**Statistical Analysis Plan (SAP)**

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**CONFIDENTIAL**

# A PHASE II STUDY EVALUATING THE EFFICACY AND THE SAFETY OF FIRST-LINE CHEMOTHERAPY COMBINED WITH TG4010 AND NIVOLUMAB IN PATIENTS WITH ADVANCED NON-SQUAMOUS NON-SMALL-CELL LUNG CANCER (NSCLC)

Study phase: II

**PROTOCOL N° TG4010.24**

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**COORDINATING** [redacted]

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# DOCUMENT APPROVAL

SPONSOR'S OFFICER(S)

[redacted]

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## LIST OF ABBREVIATIONS

| ABBREVIATIONS | MEANING OF ABBREVIATIONS IN DOCUMENT |
|---|---|
| AE | Adverse Event |
| AEOSI | Adverse Event of Special Interest |
| ALK | Anaplastic Lymphoma Kinase |
| ATC | Anatomical Therapeutic Chemical |
| AUC | Area Under the Curve |
| BMI | Body Mass Index |
| BOR | Best Overall Response |
| BSA | Body Surface Area |
| [redacted] | [redacted] |
| CI | Confidence Interval |
| CM | Concomitant Medication |
| CR | Complete Response |
| CRA | Clinical Research Associate |
| CRO | Contract Research Organization |
| CS | Clinically Significant |
| CT | Computed Tomography |
| CTCAE | Common Terminology Criteria for Adverse Events |
| [redacted] | [redacted] |
| D | Day |
| DCR | Disease Control Rate |
| DNA | Deoxyribonucleic acid |
| DoR | Duration of Response |
| ECG | Electrocardiogram |
| ECOG | Eastern Cooperative Oncology Group |
| eCRF | Electronic Case Report Form |
| EGFR | Epidermal Growth Factor Receptor |
| EOS | End of Study |
| EOT | End of Treatment |
| EPP | Evaluable Patients' Population |
| FAS | Full Analysis Set |
| FU | Follow Up |
| GCP | Good Clinical Practice |
| HBV | Hepatitis B Virus |
| HCV | Hepatitis C Virus |
| HIV | Human Immunodeficiency Virus |
| [redacted] | [redacted] |
| HR | Hazard Ratio |
| ICF | Informed Consent Form |
| IDMC | Independent Data Monitoring Commitee |
| IHC | Immunohistochemistry |
| IMAE | Immune-Mediated Adverse Event |
| IMP | Investigational Medicinal Product |
| INT | Integer part |
| IU | International Unit |
| M | Month |
| MAX | Maximum |
| MEDDRA | Medical Dictionary for Regulatory Activities |
| MIN | Minimum |
| MUC1 | Mucine 1 |
| N | Number |
| NA | Not Applicable |
| NCI-CTCAE | National Cancer Institute's Common Terminology Criteria for Adverse Events. Also referred as CTCAE in the text |
| NCS | Non Clinically Significant |
| NSCLC | Non-Small-Cell Lung Cancer |
| NE | Not evaluable |
| ORR | Objective Response Rate |
| OS | Overall Survival |
| PD | Progressive Disease |
| PD-L1 | Programmed Death Ligand-1 |

| ABBREVIATIONS | MEANING OF ABBREVIATIONS IN DOCUMENT |
|---|---|
| PFS | Progression Free Survival |
| PFU | Plaque Forming Unit |
| PR | Partial Response |
| PS | Performance Status |
| PT | Prefered Term |
| RDI | Relative Dose Intensity |
| RECIST | Response Evaluation Criteria In Solid Tumors |
| [redacted] | [redacted] |
| SAE | Serious Adverse Event |
| SAF | Safety Analysis Set |
| SC | Subcutaneous |
| sd | Standard deviation |
| SD | Stable Disease |
| SET | Safety Evaluable Set |
| SI units | International System of units |
| SOC | System Organ Class |
| TNM | Tumour Nodes (Lymph) Metastasis |
| ULN | Upper Limit of Normal |

[redacted]

## 2 STUDY DESIGN

### 2.1 Overall study design and plan description

This is a multicenter, single arm, open label phase II study in chemotherapy-naïve for advanced stage of the disease and immunotherapy-naïve patients with advanced non-squamous NSCLC. Only patients with PD-L1 membrane staining on < 50% of tumor cells by immunohistochemical (IHC) staining in the submitted tumor sample will be included.

Patients will receive TG4010 + nivolumab + chemotherapy from C1D1.

TG4010 will be administered weekly for 6 weeks (C3D1) and every 3 weeks thereafter until disease progression or death or premature discontinuation due to any reason.

Nivolumab will be given every 3 weeks until disease progression or death or premature discontinuation due to any reason or for a maximum of 24 months whichever occurs first.

Platinum-doublet chemotherapy will be administered as 21-day cycle for 4 cycles followed by pemetrexed in patients candidate for maintenance therapy. Pemetrexed will be administered until disease progression or death or premature discontinuation due to any reason.

Evaluation of efficacy and safety will be performed.

Tumor assessment will be performed at baseline and then every 6 weeks until documented disease progression or for a period of 9 months after the start of study treatment. Beyond 9 months, the evaluation will be performed every 12 weeks until documented disease progression. Locally performed tumor evaluations based on RECIST 1.1 will be used for efficacy assessment [redacted]

Toxicities will be graded according to National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI-CTCAE), version 4.03.

Patients will have a safety follow-up of 100 days after last study treatment administration.

An Independent Data Monitoring Committee (IDMC) will be set up for the purpose of reviewing clinical data and the conduct of the study. The IDMC will meet:

- To review safety data at an interim safety analysis once 6 patients have been treated with the triple combination (TG4010 + nivolumab + chemotherapy) for at least 6 weeks (at least 2 cycles of the triple combination) or have discontinued the study treatment due to treatment-related toxicity (safety evaluable set).
- To review efficacy and safety data at study completion.

In addition to the planned meetings and based on the continuous safety assessments during the study, the Sponsor will evaluate the need for additional ad-hoc meeting(s) of the IDMC to analyze patients' safety data.

### 2.2 Number of centers and patients

It is anticipated that around 10 sites will participate in the study to include a total of 39 patients to obtain 35 evaluable patients. A patient will be considered as non-evaluable if the minimum exposure is not met (i.e. at least 2 nivolumab administrations, 2 chemotherapy administrations and 6 TG4010 injections) except if patient has progressed or died due to underlying disease before or at the first evaluation.

## 3 STUDY OBJECTIVES

### 3.1 Primary objective

The primary objective of this study is to evaluate the anti-tumor activity in terms of objective response rate (ORR) by using RECIST 1.1 in chemotherapy-naïve and immunotherapy-naïve advanced, non-squamous NSCLC patients with PD-L1 membrane staining <50% of tumor cells receiving first-line chemotherapy (pemetrexed + carboplatin or cisplatin followed by pemetrexed maintenance therapy) plus TG4010 and nivolumab.

### 3.2 Secondary objectives

Secondary objectives include:

- Evaluation of the efficacy of treatments with respect to:
  - Progression Free Survival (PFS)
  - Disease Control Rate (DCR)
  - Overall Survival (OS)
- Description of duration of response (DoR)
- Evaluation of the safety profile

# 4 STUDY DURATION

The recruitment started in Q1 2018 and completed in Q2 2019. Primary endpoint analysis is expected in Q4 2019.

# 5 TREATMENT PLAN

## 5.1 Randomization

No randomization is planned in this study.

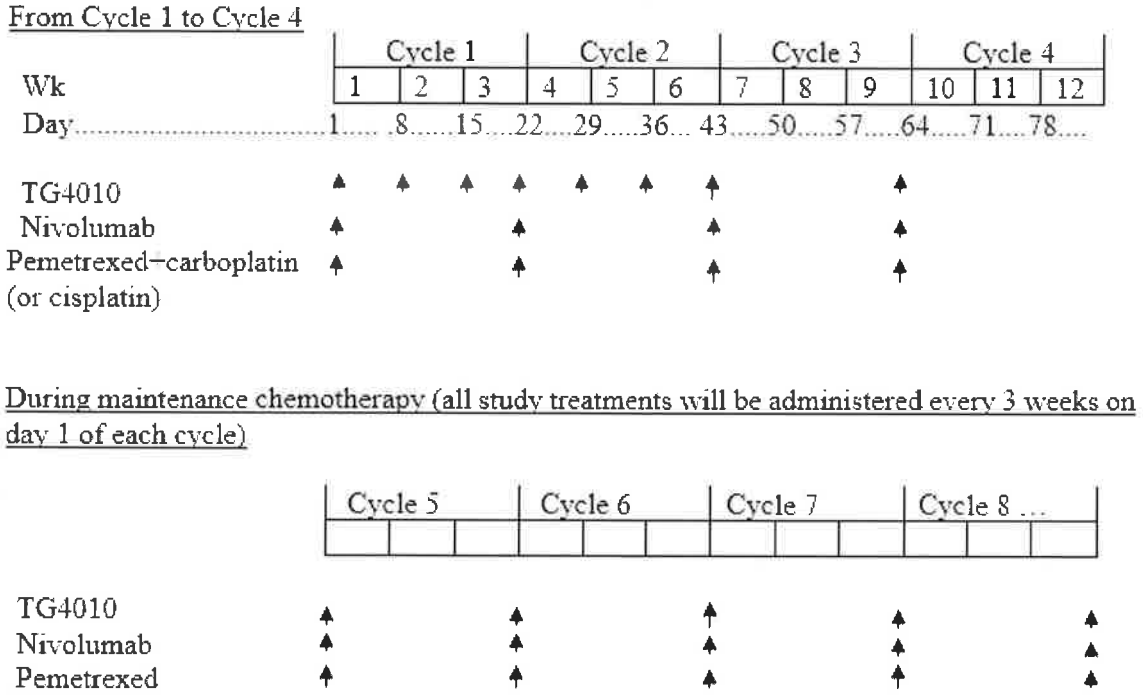
## 5.2 Duration of Treatment

Patients will receive TG4010 + nivolumab + chemotherapy from C1D1.

- TG4010 will be administered weekly for 6 weeks (C3D1) and every 3 weeks thereafter on day 1 of each cycle.
- Nivolumab will be given every 3 weeks on day 1 of each cycle.

- Platinum-doublet chemotherapy will be administered as 21-day cycle for 4 cycles followed by pemetrexed in patients candidate for maintenance therapy.

**Figure 1 :** Schedule of administration of study drugs




TG4010, nivolumab and pemetrexed as maintenance therapy (if applicable) will be administered until disease progression or death or premature discontinuation due to any reason whichever occurs first and for a maximum of 24 months for nivolumab.

Patients who are withdrawn from study treatment for reasons other than disease progression will be followed until progression of the disease or until the date of last contact if the patient is lost to follow-up or withdraws consent.

## 6 DEFINITION OF THE POPULATIONS TO BE ANALYZED

### 6.1 Patients classification

Full Analysis Set (FAS): all patients who received any component of the study treatment will be included in the FAS. Any patient who is assigned a patient number, but does not receive any study treatment will not be included in the FAS. This is the primary dataset for analyses of demography, protocol deviations and baseline characteristics. Efficacy analyses will be repeated on the FAS.

Safety Analysis Set (SAF): consists of all patients entered into the study who received at least one dose of IMP (TG4010, nivolumab). The SAF will be the primary population for the safety analyses. If FAS and SAF contain the same patients, all analyses planned on FAS will be done only on SAF.

Safety Evaluable Set (SET): consists of the first 6 patients entered into the study and who have been treated with TG4010, nivolumab and chemotherapy for at least 6 weeks (at least 2 cycles of the triple combination) or have discontinued the study treatment due to treatment-related toxicity. The SET will be the primary population for the Interim safety analysis.

Safety analyses based on the SET will be reviewed and evaluated by the IDMC.

Evaluable Patients' Population for tumor response (EPP): consists of all evaluable patients without major protocol deviations who have at least one baseline and one post-baseline evaluable CT-scan after study treatment start, except patients with early disease progression or death due to lung cancer. The EPP will be the primary population for efficacy analyses. A patient will be considered as non-evaluable if the minimum exposure is not met (i.e. at least 2 nivolumab administrations, 2 chemotherapy administrations and 6 TG4010 injections) except if patient has progressed or died due to underlying disease before or at the first evaluation.

## 6.2 Major protocol deviations

The identification of major protocol deviations is critical for the EPP definition. A protocol deviation will be classified as major, i.e., leading to exclusion of patient from the EPP, only:

- if the protocol deviation is very likely to confound the scientific analysis of the primary endpoint or if it precludes any meaningful assessment
- if it is in direct conflict with the population definition given in the title of the study (i.e. patient diagnosis, stage of disease or use of prior treatment does not correspond to the intended patient population to be studied).

A list of deviations shall be generated by CRO biostatistician according to the Protocol and in agreement with Transgene. Furthermore, deviations reported by Data Management and CRAs

shall also be taken into account to define the final deviations list of the Study. GCP deviations (including protocol deviations, applicable SOPs deviations, etc.) must be tracked. The criticality of each deviation will be established during the data review meeting (at the latest).

Anticipated but not limited major deviations are:

- No target lesion at baseline
- Previous antineoplastic therapy (as per protocol)
- Histologically confirmed squamous NSCLC
- Not stage IIIb/IV NSCLC and no delayed relapse of any stage amenable to surgery or radiotherapy with curative intent
- PD-L1 expression by immunohistochemistry (IHC) $\geq$ 50%

# 7 STATISTICAL DESIGN

## 7.1 Sample size determination

Hypotheses

As the patient survival benefit may be correlated with either radiological response of tumors or/and prolonged stabilization of the disease, the analysis of efficacy will consider ORR as primary endpoint. A response rate of 30% with the combination of TG4010 + nivolumab + chemotherapy in these patients would be considered disappointing, while a response rate of 50% or more would be promising and would encourage further study of the proposed regimen in these patients. The null hypothesis for response rate $H_0$ is set at 30%, the alternate hypothesis of efficacy is set at $H_1$=50%, the type I error $\alpha$ is set at 5% one sided and the power is set at 80%.

Statistical Design

Under these hypotheses, a one-stage design will be used leading to a sample size of 35 evaluable patients (implemented in EAST® 6.4) with a test proportion with normal approximation to the binomial distribution. [redacted]

## 7.2 Interim safety analysis

An interim safety analysis will be performed once 6 patients have been treated with the triple combination (at least 2 cycles of the triple combination TG4010 + nivolumab + chemotherapy) for at least 6 weeks or have discontinued the study treatment due to treatment-related toxicity. The IDMC will review clinical trial data to ensure patient safety, integrity, and scientific rigor. These safety analyses will be based on the SET.

## 7.3 Data Review Meeting

A data review meeting will occur:

- Before the lock for final statistical analysis
- Before follow-up analysis

Data listings will be produced before the data review meeting.

## 7.4 Missing data

Measurements that were not performed or not recorded are treated as missing data.

No imputation will be done for missing data, except for missing and incomplete dates for birth, adverse events (AE) and concomitant medications (CM) as detailed below. Missing data will be noted as missing in appropriate tables.

Imputation Rules for Partial or Missing Start Dates for AE:

- If the month and year are present, impute the day by the first day of that month. If the month and year are the same as those of the date of first dose, impute the day with the day of first study treatment administration.
- If only the year is present, impute by January 1st. If the year is the same as the year of the date of first dose, impute by the date of first study treatment administration.
- If the start date is entirely missing, impute by the date of first study treatment administration.

Imputation Rules for Partial or Missing Stop Dates for AE:

- If the month and year are present, impute the day by the last day of that month.

- If only the year is present, impute by December 31st of that year.
- If the stop date is entirely missing, assume the event or medication is ongoing.

Imputation Rules for Partial or Missing Start Dates for CM if Reason for use is "*Medical History*" or "*Signs and Symptoms*" (otherwise same rule as AE):

- If the month and year are present, impute the day by the first day of that month.
- If only the year is present, impute by January 1st.
- If the start date is entirely missing, impute date of ICF signature.

## 7.5 Definitions and Derived variables

### 7.5.1 Definitions

Baseline: Unless otherwise specified, baseline is the last measurement taken prior to the first injection of any component of the study treatment (TG4010, nivolumab or chemotherapy).

C1D1: Date of first administration of any component of the study treatment (TG4010, nivolumab or chemotherapy).

Study day: For post-treatment measurements, study day will be calculated using the start date of treatment as the origin, i.e. the study day will be calculated as (date of assessment) – (start date of study treatment) +1. Then study day 1 (C1D1) will be the first day of injection of any component of the study treatment (TG4010, nivolumab or chemotherapy).

For prior treatment measurements, the study day will be negative and calculated as (date of assessment) – (start date of study treatment).

Cut-off date: For a given analysis (interim safety analysis, final and follow-up analysis), data in the database with a date prior or equal to the cut-off date must be as clean as possible for interim safety analysis and clean for primary endpoint analyses for final and follow-up analysis. The cut-off date will be the date of the export.

All AE or concomitant medications with start date before or on the cut-off date and end date after the cut-off date will be reported as 'continuing at the cut-off date'. The end date will be considered

as missing data and will be displayed as such in listing.

Study treatment period: From the date of the first administration of one component of the study treatment (TG4010, nivolumab or chemotherapy) to the date of last administration of all components of the study treatment. In case all the components of study treatment are not stopped on the same day, the latest date will be used.

First treatment period: From the date of the first administration of one component of the study treatment (TG4010, nivolumab or chemotherapy) to the last doublet-chemotherapy administration + 20 days if no maintenance or first administration of maintenance - 1 day if maintenance.

Maintenance period: from first administration of study treatment after stopping doublet-chemotherapy administration to end date of study treatment. Note that the maintenance period will be part of the study treatment period.

End of study: Date of last patient inclusion (LPI) plus 18 months, to get information on PFS and OS data.

### 7.5.2 Derived variables

The following conventions will be used:

- 1 month corresponds to 365.25/12=30.4375 days.
- 1 year corresponds to 365.25 days.
- Temperature (°C):
    - from F to °C: Temperature (°C) = (Temperature (F) -32) / 1.8
- Weight (kg):
    - from Lbs to kg: weight (kg) = weight (lbs) * 0.45
- Height (cm):
    - from Inch to cm: height (cm) = height(inch) x 2.54

The following variables will be calculated:

- Study day

- If date of assessment is on or after the date of first study treatment administration
  - Date of assessment – date of first study treatment administration + 1
- If date of assessment is before date of first study treatment administration
  - Date of assessment - date of first study treatment administration

- Age:
  - if the whole Birth date is available:
    - floor((date of first informed consent signature – date of birth + 1)/365.25)
  - if only Year and Month from Birth date available:
    - floor((date of first informed consent signature - 15,Month,Year(date of birth))/365.25)
  - if only Birth year is available:
    - floor((date of first informed consent signature - 1,JULY,Year(date of birth))/365.25)

- Body Mass Index (BMI): Weight (kg) / Height$^2$ (m)
- Duration of an event (Day): End date – Start date + 1
- Smoking habits:
  - Pack-years smoked cigarettes = Number of cigarettes smoked per day / 20 * Number of years patient smoked.
  - Duration of smoking (years) = (stop date of smoking or in case of current smoker, the date of first informed consent signature – start date of smoking)/365.25, rounded to one digit.

    Imputation rules for partial or missing start dates:
    - If month and year are present, impute the day by the first day of that month.
    - If only the year is present, impute by January 1$^{st}$ of that year.
    - If the start date is entirely missing, no imputation will be done.

    Imputation rules for partial or missing stop dates in case of ex-smoker:

- If month and year are present, impute the day by the last day of that month. If the month and year are the same as those of the date of first informed consent signature, impute by the date of first informed consent signature.
- If only the year is present, impute by December 31st of that year. If the year is the same as the year of the date of first informed consent signature, impute by the date of the first informed consent signature.

- Time since initial diagnosis (months): (date of first study treatment administration – date of initial diagnosis)/30.4375
- Time since sample collection for PD-L1 testing (days): date of PD-L1 test – collection date of tumor sample used for PD-L1 testing

The following time-to-event variables will be calculated:

- PFS expressed in months = (MIN(Date of first radiologically documented tumor progression, Date of death from any cause) – date of first study treatment administration +1)/30.4375 if the patient has a PFS event

or (Date of last evaluable tumor assessment – date of first study treatment administration +1)/30.4375 in case of censoring.

Individual patient's PFS will be censored if no progression or death is observed at the cut-off date for analysis or at the date when a further treatment (other than those planned in the protocol) is started. The censoring date will be the date of the last evaluable tumor assessment before the cut-off date or start of further therapy.

As sensitivity analysis, the censoring date will be the date of last visit without any clinical progression before the cut-off date or start of further therapy.

- OS expressed in months = (Date of death from any cause – date of first study treatment administration + 1)/30.4375 for patients with available death date

or (Date of last contact – date of first study treatment administration +1) /30.4375 in case of censoring.

- DoR expressed in weeks for patients whose objective response was confirmed CR or PR = (MIN(Date of first documented disease progression, date of death from underlying disease) – Date of first documented response +1)/7

or (Date of the last evaluable tumor assessment – Date of first documented response +1)/7 in case of censoring.

[redacted]

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

Body Surface Area (BSA):

Calculation of BSA($m^2$): 0.007184 x (weight(kg)$^{0.425}$) x (height(cm)$^{0.725}$) based on DuBois & DuBois formula.

For each time point where BSA is calculated, the corresponding weight will be used.

All laboratory parameters will be expressed in the International System (SI) of units. Laboratory values recorded as "value < x" or "value > x" will be handled as equal to:

- x – 0.001 if value recorded as "value < x"
- x + 0.001 if value recorded as "value > x"

for the calculation of descriptive parameters and for the value derived in standard SI units. Other methods could be investigated for specific parameters. In individual listings they will be presented as "< x" or "> x".

Creatinine Clearance (CRCL):

Creatinine clearance will be recalculated with Cockroft formula.

CRCL(Male) (mL/min) = 1.23 x weight (kg) x (140 - Age)/creatinine(umol/l)

CRCL(Female) (mL/min) = 1.04 x weight (kg) x (140 - Age)/creatinine(umol/l)

For calculation of CRCL at C1D1, the screening value for creatinine will be used in combination with the C1D1 weight. For the remaining time points, creatinine and weight values of corresponding time points will be used. If weight is missing, the last available weight will be used.

Cumulative dose, dose intensity, Relative Dose Intensity for Pemetrexed will be displayed by treatment period (during first treatment period and maintenance and overall).

All laboratory parameters will be expressed in the International System (SI) of units and the intensity grade calculated using appropriate common terminology criteria for adverse events (CTCAE version 4.03). A grade of 0 will be assigned when the value is within normal limits. (In the case a local laboratory normal range overlaps into the higher (i.e., non-zero) CTC grade, the laboratory value will still be taken as within normal limits and assigned a CTC grade of zero.). When normal limits are missing and needed for grade intensity, the grade will be set as missing. If normal limits are missing but not needed, grade intensity will be calculated as usual with CTCAE ranges.

# 8 STATISTICAL METHODS

## 8.1 General principles

Statistical summaries described in this plan will be produced using SAS® software version 9.3 or higher. The tables, listings and graphics will be prepared in landscape format.

Continuous variables will be described using: number of observations (N), arithmetic mean (Mean), standard deviation (sd), minimum (MIN), median (Median), the interquartile range (Q1-Q3) and maximum (MAX). One additional decimal point for mean, median, Q1 and Q3, and 2 additional decimal points for sd will be used. Data with more than 4 decimal places (if any), may not follow this rule: so, 4 decimal places will be used.

Categorical variables will be presented using the number of observations (N) and percentages (%). Proportions will be displayed with one decimal and estimated with their exact {Clopper & Pearson, 1934} 95% CIs when appropriate.

All statistical testing will be two-sided at the 0.05 level without adjustments for multiplicity testing, unless specified otherwise. P-values will be presented to 4 decimal places. Any p-value less than 0.0001 will be presented as <0.0001, even if it would normally round up to 0.0001.

## 8.2 Patient enrollment and disposition

### 8.2.1 Screening status

The number of patients screened (who signed informed consent) will be displayed. All consented patients who did not receive any component of the study treatment will be considered as screen

failure and reported in the study report. This number of patients and the primary reason for non-inclusion will also be displayed. Percentages are calculated over the number of patients screened.

A listing will present all screen failures with the reason(s) for non-inclusion.

### 8.2.2 Population

A table "Study Populations" will display, for interim safety analysis, the number and percentage of patients (percentages based on included patients) with:

- Patients who received any component of the study treatment (FAS)
- Patients included in the SAF population (who received at least one dose of IMP (TG4010, nivolumab))
- Patients included in SET population (first 6 patients recruited in the study and treated with TG4010, nivolumab and chemotherapy for at least 6 weeks (at least 2 cycles of the triple combination) or who have discontinued the study treatment due to treatment-related toxicity)

A table will display, for the final analysis and follow-up analysis, the number and percentage of patients (percentages based on included patients) separating:

- Patients who received any component of the study treatment (FAS)
- Patients included in the EPP population (evaluable patients without any major protocol deviation)
- Patients not included in the EPP population, with the main reason for non-inclusion. The main reason for non-inclusion in the EPP will also be listed
- Patients included in the SAF population (who received at least one dose of IMP (TG4010, nivolumab))

A listing will present reason for non-inclusion in each population.

A disposition table "Summary of patients' disposition" will display the number of patients under study treatment in each treatment period (during maintenance or first treatment period) and the number of patients who discontinue the study and the reason for study completion/premature

discontinuation.

As example, the following information will be listed for each patient with:

- Did the patient receive the first treatment period? With chemo, with IMP (Yes/No)
- Did the patient receive the maintenance treatment? With pemetrexed, with IMP (Yes/No)
- Discontinued the IMPs? (Yes/No)
- Date of end of treatment
- Reason for study treatment withdrawal
- Date of end of study
- Main reason for study discontinuation.

### 8.2.3 Status at the end of study treatment

The number and percentage of patients having withdrawn from the study treatment will be summarized with the primary reason for withdrawal ("*End of treatment*" form of eCRF). The percentage will be based on the FAS.

## 8.3 Analysis of demographic and baseline characteristics

These analyses will be based on the SET for the interim safety analysis and on the EPP and FAS for the final analysis.

### 8.3.1 Demographic and baseline characteristics

The following demographic and baseline characteristics will be listed and summarized with the following items:

- Country
- Gender
- Race, ethnicity
- Age (years) at informed consent signature
- Smoking habits (status, Pack-years smoked cigarettes, duration of smoking)

- BMI (kg/m²)
- Prior Cancer therapy (Yes/No)
- MUC1 expression and staining
- ECOG performance status (0 / 1 / 2 / 3 / 4)
- [redacted]

The following baseline characteristics will be listed and summarized

- Physical examination, vital signs and echocardiography (Normal / Abnormal NCS / Abnormal CS)
- Electrocardiogram (Normal / Abnormal NCS / Abnormal CS)
- Hematology and Biochemistry
- Thyroid function: TSH, FT3 and FT4
- HIV/HBV/HCV Serology (Positive / Negative / Not Done) (listing only)
- Medical history and current medical conditions presented by SOC and PT
- Signs and symptoms at baseline with CTCAE Grade presented by SOC and PT. "*Signs and Symptoms*" form of eCRF include information observed before first study treatment administration.

'Medical history and current medical conditions' and 'signs and symptoms' presented by SOCs will be sorted in alphabetic order and PTs within SOCs will be sorted in descending number of counts according to the overall column.

### 8.3.2 History of studied disease

The following variables will be listed and summarized with the following items:

- Time since initial diagnosis (months)
- Stage at initial diagnosis and at baseline
- Histology type

- Number of organs involved (target and non-target lesions)
- PD-L1 expression by immunohistochemistry (IHC) with time since sample collection

[redacted]

Prior cancer therapy details will be listed and summarized with the following items:

- Number of patients with prior cancer therapy
- Type of Therapy (Chemotherapy / Radiotherapy / Surgery…)
- Setting (Adjuvant / Neo-Adjuvant)
- Procedures / treatments with corresponding start and end dates (listing only)

### 8.3.3 Concomitant diseases

Concomitant diseases are diseases present at the ICF signature. Concomitant diseases will be included in the Medical History. Medical History will be listed and summarized. Signs and symptoms will be listed and summarized separately.

## 8.4 Stratification factors

No stratification is planned in this study.

## 8.5 Protocol eligibility criteria

The eligibility criteria not respected will be listed for each patient included in the study.

## 8.6 Protocol deviations summaries

All protocol deviations for included patients will be presented by patient in data listings with a distinction between deviations at inclusion and deviations during the study.

The number of patients with at least one protocol deviation will be summarized by type of deviation and overall with a distinction between deviations at inclusion and deviations during the study. All protocol deviations will be reviewed before database lock during each Data Review Meeting (before final and post-lock analysis).

## 8.7 Treatments

### 8.7.1 Study treatment

Duration of study treatment exposure, cumulative dose, dose intensity and Relative Dose Intensity (RDI) will be listed and summarized for each of the study treatment components (i.e., IMPs, chemotherapy).

In addition, the duration of exposure to study treatment will be categorized into time intervals (3 weeks); frequency counts and percentages will be presented for the number of patients in each interval. The number of cycles of chemotherapy received will be summarized. The number of patients receiving pemetrexed during maintenance period and the number of cycles will be also summarized. In addition, the number of injections of IMPs in the first study treatment period, the maintenance period and overall will be summarized.

The SAF will be used for all summaries and listings of study treatment and analysis will be repeated in the SET, FAS and EPP.

- The number of patients with dose changes will be presented by study treatment component (i.e., platinum-doublet, pemetrexed during maintenance period). The number of dose changes (increase and decrease) per patient will also be tabulated. In addition, the total number of dose changes will be displayed.
- The number of patients with dose cancellations will be presented by study treatment component (i.e., IMPs, chemotherapy, pemetrexed during maintenance period), along with reasons for the dose cancellation. The number of dose cancellations per patient along with reasons will also be tabulated. In addition, the total number of dose cancellations will be displayed.
- The number of patients with dose delays will be presented by study treatment component (i.e., IMPs, chemotherapy, pemetrexed during maintenance period), along with reasons for the dose delay. The number of dose delays per patient along with reasons will also be tabulated. In addition, the total number of dose delays will be displayed.
- The number of patients with dose stopped will be presented by study treatment component (i.e., IMPs, chemotherapy, pemetrexed during maintenance period).

In addition, a table summarizing the regimen received by patients (pemetrexed-cisplatin, pemetrexed-carboplatin, pemetrexed, IMPs) according to the study treatment period.

[redacted]

### 8.7.3 Subsequent anti-cancer therapies

All antineoplastic therapies given after end of treatment will be coded using the WHO Drug Dictionary and ATC classification. For patients who prematurely discontinued the study treatment (for another reason than progressive disease), all subsequent anti-cancer therapies will also be collected and coded in the same way.

All anti-cancer therapies will be listed and summarized by means of frequency counts and percentages using the FAS and EPP.

## 8.8 Analysis of efficacy

All the efficacy analyses will be based on the EPP population which is the primary dataset.

Efficacy analyses will be repeated on the FAS. All efficacy variables will be listed in dedicated listings by patient.

### 8.8.1 Primary efficacy endpoint and analysis

The primary objective of the study is the evaluation of Objective response rate (ORR) which is the proportion of patients, whose best overall response is either CR or PR, confirmed at least 4 weeks after initial documentation in EPP [redacted]

In addition, p-value for testing the RECIST 1.1 ORR is greater than the historical control (30%) will be provided using a one-sided proportion test. Patients with best overall response "Not evaluable" will be counted as non-responders. Best overall response (BOR) per RECIST v1.1 [redacted] is defined as the best response designation recorded between the date of first dose and the date of first documented progression per RECIST 1.1 or the date of subsequent cancer therapy, whichever occurs first. CR or PR determinations included in the BOR assessment must be confirmed by a second scan no less than 4 weeks after the criteria for response are first met. For patients without documented progression or subsequent therapy, all available response designations should contribute to the BOR assessment.

### 8.8.2 Secondary efficacy endpoints and analyses

The endpoints for secondary objectives of the study are defined as follows:

- Progression Free Survival (PFS): time from the date of the first study drug administration to the date of first documented tumor progression or death due to any cause, whichever occurs first. If a patient has not had a PFS event and is not known to have died at the cut-off date for analysis, PFS will be censored at the date of last evaluable tumor assessment before the cut-off date. Sensitivity analysis will be performed using the last visit without progression as censoring date. The percentage of patients without progression will also be presented over time considering the proportions of patients having not progressed at 6, 9 and 12 months, along with corresponding 95% CIs. At these timepoints the restricted mean non-progression time with 95% confidence interval will be calculated. A graphical

representation will be done using a Kaplan-Meier curve with 95% confidence interval.

- Disease control rate (DCR): proportion of patients whose best overall response is either CR, PR, or stable disease (SD).
- Overall Survival (OS): time from the first study drug administration to the date of death due to any cause. If a patient is not known to have died at the cut-off date for analysis, survival will be censored at the date of last contact. The percent survivors over time will also be presented considering the proportions of patients alive at 9, 12, 18, and 24 months, along with corresponding 95% CIs. At these timepoints the restricted mean survival time (RMST) with 95% confidence interval will be calculated. A graphical representation will be done using a Kaplan-Meier curve with 95% confidence interval.
- Duration of Response (DoR): applies only to patients whose best overall response is CR or PR. The start date is the date of first documented response (CR or PR) and the end date is the date of first documented disease progression or the date of death due to underlying cancer. DoR will be censored if progression or death due to underlying cancer is not observed at the cut-off date for the analysis, or death due to another cause than underlying cancer or start of subsequent anti-cancer therapy. The censoring date will be the date of the last evaluable tumor assessment without progression. Graphical representations will be done using a Kaplan-Meier curve with 95% confidence interval and swimmer plot. Sensitivity analysis considering the last visit without any progression will be performed.
- Efficacy will also be evaluated with respect to PFS and OS in patients subdivided according to their response of CR or PR, using a landmark analysis at 4 months to avoid length-biased sampling {Anderson JR, 2008}. These analyses will be interpreted with due caution.

[redacted]

[redacted]

## 8.9 Analysis of safety

An interim safety analysis will be performed once 6 patients have been treated with the triple combination (TG4010 + nivolumab + chemotherapy) for at least 6 weeks or have discontinued the study treatment due to treatment-related toxicity. Safety analyses will be based on the SET. Safety

data will be reviewed by an IDMC.

For final analysis and follow-up analysis, safety analyses will be based on SAF. Safety summary tables will include all safety assessments collected up to 100 days after last study treatment administration.

### 8.9.1 Adverse Events

#### 8.9.1.1 Definitions

Collection of AEs/SAEs starts from the date of signature of the ICF up to the safety follow-up visits (100 days after the last administration of any study treatment administration). After this period, investigators should only report SAEs that are considered as related to IMP(s) (TG4010 and/or nivolumab).

- If a non-serious event occurs during the screening period (i.e., after ICF signature and before study treatment administration on C1D1), it will be recorded either on a "Medical history and current medical conditions" page for an identified syndrome (e.g., pneumonia) or on a "Signs and symptoms" page for symptoms with no associated syndrome (e.g., diarrhoea).
- From the first study treatment administration (C1D1), AEs will be recorded on an "AE" page. In case of worsening of an event which started before C1D1, an AE page will be completed using a verbatim starting by "worsening of…".

All SAEs including those occurring during the screening period will be collected and listed separately.

SAEs occurring more than 100 days after the last study treatment administration and evaluated by the Investigator as related to the IMP(s) should be collected and reported to Transgene indefinitely even after end of study. Only SAEs occurring prior to end of study will be reported in the eCRF.

All adverse events (AE) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) central coding dictionary using latest version available. NCI-CTCAE version 4.03, dated June 14, 2010 will be used for grading intensity of the events.

All AEs are reported on the "*Adverse Events*" section of eCRF. Safety analyses will be based on SAF. Patients receiving only chemotherapy (not included in the SAF) will be listed separately.

#### 8.9.1.2 AEs Analysis

Adverse Event (AE)

AE summaries will include all AEs starting on or after study day 1 (i.e. on or after the day of the first intake of study treatment) and starting no later than 100 days after the end date of study treatment.

For the analyses, the number and percentage of patients with at least one AE will be summarized in a frequency table by body system organ class (SOC) and preferred terms (PT) as per MedDRA dictionary. The number of events will be also summarized in the same table. The table will be displayed by descending order based on the number of patients. Each patient will be counted only once within each classification (SOC / PT).

SAEs occurring after signing the Informed Consent Form (ICF) but before starting study treatment, including those observed in patients never treated with the IMP, will be listed separately from those occurring after treatment start.

Serious Adverse Event (SAE)

The SAEs are the adverse events with the item "*Is this adverse event Serious?*" ticked "*Yes*" in "*Adverse Events*" form of the eCRF. If the item is missing, the Adverse Event will be considered as Serious.

AEs related to Infusion and study procedure

AEs related to Study Procedure are the adverse events with the item "*Is this an injection site reaction*?" or "*Is this event related to other study procedure*?" ticked "*Yes*" in "*Adverse Events*" form of the eCRF. If the item is missing, the Adverse Event will be considered as related to Study Procedure.

AEs related to TG4010

AEs related to TG4010 are the adverse events with the item "*Relationship to TG4010*" ticked "*Related*" in "*Adverse Events*" form of the eCRF. If the item is missing, the Adverse Event will be considered as related to TG4010.

AEs related to Nivolumab

AEs related to Nivolumab are the adverse events with the item "*Relationship to Nivolumab*" ticked

"*Related*" in "*Adverse Events*" form of the eCRF. If the item is missing, the Adverse Event will be considered as related to Nivolumab.

AEs related to IMP (TG4010 + Nivolumab)

AEs related to IMP are the adverse events related to either TG4010 or Nivolumab (or both).

AEs of Special Interest (AEOSI)

A list of AEs of Special Interest will be defined including at least injection site reactions and some expected related AEs (e.g. Fatigue).

AE leading to study treatment discontinuation (any component)

AE leading to discontinuation are the AEs with the items "*Action taken with TG4010*" or "*Action taken with Nivolumab*" or "*Action taken with Chemotherapy*" ticked "*Stopped*".

AE leading to death

The AE leading to death are the AEs with the item

- "*Intensity grade*" ticked "*Grade 5 - Fatal*" or
- "*Outcome*" ticked "*Fatal*"

#### 8.9.1.3 Listings

All AEs will be listed with the following items:

- Patient Number
- Age / Gender
- Preferred term (PT), System Organ class (SOC) and the verbatim
- Date of onset and date of end
- Intensity grade (Grade 1 / Grade 2 / Grade 3 / Grade 4 / Grade 5)
- Outcome (Recovered / Recovered with sequelae / Not recovered / Fatal / Unknown)
- Relation to TG4010 (Related/Not Related) and Action taken regarding TG4010
- Relation to Nivolumab (Related/Not Related) and Action taken regarding Nivolumab

- Relation to Platinum-based Doublet Chemotherapy (Related/Not Related) and Action taken regarding Platinum-based Doublet Chemotherapy
- Injection Site Reaction (Y/N)
- Relation to Other Study Procedure (Related/Not Related)
- Action regarding the event
- Evaluation of seriousness
- Event potentially immune-mediated (Y/N)

Moreover, the following sub-listings will be provided:

- IMP-related AEs
- SAEs
- IMP-related SAEs
- AEs leading to discontinuation
- Grade 3/4 adverse events
- Fatal AEs
- Pre-treatment SAEs

#### 8.9.1.4 Tables

An overview table will be presented with the number and percentage of patients for each of the following categories (the number of events will be also provided):

- with at least one AE

[redacted]

[redacted]

The number and percentage of patients for each category above will be summarized by body system organ class (SOC) and preferred terms (PT) as per MedDRA dictionary. The number of events will be also summarized in the same table.

Table for AEs, AEs related to IMP, AEs related to TG4010, AEs related to Nivolumab and AEs related to IMP and/or chemotherapy will also be presented by grade and summarized by system organ class (SOC) and preferred terms (PT) as per MedDRA dictionary.

### 8.9.2 Laboratory abnormalities

The analyses will include all laboratory assessments collected no later than 100 days after treatment discontinuation. All laboratory assessments will be listed and those collected during 100 days after study treatment discontinuation will be flagged in the listings.
Laboratory parameters (hematology, biochemistry and urinalysis) will be graded using the NCI-CTCAE version 4.03, dated June 14, 2010.
Listings of laboratory data will be provided by visit and displaying the Standard International (SI) units converted laboratory parameters with at least value, change from baseline, reference range, high/low, grade and shift from baseline value (Normal/Abnormal). A separate listing will display notable laboratory abnormalities (i.e., newly occurring CTCAE Grade 3 or 4 laboratory toxicities).
Laboratory data at baseline (last measurement taken prior to the first injection of any component of the study treatment (TG4010, nivolumab or chemotherapy) will be summarized by presenting descriptive statistics of raw data for all hematologic and biochemical laboratory parameters (including troponin and D-Dimers). All values will be displayed in Standard International (SI) units.
A shift table of baseline CTCAE grade versus worst post-baseline CTCAE grade during study will be presented for hematology and biochemistry parameters. Note that for parameters with two directions abnormalities (hypo/hyper), two tables will be presented.

### 8.9.3 Other safety data

Other safety data (e.g., vital signs, electrocardiogram) will only be listed, notable values will be flagged, and any other information collected will be listed as appropriate.

## 9 CHANGES FROM THE PROTOCOL

No change from the protocol

[redacted]

[redacted]

[redacted]

[redacted]