Clinical Study Protocol

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
Amended Version 4.0 – 13 March 2018

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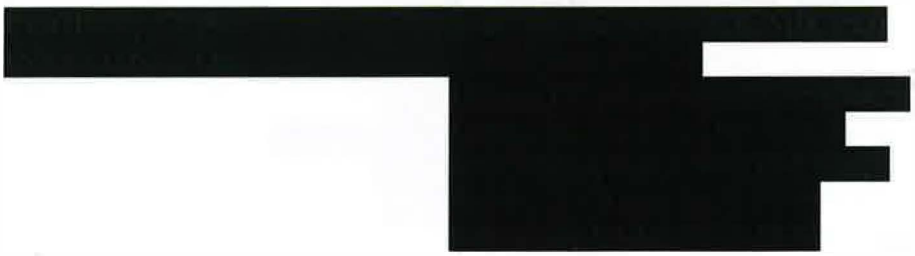

SPONSOR:

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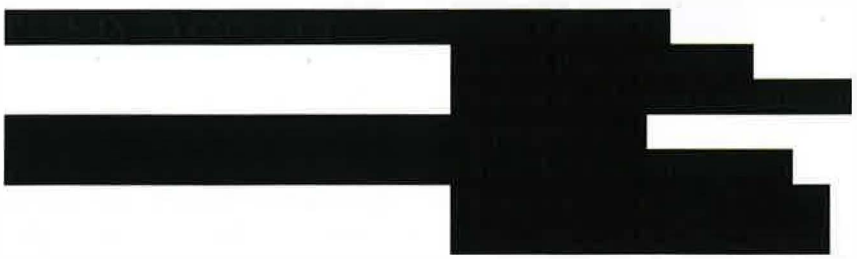

INVESTIGATORS / STUDY ADMINISTRATIVE STRUCTURE

NAMES AND CONTACT DETAILS

[redacted]

Centers / Investigators

The complete Investigator list is available in the Investigator Site File and in the Trial Master File kept by the Sponsor or its designee.

[redacted]

A complete list of details for the Contract Research Organization (CRO), the central laboratory/ies and the independent review committee(s) is available in the Investigator Site File and in Transgene files.
During the study, if applicable, the administrative structure will be updated in the Investigator Site File and in Transgene files.

DOCUMENT APPROVAL

[redacted]

SYNOPSIS

Sponsor: Transgene S.A.
IMPs: TG4010
Nivolumab

Study Title
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)

Coordinating / Principal Investigator(s)
[redacted]

Investigational Center(s)/Country(ies): including but not limited to Belgium, Denmark, France, Hungary, USA

Study N°: TG4010.24

Study Period: Q4 2017 – Q1 2020 | **Clinical Phase:** II

Objectives

Primary objective
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 on <50% of tumor cells receiving first-line chemotherapy (pemetrexed + carboplatin or cisplatin followed by pemetrexed maintenance therapy) plus TG4010 and nivolumab.

Secondary objectives
- To evaluate the efficacy with respect to:
  - Progression Free Survival (PFS)
  - Disease Control Rate (DCR)
  - Overall Survival (OS)
- To describe duration of response (DoR)
- To evaluate the safety profile
- [redacted]

Methodology
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 < 50% of tumor cells expressing PD-L1 by immunohistochemical (IHC) staining of PD-L1 protein in the submitted tumor sample will be included.
Patients will receive TG4010 + nivolumab + chemotherapy from C1D1.

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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 whichever occurs first.

Nivolumab will be given every 3 weeks from C1D1 until disease progression, or death or premature discontinuation due to any reason or for a maximum of 24 months whichever occurs first. Patients who achieve a confirmed complete response (CR) MAY discontinue nivolumab earlier after specific consultation and agreement between the Investigator and Transgene Medical Monitor when benefit/risk justify discontinuation.

Platinum-doublet chemotherapy will be administered for a total of 4 cycles (21-day cycle). In patients candidate for maintenance therapy, pemetrexed will be administered until disease progression or death or premature discontinuation due to any reason whichever occurs first.

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. In case the study treatment discontinuation is not due to progressive disease or death, response assessment should continue until progression of the disease or until the date of last contact if the patient is lost to follow-up or withdraws consent.

Toxiciti(es) 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.
- To review efficacy and safety data at study completion.

[redacted]

Number of Patients
A total of 39 patients are planned to be enrolled in this study to obtain 35 evaluable patients for tumor response.

Inclusion criteria

1. Signed informed consent in accordance to ICH-GCP and national/local regulation before any protocol-related procedures that are not part of normal patient care
2. Female or male patients age > 18 years-old
3. Eastern Cooperative Oncology Group (ECOG) performance Status 0 or 1 at study entry
4. Life expectancy of at least 3 months
5. Histologically confirmed non-squamous NSCLC (adenocarcinoma, large cell carcinoma, undifferentiated carcinoma or other)
6. Stage IIIB-IV cancer or delayed relapse of any stage not amenable to surgery or radiotherapy with curative intent. Patients with stage IIIB must not be eligible to radiotherapy

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[redacted] PD-L1 expression by immunohistochemistry (IHC) in < 50% of tumor cells using 22C3 pharmDx assay kit [redacted]

8. Prior treatment:
   patients must be treatment-naïve for the advanced stage of the disease. [redacted]
9. At least one measurable lesion by CT scan based on RECIST 1.1 performed within 28 days prior to start of study treatment and excluding the lesion used for biopsy
10. Adequate hematological, hepatic, and renal functions:
    - Hemoglobin ≥ 10.0 g/dL
    - White Blood Cells (WBC) ≥ 2.0 x 10^9/L, including
      - Neutrophils ≥ 1.5 x 10^9/L
      - Total lymphocytes count ≥ 0.5 x 10^9/L
    - Platelets count ≥ 100 x 10^9/L
    - Serum alkaline phosphatase ≤ 3 x ULN in the absence of liver or bone metastases and ≤ 5 x ULN in patients with documented bone or liver metastases
    - Total bilirubin ≤ 1.5 x ULN (except patients with Gilbert Syndrome who must have a total bilirubin level of < 3.0 x ULN)
    - Serum transaminases (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) ≤ 3 x ULN
    - Serum creatinine ≤ 1.5 x ULN or calculated creatinine clearance > 50 mL/min (using the Cockcroft-Gault formula)
11. Women of childbearing potential (WOCBP) must have a negative serum pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 72 hours prior to the start of study treatment
12. Highly effective contraception defined as:
    - Hormonal methods of contraception including combined oral contraceptive pills, vaginal ring, injectables, implants, intrauterine devices (IUDs) such as Mirena and Nonhormonal IUDs such as ParaGard for WOCBP patient or male patient's WOCBP partner
    - Tubal ligation
    - Vasectomy
    - Sexual abstinence
13. Women of childbearing potential (female patients not menopaused since ≥ 1 year) must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug(s) plus 5 half-lives of study drug plus 30 days (duration of ovulatory cycle) for a total of 5 months post-treatment completion
14. Men who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug (s) plus 5 half-lives of study drug(s) plus 90 days (duration of sperm turnover) for a total of 7 months post-treatment completion

Exclusion criteria

1. Patients having Central Nervous System (CNS) metastases. Patients who have had brain metastases surgically removed or irradiated with no residual disease confirmed by imaging and not treated by corticosteroids are allowed
2. Patients with pericardial effusion

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3. Prior exposure to cancer immunotherapy including cancer vaccines, anti-PD-1, anti-PD-L1, anti-PD-L2, anti-cytotoxic T-Lymphocyte antigen-4 (CTLA-4) antibody or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways
4. Patients with EGFR activating mutations or ALK-rearrangements (tests mandatory) leading to eligibility for TKI treatment or other routinely assessed mutations/rearrangements for which a TKI is commercially available
5. Prior history of other malignancy except basal cell carcinoma of the skin, cervical intra-epithelial neoplasia, and other cancer curatively treated with no evidence of disease for at least 3 years
6. Patients with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of start of study treatment. Inhaled or topical steroids, and adrenal replacement steroid doses > 10 mg daily prednisone equivalent, are permitted in the absence of active auto-immune disease
7. Patients with an active, known or suspected autoimmune disease. Patients with type I diabetes mellitus, hypothyroidism only requiring hormone replacement, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll
8. Patients with interstitial lung disease that is symptomatic or may interfere with the detection or management of suspected drug-related pulmonary toxicity
9. Patients with grade ≥ 2 neuropathy
10. Signs or symptoms of infection within 14 days prior to start of study treatment or active infection requiring systemic therapy
11. Positive serology for Human Immunodeficiency Virus (HIV) or Hepatitis C Virus (HCV); presence in the serum of the Hepatitis B surface antigen (HBsAg) at baseline
12. Patients with any underlying medical condition that the treating physician considers might be aggravated by treatment or which is not controlled (e.g., elevated troponin or creatinine, uncontrolled diabetes)
13. History of any of the following cardiovascular conditions within 12 months of enrollment: cardiac angioplasty or stenting, myocardial infarction, unstable angina, coronary artery by-pass graft surgery, symptomatic peripheral vascular disease, class III or IV congestive heart failure, as defined by the New York Heart Association
14. Left ventricular ejection fraction (LVEF) less than the Lower Limit of Normal as assessed by echocardiography (or MUGA scan)
15. Patients with major surgery within 4 weeks prior to the start of the study treatment and patients with stage IIIB eligible to radiotherapy. Patients with stage IV may have received radiation therapy aimed at local palliation (except thoracic radiotherapy and provided that the field irradiated does not include the unique measurable lesion) if completed 2 weeks before study treatment start.
16. Pregnant or nursing (lactating) women
17. Patients with an organ allograft
18. Any known allergy to eggs, gentamicin or history of allergy or hypersensitivity to study drug components
19. Participation in a clinical study with an investigational product within 4 weeks prior to the start of the study treatments
20. Patients unable or unwilling to comply with the protocol requirements
21. Prisoners or patients who are involuntarily incarcerated
22. Patients who are compulsorily detained for treatment of either a psychiatric or physical (eg, infectious disease) illness

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Dose, Mode of Administration

In this study, the study treatments are the following: TG4010 and nivolumab as Investigational medicinal products (IMP) and first-line chemotherapy (pemetrexed plus carboplatin or cisplatin followed by pemetrexed as maintenance as non-IMP treatments as corresponding to standard of care).

TG4010

TG4010 is a suspension of recombinant Modified Vaccinia virus strain Ankara (MVA), a significantly attenuated strain of Vaccinia virus, carrying coding sequences for the human MUC1 antigen and for the human Interleukin-2 (IL2) in a formulation medium.
Patients will receive SC injections of TG4010 at the dose of 1 x 10^8 PFU weekly for 6 weeks and then once every 3 weeks until disease progression or death or premature discontinuation due to any reason.

Nivolumab

Nivolumab will be administered as an IV infusion over at least 30 minutes at a dose of 360 mg once 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.

Chemotherapy:

Pemetrexed 500 mg/m2 on day 1 and carboplatin AUC 6 (or cisplatin 75 mg/m²) on day 1 every 21 days for 4 cycles.
Pemetrexed should be given as maintenance therapy in eligible patients after 4 cycles of platinum-based chemotherapy. Pemetrexed at the dose of 500 mg/m2 will be administered until disease progression or death or premature discontinuation due to any reason.

When the 2 IMPs (TG4010 and nivolumab) and chemotherapy are given on the same day, TG4010 will be administered first, then nivolumab and then pemetrexed followed by carboplatin (or cisplatin).
No dose reduction will be allowed for TG4010 or nivolumab. Dose reductions for chemotherapy will occur according to EU Summary of Product Characteristics (SmPC) and United States Product Insert (USPI).

According to standard practice, the start of a new cycle of chemotherapy will be delayed if toxicity does not allow a new administration of chemotherapy. In this case, TG4010 and nivolumab administrations will also be delayed.

- If TG4010 is delayed or stopped for toxicity, nivolumab will also be delayed or stopped but chemotherapy will continue as planned unless criteria for chemotherapy delay or discontinuation are also met.
- If nivolumab is delayed or stopped for toxicity, TG4010 dosing will also be delayed or stopped but chemotherapy should continue unless criteria for chemotherapy delay or discontinuation are also met.
- If chemotherapy is definitely stopped for toxicity, TG4010 and nivolumab should continue (or restart) as soon as criteria for retreatment are met. Note that if the reason for stopping chemotherapy is not due to intolerable toxicity, the patient should receive at least 3 cycles of the platinum-doublet.

Concomitant medications

Prohibited and or restricted treatments

- Immunosuppressive agents
- Immunosuppressive doses of systemic corticosteroids

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- Any concurrent anti-neoplastic therapy (i.e., chemotherapy other than planned per protocol, hormonal therapy, immunotherapy, extensive non-palliative radiation therapy, or standard or investigational agents for treatment of NSCLC)
- Any vaccine therapies for the prevention of infectious disease (e.g., human papilloma virus vaccine) except administration of the inactive influenza vaccine

Permitted medications/therapies

- Patients are permitted the use of topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption).
- Adrenal replacement steroid doses > 10 mg daily prednisone are permitted. A brief (less than 3 weeks) course of corticosteroids for prophylaxis (eg, contrast dye allergy) or for treatment of non-autoimmune conditions (eg, delayed-type hypersensitivity reaction caused by a contact allergen) is permitted.
- Growth factors (granulocyte colony stimulating factor or granulocyte macrophage colony stimulating factor), erythropoietin and darbepoietin alpha which may be prescribed at the investigator's discretion
- Radiotherapy for pain relief (e.g., bone metastases) is permitted. A minimum interval of one week should have elapsed between radiotherapy (pre and post) and nivolumab administration. If lesions are in the field of radiation they will be no longer evaluable for the tumor response.
- Any medications (other than those excluded by the study protocol) that are considered necessary for the patients' welfare and will not interfere with the trial medication may be given at investigator's discretion.

Duration of Treatment

The study drugs will be administered until documented disease progression (according to RECIST 1.1), death or premature discontinuation due to any reason, whichever occurs first.
However, nivolumab will be given for up to 24 months in the absence of disease progression or unacceptable toxicity. Patients who achieve a confirmed complete response (CR) MAY discontinue nivolumab earlier after specific consultation and agreement between the Investigator and Transgene Medical Monitor when benefit/risk justify discontinuation.

Patients who are withdrawn from study treatment for reasons other than disease progression will be followed until documented disease progression or death due to any cause or the date of cut-off whichever occurs first.

Criteria for Evaluation / Endpoints

Efficacy assessment

Efficacy assessments will be based on local evaluations according to RECIST 1.1.
Patients should have at least one measurable lesion by CT-scan (minimum size not less than 10 mm). All target lesions (measurable) and non-target lesions (measurable or not) will have to be recorded.
Chest and abdominal (and pelvis if lesion suspected) CT-scan (mandatory for chest) or MRI will be performed within 28 days prior to start of study treatment, then every 6 weeks for 9 months and thereafter every 12 weeks until progression; cerebral CT scan or MRI is mandatory at baseline. For patients with brain metastases history, cerebral CT-scan or MRI should be performed every 12 weeks or as clinically indicated.

Will be evaluated:

- Best Overall Response (BOR): the best response designation recorded between the date of first dose and the date of first documented tumor progression per RECIST 1.1 or the date of subsequent cancer therapy, whichever occurs first. Objective response rate (ORR) is defined as the proportion of patients with a BOR of CR or PR: confirmed complete responses (CR) and partial responses (PR).

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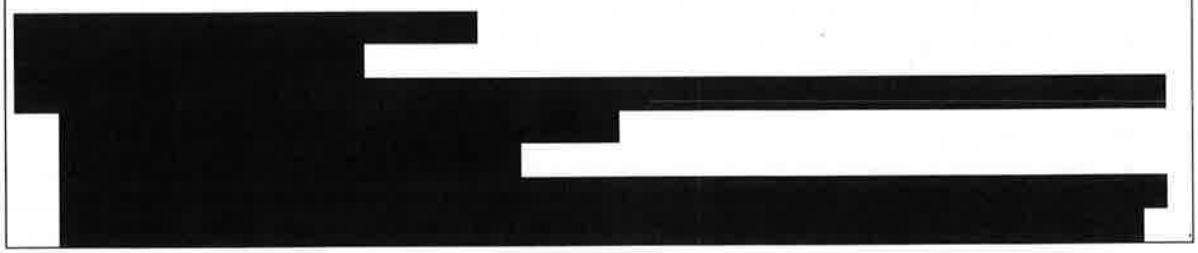
- Progression Free Survival (PFS): time from the date of first study treatment administration to the date of first documented tumor progression or death due to any cause, whichever occurs first. If a patient has not had a PFS event at the cut-off date for analysis or at the date when a subsequent cancer therapy (other than those planned as study treatment in the protocol) is started, PFS will be censored at the date of last evaluable tumor assessment before the cut-off date or start of subsequent therapy.
- Duration of Response (DoR): applies only to patients with 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. If no progression has been observed at the cut-off date of analysis or at the date when a subsequent cancer therapy is started, DoR will be censored at the date of the last evaluable tumor assessment.
- Disease control rate (DCR): proportion of patients with CR or PR, or stable disease (SD).
- Overall Survival (OS): time from the date of first study treatment 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.

Safety assessment

- Physical examination including weight, height (only at baseline), blood pressure (BP), heart rate (HR), temperature, and oxygen saturation by pulse oximetry at rest (also monitor amount of supplemental oxygen if applicable) will be performed at baseline and at each visit prior to dosing.
- ECOG Performance Status will be evaluated at baseline and at regular intervals (3 weeks).
- Adverse Events (AE) and Serious Adverse Events (SAEs) will be reported at each visit and graded according to NCI-CTCAE, version 4.03.
- Laboratory investigations will be undertaken:
  - Complete blood cells (CBC) count with differential within 72h prior to first study treatment administration, every week during the first 6 weeks, then prior to study treatment every 3 weeks, at the end of treatment visit and at the safety follow-up visit
  - Biochemistry analyses including liver function tests (ALT, AST, total bilirubin, alkaline phosphatase), BUN or serum urea level, uric acid, creatinine and creatinine clearance, Ca, Mg, Na, K, Cl, phosphate, LDH, glucose, amylase and lipase within 72h prior to first study treatment administration, prior to study treatment administration every week during the first 6 weeks, then every 3 weeks, at the end of treatment visit and at the safety follow-up visit
  - Troponin and D-dimers within 72h prior to first study treatment administration and at C2D1, C3D1 and C4D1
  - Thyroid function: TSH, free T3 and free T4 at baseline and then TSH (reflex free T4), every 6 weeks and at the end of treatment visit
- Electrocardiogram (12 leads) will be performed at baseline, at C2D1 and as clinically indicated during the treatment period and at the end of treatment visit.
- Echocardiography (or MUGA scan) will be performed at baseline on all patients. Patients who develop new pericardial effusions while on study must be followed by echocardiography (or MUGA scan).



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Nivolumab

[redacted]

Statistical Methods

Full Analysis Set (FAS): all patients included and 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.

Safety Analysis Set (SAF): consists of all patients entered into the study who received at least one dose of IMP (TG4010, nivolumab).

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.

Evaluable Patients' Population for tumor response (EPP): consists of all patients without major protocol deviation and have at least one baseline and one post-baseline evaluable CT-scan after study treatment start except early disease progression and death due to lung cancer. The evaluable patients' population will be the primary population for efficacy analyses[redacted]

For the first 6 patients, safety analyses will be based on the SET to be reviewed and evaluated by the IDMC. 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.

With a one-sided 0.05 alpha level, a total of 35 evaluable subjects would provide approximately 80% power in order to detect a response rate of 50% versus 30% with a proportion test. [redacted]

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ABBREVIATIONS / DEFINITION OF TERMS

ABBREVIATIONS	MEANING OF ABBREVIATIONS IN DOCUMENT
ADA	Anti-drug Antibody
ADCC	Antibody Dependent –Cell mediated Cytotoxicity
ADR	Adverse Drug Reaction
AE	Adverse Event
AEOSI	Adverse Event of Special Interest
ALK	Anaplastic Lymphoma Kinase
ALT	Alanine amino-transferase (= SGOT)
APCs	Antigen Presenting Cells
AST	Aspartate amino-transferase (= SGPT)
ATC	Anatomical Therapeutic Chemical
AUC	Area Under the Curve
BOR	Best Overall Response
[redacted]	[redacted]
CI	Confidence Interval
CIN	Cervical Intraepithelial neoplasia
CNS	Central Nervous System
CR	Complete Response
CRA	Cytokine Release Assays
CRC	Colorectal Cancer
CRO	Contract Research Organization
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
[redacted]	[redacted]
CTLA-4	Cytotoxic T-Lymphocyte Antigen-4
D	Day
DC	Dendritic Cells
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
FAS	Full Analysis Set
FACS	Fluorescence-activated cell sorter
FFPE	Formalin-fixed, paraffin-embedded
FDG-PET	Fluorodeoxyglucose Positron Emission Tomography
GCP	Good Clinical Practice
GMO	Genetically Modified Organism
HBV	Hepatitis B Virus
HBsAg	Hepatitis B Surface Antigen
hCG	Chorionic Gonadotropin Hormone
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HLA	Histocompatibility Leukocyte Antigen
HPV	Human Papilloma Virus
HR	Hazard Ratio
IB	Investigator's brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ICMJE	International Committee of medicinal Journal Editors
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee

Ig	Immunoglobulin
IHC	Immunohistochemistry
IL	Interleukin
IM	Intramuscular
IMAE	Immune-Mediated Adverse Event
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
ITT	Intent To Treat
IU	International Unit
IUD	Intrauterine devices
IV	Intravenous
LDH	Lactate Dehydrogenase
LFT	Liver Function Test
LVEF	Left Ventricular Ejection Fraction
M	Month
mCRPC	Metastatic Castration-Resistant Prostate Cancer
MAb	Monoclonal Antibody
mL	Milliliters
MTD	Maximal Tolerated Dose
MRI	Magnetic Resonance Imaging
MUGA scan	Multigated Acquisition scan
MVA	Modified Virus of Ankara
NCI-CTCAE	National Cancer Institute's Common Terminology Criteria for Adverse Events. Also referred as CTCAE in the text
[redacted]	[redacted]
ORR	Objective Response Rate
OS	Overall Survival
[redacted]	[redacted]
PD	Progressive Disease
PD-1	Programmed Death-1
PD-L1 & PD-L2	Programmed Death Ligand-1 & Programmed Death Ligand-2
PFS	Progression Free Survival
PFU	Plaque Forming Unit
PK	Pharmacokinetic
PR	Partial Response
PS	Performance Status
RCC	Renal Cell Carcinoma
RECIST	Response Evaluation Criteria In Solid Tumors
[redacted]	[redacted]
RP2D	Recommended Phase 2 Dose
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SC	Subcutaneous
SD	Stable Disease
SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
[redacted]	[redacted]
TMF	Trial Master File
TRAE	Treatment Related Adverse Event
ULN	Upper Limit of Normal
USPI	United States Product Insert
WBC	White Blood Cells

ABBREVIATIONS / DEFINITION OF TERMS (Cont.)

DEFINITIONS

Consented patient	A patient who has signed the Informed Consent Form (ICF) to undergo procedures required to verify the eligibility criteria before inclusion into the trial.
Screening failure patient	A patient who signed the ICF but did not satisfy to all inclusion and exclusion criteria.
Baseline (=screening)	Period during which all the procedures are performed to verify the eligibility criteria before inclusion. The period of baseline should not exceed 28 days.
Included patient	A patient who signed the ICF, who satisfied all inclusion and exclusion criteria at baseline and who received the study treatments at Cycle 1 Day 1.
Cycle 1, Day 1	First administration of any component of the study treatment. At D1 this should be TG4010 + nivolumab + chemotherapy.
Treated patient	A patient having received at least one administration among the following study treatments: Investigational Medicinal Product (IMP: TG4010, nivolumab), chemotherapy, as planned by the protocol.
Ongoing patient	A patient included, presently treated according to the protocol requirements.
Discontinued patient	A patient who discontinued the study treatment whatever the reason.
Protocol deviations	All non-adherences to following protocol requirements: study inclusion or exclusion criteria, conduct of the study, patient management or patient assessment.
IMP	Investigational Medicinal Product i.e. TG4010 or nivolumab
Study treatment	TG4010, nivolumab and chemotherapy.
End of study treatment	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.
Safety follow-up visit	Last visit according to protocol. Two safety follow-up visits will be performed: 30 days and 100 days after last treatment administration.
Follow-up for PFS	In case the study treatment discontinuation is not due to progressive disease (or death), patients will be followed off-study treatment until progression of the disease, end of study, or relapse, lost to follow-up, withdrawal of consent or death whichever occurs first.
Follow-up for OS	Patients will be followed up for survival until end of study, lost to follow-up, withdrawal of consent or death whichever occurs first.
End of study	The end of the study is defined as the date of last patient inclusion (LPI) plus 18 months, to get information on PFS and OS data.

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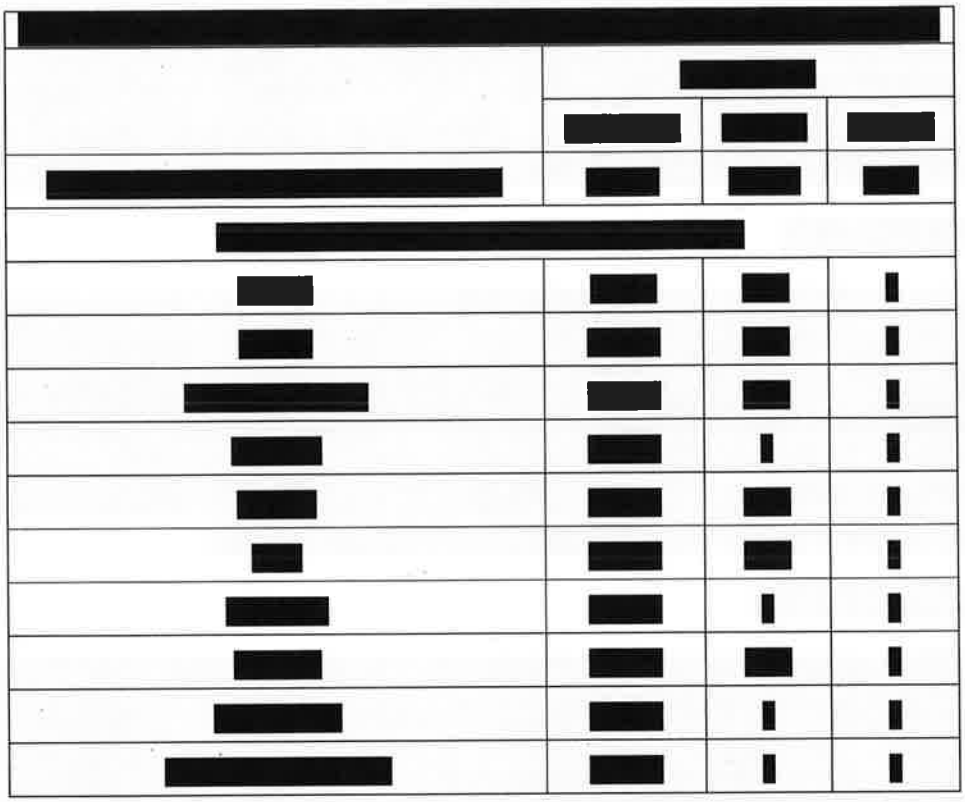

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2. OBJECTIVES

2.1. Primary objective

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.

2.2. Secondary objectives

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

[redacted]

3. STUDY DESIGN

3.1. Overall study design and plan description

3.1.1. Overall design and treatment plan

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 whichever occurs first.
Nivolumab will be given every 3 weeks from C1D1 until disease progression, or death or premature discontinuation due to any reason or for a maximum of 24 months whichever occurs first. Patients who achieve a confirmed complete response (CR) MAY discontinue nivolumab earlier after specific consultation and agreement between the Investigator and Transgene Medical Monitor when benefit/risk justify discontinuation.

Platinum-doublet chemotherapy will be administered as 21-day cycle for 4 cycles. In patients candidate for maintenance therapy, pemetrexed will be administered until disease progression or death or premature discontinuation due to any reason whichever occurs first.

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. In case the study treatment discontinuation is not due to progressive disease or death, response assessment should continue until progression of the disease or until the date of last contact if the patient is lost to follow-up or withdraws consent.

Toxiciti(es) 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)
- 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 analyse patients' safety data.

[redacted]

3.1.2. Number of centers and patients

It is anticipated that around 10 sites will participate in the study to include a total of 39 patients.

3.1.3. Patient accrual and duration of study

This study is expected to start in Q4 2017 and to be completed by Q1 2020 (primary objective).

In case of no safety concerns and for the further conduct of the study it is understood that the accrual rate is based on reasonable planning expectations. In particular, it must take into account the observed distribution of patients regarding the PD-L1 expression cutoff used to define inclusion criterion (<50%). The actual accrual rate should be compared to the expected rate on an ongoing basis. If problems with recruitment are encountered this should be discussed with Transgene as early as possible in order to institute measures to meet the above timelines.

3.2. Discussion of the Overall Study Design

3.2.1. Investigational plan

The study is designed as a phase II trial to evaluate the efficacy and safety of first-line chemotherapy combined with TG4010 and nivolumab in advanced, non-squamous NSCLC patients.

The primary efficacy endpoint of the study is objective response rate. [redacted]

3.2.2. Dose selection of IMPs

3.2.2.1. TG4010

Patients will receive weekly SC injections of TG4010 at the dose of 1 x 10^8 PFU for 6 weeks then every 3 weeks [redacted]

3.2.2.2. Nivolumab

Nivolumab will be administered as an IV infusion over at least 30 minutes at a dose of 360mg once every 3 weeks.

[redacted]

[redacted]

4. STUDY ENROLLMENT AND WITHDRAWAL

4.1. Study Population

4.1.1. Inclusion criteria

Patients must satisfy all the following inclusion criteria before they are allowed to participate in the study:

1. Signed informed consent in accordance to ICH-GCP and national/local regulation before any protocol-related procedures that are not part of normal patient care
2. Female or male patients age > 18 years-old
3. Eastern Cooperative Oncology Group (ECOG) performance Status 0 or 1 at study entry (APPENDIX 1)
4. Life expectancy of at least 3 months
5. Histologically confirmed non-squamous NSCLC (adenocarcinoma, large cell carcinoma, undifferentiated carcinoma or other)
6. Stage IIIB-IV cancer or delayed relapse of any stage not amenable to surgery or radiotherapy with curative intent. Patients with stage IIIB must not be eligible to radiotherapy
7. [redacted]PD-L1 expression by immunohistochemistry (IHC) in < 50% of tumor cells using 22C3 pharmDx assay kit[redacted]
8. [redacted]Prior treatment: patients must be treatment-naïve for the advanced stage of the disease. [redacted]
9. At least one measurable lesion by CT scan based on RECIST 1.1 performed within 28 days prior to start of study treatment and excluding the lesion used for biopsy
10. Adequate hematological, hepatic, and renal functions:
    - Hemoglobin ≥ 10.0 g/dL
    - White Blood Cells (WBC) ≥ 2.0 x 10^9/L, including
        - Neutrophils ≥ 1.5 x 10^9/L
        - Total lymphocytes count ≥ 0.5 x 10^9/L
    - Platelets count ≥ 100 x 10^9/L

- Serum alkaline phosphatase ≤ 3 x ULN in the absence of liver or bone metastases and ≤ 5 x ULN in patients with documented bone or liver metastases
- Total bilirubin ≤ 1.5 x ULN (except patients with Gilbert Syndrome who must have a total bilirubin level of < 3 x ULN)
- Serum transaminases (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) ≤ 3 x ULN
- Serum creatinine ≤ 1.5 x ULN or calculated creatinine clearance > 50 mL/min (using the Cockcroft-Gault formula)

11. Women of childbearing potential (WOCBP) must have a negative serum pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 72 hours prior to the start of study treatment
12. Highly effective contraception defined as:
    - Hormonal methods of contraception including combined oral contraceptive pills, vaginal ring, injectables, implants, intrauterine devices (IUDs) such as Mirena and Nonhormonal IUDs such as ParaGard for WOCBP patient or male patient's WOCBP partner
    - Tubal ligation
    - Vasectomy
    - Sexual abstinence
13. Women of childbearing potential (female patients not menopaused since ≥ 1 year) must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug(s) plus 5 half-lives of study drug plus 30 days (duration of ovulatory cycle) for a total of 5 months post-treatment completion
14. Men who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug (s) plus 5 halflives of study drug(s) plus 90 days (duration of sperm turnover) for a total of 7 months post-treatment completion

4.1.2. Exclusion criteria

If any of the following criterion apply, the patient must not enter the study.

1. Patients having Central Nervous System (CNS) metastases. Patients who have had brain metastases surgically removed or irradiated with no residual disease confirmed by imaging and not treated by corticosteroids are allowed
2. Patients with pericardial effusion
3. Prior exposure to cancer immunotherapy including cancer vaccines, anti-PD-1, anti-PD-L1, anti-PD-L2 , anti-cytotoxic T-Lymphocyte antigen -4 (CTLA-4) antibody or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways
4. Patients with EGFR activating mutations or ALK-rearrangements (tests mandatory) leading to eligibility for TKI treatment or other routinely assessed mutations/rearrangements for which a TKI is commercially available
5. Prior history of other malignancy except basal cell carcinoma of the skin, cervical intra-epithelial neoplasia, and other cancer curatively treated with no evidence of disease for at least 3 years

6. Patients with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of start of study treatment. Inhaled or topical steroids, and adrenal replacement steroid doses > 10 mg daily prednisone equivalent, are permitted in the absence of active auto-immune disease
7. Patients with an active, known or suspected autoimmune disease. Patients with type I diabetes mellitus, hypothyroidism only requiring hormone replacement, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll
8. Patients with interstitial lung disease that is symptomatic or may interfere with the detection or management of suspected drug-related pulmonary toxicity
9. Patients with grade ≥ 2 neuropathy
10. Signs or symptoms of infection within 14 days prior to start of study treatment or active infection requiring systemic therapy
11. Positive serology for Human Immunodeficiency Virus (HIV) or Hepatitis C Virus (HCV); presence in the serum of the Hepatitis B surface antigen (HBsAg) at baseline
12. Patients with any underlying medical condition that the treating physician considers might be aggravated by treatment or which is not controlled (e.g., elevated troponin or creatinine, uncontrolled diabetes)
13. History of any of the following cardiovascular conditions within 12 months of enrollment: cardiac angioplasty or stenting, myocardial infarction, unstable angina, coronary artery by-pass graft surgery, symptomatic peripheral vascular disease, class III or IV congestive heart failure, as defined by the New York Heart Association
14. Left ventricular ejection fraction (LVEF) less than the Lower Limit of Normal as assessed by echocardiography (or MUGA scan)
15. Patients with major surgery within 4 weeks prior to the start of the study treatment and patients with stage IIIB eligible to radiotherapy. Patients with stage IV may have received radiation therapy aimed at local palliation (except in case of thoracic radiotherapy and provided that the field irradiated does not include the unique measurable lesion) if completed 2 weeks before study treatment start.
16. Pregnant or nursing (lactating) women
17. Patients with an organ allograft
18. Any known allergy to eggs, gentamicin or history of allergy or hypersensitivity to study drug components
19. Participation in a clinical study with an investigational product within 4 weeks prior to the start of the study treatments
20. Patients unable or unwilling to comply with the protocol requirements
21. Prisoners or patients who are involuntarily incarcerated
22. Patients who are compulsorily detained for treatment of either a psychiatric or physical (eg, infectious disease) illness

4.2. Criteria for patient withdrawal and replacement

4.2.1. Premature discontinuation of study treatment

Patients may discontinue the study treatment prematurely if any of the following occur:

- Adverse event(s) according to the Investigator's evaluation
- Investigator's determination that patient's further participation in the study is not in the patient's best interest
- Patient's consent withdrawal
- Critical protocol deviation (including pregnancy)
- Lost to follow up

In case of premature withdrawal from the trial, the Investigator will obtain all the required details and document the date of and the reason for the discontinuation in the eCRF. In any case of treatment discontinuation not related to disease progression or death, the patient will be followed per protocol until documentation of progressive disease.

If the reason for stopping the treatment is an AE, the specific event will be recorded in the eCRF. The Investigator will make thorough efforts to document the outcome.
As far as possible, no patient should leave the study without having undergone the 2 safety follow-up visits.

4.2.2. Replacement policy

Whatever the reason for withdrawal, except for disease progression or death due to lung cancer, patients considered as non-evaluable for tumor response will be replaced.

4.3. Premature termination or suspension of the study

The study may be put "on-hold" or terminate under any of the following circumstances:

- Sponsor's decision
- Health Authorities' decision
- IDMC recommendation in case of a safety concern. However, in this latter case, the final decision as to whether to continue the study will be taken by the Sponsor

If the study needs to be terminated, Transgene and the Investigator will assure that adequate consideration is given to the protection of the patients. Transgene will notify the Health Authorities and the IEC(s)/IRB(s), any other committees and BMS of the premature study termination according to local regulations.

Should the study be prematurely stopped or put "on-hold" upon Health Authorities' decision, Transgene will inform immediately the Investigators and BMS in written including measures to be implemented.
If the study is prematurely discontinued, all study data must be returned to Transgene. In addition, the site must conduct final disposition of all unused study drugs in accordance with Transgene procedures for the study.

4.4. Definition of End of Study (EOS)

The end of the study will be defined as the date of last patient inclusion (LPI) plus 18 months to get information on the PFS and OS.

5. STUDY TREATMENTS

In this study the IMPs are TG4010 and nivolumab.

Non-IMP medications are chemotherapy (pemetrexed, carboplatin or cisplatin).
Note: all non-IMP medications will be administered according to local labeling.

5.1. Investigational Medicinal Products (IMPs)

The IMPs are TG4010 and nivolumab.

5.1.1. TG4010 (MVA-MUC1-IL2)

5.1.1.1. Characteristics and formulation

TG4010 is a suspension of recombinant Modified Vaccinia virus strain Ankara (MVA strain), a significantly attenuated strain of Vaccinia virus, carrying coding sequences for the human MUC1 antigen and human interleukin-2 (IL2).

[redacted]

[redacted]

5.1.1.3. Conditions of storage and use

TG4010 must be stored at -20°C +/- 5°C (between -15°C and -25°C), which is equivalent to -4°F± 9°F (between + 5°F and -13°F), in an alarmed and monitored freezer in a secure place with restricted access until use under the supervision of the study Pharmacist / Investigator (or his/her delegate). The vials will be dispensed only with the written authorization of the Investigator to staff that have been specifically designated and trained for this study.

TG4010 is a Genetically Modified Organism (GMO[redacted]

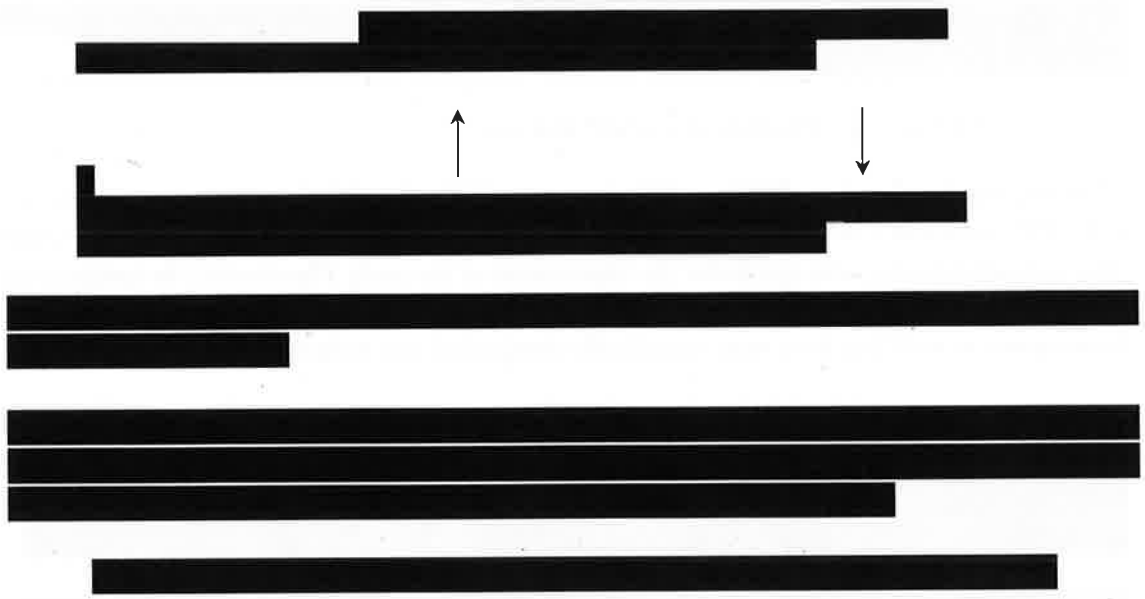
[redacted]

5.1.1.4. Preparation and administration procedure

TG4010 doses will be prepared and handled according to the instructions provided in a Preparation procedure provided by Transgene.

[redacted]

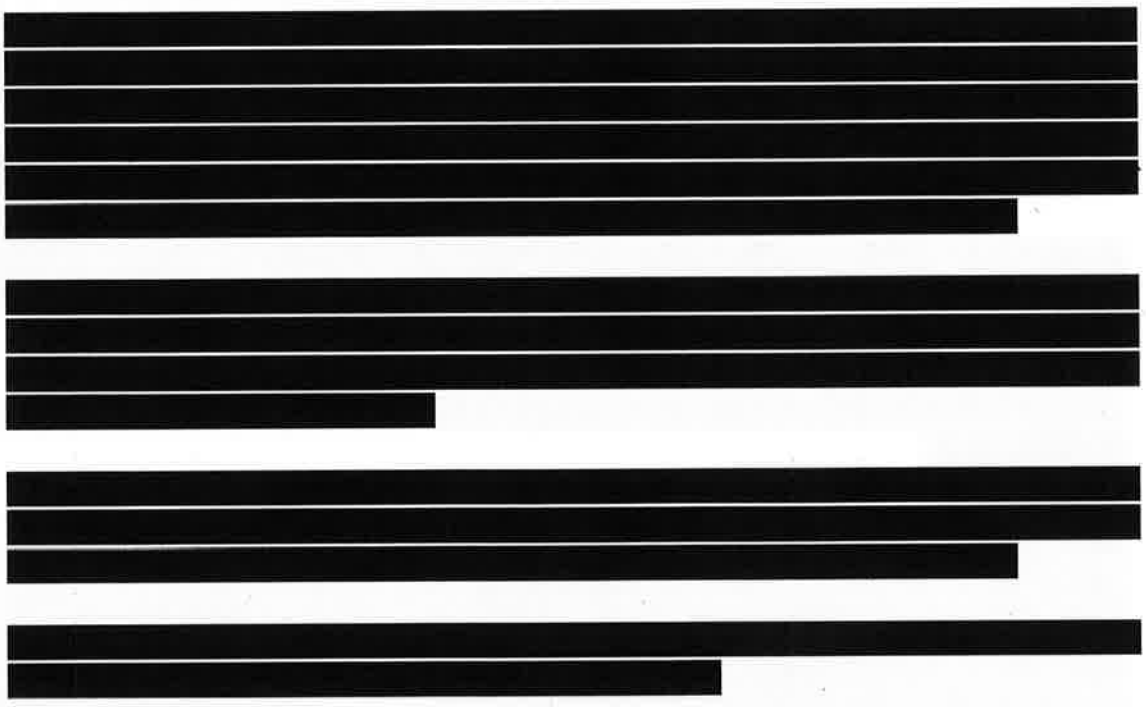
[redacted]



5.1.1.5. Disposal and destruction or return

During the course of the study based on Transgene's request and at termination of the study all unused TG4010 will be destroyed locally or returned to the supply provider contracted by Transgene.

[redacted]



5.1.1.6. Supplier

TG4010 will be supplied on behalf of Transgene for this study at no cost to the study participant.

5.1.2. Nivolumab

5.1.2.1. Characteristic, packaging and labeling

Nivolumab Injection, 100 mg/10 mL (10 mg/mL), is a clear to opalescent, colorless to pale yellow liquid, which may contain light (few) particulates. The drug product is a sterile, non-pyrogenic, single-use, isotonic aqueous solution formulated at 10 mg/mL in sodium citrate, sodium chloride, mannitol, diethylenetriaminepentacetic acid (pentetic acid), and polysorbate 80 (Tween™ 80), pH 6.0 and includes an overfill to account for vial, needle, and syringe holdup [redacted]

[redacted]

5.1.2.2. Conditions of storage and use

In accordance with its EU SmPC and United States Product Insert (USPI), nivolumab vials must be stored in a refrigerator at 2°C to 8°C (36°F to 46°F) in the original package in order to protect from light.

[redacted]

5.1.2.3. Preparation and administration procedures

Nivolumab injection is to be administered as an IV infusion through a 0.2-micron to 1.2-micron pore size, low-protein binding polyethersulfone membrane in-line filter at the protocol-specified doses. It is not to be administered as an IV push or bolus injection but as an infusion of at least 30 minutes.

[redacted]

[redacted]

[redacted]

5.1.2.4. Disposal and destruction or return

During the course of the study based on Transgene's request and at termination of the study all unused nivolumab will be destroyed locally or returned to the supply provider contracted by Transgene.

[redacted]

5.1.2.5. Supplier

Nivolumab will be supplied for this study at no cost to the study participant.

5.2. Non-Investigational Medicinal Product (non-IMP)

5.2.1. Pemetrexed plus platinum (carboplatin or cisplatin)

Chemotherapy will be given as 21-day cycles for 4 cycles or until disease progression or discontinuation due to any reason whichever occurs first. The chemotherapy regimen to be administered is the following:

- Pemetrexed: 500 mg/m² on D1 of each cycle
- Carboplatin = AUC 6 or Cisplatin 75 mg/m² on D1 of each cycle

The next course of chemotherapy on D22, i.e., 3 weeks after start of the current chemotherapy cycle and corresponding to D1 of this new cycle.
Pemetrexed and cisplatin dosing calculations should be based on the body surface area calculation. The dose may remain the same if the patient's weight is within 10% weight used to calculate the previous dose. All doses should be rounded up or to the nearest milligram per institutional standard.

The carboplatin dose will be calculated using the Calvert formula as follows:
Carboplatin dose (mg) = Target AUC x [(CrCl (mL/min) + 25]

Creatinine clearance (CrCl) calculation is based on the Cockroft-Gault formula and should include the most recent serum creatinine and most recent weight. NOTE: If calculation of the CrCl by the Cockroft-Gault formula yields a result of > 125 mL/min, then a CrCl should be calculated by an alternative formula per institutional standards or capped at 125 mL/min.

The dose of carboplatin may be capped per local standards.

Premedication for use with pemetrexed: Oral corticosteroid should be given according to local standards at a dose equivalent to dexamethasone 4 mg BID on the day prior to, the day of, and the day after the administration of pemetrexed. Oral folic acid 350 to 1000 mcg daily should be given starting 1 week prior to the first dose of pemetrexed, with at least 5 doses of folic acid administered in the 7 days prior to the first dose. Oral folic acid should be continued daily throughout the treatment with pemetrexed and for 21 days after the last dose of pemetrexed. Intramuscular (IM) injection of vitamin B12 1000 mcg should be given approximately 1 week prior to the first dose of pemetrexed and repeated every 3 cycles thereafter during pemetrexed treatment. Subsequent injections of vitamin B12 may be given on the same day as pemetrexed.

Premedications for use with pemetrexed/carboplatin or cisplatin: Antiemetic premedication will be administered according to local standards. Recommended antiemetic treatments are dexamethasone (dosing according to local standards; an equivalent dose of another corticosteroid may be substituted) and a 5-HT3 receptor antagonist (type per investigator discretion and local standards-of-care). Additional use of antiemetic premedication may be employed at the discretion of the Investigator.

All patients who will be receiving cisplatin should have audiometric testing performed prior to initiation of therapy and prior to subsequent doses of cisplatin, or as per local standards of care. Cisplatin will be administered to patients at least 30 minutes following the end of pemetrexed infusion. Pretreatment hydration for cisplatin can follow local standard of care.

Patients who discontinue cisplatin alone will be switched to pemetrexed/carboplatin for the remainder of the platinum doublet cycles (4 cycles in total). Dosing for pemetrexed/carboplatin for such patients should follow the instructions in the Pemetrexed/Carboplatin with Pemetrexed Continuation Maintenance.

Doses of pemetrexed and/or carboplatin or cisplatin may be interrupted, delayed, reduced, or discontinued depending on how well the patient tolerates the treatment. See Sections 6.5.1 and 6.5.2 for additional details.

5.2.2. Maintenance therapy by pemetrexed

After Cycle 4, pemetrexed is to be prescribed to patients candidate for maintenance therapy according to local labelling until disease progression or premature discontinuation due to any reason (*e.g.* AE) or toxicity.
Pemetrexed will be administered at the dose of 500 mg/m² every 3 weeks on D1 of each cycle in combination with TG4010 and nivolumab.

In patients who required pemetrexed dose reduction due to toxicity during the pemetrexed/platinum combination cycles, the dose of pemetrexed may be escalated to 500 mg/m² after the discontinuation of the platinum compound, at the investigator's discretion and according to local standards, if the prior toxicity was felt to be related mainly to platinum.

6. TREATMENT PLAN

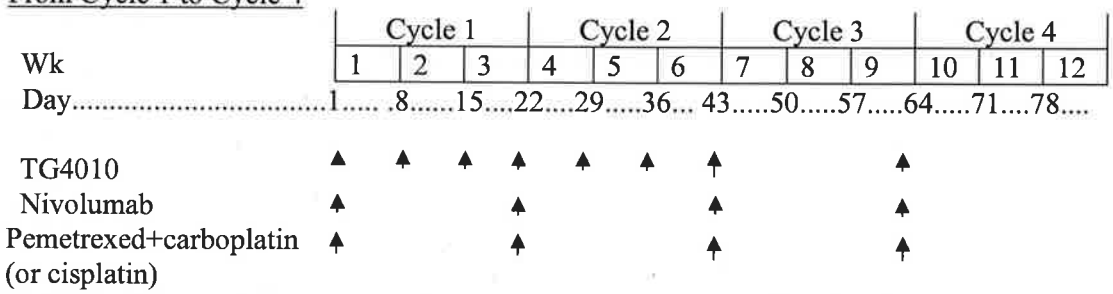
6.1. Selection and timing of dosing

Patients will receive TG4010 plus nivolumab plus pemetrexed-carboplatin (or cisplatin).
Patients will receive TG4010 at 1 x 10^8 PFU starting on Day 1 of first chemotherapy cycle on a weekly basis for 6 weeks and then once every 3 weeks.
Patients will receive nivolumab at the dose of 360 mg by IV infusion over at least 30 minutes on Day 1 of first chemotherapy cycle and then once every 3 weeks.
Patients will receive pemetrexed at a dose of 500 mg/m² as a 10-minutes IV infusion with carboplatin at a dose of AUC 6 as a 30-minutes IV infusion or with cisplatin at a dose of 75 mg/m² as 120-minutes IV infusion on Day 1 of a 3-week treatment cycle, for 4 cycles (Figure 1).
After cycle 4, patients with stable disease or response will discontinue the platinum compound (carboplatin or cisplatin) and will continue TG4010 plus nivolumab and pemetrexed at the same dose and schedule on Day 1 of a 3-week treatment cycle. Treatment will continue until progression, unacceptable toxicity, withdrawal of consent, or the study ends, whichever occurs first. Nivolumab will be administered up to a maximum of 24 months. In patients who required pemetrexed dose reduction due to toxicity during the pemetrexed + carboplatin (or cisplatin) combination cycles, the dose of pemetrexed may be escalated to 500 mg/m² after the discontinuation of the platinum compound at the investigator's discretion and according to local standards, if the prior toxicity was felt to be related mainly to the platinum compound.

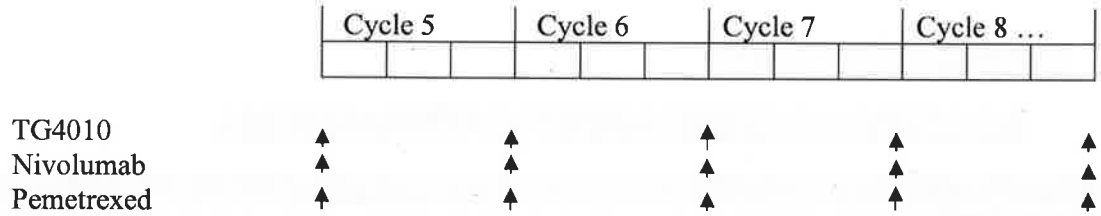
TG4010 will be administered first, then nivolumab and then pemetrexed with carboplatin (or cisplatin), no sooner than 30 minutes after completion of nivolumab infusion.

Figure 1 : Schedule of administration of study drugs

From Cycle 1 to Cycle 4



During maintenance chemotherapy (all study treatments will be administered every 3 weeks on day 1 of each cycle)



6.2. Treatment duration

The study treatment will be administered until documented disease progression (according to RECIST 1.1), death or premature discontinuation due to any reason, whichever occurs first.

However, nivolumab will be given for up to a maximum of 24 months in the absence of disease progression or unacceptable toxicity. Patients who achieve a confirmed complete response (CR) MAY discontinue nivolumab earlier after specific consultation and agreement between the Investigator and Transgene Medical Monitor when benefit/risk justify discontinuation.

TG4010 will be continued.

6.2.1. On study period

The trial duration includes a 28-day screening period (decision will be made in this period for patients' trial inclusion if all eligibility criteria are met), a treatment period which may last up to disease progression, unacceptable toxicity, withdrawal from the trial occurs for any reason. An end-of-treatment visit will be completed as soon as all study treatments are permanently discontinued. Safety follow-up should continue up to 100 days after the last study treatment administration (safety follow-up visit at 30 days and at 100 days after end of study treatment).

During the study, depending on the response, the following rules for study treatment duration will apply:

- Patients with a response of CR/PR/SD will continue to receive study treatment until documented disease progression, development of unacceptable toxicity or discontinuation due to any reason whichever occurs first. However, nivolumab will be given for up to a maximum of 24 months in the absence of disease progression or unacceptable toxicity. TG4010 and pemetrexed (if applicable) will be continued.
- Individual participants with confirmed CR will be given the option to discontinue nivolumab earlier, on a case by case basis, after specific consultation and agreement between the Investigator and Transgene Medical Monitor, in settings where benefit/risk justify discontinuation of study therapy. TG4010 and pemetrexed (if applicable) will be continued.
- Patients with documented progressive disease (PD) based on RECIST *v*1.1 will stop study treatment

Patients who are withdrawn from study treatment for reasons other than disease progression or death will be followed until documented disease progression or death or the cut-off date whichever occurs first.

[redacted]

[redacted]

6.4. Method of assigning patients to treatment groups

6.4.1. Recruitment

Upon signing the informed consent form (ICF), the patient will be assigned an identification number.
The center number is assigned by the Sponsor to the investigational site. At each site, the first patient screened is assigned patient number 01, and subsequent patients are assigned consecutive numbers. Once assigned to a patient, the patient number will not be reused.
The screening process will start and is defined as the baseline period. The baseline lasts at most 28 days. Tests performed per standard of care (e.g., CT-scan) prior to ICF signature may not need to be repeated if collected within 28 days prior to start of study treatment.
If the patient fails to be included for any reason, the reason for non-inclusion (e.g. withdrawal of consent, exclusion criteria) and a minimum of other parameters (e.g., date of ICF signature, demographics and disease characteristics) will be entered in the eCRF. Under no circumstances will patient screened for the study be permitted to be re-screened for a second time in the study.

6.4.2. Randomization

NA

6.5. Toxicity management and safety review

6.5.1. Dose modification, dose delay and criteria to resume dosing

No intra-patient dose reduction will be allowed for TG4010 or nivolumab. Dosing of TG4010 and nivolumab should be delayed according to the criteria in Section 6.5.1.1.

- If TG4010 is delayed or stopped for toxicity, nivolumab will also be delayed or stopped but chemotherapy will continue as planned unless criteria for chemotherapy delay or discontinuation are also met.
- If nivolumab is delayed or stopped for toxicity, TG4010 dosing will also be delayed or stopped but chemotherapy should continue unless criteria for chemotherapy delay or discontinuation are also met.

Dose reductions for chemotherapy will occur according to EU Summary of Product Characteristics (SmPC) and United States Product Insert (USPI) as detailed in Section 6.5.1.2.

- According to standard practice, the start of a new cycle of chemotherapy will be delayed if toxicity does not allow a new administration of chemotherapy. In this case, TG4010 and nivolumab administrations will also be delayed.
- If chemotherapy is definitely stopped for toxicity, TG4010 and nivolumab should continue (or restart) as soon as criteria for retreatment are met. Note that if the reason for stopping chemotherapy is not due to intolerable toxicity, the patient should receive at least 3 cycles of the platinum-doublet.

6.5.1.1. Dose delay

Dose delay for TG4010

The hematological threshold to allow the administration of TG4010 is defined as neutrophils $\geq 0.5 \times 10^9$/L.

If a Grade 1-2 AE occurs TG4010 should be administered as planned.

In case ≥ Grade 3 AE possibly, probably or definitely suspected to be related to TG4010 occurs, the administration of TG4010 will be delayed and the patient should come in for his/her next, regularly scheduled visit.

If TG4010 is delayed, nivolumab will also be delayed but chemotherapy will continue as planned unless criteria for chemotherapy delay are also met.

Dose delay for nivolumab

Dose delay criteria apply for all nivolumab-related adverse events.

Nivolumab administration should be delayed for the following:

- Grade 2 pneumonitis or interstitial lung disease
- Grade ≥ 2 non-skin, drug-related adverse event, except for fatigue
- Grade 2 drug-related creatinine, AST, ALT and/or total bilirubin abnormalities
- Grade ≥ 3 skin, drug-related adverse event
- Grade ≥ 3 drug-related laboratory abnormality, with the following exceptions:
  - Grade 3 lymphopenia or asymptomatic amylase or lipase does not require dose delay
  - Concurrent AST or ALT ≥ 3 x ULN **and** total bilirubin ≥ 2 x ULN requires discontinuation
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants dose delay/omission of study medication.

If nivolumab is delayed > 6 weeks, the patient must be permanently discontinued from both IMPs (nivolumab, TG4010) except as specified in Dose Discontinuation Criteria (see Section 6.5.2).

Dosing delay for chemotherapy

In the case chemotherapy needs to be delayed, TG4010 and nivolumab will also be delayed.

Dosing of both drugs in the platinum doublet chemotherapy regimen selected should be delayed for any of the following on the Day 1 of each cycle:

- Absolute neutrophil count (ANC) < 1.5 x 10^9/L
- Platelets < 100 x 10^9/L
- Any Grade ≥ 2 non-skin, non-hematologic, drug-related adverse event (excluding Grade 2 alopecia, Grade 2 fatigue, and Grade 2 laboratory abnormalities)
- Any Grade ≥ 3 skin, drug-related adverse event
- Any Grade ≥ 3 drug-related laboratory abnormality, with the following exceptions for lymphopenia, AST, ALT, or total bilirubin:
  - Grade 3 lymphopenia does not require dose delay.
  - If a patient has a baseline AST, ALT or total bilirubin that is within normal limits, delay dosing for drug-related Grade ≥ 2 toxicity.
  - If a patient has baseline AST, ALT, or total bilirubin within the Grade 1 toxicity range, delay dosing for drug-related Grade ≥ 3 toxicity.
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of study medication.

Investigators should consult local labeling for the chemotherapy drugs being administered to any given patient for additional guidance on dose delays.
In addition, patients receiving cisplatin with pemetrexed must discontinue cisplatin if the calculated creatinine clearance decreases to < 50 mL/min (based on the Cockroft Gault formula).

6.5.1.2. Dose reductions

Dose reductions for TG4010 or nivolumab

There will be no dose reduction for TG4010 or nivolumab.

Dose reduction for pemetrexed plus platinum (carboplatin or cisplatin)

Dose adjustments at the start of a subsequent cycle should be based on nadir hematologic counts or maximum non-hematologic toxicity from the preceding cycle of therapy. Treatment may be delayed to allow sufficient time for recovery. Upon recovery patients should be retreated using the guidelines in Tables 3, 4 and 5, which are applicable for pemetrexed used as a single agent or in combination with cisplatin. Treatment with pemetrexed should be discontinued if a patient experiences any hematologic or non-hematologic Grade 3 or 4 toxicity after 2 dose reductions or immediately if Grade 3 or 4 neurotoxicity is observed. Cases of radiation pneumonitis have been reported in patients treated with radiation either prior, during or subsequent to their pemetrexed therapy. Particular attention should be paid to these patients and caution exercised with use of other radiosensitising agents.

Dose Reductions for Hematologic Toxicity

Dose modifications for hematologic toxicities (according to CTCAE version 4.03) are summarized in Table 3. Dose adjustments are based on nadir blood counts (assessed as per local standards) since the preceding drug administration. Dose level adjustments for pemetrexed plus carboplatin (or cisplatin) are relative to that of the preceding administration. Generally, both chemotherapy agents should be dose reduced together for hematologic toxicity. After the first cycle, growth factors may be used to assist hematologic recovery. Use local standards of care in the use of these supportive measures. Additionally, prophylactic antibiotics may be used according to local standards of care. Please report any antibiotic or growth factor use on the eCRF.

Table 3 : Dose Modifications for Hematologic Toxicities (based on nadir counts)

Toxicity	Pemetrexed	Carboplatin	Cisplatin
Neutrophil Count Decreased			
Nadir Absolute Neutrophils Count (ANC) <500/mm^3 (or <0.5 x 10^9/L) and nadir platelets ≥ 50,000/mm^3 (or 50 x 10^9/L)	75% of previous dose	75% of previous dose	75% of previous dose
Platelet Count Decreased			
Nadir platelets < 50,000/mm^3 (or <50 x 10^9/L) regardless of nadir ANC	75% of previous dose	75% of previous dose	75% of previous dose
Nadir platelets < 50,000/mm^3 (or <50 x 10^9/L) with bleeding regardless of nadir ANC	50% of previous dose	50% of previous dose	50% of previous dose

Dose Reductions for Non-Hematologic Toxicities

Dose adjustments for pemetrexed plus carboplatin (or cisplatin) for non-hematologic toxicities during treatment are described in Table 4 and Table 5. All dose reductions should be made based on the worst grade toxicity.

Patients experiencing any of the toxicities detailed below during the previous cycle should have their chemotherapy delayed until retreatment criteria are met (per Section 6.5.1.3) and then reduced for all subsequent cycles as displayed below or discontinued as appropriate. Dose levels for the 2 drugs are not linked and may be reduced independently, as summarized in the table below.

Table 4: Dose Modifications for Non-hematologic Toxicities except Neurotoxicity			
Toxicity	**Pemetrexed**	**Carboplatin**	**Cisplatin**
Any grade 3 or 4 toxicities except mucositis	75% of previous dose	75% of previous dose	75% of previous dose
Any diarrhea requiring hospitalization (irrespective of grade) or grade 3 or 4 diarrhea	75% of previous dose	75% of previous dose	75% of previous dose
Grade 3 or 4 mucositis	50% of previous dose	100% of previous dose	100% of previous dose

Table 5 : Dose Modification for Neurotoxicity			
Toxicity	**Pemetrexed**	**Carboplatin**	**Cisplatin**
Neuropathy Grade 0 or 1	100% of previous dose	100% of previous dose	100% of previous dose
Neuropathy Grade 2	100% of previous dose	100% of previous dose	50% of previous dose
Neuropathy Grade 3 or 4	Discontinue	Discontinue	Discontinue

6.5.1.3. Criteria to Resume Dosing

Criteria to resume TG4010 dosing

Patients may resume treatment with TG4010 when drug-related AE(s) resolve(s) to Grade ≤ 2 or baseline.

Criteria to resume nivolumab dosing

If the decision is to resume nivolumab dosing, the patient should restart treatment on the next regularly scheduled nivolumab dosing visit. Skipped doses are not to be replaced. If treatment is delayed > 6 weeks, the patient must be permanently discontinued from both IMPs, except as specified in Dose Discontinuation Criteria.

Tumor assessments for all patients should continue as per protocol ***even if dosing is delayed.***
Patients may resume treatment with nivolumab when the drug-related AE(s) resolve to Grade ≤1 or baseline value, with the following exceptions:

- Patients may resume treatment in the presence of Grade 2 fatigue
- Patients who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity
- For patients with Grade ≥ 2 AST/ALT or Total Bilirubin abnormalities meeting dose delay parameters, dosing may resume when laboratory values return to baseline and management with corticosteroids, if needed, is complete

- Patients with combined Grade 2 AST/ALT **AND** total bilirubin values meeting discontinuation parameters should have treatment permanently discontinued
- Drug-related pulmonary toxicity, diarrhea, or colitis, must have resolved to baseline before treatment is resumed. Patients with persistent Grade 1 pneumonitis after completion of a steroid taper over at least 1 month may be eligible for retreatment if investigator allows.
- Patients who received systemic corticosteroids for management of any drug-related toxicity must be off corticosteroids or have tapered down to an equivalent dose of prednisone ≤10 mg/day
- Grade 3 drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment if investigator allows. Grade ≥ 3 ~~Grade 4~~ adrenal insufficiency requires definitive discontinuation

If the criteria to resume treatment are met, the patient should restart treatment at the next scheduled timepoint per protocol. However, if the treatment is delayed past the next scheduled timepoint per protocol, the next scheduled timepoint will be delayed until dosing resumes.

Criteria to resume pemetrexed plus carboplatin or cisplatin dosing

- Patients may resume treatment with pemetrexed plus carboplatin or cisplatin when the ANC returns to ≥ 1.5 x 10^9/L, the platelet count returns to ≥ 100 x 10^9/L and all other drug-related toxicities have returned to baseline or Grade ≤ 1 (or Grade ≤ 2 for alopecia and fatigue).
- If a patient fails to meet criteria for reinitiating treatment, then treatment should be delayed, and the patient should be re-evaluated weekly or more frequently as clinically indicated. Any patient who fails to recover from toxicity attributable to pemetrexed plus carboplatin (or cisplatin) to baseline or Grade ≤ 1 (except Grade 2 alopecia and fatigue) within 6 weeks from the last dose given should discontinue the drug(s) that caused the delay.
- When resuming pemetrexed plus carboplatin (or cisplatin) treatment, please follow the dose reduction recommendations in Section 6.5.1.2.
- Note that patients receiving pemetrexed + cisplatin who meet criteria to discontinue cisplatin alone will be switched to pemetrexed + carboplatin for the remainder of the platinum-doublet cycles (4 cycles in total).

6.5.2. Treatment Discontinuation Criteria

For all patients global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as symptomatic deterioration in the source data and in the eCRF. Every effort should be made to document objective progression (ie, radiographic confirmation) even after discontinuation of treatment.

6.5.2.1. TG4010 dose discontinuation

Should TG4010 be permanently discontinued, nivolumab will also be discontinued.

6.5.2.2. Nivolumab Dose Discontinuation

Should nivolumab be permanently discontinued, TG4010 will also be discontinued.
Treatment with nivolumab should be permanently discontinued for any of the following:

- Any Grade ≥ 2 drug-related uveitis or eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within the treatment re-initiation period OR requires systemic treatment.
- Any Grade ≥ 3 non-skin, drug-related adverse event lasting > 7 days, or recurs with the following exceptions for uveitis, pneumonitis, bronchospasm, diarrhea, colitis, neurologic toxicity, hypersensitivity reactions, infusion reactions, endocrinopathies, and laboratory abnormalities:
  - Grade ≥ 3 drug-related uveitis, pneumonitis, bronchospasm, diarrhea, colitis, neurologic toxicity, hypersensitivity reaction of any duration or Grade 3 infusion reaction (see Section 6.5.3) requires discontinuation
  - Grade 3 drug-related endocrinopathies adequately controlled with only physiologic hormone replacement do not require discontinuation except Grade 3 adrenal insufficiency which requires dicontinuation
  - Grade ≥ 3 drug-related laboratory abnormalities do not require treatment discontinuation except:
    - Grade 3 drug-related thrombocytopenia > 7 days or associated with bleeding requires discontinuation.
    - Grade ≥ 3 drug-related AST, ALT or Total Bilirubin requires discontinuation.
    - Concurrent AST or ALT ≥ 3 x ULN **AND** total bilirubin ≥ 2 × ULN requires discontinuation
- Any Grade 4 drug-related adverse event or laboratory abnormality, except for the following events, which do not require discontinuation:
  - Grade 4 neutropenia ≤ 7 days
  - Grade 4 lymphopenia or leukopenia or asymptomatic amylase or lipase
  - Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset
- Grade 4 drug-related endocrinopathy adverse events requires definitive discontinuation regardless of control with hormone replacement
- Dosing delay of nivolumab which results in treatment interruption of > 6 weeks requires treatment discontinuation with the following exceptions:
  - Dosing delays to allow for prolonged steroid tapers to manage drug-related adverse events are allowed.
  - Dosing delays lasting > 6 weeks from the previous dose that occur for non-drug-related reasons may be allowed if approved by the Transgene Medical Monitor.

  Prior to re-initiating treatment in a patient with a dosing delay lasting > 6 weeks, the Transgene and BMS Medical Monitors must be consulted. Tumor assessments should continue as per protocol even if dosing is delayed. Periodic study visits to assess safety and

laboratory studies should also continue every 3 weeks or more frequently if clinically indicated during such dosing delays.

- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the patient with continued nivolumab dosing.

The assessment for discontinuation of nivolumab should be made separately from the assessment made for discontinuation of chemotherapy doublet. If criteria for discontinuation for nivolumab are met before the nivolumab plus platinum doublet chemotherapy cycles have been completed, platinum doublet chemotherapy may continue until 4 cycles (maximum) have been given.

6.5.2.3. Pemetrexed plus carboplatin (or cisplatin)

Except where specified below, both chemotherapy drugs should be discontinued for any of the following:

- Any Grade ≥ 3 peripheral neuropathy.
- Grade ≥ 3 drug-related thrombocytopenia associated with clinically significant bleeding.
- Any drug-related liver function test (LFT) abnormality that meets the following criteria requires discontinuation:
  - AST or ALT ≥ 5-10 x ULN for > 2 weeks
  - AST or ALT ≥ 10 x ULN
  - Total bilirubin ≥ 5 x ULN
  - Concurrent AST or ALT ≥ 3 x ULN and total bilirubin ≥ 2 x ULN
- Any drug-related adverse event which recurs after 2 prior dose reductions for the same drug-related adverse event (as specified in Section 6.5.1.2) requires discontinuation of the drug(s) which was/were previously dose reduced.
- Any Grade ≥ 3 drug-related hypersensitivity reaction or infusion reaction requires discontinuation of the drug(s) felt to be causing the reaction. The drug not felt to be related to the hypersensitivity reaction or infusion reaction may be continued.
- Any Grade 4 drug-related adverse event which the investigator deems is inappropriate to be managed by dose reduction(s) requires discontinuation of the drug(s) felt to be causing the event. The drug not felt to be related to the event may be continued.
- Any event that leads to delay in dosing of any study drug(s) for > 6 weeks from the previous dose requires discontinuation of that drug(s) with the following exception:
  - Dosing delays lasting > 6 weeks from the previous dose that occur for non-drug-related reasons may be allowed. Prior to re-initiating treatment in a patient with a dosing delay lasting > 6 weeks, the Medical Monitor must be consulted. Tumor assessments should continue as per protocol even if dosing is delayed. Periodic study visits to assess safety and laboratory studies should also continue every 3 weeks or more frequently if clinically indicated during such dosing delays.
- Any adverse event, laboratory abnormality, or undercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the patient with continued pemetrexed-carboplatin (or cisplatin) dosing. Investigators should consult local labeling for

the chemotherapy drugs being administered to any given patient for additional guidance on dose discontinuation.

- A total of 4 cycles of chemotherapy should be given prior to starting pemetrexed maintenance treatment. However, patients who experience Grade 4 treatment-related hematologic toxicity, or Grade 3 treatment-related non-hematologic toxicity, may start maintenance therapy after 3 cycles of platinum-doublet chemotherapy. The nature and grade of the toxicity must be clearly noted, and the medical monitor must be notified.
- Note that patients receiving pemetrexed/cisplatin who discontinue cisplatin alone will be switched to pemetrexed/carboplatin for the remainder of the platinum doublet cycles (4 cycles in total).

6.5.3. Management of nivolumab infusion reaction

Since nivolumab contains only human immunoglobulin protein sequences, they are unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgia, hypotension or hypertension, bronchospasm, or other symptoms. All Grade 3 or 4 infusion reactions should be reported within 24 hours to the study medical monitor and reported as an SAE if it meets the criteria. Infusion reactions should be graded according to NCI-CTCAE (Version 4.03) guidelines.

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

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

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

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

- Stop the nivolumab infusion, begin an IV infusion of normal saline, and treat the patient with diphenhydramine 50 mg IV (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg; remain at bedside and monitor patient until resolution of symptoms. Corticosteroid and/or bronchodilator therapy may also be administered as appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor patient closely. If symptoms recur, then no further nivolumab will be administered at that visit. Administer diphenhydramine 50 mg IV, and remain at bed side and monitor the patient until resolution of symptoms. The amount study drug diffused must be recorded on the eCRF.

- For future infusions, the following prophylactic pre-medications are recommended: diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg should be administered at least 30 minutes before nivolumab infusions. If necessary, corticosteroids (up to 25 mg of SoluCortef or equivalent) may be used.

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

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

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

6.5.4. Data Monitoring Committee

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 of an interim safety analysis once 6 patients have been treated with the triple combination (TG4010 + nivolumab + chemotherapy) for at least 6 weeks.
- To review efficacy and safety data at study completion.

In addition to the scheduled meeting and based on the continuous safety assessments, the Sponsor will evaluate the need for additional ad-hoc meeting(s) of the IDMC to analyse patient safety data.
Safety data will be reviewed regularly for any late-emerging toxicities.

The IDMC will be composed of 2 independent clinicians. Representatives of Transgene (Medical monitor, Pharmacovigilance physician) and BMS (Medical monitor) will be invited to all meetings to present clinical data and respond to any specific questions the IDMC may have on the conduct of the study. Additional study team members may attend if deemed necessary (Clinical trial manager, Statistician). If deemed appropriate, the coordinating investigators and the study investigators of the concerned centers will be invited for cases requiring specific explanation. The Sponsor can appoint any additional independent expert if needed.

A charter describing the responsibilities of the IDMC as well as the working procedures will be provided in a separate document.

6.6. Treatment compliance

6.6.1. Dispensing and accountability

The IMPs will only be dispensed, according to Investigator's prescription, to patients who meet all selection criteria.

The Investigator / Pharmacist or delegated person will maintain IMPs accountability records for TG4010 as well as for nivolumab, detailing the dates and quantities dispensed for each patient along with IMP packaging batch numbers, box and vial numbers.

IMPs accountability records will be verified by the monitor during site visits. All used and unused IMPs will be accounted for. All unused IMPs will be destroyed locally or returned to Transgene and/or its IMP supply provider, providing destruction or return certificates.

The Investigator / Pharmacist or delegated person will also maintain a Non-IMP medications (chemotherapeutic treatments such as pemetrexed and carboplatin or cisplatin) accountability log detailing the dates and quantities dispensed for each patient along with brand names or International Non-proprietary Names (INN), packaging batch numbers, treatment numbers if applicable. Non-IMP accountability records will be verified by the monitor during site visits.

6.6.2. Assessment of compliance

The compliance for the IMPs will be monitored through the IMP(s) accountability logs and information reported on the eCRF pages.

6.7. End of treatment

An end of treatment visit will be performed as soon as all treatments are discontinued.

The Investigator will obtain all the required details and document the date and the reason for study treatment discontinuation on the eCRF "end of treatment" form.
The patient will then be followed for PFS (if applicable), safety (safety visits), subsequent therapies and survival.

6.8. Safety follow-up visits

All patients (if alive) who discontinue the study treatment, will be evaluated for safety up to 100 days after last dose of study drug including those who refuse to return for a visit who will be contacted by phone. A first "safety follow-up visit" will occur 30 days after last treatment administration and a second "safety follow-up visit" will occur 100 days after last treatment administration. These visits are to be completed in the eCRF.
All adverse events, concomitant medications, significant non-drug therapies within 100 days after the last study treatment administration will be collected.

6.9. End of study

An "end of study" form will be completed as soon as the disease progression is documented and the 2 safety follow-up visit have been performed. However, overall survival follow-up will be collected.

6.10. Medical care of patients after end of study

After a patient has completed the trial or has withdrawn early, usual treatment will be administered, if required, in accordance with the trial site's standard of care and generally accepted medical practice and depending on the patient's individual medical needs.
Upon withdrawal from trial treatment, patients may receive whatever care they and their physicians agree upon.

6.11. Follow-up for PFS and subsequent therapy

In case the study treatment discontinuation is not due to progressive disease or death, the patient will be followed for PFS until progressive disease by RECIST 1.1 or until the date of last contact if the patient is lost to follow-up or withdraws consent. A CT scan or MRI of measurable and non-measurable disease must be obtained every 6 weeks until disease progression or for a period of 9 months after the start of study treatment. Beyond 9 months, the evaluations will be performed every 12 weeks until disease progression.
Tumor assessments will be recorded in the eCRF. All subsequent cancer therapies (if applicable) must be recorded in the eCRF with start and end dates.

6.12. Follow-up for survival and subsequent therapy

From the end of treatment date, all subsequent therapies for cancer (if applicable) must be recorded in the eCRF with start and end dates.
From the safety follow-up visit (or last PFS follow-up visit), the patient will be followed every 3 months for survival until death or the date of last contact if the patient is lost to follow-up or informed consent withdrawal. Survival data may be determined from review of publicly available databases (where local regulations allow).

7. STUDY VISITS AND PROCEDURES

A flow-chart shown in APPENDIX 2 summarizes the evaluations to be performed along with the time points for each parts of the study and the data to be collected in the eCRF. If not otherwise specified, when an assessment is planned on the same day as treatment administration, it will be done prior to it.

7.1. Evaluations description

The following parameters will be measured during the course of the study:

Inclusion/exclusion criteria
Patient eligibility is to be established by the investigator by confirming all inclusion/exclusion criteria are met. Deviation of any eligibility criterion excludes a patient from enrolment into the study.

Demography
- Date of birth, gender
- Child bearing potential status
- Smoking habits (previous / current smokers, never smokers)

History of studied disease
- Date of diagnosis and stage at diagnosis
- Histology type
- EGFR mutations (including T790M mutation status), ALK-rearrangement and if available ROS1-rearrangement, BRAF and KRAS status and other molecular tests if performed
- Prior cancer therapy

Relevant medical history and current medical conditions
- Relevant medical history with established diagnosis (e.g., cholecystectomy, ongoing arterial hypertension) present or recovered at ICF signature
- Syndrome / pathology with established diagnosis (e.g., gastro-oesophageal reflux) starting during the screening period (from signature of ICF up to C1D1) either recovered or ongoing

Signs and symptoms pre-treatment
- Relevant signs and symptoms (e.g., cough, dyspnea, pain) present at the signature of the ICF or starting during the screening period

Clinical evaluation
- Physical examination of the major organ system, including weight, height (only at baseline), blood pressure (BP), heart rate (HR), temperature, and oxygen saturation by pulse oximetry at rest (also monitor amount of supplemental oxygen if applicable)
- PS on ECOG scale (APPENDIX 1)

Cardiac evaluation
- Electrocardiogram (12 leads)
- Echocardiography (or multigated acquisition (MUGA) scan) at baseline
- In case of potential symptoms of myocarditis / pericarditis during study treatment (such as chest pain, shortness of breath, heart palpitations, and reduced tolerance to exercise), cardiac laboratory analyses (e.g.; creatinine kinase-myocardial band, troponin), ECG and echocardiography (or MUGA scan) will be requested. If abnormal findings indicate possible myo- or pericarditis, the patient will be referred to consulting a cardiologist.

Safety assessment (up to 100 days after last study treatment administration)
- All SAEs from ICF signature

- New AEs including worsening of pre-existing medical condition or signs/symptoms (e.g., worsening of arterial hypertension, worsening of pain) from C1D1
- Follow-up of all ongoing AEs

Concomitant medications and significant non-drug therapies (up to 100 days after last study treatment administration)

Laboratory evaluation (blood analyses)

- Hematology: complete blood cell (CBC) count including Red Blood Cells, hemoglobin, hematocrit, WBC and differentials, platelets
- Biochemistry: including liver function tests (ALT, AST, total bilirubin, alkaline phosphatase), BUN or serum urea level, uric acid, creatinine and creatinine clearance, Ca, Mg, Na, K, Cl, phosphate, LDH, glucose, amylase and lipase
- Troponin and D-dimers
- TSH, free T3, and free T4
- HIV and HCV serology; detection of HBs antigen
- Pregnancy test (for women of child bearing potential)

[redacted]

PD-L1 testing

Tumor tissue (fresh tumor sample or archived tissue collected within 3 months prior to start of study treatment at baseline). [redacted]

Tumor evaluation

- Efficacy assessments will be based on local evaluations according to RECIST 1.1.
- Patients should have at least one measurable lesion by CT-scan (minimum size not less than 10 mm). All target lesions (measurable) and non-target lesions (measurable or not) will have to be recorded and must be assessed using the same methods and techniques over the whole study period.
- Chest CT-scan (mandatory) and CT or MRI of the abdomen (and pelvis if lesion suspected) and brain (and other established assessments of tumor burden if CT/MRI imaging is insufficient for the individual patient). In case of bone pain, an adequate radiological and/or isotopical exploration is to be performed to research metastases.
- Tumor assessment will be performed within 28 days prior to start of study treatment. Patients will be evaluated every 6 weeks, with a time window allowed of +/-7 days, from start of treatment until documented progression or for a period of 9 months after start of study treatment, whichever occurs first. Beyond 9 months of treatment, the evaluations will be performed every 12 weeks until documented progression.

- For patients with brain metastases history, cerebral CT-scan or MRI should be performed every 12 weeks or sooner if clinically indicated.

Further antineoplastic therapies
All subsequent therapies given for cancer after the patient discontinued study treatment will be collected in the eCRF.

7.2. Baseline

The following evaluations must be performed within 28 days prior to the initiation of treatment:

- Inclusion/exclusion criteria check
- Physical examination of the major organ system, including weight, height, blood pressure (BP), heart rate (HR), temperature, and oxygen saturation by pulse oximetry at rest (also monitor amount of supplemental oxygen if applicable)
- PS on ECOG scale
- Demography
- History of studied disease
- Previous antineoplastic therapy (including chemotherapy neo/adjuvant, surgery and radiotherapy),
- Relevant medical history / current medical conditions and signs and symptoms
- TSH, free T3, and free T4
- HIV and HCV serology; detection of HBs antigen
- Echocardiography (or MUGA scan)
- [redacted]
- Serious adverse events reporting (from the date of signature of the ICF)
- Concomitant medications and significant non-drug therapies collection and medications administered during the month prior to C1D1
- Tumor evaluation
  - Chest CT-scan (with contrast)
  - Cerebral CT-scan or MRI (mandatory at baseline)
  - CT scan or MRI imaging of the abdomen (+/-pelvis) and other established assessments of tumor burden if CT/MRI imaging is insufficient for the individual patient. In case of bone pain, an adequate radiological and/or isotopical exploration is to be performed to research metastases
- [redacted] Results of the PD-L1 test performed using the Dako PD-L1 IHC 22C3 pharmDx assay kit on fresh tumor sample from biopsy or archived [redacted]

Note: tests performed per standard of care (e.g., CT-scan) prior to ICF signature may not need to be repeated if collected within 28 days prior to start of study treatment.

As far as possible, the test result for PD-L1 expression should be already obtained to confirm patient's eligibility for the trial prior further evaluations described below. In the event assessment of PD-L1 expression is not feasible , the patient will not be enrolled.
The following evaluations must be performed within 72 hours prior to the first dose:

- Inclusion/exclusion criteria check
- 12-leads Electrocardiogram
- Blood analyses:
  - Hematology: CBC count including Red Blood Cells, hemoglobin, hematocrit, WBC and differentials, platelets
  - Biochemistry: including LFTs (ALT, AST, total bilirubin, alkaline phosphatase), BUN or serum urea level, uric acid, creatinine and creatinine clearance, Ca, Mg, Na, K, Cl, phosphate, LDH, glucose, amylase and lipase
  - Troponin and D-dimers
  - Pregnancy test for women of childbearing potential

7.3. During the study treatment period

12 lead-ECG and any additional laboratory analyses (e.g, troponin) will be performed as clinically indicated. Patients who develop new pericardial effusion while on study must be followed by echocardiography (or MUGA scan).
For patients with brain metastases history, cerebral CT-scan or MRI should be performed every 12 weeks or as clinically indicated.

The time windows allowed for the visits are:

- +/- 1 day for the first 6 weeks of study treatment
- +/- 3 days for the further study treatment beyond the first 6 weeks

After Cycle 1 day 1, pre-dose laboratory procedures can be conducted up to 24 hours prior to dosing.
The time window allowed for tumor evaluation is +/-7 days.

7.3.1. Cycle 1

C1D1:

- Physical examination of the major organ system, including weight, blood pressure (BP), heart rate (HR), temperature, and oxygen saturation by pulse oximetry at rest (also monitor amount of supplemental oxygen if applicable)
- Performance status
- Adverse events reporting
- Concomitant medications and non-drug therapies collection

[redacted]

- TG4010 SC injection
- Nivolumab administration
- Chemotherapy (pemetrexed + platinum) administration

C1D8:

- Physical examination of the major organ system, including weight, blood pressure (BP), heart rate (HR), temperature, and oxygen saturation by pulse oximetry at rest (also monitor amount of supplemental oxygen if applicable)
- Adverse events reporting
- Concomitant medications and non-drug therapies collection
- Prior to study treatment administration
  - Hematology
  - Biochemistry
- TG4010 SC injection

C1D15:

- Physical examination of the major organ system, including weight, blood pressure (BP), heart rate (HR), temperature, and oxygen saturation by pulse oximetry at rest (also monitor amount of supplemental oxygen if applicable)
- Adverse events reporting
- Concomitant medications and non-drug therapies collection
- Prior to study treatment administration
  - Hematology
  - Biochemistry
- TG4010 SC injection

7.3.2. Cycle 2

C2D1:

- Physical examination of the major organ system, including weight, blood pressure (BP), heart rate (HR), temperature, and oxygen saturation by pulse oximetry at rest (also monitor amount of supplemental oxygen if applicable)
- Performance status
- 12-leads Electrocardiogram
- Adverse events reporting
- Concomitant medications and non-drug therapies collection
- Prior to study treatment administration
  - Hematology
  - Biochemistry
  - Troponin and D-dimers
  - [redacted]
- TG4010 SC injection
- Nivolumab administration
- Chemotherapy (pemetrexed + platinum) administration

C2D8:

- Physical examination of the major organ system, including weight, blood pressure (BP), heart rate (HR), temperature, and oxygen saturation by pulse oximetry at rest (also monitor amount of supplemental oxygen if applicable)
- Adverse events reporting
- Concomitant medications and non-drug therapies collection
- Prior to study treatment administration
  - Hematology
  - Biochemistry
- TG4010 SC injection

C2D15:

- Physical examination of the major organ system, including weight, blood pressure (BP), heart rate (HR), temperature, and oxygen saturation by pulse oximetry at rest (also monitor amount of supplemental oxygen if applicable)
- Adverse events reporting
- Concomitant medications and non-drug therapies collection
- Prior to study treatment administration
  - Hematology
  - Biochemistry
- TG4010 SC injection

[redacted]

7.3.3. Cycle 3

C3D1:

- Physical examination of the major organ system, including weight, blood pressure (BP), heart rate (HR), temperature, and oxygen saturation by pulse oximetry at rest (also monitor amount of supplemental oxygen if applicable)
- Performance status
- Adverse events reporting
- Concomitant medications and non-drug therapies collection
- Tumor evaluation for identified lesions as at Baseline. Additional CT or MRI may be performed if clinically indicated
- Prior to study treatment administration
  - Hematology
  - Biochemistry
  - Troponin and D-dimers
  - TSH (reflex T4)
  - Pregnancy test for women of childbearing potential

[redacted]

- TG4010 SC injection
- Nivolumab administration

- Chemotherapy (pemetrexed + platinum) administration

7.3.4. Cycle 4

C4D1:

- Physical examination of the major organ system, including weight, blood pressure (BP), heart rate (HR), temperature, and oxygen saturation by pulse oximetry at rest (also monitor amount of supplemental oxygen if applicable)
- Performance status
- Adverse events reporting
- Concomitant medications and non-drug therapies collection
- Prior to study treatment administration
  - Hematology
  - Biochemistry
  - Troponin and D-dimers
- TG4010 SC injection
- Nivolumab administration
- Chemotherapy (pemetrexed + platinum) administration

7.3.5. From Cycle 5 and Odd number cycles (Cycle 7, 9...)

D1:

- Physical examination of the major organ system, including weight, blood pressure (BP), heart rate (HR), temperature, and oxygen saturation by pulse oximetry at rest (also monitor amount of supplemental oxygen if applicable)
- Performance status
- Adverse events reporting
- Concomitant medications and non-drug therapies collection
- Tumor evaluation for identified lesions as at baseline is to be performed every 6 weeks for the first 9 months from start of study treatment, then every 12 weeks beyond 9 months of treatment. Additional CT or MRI may be performed if clinically indicated
- Prior to study treatment administration
  - Hematology
  - Biochemistry
  - TSH (reflex T4)
  - Pregnancy test for women of childbearing potential
- TG4010 SC injection
- Nivolumab administration (for up to 24 months maximum)
- Chemotherapy (pemetrexed in maintenance) administration

7.3.6. From Cycle 6 and Even number cycles (Cycle 8, 10...)

D1:

- Physical examination of the major organ system, including weight, blood pressure (BP), heart rate (HR), temperature, and oxygen saturation by pulse oximetry at rest (also monitor amount of supplemental oxygen if applicable)
- Performance status
- Adverse events reporting
- Concomitant medications and non-drug therapies collection
- Prior to study treatment administration
  - Hematology
  - Biochemistry
- TG4010 SC injection
- Nivolumab administration (for up to 24 months maximum)
- Chemotherapy (pemetrexed in maintenance) administration

7.4. End of treatment visit

This visit should be completed as soon as all the components of the study treatment are stopped. The following evaluations will be conducted:

- Physical examination of the major organ system, including weight, blood pressure (BP), heart rate (HR), temperature, and oxygen saturation by pulse oximetry at rest (also monitor amount of supplemental oxygen if applicable)
- Performance status
- Adverse events reporting
- Concomitant medications and non-drug therapies collection
- Hematology
- Biochemistry
- TSH, free T3, and free T4
- Pregnancy test for women of childbearing potential
- 12-leads Electrocardiogram
- [redacted]
- Subsequent cancer therapies reporting if applicable

7.5. Safety follow-up visits

This first safety follow-up visit should occur not less than 30 days after the last study treatment administration. The following evaluations will be conducted:

- Physical examination of the major organ system, including weight, blood pressure (BP), heart rate (HR), temperature, and oxygen saturation by pulse oximetry at rest (also monitor amount of supplemental oxygen if applicable)
- Adverse events reporting
- Concomitant medications and non-drug therapies collection
- Hematology

- Biochemistry
- Subsequent cancer therapies reporting if applicable

The second safety follow-up visit will occur not less than 100 days after the last study treatment administration. Same evaluations as for the first visit will be performed except laboratory analyses which will be performed only in case of abnormalities observed at the previous visit.

7.6. Post-study follow-up

For patients who stopped the study treatment for a reason other than progressive disease (e.g., AE), tumor evaluation should be obtained every 6 weeks until documented progression by RECIST *v*1.1 or for a period of 9 months after the start of study treatment. Beyond 9 months, the evaluations will be performed every 12 weeks until progression by RECIST *v*1.1. Tumor measurements will be recorded on the eCRF with the date and method of tumor assessment and the response evaluation. This follow-up should be done even if patients start subsequent cancer therapies.

Subsequent cancer therapies, given after end of study treatment will be reported on the eCRF with the start date and end date.

From the safety follow-up visit, the patient will be followed for survival every 3 months and up to 5 years or until death or until the date of last contact if the patient is lost to follow-up or withdraws consent for collection of long-term data (phone call is considered as a follow-up).

[redacted]

[redacted]

8. ASSESSMENT OF EFFICACY

The assessment of efficacy is based on Response Evaluation Criteria in Solid Tumors (RECIST) *v*1.1 [redacted]

For efficacy evaluation, patients must have at least one measurable lesion (excluding lesion used for biopsy) by CT/MRI scan (minimum size not less than 10 mm) at baseline and one valid post-baseline assessment. Each identified and reported lesion at baseline must be followed at subsequent evaluations.

Tumor assessment will be performed LOCALLY according to investigator's assessment every 6 weeks from the start of study treatment until documented progression or for a period of 9 months after start of study treatment, whichever occurs first. Beyond 9 months after start of study treatment, the evaluations will be performed every 12 weeks until documented progression. The same schedule of tumor evaluation will be applied for patients who stopped the study treatment for any reason other than progressive disease. The time window allowed for tumor evaluation is +/-7 days.

For all patients, tumor response assessment will be performed by CT scan or MRI (if MRI is used, chest CT-scan is mandatory) imaging of the chest/abdomen (+/-pelvis plus other regions as specifically required for specific tumor types) and other established assessments of tumor

burden if CT/MRI imaging is insufficient for the individual patient. All the scans performed at baseline and other imaging performed as clinically required (other supportive imaging) need to be repeated at subsequent visits. Brain CT-scan or MRI is required at baseline only. However, for patients with brain metastases history, cerebral CT-scan or MRI should be performed every 12 weeks or as clinically indicated.

[redacted]

Data of locally performed tumor evaluations will be used for efficacy assessment.
To assess objective response, the tumor burden at baseline will be estimated and used for comparison with subsequent measurements. At baseline, tumor lesions will be categorized in target and non-target lesions [redacted]

[redacted]

9. ASSESSMENT OF SAFETY

Safety assessments will consist of monitoring and reporting of all adverse events (AEs) and serious adverse events (SAEs), physical examination findings including vital signs and laboratory tests (see APPENDIX 2).

Adverse events / Adverse reactions
An ***Adverse Event (AE)*** is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation patient administered study treatment and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory finding), symptom, or disease temporally associated with the use of study treatment, whether or not considered related to the study treatment.

Adverse reaction (AR)
All noxious and unintended responses to a medicinal product related to any dose or to a study specific procedure.

The causal relationship to study treatment can be one of the following:
Related: There is a reasonable causal relationship between study treatment administration and the AE.
Not related: There is not a reasonable causal relationship between study treatment administration and the AE.
The term "reasonable causal relationship" means there is evidence to suggest a causal relationship.

9.1. Serious adverse events

A ***Serious Adverse Event (SAE)*** is any untoward medical occurrence that at any dose:

- results in death
- is life-threatening (defined as an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- requires inpatient hospitalization or causes prolongation of existing hospitalization (see NOTE below)
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the patient or may require intervention (e.g., medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.) Potential drug induced liver injury (DILI) is also considered an important medical event.

Suspected transmission of an infectious agent (eg, pathogenic or nonpathogenic) via the study drug is an SAE.
Although pregnancy, overdose and cancer are not always serious by regulatory definition, these events must be handled as SAEs. (see Section 9.69.6).

[redacted]

Suspected Unexpected Serious Adverse Reaction (SUSAR):

A SUSAR is any unexpected SAE considered as related to the study treatment or to a study specific procedure.
Expected adverse events are those adverse reactions that are listed or characterized in the reference document (e.g. Package Insert. or I.B).
Unexpected adverse reactions are those not listed in the reference document or not identified. This includes adverse events for which the specificity or severity is not consistent with the description in the reference document.

9.2. Immune-mediated adverse events

Immune-mediated adverse events (IMAEs) are AEs consistent with an immune-mediated mechanism or immune mediated component for which non-inflammatory etiologies (e.g., infection or tumor progression) have been ruled out. IMAEs can include events with an alternate etiology which were exacerbated by the induction of autoimmunity. Information suporting the assessment will be collected on the eCRF.

[redacted]

9.3. Time period for collection

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 an 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/ current 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 recorded in the Sponsor's safety database.

For screening failure patients (i.e. who signed the ICF but failed to be included), all SAEs will be collected and recorded in the Sponsor's safety database. See Section 9.6 for special situations.

9.4. Adverse event / Serious adverse event management

9.4.1. Data collection

Reporting in eCRF

At each visit, all AEs whether volunteered by the patient, discovered by study personnel during questioning, or detected through physical examination, laboratory test, or other means will be reported appropriately on the page "Adverse Events" of the eCRF (= AE page). The following items must be documented:

- nature of the event with self-explanatory and concise medical terminology (if possible indicate a diagnosis or syndrome instead of symptoms),
- date of onset and date of end (i.e. actual dates when the event starts and is resolved rather than dates when the Investigator is informed),
- intensity,
- evaluation of seriousness,
- relation to study treatment (separate evaluation for TG4010, nivolumab and chemotherapy), or to study procedures,
- action taken regarding the study treatment (separately for TG4010, nivolumab and chemotherapy),
- action taken regarding the event,
- outcome.

Every AE must be assessed by the investigator with regards to whether it is considered immune-mediated. For events which are potentially immune-mediated, additional information will be collected on the eCRF.

AE / AR requiring therapy must be treated with recognized standards of medical care to protect the health and well-being of the patient. Any treatment given will be reported on the page "Concomitant medication" of the eCRF.

Appropriate resuscitation equipment and medicines must be available to ensure the best possible treatment of an emergency situation.

[redacted]

Intensity

The intensity of AE/SAE will be graded according to the NCI-CTCAE (version 4.03) which will be provided to the Investigators.

Should an event be missing in the CTCAE, the following 5-point scale is to be used:

- Mild: Discomfort noticed, but no disruption of normal daily activity
- Moderate: Discomfort sufficient to affect normal daily activity
- Severe: Inability to work or perform normal daily activity
- Life-threatening: Risk of death at the time of the event
- Fatal: The patient died

The correspondence between the two scales is as follows:

CTCAE	5-point scale
1	Mild
2	Moderate
3	Severe
4	Life-threatening
5	Fatal

Any increase in severity category during the course of an adverse event should be reported on the AE pages of the eCRF with corresponding dates.

Causality

The relationship to the IMPs and/or chemotherapy (separate evaluation for TG4010, nivolumab and chemotherapy) of each AE/SAE will be evaluated by the Investigator with the "global introspection" method using the following levels:

- **Not related**: the temporal relationship of the clinical event to the administration of study treatments (separate evaluation) makes a causal relationship unlikely; and other drugs, therapeutic interventions or underlying conditions provide a sufficient explanation for the observed event.
- **Related**: the temporal relationship of the clinical event to the administration of the study treatments (separate evaluation) makes a causal relationship possible; and other drugs, therapeutic interventions or underlying conditions do not provide a sufficient explanation for the observed event. A clear-cut temporal association with improvement on cessation of the study treatments or recurrence upon rechallenge may also be observed.

Outcome

The outcome is rated as follows:

- recovered,
- not recovered,

- recovered with sequelae
- fatal,
- unknown,

Note on "fatal": this outcome is to be used only for the event leading to death. The outcome of all other events at the time of the death must be reported. The outcome of ongoing ones is reported as "not recovered".

Action taken regarding the IMPs (TG4010, nivolumab) and chemotherapy
Action taken will be provided separately for each study treatment.

- None: administration continues as planned in the protocol, or has not yet been administered and no action is planned
- Delayed/cancelled: administration following the occurrence of the event is delayed (or cancelled for IMPs if chemotherapy is not delayed)
- Dose changed: the dose administered is not as planned per protocol (applicable only for chemotherapy)
- Stopped: administration is definitively stopped
- Not applicable: administration is already stopped (or study treatment not started yet)

Action taken regarding the event:

- New treatment prescribed or change in concomitant medication
- Hospitalization or prolongation of hospitalization
- Non-drug therapy implemented
- None
- Other (to be specified)

9.4.2. Follow-up

Once an AE is detected, it must be proactively followed until its resolution or 100 days after the last study treatment administration.
However, the AEs listed below must be followed until they are resolved or stable or returned to baseline status, which may occur after the safety follow-up visit planned by the protocol:

- AE evaluated as related to the IMP(s)
- SAEs
- Any other significant AE as recommended by Transgene

Transgene or its representative reserves the right to ask for further information on any AE/SAE that may be considered of interest or when the event is not previously documented in the IB (new occurrence) or Package Insert and is thought to be related to the IMP(s).

9.4.3. Documentation

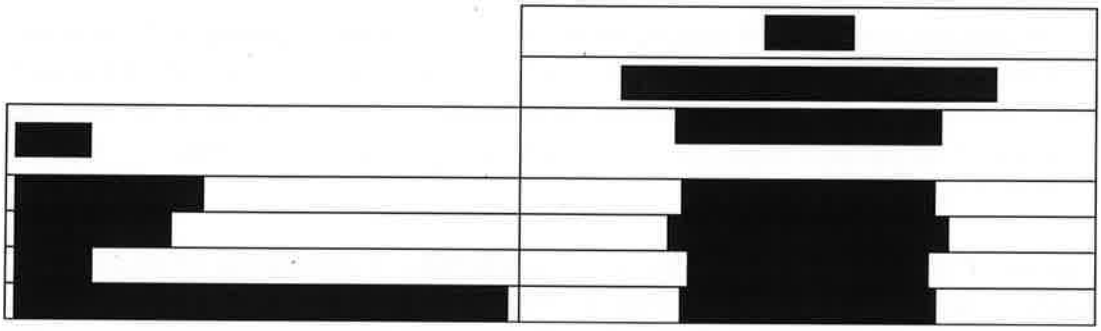
All AEs/SAEs will be reported in the source document with at least the nature, the date of onset and end, the causality, and the treatment (if applicable).

Copies of SAE form will be filled in the Investigator Site File along with copies of any correspondence with the Independent Ethics Committee (IEC) / Institutional Review Board (IRB). The Investigator Site File will also include copies of notification letters and/or faxes with forms sent to Health Authorities and Gene Therapy Bodies if appropriate.

9.5. Serious Adverse Event / Serious Adverse Reaction / Suspected Unexpected Serious Adverse Reaction notification

Reporting to Transgene

Any SAE occurring during the course of the study (from the signature of ICF and up to 100 days after last study treatment administration whether or not related to the IMP(s) / other study treatments MUST be reported to Transgene. The Investigator must complete and send (preferably by email otherwise by fax) a "Serious Adverse Event Form" to Transgene within 24 HOURS of occurrence or knowledge of the event.



An Investigator's designee may complete the SAE form; however, the Investigator must sign it. The form can be sent to Transgene with the designee's signature if the Investigator's signature cannot be obtained within one working day. The Investigator's signature must be obtained as soon as possible, as well as his/her evaluation of the relationship to the study treatment (IMP(s) and chemotherapy if applicable). The signed form must be sent (preferably by email otherwise by fax) to Transgene immediately.

The SAE form should be completed in English.

Follow-up information (e.g., complications or progression of the initial SAE) must be notified to Transgene by the Investigator within the same time frame as the occurrence by using a new "SAE form" with the box "follow-up" ticked and sent to the Transgene.

The follow-up information should describe whether the event has resolved or continues, if and how it was treated and whether the patient continued or withdrew his/her consent.

Transgene or its representative may request further information as needed.

All SAEs will be followed to resolution or stabilization.

Notification to Regulatory Authorities / Gene Therapy Bodies / Ethics Committee

The Sponsor or its representative will be responsible for reporting of SUSAR and any other SAEs to Regulatory Authorities, IEC(s) / IRB(s) and Gene Therapy Bodies as per local regulation. In case of a SUSAR, the Sponsor or its representative will inform all investigators

involved in the study that such an event has been reported. The Investigator is responsible for informing local Ethics Committee of SUSARs, any other SAEs, and any follow-up information as per local regulations.

9.6. Special situations

Serious Adverse Reactions related to-non IMPs (chemotherapy)
There is no need for the Sponsor to report as SUSARs adverse reactions related to the chemotherapy (considered as a non-IMP) received by the subject and without interaction with the IMP.

Pregnancy
Study treatments must be discontinued immediately when a patient becomes pregnant.
The occurrence of a pregnancy must be handled as a SAE and reported to Transgene by the Investigator within 24 HOURS using a "Pregnancy form":

- The first part of the form is used to collect information at the beginning of the pregnancy. It should be completed and reported as soon as possible and within 24 hours of knowledge
- The second part of the form is to collect information about the outcome of the pregnancy. It should be reported within the same time frame and even if the patient was withdrawn from the study

Pregnancies have to be followed up to the completion or termination of the pregnancy, collecting information about the pregnancy and knowledge of the new-born medical status. Pregnancy outcomes must be collected for the female partners of any males who took the IMP(s). Consent to report information regarding these pregnancy outcomes should be obtained from the mother.
Pregnancy itself is not considered as an AE. However, any problem met during the pregnancy should be reported as an AE or a SAE. Spontaneous or induced abortions as well as ectopic pregnancy should be considered as serious. Similarly, any congenital anomaly/birth defect in a child born to a female patient exposed to anyof the IMPs should be reported as an SAE.
The time period for collecting new pregnancies is from the first administration of the IMP(s) up to 5 months after the last study treatment administration for female patients and up to 7 months after the last study treatment administration for male patient's partner.

Overdose
An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important.
For this study, any dose of IMP greater than the assigned dose, and considered excessive and medically important by the Investigator, will be considered an overdose.

All occurrences of overdose must be reported as SAEs (see Section 9.5).
In the event of an overdose, the Investigator or treating physician should:

- Contact the Medical Monitor immediately
  - Closely monitor the participant for AEs/SAEs and laboratory abnormalities until the corresponding drug can no longer be detected systemically

- Obtain a plasma sample for PK if requested by the Medical Monitor (determined on a case by case basis)

- Document the quantity of the excess dose as well as the duration of the overdosing in the eCRF

[redacted]

[redacted]

Other safety considerations

Any significant worsening noted during interim or final physical examinations, electrocardiogram, x-ray filming, any other potential safety assessment required or not required by protocol should also be recorded as a nonserious or serious AE, as appropriate, and reported accordingly.

9.7. Laboratory values, vital signs, physical findings and other safety data

Laboratory tests results will be recorded on the laboratory results forms of the eCRF.
Clinically relevant abnormal laboratory or tests results, clinically relevant abnormal findings in vital signs measurements, physical examinations or ECGs will be reported by the Investigator and followed until normal, stabilization or back to baseline value or until the safety follow-up visit if they are not related to IMP(s). If related to IMP(s), they should be followed even after the safety follow-up visit (see Section 9.4.2).
Any laboratory result abnormality fulfilling the criteria for a serious adverse event (SAE) should be reported as such, in addition to being recorded as an AE on the eCRF.

Any treatment-emergent abnormal laboratory result which is clinically significant, i.e., meeting one or more of the following conditions, should be recorded as a single diagnosis on the adverse event form in the eCRF:

- accompanied by clinical symptoms
- leading to a change in study medications (e.g. interruption or permanent discontinuation)
- requiring corrective treatment or clinical management

10. STATISTICAL METHODS PLANNED AND SAMPLE SIZE

10.1. Data sets analyzed

Full Analysis Set (FAS): all patients included and 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.

Safety Analysis Set (SAF): consists of all patients entered into the study who received at least one dose of IMP (TG4010, nivolumab).

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

Evaluable Patients' Population for tumor response (EPP): consists of all patients without major protocol deviation and have at least one baseline and one post-baseline evaluable CT- after study treatment start except early disease progression and death due to lung cancer. The evaluable patients' population will be the primary population for efficacy analyses.

10.2. Determination of sample size

With a one-sided 0.05 alpha level, a total of 35 evaluable subjects would provide approximately 80% power in order to detect a response rate of 50% versus 30% with a proportion test [redacted]

10.3. Study endpoints

10.3.1. Primary endpoint

Objective Response Rate (ORR), defined as the number of patients whose best overall response is either CR or PR according to RECIST v1.1 divided by the number of patients in the set of 'evaluable patients' population for tumor response (or FAS as appropriate).
Best Overall Response (BOR) per RECIST v1.1 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 subjects without documented progression or subsequent therapy, all available response designations should contribute to the BOR assessment.

10.3.2. Secondary endpoints

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.
- [redacted]Disease control rate (DCR): proportion of patients whose best overall response is either CR, PR, or stable disease (SD). [redacted]
- Overall Survival (OS): time from the first study drug administration to the date of death due to any cause.

- 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.
- Safety: the assessment of safety of the combination will be based mainly on the frequency of AEs, SAEs, AEOSI, IMAE and on the number of laboratory values that fall outside of predetermined ranges. Other safety data (e.g., ECG, vital signs) will be considered as appropriate.

[redacted]

10.4. Statistical and analytical plans

10.4.1. Efficacy analyses

The analyses of the efficacy endpoints will be performed on the EPP. As supportive analyses, these analyses will be repeated in the FAS. The primary analysis of efficacy will be based on the RECIST *v*1.1.

- **Objective Response Rate (ORR)**

ORR is defined as the number of patients whose best overall response is either CR or PR, according to RECIST *v*1.1, divided by the number of patients in the considered set of patients' population (EPP or FAS). Proportions of patients with a best overall response of CR or PR will be presented with corresponding 90% confidence interval based on Normal approximation. In addition, p-value for testing the RECIST 1.1 ORR is greater than the historical control will be provided using proportion test. Patients with best overall response "Not evaluable" will be counted as non-responder.

Patients with best overall response 'not evaluable' will be summarized by reason for being Not evaluable. Analyses of ORR will be performed after a follow-up of at least 18 weeks.

- **Progression Free Survival (PFS)**

PFS (in months) is defined as the 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. PFS will be censored if no progression or death is observed at the cut-off date for analysis, or at the date when a subsequent cancer therapy (other than those planned in the protocol) is started. The censoring date will be the date of the last evaluable tumor assessment or the date of last visit without progression before the cut-off date or start of subsequent cancer therapy.

PFS will be presented descriptively using Kaplan-Meier curves. Summary statistics from the Kaplan-Meier distributions will be determined, including median PFS and 25% and 75% quartiles with corresponding 95% confidence intervals (CIs). The proportions of patients remaining progression-free at 6, 9 months and 12 months, along with 95% CIs will also be provided. In addition, given the expected delayed response due to the mechanism of action of the study treatment, restricted mean PFS time will also be calculated.

- **Disease Control Rate (DCR)**

Disease control rate (DCR) is defined as the proportion of patients whose best overall response is either CR, PR, or stable disease (SD).

- **Overall Survival (OS)**

OS is defined as the time from the date of the first study drug administration to the date of death due to any cause. If a patient is not known to have died, survival will be censored at the date of last contact.
OS will be summarized by treatment arm. A Kaplan-Meier curve will be constructed. Median OS and 25% and 75% quartiles will be presented along with 95% CIs. In addition, the Kaplan-Meier estimates with 95% confidence intervals at 12, 18 and 24 months will be presented. In addition, given the expected delayed response due to the mechanism of action of the study treatment, restricted mean survival time will also be calculated.

- **Duration of Response (in case of CR or PR)**

Duration of response in months (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 event defined as first documented disease progression or death due to lung cancer. If no progression has been observed at the cut-off date of analysis or at the date when a subsequent cancer therapy is started, DoR will be censored at the date of the last evaluable tumor assessment before the cut-off date or before the start of subsequent cancer therapy, whichever occurs first.

A Kaplan-Meier curve of DoR will be constructed. Median DoR, 25% and 75% quartiles, will be presented along with 95% confidence intervals for each treatment arm. In addition, the Kaplan-Meier estimates with 95% confidence intervals at 3, 6, and 9 months will be presented.

10.4.2. Safety analyses

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. For the first 6 patients, safety analyses will be based on the SET. Safety data will be reviewed by an IDMC.

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.

Adverse Events

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.

All AEs, significant AEs, AEs leading to discontinuation of study treatment (overall and by component: TG4010, nivolumab, and chemotherapy), severe AEs (Grade 3 or 4) and serious AEs (SAE), IMAEs or AEs of special interest (AEOSI) (e.g., injection site reactions) will be listed and summarized by System Organ Class (SOC) and Preferred Term (PT), intensity (based on the NCI-CTCAE grades, also referred as CTCAE), relationship to study treatment (TG4010 / nivolumab / chemotherapy).

AEs will be summarized by presenting the number and percentage of patients having at least one AE. Data will be presented by SOC and PT using MedDRA coding. A patient with multiple occurrences of an AE will be counted only once in the AE category.

Separate AE summaries will be presented by SOC, PT, and maximum CTCAE grade. A patient with multiple grades for an AE will be summarized under the maximum CTCAE grade recorded for the event. In the summaries presented by grade, all AEs will be pooled.

Specific tables will summarize related AEs to IMP or to other study component, IMAEs and AEOSI (e.g; injection site reactions).

The frequency of CTCAE Grade 3 and 4 AEs will be summarized separately.

Written narratives will be produced for all SAEs and unexpected or other significant AEs that are judged to be clinically relevant.

Adverse events/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.

Fatal Events

All fatal events will be listed and summarized by SOC and PT. The nature of the event leading to death should be recorded. Sudden/unexplained death will be coded as "death".

Fatal events will be summarized by presenting the number and percentage of patients who died. Data will be presented by SOC and PT using MedDRA coding.

Fatal events occurring after signing the Inform Consent Form (ICF) but before starting study treatment, including those observed in patients included but never treated with the IMPs, will be listed separately from those occurring after treatment start.

Laboratory abnormalities

The summaries 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.

All laboratory values will be converted into SI units and will have a severity grade calculated using appropriate common terminology criteria for AEs (NCI-CTCAE, version 4.03). A listing of laboratory values will be provided by laboratory parameter and patient. A separate listing will display notable laboratory abnormalities (i.e., newly occurring CTCAE Grade 3 or 4 laboratory toxicities). The frequency of these notable laboratory abnormalities will be displayed by parameter. The shift tables using CTCAE grades to compare baseline to the worst post-baseline value will be produced for all relevant safety measures as described in the statistical analysis plan. Note that for parameters with two directions abnormalities (hypo/hyper), two tables will be presented.

Other safety data

Other safety data (e.g., vital signs, electrocardiogram) will be listed, notable values will be flagged, and any other information collected will be listed as appropriate. Any statistical procedures performed in order to explore the data will be used only to highlight any interesting comparisons that may warrant further consideration.

[redacted]

10.5. Methods of analysis

10.5.1. General considerations

Statistical summaries will be produced using SAS® software version 9.4 or higher. Continuous variables will be described using the number of observations (N), arithmetic mean (Mean), standard deviation (SD), minimum (MIN), median (Median), and maximum (MAX). Means will be further described with 95% confidence intervals (CIs) when appropriate. Categorical variables will be summarized by frequency (N) and percentage (%). Proportions will be estimated with their 95% CIs when appropriate.

10.5.2. Disposition of patients

The number of screen failure patients and reasons for screen failure will be summarized. A patient listing will be provided with the reason of screen failure.
The disposition data will be presented by patient in data listings and in a summary table on:

- Number of patients included
- Number of patients included in each population: FAS, SAF, SET, EPP
- Number of patients excluded from the populations and reasons for exclusion
- The number of patients who discontinued IMP(s) and reasons for discontinuation
- Number of patients who discontinued all study treatments and reasons for discontinuation

10.5.3. Demographic and baseline characteristics

Baseline demographics and disease characteristics data will be listed and summarized. Qualitative data (e.g., gender, PS, smoking status) will be summarized by means of contingency tables, and quantitative data (e.g., age and body weight) will be summarized by appropriate descriptive statistics (mean, standard deviation, median, minimum, and maximum).
Summaries will be provided overall for the FAS and for key subpopulations, i.e. SAF and EPP.

10.5.4. Treatments

10.5.4.1. Prior anti-cancer therapies

Prior antineoplastic therapies will be listed and summarized (surgery, radiotherapy, chemotherapy neo/adjuvant for early stage). The FAS will be used for all summaries and listings of prior anti-cancer therapies.

10.5.4.2. Study treatments

Exposure to TG4010, will be provided by listing and summarizing the number of injections and the duration of treatment.
Exposure to nivolumab will be provided by listing and summarizing the number of infusions, the cumulated dose and the duration of treatment.
The SAF will be used for all summaries and listings of study treatment.
The number of patients with dose omission / dose delay will be presented by study treatment component , along with reasons for the dose omission.

[redacted]

10.5.4.4. Subsequent cancer therapy

All subsequent cancer therapies given after discontinuation of study will be collected with their start date and end date. They will be coded using WHO Drug dictionary including the ATC classification and listed and summarized by active ingredient by means of frequency counts and percentages using the SAF and EPP.

10.6. Protocol deviations

Any protocol deviation will be discussed with the Investigator on a case by case basis and tracked in a deviations log.
Major and minor protocol deviations at study entry and during the study will be described in the statistical analysis plan in order to determine the eligible population.

11. CHANGES IN THE CONDUCT OF THE STUDY

Changes to this protocol will be effected through amendments issued by Transgene after mutual agreement of the Investigator(s) and Transgene. Both the Investigator(s) and Transgene will sign the amendments. When applicable, amendments are submitted to Health Authorities and the Independent Ethics Committee (IEC(s) and any other committees by Transgene or the sub-contractor or the Coordinating / Principal Investigator according to local regulations.

Authorization / approval will be required before implementation of any change to the protocol which could significantly affect the safety of patients, the scope of the investigation, the scientific quality of the study or any other aspect of the study. Other changes will be provided when required by local laws to IEC(s) and any other committees for information only.

An amendment intended to eliminate an apparent immediate hazard to patients may be implemented immediately. Such an amendment must be notified as soon as possible to Regulatory Authorities IEC(s) and any other committees as locally required for authorisation / approval.

12. ETHICAL CONSIDERATIONS

12.1. Independent Ethics Committee/Institutional Review Board

Before starting the study, the protocol, the written patient information sheet and informed consent form, and any other document specifically requested must be reviewed and approved by an IEC complying with the requirements of relevant local law.
Before enrollment of patients, Transgene must obtain from the IEC(s) / IRB(s)

- A written authorization / approval,
- The list of members having participated in the meeting including their qualification

In addition, IEC written approval must be obtained by Transgene for protocol amendment as described in Section 11.

12.2. Informed consent

The Investigator or his/her delegate will obtain a voluntary written consent from each patient after an appropriate explanation of the aims, methods, anticipated benefits, risks and any other aspect of the study relevant to the patient's decision to participate. Consent forms and all verbal study related information must be in a language fully comprehensible to the prospective patient. Patients will be informed that they are free not to participate in the study and that they may withdraw consent to participate at any time. They will be told which alternative treatments are available if they refuse to take part and that such refusal will not prejudice future treatment.
Patients will be informed that their records, including medical history, may be examined by competent authorities and authorized persons but that personal information will be treated as strictly confidential and will not be publicly available.

A written "patient information sheet" will be given to each patient to complete the verbal information. This written form should be reviewed orally with the patient. Patient must be given ample opportunity to inquire about details of the study.
The "patient information sheet" will explain that the data collected for this study will be stored in a computer database, with confidentiality maintained in accordance with national data legislation. All data computer processed will be identified by patient initials and number only.

Informed consent shall be documented by the use of a written consent form approved by the IEC and signed and dated by the Investigator and the patient before any exposure to a study-related procedure, including screening tests for eligibility. Any new version of the ICF will be signed by all ongoing patients.

Should a patient start with the study treatment more than one month after having signed the informed consent form, whatever the reason, it would be ethical to ask him/her to reconfirm his/her willingness to participate to the study by signing a new consent form.
A copy of each signed informed consent form must be given to the patient and to his/her legally authorized representative. The originals are filed at the study site in the Investigator Site File.

12.3. Confidentiality of patient data

The Investigator must assure that patients' anonymity is maintained and that their identities are protected from unauthorized parties. On eCRFs or other documents collected by Transgene or its representative, patients should not be identified by their names, but by an identification code system.
The Investigator should keep a patient identification log showing codes, names and addresses of all patients consented. A copy of this log without names and addresses will be filed at Transgene after study completion.

13. REGULATORY CONSIDERATIONS

This study will be conducted in accordance with:

- The updated Declaration of Helsinki adopted by the World Medical Association,
- The ICH (International Conference on Harmonization) Good Clinical Practice (GCP) guidelines, and
- The local regulatory requirements.

13.1. Regulatory approval / authorization

The regulatory authorization / approval for conducting the study will be obtained from Regulatory Authorities in accordance with local regulatory requirements. Additional authorizations / approvals will be obtained from the national gene therapy and viral safety committees, as required. All approvals must be obtained before a patient is exposed to a study-related procedure, including baseline screening tests for eligibility.

13.2. Investigators' obligations

Before the study starts, the Investigator shall provide Transgene with his/her curriculum vitae and complete a list giving the names, functions and authorized activities of all persons who will exercise any kind of responsibility in carrying out of the study. CVs of these people will also be collected.
The Investigator also provides to the site staff appropriate training. The staff training will be documented in the Investigator Site File.

The Investigator ensures the quality of the study through strict observance of the protocol, Good Clinical Practice and local regulations. Investigator must ensure that the study has been authorized / approved by all Regulatory Authorities, IEC and any other committees prior to enrolling patients and on an ongoing basis as locally required.

Investigator is required to obtain written informed consent from each patient prior a patient is exposed to a study-related procedure, including baseline screening tests for eligibility.

13.3. Insurance

Transgene certifies having taken out a civil liability insurance policy covering liability with regard to the participants in this study.

14. QUALITY CONTROL AND QUALITY ASSURANCE

14.1. Periodic monitoring

The monitor will contact and visit the Investigator periodically to evaluate study progress and protocol compliance. For this study, the average frequency of the monitoring visits is intended to be approximately every 6 weeks with the first visit occurring as soon as possible after the first patient inclusion. Intervals may be adjusted according to patient accruals, protocol changes or site performance.

The Investigator and any study staff member will co-operate with the monitor to ensure that any problems are resolved.

14.2. Audit and inspection

The main purposes of an audit or inspection are to confirm that the rights and well-being of the patients have been adequately protected, and that all data relevant for the evaluation of the IMP have been processed and reported in compliance with GCP and applicable regulatory requirements.
The sponsor is responsible for making sure that both his representatives (monitor, clinical research assistant) and the investigator fulfil their requirements as specified by the GCP guidelines. The audit can be made internally at Transgene and at the investigational site or at the Services Provider. Possibility to have a direct access to all study documentation is compulsory. The practical conditions for the audit will be discussed between the investigator and the Clinical Quality Assurance Department.
The Health Care Authorities may inspect any investigation site or the sponsor during the course of the study or following its completion, to verify the conduct of the study and quality of the data. The investigator will provide direct access to source documents.
After appropriate notification, the Investigator will make all study-related source data and documents available to a quality assurance auditor mandated by Transgene, or to domestic or foreign regulatory inspectors.

15. DATA HANDLING AND RECORD KEEPING

15.1. Source data and documents

Source data are all information available in original source document or certified copies of source document of any clinical findings, observations, or other activities that are necessary for the reconstruction and evaluation of the study.

The Investigator will record at least the following information in the source documents for all consented patients: date of birth, gender, medical history, reference to the study, visit dates, study treatments administrations, concomitant medications, evaluation criteria and nature of adverse events with date of start and end and relationship to study treatments. The location of each source data will be identified on a dedicated form.

When computerised systems are used in the original recording of data, the following criteria should be met:

- documented evidence that the computer system has been validated,
- the system provides adequate security to ensure that only authorized persons can enter/change data and allows audit trail of entries / changes,
- existence of procedure for manual data entry in case of system break down,
- if no electronic signature is in place, the Investigator agrees to print out data periodically and to sign the printouts, and
- when possible, compliance with CFR part 11.

The Investigator will permit study-related monitoring, audit(s), and regulatory inspection(s), with a direct access to all the required source documents each time it is necessary provided that patient confidentiality is protected.

15.2. Case report forms

Electronic Data Capture (EDC) will be used for this study, meaning that all CRF data will be entered in electronic forms at the investigational site for each screened patient.
All data must be entered in English.
The eCRFs should always reflect the latest observations on the patients participating in the study. Therefore, the eCRFs are to be completed as soon as possible after the patient's visit. The Investigators must verify that all data entries in the eCRFs are accurate and correct. If some assessments are not done, or if certain information is not available, not applicable, or unknown, the Investigators should indicate this in the eCRF. The Investigators will be required to electronically sign off the all clinical data collected.

The Monitors will review the eCRFs and evaluate them for completeness and consistency. The eCRF will be compared with the source documents to ensure that there are no discrepancies.
All entries, corrections, and alterations are to be made by the Investigator or his/her delegate. Once clinical data have been submitted, corrections to the data fields will be audit trailed, meaning that the reason for change and the name of the person who performed the change, together with time and date, will be logged. Roles and rights of the site personnel responsible for entering the clinical data into the eCRF will be determined in advance and documented on the "delegation form".
If additional corrections are needed, the Monitors, Data Manager(s) or authorized Transgene's medical monitors will raise a query in the EDC application.

After database lock, the Principal Investigator will receive a CD-ROM/DVD of the patient data for archiving at the investigational site.

16. CLINICAL STUDY REPORT AND PUBLICATION

16.1. Clinical study report

All relevant data will be reported in a clinical study report which will be prepared by Transgene/CRO and submitted for comments and signature to the coordinating / principal Investigator. The final report is used for regulatory purposes by Transgene according to local regulations and provided to each Investigator once finalized.

16.2. Confidentiality of study data

Any information provided by Transgene, including nonclinical data, protocols, eCRFs, verbal and written information, and results of the study will be kept strictly confidential and confined to the clinical personnel involved in conducting this study, and no disclosure shall be made except in accordance with any right of publication granted to the Investigator by Transgene.

16.3. Publication policy

The results of this study may be published or presented at scientific meetings. If this is envisaged, the coauthors agree to submit all manuscripts or abstracts to Transgene prior to scientific meeting or journal submission allowing for reasonable time to review, consistent with Transgene policy. This allows the sponsor to protect proprietary information and to provide medical/scientific review. For intellectual property protection purposes, Transgene can request the coauthors to delay publication or presentation of results.

Consistent with Good Publication Practices (GPP2), authorship is to follow the criteria outlined by the International Committee of Medical Journal Editors (ICMJE), and/or follow the policies outlined by the journal or scientific congress. Financial support for medical writing assistance or travel provided to the authors is also to be acknowledged.

In accordance with consistent editorial practice, Transgene supports the publication of primary study results from multicenter studies in their entirety prior to any secondary analyses. Publication of individual center data unless ancillary study / data is discouraged. A publication in which the contribution of the sponsor's personnel exceeded that of conventional monitoring will be considered for co-authorship provided all other criteria of ICMJE are met.

17. ARCHIVING

17.1. Investigator site file

In accordance with the ICH GCP standards, the Investigator is responsible for on-site storage and maintenance of all records pertaining to the study for the maximum period of time required by local requirements.

No study site document may be destroyed without prior written agreement between the Investigator and Transgene. Transgene must be notified if the Investigator assigns the study documentation to another party or moves it to another location.

If the Investigator cannot guarantee this archiving requirement on site for any or all of the documents, special arrangements must be made between the Investigator and Transgene to store the documents in a sealed container off-site so they can be returned sealed to the Investigator in case of an audit/inspection.

17.2. Trial master file

Transgene will archive the trial master file (TMF) in accordance with GCP and applicable regulatory requirements, and will inform the Investigator when the archiving of the study documentation is no longer required.

[redacted]

[redacted]

[redacted]

19. APPENDICES

APPENDIX 1: PERFORMANCE STATUS (ECOG) SCALE

0: Fully active, able to carry on all pre-disease performance without restriction.

1: Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g. light house work, office work.

2: Ambulatory and capable of self care but unable to carry out any work activities. Up and about more than 50% of waking hours.

3: Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.

4: Completely disabled. Cannot carry out any self-care. Totally confined to bed or chair.

APPENDIX 2: STUDY FLOW-CHART

	Baseline		Cycle 1			Cycle 2			Cycle 3	Cycle 4	Cycle 5 and beyond (Q 3 weeks)	End of treatment visit (EOT)	Safety follow-up visit 1	Safety follow-up visit 2	PFS-FU visit [h]	OS-FU [i]
Study days	-28 / 0	-3 / 0	C1 D1	C1 D8	C1 D15	C2 D1	C2 D8	C2 D15	C3 D1	C4 D1	From C5D1		EOT + 30 days	EOT + 100 days		
Administration TG4010			↘	↘	↘	↘	↘	↘	↘	↘	↘					
Administration Nivolumab			X			X			X	X	X					
Pemetrexed + Platinum			X			X			X	X						
Pemetrexed in maintenance if applicable											X					
Demography, history of studied disease, relevant medical history / current medical conditions and signs and symptoms [b]	X															
Eligibility criteria check	X	X														
Physical examination[a]	X		X	X	X	X	X	X	X	X	X	X	X	X		
Performance status	X		X			X			X	X	X	X				
ECG [j]		X				X						X				
Echocardiography [j,k]	X															
Adverse events reporting	X[e]		X	X	X	X	X	X	X	X	X	X	X[f]	X[f]		
Concomitant medications and significant non-drug therapies collection	X[b]		X	X	X	X	X	X	X	X	X	X	X[f]	X[f]		
Tumor evaluation (RECIST 1.1)[g]	X		every 6 weeks (± 7 days) up to 9 months then every 12 weeks until disease progression or lost to follow-up or withdrawal of consent													
Subsequent cancer therapies												X	X	X	X	X
Hematology		X		X[c]	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]	X	X	X[p]		
Biochemistry [n]		X		X[c]	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]	X	X	X[p]		
Troponin & D-dimers [l]		X				X[c]			X[c]	X[c]						
Free T3, free T4, TSH	X								X[c,o]		X[c,d,o]	X				

	Baseline		Cycle 1			Cycle 2			Cycle 3	Cycle 4	Cycle 5 and beyond (Q 3 weeks)	End of treatment visit (EOT)	Safety follow-up visit 1	Safety follow-up visit 2	PFS-FU visit [h]	OS-FU [i]
Study days	**-28 / 0**	**-3 / 0**	**C1 D1**	**C1 D8**	**C1 D15**	**C2 D1**	**C2 D8**	**C2 D15**	**C3 D1**	**C4 D1**	**From C5D1**		**EOT + 30 days**	**EOT + 100 days**		
HIV and HCV serology; detection of HBsAg	X															
Pregnancy test		X [l]							X		X [d]	X				
[redacted]			■													
[redacted]			■			■			■							
[redacted]	■							■				■				

[a] Physical examination including: weight, height (only at baseline),blood pressure (BP), heart rate (HR), temperature, and oxygen saturation by pulse oximetry at rest (also monitor amount of supplemental oxygen if applicable)
[b] From the date of signature of the ICF and before first study treatment administration for medical history, current medical conditions, signs and symptoms
[c] To be performed prior to study treatment administration
[d] Every 6 weeks
[e] From first study treatment administration except for SAE which must be collected from signature date of the ICF
[f] Occurred within 30 days after the last study treatment administration for safety follow-up visit 1 and 100 days after the last study treatment administration for SFU visit 2
[g] Includes: chest and abdominal (and pelvis if lesion suspected) CT scan (mandatory for chest) or MRI every 6 weeks for 9 months and thereafter every 12 weeks; cerebral CT scan or MRI (mandatory at baseline. For patients with brain metastases history, cerebral CT-scan or MRI should be performed every 12 weeks or sooner if clinically indicated).
[h] For patients who discontinued study treatment before progressive disease (every 6 weeks for 9 months from treatment start and every 12 weeks thereafter).
[i] Long-term follow-up for survival, every 3 months after the safety follow-up visit or last PFS follow-up visit (may be performed by phone contact) up to 5 years
[j] And as clinically indicated
[k] Patients who develop new pericardial effusions while on study must be followed by echocardiography (or MUGA scan).
[l] To be performed within 72 hours prior to first study treatment administration
[redacted]
[n] Includes the following: liver function tests (ALT, AST, total bilirubin, alkaline phosphatase), BUN or serum urea level, uric acid, creatinine, creatinine clearance, Ca, Mg, Na, K, Cl, phosphate, LDH, glucose, amylase and lipase at baseline, every week during the first 6 weeks, then prior to each dose of study drug every 3 weeks, at the end of treatment visit and at the safety follow-up visit
[o] TSH (reflex T4) only during the study treatment period
[p] To be performed in case of abnormalities at the previous safety follow-up visit
[redacted]

Time window for tumor evaluation: +/- 7 days
Time windows for visits: +/- 1 day for cycle 1 and 2, and +/- 3 days from cycle 3.

[redacted]

[redacted]

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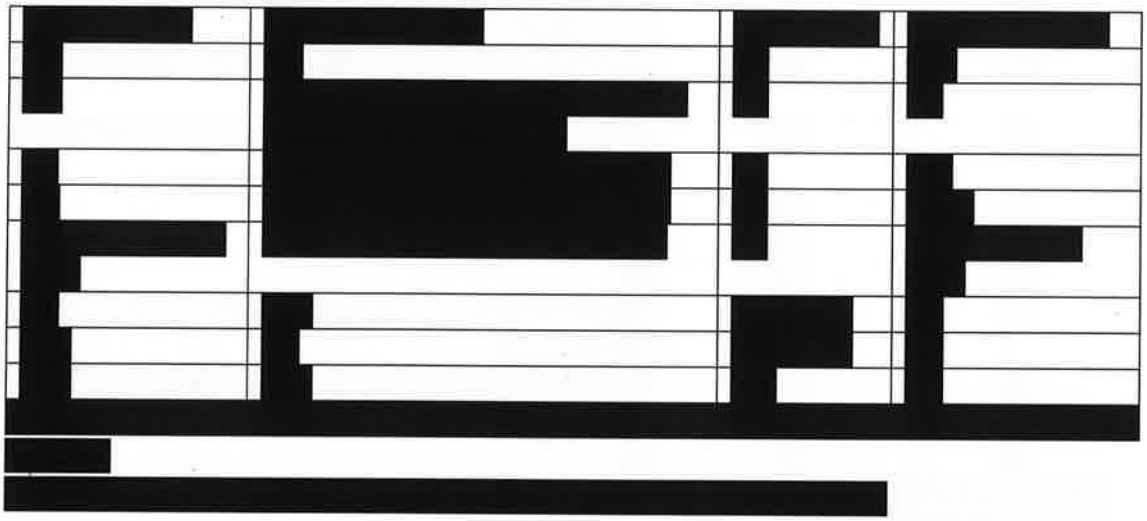
[redacted]



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