Clinical Study Protocol

CONFIDENTIAL

A phase I trial evaluating a mutanome-directed immunotherapy in patients with high grade serous carcinoma (HGSC) of the ovary, fallopian tube or peritoneum who experience an asymptomatic relapse

Study phase: I

PROTOCOL N° TG4050.01
Version 9.0 / 12 September 2023

EudraCT N°: 2018-003266-14

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During the study, if applicable, the administrative structure will be updated in the Investigator Site File and in Transgene files.

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Previous Electronic Signatures:

There are no signatures for any previous versions.

SYNOPSIS

Sponsor: Transgene
IMP: TG4050, an MVA based, mutanome-targeted individualized immunotherapy

Study Title
A phase I trial evaluating a mutanome-directed immunotherapy in patients with high grade serous carcinoma (HGSC) of the ovary, fallopian tube or peritoneum who experience an asymptomatic relapse

Study N°:TG4050.01

EudraCT N°: 2018-003266-14

Coordinating / Principal Investigator: Matthew Block, Mayo Clinic, Rochester, USA

Investigational Centers/Countries: USA (3 sites from Mayo Clinic) and France (3 sites)

Study Period: Q4 2019-Q4 2024 | **Clinical Phase:** I

Objectives

Primary objective: to evaluate the safety and tolerability of multiple subcutaneous (SC) injections of a neoantigen-directed active immunotherapy (TG4050) in ovarian, fallopian or peritoneal HGSC patients with an asymptomatic relapse.

Secondary objectives: to evaluate:

- Failure to provide TG4050
- Failure to treat with TG4050
- CA-125 doubling time and half-life as appropriate, time to normalization and response according to Gynecological Cancer InterGroup (GCIG) criteria
- Time to measurable relapse in Cohort A and Time to progression in Cohort B per RECIST 1.1
- Tumor response by using RECIST 1.1

Translational research endpoints:

CCI [redacted]

Methodology

This is a multicenter, open-label, single arm phase I study evaluating TG4050, an individualized active immunotherapy which refers to a mutanome-directed immunotherapy based on a Modified Vaccinia virus Ankara (MVA) vaccine specifically designed to target tumor-specific antigens identified in each ovarian, fallopian or peritoneal HGSC patient with an asymptomatic relapse.

The study will consist of 2 parts for each patient:

- A screening period starting at least 6 months after completion of standard first-line treatment including a platinum-based chemotherapy in patients with high risk serous fallopian, peritoneal or ovarian cancer who underwent cytoreductive surgery and achieved clinical complete response after platinum-based chemotherapy as demonstrated by non-evidence of disease on the last CT-scan and normal CA-125. High risk is defined by high grade and stage IIIC or stage IV disease. For each of those patients, an individualized, mutanome-directed immunotherapy TG4050 will be assembled.

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- A treatment period with TG4050 monotherapy starting in:
    - Cohort A: when patients develop an asymptomatic relapse defined on the basis of progressive serial elevations of serum CA-125 (GCIG criteria) or documentation of low volume radiological disease with CA-125 > Upper Limit of Normal (ULN). Low volume radiological disease is defined as radiologically visible disease excluding intra-hepatic or intra-splenic metastases, ascites or pleural effusion thought to require drainage
    - Cohort B: when patients develop an asymptomatic relapse with measurable disease excluding intra-hepatic or intra-splenic metastases, ascites or pleural effusion thought to require drainage, whatever serum CA-125 level and for whom further treatment is not planned within 2 months. Longest diameter on CT-scan must not exceed 2 cm for non-nodal lesions and 2.5 cm in short axis for nodal lesions

Patients will receive TG4050 up to a total of 20 injections or until disease progression justifying initiation of further treatment, unacceptable toxicity including occurrence of a dose-limiting toxicity, or patient withdrawal for any reason, whichever occurs first.

A safety run-in phase will be conducted in the first 3 treated patients from Cohort A or B who will be observed during the 6 weeks after the first administration of TG4050. During this phase, each patient will be monitored for 4 weeks after the first injection of TG4050 before the next patient can be enrolled.
Enrolment of the next patients will be allowed if none of the 3 patients has experienced during the six weeks run-in phase:

- any grade ≥3 toxicity that is at least possibly related to TG4050, with the following exception: pre-existing grade 2 fatigue at baseline that would worsen up to grade 3
- any death

The occurrence of any of those events will trigger a study hold. An evaluation of the cause of toxicity will be performed and corrective measures, if appropriate, will be proposed before recruitment in the study can be reinitiated.

Beyond the safety run-in phase, a dose-limiting toxicity is defined as any treatment-emergent AE ≥3 toxicity that is at least possibly related to TG4050, with the following exceptions: pre-existing grade 2 fatigue at baseline that would worsen up to grade 3.

In any case, patients experiencing a dose-limiting toxicity will discontinue study treatment permanently.

An Independent Data Monitoring Committee (IDMC) will be set up for the purpose of reviewing patients' safety data and the conduct of the study.
The IDMC will meet at completion of the safety run-in phase to analyze and review the safety data of the first 3 patients from Cohort A or B. The IDMC will then recommend whether it is possible to pursue patient enrolment as per study protocol. In addition to the review of the first 3 patients, the IDMC will review safety data of all patients included every 3 months during the first year and every 6 months thereafter.
Ad hoc meetings may be held upon necessity.

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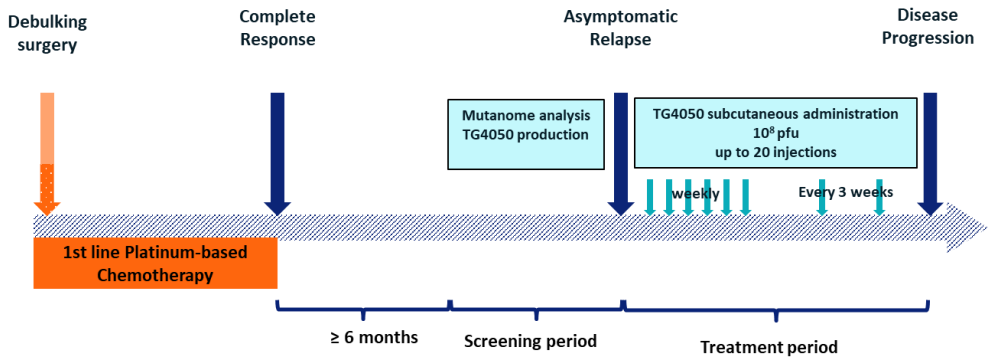
Graphical synopsis



Number of Patients

- Screening period: an approximate number of 60 patients will participate.
- Treatment period:
  - Cohort A: at least 13 patients will be enrolled to allow sufficient number of patients evaluable for safety, efficacy and immunological analyses.
  - Cohort B: Number of patients included at the time of full accrual in Cohort A with a maximum of 10 patients.

Inclusion criteria

Screening period

1- Signed written 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 patients ≥ 18 years of age
3- Histologically confirmed high grade, stage IIIC or stage IV (FIGO staging) serous ovarian, fallopian or primary peritoneal carcinoma with abnormal CA-125 at diagnosis
4- Patients who have undergone primary debulking surgery or interval debulking surgery and completed a total of at least 5 cycles of taxane-platinum combination. Note: patients may have received concurrent or maintenance bevacizumab or a PARP inhibitor.
5- Patients must have achieved a complete response to therapy, as demonstrated by no residual disease on most recent CT scan and normal CA-125.
6- Patient who remains disease free at least 6 months from last prior dose of cytotoxic chemotherapy (maintenance therapy with bevacizumab or a PARP inhibitor is allowed).
7- Available tumor tissue, banked from previous abdominal debulking surgery and/or from a core needle biopsy performed at diagnosis if the patient received neoadjuvant chemotherapy, and peripheral blood samples for exome and transcriptome sequencing.

Treatment period

8- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 at treatment period initiation
9- Patients who have developed an asymptomatic relapse as defined by
   - Cohort A: CA-125 ≥ 2 times ULN on 2 occasions at least 1 week apart (GCIG criteria) or low volume radiological disease and CA-125 > ULN. Low volume radiological disease is defined as radiologically visible disease excluding intra-hepatic or splenic metastases, ascites or pleural effusion thought to require drainage.
   - Cohort B: patient asymptomatic with measurable disease, excluding intra-hepatic or splenic metastases, ascites or pleural effusion thought to require drainage, whatever serum CA-125 level and for whom further treatment is not planned within 2 months. Longest diameter on CT-scan must not exceed 2 cm for non-nodal lesions and 2.5 cm in short axis for nodal lesions.

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10- Adequate hematological, hepatic and renal functions:
- Hemoglobin ≥ 9.0 g/dL
- Neutrophils count ≥ 1.5 $x10^9$/L
- Lymphocytes count ≥ 0.9 $x10^9$/L
- Platelets count ≥ 100 $x10^9$/L
- Total bilirubin ≤ 1.5 x ULN (except for patients with Gilbert's syndrome)
- Aspartate aminotransferase (AST) ≤ 2.5 x ULN
- Calculated creatinine clearance ≥ 45 mL/min using the Cockroft & Gault formula or ≥ 45 mL/min/1.73m² using other methods

11- Patients who received standard maintenance therapy will stop before initiation of TG4050 administration. A free-interval of at least 30 days will be respected before first dosing of TG4050 except for PARP inhibitor (at least 14 days).

Exclusion criteria

Screening period

1- Patient having received any cancer immunotherapy including cancer vaccines, any antibody/drug targeting T cell co-regulatory proteins such as anti-PD1, anti-PDL1 or anti-CTLA-4
2- Patients with other active malignancy ≤ 3 years prior to registration except non-melanoma skin cancer, stage 0 in situ carcinoma and recent early stage papillary thyroid cancer. If there is an history of prior malignancy, patient must not be receiving other specific treatment for their cancer
3- Patient post-organ transplantation, including allogeneic stem cell or bone marrow transplantation. History of blood transfusion within 3 weeks prior to study entry visit.
4- Known history of positive testing for Human Immunodeficiency Virus (HIV) or known AIDS (Acquired Immune Deficiency Syndrome)
5- Any known allergy or reaction to eggs or attributed to compounds of similar chemical or biological composition to therapeutic vaccines/immunotherapeutic products
6- Positive serology for Hepatis C Virus (HCV) or positive serum Hepatitis B surface antigen (HBsAg) within 3 months prior to or at study entry (tests required)

Treatment period

7- Measurable disease associated with the appearance of symptoms justifying initiation of further treatment.
8- Major surgery within 4 weeks prior to treatment start
9- Treatment with another investigational agent within 30 days prior to TG4050 treatment initiation.
10- Patients under chronic treatment with systemic corticosteroids or other immunosuppressive drugs for a period of at least 4 weeks and whose treatment was not stopped 2 weeks prior to TG4050 treatment initiation planned date, with the exception of patients with adrenal insufficiency who may continue corticosteroids at physiological replacement dose, equivalent to ≤ 10 mg prednisone daily. Steroids with no or minimal systemic effect (topical, inhalation) are allowed.
11- Vaccination for the prevention of infectious diseases with a live vaccine during the four-week period prior to TG4050 treatment initiation planned date. Furthermore, patients should not receive any live vaccine during the period of study treatment administration.
12- Patient with any underlying medical condition, that in the opinion of the investigator, could make the patient inappropriate for entry into this study or interfere significantly with the proper assessment of safety or toxicity of the study treatment.
13- Uncontrolled intercurrent illness including, but not limited to ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia or psychiatric illness/social circumstances that could limit compliance with study requirements.
14- History of myocardial infarction ≤ 6 months.

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IMP: Dose, Mode of Administration

In this study, the Investigational Medicinal Product (IMP) is TG4050.

- The IMP is an individualized MVA construct, mutanome-directed immunotherapy tailored to each patient and derived from a replication deficient strain of vaccinia virus (Modified Vaccinia virus Ankara, MVA).
- The individualized TG4050 construct will be assembled for each patient during the screening period. Study treatment will be started when a patient develops an asymptomatic relapse.
- Patients will receive subcutaneous (SC) injections of TG4050 at a dose of $1x10^8$ PFU weekly for the first 6 weeks and then every 3 weeks up to a total of 20 injections unless disease progression justifying initiation of further treatment, unacceptable toxicity including occurrence of a dose-limiting toxicity, or patient withdrawal for any reason, whichever occurs first.

Reference / Associated Therapy

Permitted medicines and therapies:

- Any medications that are considered necessary for the patients' welfare and will not interfere with the trial medication may be given at investigator's discretion.
- The use of the following drugs will not be restricted during the course of the study: G-CSF, erythropoietin, antiemetics and analgesics.
- Topical, ocular, intra-articular, intranasal and inhalational corticosteroids (with minimal systemic absorption)
- The use of systemic corticosteroids during the study is restricted as follows: for short term treatment (≤7 days) of allergic reactions, or for replacement for adrenal insufficiency at doses equivalent to ≤ 10 mg prednisone daily.

Non-permitted medicines and therapies during the study treatment period:

- Immunosuppressive agents
- Immunosuppressive doses of systemic corticosteroids per restrictions described above.
- Any concurrent antineoplastic therapy
- Any live vaccine for the prevention of infectious disease
- Any other investigational agent

Duration of Study Treatment

TG4050 will be administered up to a total of 20 injections or until disease progression justifying initiation of further treatment, unacceptable toxicity including occurrence of a dose-limiting toxicity, or patient withdrawal for any reason whichever occurs first.

Criteria for Evaluation

Failure to provide rate

The proportion of patients for whom TG4050 cannot be provided and the reason for not being able to provide the vaccine will be recorded.

Failure to treat rate

The proportion of patients who cannot receive TG4050 and the reason that prevents the patient from being treated will be recorded.

Safety assessment

The following evaluations will be performed:

- Physical examination including vital signs, body weight and performance status every week for the first 6 weeks and then every 3 weeks.
- AEs and Serious Adverse Events (SAEs) will be reported and graded according to NCI CTCAE, version 5 at each visit.
- Laboratory investigations will be undertaken:

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- Complete blood count (CBC) including Red Blood cells (RBC), White Blood cells (WBC) and differential, Hemoglobin (Hb) and platelets at baseline, every week up to week 6, then every 3 weeks up to Month 6 (Day 190), thereafter every 12 weeks, and at the end of treatment visit.
- Biochemistry analyses including: AST, ALT, alkaline phosphatases, total bilirubin, glucose, electrolytes (sodium, potassium, magnesium and bicarbonates), creatinine and creatinine clearance at baseline, every week up to week 6, then every 3 weeks up to Month 6 (Day 190), thereafter every 12 weeks, and at the end of treatment visit.

- ECG at baseline, every 3 weeks for the first 6 weeks and then every 6 weeks up to Day 169, thereafter every 12 weeks, and at the end of treatment visit.

Efficacy assessment

- CA-125 determined in an accredited central laboratory will be measured within 7 days prior to treatment initiation and then every 3 weeks throughout the treatment period. CA-125 doubling time and half-life as appropriate, time to normalization and response according to GCIG criteria will be assessed.
- Tumor response will be evaluated by using RECIST 1.1. A CT-Scan of the pelvis and abdomen (or MRI) and X ray or preferably CT-scan of the chest will be performed within 21 days prior to treatment initiation, on Day 43 and then every 9 weeks.

Immune responses

Patient samples collection:

- Cytapheresis for collection of PBMC will be performed prior to first treatment administration and 9 weeks (D64) after treatment initiation. In case a patient is withdrawn prior to D64, a cytapheresis is to be performed at end of treatment visit. If the post-baseline cytapheresis is not clinically feasible, it can be replaced by a 150 ml blood draw.

- Blood samples (prior to study treatment administration, when applicable) at baseline, on Day 8, Day 22, Day 43, Day 64, Day 85, Day 211 and at the end of treatment visit for extraction of serum, plasma and PBMC for longitudinal monitoring of response.

Blood samples will be collected to assess the following parameters:

- Whole blood cell phenotype on fresh blood samples by multiparametric flow cytometry (FACS). Proposed assessments include counting and phenotyping of memory and naïve T cells, regulatory T cells, CD8 T cells, B cells, NK cells, innate like T cells as well as relevant activation markers
- Quantification of immune related soluble factors, cytokines, antibody responses to neoantigens and virus
- Peripheral Blood Mononuclear Cells (PBMC) from whole blood to assess specific cellular immune responses against neoantigens
- HLA Genotyping (class I and II)
- Circulating tumor and immune markers

Tumor sample(s) will be collected to assess:

- Density of tumor infiltrating lymphocytes (TILs) and phenotyping of the infiltrated cells (cell type and activation markers) (Immunoscoring)
- PD-L1 and other relevant immune related factor expression by IHC assessment
- Transcriptomic analysis of whole tumor and purified immune cell populations
  - Evaluation of tumor mutation load

Statistical Methods:

This is a phase I first-in-man study. No formal sample size calculation is planned.
Descriptive statistics will be used to present patient demographic and baseline characteristics, as well as safety, efficacy and immune data.

TABLE OF CONTENTS

ABBREVIATIONS / DEFINITION OF TERMS

ABBREVIATIONS	MEANING OF ABBREVIATIONS IN DOCUMENT
AE	Adverse Event
ALT	Alanine amino-transferase (= SGOT)
AR	Adverse Reaction
AST	Aspartate amino-transferase (= SGPT)
BRCA 1 & BRCA 2	Breast Cancer 1 & Breast Cancer 2
CBC	Complete Blood Count
CI	Confidence Interval
CR	Complete Response
CRO	Contract Research Organization
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	Circulating Tumor DNA
CTL	Cytotoxic T Lymphocytes
D	Day
DLT	Dose Limiting Toxicity
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
FACS	Fluorescence-activated cell sorter
GCIG	Gynecologic Cancer InterGroup
GCP	Good Clinical Practice
GMO	Genetically Modified Organism
GOG	Gynecologic Oncology Group
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HGSC	High Grade Serous Carcinoma
HIV	Human Immunodeficiency Virus
HLA	Histocompatibility Leukocyte Antigen
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
IHC	Immunohistochemistry
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
M	Month
mL	Milliliters
MRI	Magnetic Resonance Imaging
MVA	Modified Vaccinia virus of Ankara
NCI-CTCAE	National Cancer Institute's Common Terminology Criteria for Adverse Events. Also referred as CTCAE in the text
NK	Natural Killer
PBMC	Peripheral Blood Mononuclear Cells
PD-1	Programmed Death-1
PD-L1	Programmed Death Ligand-1
PFS	Progression Free Survival
PFU	Plaque Forming Unit
PS	Performance Status
RBC	Red Blood Cells
RECIST	Response Evaluation Criteria In Solid Tumors
RNA	Ribonucleic Acid
SAE	Serious Adverse Event
SAF	Safety Analysis Set

SC	Subcutaneous
sd	standard deviation
SOC	Standard of Care
SUSAR	Suspected Unexpected Serious Adverse Reaction
TSAs	Tumor Specific Antigens
TIL	Tumor Infiltrating Lymphocytes
TMF	Trial Master File
TCR	T Cell Receptor
ULN	Upper Limit of Normal
WBC	White Blood Cells

1. INTRODUCTION

1.1. Disease background

After initial surgical diagnosis, staging and cytoreduction, the standard primary chemotherapy for women with advanced epithelial ovarian, fallopian or peritoneal primary cancer consists of taxane and a platinum salt in combination, usually carboplatin and paclitaxel.
Despite the high response rate for front-line therapy with more than 70 % of patients achieving a clinical response, the majority of patients with advanced ovarian cancer will subsequently relapse. In the past 5 years, bevacizumab combined with front-line chemotherapy and then given in maintenance was shown to provide a statistically and clinically significant improvement in PFS (Burger R.A. et al., 2011; Perren T.J. et al., 2011). In the GOG-0218 trial (Burger R.A. et al., 2011) which enrolled incompletely resected stage III and stage IV epithelial ovarian cancer and mostly grade 3 disease (71.2 %), median PFS was increased from 10.3 months in the control arm to 14.1 months in the concomitant and maintenance bevacizumab arm. However, no statistically significant difference in OS was observed in the final study analysis (Burger R.A. *et al.*, 2018). The development of several PARP inhibitors has been an important advance in the treatment of ovarian cancer. More recently, their use as maintenance therapy was approved based on PFS improvement in particular in patients with homologous recombination deficiency tumors (Pujade-Lauraine E. *et al.*, 2017). Hence, there is still a clear unmet medical need and new treatment approaches are strongly awaited to improve the outcome of high-grade serous carcinoma (HGSC) of the ovary, fallopian tube and peritoneum.

One potentially attractive approach is tumor mutanome directed immunotherapy since ovarian cancer may be recognized and attacked by the immune system. Tumor infiltrating T cells were detected and their presence was shown to correlate with improved clinical outcome in advanced ovarian cancer (Zhang L. et al., 2003). Stimulation of the immune system with a vaccine may provide an opportunity to leverage long-term anti-tumor immune response while maintaining an excellent safety profile. On a longer term, such approach can potentially constitute a medical option in an indication of high medical need. Moreover, studies have demonstrated that residual disease or remanence of micrometastasis is a major prognostic factor for clinical recurrence (Braun S. et al., 2001). Micrometastases are scattered cancer cells with relatively low rates of replication, which may explain the lack of efficacy of cytotoxic therapy but may constitute an ideal target for immune mediated response.

1.2. Study population rationale

Patients with ovarian, fallopian or peritoneal cancer in the context of minimal residual disease will be enrolled. These patients have achieved complete clinical response after surgery and standard platinum-based therapy and will be enrolled when rise in serum CA-125 predicts a slow disease recurrence.

Indeed, despite the high response rate for front-line therapy the majority of patients with advanced ovarian cancer will subsequently relapse. A substantial number of patients develop a biochemical relapse based on increased CA-125 measurement without clinical symptoms which can be associated with a low volume disease on CT-scan. For this group of patients, no survival benefit has been demonstrated from early chemotherapy treatment which means that patients participating into the present study will not be deprived from their standard of care treatment. The median lead time between CA-125 rise and initiation of second-line chemotherapy for clinical recurrence was reported to be 4.8 months (Rustin G.J. *et al.*, 2010). This might be

explained by the low rate of proliferation of cancer cells at this stage of the disease. Additionally, before biochemical relapse, tumor cells are scattered and may be accessible to immune intervention as immunosuppressive properties of the disease may be lower than what would be encountered in larger tumors.

Tumor infiltrating T cells were detected and their presence was shown to correlate with improved clinical outcome in advanced ovarian cancer. (Zhang L. et al., 2003). Taken together these properties of tumor cells at this stage of the disease make them promising target for cell mediated immune anti-tumor reaction.

The time interval from completion of chemotherapy will be at least 6 months since only patients with platinum sensitive relapse are eligible for the study. Although we recognize that the complex interplay between chemotherapy induced lymphopenia and chemotherapy, we consider that this time interval would presumably be sufficient for recovery of patients from immune-compromising effect of chemotherapy. In addition, patients are required not to have been treated with chronic systemic corticosteroids or other immunosuppressive drugs for a period of at least 4 weeks before study entry and up to 2 weeks prior to first TG4050 treatment administration. Other parameters reflecting immune status of the patient may be included in the protocol as appropriate based on the recent state of the art.

The present feasibility and safety clinical trial is then conducted in high grade serous ovarian, fallopian or peritoneal cancer patients with platinum-sensitive asymptomatic relapse after debulking surgery followed by platinum-based therapy.

1.3. TG4050 background

TG4050 is an immunotherapeutic product manufactured specifically for a given patient based on identification of tumor specific somatic mutations. Briefly, tumor specific mutations expressed in the tumor tissue are detected by comparing the tumor and healthy tissue exomes by massively parallel sequencing; evidence of expression of identified mutation is obtained through sequencing of tumor cells transcriptome (RNAseq). Subconsequently, mutated sequences are used to design a synthetic gene and cloned in a modified vaccinia Ankara viral vector (Bendjama K. and Quemeneur E., 2017).

The Modified Vaccinia virus Ankara (MVA) has been generated through serial passages in chicken embryo fibroblasts. It has been used safely and effectively for smallpox vaccination in more than a hundred thousand individuals. The MVA has lost the pathogenicity of its parental virus, the Chorioallantois Vaccinia virus Ankara, through alterations of its genome, i.e. 15% of genome loss. The virus is replication defective in human cells, ensuring its safety and tolerability for clinical use but replicative in avian cells. This feature enables the use of an egg-based manufacturing process. It has served as an effective vector in previous attempts to develop viral-based immunotherapies, in particular, the vector has been used for the production of several Transgene's IMPs tested in phase 1 and phase 2 clinical studies. The long track record of clinical use of the MVA demonstrates an excellent safety profile and is not associated with cardiac safety issues like with replicative vaccinia virus (Elizaga M.L. et al., 2013), (Zitzmann-Roth E.M. et al., 2015).

The use of cancer specific immunogenicity has been validated through a wealth of evidence preclinically and clinically. Tumor infiltration with cytotoxic T cell has been long known as a factor of positive prognostic. More recently, molecular characterization of tumor tissues demonstrated that antigens arising from tumor specific mutations are the main targets of

cytotoxic T cells (Schumacher T.N. et al., 2015). Therapeutics stimulating the immune system has leveraged successfully activity of these cells by bypassing the propensity of tumors to escape immune control by inhibiting effector cells. Therapies such as immune checkpoint inhibitors (ICI) have yielded high clinical efficacy by inhibiting pathways used by the tumor to downregulate the immune response (e.g., PD-1/PD-L1). One downside in such approach is that it remains limited to a relatively reduced fraction of patients whose immune profile is compatible with such intervention. Indeed, ICI therapy implies that there is a pre-existing immune response in patients, yet, tumors are also known to be able to inhibit priming of a cellular response by various mechanisms.

The strategy behind TG4050 is to use the natural sensitivity of the immune system to trigger a response against tumor specific antigens (TSAs), by priming the immune system outside of the tumor environment. This response may then lead to a cytotoxic activity of T cells and improvement of patient outcome. Potentially, such approach may be used synergistically with other immune modulators.

In the present study, TG4050 IMP is designed based on samples collected prior to the adjuvant chemotherapy and the therapy is only administered at the time of biochemical progression. Given the well documented high genomic instability of ovarian serous carcinoma (Vollebergh M.A. et al., 2012), and the tendency of chemotherapeutic agents to induce somatic mutation (Gercel-Taylor C. et al., 2005), the relevance of administrating after chemotherapy a GTMP targeting mutations identified prior to the said chemotherapy may be questioned. The recent work by (Arend R.C. et al., 2018) studied the relationship between mutation load and neoadjuvant therapy in ovarian carcinoma. Results from molecular profiling of serous ovarian carcinoma in 19 patients demonstrate that while mutation load may be affected by chemotherapy, the vast majority of mutations detected before and after neoadjuvant chemotherapy were the same (O'Donnell T. et al., 2018). Additionally, recent studies document differences of mutational profile between primary and metastatic tumor. While there is a significant evolution of the mutational landscape, on average 61% of mutations present in the primary tumor are found in a metastatic lesion (Masoodi T. *et al.*, 2020). This suggests that while new mutations may be induced by treatment or natural evolution of the disease, mutations that appeared earlier in the history of the disease are likely to be conserved. Also, the use of up to 30 epitope targets mitigate the risk of loss of immune escape. In order to validate this assumption, the genomic profile of tumors will be studied at recurrence.

1.4. Translational research rationale

Besides the assessment of safety and tolerability, the current study is intended to provide critical data on the mechanism of action of TG4050. We aim at generating data that may help validating TG4050 as an effective tool for the development of tumor specific immune responses and obtain preliminary data on the antitumor efficacy of this individualized therapy.

Material banked at diagnosis or after surgery will be used to identify tumor specific mutations and evaluate level of expression of tumor specific mutations. Sequencing data will be used to describe mutational load and impact of clinical covariates on the frequency of mutations.

CCI [redacted]

CCI [redacted]

[redacted]

[redacted]

[redacted]

1.5. Summary of the overall benefits and risks

1.5.1. Expected benefits

TG4050 is an individualized mutanome-directed active immunotherapy designed to trigger a specific immune response against patient tumor specific antigens. It is expected that this specific response will induce a cytotoxic activity of T cells towards tumor cells potentially leading to an improved disease outcome.

1.5.2. Potential risks

Based on the clinical experience collected for several MVA vector-based immunotherapy products investigated by Transgene, the following related adverse events were the most common events in clinical trials:

- Injection site reactions of grade 1 and 2 based on the NCI CTCAE version 5 including erythema, inflammation, pain, hemorrhage, pruritus, induration, bruising
- Lymphadenopathy
- Headache
- Pyrexia
- Fatigue
- Nausea and vomiting
- Influenza like illness

1.5.3. Measures taken to mitigate the risks

The risks-benefits relationship has been carefully considered in the planning of the study. Based on the clinical data available to date on other MVA vector-based immunotherapy products, the conduct of this study is considered justifiable using the dose and dosage regimen of TG4050 specified in the study protocol. An Independent Data Monitoring Committee (IDMC) is planned for the ongoing assessment of the risk-benefit ratio. The trial shall be discontinued in the event of any new finding that indicates a deterioration of the risk-benefit ratio and would render continuation of the trial unjustifiable.

This clinical trial will be conducted in compliance with the clinical study protocol, GCP (ICH E6 R2) and the applicable national regulatory requirements.

2. OBJECTIVES

2.1. Primary Objective

To evaluate the safety and tolerability of multiple subcutaneous (SC) injections of a neoantigen-directed active immunotherapy in ovarian, fallopian or peritoneal high-grade serous carcinoma (HGSC) patients with an asymptomatic relapse.

2.2. Secondary objectives

To evaluate:

- Failure to provide TG4050
- Failure to treat with TG4050
- CA-125 doubling time and half-life as appropriate, time to normalization and response according to GCIG criteria
- Time to measurable relapse in Cohort A and Time to progression in Cohort B per RECIST 1.1
- Tumor response by using RECIST 1.1

2.3. Translational research

The following exploratory endpoints will be also investigated:

- CCI

3. STUDY DESIGN

3.1. Overall study design and plan description

This is a multicenter, open-label, single arm phase I study evaluating TG4050, an individualized active immunotherapy which refers to a mutanome-directed immunotherapy based on a Modified Vaccinia virus Ankara (MVA) vaccine specifically designed to target patient-specific immunogenic mutations.

The vaccine will be administered at the time of asymptomatic relapse in patients with ovarian, fallopian or peritoneal HGSC as a single agent during the treatment period. Patients will receive TG4050 at $1x10^8$ PFU by subcutaneous (SC) injections weekly for the first 6 weeks and then every 3 weeks up to a total of 20 injections unless disease progression justifying initiation of further treatment, unacceptable toxicity including occurrence of a dose-limiting toxicity, or patient withdrawal for any reason, whichever occurs first.
A safety run-in phase will be conducted in the first 3 treated patients from Cohort A or B who will be observed during the 6 weeks after the first administration of TG4050.
During this phase, each patient will be monitored for 4 weeks after the first injection of TG4050 before the next patient can be enrolled.
Enrolment of the next patient will be allowed if none of the 3 patients has experienced during the 6 weeks run-in phase:

- any grade ≥3 toxicity that is at least possibly related to TG4050, with the following exception: pre-existing grade 2 fatigue that would worsen up to grade 3
- any death.

The occurrence of any of those events will trigger study hold. An evaluation of the cause of toxicity will be performed and corrective measures if appropriate, will be proposed before recruitment in the study can be reinitiated.

The study will consist of 2 parts for each patient:

- A screening period which will start at least 6 months after completion of standard first-line treatment including a platinum-based chemotherapy. Only patients with histological confirmation of serous carcinoma of the ovary, fallopian tube or peritoneum and having high risk cancer defined as high grade and stage IIIC or stage IV disease who achieved a complete response after chemotherapy defined as non-evidence of disease on the last CT-scan and normal CA-125, and from whom tumor tissue is available for tumor neoantigen identification can be included in the screening period.
  For those patients, tumor tissue which have been banked at the time of abdominal surgery (or at the time of diagnosis if the patient received neoadjuvant chemotherapy) and blood samples will be tested for TSAs identification. TSAs will be used to manufacture an individualized TG4050 mutanome-directed immunotherapy. Manufacturing will take approximately 12 weeks for the vaccine to be prepared in accordance with GMP procedures.
  During the screening period, patients will be regularly followed per standard medical practice and with serum CA-125 measurements performed in an accredited central laboratory at least every 90 to 120 days and imaging in the event of CA-125 increase and/or clinical symptoms. If the patient did not relapse after 2 years of follow-up, this

follow-up may be performed at least every 6 months (+1 month) according to Investigator's standard practice. Circulating tumor DNA will be followed in peripheral samples from study entry and measured in a central laboratory. If a suspicious but indeterminate nodule is identified at study entry, repeat imaging should be obtained 3 months after (+/- 2 weeks) to determinate whether the nodule is malignant. Alternatively, a biopsy may be obtained.
Patients who have developed an asymptomatic relapse according to the below definitions are eligible for the treatment period provided they meet the other treatment period eligibility criteria.

- A treatment period which will start
  - Cohort A: when patients develop an asymptomatic relapse defined on the basis of progressive serial elevations of serum CA-125 (GCIG criteria) or low volume radiological disease with CA-125 > Upper Limit of Normal (ULN). Low volume radiological disease is defined as radiologically visible disease excluding intra-hepatic or splenic metastases, ascites or pleural effusion thought to require drainage.
  - Cohort B: when patients develop an asymptomatic relapse with measurable disease, excluding intra-hepatic or splenic metastases, ascites or pleural effusion thought to require drainage, whatever serum CA-125 level and for whom further treatment is not planned within 2 months. Longest diameter on CT-scan must not exceed 2 cm for non-nodal lesions and 2.5 cm in short axis for nodal lesions

Patients will stop maintenance therapy if any and will receive TG4050.

All treated patients will be followed for:

- Safety assessments performed on a weekly basis for the first 6 weeks and every 3 weeks thereafter.
- Serum CA-125 levels assessed in an accredited central laboratory within 7 days prior to treatment initiation and then every 3 weeks and imaging performed within 21 days prior to treatment initiation, at Day 43 and then every 9 weeks.
- Immune responses evaluated in the blood at baseline and on Days 8, 22, 43, 64 ,85 and 211; in the tumor at the time of RECIST defined disease progression

A schematic illustration of the trial design is shown below.

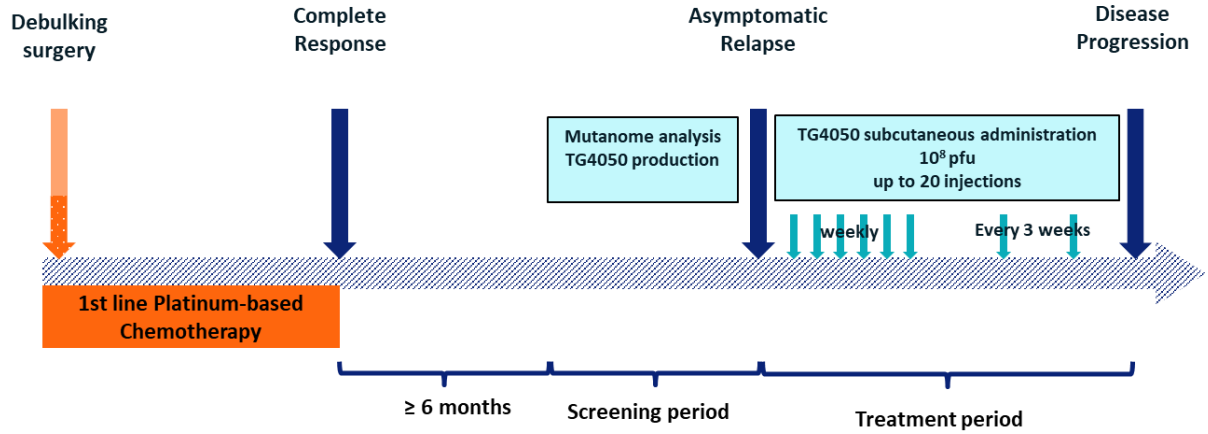


Figure 1: Overall study design

3.2. Number of centers and patients

In the screening period, an approximate number of 60 patients will be included.
In the treatment period:

- Cohort A: at least 13 patients will be enrolled to allow sufficient number of patients evaluable for safety, efficacy and immunological analyses.
- Cohort B: number of patients included at the time of full accrual in Cohort A with a maximum of 10 patients.

The study will be a multicenter one with 3 centers from Mayo Clinic in the US and 3 centers in France.

3.3. Discussion of Study Design

The first-in-man study of TG4050 is designed as a phase I trial to evaluate primarily the safety of TG4050 administered alone in stage IIIC or stage IV HGSC patients with an asymptomatic relapse. This clinical setting will also allow the evaluation of serum CA-125 doubling time and half-life as appropriate, time to normalization, response according to GCIG criteria and immune response to TG4050.

The screening period will run from at least 6 months after completion of first-line platinum-based chemotherapy to the documentation of an asymptomatic relapse. Patients who achieved a complete response as demonstrated by non-evidence of disease on the last CT-scan and normal CA-125 can be enrolled. Archived tumor tissue collected at the time of abdominal surgery and/or at diagnosis will be used for TSAs identification and subsequent individualized TG4050 MVA construct manufacturing. If the patient has received neoadjuvant chemotherapy, the tumor tissue must be obtained from a core needle biopsy (18G minimum) performed at diagnosis.

The treatment period will run from the documentation of asymptomatic relapse until a total of 20 injections of TG4050 unless disease progression justifying initiation of further treatment, unacceptable toxicity including occurrence of a dose-limiting toxicity or patient withdrawal for any reason whichever occurs first.

A safety run-in phase will be conducted in the first 3 treated patients from Cohort A or B who will be observed during the 6 weeks after TG4050 first dose. For patients presenting with a biochemical relapse detected on the basis of raised serum CA-125 concentration alone, no survival benefit has been demonstrated from early chemotherapy treatment compared to delayed treatment on the basis of clinical relapse (Rustin G.J. *et al.*, 2010). The lead time between CA-125 increase and clinical recurrence was shown to be 4.8 months on average which will allow to investigate the tolerance of TG4050. This time period will allow to capture immune response to TG4050 and its possible impact on CA-125 doubling time and half-life as appropriate, time to normalization and response. In current practice, second-line treatment is rarely initiated when relapse is asymptomatic, even in the presence of small measurable lesions, and the patient is usually followed with a CT-scan performed 2 months later. National Comprehensive Cancer Network guidelines endorse delaying treatment until clinical relapse.

This patient population may benefit from study treatment and will be evaluated separately in Cohort B.

3.4. Dose and schedule selection

Dose and schedule for TG4050 administration have been selected on the basis on the broad clinical experience gathered on TG4010, an MVA carrying coding sequences for the human MUC1 antigen and human interleukin 2 also developed by Transgene. As of end 2018 a total of 354 cancer patients, mostly non-small cell lung cancer (NSCLC) patients, received SC injections of TG4010 at a dose of $1x10^8$ PFU weekly for 6 weeks followed by every 3 weeks administrations.

• Rationale for the route of administration

In pre-clinical experiments, SC and IM administrations of research grade TG4010 resulted in similar anti-tumoral activity as measured by survival in the RMA-MUC1 prophylactic mouse model. This finding was repeated with the other Transgene MVA-based gene therapy products. The SC route has been chosen from phase II studies of TG4010 and other MVA-based products as it appears a more effective route of administration to initiate an immune reaction which is the expected mechanism of action for Transgene MVA-based products. It has been demonstrated as a safe and immunogenic route in the clinic with MVA-based products.

• Rationale for the dose and regimen:

In TG4010 development, phase II clinical trials were conducted testing different doses and schedules of administration of the study drug.
The dose of $1x10^8$ PFU was selected based on its good tolerance and immunogenicity.
With its design targeting patient specific neoantigens, TG4050 products should target more immunogenic antigens that the ones targeted by MVA-based products already tested in clinic by Transgene. It is envisaged that a critical dose threshold needs to be reached to achieve an immunogenic response disregarding the nature and immunogenicity of the patient specific antigens carried by the MVA vector. This was consolidated by a pre-clinical experiment in HLA-A2 mice who received different doses of MVA constructs representative of TG4050 and showed response with no dose-response effect.
Sticking with a dose of $1x10^8$ PFU which allowed immunogenic response with an MVA-based product carrying a weak antigen sequence (i.e.: MUC1 antigen for TG4010) should then be relevant for TG4050. The high specificity of TG4050 antigens to the human tumor should prevent from autoimmune reaction.
In prostate cancer patients the change in PSA doubling time from before treatment to during treatment was statistically significant in patients who received TG4010 weekly for 6 weeks then every 3 weeks while this change was not significant in those who received TG4010 every 3 weeks. Therefore, this treatment regimen was used in all subsequent studies.

• Rationale for repeated administrations scheme:

Therapeutic vaccines do not directly target the tumor but they rather aim at activating and amplifying immune reactions against the tumor. Immune responses often take time to develop and can potentially be enhanced by continued booster vaccinations. Then a repeated schedule of administration was selected for TG4010 as well as the other Transgene MVA-based products and is also applied to TG4050 in the clinic. This repeated dose study regimen was shown to be

well tolerated, grade 1 or 2 injection site reactions being the most frequent Adverse Events (AEs). Importantly this regimen of TG4010 in combination with standard chemotherapy was shown to improve patient outcome in a randomized placebo-controlled, double-blind phase 2 study comparing the combination with chemotherapy and placebo in 222 first-line NSCLC patients (Quoix E. *et al.*, 2016). Consistent with repeated injections of TG4010, development of CD8+ T cell response to MVA-specific epitopes were observed at different timepoints and more frequently in the TG4010 arm in comparison to the placebo arm in this phase 2 clinical trial (Tosch C. *et al.*, 2017). Interest of repeated administrations was also evidenced with MVA-based products not developed by Transgene. For instance, CD4+ and CD8+ T-cell responses to MVA or Dryvax were reported in subjects vaccinated with TBC-MVA and responses were augmented after three doses of MVA compared to one dose (Parrino J. et al., 2007).
From an immunologic perspective, there is a theoretical possibility of T cell cross-reactivity with repeated administrations of TG4050. This potential risk was previously monitored in TG4010 clinical trials assessing repeated administrations of $1x10^8$ PFU through auto-immunity parameters assessment (e.g. anti-DNA antibodies, anti-nuclear antibodies, thyroid stimulating hormone, anti-thyroperoxidase antibodies). While some of these antibodies increased slightly during study compared to pre-treatment level, it was never considered clinically significant by the investigators. There was also no clinical evidence of auto-immunity to glandular mucins reported (Sjogren's syndrome). No further autoimmunity clinical issue is expected with TG4050 as it targets mutations of patient specific tumor antigen and it has a different mechanism of action from checkpoint blockade. Overall the good tolerance and the efficacy of the proposed TG4050 regimen have been established for an MVA-based product developed by Transgene.

TG4050 will be administered at $1x10^8$ PFU by subcutaneous (SC) injections weekly for the first 6 weeks and then every 3 weeks up to a total of 20 injections unless disease progression justifying initiation of further treatment, unacceptable toxicity including occurrence of a dose-limiting toxicity, or patient withdrawal for any reason, whichever occurs first.

4. STUDY POPULATION

4.1. Inclusion criteria

Screening period

1. Signed written 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 patients ≥ 18 years of age
3. Histologically confirmed high grade, stage IIIC or stage IV (FIGO staging) serous ovarian, fallopian or primary peritoneal carcinoma with abnormal CA-125 at diagnosis.
4. Patients who have undergone primary debulking surgery or interval debulking surgery and completed a total of at least 5 cycles of taxane-platinum combination. Note: patients may have received concurrent or maintenance bevacizumab or a PARP inhibitor
5. Patients must have achieved a complete response to therapy, as demonstrated by no residual disease on most recent CT scan and normal CA-125.
6. Patient who remains disease free at least 6 months from last prior dose of cytotoxic chemotherapy (maintenance therapy with bevacizumab or a PARP inhibitor is allowed).

7. Available tumor tissue, banked from previous abdominal debulking surgery and/or from a core needle biopsy performed at diagnosis if the patient received neoadjuvant chemotherapy, and peripheral samples to be submitted to complete exome and transcriptome sequencing.

Treatment period:

8. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 at treatment period initiation.
9. Patients who have developed an asymptomatic relapse as defined by:
    - Cohort A: CA-125 ≥ 2 times Upper Limit of Normal (ULN) on 2 occasions at least 1 week apart (GCIG criteria) or low volume radiological disease and CA-125 > ULN. Low volume radiological disease is defined as radiologically visible disease excluding intra-hepatic or intra-splenic metastases, ascites or pleural effusion thought to require drainage
    - Cohort B: patient asymptomatic with measurable disease excluding intra-hepatic or splenic metastases, ascites or pleural effusion thought to require drainage, whatever serum CA-125 level and for whom further treatment is not planned within 2 months. Longest diameter of measurable lesion on CT-scan must not exceed 2 cm for non-nodal lesions and 2.5 cm in short axis for nodal lesions
10. Adequate hematological, hepatic and renal functions:
    - Hemoglobin ≥ 9.0 g/dL
    - Neutrophils count ≥ 1.5 x 10^9/L
    - Lymphocytes count ≥ 0.9 x 10^9/L
    - Platelets count ≥ 100 x 10^9/L
    - Total bilirubin ≤ 1.5 x ULN (except for patients with Gilbert's syndrome)
    - Aspartate aminotransferase (AST) ≤ 2.5 x ULN
    - Calculated creatinine clearance ≥ 45 mL/min using the Cockcroft-Gault formula or ≥ 45 mL/min/1.73m² using other methods

Note: for Cockroft-Gault formula:

$$\text{Creatinine clearance for females (mL/min)} = \frac{(140 - \text{age})(\text{weight in kg})(0.85)}{(72)(\text{serum creatinine in mg/dL})}$$

$$\text{Creatinine clearance for females (mL/min)} = \frac{(140 - \text{age})(\text{weight in kg})(1.04)}{(\text{serum creatinine in } \mu\text{mol/L})}$$

11. Patients who received standard maintenance therapy will stop before initiation of TG4050 administration. A free interval of at least 30 days will be respected before first dosing of TG4050 except for PARP inhibitors (at least 14 days).

4.2. Exclusion criteria

Screening period

1. Patient having received any cancer immunotherapy including cancer vaccines, any antibody/drug targeting T cell co-regulatory proteins such as anti-PD1, anti-PDL1 or anti-CTLA-4
2. Patients with other active malignancy ≤ 3 years prior to registration except non-melanoma skin cancer, stage 0 in situ carcinoma and recent early stage papillary thyroid cancer. If there is an history of prior malignancy, patients must not be receiving other specific treatment for their cancer.
3. Patient post-organ transplantation, including allogeneic stem cell or bone marrow transplantation. History of blood transfusion within 3 weeks prior to study entry visit.
4. Known history of positive testing for Human Immunodeficiency Virus (HIV) or known AIDS (Acquired Immune Deficiency Syndrome).
5. Any known allergy or reaction to eggs or attributed to compounds of similar chemical or biological composition to therapeutic vaccines/immunotherapeutic products.
6. Positive serology for Hepatis C Virus (HCV), or positive serum Hepatitis B surface antigen (HBsAg) within 3 months prior to or at study entry (tests required).

Treatment period

7. Measurable disease associated with the appearance of symptoms justifying initiation of further treatment.
8. Major surgery within 4 weeks prior to treatment start
9. Treatment with another investigational agent within 30 days prior to TG4050 treatment initiation.
10. Patients under chronic treatment with systemic corticosteroids or other immunosuppressive drugs for a period of at least 4 weeks and whose treatment was not stopped 2 weeks prior to TG4050 treatment initiation planned date, with the exception of patients with adrenal insufficiency who may continue corticosteroids at physiological replacement dose, equivalent to ≤ 10 mg prednisone daily. Steroids with no or minimal systemic effect (topical, inhalation) are allowed.
11. Vaccination for the prevention of infectious diseases with a live vaccine during the four-week period prior to TG4050 treatment initiation planned date. Furthermore, patients should not receive any live vaccine during the period of study treatment administration.
12. Patient with any underlying medical condition that, in the opinion of the investigator, could make the patient inappropriate for entry into this study or interfere significantly with the proper assessment of safety or toxicity of the study treatment.
13. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.
14. History of myocardial infarction ≤ 6 months.

4.3. Criteria for patient premature withdrawal

4.3.1. Premature withdrawal from the trial

Patients are free to discontinue the trial at any time without giving reasons.
A patient must be withdrawn in the event of any of the following:

- Withdrawal of the patient's consent
- Participation in any other trial during the duration of this trial

4.3.2. Withdrawal from study treatment period

Patients must discontinue the study treatment (i.e., for another reason than disease progression or death) if any of the following occurs:

- Significant clinical deterioration (clinical progression), defined as new symptoms that are deemed by the investigator to be clinically significant and due to cancer growth. However, every effort should be made to document objective progression even after discontinuation of treatment
- Occurrence of a dose-limiting toxicity i.e any treatment-emergent AE grade ≥3 toxicity that is at least possibly related to TG4050, with the following exception: pre-existing grade 2 fatigue at baseline that would worsen up to grade 3
- Physician's decision that further participation in the study is not in the patient's best interest
- Patient's request at any time for any reason
- Protocol violation
- Lost to follow up
- TG4050 expiry date reached

For any discontinuation, the Investigator will obtain all the required details and document the date and the reason for the discontinuation in the eCRF. In any case of treatment discontinuation not related to disease progression the patient will be followed per protocol until documentation of disease progression.
If the reason of 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 end of treatment visit and the safety follow-up visit.

4.3.3. Replacement policy

In the safety run-in phase part of the trial (3 first patients), only patients who do not complete the DLT observation period (the first 6 weeks of study treatment) for other reasons than a DLT or who are not evaluable for safety analysis will be replaced. Evaluable patients' populations are defined in section 9.1.
If some patients have not progressed within 36 months after vaccine manufacture, patients will be withdrawn from study. Patients will not be replaced.

4.4. Definition of end of study

The end of study is defined as the date of the last patient last visit.

The end of study page in the eCRF will be filled in when patient withdraws the study due to any reason or if the patient dies or progresses. The patient will be considered as completer if she received the 20 injections or progresses or dies or withdraws due to a DLT before the end of treatment.
In addition, the shelf life of TG4050 is 48 months. Considering the planned duration of treatment lasting around 11 months with pre-treatment assessments of around 1 month (confirmation of asymptomatic relapse and baseline visit), patients will need to start treatment at least 12 months before the expiry date. Otherwise, patients will be withdrawn from the trial prior treatment period initiation and their end of study would be defined as the date of study withdrawal.

5. REGISTRATION PROCEDURES

The study design will require two registration procedures, one for the screening period and the other for the treatment period.

5.1. Screening period

At least six months after chemotherapy completion, the patient who meets the eligibility criteria will sign an informed consent form (ICF) and will be assigned a 15-digit identification number which is a combination of the study code (TG4050-01), the 4-digit center number and the 3-digit patient number. The center number is assigned by Transgene to the investigational site. At each site the first patient screened is assigned patient number 001 and subsequent patients are assigned consecutive numbers. Once assigned to a patient, the patient number will not be reused.
For patients having archived tumor tissue, eligibility will be verified. If the patient is not included for any reason, the reason for non-inclusion and a minimum of other parameters (date of ICF signature, demographics and disease characteristics) will be entered in the eCRF.

5.2. Treatment period

At the time of asymptomatic relapse, the patient for whom TG4050 is available will start treatment period. The patient will keep the same identification number for the treatment period. The baseline assessment will last at most 21 days. Tests performed per standard of care (e.g., CT-scan) may not need to be repeated if collected within 28 days prior to start of study treatment.
If the patient is not included for any reason, the reason for non-inclusion and a minimum of other parameters (results of the baseline assessment) will be entered in the eCRF.

6. STUDY VISITS AND PROCEDURES

A flow chart in Appendix II summarizes the evaluations to be performed along with the timepoints for each period of the study and the data to be collected in the eCRF.

6.1. Screening period

6.1.1. Evaluation description

- **Demography**

- Date of birth

- **History of HGSC cancer**
  - Date of diagnosis and abdominal surgery
  - Confirmation of the High Grade
  - Confirmation of the Stage at diagnosis (IIIC or IV)
  - Confirmation of the Histologic type (Serous)
  - Primary tumor location
    - BRCA 1 and 2 status and other molecular characteristics if available (e.g: other mutations of interest, Human Recombination Deficiency status by Genomic Instability Score, Loss of Heterozygosity testing, Telomeric Allelic imbalance or Large scale transition or other metrics)
  - Prior antineoplastic therapies, including date, setting and type of chemotherapy and date of documentation of response
  - Maintenance therapy if any

- **Relevant medical history**
  - Relevant medical history with established diagnosis present or recovered at ICF signature

- **Clinical evaluation**
  - Physical examination of the major organ systems, including vital signs (body temperature, pulse rate and blood pressure) and weight (height to be collected at screening only)

- **Concomitant medications and significant non-drug therapies**

- **Reporting of Serious Adverse reactions (SARs)** caused by a protocol required procedure

- **Blood sampling**
  - HCV serology; detection of Hbs antigen if not performed within 3 months prior to study entry.
  - Blood sampling needed for HLA typing and generation of reference exome

- **Tumor tissue availability**
  - Tumor tissue obtained at the time of abdominal surgery and/or at the time of diagnosis if the patient received neoadjuvant chemotherapy (18G core needle biopsy) will be used for TSAs identification and translational research (see protocol section 8.2.6).

- **CA-125 assessed in an accredited central laboratory**
  - Serum concentration will be assessed as per standard medical practice and at least every 90 to 120 days from study entry. If the patient did not relapse after 2 years of follow-up, this follow-up may be performed at least every 6 months (+1 month) according to Investigator's standard practice.

- **CtDNA assessed in a central laboratory:** every 90 to 120 days from study entry. If the patient did not relapse after 2 years of follow-up, this follow-up may be performed at least every 6 months (+1 month) according to Investigator's standard practice.

- **Tumor imaging**
  - Regular visits will be scheduled as per standard medical practice. CA-125 increase above ULN or occurrence of symptoms or clinical signs will be an indication for imaging.

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

6.1.2. Study entry visit

Once the informed consent is signed, the following will be performed:

- Collection of demographics data
- Recording of history of HGSC and relevant medical history
- Complete response (non-evidence of disease) checked on imaging performed within 28 days prior to or at study entry visit. If a suspicious but indeterminate nodule is identified at study entry, repeat imaging should be obtained 3 months after (+/- 2 weeks) to determinate whether the nodule is malignant. Alternatively, a biopsy may be obtained
- Physical examination of major organ systems, including vital signs, weight and height
- Recording of concomitant medications and significant non-drug therapies
- HCV serology; detection of HBs antigen if not performed within 3 months prior to study entry
- CA-125 concentration
- ctDNA measurement
- Verification of eligibility criteria
- Request for TG4050 manufacturing
  - Tumor tissue sample banked to be sent to sequencing/central laboratory
  - Blood sample collected to be sent to sequencing/central laboratory

6.1.3. Follow-up visits in patients with Complete Response

Follow-up visits will be performed at least every 90 to 120 days in accordance with standard medical practice and include:

- Physical examination, including vital signs and weight (according to local practice, physical examination and vital signs can be done every 6 months beyond 2 years after surgery)
- Concomitant medications and significant non-drug therapies
- CA-125 concentration
- ctDNA measurement
- Imaging per standard practice and if symptoms or clinical signs occur or if CA-125 increases.

If the patient did not relapse after 2 years, these follow-up visits may be performed at least every 6 months (+1 month) according to Investigator's standard practice.

6.1.4. **Asymptomatic relapse study visit**

Each time CA-125 value is above the ULN during the follow-up post-chemotherapy, an asymptomatic relapse assessment will be conducted at least one week later per regular medical practices with:

- Physical examination, including vital signs and weight
- Concomitant medications and significant non-drug therapies
- CA-125 concentration (for increase confirmation)
- Imaging

Based on CA-125 serum concentration and imaging monitoring in asymptomatic relapse study visit, it will be considered that a patient has developed an asymptomatic relapse when:
Cohort A:

- the patient has CA-125 ≥ 2 times ULN on 2 occasions at least 1 week apart

or

- the patient has low volume radiological disease and CA-125 > ULN. Low volume radiological disease is defined as radiologically visible disease excluding intra-hepatic or intra-splenic metastases, ascites or pleural effusion thought to require drainage.

Cohort B:

- the patient is asymptomatic but develops measurable disease excluding intra-hepatic or intra-splenic metastases, ascites or pleural effusion thought to require drainage, whatever serum CA-125 level and for whom further treatment is not planned within 2 months. Longest diameter on CT-scan must not exceed 2 cm for non-nodal lesions and 2.5 cm in short axis for nodal lesions.

When a patient has developed an asymptomatic relapse, a request for clinical supply of TG4050 individualized product will be sent by the clinical site to Transgene.

6.2. Treatment period

Treatment with TG4050 will be initiated in eligible patients for whom the individualized MVA construct is available.
Patients not eligible or for whom the individualized TG4050 product is unavailable will continue to benefit from routine medical monitoring and will receive SOC in case of recurrence as per normal practice.

6.2.1. **Evaluation description**

The following parameters will be measured during this period:

- **Inclusion/exclusion criteria**
  Patient eligibility is to be established by the investigator by confirming that all the treatment period inclusion / exclusion criteria are met. Deviation from any eligibility criterion excludes a patient from registration into the treatment period.

- **Current medical conditions**
  - Syndrome/pathology with established diagnosis starting during the screening period either recovered or ongoing
  - “Signs and symptoms” symptoms with no associated syndrome (e.g., diarrhea) see section 8.2

- **Clinical evaluation**
  - Physical examination of major organ systems, including vital signs (body temperature, pulse rate and blood pressure) and weight
  - PS on ECOG scale (see APPENDIX I)

- **Concomitant medications and significant non-drug therapies**

- **Electrocardiogram (12 leads)**
  - At baseline, every 3 weeks for the first 6 weeks and then every 6 weeks up to Day 169, thereafter every 12 weeks, and at the end of treatment visit

- **Safety assessments**
  - AEs/SAEs collection see section 8.2
  - Follow-up of all ongoing AEs

- **Laboratory assessments**
  - CBC including RBC, Hb, WBC and differential, platelets
  - Biochemistry including AST, ALT, alkaline phosphatases, total bilirubin, glucose, electrolytes (sodium, potassium, magnesium and bicarbonates), creatinine and creatinine clearance

- **Blood sampling and cytapheresis** for translational research; if the post-baseline cytapheresis procedure is not clinically feasible, it can be replaced by a 150 ml blood draw.

  CA-125 evaluation in an accredited central laboratory, serum concentration will be assessed every 3 weeks

- **Tumor imaging**
  - A CT-Scan of the pelvis and abdomen (or MRI) and X-ray or preferably CT-scan of the chest will be performed within 21 days prior to treatment initiation, on Day 43 and then every 9 weeks with a time window of +/- 7 days until disease progression justifying initiation of further treatment

6.2.2. **Baseline visit**

The following procedures will be performed within 21 days prior to treatment start:

- Inclusion/exclusion check
- Physical examination, including vital signs and weight
- PS on ECOG scale
- Current medical conditions and signs/symptoms see section 8.2
- Concomitant medications
- Electrocardiogram
- Tumor assessment by imaging procedures if the previous imaging has been performed more than 4 weeks before treatment start

The following procedures must be performed within 7 days prior to the first dose:

- Inclusion/exclusion check
- Blood analyses including:
  - CBC including RBC, Hb, WBC and differential, platelets
  - Biochemistry tests
  - CA-125 concentration
  - Blood sample and cytapheresis for translational research

6.2.3. Study visits during the treatment period

The time windows allowed for the visits are:

- +/- 1 day for the first 6 weeks
- +/- 7 days beyond the first 6 weeks

During the first 6 weeks
On a weekly basis, the following investigations must be performed:

- Physical examination, including vital signs and weight
- PS on ECOG scale
- Adverse events reporting
- Concomitant medications
- CBC including RBC, Hb, WBC and differential, platelets
- Biochemistry tests

On an every three-weeks basis, the following investigations must be performed:

- CA-125 concentration
- Electrocardiogram

For translational research:

- CCI [redacted]

Imaging at Day 43

Beyond 6 weeks
On an every three-week basis, the following investigations must be performed:

- Physical examination, including vital signs and weight
- PS on ECOG scale
- Adverse events reporting
- Concomitant medications
- CA-125 concentration

CBC including RBC, Hb, WBC and differential, platelets & Biochemistry every 3 weeks up to Month 6 (Day 190), thereafter every 12 weeks.

ECG every 6 weeks up to Day 169, thereafter every 12 weeks.

From Day 43, tumor assessments by imaging procedures must be performed every 9 weeks.

For translational research:

- CCI [redacted]

- Cytapheresis on Day 64; if not clinically feasible, the cytapheresis procedure can be replaced by a 150 ml blood draw.

6.2.4. End of treatment visit

An end of treatment visit will be performed within 7 days after study treatment is completed or stopped for whatever reason (disease progression, unacceptable toxicity including dose-limiting toxicity or, patient withdrawal due to any reason). The end of treatment visit and the last visit planned for treatment administration can be performed on the same day provided that all evaluations and blood samples required at both visits are performed (except if repeated exams).

The following evaluations will be conducted:
- Physical examination, including vital signs and weight
- PS on ECOG scale
- Adverse events reporting
- Concomitant medications
- CBC including RBC, Hb, WBC and differential, platelets
- Biochemistry tests
- Electrocardiogram
- Reporting of subsequent cancer therapy if applicable
- For translational research, a blood sample and tumor sample will be collected at the time of documented disease progression when clinically feasible.
- Cytapheresis: in case patient is withdrawn prior to Day 64, a cytapheresis is to be performed at the end of treatment visit. If not clinically feasible, it can be replaced by a 150 ml blood draw.

6.2.5. Follow-up for secondary activity endpoints

In case the study treatment discontinuation is not due to progressive disease or death, the patient will be followed for secondary endpoints (CA-125 evaluation, Time to measurable relapse or progression justifying initiation of further treatment) or until the date of last contact if the patient is lost to follow-up or withdraws consent. A CT-scan or MRI as well as CA-125 measurement must be obtained every 9 weeks until disease progression and recorded in the eCRF. All subsequent antineoplastic therapies (if applicable) must be recorded in the eCRF with start and end dates.

6.2.6. Safety Follow-up visit

A safety follow-up visit will be performed at least 30 days (+14 days allowed) after the last dose of study treatment.

The following evaluations will be conducted and recorded in eCRF:
- Physical examination, including vital signs and weight
- PS on ECOG scale
- Adverse events reporting
- Concomitant medications
- Reporting of subsequent cancer therapy if applicable

For patients who refuse to return for a visit, they will be contacted by phone to obtain this information if possible.

7. TREATMENT PLAN FOR TREATMENT PERIOD

7.1. Investigational Medicinal Product (IMP) characteristics

In this clinical trial, the Investigational Medicinal Product (IMP) is TG4050.

TG4050 is a suspension of a recombinant MVA strain, a significantly attenuated strain of Vaccinia virus, containing DNA sequences coding for several patient tumor specific antigens (TSAs).

CCI

TG4050 will be supplied along with a Technical Sheet detailing its characteristics.

7.1.1. Manufacturing

For patients who meet screening period eligibility criteria, tumor tissue which have been banked at the time of surgery and/or at the time of diagnosis if the patient received neoadjuvant chemotherapy (18G core needle biopsy), and blood samples will be tested for TSAs identification. TSAs will be used to manufacture an individualized TG4050 mutanome-directed immunotherapy. Manufacturing will take approximately 12 weeks for the vaccine to be prepared in accordance with GMP procedures.

In case of TG4050 individualized construct unavailability in due time or no injection of TG4050 manufactured product for any reason, the reason will be documented as a Failure to provide or a Failure to treat and the patient will be withdrawn from the study. They will continue to benefit from routine medical monitoring and will receive SOC in case of recurrence as per normal practice.

Due to rapid progression of the disease, another round of manufacturing attempt could not be considered in case of Failure to provide or Failure to treat.

7.1.2. Packaging and labeling

TG4050 is supplied as a frozen suspension filled in individual 2-mL glass vials (Type I glass). Each vial is intended for single use (i.e., 1 injection to 1 patient). The recoverable volume of TG4050 in each vial is 0.5 mL with an infectious titer of $1x10^8$ PFU. TG4050 is a colorless to whitish clear or slightly turbid liquid, with possible presence of product particles or filaments.

The primary label on the vial as well as the secondary label on the secondary packaging are in the language of countries where the study is to be performed. Labels are compliant with local regulatory requirements.

Packaging for shipment of TG4050 is compliant with the IATA (International Air Transport Association) and ADR (International Carriage of Dangerous Goods by Road) regulations for air and road transport of infectious substances (UN 373 regulations). TG4050 is shipped in proper transport conditions with the official transport designation "Biological Substance, Category B" by a carrier specialized in Genetically Modified Organisms (GMO) transportation.

7.1.3. Conditions of storage and use

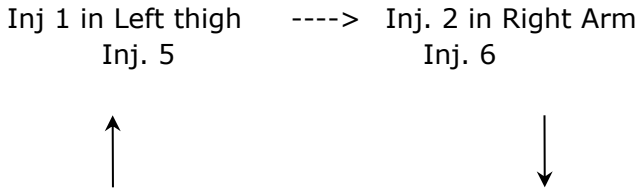
TG4050 must be stored at -20°C +/- 5°C (between -15°C and -25°C), which is equivalent to -4°F +/- 9°F (between +5°F and -13°F), in an alarmed and monitored freezer in a secure place with restricted access until use under the supervision of the study Pharmacist / Investigator (or his/her delegate). The vials will be dispensed only with the written authorization of the Investigator to staff that have been specifically designated and trained for this study.
TG4050 is a Genetically Modified Organism (GMO). As such, and whenever relevant, it must be handled according to national regulatory requirements. The Investigator's Brochure, as well as the Technical Sheet provided by Transgene provide instructions for TG4050 handling (biosafety requirements, preparation, administration, destruction) and incident management.
During all TG4050 handlings, lab coat, goggles, gloves and mask must be worn. All transport of TG4050 (vial or syringe containing the dose to be injected) must be done using a leakproof container/bag.

7.1.4. Preparation and administration procedure

TG4050 doses will be prepared and handled according to the instructions provided in a Preparation Procedure provided by Transgene.

TG4050 must be prepared under aseptic conditions in compliance with requirements for every human injectable preparation. Aseptic conditions mean the standard hospital conditions for injectable preparations that ensure the sterility of the TG4050 solutions.

Each TG4050 dose will be administered by a single SC injection. Four injection sites will be used (left and right arm, left and right thigh) according to a rotation schedule. It is preferable that the first injection is administered in either the right or left thigh. The second injection is to be given in the opposite side arm, the third in the same side thigh, and the fourth in the opposite side arm. For example, if the left thigh is the site of the first vaccination, the second vaccination would be in the right arm, the third in the right thigh, and the fourth in the left arm. This pattern is recommended and will be repeated for subsequent injections.



Inj. 4 in Left Arm ←--- Inj. 3 in Right Thigh
Inj. 8 Inj. 7

If the pattern cannot be followed exactly, it is more important to alternate between the arms and thighs than side to side.

In case of incident while handling TG4050, the actions recommended are described in the Technical Sheet.

Any incident must be documented by a written report to be sent as soon as knowledge of the event to Transgene Medical Department or its designee:

Emergency 24-hour telephone number (international): (33) (0)3 68 33 28 80

7.1.5. Disposal and destruction or return

During the course of the study based on Transgene's request and at termination of the study all unused TG4050 will be destroyed locally or returned to Transgene.

For local destruction, the Investigator/Pharmacist or delegated person will ensure that destruction is performed according to written instructions for disposal of TG4050 and waste generated during the TG4050 preparation and administration (e.g. injected and non-injected syringes, needles, gloves, etc.) available in the TG4050 Investigator's Brochure and the Technical Sheet, and will not expose humans to any risks from TG4050. A certificate of destruction will be completed and provided to Transgene (copy retained by the site).

Alternatively, unused vials of TG4050 may be returned to Transgene with the appropriate documentation. Transgene will coordinate the return of unused vials of TG4050. A certificate of return will be completed and provided to Transgene (copy retained by the site).
All along the study, the monitor will verify that all used TG4050 vials and waste linked to TG4050 handling are disposed locally, all unused/expired vials are returned or destroyed locally, and no product remains on site upon completion or termination of the study.
Accurate records of TG4050 received at, dispensed from, returned to and disposal of by the study site should be recorded appropriately on the drug log.

7.1.6. Supplier

TG4050 will be supplied by Transgene for this study at no cost to the study participant.

7.2. Treatment duration

Study treatment will be administered up to a total of 20 injections unless disease progression justifying initiation of further treatment, unacceptable toxicity including occurrence of a dose-limiting toxicity, or patient withdrawal due to any reason, whichever occurs first.

7.3. Treatment modification

No dose reduction is allowed.
If a grade 1 occurs, TG4050 should be administered as planned. In case a grade ≥ 2 treatment-emergent AE occurs, that is at least possibly related to TG4050, the administration of TG4050 will be delayed until resolution to grade ≤1 with the following exceptions: fatigue and injection site reactions which are common vaccine-associated AEs. The decision to restart TG4050 or to permanently discontinue study treatment will be discussed between the investigator and Transgene.

7.4. Treatment compliance

7.4.1. Dispensing and accountability

TG4050 will only be dispensed, according to Investigator's prescription, to patients who meet all eligibility criteria.
The Investigator / Pharmacist or delegated person will maintain IMP accountability records for TG4050, detailing the dates and quantities dispensed for each patient along with IMP packaging batch numbers, box and vial numbers.
IMP accountability records will be verified by the monitor during site monitoring visits. All used and unused IMP will be accounted for. All unused IMP will be destroyed locally or returned to Transgene, providing destruction or return certificates (see sections 7.1.5 and 7.1.6).

7.4.2. Assessment of compliance

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

7.5. Concomitant medications

7.5.1. Prohibited and/or restricted medications during study treatment

The following medications are prohibited (unless utilized to treat a drug-related adverse event):

- Immunosuppressive agents
- Immunosuppressive doses of systemic corticosteroids (except as stated in Section 7.5.3)
- Any concurrent anti-neoplastic therapy (ie, chemotherapy, hormonal therapy, immunotherapy, radiation therapy, or another standard or investigational agents for treatment of ovarian cancer)
- Any live vaccine for the prevention of infectious disease
- Any other investigational agent

The following non-drug therapies must not be used during the study (and within 28 days before the start of trial treatment):

- Herbal remedies with immunostimulating properties (e.g., mistletoe extract) or known to potentially interfere with major organ function (e.g., hypericin)
- Major surgery

If the use of a non-permitted concomitant therapy becomes necessary during the trial, the patient should be withdrawn from trial treatment (Transgene may be contacted to discuss whether the trial treatment must be discontinued).

7.5.2. Permitted medications/therapies

- Patients are permitted the use of topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption).
- The use of the following drugs will not be restricted during the course of the study: G-CSF, erythropoietin, antiemetics and analgesics.
- The use of systemic corticosteroids during the study is restricted as follows: for short term treatment (≤7 days) of allergic reactions, or for replacement for adrenal insufficiency at doses equivalent to ≤ 10 mg prednisone daily.
- 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.

7.6. 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 study treatment, patients may receive whatever care they and their physicians agree upon.

8. EVALUATION

8.1. Evaluation of screen failure

The percentage of patients who cannot be enrolled in the treatment period and the reason that prevents patients from being treated will be evaluated.
The reasons can be:

- Failure to provide the vaccine (e.g., no mutations identified) or failure to treat (e.g., non-eligibility of the patients for the treatment period)
- Lost to follow-up

8.2. Evaluation during the treatment period

8.2.1. Efficacy evaluation

<u>CA-125 evaluation</u>
CA-125 concentration assessed in an accredited central laboratory will be measured every 3 weeks from the start of study treatment until treatment discontinuation for any reason including documented disease progression by RECIST 1.1. For patients who stopped the study treatment before documentation of disease progression, CA-125 measurements should then be performed every 9 weeks until documented progression. A CA-125 response is defined as at least a 50 %

reduction in CA-125 concentrations from a pretreatment sample according to GCIG criteria. The response must be confirmed and maintained for at least 28 days.
CA-125 doubling time and half-life as appropriate, time to normalization will also be analyzed during the study treatment period.

Tumor evaluation
Tumor response will be evaluated according to RECIST 1.1. Tumor assessment will be performed within 21 days prior to treatment start, at Day 43 and then every 9 weeks until disease progression justifying further treatment and will require CT-scans of the pelvis and abdomen and (X-ray or preferably CT-scan) of the chest. MRI can be used for patients who are allergic to radiographic contrast media. Throughout the study, the same assessment technique must be used.

8.2.2. **Safety evaluation**

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 II).
The safety assessments will be performed according to the schedule of assessments in Appendix II-B.

8.2.2.1. Definitions

Treatment-Emergent Adverse Event (TEAE)
A treatment-emergent adverse event (TEAE) is defined as a sign or symptom that emerges during treatment or within 30 days after the last dose of the study drug, having been absent pre-treatment or that has worsened relative to the pre-treatment state.
Adverse Event (AE)
An Adverse Event 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.

Dose-limiting toxicity (DLT)
Any of the following treatment-emergent AE occurring during the first 6 weeks after TG4050 administration:

- any grade ≥3 toxicity that is at least possibly related to TG4050, with the following exception: pre-existing grade 2 fatigue at baseline that would worsen up to grade 3
- any death.

The occurrence of one of those events in the initial 3 treated patients will trigger study hold.

Beyond the safety run-in phase, a dose-limiting toxicity is defined as any treatment-emergent AE grade ≥3 toxicity that is at least possibly related to TG4050, with the following exception: pre-existing grade 2 fatigue at baseline that would worsen up to grade 3.

In any case, patients experiencing a dose-limiting toxicity will discontinue study treatment permanently.

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 (e.g., pathogenic or nonpathogenic) via the study drug is an SAE.

Although overdose and cancer are not always serious by regulatory definition, these events must be handled as SAEs. (see Section 8.2.4).

NOTE

The following situations do not need to be reported as SAEs:

- Elective hospitalization for pre-existing conditions that have not been exacerbated by trial treatment.
- Hospitalization which was planned before the patient consented for study participation and where admission did not take longer than anticipated.
- Hospitalization planned for protocol related treatment or protocol related procedure as per institutional standard timelines.
- Social and/or convenience admission to a hospital.
- Medical or surgical procedure (e.g., endoscopy, appendectomy); the condition that leads to the procedure is an (S)AE.
- Situations where an untoward medical occurrence did not occur (palliative care, rehabilitation, overdose without occurrence of an adverse event).
- Hospitalization for anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

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., IB).
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.

8.2.2.2. Time period for collection

From the date of signature of ICF and up to first TG4050 administration, only serious adverse reactions (SARs) caused by a protocol-required procedure will be collected and reported (refer to section 8.2.2. and 8.2.3). The only protocol-required procedure concerned is the specific blood sample taken during the screening period.
AEs, SAEs, or procedure related ARs that occur between ICF signature and 3 weeks prior to first administration, and that are considered by the investigator as particularly relevant to the patient's condition, will be collected as a current medical history.
If an event occurs during the period from 21 days before and up to first TG4050 administration, 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., diarrhea).

From the first TG4050 administration and in case of worsening of a sign and symptoms which started 21 days before first TG4050 administration, an AE page will be completed using a verbatim starting by "worsening of..."
From the initiation of TG4050 treatment up to the safety follow-up visit (at least 30 days after the last administration of study treatment), all AEs and SAEs should be collected and recorded on the eCRF. During this period all SAEs should also be reported to Transgene.
All SARs related to a study specific procedure occurring during the screening period and all SAEs occurring during the treatment period will be recorded in Transgene safety database.

SAEs occurring more than 30 days after administration of the last dose of TG4050 and evaluated by the investigator as related to TG4050 should be collected and reported to Transgene indefinitely even after study closure. These will however not be reported in the eCRF after Database lock.

8.2.2.3. Adverse event / Serious adverse event management

8.2.2.4. 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 or to study procedures,
- action taken regarding the study treatment,
- action taken regarding the event,
- outcome.

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.

Intensity
The intensity of AE/SAE will be graded according to the NCI-CTCAE (version 5) 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 or decrease 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 IMP of each AE/SAE will be evaluated by the Investigator with EudraVigilance Clinical Trial Module" (EVCTM) method using the following levels:

- **No reasonable possibility** (i.e. no facts (evidence) or arguments to suggest a causal relationship): the temporal relationship of the clinical event to the administration of study

treatments makes a causal relationship unlikely; and other drugs, therapeutic interventions or underlying conditions provide a sufficient explanation for the observed event.

- **Reasonable possibility** (i.e. facts (evidence) or arguments to suggest a causal relationship): the temporal relationship of the clinical event to the administration of the study treatments 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 treatment or recurrence upon rechallenge may also be observed.

Outcome

The outcome is rated as follows:

- recovered,
- not recovered,
- worsening
- recovering,
- 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 IMP

- None: administration continues as planned in the protocol
- Delayed: administration following the occurrence of the event is delayed
- Cancelled: administration following the occurrence of the event is cancelled
- 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)

8.2.2.5. Follow-up

Once an AE is detected, it must be proactively followed until its resolution or 30 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
- 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) is thought to be related to the IMP.

8.2.2.6. 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.

8.2.2.7. Notification to investigators

In case of a grade ≥ 3 AE suspected to be related to TG4050 occurs, Transgene or its representative will inform all investigators involved in the study that such an event has been reported as soon they became aware.

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

Reporting to Transgene
Any SAE occurring during the screening period (after ICF signature and before TG4050 treatment initiation) related to a study specific procedure (specific blood sample taken during the screening period) MUST be reported to Transgene.
Any SAE occurring during the treatment period (from TG4050 treatment initiation and up to 30 days after last study treatment administration) whether or not related to TG4050 MUST be reported to Transgene.
SAEs occurring more than 30 days after administration of the last dose of TG4050 and evaluated by the investigator as related to TG4050 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.

	France
	Pharmacovigilance Physician
Name	PPD
Phone number	PPD
Fax number	PPD
Email	PPD
Emergency 24-hour telephone number	PPD

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. The signed form must be sent (preferably by email otherwise by fax) to Transgene immediately.
The SAE form must 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
Transgene 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, Transgene 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 Committees, IRB(s) of SUSARs, any other SAEs, and any follow-up information as per local regulations.
Transgene or its representative is responsible for ensuring that all AEs and SAEs that are observed or reported during the study are collected and reported to the FDA in accordance with CFR 312.32 (IND Safety Reports).

8.2.4. Special situations

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 8.2.3).
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
- Document the quantity of the excess dose as well as the duration of the overdosing in the eCRF

Decisions regarding dose interruptions or modifications secondary to an overdose will be made by the Investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

Any overdose should be reported to Transgene within 24 HOURS and documented and followed-up using an "Overdose form". In addition, any associated symptoms should be reported as an AE or SAE.

Other safety considerations

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

8.2.5. 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 the IMP. If related to the IMP, they should be followed even after the safety follow-up visit (see Section 8.2).
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

8.2.6. Translational research and exploratory evaluations

Mutational load and impact of vaccination on tumor mutational profile; specifically, tumor exome and transcriptome sequencing prior to initiation of treatment will allow identification of tumor specific mutations and their respective level of expression in tumor tissue. CCI

CCI [redacted]

CCI [redacted]

9. STATISTICAL METHODS PLANNED AND SAMPLE SIZE

9.1. Data sets analyzed

9.1.1. Screening period

All patients having signed the ICF will be considered as screened patients and included in the screening population (SCR). The percentage of patients not treated afterwards and the corresponding reason, will be analyzed. Available data from screen failed patients will be listed separately and presented according to the statistical plan.

9.1.2. Treatment period

Patients will be enrolled in separate cohorts at the time of treatment initiation according to:

- Cohort A: patients develop an asymptomatic relapse defined on the basis of progressive serial elevations of serum CA-125 (GCIG criteria) or documentation of low volume radiological disease with CA-125 > Upper Limit of Normal (ULN). Low volume radiological disease is defined as radiologically visible disease excluding intra-hepatic or intra-splenic metastases, ascites or pleural effusion thought to require drainage.

- Cohort B: patients develop an asymptomatic relapse with measurable disease excluding intra-hepatic or splenic metastases, ascites or pleural effusion thought to require drainage, whatever serum CA-125 level and for whom further treatment is not planned within 2 months. Longest diameter on CT-scan must not exceed 2 cm for non-nodal lesions and 2.5 cm in the short axis for nodal lesions.

Safety Analysis Set (SAF): all patients included and who received at least one dose of TG4050 will be included in the SAF. This is the primary dataset for safety analyses.

Evaluable Safety Set (ESAF): first 3 patients in SAF who completed the first 6 weeks of treatment or discontinued due to a DLT. Patients who are not evaluable for safety analysis during the run-in phase, or who are withdrawn for other reasons than toxicity, will be replaced.

Evaluable Per-Protocol Set (EPP): all included patients in each cohort without any major protocol deviation who received at least the 6 first weekly injections of TG4050 corresponding to the treatment induction phase and have at least two baseline and two post-baseline evaluations of CA-125 and one baseline and one post-baseline CT-scan or MRI.

Modified Evaluable Per-Protocol (mEPP): patients from EPP in each cohort who are evaluable for immune response meaning at least one pre-dose evaluation and one post-baseline evaluation.

9.2. Determination of sample size

No formal sample size calculation is planned.

9.3. Study endpoint

9.3.1. Primary endpoint

Adverse events will be assessed throughout the treatment period and graded according to NCI CTCAE version 5.

9.3.2. Secondary endpoints

- Failure to provide rate: percentage of patients for whom TG4050 cannot be provided and the reason for not being able to provide the vaccine will be recorded.
- Failure to treat rate: percentage of patients who cannot receive TG4050 and the reason that prevent patient from being treated.
- CA-125 doubling time and half-life as appropriate
- Time to normalization of CA-125
- Response according to GCIC criteria
- Time to measurable relapse in Cohort A and Time to progression in Cohort B per RECIST 1.1
- Tumor response according to RECIST 1.1

9.3.3. Translational research

The following exploratory endpoints will be investigated:

- CCI

- Quantification of tumor and immune related biomarkers

9.4. Statistical and analytical plans

9.4.1. Safety analyses for the treatment period

All safety analyses will be performed and summarized in the SAF. Safety analyses will also be conducted in each cohort of treated patients.

Adverse events

AE summaries will include all TEAEs corresponding to AEs that have started on or after the day of first study treatment administration or that have worsened on or after first TG4050 administration and starting no later than 30 days after the date of last study treatment administration. All AEs, significant AEs, AEs leading to discontinuation of study treatment, severe AEs (Grade 3 or 4) and serious AEs (SAE) will be listed and summarized by System Organ Class (SOC) and Preferred Term (PT), intensity (based on the NCI CTCAE grades, relationship to TG4050).

Written narratives will be produced for all SAEs and unexpected or other significant AEs that are judged to be of special interest because of their clinical importance.

Adverse events/SAEs occurring after signing the Informed Consent Form (ICF) but before starting study treatment, including those observed in patients screened but not included will be listed separately from those occurring after treatment start.

SAEs occurring more than 30 days after administration of the last dose of TG4050 and evaluated by the investigator as related to TG4050 will be listed separately.

Fatal Events

All fatal events will be listed and summarized by System Organ Class (SOC) and Preferred Term (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 in patients screened but not included will be listed separately from those occurring after treatment start.

Laboratory abnormalities

The summaries will include all laboratory assessments collected from baseline assessment until 30 days after treatment discontinuation. All laboratory assessments will be listed and those collected during 30 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 5). 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.

9.4.2. Efficacy analyses for the treatment period

The analysis of the efficacy endpoints will be performed on the evaluable population (EPP) for efficacy in each cohort of treated patients.
CA-125 doubling time and half-life as appropriate, time to normalization and response according to GCIG as well as time to measurable relapse or progression will be analyzed.
Time to measurable relapse in Cohort A and Time to progression in Cohort B per RECIST 1.1
Tumor response according to RECIST 1.1. will be analyzed.

9.4.3. Translational research

A statistical analysis plan dedicated to translational research will be provided separately.

9.5. Methods of analysis

9.5.1. 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) where appropriate. Categorical variables will be summarized by frequency (N) and percentage (%). Proportions will be estimated with their 95% CIs when appropriate.

9.5.2. 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.

9.5.3. Demographic and baseline characteristics

Baseline demographics and disease characteristics data will be listed and summarized. Qualitative data will be summarized by means of contingency tables, and quantitative data will be summarized by appropriate descriptive statistics (mean, standard deviation, median, Q1, Q3, minimum, and maximum).

9.5.4. Treatments

9.5.4.1. Prior anti-cancer therapies

Prior antineoplastic therapies will be listed and summarized (surgery, chemotherapy, other therapies).

The SAF set will be used for all summaries and listings of prior anti-cancer therapies and results will also be provided for each cohort of treated patients.

9.5.4.2. Study treatment

Exposure to TG4050 will be provided by listing and summarizing the number of injections and the duration of treatment.
The SAF will be used for all summaries and listings of study treatment. Analyses will be displayed separately for each cohort of treated patients.
The number of patients with dose omission will be presented along with reasons for the dose omission.

9.5.4.3. Concomitant medications

Medications and/or non-drug therapies taken by the patient during the month prior to start of the study treatment, as well as all medications and significant non-drug therapies taken during the course of the study up to 30 days after the last study treatment administration, will be collected with their start date and end date, reason for prescription, route of administration and dose.
The concomitant medications (i.e., ongoing at the start of study treatment or taken during the course of the study) will be coded using WHO Drug dictionary including the Anatomical Therapeutic Chemical (ATC) classification and will be listed and summarized by active ingredient by means of frequency counts and percentages.
The SAF will be used for all above mentioned concomitant medication tables.

9.6. Protocol deviations

Any protocol deviations impacting statistical analyses will be classified as major and the list will be described in the statistical analysis plan in order to determine the evaluable population for efficacy. All these protocol deviations for included patients will be presented by patient in data listings with a distinction between deviations at inclusion and deviations during the study.
The number of patients with at least one major protocol deviation will be summarized by type and overall with a distinction between deviations at inclusion and deviations during the study.

10. CHANGES IN THE CONDUCT OF THE STUDY

10.1. Protocol amendments

Changes to this protocol will be performed 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 authorization / approval.

10.2. Premature termination or suspension of the study

During the safety run-in phase, the study may be suspended and an IDMC ad-hoc meeting immediately called if at least one of the following events occur:
- any grade ≥3 toxicity that is at least possibly related to TG4050, with the following exception: pre-existing grade 2 fatigue at baseline that would worsen up to grade 3
- any death.

Beyond the safety run-in phase, the study may be suspended or terminated under any of the following circumstances:
- Sponsor's decision
- Health Authorities' decision
- Any death, unrelated to progressive disease, which occurs within 30 days after TG4050 administration
- IDMC recommendation in case of a safety concern. However, in this case, the final decision as to whether or not to continue the study will be taken by Transgene.

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 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 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.

11. ETHICAL CONSIDERATIONS

11.1. 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 and the list of members having participated in the meeting including their qualification.

In addition, IEC / IRB written approval must be obtained by Transgene for protocol amendment as described in Section 10.1.

11.2. 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 (for instance, the European General Data Protection Regulation for European countries).

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.

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.

11.3. 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.

For European countries:
Confidentiality of patients' medical records will be maintained in accordance with the applicable data privacy laws such as, for instance, the European General Data Protection Regulation (Regulation EU 2016/679 of 27 April 2016 on the protection of natural persons regarding the processing of personal data and on the free movement of such data).

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.

11.4. Independent Data Monitoring Committee

11.4.1. Responsibilities of the Independent Data Monitoring Committee

Members of the IDMC will be responsible for reviewing primarily the safety data as well as the conduct of the study.

The IDMC will review the safety data of the 3 first patients from Cohort A or B at the end of the safety run-in phase of the treatment period.
In addition to the review of the first 3 patients, the IDMC will review safety data of all patients included every 3 months during the first year and every 6 months thereafter.
Safety reviews by the IDMC may also be called by Transgene on an *ad hoc* basis upon necessity.

11.4.2. Safety reviews to investigators

The outcome(s) of any safety review conducted by the IDMC during the study will be shared with all participating investigators including corrective measures, if appropriate. Timelines of communication to participating investigators will be specified in the IDMC charter. Written and signed recommendations from the IDMC will be available within 24 hours.

Further details on the organization, roles, and responsibilities of this committee will be established in an Independent Data Monitoring Committee charter signed by its members.

12. REGULATORY CONSIDERATIONS

This study will be conducted in accordance with:
- The updated Declaration of Helsinki adopted by the World Medical Association,
- The ICH E6 (R2) (International Conference on Harmonization) Good Clinical Practice (GCP) guidelines, and
- The local regulatory requirements.

12.1. 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 committee, as required. All approvals must be obtained before a patient is exposed to a study-related procedure, including baseline screening tests for eligibility.

12.2. 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 supervising any individual or party to whom trial-related duties and functions conducted at the site have been delegated. When trial-related duties or functions are delegated to parties, the investigator should ensure the individual or party is qualified to perform the delegated tasks and should implement procedures to ensure the integrity of the trial-related duties and functions performed and any data generated.

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.

12.3. Insurance

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

13. QUALITY CONTROL AND QUALITY ASSURANCE

13.1. Monitoring

The monitor will contact and visit the Investigator periodically to evaluate study progress and protocol compliance 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. Remote monitoring is allowed in the respect of maintaining confidentiality and integrity of medical data.

Monitoring activities are based on instructions given within the Monitoring Plan and could be complemented by Central monitoring activities.
During the visit, the Investigator and any study staff member will co-operate with the monitor to ensure that any problems are resolved.

13.2. 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.
Transgene 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 investigational site or Transgene 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.

14. DATA HANDLING AND RECORD KEEPING

14.1. 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 treatment administrations, concomitant medications, evaluation criteria and nature of adverse events with date of start and end and relationship to study treatment. The location of each source data will be identified on a dedicated form.

If computerized systems are used to record subjects' source data (i.e. subjects' electronic source documents), 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 people can access the system (log in / password) to enter/change data,
- the system allows audit trail of entries / changes,
- existence of a back-up system,
- existence of data security in case of a system break down,

- the users of the system are trained to the system,
- a user list is maintained,
- existence of a written procedure covering these aspects,
- servers containing data are physically protected,
- if an electronic signature is used:
    - the log in and password are entered upon signature
    - the electronic signature is timestamped
- if no electronic signature is in place, the PI agrees to print out subjects' source data periodically and to sign the printouts.

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.

14.2. 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 by the investigator.
The eCRFs should always reflect the latest observations on the patients participating in the study. Therefore, the eCRFs are to be completed without any delay 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 all the 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 or confirmation are needed, the Monitors, Data Manager(s) or authorized Transgene's medical monitors will raise a query.

After database lock, the Principal Investigator will receive a copy of the patient eCRF data for archiving at the investigational site.

15. CLINICAL STUDY REPORT AND PUBLICATION

15.1. 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.

15.2. 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.

15.3. 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 Transgene 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 Transgene's personnel exceeded that of conventional monitoring will be considered for co-authorship provided all other criteria of ICMJE are met.

16. ARCHIVING

16.1. 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.

16.2. 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.

17. APPENDICES

APPENDIX I: PERFORMANCE STATUS (ECOG) SCALE
APPENDIX IIA STUDY FLOW CHART (screening period)
APPENDIX IIB: STUDY FLOW CHART (treatment period)

18. REFERENCES

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APPENDIX I

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 II-A: STUDY FLOW-CHART

Screening-period

	Study entry (At least six months after first-line CT)	Follow-up in CR patients	Asymptomatic relapse
ICF	**X**		
History of HGSC, relevant medical history	**X**		
Inclusion/exclusion criteria check	**X**[(1)]		**X**
Physical examination	**X**	**X**	**X**
Concomitant medications	**X**	**X**	**X**
HCV, HBsAg	**X**		
Blood sampling (for sequencing/central laboratory)	**X**		
Archived tumor tissue (for sequencing/central laboratory)	**X**		
CA-125 concentration	**X**	**X**	**X**[(2)]
ctDNA measurement	**X**	**X**	
Imaging	**X**[(3)]	**X** [(4)]	**X**[(2)]
Request for clinical supplies			**X**

[(1)] Check that complete response has been achieved. If a suspicious but indeterminate nodule is identified at study entry, repeat imaging should be obtained 3 months after (+/- 2 weeks) to determinate whether the nodule is malignant. Alternatively, a biopsy may be obtained.
[(2)] Cohort A: CA-125 ≥ 2 x ULN on 2 occasions at least 1 week apart; or low volume radiological disease and CA-125 > ULN
Cohort B: patient asymptomatic with measurable disease whatever serum CA-125 level and for whom further treatment is not planned within 2 months.
[(3)] Imaging performed within 28 days prior to study entry visit can be used
[(4)] Imaging indicated if symptoms or clinical signs occur or if CA-125 increases or as current medical practice

APPENDIX II B: STUDY FLOW-CHART

Treatment period

	Baseline		**First 6 weeks**							**Beyond 6 weeks**		**End of treatment visit**	**Safety Follow-up visit**	**Observation [6]**
	≤ 21 days prior to treatment start	≤ 7 days prior to treatment start	D1	D8 (W1) +/- 1 day	D15 (W2) +/- 1 day	D22 (W3) +/- 1 day	D29 (W4) +/- 1 day	D36 (W5) +/- 1 day	D43 (W6) +/- 1 day	Q3 weeks +/- 7 days	Q9 weeks +/- 7 days	Within 7 days after treatment stop	At least 30 days after last study treatment administration (+ 14 days)	Q9weeks +/- 7 days
TG4050 Administration [9]			X	X	X	X	X	X	X	X				
Inclusion/exclusion criteria check	X	X												
Current medical conditions	X													
Physical examination	X		X	X	X	X	X	X	X	X		X	X	
Performance status	X		X	X	X	X	X	X	X	X		X	X	
ECG	X					X			X	X[3]		X		
AEs/SAEs reporting[7]	X		X	X	X	X	X	X	X	X		X	X	
Concomitant medications	X		X	X	X	X	X	X	X	X		X	X	
CBC		X		X[8]	X[8]	X[8]	X[8]	X[8]	X[8]	X[8]		X		
Biochemistry		X		X[8]	X[8]	X[8]	X[8]	X[8]	X[8]	X[8]		X		
Blood samples + cytapheresis for translational research		X[1]		X[1]		X[1]			X[1]	X[1]		X[1]		

	Baseline		**First 6 weeks**							**Beyond 6 weeks**		**End of treatment visit**	**Safety Follow-up visit**	**Observation (6)**
	≤ 21 days prior to treatment start	≤ 7 days prior to treatment start	D1	D8 (W1) +/- 1 day	D15 (W2) +/- 1 day	D22 (W3) +/- 1 day	D29 (W4) +/- 1 day	D36 (W5) +/- 1 day	D43 (W6) +/- 1 day	Q3 weeks +/- 7 days	Q9 weeks +/- 7 days	Within 7 days after treatment stop	At least 30 days after last study treatment administration (+ 14 days)	Q9 weeks +/- 7 days
Tumor samples for translational research												X(2)		
CA-125 concentration		X				X			X	X				X
Tumor assessment	X(4)								X		X(5)			X

(1) Blood samples for translational research will be collected at baseline, on CCI [redacted], cytapheresis at baseline and on Day 64 or at the end of treatment visit if patient is withdrawn prior to Day 64.

(2) Tumor samples for translational research will be collected at the time of clinical recurrence

(3) ECG every 6 weeks up to Day 169, thereafter every 12 weeks

(4) Imaging to be performed only if the previous imaging has been performed more than 4 weeks before treatment start.

(5) Tumor assessment by imaging procedures will be performed on Day 43 and every 9 weeks thereafter

(6) For patients who stopped study treatment before documentation of disease progression

(7) AEs reported up to 30 days after last treatment, only SAEs related to IMP thereafter

(8) CBC including RBC, Hb, WBC and differential, platelets & Biochemistry every week up to Week 6, then every 3 weeks up to Month 6 (Day190), thereafter every 12 weeks

(9) TG4050 will be administered up to a total of 20 injections or until disease progression justifying initiation of further treatment, unacceptable toxicity including occurrence of a dose-limiting toxicity, or patient withdrawal for any reason whichever occurs first.