

13.13. Trial Record Retention

Essential documents and eCRF data should be retained during 25 years.

14. ADMINISTRATIVE CONSIDERATIONS

The following administrative items are meant to guide each study site Investigator in the conduct of the study but may be subject to change based on industry and government SOPs or working practice documents or guidelines.

14.1. Legal Considerations

The current clinical trial will be conducted in accordance with the protocol, the principles established in the current revised version of the Declaration of Helsinki (Annex 1) and the applicable regulatory requirements, particularly the ICH Tripartite Harmonized Guidelines for good clinical practice (1996), the Regulation (EU) 536/2014 relative to clinical trials on medicinal products for human use and the locally applicable regulations (e.g., In Spain, the Royal Decree on Clinical Trials 1090/2015).

14.2. Ethics committee review

ICH guidelines require that approval be obtained from Health Authorities and an Ethics Committee before human subjects can participate in research studies. Prior to the trial onset, the protocol, informed consent, advertisements to be used for subject recruitment (if applicable), and any other written information regarding this trial to be provided to the subject will be approved by the Ethics Committee. The clinical study will only be started when both the Health Authorities and an Ethics Committee have considered that the expected benefits for the trial subject and society justify the risks; in addition, the trial will only be continued if compliance with this criterion is constantly supervised.

APICES will obtain Ethics Committee approvals on behalf of the sponsor and investigators. All regulatory approvals should be signed by the Ethics Committee Chairman or designee and must identify the Ethics Committee name and address, the clinical protocol by title and/or protocol number and the date approval and/or favorable opinion was granted. Documentation of all Health Authorities and Ethics Committee approvals and of the Ethics Committee compliance with ICH E6(2) will be maintained by the site and will be available for review.

14.3. Modifications of the protocol

Any change in the approved protocol will require a Protocol amendment. The Investigator must not make any change in the study without favourable opinion from the Ethics Committee and authorization from the Health Authorities, except as necessary to eliminate an impending and obvious risk for the subjects except when necessary to remove an apparent, immediate hazard to subjects. Protocol changes introduced to eliminate an impending and obvious risk may be implemented immediately, but must subsequently be documented in an amendment, reported to the Ethics Committee and be submitted to the relevant Health Authorities within the required timeframe.

Any substantial amendments to the protocol must be submitted in writing to the Ethics Committee and the Health Authorities for approval before the changes proposed in the amendment are implemented. Depending on the magnitude of the change, the recruitment may be temporally halted.

The sponsor does not have to notify non-substantial amendments to the Health Authorities or the Ethics Committee. However, any non-substantial amendments will be recorded and contained in the documentation when it is subsequently submitted, for example in the

subsequent notification of a substantial amendment. Documentation of any non-substantial amendments will be available on request for inspection at the trial site or the sponsor premises as appropriate.

14.4. Informed consent

A written informed consent in compliance with ICH E6 guidelines shall be obtained from each subject before being included in the study or performing any study specific procedures.

In obtaining and documenting informed consent, the Investigator should comply with the applicable regulatory requirements, and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. The consent form and any revision(s) should be approved by the Ethics Committee prior to being provided to potential subjects.

The written Informed Consent Form (ICF) should be prepared in the local language(s) of the potential subject population.

An approved informed consent form will be provided by the sponsor to investigative site.

Before a subject's participation in the study, it is the Principal Investigator's (or their designee) responsibility to obtain freely given consent in writing, from the subject after adequate explanation of the aims, methods, anticipated benefits, and potential risks of the study and before any protocol-specific screening procedures or any study drugs are administered. Subjects must have the opportunity to ask questions and receive answers and will have adequate time to decide whether or not to participate in the study. Once the Investigator is assured that the subject understands the implications of participating in the trial, the subject will be asked to give consent to participate in the trial by signing the informed consent.

The ICF should be signed and personally dated by the subject and by the physician who conducted the informed consent discussion (Principal Investigator or designee). The subject's written informed consent should also be documented in the subject's medical records.

The Investigator shall provide a copy of the signed informed consent to the subject. A second original form shall be maintained in the Investigator study file at the site.

If the informed consent is revised during the course of the trial, all active participating subjects must sign the revised form approved by the Ethics Committee.

The subject participating in a clinical trial, or his/her legal representative, may withdraw consent at any time without giving any reason and without this involving any penalty or prejudice for the participating subject.

14.5. Confidentiality

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain subject confidentiality. Each Investigator will ensure that all site personnel involved will respect the confidentiality of any information about trial subjects. Management of personal data from subjects participating in the trial, particularly as regards consent, will comply with Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data and local laws.

At each site, all records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the subject. Subject identity is confidential and may only be known by the Investigator, trial personnel, appointed auditors and monitors, and Health Authorities.

Each Investigator and all employees and coworkers involved with this trial may not disclose or use for any purpose other than performance of the trial, any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the trial. Prior written agreement from the sponsor or its designee must be collected for the disclosure of any said confidential information to other parties.

14.6. Insurance

The sponsor has contracted an insurance policy to cover the responsibilities of the investigator and other parties participating in the study, according to the applicable legislation.

- Insurance company: Chubb European Group SE
- Policy Number: ESLSC238983

14.7. Publications

The sponsor commits to responsible publication of both the positive and negative results from its clinical trials as required by all governing regulatory and health authorities.

Investigators will not publish the global study results (all sites) unless the sponsor has not done so in a suitable time period after the clinical study report (CSR) has been available. Should the Investigator(s) independently seek to publish results of this study which occur at their study site(s), they must inform the study sponsor of any/all drafts (including, but not limited to papers, manuscripts or abstracts) at least 60 days before submission to the congress, meeting or journal. The sponsor and Investigator(s) will agree with all aspects related to any proposed publications with regards to the following: 1) any proposed publications will be drafted in agreement with international recommendations, such as those from the International Committee of Medical Journal Editors (ICMJE) and all elements of the Consort Statement (2010), to maintain integrity of the trial results in all communications; 2) any proposed publications will state the Clinical Research Ethics Committees which approved the trial and the funding sources of the trial; 3) any proposed publications will occur before disclosure of results to lay people; 4) any proposed publications will not report premature or partial data prior to completion of the analysis of the overall results of the trial.

The order of the authors in the publication will be determined according to the sponsor standard operating procedures.

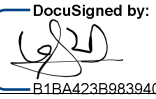
15. SPONSOR'S SIGNATURE PAGE

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)

Study code: TTCC-2019-01 / CA209-7HE / TCC277007

Version number and date: 5.0 - October, 19th, 2022

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable regulations and ICH guidelines.

Position (pre-printed name)	Signature	Signature date (DD-Mmm-YYYY)
Ricard Mesía Ico	DocuSigned by: Ricard Mesía D1B3FBC6243E419...	21-oct.-2022
Lara Iglesias Pi	DocuSigned by:  B1BA423B9839404...	28-oct.-2022

16. INVESTIGATOR'S SIGNATURE PAGE

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)

Study code: TTCC-2019-01 / CA209-7HE / TCC277007

Version number and date: 5.0 - October, 19th, 2022

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable regulations and ICH guidelines.

Principal Investigator's signature	Signature date (DD-Mmm-YYYY)
Investigator's name (capital letters)	
Investigator's signature	Signature date (DD-Mmm-YYYY)
Investigator's name (capital letters)	
Investigator's signature	Signature date (DD-Mmm-YYYY)
Investigator's name (capital letters)	

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Annex 1. Declaration of Helsinki

WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects

Adopted by the
18th WMA General Assembly, Helsinki, Finland, June 1964
and amended by the
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th General Assembly, Somerset West, Republic of South Africa, October 1996
52nd General Assembly, Edinburgh, Scotland, October 2000
Note of Clarification, added by the WMA General Assembly, Washington 2002
Note of Clarification, added by the WMA General Assembly, Tokyo 2004
59th General Assembly, Seoul, Republic of Korea, October 2008
64th General Assembly, Fortaleza, Brazil, October 2013

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words, “The health of my patient will be my first consideration,” and the International Code of Medical Ethics declares that, “A physician shall act in the patient's best interest when providing medical care.”

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician’s knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimises possible harm to the environment.

12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens.

Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by

the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised

representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention

and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports

of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

Annex 2. List of Sites / Principal Investigators

Attached in a separate file.

Annex 3. Informed Consent Form

Attached in a separate file.

Annex 4. NCI-CTC AE Criteria

Common terminology criteria for classification of adverse events version 5.0 (NCI CTC AEv5.0) are available at the following Internet address: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf

Annex 5 Cockcroft-Gault Equation

For male subjects:

$$\text{Creatinine clearance} = \frac{(140 - \text{age[years]}) \times \text{weight [kg]}}{72 \times (\text{serum creatinine[mg/dL]})} \quad \textbf{OR} \quad \frac{(140 - \text{age[years]}) \times \text{weight [kg]}}{0.81 \times (\text{serum creatinine [µmol/L]})}$$

For female subjects:

$$\text{Creatinine clearance} = \frac{0.85\ (140 - \text{age[years]}) \times \text{weight [kg}}{72 \times (\text{serum creatinine[mg/dL]})} \quad \textbf{OR} \quad \frac{0.85\ (140 - \text{age[years]}) \times \text{weight [kg]}}{0.81 \times (\text{serum creatinine[µmol/L]})}$$

Source: Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16(1):31-41.

Annex 6 Methods of Contraception Considered to be Effective

Acceptable Methods Considered Highly Effective

Birth control methods that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered as highly effective. Such methods include:

- combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - oral
  - intravaginal
  - transdermal
- progestogen-only hormonal contraception associated with inhibition of ovulation:
  - oral
  - injectable
  - implantable
- intrauterine device (IUD)
- intrauterine hormone-releasing system (IUS)
- bilateral tubal occlusion
- vasectomised partner
- sexual abstinence

Methods that are Considered Less Highly Effective

Acceptable birth control methods that result in a failure rate of more than 1% per year include:

- progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action
- male or female condom with or without spermicide
- cap, diaphragm or sponge with spermicide

Annex 7 ECOG and Karnofsky performance status

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
Severly disabled. Hospitalisation indicated though death nonimminent	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
Dead	0	5	Dead

http://www.ncbi.nlm.nih.gov/pubmed/7165009

https://oncologypro.esmo.org/Oncology-in-Practice/Practice-Tools/Performance-Scales

Annex 8 Head and neck squamous cell carcinomas

- oral cavity:
  - anterior two thirds of the tongue
  - tongue unspecified,
  - lip
  - gum
  - floor of the mouth
  - hard palate
  - palate unspecified
  - other oral cavity—including buccal mucosa and retromolar area
  - oral cavity unspecified
- oropharynx:
  - base of the tongue
  - soft palate
  - tonsil
  - uvula
  - other parts of the oropharynx
  - Waldeyer’s ring
  - oropharynx unspecified
- larynx:
  - glottis
  - supraglottis
  - subglottis
  - other and unspecified larynx subsites
  - Hypopharynx cases are classified as belonging to the larynx, including pyriform sinus

Annex 9 New York Heart Association Classification of Cardiac Disease

Class	Functional Capacity	Objective Assessment
I	Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.	No objective evidence of cardiovascular disease.
II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of minimal cardiovascular disease
III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain	Objective evidence of moderately severe cardiovascular disease
IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	Objective evidence of severe cardiovascular disease
Source: The Criteria Committee of New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. Ninth Ed. Boston, MA: Little, Brown & Co; 1994:253-256.		

Annex 10 G8 questionnaire

G8 questionnaire

	Items	Possible answers (score)
A	Has food intake declined over the past 3 months due to loss of appetite, digestive problems, chewing or swallowing difficulties?	0 : severe decrease in food intake
		1 : moderate decrease in food intake
		2 : no decrease in food intake
B	Weight loss during the last 3 months	0 : weight loss > 3 kg
		1 : does not know
		2 : weight loss between 1 and 3 kgs
		3 : no weight loss
C	Mobility	0 : bed or chair bound
		1 : able to get out of bed/chair but does not go out
		2 : goes out
E	Neuropsychological problems	0 : severe dementia or depression
		1 : mild dementia or depression
		2 : no psychological problems
F	Body Mass Index (BMI (weight in kg) / (height in m^2)	0 : BMI < 19
		1 : BMI = 19 to BMI < 21
		2 : BMI = 21 to BMI < 23
		3 : BMI = 23 and > 23
H	Takes more than 3 medications per day	0 : yes
		1 : no
P	In comparison with other people of the same age, how does the patient consider his/her health status?	0 : not as good
		0.5 : does not know
		1 : as good
		2 : better
	Age	0 : >85
		1 : 80-85
		2 : <80
	TOTAL SCORE	**0 – 17**

Bellera CA, Rainfray M, Mathoulin-Pélissier S, et al. Screening older cancer patients: first evaluation of the G-8 geriatric screening tool. Ann Oncol 2012; 23: 2166–72.

Annex 11 RECIST Criteria

The RECIST criteria can be accessed at the following internet address:

http://ctep.cancer.gov/protocolDevelopment/docs/recist_guideline.pdf

Annex 12 Combined Positive Score (CPS)

$$CPS = \frac{\text{Number of PD-L1 stained cells (tumor cells, lymphocytes, macrophages)}}{\text{Total number of viable tumor cells}} \times 100$$

Reported as a number (capped at 100)

Annex 13 Management algorithms for immune-mediated adverse reactions

These general guidelines constitute guidance to the Investigator and may be supplemented by discussions with the Medical Monitor representing the Sponsor. The guidance applies to all immuno-oncology agents and regimens.

A general principle is that differential diagnoses should be diligently evaluated according to standard medical practice. Non-inflammatory etiologies should be considered and appropriately treated.

Corticosteroids are a primary therapy for immuno-oncology drug-related adverse events. The oral equivalent of the recommended IV doses may be considered for ambulatory patients with low-grade toxicity. The lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Consultation with a medical or surgical specialist, especially prior to an invasive diagnostic or procedure, is recommended.

The frequency and severity of the related adverse events covered by these algorithms will depend on the immuno-oncology agent or regimen being used.