Investigational Drug	Paclitaxel and Carboplatin
Substance(s)	Not applicable
Study Number	
Version Number	Ver. 1.4
Date	01 Dec 2022

A Phase II Clinical Trial on Surgery After Paclitaxel/Carboplatin as Neoadjuvant Therapy in Locally Advanced Head and Neck Cancer

Sponsor:

Investigator-initiated clinical trial protocol

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PROTOCOL OVERVIEW

Clinical trial title: Phase II Clinical Trial of Surgery After Paclitaxel/Carboplatin Administration as Neoadjuvant Therapy in Locally Advanced Head and Neck Cancer (NEOS)
Phase II trial of neoadjuvant therapy with paclitaxel and carboplatin in operable locally advanced head and neck cancer patients (NEOS)
Plan Number:
Clinical trial phase: Single arm, phase II
Duration of the trial: Subject Recruitment Period: 20 Q1 22 - Q2 2024 Treatment follow-up period: 2 years after completion of treatment in the last subject Expected CSR completion timeline: October 2026
Investigational drug: Paclitaxel is an injectable drug containing a colorless-light yellow clear viscous liquid in a colorless vial and is produced in the form of a glass vial containing 0.1 g of liquid at a concentration of 6 mg/mL for intravenous use. Carboplatin is a brown vial injection solution with a colorless and transparent solution, produced in the form of a 45 mL vial containing 0.45g of liquid at a concentration of 10 mg/mL for intravenous use.
Hypotheses of the study When paclitaxel and carboplatin-guided anticancer therapy followed by surgery and then postoperative anticancer radiotherapy according to standard guidelines are administered, clinical outcomes are improved with less toxicity compared to conventional standard of care (TCF).
Objective:

Primary Objective:

To evaluate the major pathological response rate (mPR) when surgery is performed after paclitaxel and carboplatin-induced anticancer treatment in locally advanced head and neck cancer.

Secondary Objectives:

The efficacy and safety of induction anticancer will be evaluated.

Outcome indicators: Locoregional relapse rate (LRR), relapse–free survival (RFS), overall survival (OS), adverse events according to CTCAE 5.0

Exploratory Objectives:

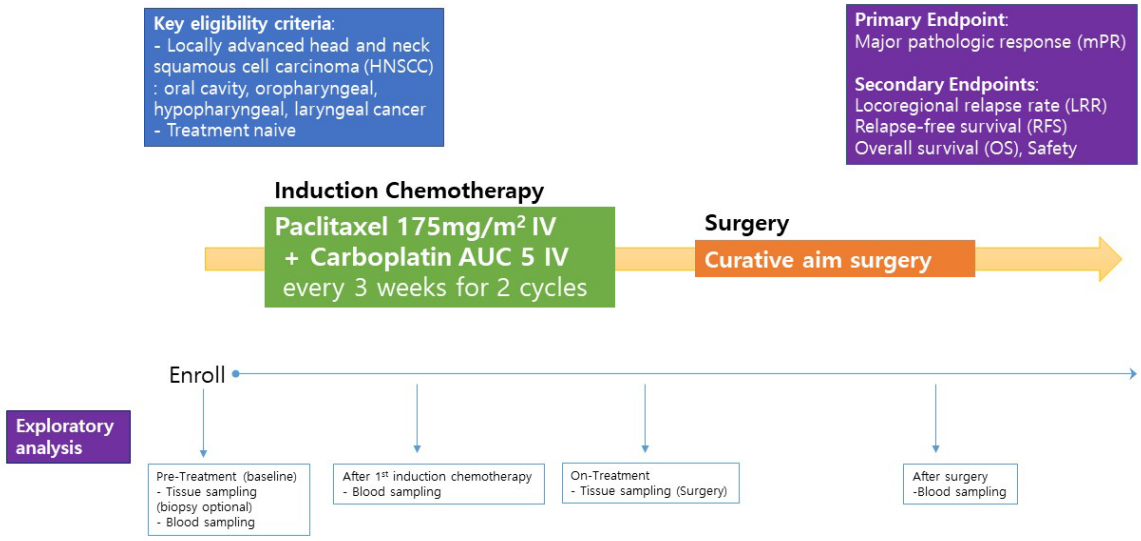
Changes in circulating tumor cells (CTCs) and changes in immunodynamics before and after paclitaxel and carboplatin-induced anticancer treatment will be investigated through the analysis of blood, biopsy specimens, and surgical specimens.

Endpoints:

Primary endpoint: Major pathological response rate (mPR)

Secondary endpoints: Locoregional relapse rate (LRR), relapse–free survival (RFS), overall survival (O S), adverse events according to CTCAE 5.0, and observation of neutropenia frequency and grade according to the use of pegylated G-CSF

Exploratory objectives: **Changes in** circulating tumor cells (CTCs), changes in immunodynamics before and after induction anticancer treatment



Trial design: Single-arm, phase II

1) Induction chemotherapy

Paclitaxel 175mg/m2

Carboplatin AUC5

Doses every 3 weeks for a total of 2 doses

Pegteograstim 6 mg Adjuvant Therapy

Dose every cycle in the judgment of the investigator

2) Surgery

Curative surgery (including transoral robotic surgery (TORS))

Surgery performed within 2-9 weeks of induction anticancer therapy

Exploratory Study

- Blood specimen collection

Baseline (required)

After first-line induction chemotherapy (mandatory)

Postoperative (mandatory)

- Tumor specimen collection

Baseline (optional)

At the time of surgery (required)

Analytics

·PD-L1 expression

Circulating tumor cells (CTCs)

·T-cell immunophenotyping using flow cytometry

·Multiplex biomarker analysis of tumor cells and immune cells in the tumor microenvironment

·RNA sequencing using fresh tumor samples collected during pre- and post-treatment resection surgery (if possible, single-cell RNA sequencing) to find potential transscriptome changes in tumor cells and immune cells

Number of test sites: 2 (Sinchon Severance Hospital. Gangnam Severance Hospital)

Number of subjects: 79 in total

Trial Population:

Patients with histologically confirmed resectable HNSCC by surgery of the oral cavity, hypopharynx, oropharynx, and larynx

Scientific Basis/Rationale

- In cases where immediate surgery is not possible in locally advanced head and neck cancer, chemoradiation (CRT) or induction chemotherapy (IC) + CRT) has been performed to preserve organ function preservation.
- The effectiveness of pre-induction anti-cancer radiotherapy has been controversial due to the inconsistent results of several phase III clinical studies. At present, it is difficult to claim the superiority of either the addition of induction anticancer therapy or chemotherapy radiotherapy alone, but in certain subgroups, induction anticancer therapy (advanced N stage such as N2c/N3) can be said to be a useful option to lower distant metastasis.
- The results of the TAX324 clinical trial showed that weekly carboplatin-based anticancer radiation or surgery after neoadjuvant Docetaxel + Cisplatin + 5FU chemotherapy resulted in an improvement in overall survival (HR 0.7, p=0.0058) and an improvement in organ maintenance rate (3 year LFS: 52% vs 32%) compared to the conventional neoadjuvant therapy Cisplatin + 5FU. However, due to the toxicity (neutropenia, nephrotoxicity) of this TPF regimen and the resulting limitations of anticancer radiation, it is difficult to apply it to all patients in actual clinical practice.
- In a retrospective study, neoadjuvant paclitaxel + carboplatin showed no difference in progression-free survival compared to TPF (p=0.15), and a statistically significant reduction in local recurrence rate (HR 0.27, p = 0.04) was identified.
- Therefore, this study expects that paclitaxel and carboplatin-guided anticancer treatment followed by surgery and postoperative anticancer radiotherapy will result in improved clinical outcomes with less toxicity compared to standard TPF-guided anticancer therapy.

Inclusion Criteria: In order to participate in this clinical trial, all of the following criteria must be met

- Patients with histologically confirmed HNSCC of the oral cavity, hypopharynx, oropharynx, and larynx that are operable and free of distant metastases

  - Stage III-IV oral cancer, laryngeal cancer, hypopharyngeal cancer, HPV-negative oropharyngeal cancer

  - Stage II-III HPV-positive oropharyngeal cancer

- Measurable disease, defined as a lesion that can be accurately measured according to RECIST 1.1
- Patient Candidate has completed the Patient Consent Form prior to initiation of any protocol-related procedures, including screening assessments;
- Adult men and women 20 years of age or older at the time of participation in the trial
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
- Patients with a life expectancy of at least 12 weeks
- Adequate and normal organ and bone marrow function as defined below:
  - Hemoglobin ≥9.0 g/dL
  - Absolute neutrophil count (ANC) ≥109 /L (1500 per mm3)
  - Platelet count ≥ 75,000 per mm3
  - Total serum bilirubin ≤1.5 times ULN at the site
  - AST (SGOT)/ALT (SGPT) ≤ 2.5 times the ULN of the testing site.
  - Creatinine clearance >40 mL/min as measured by a 24-hour urine collection specimen or creatinine clearance >40 mL/min as calculated by the Cockcroft-Gault formula (Cockcroft and Gault 1976):

    Male:

    $$\text{Creatinine clearance (mL/min)} = \frac{\text{Weight (kg)} \times (140 - \text{Age})}{72 \times \text{Serum creatinine (mg/dL)}}$$

    Women:

    $$\text{Creatinine clearance (mL/min)} = \frac{\text{Weight (kg)} \times (140 - \text{Age})}{72 \times \text{Serum creatinine (mg/dL)}} \times 0.85$$

- Women with evidence of postmenopausal status or premenopausal women with a negative urine or serum pregnancy test. Women who have been amenorrheic for 12 months without an alternative medical reason are considered postmenopausal. The following age-specific requirements apply:

  - Even if they are under 50 years of age, they are considered menopausal women if they have been amenorrheic for at least 12 months after stopping exogenous hormonal therapy and their progesterone (LH) and follicle-stimulating hormone (FSH) levels are within the

postmenopausal value range of the test site, or if they have undergone surgical sterilization (bilateral oophorectomy or complete hysterectomy).

- Women who have been amenorrheic for at least 12 months after discontinuation of all exogenous hormonal therapy, or who are radiation-induced postmenopausal with the time of their last menstrual period more than 1 year ago, or who have been surgically sterilized (bilateral oophorectomy, bilateral salpingectomy, or complete hysterectomy) are considered menopausal women.

- Patients who are willing and able to comply with the protocol for the duration of the trial, including trial treatment, scheduled visits, and the performance of tests, including follow-up

Exclusion Criteria: Patients who meet any of the following exclusion criteria will not be eligible to participate in the trial

- Patients with nasopharyngeal cancer
- Patients with previous treatment experience for head and neck cancer (including history of radiotherapy)
- Patients who have participated in other clinical trials in which an investigational drug is used within the past 1 month
- Patients who are concurrently enrolled in an observational (non-interventional) trial or in another clinical trial that is not a follow-up period of an interventional trial
- Patients who require additional chemotherapy, investigational drugs, biologics, or hormonal therapy for anticancer treatment. However, concurrent use of hormone therapy for conditions unrelated to cancer (e.g., hormone replacement therapy) is allowed.
- Patients undergoing major surgery (as defined by the investigator) within 28 days prior to the first dose of investigational drug. Note: Local surgery for independent lesions with palliative therapeutic intent is allowed.
- Uncontrolled intercurrent illness. including, but not limited to: current or active infection; symptomatic congestive heart failure; uncontrolled hypertension; unstable angina; cardiac arrhythmia; interstitial lung disease; significant chronic gastrointestinal conditions with diarrhea; Any psychiatric illness/social condition that would limit compliance with trial requirements, significantly increase the risk of adverse events, or impair the subject's ability to complete informed consent
- Patients with a history of other primary malignancies. However, the following exceptions shall be made.
    - Past malignancy that has received curative intent and has no history of known active disease within 3 years prior to the first dose of investigational drug and has a low risk of recurrence
    - Adequately treated non-melanoma skin cancer (stage I-III) or malignant lentigo with no evidence of disease
    - Adequately treated carcinoma in situ with no evidence of disease
- History of active primary immunodeficiency
- Female patients who are currently pregnant or breastfeeding, or male and female patients of childbearing potential who are not willing to use effective contraception continuously from the time of screening until Day 180 after the end of trial treatment
- Patients with known allergy or hypersensitivity to the investigational drug or its excipients
- Patients who, in the judgment of the investigator, are not suitable for participation in the trial and are expected to not comply with the trial procedures, restrictions, and requirements

Investigational drug, dose, and route of administration:

Induction chemotherapy

Paclitaxel 175 mg/m2 + Carboplatin AUC5 (calculated by Cockcroft - Gault formula) Combination therapy

A total of 2 intravenous instillation infusions every 3 weeks

Pegteograstim 6 mg adjuvant therapy, administered every cycle as judged by the investigator

Surgery within 2-9 weeks of induction anticancer therapy

Surgery

The surgery in this study refers to complete resection with the aim of cure, and minimally invasive surgery is oriented.

Clinical trial evaluation and evaluation criteria:

Effectiveness Assessment:

Major pathologic response rate (Major pathologic response rate, mPR rate)

Locoregional relapse rate (LRR)

Relapse–free survival (RFS)

Overall survival (OS)

Safety Assessment:

Serious adverse events related to the investigational drug or unexpected delay or complication of surgery

Statistical analysis and data analysis:

Variables will be compared using the student-t test, Mann-Whitney-U test, and chi-square test according to the nature of the variables. Multivariate survival analysis will be performed using a Cox proportional hazards regression model.

Major pathologic response (mPR) is defined as less than 10% of residual cancer remaining in tumor tissue resected at the time of surgery after neoadjuvant chemotherapy.

The local recurrence rate (LRR) is defined as the frequency of recurrence of the primary or cervical lymph nodes after surgery.

Recurrence-free survival (RFS) is defined as the time from the date of first administration of study drug to the date of first documented radiographic disease progression according to RECIST 1.1 by local or distant recurrence in subjects who have achieved disease-free postoperatively.

Overall survival (OS) is defined as the time from the date of first administration of the investigational drug to the date of objective disease progression or death from any cause, regardless of cause.

Sample size determination:

Total sample size: 79 people

This study is a clinical trial designed to evaluate whether Paclitaxel + Carboplatin induction anticancer therapy improves the major pathological response rate compared to conventional induction anticancer therapy (historical control) in patients with potentially operable locally advanced HNSCC.

The sample size was calculated with a one-arm binomial test with a power of 75% for the hypothesis to be accepted and a significance of 10% for the hypothesis to be rejected (α error=0.10, beta: 0.25, power=0.75). It is assumed that the mPR of the historical control induction chemotherapy is 30.0% (p1) and the mPR of Paclitaxel + Carboplatin induction chemotherapy is 41.0% (p2).

H0: p1=p2 vs. H1: p1≠p2, p1=0 at the significance level of 10%.30, p2=0.41 A 72 patients are needed to have a power of 75%, and a follow-up failure rate of 10% requires a total of 79 subjects.

Clinical trial evaluation timeline

Assessments to be performed at the time points specified in the table and whenever clinically required for the management of the subjects	**Screening**	**Baseline**	**Neoadjuvant treatment**	**Before surgery**	**Surgery**	**Follow-up Survey** [l]	**Remarks**
			Paclitaxel + Carboplatin combination therapy				
			2 cycles (every 3 weeks)				
Days	**-Within 28 days**		**Day 1 of the cycle (1, 22) (±3 Day)**			**28~56 days**	
Completion of the consent form for the subject	X						
Check for Conformity	X						
Demographics, disease status, detailed medical history	X						
Paclitaxel + Carboplatin			Paclitaxel 175mg/m2 + Carboplatin AUC5				
Physical examination [a]	X		X				
Vital signs [B]	X		X			X	
Weight	X		X			X	
ECGc	X						
Assessment of adverse events/SAEs	X		X			X	
Concomitant medications	X		X				
ECOG performance status	X		X				
Hematology, Chemistry	X		X				
Urine hCG or serum ßhCG[e]	X						
HIV, HBV, HCV screening[f]	X						
Chest x-ray	X						
Tumor assessment (CT and MRI) [g]	X			X (within 3 weeks before surgery)		X (approximately every 12 weeks after surgery)	
If applicable, collection of tissue specimens for biomarker analysis		X (Optional)			Xh		
Collection of blood specimens for biomarker analysis, if applicable		X	X (22 days)			X[h] (between 28-56 days after surgery)	

[a] A detailed physical examination will be performed at baseline and a brief physical examination will be performed at all other time points.

[b] Before and after each visit, blood pressure, pulse, respiration, and temperature will be measured as needed.

[c] A single ECG will be performed at the time of screening. After that, it will be performed whenever clinically necessary.

[d] If the screening laboratory assessment was performed within 7 days prior to Day 1, it does not need to be repeated on Day 1. Before starting the infusion, the results of the safety blood test should be available and reviewable. Blood clotting tests: prothrombin time, APTT, INR - performed at screening and only when clinically indicated.

[e] Only for women of childbearing potential before menopause

[f] Within 3 months If there are available test results, there is no need to repeat them.

[g] Time of tumor assessment: Screening, within 14 days prior to surgery, and approximately every 12 weeks according to institutional standard procedures until disease progression or recurrence is confirmed. Neck MRI, Chest CT, etc.), and if the disease progresses and the patient drops out or fails to undergo surgery, they will also be followed up according to the institution's standard procedures.

[h] If the patient drops out due to disease progression or fails to undergo surgery, it will not be collected.

[i] Visit between 28-56 days postoperatively. Based on pathological findings such as high risk factors in surgical findings (e.g., extra capsule extension [ECE+] or resection margin involvement [RM+]) or physician's decision, cisplatin-based standard post-operative concurrent chemoradiation therapy (PO-CCRTx) will be administered, which will be in accordance with the standard of care performed at each institution and will not be included in the clinical trial.

* Blood and tissue sample collection schedule and sample type for biomarker analysis

Perspective	Blood	Organization
Baseline	EDTA tube 8cc - essential	FFPE or Fresh tissue (Replace existing organization) - Select
After the first round of neoadjuvant therapy (Within 7 days of Cycle 2 Day 1 start)	EDTA tube 8cc - essential	NA
At the time of surgery	NA	Fresh frozen (tumor and NL) - essential
Postoperative (Day 28-56)	EDTA tube 8cc - essential	NA

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1. INTRODUCTION

The purpose of this clinical trial is to evaluate whether paclitaxel and carboplatin-guided anticancer therapy followed by surgery and postoperative anticancer radiotherapy in potentially operable locally advanced head and neck squamous cell carcinoma results in improved clinical outcomes, such as an increase in the rate of major pathologic response (mPR), with less toxicity compared to standard TPF-guided anticancer therapy.

1.1 Background of the disease

Head and neck squamous cell carcinoma (HNSCC) is the sixth most common cancer worldwide, with 890,000 new diagnoses and 450,000 deaths from head and neck cancer in 2018 (Bray, F. et al 2018). The most common HNSCC tumor sites are the larynx, pharynx, and oral cavity. The main risk factors for oral, laryngeal, oropharyngeal, and hypopharyngeal cancers are alcohol consumption and smoking, accounting for 75% of HNSCC cases. Human papillomavirus (HPV)) infections, especially HPV-16, are an established cause of oropharyngeal cancer (tonsils and tongue floor). The incidence of oropharyngeal cancer caused by HPV is increasing worldwide, with a large variation between less than 10 and 70% of all oropharyngeal cancers depending on the region, and it is more frequent in industrialized countries. It is not known if HPV plays an etiological role in other HNSCC sites other than the oropharynx. Treatment depends on the location of the primary tumor, disease stage, and expected oncological and functional outcomes. Early stage (stage I/II) HNSCC according to the Union for International Cancer Control (UICC)/American Joint Committee on Cancer (AJCC) staging classification is often treated with a single line of therapy, i.e., surgery or radiotherapy. Locally advanced stage (UICC/AJCC stage III/IV) is usually treated with radiotherapy, Surgery, chemotherapy, or cetuximab must be used together. The survival rate for all HNSCC patients is about 70% at 1 year and 40-60% at 5 years. Some HNSCC patients develop local recurrence or distal metastasis, which can lead to life-threatening conditions.

Squamous cell carcinoma of the head and neck (HNSCC) can carry significant morbidity in that symptoms associated with local recurrence significantly impair important basic functions such as breathing, speaking, and swallowing. In addition, pain and social isolation upon recurrence, as well as the possibility of changes in appearance due to the site of the head and neck lesion, all indicate the importance of preventing the progression of this disease, which can have serious adverse effects.

1.1.1 Induction Anticancer Therapy in Locally Advanced Head and Neck Cancer

In cases where immediate surgery is not possible in locally advanced head and neck cancer, chemoradiation (CRT) or induction chemotherapy (IC) + CRT) has been performed to preserve organ function preservation.

In head and neck cancer, induction chemotherapy was first presented in a study published by The Department of Veterans Affairs Laryngeal Cancer Study Group in 1991 (Department of Veterans Affairs Laryngeal Cancer Study Group et al 1991). In a phase III clinical study comparing radiotherapy after 3-cycle chemotherapy with Fluorouracil and Cisplatin (FP) with postoperative radiotherapy, there was no difference in 2-year survival between the two groups (68%, p=0.9846). In the group that received radiotherapy after induction chemotherapy, the local recurrence was higher than that of the operated group (p=0.0005), but the rate of distant metastasis was lower (p=0.016). In approximately 64% of patients, the larynx was preserved without resection, and this study confirmed the new role of induction chemotherapy in pursuing the preservation of organ function without adversely affecting overall survival. Subsequent studies confirmed that when docetaxel or paclitaxel was added to FP, the clinical course was improved compared to induction chemotherapy with FP alone. In the EORTC 24971/TAX 323 study (Vermorken, J. B., et al 2007), Docetaxel and FP as induction anticancer therapy prior to radiotherapy showed an improvement in median progression-free survival (mPFS 11.0 vs 8.2 months, HR 0.72, p=0.007) and overall survival (mOS 18.8 vs 14.5 months, HR 0.73, p=0.02) compared to FP alone when combined with docetaxel before radiotherapy for unresectable locally advanced head and neck cancer.In the TAX 324 study with a similar design (Posner et al. 2007), the addition of Docetaxel to FP as induction anticancer prior to weekly carboplatin-based anticancer radiotherapy in locally advanced head and neck cancer (TPF) showed an improvement in overall survival (mOS 71.0 vs 30.0 months, HR 0.70, p=0.006) and 3-year survival (62% vs 48%). In the 5-year follow up results of this TAX324 study,(Lorch et al. 2011) This trend remained the same, with TPF-guided anticancer groups showing superior survival compared to FP (5-year survival rate 52% vs 42%). On the other hand, paclitaxel was also shown to improve response rate compared to FP alone when added to FP as induction anticancer therapy prior to cisplatin-based anticancer radiotherapy (Hitt et al. 2005), improved response rate compared to FP alone (Complete response rate 33% vs 14%, p <0.001), and prolonged time to median treatment failure (mTTF 20.0 vs 12.0 months, p=0.006).

However, the effectiveness of induction chemotherapy before anticancer radiotherapy has been controversial due to inconsistent results from several phase III clinical studies. According to the DeCIDE study (Cohen, E.E. et al 2014), induction chemotherapy (Docetaxel, Cisplatin, 5-Fluorouracil (TPF)) in high-risk patients such as N2c and N3 showed better overall survival compared to anticancer radiation alone, but it was not statistically significant (p = 0.19). In the GORTEC 2007-02 study in N2b, N2c, and N3 patients without distant metastasis (Geoffrois, L. et al 2018), 5FU/carboplatin-based anticancer radiotherapy was compared with cetuximab-based radiotherapy after TPF-

guided anticancer, and there was no difference in progression-free survival between the two groups. Even given that anticancer therapy of anticancer radiation differed from the norm, the induction anticancer group showed an improvement in remote radio survival (HR 0.62, p = 0.03). In the TTCC study (Hitt, R., et al 2014), TPF-guided anticancer followed by anticancer radiation, PF-guided anticancer followed by anticancer radiation, and anticancer radiation alone were compared, and TPF-guided anticancer showed an improvement in progression-free survival compared with anticancer radiation alone in patients per protocol (HR 0.72, p = 0.03), and overall survival also tended to improve, but it was not statistically significant. In summary, it is difficult to claim the superiority of either the addition of induction anticancer therapy or anticancer radiotherapy alone at present. In certain subgroups, (advanced N stage such as N2C/N3) induction anticancer therapy is a useful option to lower distant metastasis.

1.1.2 Paclitaxel + Carboplatin combination therapy

The results of the TAX324 trial (Posner, M.R. et al 2009) showed that weekly carboplatin-based chemotherapy or surgery after neoadjuvant Docetaxel + Cisplatin + 5FU chemotherapy resulted in an improvement in overall survival (HR 0.7, p=0.0058) and an improvement in organ maintenance (3 year LFS: 52% vs 32%) compared to the conventional neoadjuvant Cisplatin + 5FU chemotherapy (3 year LFS: 52% vs 32%). However, the toxicity of this TPF regimen (neutropenia, Nephrotoxicity) and the resulting limitations of anticancer radiation, it is difficult to apply it to all patients in actual clinical practice. Meta-analysis showed that fewer patients were able to receive all three planned doses of Cisplatin 100 mg/BSA in chemotherapy (59.4% vs 80.5%) compared to chemotherapy alone (59.4% vs 80.5%). As a result, a less toxic therapy was devised.

Paclitaxel and Carboplatin have been reported to have a complete response rate of 8~33% and a partial response rate of 50~85% when used as induction chemotherapy in head and neck cancer through several studies.

In a study conducted in 1994-1999 (Dunphy et al. 1999), radiotherapy or radiotherapy after cervical lymph node surgery was administered to locally advanced head and neck cancer after three doses of paclitaxel and carboplatin-induced chemotherapy, with an overall response rate of 66%. According to the Eastern Cooperative Oncology Group Study E2399 study (Cmelak et al. 2007a), 2-year survival rate of 76% and 81% of organ preservation were achieved when weekly paclitaxel-based anticancer radiation was administered twice in locally advanced head and neck cancer, and the toxicity was relatively low and did not compromise planned follow-up chemotherapy. In another phase II study (Cmelak et al. 2007b) In locally advanced head and neck cancer, when paclitaxel and carboplatin-induced chemotherapy were administered three times, weekly paclitaxel and cisplatin or carboplatin-based anticancer radiation were administered, resulting in a two-year survival rate of 71% and an organ preservation rate of 83%. In a study (Ready et al. 2012) in which weekly paclitaxel and carboplatin-guided anticancer therapy followed by weekly paclitaxel and carboplatin-based

anticancer radiotherapy (Ready et al. 2012) showed an overall response rate of 79%, a 3-year survival rate of 67%, and a very low distant metastasis rate of 8%. In a retrospective study (Herman, L.C., et al 2014), 143In patients with locally advanced head and neck cancer, paclitaxel + carboplatin-induced anti-cancer was compared with TPF, and there was no difference in response rate and progression-free survival, and a statistically significant decrease in local recurrence rate (HR 0.27, p = 0.04) was observed, and in the case of TPF, treatment was frequently delayed due to nephrotoxicity compared to paclitaxel + carboplatin.

In addition, in contrast to the TAX 323 and 324 studies, which reported a high level of grade 3 or higher Neutropenia after TPF-induced chemotherapy at 76~83%, Paclitaxel and Carboplatin-induced anti-cancer therapy were relatively lower at 21~36%.

Therefore, this study expects that paclitaxel and carboplatin-guided anticancer treatment followed by surgery and postoperative anticancer radiotherapy will result in improved clinical outcomes with less toxicity compared to standard TPF-guided anticancer therapy.

1.2 Hypotheses of the study

When Paclitaxel + Carboplatin induction chemotherapy is administered to patients with potentially operable locally advanced HNSCC, the major pathological response rate is improved compared to the conventional Docetaxel+Cisplatin+Fluorouracil induction anticancer therapy (historical control).

2. CLINICAL TRIAL OBJECTIVES

2.1.1 Primary endpoint

I. To evaluate the major pathologic response (mPR) when surgery is performed after paclitaxel and carboplatin-induced anticancer treatment in locally advanced head and neck cancer.

2.1.2 Secondary endpoints

The efficacy and safety of induction anticancer will be evaluated.

I. In locally advanced head and neck cancer, the Locoregional relapse rate (LRR), relapse–free survival (RFS), and Overall survival (OS) of paclitaxel and carboplatin-induced chemotherapy followed by surgery will be evaluated.

II. As for adverse events according to CTCAE 5.0 evaluate. Among them, the frequency and grade of neutropenia according to the use of pegylated G-CSF will be observed.

2.1.3 Exploratory Objectives

Changes in circulating tumor cells and changes in immunodynamics before and after paclitaxel and carboplatin-induced anticancer treatment will be investigated through the analysis of blood, biopsy specimens, and surgical specimens

2.2 Clinical trial design overview

This study is a phase II, single-arm clinical trial to evaluate paclitaxel + carboplatin as neoadjuvant adjuvant treatment in patients newly diagnosed with previously naïve and potentially resectable locally advanced HNSCC, surgery for the purpose of complete resection. The trial will be conducted in accordance with Good Clinical Practices (GCP). Approximately 79 subjects will be treated according to the course below.

Induction chemotherapy

Paclitaxel 175 mg/m2 + Carboplatin AUC5 (calculated by Cockcroft - Gault formula) Combination therapy

A total of 2 intravenous instillation infusions every 3 weeks

Pegylated G-CSF (pegteograstim 6 mg) as adjuvant therapy after induction anticancer therapy may be administered as judgment of the investigator.

Surgery performed within 2-9 weeks of induction anticancer therapy

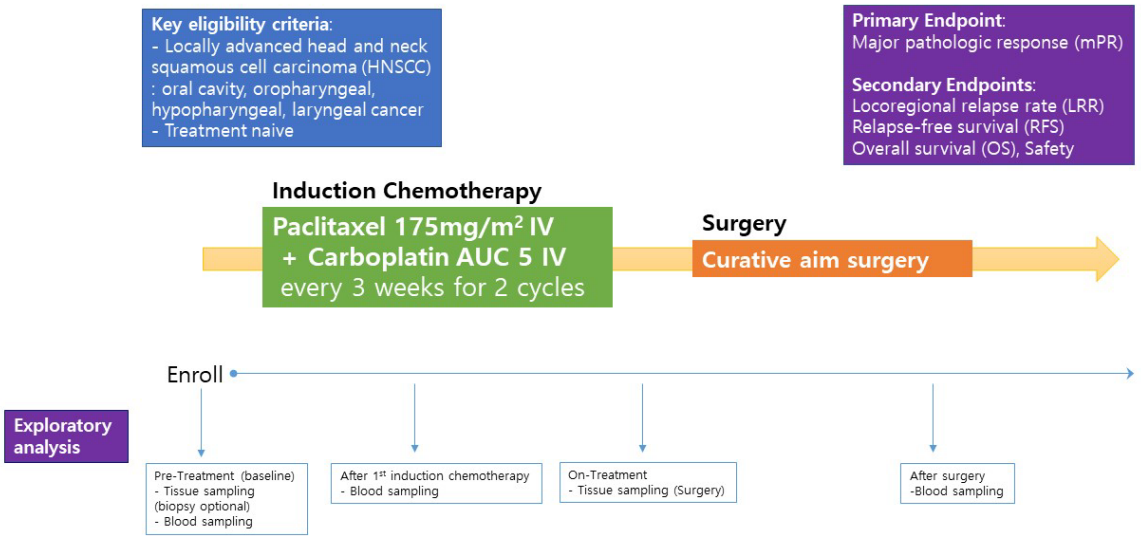
Surgery

The surgery in this study refers to complete resection with the aim of cure, and minimally invasive surgery is oriented.

Whether the subject's HNSCC status is suitable for screening will be determined based on the investigator's judgment based on the selection/exclusion criteria. Preoperative neoadjuvant treatment should be started within 5 days prior to randomization and as close as possible to the date of assignment or assignment of the subject.

Adverse events will be monitored throughout the trial and will be monitored according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5.They will be graded according to the moderate classification outlined in 0. Safety follow-up will be conducted on subjects receiving study treatment and those who have been discontinued prematurely and permanently.

2.3 Clinical trial planning



Picture 1. Clinical trial flow chart

2.4 Supervision of clinical trials to assess safety

The study may be stopped if a subject is considered to be at unnecessary risk because of a clinically significant finding that falls under any of the following criteria:

• Meets or is considered significant for individual discontinuation criteria

• Determined to have a causal relationship with the test drug

• Assessed that it is not appropriate to continue the trial

Whatever the reason for terminating the trial, all data collected from the subject at the time of permanent discontinuation or follow-up should be recorded in the CRF. All reasons for permanent suspension must be recorded.

If the clinical trial is terminated, sufficient measures will be taken to protect the rights and interests of the trial subjects.

3. SUBJECT SELECTION, ENROLLMENT, RESTRICTIONS, PERMANENT SUSPENSION AND DROPOUT

Each subject must meet all the inclusion criteria of this clinical trial and must not fall under any exclusion criteria. There are no exceptions to this rule under any circumstances.

3.1 Selection Criteria

Patients who wish to participate in this clinical trial must meet all of the following criteria:

- Patients with histologically confirmed HNSCC of the oral cavity, hypopharynx, oropharynx, and larynx that are operable and free of distant metastases

  - Stage III-IV oral cancer, laryngeal cancer, hypopharyngeal cancer, HPV-negative oropharyngeal cancer

  - Stage II-III HPV-positive oropharyngeal cancer

- Measurable disease, defined as a lesion that can be accurately measured according to RECIST 1.1
- Regionally required approvals and patient consent has been completed by the candidate prior to initiation of any protocol-related procedures, including screening assessments.
- Adult men and women 20 years of age or older at the time of participation in the trial
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
- Patients with a life expectancy of at least 12 weeks
- Adequate and normal organ and bone marrow function as defined below:
  - Hemoglobin ≥9.0 g/dL
  - Absolute neutrophil count (ANC) ≥109 /L(1500 per mm3)
  - Platelet count ≥ 75,000 per mm3
  - Total serum bilirubin ≤1.5 times ULN at the site

AST (SGOT)/ALT (SGPT) ≤ 2.5 times the ULN of the institution.

  - Creatinine clearance >40 mL/min as measured by a 24-hour urine collection specimen or creatinine clearance >40 mL/min as calculated by the Cockcroft-Gault formula (Cockcroft and Gault 1976):

Male:

$$\text{Creatinine clearance (mL/min)} = \frac{\text{Weight (kg)} \times (140 - \text{Age})}{72 \times \text{Serum creatinine (mg/dL)}}$$

Women:

$$\text{Creatinine clearance (mL/min)} = \frac{\text{Weight (kg)} \times (140 - \text{Age})}{72 \times \text{Serum creatinine (mg/dL)}} \times 0.85$$

- Women with evidence of postmenopausal status or premenopausal women with a negative urine or serum pregnancy test. Women who have been amenorrheic for 12 months without any other medical reason are considered postmenopausal. The following age-specific requirements apply:

  - Even if they are under 50 years of age, they are considered menopausal women if they have been amenorrheic for at least 12 months after stopping exogenous hormonal therapy and their progesterone (LH) and follicle-stimulating hormone (FSH) levels are within the postmenopausal value range of the test site, or if they have undergone surgical sterilization (bilateral oophorectomy or complete hysterectomy).

  - Women who have been amenorrheic for at least 12 months after discontinuation of all exogenous hormonal therapy, or who are radiation-induced postmenopausal with the time of their last menstrual period more than 1 year ago, or who have been surgically sterilized (bilateral oophorectomy, bilateral salpingectomy, or complete hysterectomy) are considered menopausal women.

3.2 Exclusion Criteria

Patients who meet any of the following exclusion criteria will not be eligible for the trial:

- Directly involved in the planning and/or conduct of this clinical trial
- Patients with nasopharyngeal cancer
- Patients with previous treatment experience for head and neck cancer (including history of radiotherapy)
- Patients who have participated in other clinical trials in which an investigational drug is used within the past 1 month
- Patients who are concurrently enrolled in an observational (non-interventional) trial or in another clinical trial that is not a follow-up period of an interventional trial
- Patients who require additional chemotherapy, investigational drugs, biologics, or hormonal therapy for anticancer treatment. However, concurrent use of hormone

therapy for conditions unrelated to cancer (e.g., hormone replacement therapy) is allowed.

- NCI CTCAE grade 2 or higher toxicity of prior anticancer therapy that has not yet resolved. However, alopecia, vitiligo, and laboratory values defined in the selection criteria are exceptions.
- Grade 2 or higher neuropathy is determined after consultation with the clinical trial physician on a case-by-case basis.
- Patients with irreversible toxicity that is not expected to worsen with investigational drug administration may participate in the trial only after consultation with the study physician.
- Patients undergoing major surgery (as defined by the investigator) within 28 days prior to the first dose of investigational drug. Note: Local surgery for independent lesions with palliative therapeutic intent is allowed.
- Uncontrolled intercurrent illness. including, but not limited to: current or active infection; symptomatic congestive heart failure; uncontrolled hypertension; unstable angina; cardiac arrhythmia; interstitial lung disease; significant chronic gastrointestinal condition with diarrhea; Any psychiatric illness/social condition that would limit compliance with trial requirements, significantly increase the risk of adverse events, or impair the subject's ability to complete informed consent
- Patients with a history of other primary malignancies. However, the following exceptions shall be made.
- Past malignancy that has received curative intent and has no history of known active disease within 3 years prior to the first dose of investigational drug and has a low risk of recurrence
    - Adequately treated non-melanoma skin cancer (stage I-III) or malignant lentigo with no evidence of disease
    - Adequately treated carcinoma in situ with no evidence of disease
- History of active primary immunodeficiency
- Female patients who are currently pregnant or breastfeeding, or male and female patients of childbearing potential who are not willing to use effective contraception continuously from the time of screening until Day 180 after the end of trial treatment
- Patients with known allergy or hypersensitivity to the investigational drug or its excipients
- Patients who, in the judgment of the investigator, are not suitable for participation in the trial and are expected to not comply with the trial procedures, restrictions, and requirements

3.3 Exclude the subject from study treatment and/or participation in the trial

Permanent suspension of investigational drugs

If the following events occur, the subject will no longer receive the investigational drug:

1. Withdrawal of consent or failure to follow up
2. Adverse events that, in the opinion of the investigator or sponsor, prohibit further administration of study treatment
3. If the subject is judged to fall under one or more clinical trial exclusion criteria that may compromise the safety of participation in the trial and continuation of the administration of investigational treatment at the time of study entry
4. Pregnancy or planning to become pregnant
5. Adverse events that meet the criteria for permanent discontinuation as defined in Chapter 9
6. Grade 3 or higher drip injection reaction
7. Non-compliance of the subject that, in the opinion of the investigator or sponsor, requires permanent discontinuation (e.g., refusal to comply with the scheduled visit schedule)
8. Initiation of new anti-cancer treatments, including other investigational drugs
9. Confirmed disease progression (PD) and judged by the investigator that further administration of the investigational drug is no longer beneficial to the subject. Regardless of the reason (withdrawal of consent, adverse reaction, etc.), a subject who permanently discontinues the administration of an investigational drug will be considered as a permanent discontinuation of the investigational treatment.

Withdrawal of consent

The subject can freely withdraw consent to the clinical trial (investigational drug and trial evaluation) at any time without being affected by future treatment.

Subjects who withdraw their consent to further study participation will no longer receive investigational drug administration or observational evaluations, but will continue to be followed up for survival until the end of the trial unless they express their intention to withdraw their consent to survival follow-up. Subjects may be suggested additional tests or study treatment checks to safely stop participating in the study.

Subjects who withdraw their consent will always be asked about the reason and whether they have had adverse events. The investigator will follow up on adverse events even if they are not required in the trial.

If the subject withdraws consent, ask the subject specifically what the scope of the withdrawal of consent is:

- Withdrawing consent to participate in future trials, including future follow-up (e.g., telephone contact to confirm survival)
- Withdrawing consent to the use of data generated in the trial
- Withdrawing consent to the use of the specimen

4. INVESTIGATIONAL DRUGS

4.1 Piclitaxel and Carboplatin

4.1.1 Formulation/Packaging/Storage

Paclitaxel

Paclitaxel is an injectable drug containing a colorless-light yellow transparent viscous liquid in a colorless vial, and is produced in the form of a glass vial containing 0.1 g of liquid at a concentration of 6 mg/mL for intravenous injection.

This drug should be diluted before the instillation injection. This drug is diluted with 0.9% sodium chloride injection solution or 5% glucose injection, 5% glucose/0.9% sodium chloride injection, and 5% glucose Ringel's solution so that the final paclitaxel concentration is 0.3~1.2 mg/ml. The solution is physiochemically stable at room temperature (15~30°C) for 27 hours.

The solution may become cloudy during solution preparation, but this is due to excipients. As a result of the sedentary simulation test through an intravenous tube equipped with a filter (0.22 microns) in the line, it was confirmed that there was no significant loss of titer.

Carboplatin

Carboplatin is a brown vial injection of a colorless and transparent solution, produced in the form of a 45 mL vial containing 0.45 g of liquid at a concentration of 10 mg/mL for intravenous use.

This drug should be administered intravenously after dispensing. Immediately before using this drug, it is prepared with water for injection, 5% glucose injection, or normal saline injection to a concentration of 10 mg/mL, and then diluted to a final concentration of 0.5 mg/mL using a diluted solution. When prepared in this way, this drug solution is stable at room temperature (25°C) for 8 hours. Since this drug does not contain antibacterial preservatives, the solution that has been dispensed for more than 8 hours should be discarded.

Pegteograstim

Pegteograstim is an injection filled with medicine in a syringe and should be stored in a shaded and refrigerated (2~8°C). Each injection contains 6 mg (0.6 ml) of

pegteograstim and is injected subcutaneously about 24 hours after completion of cytotoxic chemotherapy.

4.2 Dosage and dosage prescription

4.2.1 Dosing prescription

Paclitaxel

During the neoadjuvant treatment period, two doses of paclitaxel at a dose of 175 mg/m2 will be administered 3 weeks apart. For the calculation of the dose of paclitaxel, the body weight measured on the day of administration (prior to administration) may be used. The dose (mg) will be rounded to the first decimal place. Dosing should be performed according to site procedures, but the recommended procedure is as follows:

Paclitaxel is administered intravenously through a built-in membrane filter of 0.22 μm or less over 2-3 hours according to the product manual. Pre-dose reactions and adverse drug reactions of paclitaxel should be treated appropriately with reference to local standards such as product manuals and treatment guidelines. To prevent the development of severe hypersensitivity reactions, all patients should be premedicated before administration of this drug. Premedication can be done by administering dexamethasone 20 mg orally (or equivalent) about 12 hours and 6 hours before administration of this drug, intravenous administration of diphenhydramine 50 mg (or equivalent therapy) 30~60 minutes before administration of this drug, and intravenous administration of cimetidine (300 mg) or ranitidine (50 mg) 30~60 minutes before administration of this drug.

Carboplatin

During the neoadjuvant treatment period, two doses of carboplatin at a dose of AUC 5 will be administered 3 weeks apart.On days 1, 2, and 2, paclitaxel infusion will be administered as an intravenous infusion over 15-60 minutes.

Pegteograstim

According to the judgment of the investigator, one pegteograstim syringe (pegteograstim 6 mg) will be administered (subcutaneously) every cycle of neoadjuvant therapy and 24 hours after the completion of paclitaxel/carboplatin administration.

4.2.2 Dose Administration Monitoring

Subjects will be monitored during and after the instillation.

If adverse reactions related to instillation of grade 2 or lower occur, the drug infusion rate may be slowed down by 50% or the administration may be withheld until the event is resolved, and the infusion may be resumed at 50% of the initial rate to finish the infusion.Subjects with grade 2 or less drip-related adverse events may receive all subsequent instillation infusions at 50% of the initial rate. Acetaminophen and/or antihistamines (e.g., diphenylhydramine) or equivalent agents according to institutional standards may be administered at the discretion of the investigator. If the severity of instillation-related reactions is grade 3 or higher, the administration of the investigational drug should be permanently discontinued. For the management of subjects with instillation reactions, refer to the Toxicity Management Guidelines.

As with any antibody, there is a possibility of an allergic reaction when administering this investigational drug. Appropriate medications and medical equipment to treat acute anaphylactic reactions should be readily available nearby, and clinical trial personnel should be trained on the recognition and treatment of anaphylaxis. Sites should have emergency CPR teams and equipment on standby and take steps to ensure that the subject is admitted to the intensive care unit promptly if necessary.

5. TRIAL TREATMENT PLAN

5.1 Subject Registration

5.1.1 Registration Process

All screening and enrollment procedures will be conducted according to the evaluation schedule. Demographic data and other characteristics including date of birth or age, gender, smoking history, and race/ethnicity will be recorded according to local regulations. Standard medical history and surgical history will be investigated.

Prior to initiation of any protocol-specific procedures, including screening/baseline assessments, the patient consent form and approval in line with the local privacy legislation requirements must be secured. Subjects may optionally sign a consent form to provide tumor specimens (existing archival specimens or recently newly performed biopsy specimens) to participate in this study . This consent form is included in the principal patient consent form. Screening/baseline assessments may be conducted in multiple visits.

5.1.2 Procedures for handling incorrectly registered subjects

Patients who do not meet the suitability criteria should not receive an investigational drug under any circumstances. There are no exceptions to this rule. A study that is enrolled in a clinical trial but found to not meet the suitability criteria should be considered a screening failure and dropped out of the trial. If a patient who does not meet all of the suitability criteria accidentally initiates the incorrect dose, the investigator must immediately notify the investigator of this fact, and the investigator and the investigator should discuss whether to continue or discontinue the subject's treatment. The clinical trial team physician should ensure that all of these decisions are properly documented.

5.2 Dosage and Dosage

Intravenous instillation of paclitaxel 175 mg/m2 over 2-3 hours followed by intravenous instillation of carboplatin over 15-60 minutes on the 1st and 22nd days of the neoadjuvant treatment period (2 total doses) followed by intravenous instillation of paclitaxel 175 mg/m2 over 2-3 hours followed by intravenous instillation over 15-60 minutes (range: ± 3 days)

5.3 Dose adjustment and toxicity management

5.3.1

5.3.2 Dose adjustment for hematologic toxicity (one dose phase = 25% of the initial dose)

Adverse reactions		What to do
Grade 1-3	First occurrence	Administration may be withheld until Grade 1 or less or recovery to baseline. Treatment can be resumed without dose reduction. Consider G-CSF administration.
	Second occurrence	At the discretion of the investigator, the dose level may be lowered by one level and treatment may be resumed. Consider G-CSF administration.
	Third occurrence	Lower the dose level by two levels. Consider G-CSF administration.
Grade 3 febrile neutropenia	First occurrence	Administration may be withheld until Grade 1 or less or recovery to baseline. Lower the dose level by one notch. Consider G-CSF administration.
	Second occurrence	Lower the dose level by two levels. Consider G-CSF administration.
	Third occurrence	Permanently discontinue administration.
Grade 4 febrile neutropenia	First occurrence	Lower the dose level by two levels. Consider G-CSF administration.
	Second occurrence	Permanently discontinue administration.

5.3.3 Dose Adjustment for Non-Hematologic Toxicity

Adverse reactions		What to do
Grade 3-4 Non-	First occurrence	Administration may be withheld until Grade 1 or less or recovery to baseline. You can lower the dose level by one level.

Hematologic Toxicity	Second occurrence	Lower the dose level by two levels.
	Third occurrence	Permanently discontinue administration.
Grade 4 Laboratory Adverse Events	First occurrence	For G4 that is not clinically significant, dosing may be withheld until Grade 1 or less or recovery to baseline. If clinically significant, dosing should be withheld. Lower the dose level by one notch.
	Second occurrence	Lower the dose level by two levels.

6. LIMITATIONS DURING THE TRIAL AND COMBINATION THERAPY

6.1 Limitations during clinical trials

The following restrictions apply while the subject is receiving study treatment and before and after the specified time points:

- Female subjects of childbearing potential
  - Women of childbearing potential who are sexually active and whose male partner has not had a vasectomy must have at least 1 or more Very Effective Contraception (Table 1) from screening onwards. End of clinical trial treatment You must agree to continue using it until the 180th day. The male partner of the female test subject, who is not sterile, must use a male condom containing spermicide throughout this period. After this point, the decision to stop using contraception should be made in consultation with the attending physician. During the entire trial treatment period and during the period of extracorporeal expulsion Complete abstinencePutting it into practiceis an acceptable contraceptive method, but periodic abstinence, rhythmic methods, and extracorporeal ejaculation are not recognized as contraceptive methods. Female subjects must be In addition, Breastfeeding throughout this periodto It should be avoided.
- Male subjects with female partners of childbearing potential
  - Men who are sexually active and have a female partner of childbearing potential who have not had a vasectomy should continue to use a condom containing spermicide from screening until day 180 after the end of clinical trial treatment. Complete abstinence is an adequate form of contraception, but intermittent abstinence, rhythmic methods, and extracorporeal ejaculation are not accepted as contraceptives. Men should avoid donating sperm throughout this period.
  - (of childbearing) female partner of a male subject who is also Use at least 1 or more highly effective contraception Throughout this period Use Do (Table 1 Note).

Note: A woman of childbearing potential is defined as one who is not surgically sterile (i.e., has undergone bilateral tubal ligation, bilateral oophorectomy, or complete hysterectomy) and is not postmenopausal.

Women who have been amenorrheic for 12 months without an alternative medical reason are considered postmenopausal. The following age-specific requirements apply:

- Even if you are under 50 years old, you are considered a menopausal woman if you have been ameneorrheic for at least 12 months after stopping

exogenous hormone therapy, and your luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels are within the postmenopausal value range of the test site, or if you have undergone surgical sterilization (bilateral oophorectomy or complete hysterectomy).

- Women aged 50 years or older who have been amenorrheic for at least 12 months after discontinuation of all exogenous hormonal therapy, who are radiation-induced postmenopausal with their last menstrual period more than 1 year ago, or who have undergone chemotherapy-induced postmenopausal status more than 1 year since their last menstrual period, or who have undergone surgical sterilization (bilateral oophorectomy, bilateral salpingectomy, or complete hysterectomy) are considered menopausal women.

Defined as 1 contraceptive method with a low failure rate (i.e., less than 1% annual incidence of pregnancy) when used consistently in the correct methodBecoming Highly effective contraceptionSilver Table 1It is described in Some Contraception(e.g., male or female condoms that do not contain spermicide; female cervical caps, diaphragms, sponges that do not contain spermicide; intrauterine devices that do not contain copper); Oral hormonal contraceptives with a single ingredient of progesterone that are not the main mechanism of action are inhibition of ovulation[However,, Serajette/Desogestrel is recognized as a highly effective contraceptive method]; Triple combined oral contraceptives)is very Effective Not considered a contraceptive method.

Table 1 Highly effective contraception(Failure rate less than 1%)

Blocking method/ Intrauterine device	Hormonal preparations
• Copper T Intrauterine Device • levonorgestrel-releasing intrauterine device (e.g., Mirena®) [a]	• Implant agent: Etogestrel releasing implant: e.g., Implanon® or Norplan® • Intravaginal device: ethinylestradiol/etonogestrel-releasing intravaginal device: e.g., NuvaRing® • Injections: medroxyprogesterone injections: e.g., Depo-Provera® • Contraceptive tablets: standard and low dose combination oral contraceptives • Patch: Norelgestromine/ethinylestradiol-releasing transdermal system: e.g., Ortho Evra® • Mini-tablets: Oral contraceptives containing desogestrel based on progesterone: Currently, Cerazette is the only highly effective progesterone-based contraceptive tablet®.

[a] It is also considered a hormonal agent.

6.2 Combination treatment

The principal investigator should be promptly informed of all medications used between the time of screening and the end of the trial period (the final visit of the trial). All concomitant medications used during the trial, including natural product preparations, should be recorded in the CRF.

Restricted concomitant medications, prohibited concomitant medications, and permitted concomitant medications are listed in the table below.

6.2.1 Acceptable concomitant medications

Table 2. Adjunctive drugs

Adjunctive drugs/drug classes:	**Instructions for use:**
Concomitant medications or concomitant treatments (e.g., acetaminophen or diphenhydramine) that are deemed necessary for appropriate prophylaxis or adjuvant treatment. However, the treatment included in the above-mentioned "prohibited drugs" is not eligible.	It will be administered according to the instructions of the investigator.
Optimal adjuvant treatment (antibiotics, nutritional supplements, correction of metabolic disorders, optimal symptom control, pain management [including palliative radiotherapy for non-target lesions, etc.])	It should be used for all test subjects when necessary.
Inactivated vaccines such as influenza vaccines	It is allowed.

6.2.2 Excluded Concomitant Medications

Table 3. Prohibited Concomitant medications

Prohibited drugs/drug classes:	**Instructions for use:**
Any other investigational anticancer agent other than the drug being evaluated in this study	It should not be used together during clinical trial treatment.
Any other concurrent chemotherapy, radiotherapy, immunotherapy, or anticancer treatment other than the drugs equitable for this study	It should not be used together during the administration of the investigational drug. (Concurrent use of hormonal agents for conditions unrelated to cancer [e.g., insulin for the treatment of diabetes, hormone replacement therapy] is permitted; palliative local treatment of independent lesions except for the target lesion [e.g., local surgery or local radiotherapy] is allowed)

Prohibited drugs/drug classes:	**Instructions for use:**
Live attenuated vaccines	It should not be used until the 30th day after the final dose of the investigational drug (including standard treatment).
Substrates or inhibitors of cytochrome P450 CYP2C8 and CYP3A4 (ritonavir, saquinavir, indinavir, nelfinavir, clopidogrel)	Paclitaxel is metabolized by cytochrome P450 CYP2C8 and CYP3A4. There are no clinical trials on interactions, so caution should be exercised when co-administering this drug.

7. CLINICAL TRIAL PROCEDURES

7.1 Clinical trial procedure timeline

Several clinical and diagnostic laboratory evaluations are planned prior to enrollment in the trial, throughout the trial, and after permanent discontinuation of the investigational drug. The purpose of conducting these detailed evaluations is to ensure adequate safety and tolerability assessments. If clinically necessary, clinical evaluations and laboratory tests can be repeated more frequently. The evaluation schedule for screening and treatment period is included after the trial overview.

- The date of tumor effectiveness (RECIST) assessment will follow the original schedule as of the date of randomization (not the date of administration of trial treatment), regardless of whether the dose is withheld.
- All evaluations that should be performed at the beginning of the dosing cycle, such as laboratory evaluations, must be performed within 3 days prior to dosing.
- The test subject may postpone medication in the following situations:
    - Medication may be postponed due to adverse reactions according to toxicity management guidelines.
    - If medication is postponed for reasons other than drug-related toxicity, medication may be resumed when possible.
    - If clinically feasible, the dosing interval in subsequent cycles may be shortened to gradually align the dosing cycle with the tumor evaluation (RECIST) schedule.

7.1.1 Screening period

Unless otherwise specified, screening assessments will be performed within 28 days prior to Day 1. All patients must read, understand, and sign an IRB-approved ICF prior to initiating any trial-specific screening procedures. After signing the ICF and completing all screening procedures, patients who are deemed suitable for participation in the trial will be enrolled in the trial. Assessments that were performed prior to signing the ICF and are considered standard procedures may be replaced by a screening assessment if it falls within the 28-day range of screening.

The following procedures will be performed at the screening visit:

- Completion of the consent form for the subject
- Review of conformity criteria
- Medical history and demographics
- Detailed physical examination

- ECOG performance status
- Vital signs, weight and height
- 12-lead ECG
- Tumor biopsy (optional)
- Prior/Concomitant Medication Review
- Imaging with CT/MRI (Chest CT/Neck MRI) and/or PET CT if necessary
- Clinical laboratory tests for:
  - CBC, SMA
  - Blood clotting (PT, PTT, INR)
  - Creatinine clearance
  - Serum pregnancy test (for women of childbearing potential only)
  - Hepatitis serology
  - Urine analysis
- Chest x-ray
- HIV, HBV, HCV screening

7.1.2 Duration of Trial Treatment

For procedures that should be performed during the treatment period, please refer to the evaluation schedule. Screening procedures performed within 7 days prior to Cycle 1 Day 1 do not need to be repeated on Cycle 1 Day 1.

7.1.3 End of clinical trial treatment

End of investigational treatment is defined as the first outpatient visit after completion of induction anticancer therapy and surgery. For subjects who permanently discontinue administration and investigational procedures prior to that time, the last visit at which a decision to permanently discontinue is considered the end of treatment. All required procedures may be completed within ± 14 days of the end-of-treatment visit.

7.2 Clinical trial procedures

7.2.1 Medical history, physical examination, electrocardiogram, weight, vital signs

The findings of the medical history (collected at screening) and physical examination should also be graded at baseline according to the adverse event evaluation procedure. If the severity increases compared to the existing condition during the clinical trial, it is considered an adverse event, and if it decreases to grade or below before the start of the trial, it is considered to have resolved.

The physical examination will be performed on the trial day specified in the evaluation schedule.

7.2.2 Physical examination

A physical examination will be performed according to the evaluation schedule. In the detailed physical examination, the head, eyes, ears, nose, throat, respiratory system, cardiovascular system, gastrointestinal system, genitourinary system, musculoskeletal system, nervous system, skin, blood/lymphatic, and endocrine system are evaluated. Height will be measured at screening only. A brief physical examination will be selected and performed by the investigator based on clinical observations and symptoms.

7.2.3 Electrocardiogram

A 12-lead ECG at rest will be recorded at screening and whenever clinically necessary throughout the trial. The ECG should be performed while the subject rested in the supine position for 5 minutes and then maintained in the same position.

7.2.4 Vital signs

Vital signs (blood pressure, pulse rate, body temperature, respiratory rate) will be measured according to the assessment schedule. At each visit, they will also weigh themselves along with vital signs.

7.2.5 Clinical laboratory tests

Blood specimens and urine specimens for clinical chemistry, hematology, and urine analysis evaluation will be collected at the time specified in the evaluation schedule and whenever clinically necessary.

Clinical laboratory safety checks, including serum pregnancy tests, will be performed in an accredited clinical laboratory according to local standard procedures. Specimen tubes and specimen sizes may vary depending on the analytical method used and the laboratory's usual policies. A urine pregnancy test can be performed at a testing site

using an approved test method (urine or serum pregnancy test). If laboratory values are clinically significantly abnormal, the test should be repeated as quickly as possible (preferably within 24-48 hours).

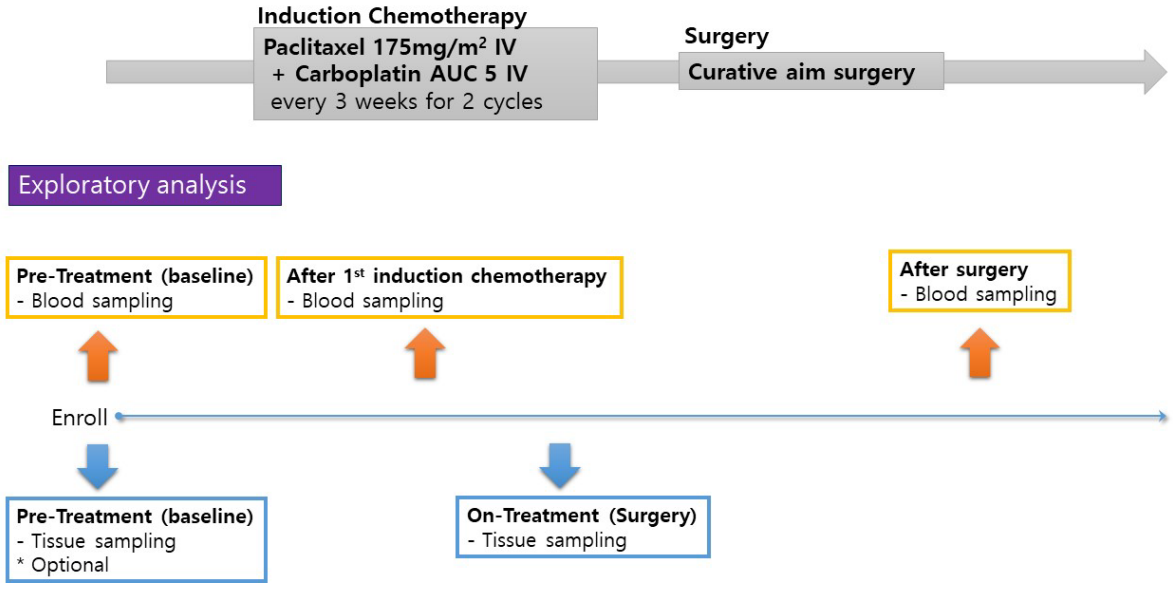
If clinically necessary according to the investigator's judgment, additional safety specimens may be collected. The collection date, collection time, and analysis results (number, unit, reference range) of the specimen are recorded in the appropriate columns of the CRF.

Other safety tests to be performed at screening include measurement of hepatitis B virus surface antigen, hepatitis C virus antibody, and HIV antibody.

7.3 Biological specimen collection procedure

In order to participate in this clinical trial, the subject must agree to the collection of biological specimens and the use of the provided specimens as described below. Tumor tissue specimens and blood specimens will be collected from all screened subjects for exploratory biomarker analysis.Samples will be collected according to the evaluation schedule presented in the schedule.

All specimens collected for biomarker analysis will be stored at the site or reference laboratory and may be used in subsequent studies related to the evaluation of biological and/or clinical response to immunotherapy.



Picture 2. Tissue specimen and blood specimen collection schedule for exploratory biomarker analysis

7.3.1 Biomarker Specimen Collection and Evaluation Methods

- Blood specimen collection schedule

Baseline (before first-line induction chemotherapy)

After the first induction chemotherapy (within 7 days before the start date of the second anticancer)

Postoperative (between 28-56 days after surgery)

- Tumor specimen collection schedule

Baseline (optional)

During surgery

Analytics

·PD-L1 expression

Circulating tumor cells

·T-cell immunophenotyping using flow cytometry

·Multiplex biomarker analysis of tumor cells and immune cells in the tumor microenvironment

·RNA sequencing using fresh tumor samples collected during pre- and post-treatment resection surgery (if possible, single-cell RNA sequencing) to find potential transscriptome changes in tumor cells and immune cells

*** Single-cell RNA sequencing (optional)**

- Single-cell RNA sequencing will be performed to identify heterogeneous gene expression programs within the tumor microenvironment and to identify transcriptional, functional, and genetic diversity relationships before and after chemotherapy treatment.
- Comparing single-cell RNA sequences to previous bulk RNA sequencing can provide information about the transscriptomes of individual cells, and barcoding each cell before starting the sequencing procedure yields a typical 1000-cell transcriptome. Therefore, single-cell RNA sequencing is the best way to comprehensively investigate changes in immune signatures after immunotherapy.

* T cell immunophenotyping using flow cytometry of blood PBMCs

i) Increase in tumor antigen-specific T cells

ii) Characterization of tumor antigen-specific T cells and TAM/MDSCs

PD-L1 test

The test method will be PD-L1 IHC 28-8 pharmDx assay.

Specimen collection for testing PD-L1

- The recommended tumor specimens for sPD-L1 status confirmation are those taken after the completion of the most recent secondary treatment. Specimens taken at this time are of the highest clinical relevance as they reflect the most recent tumor PD-L1 status.
- PD-L1 specimens should be collected through central needle biopsy using a needle of 18 gauge or larger, or incisional/excisional biopsy.

Specimen Data Collection for PD-L1 Testing

The following data fields should also be completed when specimens are collected at the test site and, if necessary, when transporting specimens:

- Subject ID code (electronic code or unique ID)
- Specimen ID code (handwritten on specimen label)
- Specimen collection date
- Slice cutting date
- Whether the sample was stored after collection
- Tumor type
- Primary cancerous site

7.3.2 Amount of blood specimen to be collected

After collecting blood samples, circulating tumor cells and peripheral blood mononucleates (PBMCs) are isolated

Baseline: 8cc

After 1st induction chemotherapy (within 7 days before the start date of 2nd chemotherapy): 8cc

・Postoperative (before the start of chemotherapy): 8cc

7.3.3 Withdrawal of consent by the subject to the biological specimen provided

If the subject withdraws their consent to the use of the specimen they have already provided, the specimen will be discarded and the action will be recorded.

The principal investigator will:

- If the biological specimen of the test subject is stored in the testing institution, it should be immediately identified and discarded, and the actions taken should be recorded.

- Immediately notify the laboratory where the specimen is stored that the subject has withdrawn consent, and ensure that the specimen is discarded, the action taken is recorded, and the record is returned to the testing site.

Notify the fact of disposal of test subject specimens.

7.3.4 Collection, storage, and disposal of personal data on the biological samples provided

The collection of personal information for the use of samples provided by the subject and the storage and disposal of samples are as follows.

- During the coding and storage procedures of specimens for genetic analysis, additional codes of specimens are assigned, and the confidentiality of the test subjects is maintained through the identification of unique numbers thereafter.

- Biological specimens of test subjects are stored and maintained in a safe place with limited access.

- Biological specimens of test subjects will be discarded after a maximum of 15 years from the end of the clinical trial.

8. DISEASE ASSESSMENT AND METHODS

Evaluate according to standard RECIST 1.1 criteria

Of note, rapid tumor progression or symptomatic progression requiring urgent medical intervention (e.g., central nervous system metastases, respiratory failure due to tumor compression, spinal cord compression) are considered clinically significant deteriorations.

9. SAFETY ASSESSMENT

The principal investigator is responsible for ensuring that all staff participating in the clinical trial are familiar with the contents of this unit.

9.1.1 Safety Parameters

9.1.1.1 Definition of adverse reaction

An adverse event is a new undesirable medical condition (other than disease progression of the cancer being evaluated) or worsening of an existing medical condition after or during exposure to a drug, regardless of whether it is believed to have a causal relationship with a drug. An undesirable medical condition can be symptoms (e.g., nausea, chest pain), signs (e.g., tachycardia, enlarged liver), or abnormal test results (e.g., laboratory results, electrocardiogram). In clinical trials, Even if no investigational treatment was administered, any undesirable medical condition that occurred at any time, including the run-in period or the period of extracorporeal discharge, is included in the adverse event.

Symptoms and signs associated with the progression of the disease should not be reported as adverse events.

The term adverse reaction encompasses both major and non-serious adverse reactions.

9.1.2 Definition of Serious Adverse Event (SAE)

A serious adverse event (SAE) is an adverse event that occurred during the trial period (i.e., screening period, run-in period, treatment period, extracorporeal discharge period, follow-up period) at any dose of investigational drug and corresponds to one or more of the following criteria:

- Causing death
- Immediately life-threatening
- Requires hospitalization or extension of existing hospitalization
- Resulting in persistent or significant disability or functional decline
- Causes congenital anomalies or birth defects in the subject's child
- Significant medical event that may endanger the subject or requires medical intervention to prevent any of the outcomes listed above

Hospitalization for symptoms and signs associated with disease progression should not be reported as a serious adverse event. In addition, hospitalization for elective treatment of pre-existing conditions that have not worsened from baseline is not considered a serious adverse event.

9.2 Evaluate safety parameters

9.2.1 Severity assessment

Assessing the severity of adverse events and SAEs is one of the many responsibilities of the investigator. The severity will be graded according to NCI CTCAE v5.0.

The severity of all other adverse events not listed in CTCAE should be determined by the investigator based on medical judgment according to the severity category defined as grade 1-5 below.

Grade 1 (mild)	Events that are usually temporary and require minimal treatment or therapeutic intervention. Overall, it does not interfere with activities of daily living.
Grade 2 (moderately)	Events that require the addition of special therapeutic interventions to mitigate them. It interferes with daily activities and causes inconvenience, but does not pose a risk of major or permanent harm to the patient.
Grade 3 (severe)	Events requiring active therapeutic intervention. It interferes with daily activities or greatly affects the patient's clinical condition.
Grade 4 (Life-Threatening)	Events and/or immediate sequelae thereof with an immediate risk of death or physical or mental impairment affecting or limiting the performance of activities of daily living
Grade 5 (Fatal)	Death as a result of an adverse reaction(Loss of life)

It is necessary to distinguish between the severity standard and the severity of adverse reactions. Severity is an indicator of the intensity of adverse events, but severity is defined according to the criteria in Chapter 9.2.1. Grade 3 adverse reactions are not necessarily SAEs. For example, a grade 3 headache lasting several hours is classified as a non-serious adverse event because it does not meet the definition of an SAE, while a grade 2 attack that resulted in hospitalization is considered an SAE.

9.2.2 Causal Assessment

The investigator evaluates the causal relationship between the investigational drug and each adverse reaction, and answers "yes" or "no" to the question, "Is there a logical possibility that the adverse reaction may have been caused by the investigational drug?" For SAEs, the causal relationship with other drugs or clinical trial procedures will also be evaluated. For SAEs that may be related to clinical trial procedures, answer "yes" to the causality question.For guidelines on the interpretation of causality questions, please refer to Appendix A of this protocol.

9.3 Recording of adverse events and serious adverse events

Adverse reactions are recorded as widely accepted medical terms or diagnoses that accurately reflect adverse reactions. The investigator will determine the severity of the adverse event, causality with the investigational drug, suspected etiology, and whether SAE criteria are met and the need for immediate reporting to the IRB and/or regulatory authorities accordingly.

For each adverse event, the following variables will be collected:

In addition, for SAEs, the following variables are also collected, as applicable:

- Adverse events (as terminology used by the investigator)
- Date the adverse event started and ended
- Maximum reported CTCAE grade
- Change in CTCAE grade
- Whether the adverse reaction is serious
- Assessment of the investigator's causality to the investigational drug (yes or no)
- Actions taken for investigational drugs
- Administration of therapeutic agents for adverse events
- Results

In addition, the following variables are collected for SAE:

- Date when the adverse event met the criteria for a serious adverse event
- Date the investigator became aware of the serious adverse event
- Whether it met the materiality criteria
- Hospitalization date
- Discharge date
- Suspected cause of death
- Date of death
- Whether an autopsy is performed
- Causality with clinical trial procedures
- Description of SAE

The revised NCI CTCAE version 5.0 rating scale will be used for all adverse events assessed by CTCAE grading. For adverse events not assessed by CTCAE grade, mild, moderate, and severe should be converted to CTCAE grade according to the recommendations of CTCAE criteria. A copy of CTCAE version 5.0 is available for

download from the Cancer Therapy Evaluation Program website (http://ctep.cancer.gov).

9.3.1 Duration and follow-up of recording adverse events and serious adverse events in clinical trials

Adverse events and SAEs will be recorded from the time of signing the consent form of the subject through the treatment period and throughout the follow-up period (until day 180 after the end of the clinical trial).

During the clinical trial, all adverse events and SAEs of each subject should be actively followed. Even if the administration is permanently discontinued/continues after completion of the clinical trial, every effort must be made to confirm whether all adverse reactions have resolved.

If the subject permanently discontinues study treatment for reasons other than disease progression and tumor evaluation continues, drug or procedure-related SAEs should be collected until the subject is confirmed to have PD and no longer undergoes tumor evaluation.

The investigator is responsible for following up all SAEs until the adverse event resolves, returns to baseline status, or stabilizes and is expected to become chronic beyond the duration of the trial.

9.3.2 Causal Collection

The investigator evaluates the causal relationship between the investigational drug and each adverse reaction, and answers "yes" or "no" to the question, "Is there a logical possibility that the adverse reaction may have been caused by the investigational drug?"

For SAEs, the causal relationship with other drugs or clinical trial procedures will also be evaluated. For SAEs that may be related to clinical trial procedures, answer "yes" to the causality question.

Guidelines for interpreting causation questions can be found in the 오류! 참조 원본을 찾을 수 없습니다.to Please refer to it.

9.3.3 Causality with clinical trial procedures

The investigator should also record the assessment of the causal relationship between the SAE and the protocol procedure in the SAE report form. This applies to both non-treatment–emergent (i.e., SAEs that occurred before administration of the investigational drug) and treatment-emergent SAEs. Protocol-related SAEs can also occur as a result of procedures or interventions required during the clinical trial (e.g., blood draw). Investigators should follow these guidelines when assessing the causality between SAEs and protocols:

- Protocol-related: Adverse event was caused by a procedure or intervention described in the protocol and no other etiology documented in the subject's medical record
- Non-protocol-related: Adverse events related to other etiologies other than the procedures or interventions described in the protocol. These other etiologies must be documented in the subject's medical record.

9.3.4 Adverse reactions based on signs and symptoms

Voluntary report by the subject or subjective question from the clinical trial staff "What health problems have you had since your last visit/last question?" All adverse events reported as answers or confirmed by observation will be collected and recorded in the CRF. When collecting adverse events, it is preferable to record the diagnosis (if possible) rather than recording a list of signs and symptoms. However, if the diagnosis is known and there are other signs or symptoms that do not usually correspond to the diagnosis, the diagnosis and each sign or symptom are recorded separately.

9.3.5 Adverse reactions based on measurement and testing

The results of laboratory tests and vital signs, which are mandatory investigations under the protocol, will be summarized in the clinical trial results report. Deterioration compared to baseline in laboratory values and vital signs, which are mandatory investigations under the protocol, will only be reported as adverse events if they meet the criteria for SAE or the reason for discontinuation of treatment with the investigational drug.

If a deterioration in laboratory values or vital signs is accompanied by post-clinical signs and symptoms, the signs or symptoms should be reported as adverse events and the associated laboratory results or vital signs should be considered additional information. If possible, the reporting investigator should use clinical terminology rather than laboratory terms (e.g., anemia rather than decreased hemoglobin levels). In the absence of clinical signs or symptoms, clinically significant deterioration of parameters that are not mandatory should be reported as adverse events.

Laboratory deterioration that is certainly due to disease progression should not be reported as adverse events/SAEs.

All new or worsening clinically significant abnormal medical results of physical examination compared to baseline assessments will be reported as adverse events.

9.3.6 Disease progression

Disease progression may be considered as a deterioration of the subject's condition due to the disease for which the investigational drug is being evaluated. This may be an increase in the severity of the disease being evaluated and/or an increase in disease symptoms. New metastases or worsening of existing metastases in the primary cancer being evaluated in the trial should be considered disease progression rather than

adverse events. Events that are clearly due to disease progression should not be reported as adverse events during clinical trials.

9.3.7 Neonatal cancer

The occurrence of new cancer should be considered an SAE. A new primary cancer is one that is not the primary cause of the administration of an investigational drug and is discovered after the subject's participation in this study.

9.3.8 Death

Any death occurring during the treatment period of the trial or within the follow-up period after the last dose of investigational drug as defined in the protocol must be reported as follows:

- Deaths that are clearly due to disease progression should be communicated to the investigator/principal investigator and recorded in the death statement column of the CRF. It should not be reported as an SAE.
- If death is not due to progression of the disease under study (or if causality is not clear), the adverse event resulting in death must be reported to the principal investigator as an SAE within 24 hours. This should also be recorded in the death statement column of the CRF.The report should include an appropriate assessment of whether disease progression was co-related and should specify the main and contributing causes of death.
- Deaths of unknown cause should always be reported as SAEs. This should also be recorded in the Statement of Death column of the CRF. Autopsies may help assess the cause of death, and if autopsies are performed, a copy of the autopsy report should be reported to AstraZeneca Patient Safety within the normal reporting deadline.

If death occurs after the last dose of investigational drug and after the safety follow-up period as defined in the protocol, it should be recorded on the death page. If the death occurred as a result of an event that began during the safety follow-up period and is believed to be due to delayed toxicity to the investigational drug, it should be reported as an SAE.

9.3.9 Reporting of Serious Adverse Events

All SAEs should be reported regardless of causal relationship to the investigational drug or trial procedure. The reporting period for SAEs is from immediately after signing the subject's consent form until Day 18 0 after the end of the trial or at the start of other anticancer therapy. The investigator is responsible for reporting SAEs to the sponsor, ethics committee, and/or regulatory authorities in accordance with local requirements.

9.3.10 Other incidents that require reporting

9.3.10.1 Overdose

The use of investigational drugs at doses exceeding the levels specified in the protocol is considered overdose. Currently, there is no established treatment method for overdose of paclitaxel or carboplatin, and the symptoms that may occur in case of overdose have not been established.

- For overdose with adverse events, the diagnosis or symptoms of adverse events should be recorded in the relevant adverse reaction column of the CRF and the overdose column of the CRF.
- Overdoses without associated symptoms will only be reported in the overdose column of the CRF.

In the event of an overdose of an investigational drug during a clinical trial, the investigator or other site representative shall notify **the IRB and regulatory authorities** immediately or no later than 24 hours after becoming aware of this fact.

In the case of overdose with SAEs, the standard reporting deadlines specified in Chapter 6.4 apply. In the case of other overdoses, they must be reported within 30 days.

9.3.10.2 Pregnancy

All pregnancies and the consequences of pregnancy shall be reported. With the following exceptions:

- Pregnancy detected before the subject starts administration of the study drug
- Pregnancy of the female partner of a male subject in the absence of contraceptive requirement for the male subject.

9.3.11 Maternal drug exposure

If a study subject becomes pregnant during the trial, the administration of the investigational drug should be stopped immediately.

Pregnancy itself is not considered an adverse event unless there is a suspicion that the investigational drug being evaluated in the clinical trial may have interfered with the effectiveness of the contraceptive. Congenital anomalies or birth defects and spontaneous miscarriages should be reported and treated as SAEs. Uncomplicated abortion should not be considered an adverse reaction. The outcome of any pregnancy (spontaneous abortion, incarcerated abortion, ectopic pregnancy, live delivery, or congenital anomaly) should be followed up and documented, even if the subject discontinues participation in the trial.

9.3.12 Drug exposure in the body

Male subjects should not plan to age 2 years or donate sperm during the trial and until 180 days after the end of the clinical trial.

The pregnancy of the subject's partner is not considered an adverse event. However, if possible, the results of any pregnancy that occurred from the date of the first dose of the investigational drug to 180 days after the end of the clinical trial (spontaneous abortion, artificial abortion, ectopic pregnancy, live delivery, or congenital anomaly) should be followed up and documented.

Once a pregnancy report is received, the investigator must obtain consent from the subject's partner before collecting information about the pregnancy. Therefore, the local clinical trial team should compile a sample of the general subject consent form according to local procedures and submit it to the appropriate Ethics Committee (EC)/Internal Review Board (IRB) prior to use.

10. STATISTICAL ANALYSIS METHODS AND SAMPLE SIZE CALCULATION

10.1 Description of the analysis set

The full analysis set (FAS) consists of all registered test subjects. Subjects who were enrolled independently of the actual treatment received but who did not receive any subsequent study treatment will also be included in the analysis.

10.1.1 Safety Assay Set

All subjects treated as in this trial

The safety analysis set consists of all subjects who have received at least one dose of test treatment.

10.1.2 Validity Analysis Set

Full Analysis Set (FAS)

10.2 Statistical analysis methods

Variables will be compared using the student-t test, Mann-Whitney-U test, and chi-square test according to the nature of the variables. Multivariate survival analysis will be performed using a Cox proportional hazards regression model.

10.2.1 Safety Analysis

Analysis of safety endpoints

Safety and tolerability will be assessed by clinical review of all relevant parameters, including adverse events, laboratory tests, and vital signs.

10.2.2 Effectiveness analysis

- Major pathologic response (mPR) is defined as less than 10% of residual cancer remaining in tumor tissue resected at the time of surgery after neoadjuvant chemotherapy.
- Locoregional relapse rate (LRR) is defined as the frequency of recurrence of primary or cervical lymph nodes after surgery.
- Relapse–free survival (RFS) is defined as the time from the date of first administration of the study drug to the date of first documented radiographic

disease progression according to RECIST 1.1 by local or distant recurrence in subjects who have achieved disease-free after surgery.

- Overall survival (OS) is defined as the time from the date of the first administration of the investigational drug to the date of objective disease progression or death from any other cause.

10.3 Sample size determination

Total sample size: 79 people

This study is a clinical trial designed to evaluate whether Paclitaxel + Carboplatin induction anticancer therapy improves the major pathological response rate compared to conventional induction anticancer therapy (historical control) in patients with potentially operable locally advanced HNSCC.

In locally advanced head and neck cancer, the pathological response rate at the time of surgery after conventional induction chemotherapy was confirmed to be 33% for Fluorouracil + Cisplatin (Licitra et al 2003) and 27.7% for Docetaxel + Cisplatin + Fluorouracil (Zhong et al 2013).

The sample size was calculated with the one-arm binomial test with 75% power for the hypothesis to be accepted and 10% for the significance of the hypothesis to be rejected (α error=0.10, beta: 0.25, power=0.75). It is assumed that the mPR of the historical control induction chemotherapy is 30.0% (p1) and the mPR of Paclitaxel + Carboplatin induction chemotherapy is 41.0% (p2).

H0: p1=p2 vs. H1: When p1≠p2, 72 subjects are required to have a power of 75% to detect a difference between p1=0.30 and p2=0.41 at a significance level of 10%, and a total of 79 subjects are required for a failure to follow-up rate of 10%.

11. ETHICS AND REGULATORY REQUIREMENTS

11.1 Ethical conduct of clinical trials

The trial will be conducted in accordance with the Declaration of Helsinki and in accordance with the International Conference on Harmonization (ICH)/Good Clinical Practice (GCP), applicable regulatory requirements and ethical principles consistent with personal data protection policies.

11.2 Review by the Ethics Committee and Regulatory Authorities

The EC/IRB must approve the final protocol, including the final version of the patient consent form and any other information/documents provided to the subject. The site director must ensure that these documents have been communicated to the EC/IRB and that the principal investigator has been communicated to the investigators and researchers. The EC/IRB's comments should be written and communicated. Before any subject is enrolled in a study, the site director must provide the principal investigator with a written EC/IRB approval letter and a notice of instructions/decision.

If the study duration is longer than one year, the site director should confirm the EC/IRB opinion on the appropriateness of continuing the study at the site at least once in a year. The principal investigator must submit a progress report to the EC/IRB through the site director at the time of re-approval of the protocol.Before any subject is enrolled in a study, the final protocol, including the final version of the consent form, must be approved by the national regulatory authority or notified to the national regulatory authority in accordance with local regulations.

11.3 Patient Consent Form

The principal investigator of each testing site warrants the following:

- Provide each patient with sufficient and appropriate oral and written information about the nature, purpose, possible risks and benefits of the clinical trial.
- Each subject is informed that the subject can stop the trial at any time
- Provide each test subject with an opportunity to ask questions and time to think about the information provided.
- Prior to any procedures related to the clinical trial, a signed and dated patient consent form will be obtained by each subject.
- Ensure that the original signed subject consent form is kept in the investigator's clinical trial file.
- Guarantee that a copy of the signed subject consent form is provided to the subject.

- Cases for subjects participating in clinical trials and all compensation provisions for subjects harmed as a result of participation in the trial are described in the EC/IRB-approved patient consent form.

11.4 Changes to the protocol and patient consent form

If there are significant changes to the protocol, those changes will be documented in the form of a revised protocol and, if necessary, a new version of the protocol (revised protocol).

The revised clinical trial protocol must also be approved by the relevant EC/IRB and, if applicable, by the national regulatory authority before implementing its contents. The revised clinical trial protocol must comply with local requirements.

If the protocol revision requires a change to the site patient consent form, the revised patient consent form must also be approved by the site EC/IRB before use.

If required by local regulations, any administrative changes will be reported to or approved by the respective EC/IRB.

12. CLINICAL TRIAL MANAGEMENT

12.1 Training of Laboratory Personnel

The principal investigator shall provide appropriate training to all these employees in connection with the exam and shall communicate any new information related to the conduct of the exam to the relevant personnel.

The principal investigator maintains the records of all personnel involved in the study (doctors, nurses, and other staff in charge).

12.1.1 Rationale data

For the storage location of the rational data, please refer to the Clinical Trial Agreement (CSA).

12.2 Clinical trial schedule and end of study

The end of this clinical trial is defined as the final visit of the last patient who is undergoing this study. This study is expected to begin in the first quarter of 2022 (enrollment of the first subject). The last study is expected to be enrolled in the fourth quarter of 2023. The end of the fourth quarter of 2023 is expected to end in the fourth quarter of 2025. The end of this clinical trial is defined as the last visit of the last patient who is undergoing this study.

13. INVESTIGATIONAL DRUGS AND OTHER TREATMENTS

13.1 Investigational Drugs

Table 4. Investigational drug used in this clinical trial

Investigational Drugs	Dosage Formulation and Strength	Manufacturer
Paclitaxel	*Infusion solution used after dilution* *6 mg/ml*	Samyang
Carboplatin	*Diluted drip solution 10 mg/ml*	Boryeong
Pegteograstim	*Glass Prefilled Syringe Injection* *1 shot of 6mg (0.6ml)*	Green Cross

14. REFERENCE LIST

Bray, F. et al 2018

Bray, F., et al., Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin, 2018. 68(6): p. 394-424.

Cmelak et al. 2007a

CMELAK, Anthony J., et al. Phase II trial of chemoradiation for organ preservation in resectable stage III or IV squamous cell carcinomas of the larynx or oropharynx: results of Eastern Cooperative Oncology Group Study E2399. Journal of clinical oncology, 2007, 25.25: 3971-3977.

Cmelak et al. 2007b

CMELAK, Anthony J., et al. Taxane-based chemoirradiation for organ preservation with locally advanced head and neck cancer: Results of a phase II multi-institutional trial. Head & Neck: Journal for the Sciences and Specialties of the Head and Neck, 2007, 29.4: 315-324.

Cohen, E.E. et al 2014

Cohen, E.E., et al., Phase III randomized trial of induction chemotherapy in patients with N2 or N3 locally advanced head and neck cancer. J Clin Oncol, 2014. 32(25): p. 2735-43.

Department of Veterans Affairs Laryngeal Cancer Study Group et al 1991

DEPARTMENT OF VETERANS AFFAIRS LARYNGEAL CANCER STUDY GROUP*. Induction chemotherapy plus radiation compared with surgery plus radiation in patients with advanced laryngeal cancer. New England Journal of Medicine, 1991, 324.24: 1685-1690.

Dunphy et al. 1999

DUNPHY, Frank R., et al. Induction paclitaxel and carboplatin for patients with head and neck carcinoma: Analysis of 62 patients treated between 1994 and 1999. Cancer, 2001, 91.5: 940-948.

Geoffrois, L. et al 2018

Geoffrois, L., et al., Induction Chemotherapy Followed by Cetuximab Radiotherapy Is Not Superior to Concurrent Chemoradiotherapy for Head and Neck Carcinomas: Results of the GORTEC 2007-02 Phase III Randomized Trial. J Clin Oncol, 2018. 36(31): p. 3077-3083.

Herman, L.C., et al 2014

Herman, L.C., et al., Comparison of carboplatin-paclitaxel to docetaxel-cisplatin-5-flurouracil induction chemotherapy followed by concurrent chemoradiation for locally advanced head and neck cancer. Oral Oncol, 2014. 50(1): p. 52-8.

Hitt et al. 2005

HITT, Ricardo, et al. Phase III study comparing cisplatin plus fluorouracil to paclitaxel, cisplatin, and fluorouracil induction chemotherapy followed by chemoradiotherapy in locally advanced head and neck cancer. J Clin Oncol, 2005, 23.34: 8636-8645.

Hitt, R., et al 2014

Hitt, R., et al., A randomized phase III trial comparing induction chemotherapy followed by chemoradiotherapy versus chemoradiotherapy alone as treatment of unresectable head and neck cancer. Ann Oncol, 2014. 25(1): p. 216-25.

Licitra et al 2003

LICITRA, Lisa, et al. Primary chemotherapy in resectable oral cavity squamous cell cancer: a randomized controlled trial. Journal of Clinical Oncology, 2003, 21.2: 327-333.

Lorch et al. 2011

LORCH, Jochen H., et al. Induction chemotherapy with cisplatin and fluorouracil alone or in combination with docetaxel in locally advanced squamous-cell cancer of the head and neck: long-term results of the TAX 324 randomised phase 3 trial. The lancet oncology, 2011, 12.2: 153-159.

Posner, M.R. et al 2007

POSNER, M.R., et al. Cisplatin and fluorouracil alone or with docetaxel in head and neck cancer. New England Journal of Medicine, 2007, 357.17: 1705-1715.

Posner, M.R. et al 2009

Posner, M.R., et al., Sequential therapy for the locally advanced larynx and hypopharynx cancer subgroup in TAX 324: survival, surgery, and organ preservation. Ann Oncol, 2009. 20(5): p. 921-7.

Ready et al. 2012

READY, Neal E., et al. Weekly paclitaxel and carboplatin induction chemotherapy followed by concurrent chemoradiotherapy in locally advanced squamous cell carcinoma of the head and neck. American journal of clinical oncology, 2012, 35.1: 6-12.

Vermorken, J. B., et al 2007

VERMORKEN, Jan B., et al. Cisplatin, fluorouracil, and docetaxel in unresectable head and neck cancer. New England Journal of Medicine, 2007, 357.17: 1695-1704.

Zhong et al 2013

ZHONG, Lai-ping, et al. Randomized phase III trial of induction chemotherapy with docetaxel, cisplatin, and fluorouracil followed by surgery versus up-front surgery in locally advanced resectable oral squamous cell carcinoma. Journal of clinical oncology, 2013, 31.6: 744.