Statistical Analysis Plan (SAP)

Version 3.0: 10JUN2025

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

EUDRACT N°2018-003266-14

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Table of Contents

LIST OF ABBREVIATIONS

ABBREVIATIONS	MEANING OF ABBREVIATIONS IN DOCUMENT
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine amino-transferase (=SGOT)
AR	Adverse Reaction
AST	Aspartate amino-transferase (=SGPT)
BMI	Body Mass Index
Bpm	Beats per minute
CI	Confidence Interval
CR	Complete Response
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
D	Day
DBP	Diastolic Blood Pressure
DLT	Dose Limiting Toxicity
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EOT	End of Treatment
EOS	End of Study
EPP	Evaluable Per-Protocol Set
FIGO	Federation of Gynecology and Obstetrics
GCIG	Gynecologic Cancer InterGroup
GCP	Good Clinical Practice
HBsAg	Hepatitis B surface Antigen
HCV	Hepatitis C Virus
HGSC	High grade serous carcinoma
ICF	Informed Consent Form
IDMC	Independent Data Monitoring Committee
INT	Integer part
IU	International Unit
LDH	Lactate Dehydrogenase
LLN	Lower Limit of Normal
M	Month
MAX	Maximum
MIN	Minimum

MRI	Magnetic Resonance Imaging
MVA	Modified Virus Ankara
N	Number
NA	Not Applicable
NCI	National Cancer Institute
NCS	Not Clinically Significant
PD	Progressive Disease
PFU	Plaque Forming Unit
PP	Per Protocol
PR	Partial Response
PS	Performance Status
PT	Preferred Term
Q1	First quartile
Q3	Third quartile
RBC	Red Blood Cells
RECIST	Response Evaluation Criteria In Solid Tumors
SAE	Serious Adverse Event
SAF	Safety set
SBP	Systolic Blood Pressure
SC	Subcutaneous
sd	Standard deviation
SD	Stable Disease
SI units	International System of units
SOC	System Organ Class
TA	Tumor Assessment
TSAs	Tumor Specific Antigens
TMB	Tumor Mutational Burden
ULN	Upper Limit of Normal
UNK	Unknown
WBC	White Blood Cells
WHO	World Health Organization

1 UPSTREAM DOCUMENTATION

The following documents were used to prepare the Statistical Analysis Plan:

- TG4050.01 Protocol-HGSC-Version 9.0_20230912
- TG4050.01_Blank CRF V8.0_20241120

2 STUDY DESIGN

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

The study consists of 2 parts for each patient:

2.1 Study parts

2.1.1 Screening period

A screening period 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 IVA disease, who achieved a complete response after chemotherapy maintained for at least 6 months and from whom tumor tissue is available for tumor neoantigens identification can be included in the screening period.

For those patients, tumor tissue which have been banked at the time of surgery 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: serum CA-125 measurements performed in an accredited central laboratory at least every 3 to 4 months and imaging in the event of CA-125 increase and/or clinical symptoms. 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. If the patient did not relapse after 2 years of follow-up, this follow-up is performed at least every 6 months (+1 month) according to the investigator's standard practice.

2.1.2 Treatment period

A treatment period with TG4050 monotherapy will start 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 > 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 documented disease progression as defined by RECIST 1.1 justifying treatment with chemotherapy, or unacceptable toxicity including occurrence of a dose-limiting toxicity, or patient withdrawal for any reason, whichever occurs first.

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 every 3 weeks after start of study treatment.
- Imaging performed within 21 days prior to treatment initiation, at day 43 and every 9 weeks after study treatment start.
- 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 documented disease progression according to RECIST 1.1.

Safety run-in phase:

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. 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 a dose-limiting toxicity 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 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.

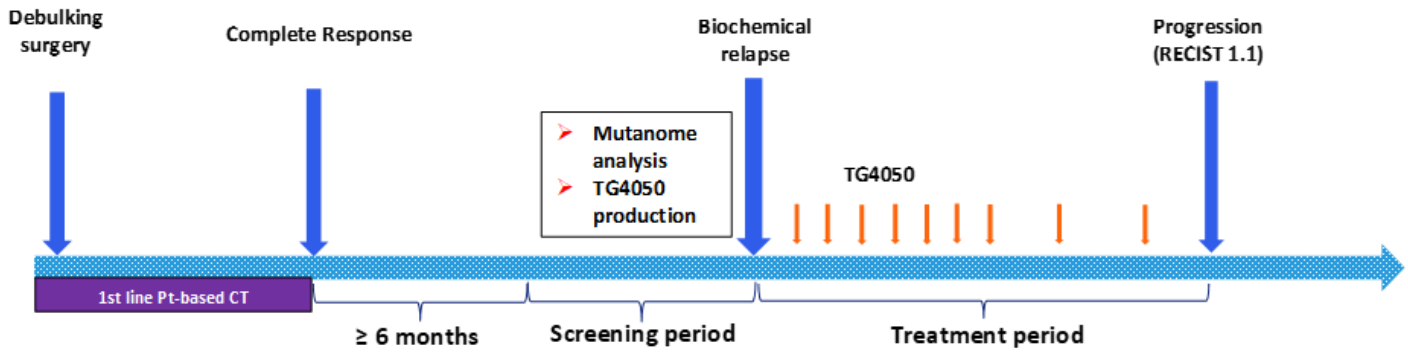
Independent Data Monitoring Committee (IDMC):

An Independent Data Monitoring Committee will be set up for the purpose of reviewing patients' safety data and 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.



Graphical study design:

2.2 Number of patients

The study will be conducted in France and US and involve 5 centers:

- An approximate number of 60 patients will be included in the screening period

Note: If some patients have not relapsed within 36 months after vaccine manufacture, they will be withdrawn from the study and will not be replaced.

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

3 STUDY OBJECTIVES AND ENDPOINTS

3.1 Primary objectives

The primary objective of the study is to evaluate the safety and tolerability of multiple subcutaneous (SC) injections of a neoantigen-directed active immunotherapy (TG4050) in ovarian, fallopian or peritoneal high grade serous carcinoma (HGSC) patients with asymptomatic relapse.

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

3.2 Secondary objectives

Secondary endpoints are to evaluate the rate of failure to provide TG4050 and failure to treat with TG4050, to evaluate, if applicable, the CA-125 doubling time/time to normalization (this analysis won't be performed given the low number of evaluable patients) and response according to GCIG criteria and time

to measurable relapse in cohort A and time to progression in cohort B per RECIST 1.1 and the tumor response according to RECIST 1.1.

3.3 Exploratory objectives

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

4 STUDY DURATION

The study started in Q4 2019. The study was stopped due to low inclusion rate in October 2024 with 6 patients treated.

5 TREATMENT PLAN

5.1 Randomization

No randomization is planned in this study.

5.2 Duration of Treatment

TG4050 will be administered up to a total of 20 injections or until disease progression according to RECIST 1.1, unacceptable toxicity including occurrence of a dose-limiting toxicity, or patient withdrawal for any reason whichever occurs first.

6 DEFINITION OF THE POPULATIONS TO BE ANALYSED

6.1 Populations

- **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.

Screening population (SCR): all patients who have signed the ICF.

- **Treatment period:**

Safety Analysis Set (SAF): all patients 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 who completed the first 6 weeks of treatment or discontinued before due to the occurrence of 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 treated patients without any major protocol deviation who received at least 6 injections of TG4050 corresponding to the treatment induction phase.
Modified Evaluable Per-Protocol (mEPP): patients from EPP who are evaluable for immune response meaning at least one pre-dose evaluation and one post-dose evaluation.
Given the small number of patients, this population won't be used.

6.2 Major protocol deviations

The identification of major protocol deviations is critical for the EPP definition. A protocol deviation classified as major, will lead to the exclusion of patient from the EPP.

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A non-exhaustive list of protocol deviations including inclusion/exclusion deviations is displayed in APPENDIX 1 – Protocol deviations.

7 STATISTICAL DESIGN

7.1 Sample size determination

No formal sample size calculation is planned for this study.

7.2 Data review Meeting

A data review meeting will occur before the lock for final statistical analysis. Data listings will be produced by project biostatistician before the data review meeting, the list of listings to produce will be defined in agreement with Project Team.

7.3 Missing data

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

No imputation will be done for missing data, except for calculation of duration with missing and incomplete dates for adverse events (AE) and missing, incomplete date for diagnosis and for concomitant medications. Missing data will be noted as missing in appropriate tables/listings.

Imputation rules for partial date of initial diagnosis:

- If the month and year are present, impute the day by the 15th day of that month.
- If only the year is present, impute by July 1st of that year.

Imputation Rules for Partial or Missing Start Dates for AE:

- If the month and year are present, impute the day by the first day of that month. If the month and year are the same as those of the date of first TG4050 injection, impute the day with the day of first injection.
- If only the year is present, impute by January 1st. If the year is the same as the year of the date of first TG4050 injection, impute by the date of first injection.

Imputation Rules for Partial or Missing Stop Dates for AE:

- If the month and year are present, impute the day by the last day of that month.
- If only the year is present, impute by December 31st of that year. If the stop date is entirely missing, assume the event is ongoing.

As prior and concomitant medications are summarized in two tables according to their start date (before or the day of first administration and after or the day of first administration), partial or missing start date of prior and concomitant medications will be imputed to discriminate them for the two tables. Missing data will be noted as missing in appropriate listings.

Imputation rules for partial or missing start date for CM:

- If the month and year are present, impute the day with the first day of that month.
- If only the year is present, impute by January 1st of that year.

- If the start date is entirely missing:
    - If the end date is after the date of ICF signature, impute the start date by the ICF signature,
    - Or, if the end date is before the ICF signature or missing, impute the start date by the date of birth.

7.4 Purpose of Safety Analyses

The safety run-in phase will be conducted in the first 3 treated patients for at least 6 weeks after TG4050 first dose. Each patient will be monitored for 4 weeks after the first injection of TG4050 before the next patient can be enrolled.

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 occurs:

- 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's 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 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.

7.5 Final Statistical Analysis

Drafts TFLs will be produced and reviewed before the database export to ensure that no critical data is missing and to check potential inconsistency in the database.

Final Analysis will be performed when all patients completed study treatment up to 20 injections or withdrew for any reasons.

7.6 Definitions and Derived variables

7.6.1 Definitions

Screened patient: A patient having consented

Re-screened patient: A patient who did not meet eligibility criteria when initially consented. This patient may fulfill criteria later and will be re-consented for screening.

Screened failed patient: A screened patient never treated in the study for any reason.

Treated patient: A patient having received at least one TG4050 dose.

Completed patient: Patient will be considered as completer if she received the treatment until:

- Disease progression or until the maximum number of administrations has been reached (20 injections of TG4050)
- occurrence of an AE due to DLT or linked to progressive disease
- Death

Baseline: Unless otherwise specified, baseline is the last measurement taken prior to the first injection of TG4050.

Baseline assessment for efficacy evaluations: In the context of baseline definition, the efficacy evaluations include in particular tumor evaluations and CA125 measurement. If baseline assessment is missing, results obtained at Day 1 can be used if assessments were performed prior to first TG4050 injection.

Baseline assessment for safety evaluations: the last available assessment before first TG4050 injection. If patients have no assessment as defined above, the baseline result will be missing. Baseline can be D1 if assessment was done before first TG4050 injection.

Study day:

- From first treatment administration, study day will be calculated using the start date of treatment as the origin, i.e. the study day will be calculated as (date of assessment) – (start date of study treatment) +1. Then study day 1 will be the first day of first study treatment administration.
- For pre-study treatment administration measurements, the study day will be negative and calculated as (date of assessment) – (start date of study treatment).

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

Time window (to check visits out of this window):

- For the visits:
  - +/-1 day for the first 6 weeks
  - +/- 7 days beyond the first 6 weeks
- For the tumor assessment:
  - Every 9 weeks with a time widow of +/- 7 days from start of treatment, CT-scan or MRI of the abdomen and pelvis are mandatory. Brain and chest CT are to be performed if lesions are suspected.

Progressive disease: as documented on tumor assessment according to RECIST 1.1.

Progressive disease will be determined according to RECIST (version 1.1) based on local evaluations. Lesions (non-target) identified at baseline, if any, will be followed post-baseline. The appearance of new lesions will also be investigated if clinically indicated.

Tumor response:

Tumor response status assessments will be evaluated by imaging performed every 9 weeks from first TG4050 administration until documented progression. Only tumor assessments performed before the start of further antineoplastic therapies (i.e. any additional secondary antineoplastic therapy or surgery) will be considered.

Per RECIST 1.1, the method used at baseline should match at all subsequent assessments, but, for a number of reasons such as site error (e.g. switch from MRI to CT) or renal dysfunction (making contrast a risk), this will not always be done. A strict implementation of RECIST would mean that any change in imaging method compared to one used at baseline should lead to unknown overall response at given assessment.

The number and percentage of patients with complete response among patients with non-measurable lesion at baseline will be presented.

End of study: The end of study is defined as the date of the last patient last visit (including safety follow-up visit). The end of study form in the eCRF will be filled in when patient withdraws the study due to any reason.

7.6.2 Derived variable

The following conventions will be used:

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

The following variables will be calculated:

- Age in years: the age at informed consent form (ICF) signature presented in whole years
  (year of ICF signature – year of birth)
- Body Mass Index (BMI) expressed in kg/m^2: Weight (kg) / Height² (m²)
- Duration of an event (in days): End date – Start date + 1
- Time since initial diagnosis (Months): (date of ICF signature – date of initial diagnosis)/30.4375

Time to measurable relapse per RECIST 1.1 (months) is defined as the time from the date of the first injection until relapse or documented progressive disease whichever occurs first. Time to measurable relapse will be censored if no progression is observed at the cut-off date for analysis. The censoring date will be the date of the last evaluable tumor assessment before the cut-off date.
Time to measurable relapse expressed in months =
((Date of documented relapse/disease progression) - date of first treatment injection) +1)/30.4375
or
(Date of last evaluable tumor assessment – date of first treatment injection +1)/30.4375 in case of censoring.

Relative Dose intensity (RDI) (%): expressed as percentage and defined as the ratio of "delivered" to the "planned" dose intensity. As the dose is always the same (10^8 / pfu), RDI is calculated as the ratio of number of injections received divided by the number of injections planned. A Relative Dose Intensity of 100% indicates that TG4050 was administered as planned, without delay and without cancellations.

Delivered Dose intensity (10^8 pfu/week):
If last dose before D43 visit (visit day ≤ 44)

- number of injections / [(Last dose date-1st dose date +7)/7]

If last dose on or after D43 visit (visit day > 44):

- number of injections / [(Last dose date-1st dose date +7*3)/7]

Planned Dose intensity (10^8 pfu/week):
If last dose before D43 visit (visit day < 42): 1
If last dose on or after D43 visit (visit day ≥ 42):
Given xx the theoretical study day of visit Dxx

$$\frac{6 + \text{Int}\left[{}^{(\text{xx} - 1 + 21 - 7\text{x}6)}/_{21}\right]}{(\text{Last dose date} - \text{1st dose date} + 21)/7}$$

For example, at visit D85; then number of injections should be: 6 + int((85-1+21-42)/21) = 9

Duration of exposure (weeks): (Last dose date-1st dose date + 1)/7

All laboratory parameters will be expressed in the International System (SI) of units and the intensity grade using CTCAE version 5. A grade of 0 will be assigned when the value is within normal limits. In the case a local laboratory normal range overlaps into the higher (i.e., non-zero) CTC grade, the laboratory value will still be taken as within normal limits and assigned a CTC grade of 0. When normal limits are missing and needed for intensity grade determination, the grade will be set at missing. If normal limits are missing but not needed, grade intensity will be calculated as usual with CTCAE ranges.

Laboratory values recorded as "value < x" or "value > x" will be handled as the formula:

- $x = x * \sum_{i=1}^{n+2}(9 * 10^{-i})$ if value recorded as "value < x" with n denoted the number of significant digits
- $x = x * (1 + 10^{-n+2})$ if value recorded as "value > x" with n denoted the number of significant

digits

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

Creatinine Clearance (CRCL):
Creatinine clearance equation could be expressed as 3 methods: Cockroft / CKD EPI / MDRD

With Cockroft formula Creatinine Clearance will be recalculated:

CRCL(Females) (mL/min) = 1.04 x weight (kg) x (140 - Age)/creatinine(µmol/L)

CRCL (Females) (mL/min) = [(140 – age)(weight (kg)) x (0.85)]/(72) (serum creatinine in mg/dL)

For the remaining time points, creatinine and weight values of corresponding time points will be used. If weight is missing, the closest compared to the actual date weight will be used.

8 STATISTICAL METHODS

8.1 General principles

Statistical summaries will be produced using SAS® software version 9.4. The tables, listings and graphics will be prepared in landscape format.

Drafts TFLs will be produced and reviewed before the database lock to ensure that no data is missing and to check for potential inconsistency in the database.

Continuous variables will be described using the number of observations (N), arithmetic mean (Mean), standard deviation (sd), minimum (MIN), median (Median), the interquartile range (Q1-Q3) and maximum (MAX). Means will be further described with 95% confidence intervals (CIs) where appropriate. One additional decimal point for mean, median, Q1 and Q3, and 2 additional decimal points for sd will be used. Data with more than 3 decimal places (if any), may not follow this rule: so, 3 decimal places will be used.

Categorical variables will be summarized by frequency (N) and percentage (%). Proportions will be estimated with their exact (Clopper-Pearson) 95% CIs when appropriate.

8.2 Patient enrollment and disposition

8.2.1 Screening status

The number of patients screened (i.e., who signed informed consent) will be displayed. All patients who failed to meet eligibility criteria after ICF signature will be considered as screening failure and reported in the study report. The number of these patients and the primary reason for non-inclusion will be also displayed. Percentages will be calculated over the number of patients screened.

A listing will be performed to present all screen failures with the reason(s) of non-inclusion for each part (screening period and treatment period). The number of screening failure patients and reasons for screening failure and reasons will be summarized.

8.2.2 Patient's populations

The disposition data will be presented by patient in data listings and the following items will be presented in a summary table:

- The number of patients included who received at least one dose of TG4050 (**SAF**)
- The number of patients excluded from the populations and reasons for exclusion
- The number of patients who discontinued TG4050 and reasons for discontinuation TG4050

8.3 Analysis of demographic and baseline characteristics

Analyses will be based on the SAF / EPP populations.

8.3.1 Demographic and baseline characteristics

Baseline demographics and disease characteristics data will be listed and summarized on SAF population.

The following continuous variables will be included:

- Date of ICF signature (listing only)
- Age at initial informed consent signature (years)
- Body Mass Index (BMI) (in kg/m²)

The following categorical variables will be summarized using the categories reported in the eCRF:

- PS on ECOG scale (0 / 1 / 2 / 3 / 4)

In addition, hematology and biochemistry at baseline will be also analyzed.

8.3.2 History of studied disease

The following variables will be listed and/or summarized:

- Time since initial diagnosis (months)
- Stage before surgery (IIIC / IVA / Other)
- Stage after surgery (on resected tumor)
- Histological type (Serous carcinoma / Other)
- Primary tumor location (Ovary(ies) / Fallopian tube(s) / Peritoneum / Lymph node / Other)
- Presence of BRCA1/BRCA2 (Yes / No / Not Known)
- Other molecular tests (if applicable)
    - Result of test (Yes/No)
- Tumor totally resected (Yes / No)
    - If No: size of residual disease: microscopic / <=1cm / >1cm
- Date of post-adjuvant chemotherapy imaging
- Response on last imaging post-adjuvant chemotherapy (CR (non-evidence of disease) / PR / SD / PD / NE / Suspicious indeterminate nodule)
-

8.3.3 Vital signs and electrocardiograms at baseline

The following variables will be listed and/or summarized:

- Weight (in Kg), Height (in cm)
- Body temperature (°C)
- Pulse rate (bpm)

- Systolic and Diastolic Blood Pressure (mmHg)
- Electrocardiogram (Normal / Abnormal Not Clinically Significant (NCS) / Abnormal Clinically Significant (CS))

8.3.4 Serology

HCV Serology and detection of HBsAg and Blood sampling (for HLA typing) will be listed and/or summarized:

- HCV serology (Positive / Negative / Not Available)
- Hepatitis B surface Antigen (HBsAg) (Positive / Negative / Not Available)

8.3.5 Manufacturing

Request to TG4050 Manufacturing will be listed:

- Type of sample (Frozen / Formalin-fixed)
- Tumor sample identification and date of shipment
- Date of blood sampling
- Blood sample identification
- Date of shipment

8.3.6 Prior anti-cancer therapies

SAF population will be used for all summaries and listings of prior anti-cancer therapies.
The SAF set will be used for all summaries and listings of prior anti-cancer therapies.

Prior anti-cancer therapies medications will be listed and summarized with the following items:

- Number of patients with previous therapy medication
- Medication (only listings)
- Type of therapy (Chemotherapy / Monoclonal antibody / PARP inhibitor / Other)
- Administration setting (Adjuvant / Neoadjuvant / Maintenance / Other)
- Time between last dose and first dose (days) for each type of prior anti-cancer therapy (months)
- Number of cycles of chemotherapy
- Time between last administration of chemotherapy and ICF signature (months)
- Duration of treatment (months)

8.3.7 Imaging until asymptomatic relapse

During the screening period imaging will be performed in case of CA-125 increase or if symptoms or clinical signs occur. Data related to the imaging will be listed.

8.3.8 CA-125 serum concentration in blood

CA-125 serum concentration in blood will be analyzed centrally (normal ranges 0 to 35 U/mL). Data related will be listed. If data are collected and recorded in eCRF, all data will be pooled and in case of data available at the same date locally and centrally, priority will be given to central data.

8.3.9 Relevant Medical History and current Medical Conditions / Signs and Symptoms

The number and percentage of patients with relevant medical history/current medical conditions will be presented by system organ class (SOC) and preferred term (PT) in the SAF.

Signs and Symptoms with CTCAE grade will be also presented by system organ class (SOC) and preferred term (PT) in the SAF.

Tables will be presented by SOC sorted in alphabetic order and PTs within SOC sorted by descending number of counts according to the overall column.

8.4 Stratification factors

No stratification is planned in this study

8.5 Protocol deviation

8.5.1 Protocol deviation eligibility criteria

Deviations from Protocol eligibility criteria collected in the eCRF will be summarized and listed by treatment arm.

8.5.2 Protocol deviation summaries

The number and percentage of patients in the SAF with important protocol deviations will be tabulated by the deviation type and category. All protocol deviations will be listed.
Any protocol deviations impacting statistical analyses will be classified as major. 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 (Section 6.2).

8.6 Treatments

The treatment information will be based on the SAF population.

8.6.1 Study treatment

Duration of TG4050 exposure, number of TG4050 injections and Relative Dose Intensity (RDI) will be provided by listing. The total number of injections will also be displayed.

The safety population will be used for all listings of study treatment.

8.6.2 Prior and Concomitant medications

8.6.2.1 Prohibited and/or restricted medications during study treatment

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

- Immunosuppressive agents
- Immunosuppressive doses of systemic corticosteroids (except refer protocol)
- Any concurrent anti-neoplastic therapy (i.e. 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

These medications and non-drug therapies will be tracked in the listings of concomitant medications and medical history to identify potential deviations.

8.6.2.2 Prior and/or Concomitant medications

Prior and concomitant medications are:

- Medications and/or non-drug therapies taken by the patient prior to start TG4050, continuing or not after the start of the study treatment
- All medications and non-drug therapies taken during the treatment period of the study starting from Day 1 up to 30 days after the last study treatment administration

Prior and concomitant medications will be coded using the WHO Drug Dictionary using latest available including the Anatomical Therapeutic Chemical (ATC) classification and will be listed and summarized by active ingredient by means of frequency counts and percentages.

A table with the frequency and percentage of patients with medications started before D1 ongoing or not at D1 and a second table with the frequency and percentage of patients with Concomitant medications started on or after D1 will be displayed.

The SAF will be used for all above mentioned concomitant medication tables.

8.6.3 End of treatment (EOT) and End of study (EOS) visits

8.6.3.1 End of treatment

The following information will be listed for each patient and will be summarized with:

- Primary reason for study treatment discontinuation (Maximum number of TG4050 administered / Documented progressive disease / Adverse Event / Investigator's decision / Protocol deviation / Patient's consent withdrawal / Lost to follow-up / Other)
- Date of start/end of treatment (in listing only)

8.6.3.2 End of study

The following information will be listed for each patient:

- Primary reason for study completion/discontinuation
- Date of study completion (listing only)
- Date of death (listing only)
- Primary cause of death (Underlying disease / Not Known / Other)

8.7 Analysis of patients not treated

In case of TG4050 individualized product unavailability in due time or TG4050 manufactured product not administered 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. The patient will continue to benefit from routine medical monitoring and will receive SOC in case of recurrence as per normal practice.

- **Failure to treat**

Patients who cannot receive TG4050 at the time of planned treatment will be listed. The reason that prevents a patient from being treated will be recorded. Reasons can be Inclusion/exclusion criteria for treatment period not met, lost to follow-up, ICF withdrawn, Adverse Event or Failure to provide. The reason of failure to treat will be listed by type (SCOS report and eCRF page "End of study").

- **Failure to provide**

Patients for whom TG4050 cannot be provided according to the SCOS report will be listed. Reasons for not being able to provide the vaccine will also be recorded. Reasons for failure to provide can be any issue at any step of TG4050 production. The reason of failure to provide will be listed by type (SCOS report and eCRF page "End of study").

8.8 Analysis of efficacy

- **Time to measurable relapse will be analyzed according to RECIST 1.1**

The time from the date of C1D1 to the date of first detection of recurrence documented by imaging procedures, whichever occurs first (a sensitive analysis could be performed on the time to measurable relapse including the death due to ovarian cancer). Time to measurable disease will be censored if no recurrence is observed at the cut-off date for analysis. For patients who stopped the study treatment before documentation of disease progression, tumor assessment should be performed every 9 weeks until

documented disease progression according to RECIST 1.1.

The censoring date will be the date of the last evaluable tumor assessment before the cut-off date.

- **Tumor response according to RECIST 1.1. (in case at least one non measurable lesion is present at baseline)**

Tumor response will be evaluated according to RECIST 1.1. Tumor assessment will be performed within 21 days prior to treatment start and then every 9 weeks until documented disease progression 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. Response will be displayed, and results will be listed

8.9 Exploratory endpoints and analyses: translational research

CCI

8.10 Safety analyses for the treatment period

The primary objective is to evaluate the safety and tolerability of multiple subcutaneous (SC) injections of a neoantigen-directed active immunotherapy (TG4050) in ovarian, fallopian or peritoneal high-grade serous carcinoma (HGSC) patients with asymptomatic relapse.

All safety analyses will be performed and summarized in the SAF.

8.10.1 Adverse Events (AEs)

8.10.1.1 Definitions

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.

Treatment-emergent adverse Event (AE):

A treatment-emergent adverse event (TEAE) is defined as a sign or symptom that emerges during treatment or within 30 days of the last dose of the study drug, having been absent pre-treatment or that has worsened relative to the pre-treatment state. Any adverse event deemed related to study drug will also be considered a TEAE regardless of elapsed time since last study drug dose.

Adverse reaction (AR):

All noxious and unintended responses to a medicinal study product (TG4050) 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.

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.

8.10.1.2 AEs analysis

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.

For these analyses, the number and percentage of patients with at least one AE will be summarized in a frequency table by System Organ Class (SOC) and Preferred Term (PT) as per MedDRA dictionary. The number of events will also be summarized in the same table. Tables will be presented by SOC sorted in alphabetic order and PTs within SOC sorted by descending number of counts according to the overall column.

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.

Serious Adverse Events (SAEs)

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.

AEs or 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 flagged.

a. Listings

All AEs will be listed with the following items:

- Patient Number
- Age
- Verbatim, Preferred term (PT) and System Organ class (SOC)
- Date of onset and date of end (study day)
- Duration of the AE in days
- Outcome (Recovered / Recovered with sequelae / Not recovered / Fatal / Unknown / Worsening)
- Evaluation of seriousness (Yes/No)
- Date of seriousness
- Intensity grade (Grade 1/ Grade 2 / Grade 3 / Grade 4 / Grade 5)
- Injection Site Reaction (Yes / No)
- Related to other study procedure (Yes /No)
- Dose Limiting Toxicity (Yes / No)

- Relation to TG4050 (Related[1]/ Not Related[2])
- Action taken regarding TG4050 (None / Delayed / cancelled / Stopped / Not applicable)
- Action regarding the event (none, hospitalization….)

Moreover, the following sub-listings will be provided:

- Dose Limiting Toxicity AEs
- TG4050-related AEs
- SAEs
- TG4050-related SAEs
- AEs leading to discontinuation
- Grade 3/4 adverse events
- Fatal AEs
- Deaths
- Pre-treatment SAEs

b. Tables

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

- with at least one AE
- with dose limiting Toxicity AEs
- with at least one AE related to TG4050
- with at least one injection site reaction
- with at least one AE related to other study procedure
- with at least one AE leading to treatment discontinuation
- with at least one AE related to TG4050 and leading to treatment discontinuation
- with at least one SAE
- with at least one SAE related to TG4050
- with at least one grade 3/4 AE
- with at least one grade 3/4 AE related to TG4050
- with fatal AE

[1] Related : reasonable possibility
[2] Not related : no reasonable possibility

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

Table for AEs, AEs related to TG4050 will also be presented by grade and summarized in a frequency table by body system organ class (SOC) and preferred terms (PT) as per MedDRA dictionary.

Tables will be presented by SOC sorted in alphabetic order and PTs within SOC sorted by descending number of contents according to the overall column.

8.10.2 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 more than 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.

8.10.3 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.

Vital signs

All vital signs (SBP and DBP in mmHg, pulse rate in bpm, temperature in °C and body weight in kg, BMI in kg/m^2) will be listed by patient. Vital signs at baseline will be summarized using descriptive statistics. All these results will be presented for SAF.

ECOG

ECOG performance status will be listed by patients. ECOG at baseline will be summarized using descriptive statistics. All these results will be presented for SAF.

9 DOCUMENT HISTORY

	Changes compared to previous version
Version 1.0 – 05AUG20	

Version 2.0 – 23SEP20	
Version 3.0 – 04JAN24	Table 14.1.2.1 -7:9 CA-125 were removed 14.2 Efficacy data Tables were removed. 16.2.6-6:12 listings were removed. 14.2.2 -5:8 Figures were removed EPP Listings/Tables were removed CCI [redacted]

10 LIST OF TABLES, FIGURES AND LISTINGS

10.1 Tables, figures and graphs

10.2 Listings

Listing number	Title
16.2	**PATIENS DATA LISTINGS**
16.2.1	***Discontinued patients***
Listing 16.2.1.1	Screen failure patients and non-inclusion reasons – SCR
Listing 16.2.1.2	Patients' disposition – SAF
16.2.2	***Protocol deviation for enrolled patients***
Listing 16.2.2.1	Protocol deviations at inclusion for treated patients – SAF
Listing 16.2.2.2	Protocol deviations during study for treated patients – SAF
16.2.4	***Demographic data and Baseline characteristics by patient (enrolled patients)***
Listing 16.2.4.1.1:2	Demographic and baseline characteristics: SCR/SAF
Listing 16.2.4.2.1:2	History of studied disease – SCR/SAF
Listing 16.2.4.3. 1:2	Prior Anti-Cancer Therapy: Medication – SCR/SAF
Listing 16.2.4.4.1	Relevant Medical History and current Medical Conditions – SAF
Listing 16.2.4.5.1:2	CA-125 concentration at study entry and during screening period – SCR/SAF
Listing 16.2.4.6	Signs and symptoms at baseline – SAF
Listing 16.2.4.7	Serology – SCR/SAF
16.2.5	***Compliance and study conduct data***
Listing 16.2.5.1	TG4050 administration – SAF
Listing 16.2.5.2	TG4050 administration per patient – SAF
Listing 16.2.5.3	Delayed, cancelled or stopped administration of TG4050 (Listing) – SAF
Listing 16.2.5.4	Discontinuation of study treatment and study (Table) – SAF
Listing 16.2.5.5	Prior and concomitant medications (on or after D1) – SAF
Listing 16.2.5.6	Prior and concomitant medications (before D1) – SAF
Listing 16.2.5.7	Further anti-cancer therapies – SAF
16.2.6	***Individual efficacy response data by patient (enrolled patients)***
Listing 16.2.6.1	CA-125 concentration during treatment period – SAF
Listing 16.2.6.2	Failure to treat/provide – SCR
Listing 16.2.6.3	Objective tumor assessments by evaluation – SAF
Listing 16.2.6.4	Detailed tumor assessment – SAF
Listing 16.2.6.5	Time to measurable relapse / Time to Progressive Disease – SAF
16.2.7	***Adverse event listings by patient***
Listing 16.2.7.1	Adverse events – SAF
Listing 16.2.7.2	Adverse events related to TG4050 – SAF
Listing 16.2.7.3	Serious Adverse events before treatment – SAF
16.2.8	***Listing of individual laboratory measurements by patient***
Listing 16.2.8.1	Laboratory parameters – Hematology – SAF
Listing 16.2.8.2	Laboratory parameters – Biochemistry – SAF
Listing 16.2.8.3	Other Laboratory parameters – SAF
Listing 16.2.8.4.1:2	Molecular Characterization tests – SCR/SAF
Listing 16.2.8.5	Vital Signs and, physical examination– SAF
Listing 16.2.8.6	Electrocardiogram and ECOG PS – SAF

Listing 16.2.9.1 Request for TG4050 manufacturing – SCR

11 REFERENCE

Clopper, C. J., and Pearson, E. S. The Use of Confidence or Fiducial Limits Illustrated in the Case of the Binomial, Biometrika 1934;26,404–413

12 APPENDIX

12.1 Appendix 1 – Protocol deviations

Anticipated but not limited deviations for eligibility criteria are:

Screening period:

Category	Period	Deviation Code	Standard name of the deviation	Criticality
Inclusion criteria	Screening	INC01	Written informed consent not signed in accordance to ICH-GCP and national/local regulation before any protocol-related procedures that are not part of normal patient care	Major
Inclusion criteria	Screening	INC02.01	Male patients	Major
Inclusion criteria	Screening	INC02.02	Patients < 18 years of age	Major
Inclusion criteria	Screening	INC03.01	Histologically not confirmed high grade, stage IIIC or stage IVA serous ovarian, fallopian or primary peritoneal carcinoma	Major
Inclusion criteria	Screening	INC03.02	High grade, stage IIIC or stage IVA serous ovarian, fallopian or primary peritoneal carcinoma with normal CA-125 diagnosis	Major
Inclusion criteria	Screening	INC04	Patients have not undergone primary debulking surgery or not completed standard first-line platinum-based chemotherapy (at least 5 cycles of taxane-platinum combination) for whom tumor tissue has been banked from previous abdominal debulking surgery	Major
Inclusion criteria	Screening	INC05.01	Patients have not achieved a complete response to therapy, as demonstrated by no residual disease on most recent CT scan	Major
Inclusion criteria	Screening	INC05.02	Patients have CA-125 increasing by > 25% and > 10 UI/mL from nadir	
Inclusion criteria	Screening	INC06	Patient doesn't remain disease-free during at least 6 months after last dose of cytotoxic chemotherapy (maintenance therapy with bevacizumab or a PARP inhibitor is allowed)	Major

Inclusion criteria	Screening	INC07	No tumor tissue and peripheral blood samples available for exome and transcriptome sequencing	Major
Exclusion	Screening	EXCL01.1	Patient having received neoadjuvant chemotherapy prior to debulking surgery	Major
Exclusion	Screening	EXCL01.2	Patient having received cancer immunotherapy including cancer vaccines, any antibody/drug targeting T cell co-regulatory proteins such as anti-PD1, anti PDL1 or anti CTLA-4	Major
Exclusion	Screening	EXCL02	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 are excluded. If there is an history of prior malignancy, patients must not be receiving other specific treatment for their cancer	Major
Exclusion	Screening	EXCL03	Patient post-organ transplantation, including allogeneic stem cell or bone marrow transplantation. History of blood transfusion within 3 weeks prior to study entry visit	Major
Exclusion	Screening	EXCL04	Known history of positive testing for Human Immunodeficiency Virus (HIV) or known AIDS (Acquired Immune Deficiency Syndrome)	Major
Exclusion	Screening	EXCL05	Any known allergy or reaction to eggs or attributed to compounds of similar chemical or biological composition to therapeutic vaccines/immunotherapeutic products	Major
Exclusion	Screening	EXCL06	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)	Major

Treatment period:

Category	Period	Deviation Code	Standard name of the deviation	Criticality
Inclusion criteria	Treatment	INC08	If required, new ICF not signed before started treatment	Major
Inclusion criteria	Treatment	INC09	Eastern Cooperative Oncology Group (ECOG) performance status > 1 at treatment period initiation	Major
Inclusion criteria	Treatment	INC10	Patients who have not developed an asymptomatic relapse as defined by 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	Major
Inclusion criteria	Treatment	INC11	Inadequate hematological, hepatic, and renal functions: o Hemoglobin < 9.0 g/dL o Neutrophils count < 1.5 x10^9/L o Lymphocytes count < 0.9 x10^9/L o Platelets count <100 x10^9/L o Total bilirubin > 1.5 x ULN (except for patients with Gilbert's syndrome) o Aspartate aminotransferase (AST) > 2.5 x ULN o Calculated creatinine clearance < 45 mL/min using the Cockroft & Gault formula or < 45 mL/min/1.73m² using other methods	Major
Inclusion criteria	Treatment	INC12	Patients who received standard maintenance therapy within 30 days prior to TG4050 treatment (or within 14 days for PARP inhibitor)	Major
Exclusion criteria	Treatment	EXCL07	Measurable disease according to RECIST 1.1	Major

Exclusion criteria	Treatment	EXCL08	Major surgery within 4 weeks prior to treatment start	Major
Exclusion criteria	Treatment	EXCL09	Treatment with another investigational agent within 30 days prior to TG4050 treatment initiation	Major
Exclusion criteria	Treatment	EXCL10	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 4 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.	Major
Exclusion	Treatment	EXCL11	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	Major
Exclusion	Treatment	EXCL12	Patients 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	Major
Exclusion	Treatment	EXCL13	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	Major
Exclusion	Treatment	EXCL14	History of myocardial infarction ≤ 6 months	Major

12.2 Appendix 2 - SI units and conversion factors

Unit	Parameters
10^{12}/L	RBC count
g/L	Hemoglobin
10^{9}/L	WBC count, neutrophils, lymphocytes, basophils, eosinophils, basophils, monocytes, platelet count
IU/L	ALT, AST, ALP, LDH
µmol/L	Total bilirubin, creatinine
mL/min	Creatinine clearance
mmol/L	Sodium, potassium, magnesium, bicarbonate, glucose

Bilirubin (584.7 g/mol): https://pubchem.ncbi.nlm.nih.gov/compound/5280352
1 mg/dL = (0.01 g/L) x (1/584.7) mol/g
= 0.01/584.7 mol/L
= 10000/584.7 µmol/L
= 17.10 x 1 µmol/L

Glucose (180.16 g/mol): https://pubchem.ncbi.nlm.nih.gov/compound/79025
1 mg/dL = (0.01) g/L x (1/180.16) mol/g
= 0.01/180.16 mol/L
= 10/180.16 mmol/L
= 0.055506 mmol/L

Sodium (22.989769 g/mol): https://pubchem.ncbi.nlm.nih.gov/compound/Sodium
1 mg/dL = (0.01) g/L x (1/22.989769) mol/g
= 0.01/22.989769 mol/L
= 10/22.989769 mmol/L
= 0.43497610 x 1 mmol/L

Potassium (39.098 g/mol): https://pubchem.ncbi.nlm.nih.gov/compound/Potassium
1 mg/dL = (0.01) g/L x (1/39.098) mol/g
= 0.01/39.098 mol/L
= 10/39.098 mmol/L
= 0.25577 x 1 mmol/L

Magnesium (24.305 g/mol): https://pubchem.ncbi.nlm.nih.gov/compound/magnesium
1 mg/dL = (0.01) g/L x (1/24.305) mol/g

= 0.01/24.305 mol/L
= 10/24.305 mmol/L
= 0.41144 x 1 mmol/L

Bicarbonate (61.017 g/mol): https://pubchem.ncbi.nlm.nih.gov/compound/Bicarbonate
1 mg/dL = (0.01) g/L x (1/61.017) mol/g
= 0.01/61.017 mol/L
= 10/61.017 mmol/L
= 0.16389 x 1 mmol/L

Creatinine (113.12 g/mol): https://pubchem.ncbi.nlm.nih.gov/compound/588
1 mg/dL = (0.01) g/L x (1/113.12) mol/g
= 0.01/113.12 mol/L
= 10000/113.12 µmol/L
= 88.402 x 1 µmol/L

Summary of conversion factors when molecular weight is needed:

Parameters	**Units**	**Conversion factor**
Total Bilirubin	mg/dL to µmol/L	17.10
Creatinine		88.402
Sodium	mg/dL to mmol/L	0.43497610
Potassium		0.25577
Magnesium		0.41144
Bicarbonate		0.16389
Glucose		0.055506

Trivial conversion into SI units using factor of 10 (e.g. conversion of mg/dL to mg/L) are not detailed but will be performed

12.3 Appendix 3 - Laboratory parameters graded according to CTCAE v5.0

Lab Test Name	**SI Unit**	**CTCAE v5.0 – AE Term for decreased**	**CTCAE v5.0 – AE Term for increased**
Hemoglobin	g/L	Anemia	Hemoglobin Increased
Leukocytes	10^9/L	White blood cell decreased	Leukocytosis
Neutrophils	10^9/L	Neutrophil count decreased	
Lymphocytes	10^9/L	Lymphocyte count decreased	Lymphocyte count increased
Platelets	10^9/L	Platelet count decreased	
Glucose	mmol/L	Hypoglycemia	Hyperglycemia
Alanine aminotransferase	IU/L		Alanine aminotransferase increased
Aspartate aminotransferase	IU/L		Aspartate aminotransferase increased
Total Bilirubin	µmol/L		Blood bilirubin increased
Alkaline phosphatase	IU/L		Alkaline phosphatase increased
Creatinine	µmol/L		Creatinine increased
Magnesium	mmol/L	Hypomagnesemia	Hypermagnesemia
Potassium	mmol/L		Hyperkalemia
Sodium	mmol/L	Hyponatremia	hypernatremia