Clinical Study Protocol

CONFIDENTIAL

A phase Ib/II trial evaluating the combination of TG4001 and avelumab in patients with HPV-16 positive recurrent or metastatic malignancies

Study phase: Ib/II

PROTOCOL N° TG4001.12
Final Version 10.0 / 06 December 2023

EudraCT N°2016-002799-28
NCT N°03260023

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INVESTIGATORS / STUDY ADMINISTRATIVE STRUCTURE

NAMES AND CONTACT DETAILS

Principal / Coordinating Investigator

[redacted]

Centers / Investigators

The complete Investigator list is available in the Investigator Site File and in the Trial Master File at Transgene

Transgene's Staff

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Statistician

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

DOCUMENT APPROVAL

SPONSOR'S OFFICER(S)

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[redacted]

STATISTICIAN

[redacted]

COORDINATING INVESTIGATOR

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SYNOPSIS

Sponsor: Transgene
Active substances: TG4001
Avelumab

Study Title
A phase Ib/II trial evaluating the combination of TG4001 and avelumab in patients with HPV-16 positive recurrent or metastatic malignancies.

Study N°: TG4001.12

EudraCT N°: 2016-002799-28
IND N°: 8147

Coordinating / Principal Investigator: [redacted]

Investigational Center(s) / Country(ies):
Phase Ib: 3 in France
Phase II part 1: up to 20 in at least France, Spain and UK
Phase II part 2: up to 25 in at least France, Spain, UK, Italy, and US

Study Period: Q3 2017 – Q4 2024	**Clinical Phase:** Ib/II

Objectives
Primary objectives:
Phase Ib: To evaluate the safety and tolerability of the combination of TG4001 plus avelumab in patients with recurrent or metastatic HPV-16 positive advanced malignancies

Phase II part 1: To evaluate the efficacy of TG4001 combined to avelumab in terms of Overall Response Rate (ORR) by using RECIST 1.1 in patients with recurrent or metastatic (R/M) HPV-16 positive advanced malignancies including oropharyngeal SCCHN

Phase II part 2: To compare the Progression-Free Survival (PFS) of TG4001 in combination with avelumab vs avelumab alone in patients with recurrent or metastatic (R/M) HPV-16 positive advanced malignancies and without liver metastases at baseline. PFS will be evaluated based on RECIST 1.1.

Secondary objectives: To evaluate the combination of TG4001 and avelumab with respect to:

- Overall response rate (ORR) by using RECIST 1.1 (phase Ib and phase II part 2)
- Progression Free Survival (PFS, phase Ib and phase II part 1)
- Overall Survival (OS)
- Duration of Response (DoR)
- Disease control rate (DCR)
- Safety profile (phase II)
- Percentage of patients with liver metastases at baseline who have disease progression at D43 (phase II part 2)

Exploratory objectives

- [redacted]

- [redacted]

Methodology

This is a multicenter, open label phase Ib/II study evaluating the combination of TG4001 and avelumab in patients with HPV-16 positive advanced malignancies.

The phase II consists of two parts: phase II part 1 is a single arm study (TG4001 with avelumab) and phase II part 2 is a randomized, controlled two arms study (TG4001 with avelumab vs avelumab alone).

In the phase Ib: safety will be assessed in consecutive cohorts of 3 to 6 patients at increasing doses of TG4001 in combination with avelumab according to a 3+3 design (See Table below). There will be no intra-patient dose escalation.

Patients will receive TG4001 on a weekly basis on Days 1, 8, 15, 22, and 29, then once every 2 weeks (starting on Day 36) until Month 6 (from Day 1 of study treatment), thereafter once every 12 weeks, until disease progression, unacceptable toxicity, patient withdrawal from study for any reason or for a maximum of 2 years, whichever occurs first. Avelumab will be given once every 2 weeks starting from Day 8 (one week after the first vaccine dose), until disease progression, unacceptable toxicity, patient withdrawal from study for any reason or for a maximum of 2 years, whichever occurs first.

Beyond 2 years of treatment and based on the clinical judgement of the investigator the patient could continue to receive study treatments according to the Study Flow-Chart (APPENDIX IIIB).

Dose escalation (3+3 design)

Two dose levels are planned for TG4001: doses of 5 x 10^6 PFU (DL1) and 5 x 10^7 PFU (DL2) in combination with avelumab at 10 mg/kg. Depending on the nature of the dose limiting toxicity (DLT) observed at these two DLs, alternative schedule for TG4001 (Q4W) may be tested with the combination. In that case, a minimum of 6 additional patients will be included. Implementation of this alternative schedule will be subject to a substantial amendment to this clinical study protocol.

Dose level	TG4001 dose	Avelumab dose	Number of patients
DL1	5 x 10^6 PFU	10 mg/kg	3 – 6
DL2	5 x 10^7 PFU	10 mg/kg	3 – 6

A minimum of 3 patients will be required at each dose level. If the maximum tolerated dose (MTD) is reached where 1 of 3 patients experiences a DLT, the cohort will be expanded with 3 additional patients at the same DL (a maximum of 6 patients will be enrolled at each DL).

Enrolment within a given cohort: The first patient will be monitored for 2 weeks (i.e. 7 days after the first administration of both products in combination) before the next 2 patients of the cohort can be enrolled simultaneously. In case the cohort must be extended by 3 additional patients for occurrence of a DLT among the first 3 treated patients, an interval of 2 weeks will be applied between the first additional patient and the 2 additional next patients.

Dose escalation rules and definition of MTD:

All patients in a given DL must complete the first 4 weeks treatment from [Day 1 to Day 28] before dose escalation to the next dose level will occur.

Patients who experience a DLT will be withdrawn from the study treatment and will not be replaced.

Patients who are not evaluable for DLT or who are withdrawn from the study during the first 4 weeks of study treatment for other reasons than a DLT, will be replaced. Doses are escalated until MTD is reached as follows.

Number of DLTs / evaluable patients	Rule
0/3	Accrue 3 new patients at the next dose level
1/3	Accrue 3 additional patients at current dose level
≥ 2/3	Stop current dose = unacceptable dose

	MTD = dose immediately below
1/6	Accrue 3 new patients at the next dose level
≥ 2/6	Stop current dose = unacceptable dose
	MTD = dose immediately below

The dose level at which unacceptable toxicity in at least 2/3 or 2/6 patients occurs will be considered as the unacceptable dose. The MTD will be considered as the dose immediately below. If no DLT in more than 1/3 or 1/6 is observed, the MTD will be considered as the recommended dose for the phase II (RP2D).

A total of 6 patients will be treated at the MTD.

If at both Dose Levels no DLT in more than 1/3 or 1/6 patients is observed, the MAD, Maximum Administered Dose (DL2), will be considered as the recommended dose for the phase II (RP2D).

Upon completion of phase Ib and for the purpose of clarification RP2D for TG4001 corresponds to DL2, i.e. 5 x 10^7 PFU.

Dose limiting toxicity (DLT) will be assessed in each included and treated patient during the first 4 weeks [Day 1 to Day 28] of dosing (4 injections of TG4001 and 2 injections of avelumab) and includes the following toxicities:

- Grade ≥ 3 drug related adverse event (AEs). However, fatigue, nausea/vomiting adequately treated with anti-emetics, endocrinopathies adequately controlled with one physiologic hormone replacement, skin toxicity and single laboratory values out of normal range without any clinical correlate, asymptomatic grade ≥3 lipase or amylase elevation, tumor flare defined as local pain, irritation, or rash localized at sites of known or suspected tumor or a transient Grade 3 infusion adverse event are excluded.
- Liver function test abnormality:
  - AST or ALT > 5 x ULN
  - Total bilirubin > 3 x ULN
  - Concurrent AST or ALT > 3 x ULN and total bilirubin > 2 x ULN
- Drug related AE requiring treatment interruption for more than 2 weeks

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

An Independent Data Monitoring Committee (IDMC) will be set up during the study for the purpose of reviewing patient safety data, efficacy data and the conduct of the study.
During the phase Ib of the study, the safety data of all enrolled and treated patients will be collected and evaluated by the Investigators, Transgene and Merck KGaA / EMD Serono on an ongoing basis.
The IDMC will meet before each new cohort begins to analyse and review the safety data of all patients in the previous cohort. The IDMC will then recommend whether it is possible to do the dose escalation as per the study design.
At the end of the phase Ib and depending on the nature of the toxicities, the safety data of all patients will be analyzed and discussed with the IDMC which will make recommendation to the sponsor on the conduct of the study. DLT evaluation is performed 4 weeks after the last patient enrolled in the phase Ib had first dose of study treatments.
During the phase II part 1 of the study the IDMC will review safety data at interim analysis. Ad hoc meetings may be held upon necessity.
During the phase II part 2 of the study and in addition to safety review the IDMC will evaluate efficacy results at interim analysis.

In the phase II part 1 patients will be treated at the established RP2D for TG4001, i.e. 5 x 10^7 PFU in combination with avelumab until disease progression, death, or unacceptable toxicity, or study withdrawal for any reason, or for a maximum of 2 years, whichever occurs first.
In the phase II part 2 patients will be treated at the established RP2D for TG4001, i.e. 5 x 10^7 PFU in combination with avelumab 800 mg Q2W (combination arm) or with avelumab 800 mg Q2W alone

(monotreatment arm) until disease progression, death, or unacceptable toxicity, or study withdrawal for any reason, or for a maximum of 2 years, whichever occurs first.
Beyond 2 years of treatment and based on the clinical judgement of the investigator the patient could continue to receive study treatments according to the Study Flow-Chart (APPENDIX IIIB and D).

In the phase II part 1, evaluation of efficacy and further evaluation of safety of the combination of TG4001 and avelumab will be performed in a single arm of patients with recurrent or metastatic HPV-16 positive advanced malignancies including HPV-16 positive oropharyngeal SCCHN.

In the phase II part 2, evaluation of efficacy of the combination of TG4001 and avelumab will be performed in a randomized, open-label controlled study comparing TG4001 in combination with avelumab (combination arm) to avelumab alone (monotreatment arm) in patients with selected HPV-16 positive recurrent or metastatic malignancies.
In patients without liver metastases at baseline, randomization will be conducted equally in a 1:1 ratio TG4001 with avelumab (combination arm) versus avelumab alone (monotreatment arm). A stratification will be done on primary tumor site.
In patients with liver metastases at baseline, randomization will be conducted equally in a 1:1 ratio TG4001 with avelumab versus avelumab alone, no stratification will be performed.

In both phases tumor response will be evaluated at baseline and then every 6 weeks until disease progression. Beyond 9 months after start of treatment, tumor evaluation will be performed every 12 weeks until disease progression.
Tumor evaluations will be based on local assessment using RECIST 1.1.
All patients will be followed up until disease progression or death due to any cause or the date of data cut-off, whichever occurs first.

Number of Patients
Phase Ib: a maximum of 12 evaluable patients depending on the safety of the combination
Phase II part 1: at least 22 evaluable patients until the first stage of the Simon design
Phase II part 2:

- For patients without liver metastases a sample size of 50 patients (25 patients in each arm) is estimated to reach the number of PFS events required for Interim Analysis. PFS analysis is performed when 37 PFS events have been observed. [redacted]
- For patients with liver metastases at baseline a sample size of [redacted] is planned.

Inclusion criteria
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 (for phase II part 2: part of normal patient care can be: e.g. CT or MRI, biopsy, determination of HPV-16 positivity by specified central laboratory)
2. Female or male patients, aged at least 18 years (no upper limit of age for phase Ib and phase II part 1), 18 to 80 years of age (for phase II part 2)
3. Eastern Cooperative Oncology Group (ECOG) Performance Status 0 or 1 (Appendix I)
4. Life expectancy of at least 3 months
5. Patients with histologically or cytologically documented metastatic or refractory/recurrent HPV-16+ cancer (determined in an accredited central laboratory using a validated assay)
6. Phase Ib and Phase II part 1: Patients with HPV-16+ cancers including oropharyngeal squamous cell carcinoma of the head and neck (SCCHN), cervical, vulvar, vaginal, penile, and anal cancer

Phase II part 2: Patients with HPV-16+ cancers including cervical, vulvar, vaginal, penile, and anal cancer

7. Disease MUST not be amenable to curative surgery resection or curative radiotherapy with documented disease progression after concertation with multidisciplinary board
8. Prior therapy
   Phase Ib and Phase II part 1:
   - Patients MAY have received up to two prior lines of systemic chemotherapy for the management of metastatic or recurrent disease; for SCCHN, patients MUST have previously been exposed to platinum-based therapy, either as part of definitive chemo-radiation OR as first line systemic treatment for metastatic disease which may include cetuximab. Patients with recurrence/progression within 6 months of prior multimodal therapy using platinum-based therapy are eligible. Patients with cervical cancer may have undergone surgery and/or received definitive radiation or chemo-radiation therapy for localized disease. Patients MUST have been exposed to platinum–based chemotherapy for metastatic disease which may include bevacizumab. Patients with platinum-refractory disease will be eligible

   Phase II part 2:
   - For recurrent/metastatic disease no more than one prior line of chemotherapy which can contain a platinum
   - Prior treatment for recurrent or metastatic disease is not required for:
     - Patients with recurrence/progression within 6 months after completion of prior multimodal therapy for localized or locally advanced disease not amenable to curative treatment
     - Patients who are unsuitable for platinum-based therapy
     - Patients who refuse chemotherapy or other standard therapies for the treatment of metastatic or recurrent disease. The benefit of an immunotherapy over standard therapies must be validated by the medical board and duly documented.

   A minimum of 4 weeks interval should have elapsed between the completion of the last chemotherapy and study treatment start

   A minimum of 4 weeks interval between palliative bone directed radiotherapy and the start of the study treatment provided that radiation therapy does not affect the unique measurable lesion, if applicable
9. Phase II part 2: For patients with hepatic metastases
   - no more than 3 hepatic lesions in total (target and non-target lesions)
   - maximum size of hepatic target disease ≤ 30 mm according to RECIST 1.1
10. Phase Ib and Phase II part 1: **Availability of tumor tissue from biopsy:** at least 2 fresh tumor tissue samples are to be collected. Tumor tissue may come either from the local tumor or distant metastasis. Cytological material is not accepted

    Phase II part 2:
    - Availability of archived or fresh tumor tissue for the determination of HPV-16 positivity.

    Patients must agree to undergo a core or excisional biopsy of a tumor lesion not previously irradiated (at least 2 fresh tissue samples to be collected). An archival sample obtained within one year prior to randomization is acceptable only if tumor is not accessible. Tumor tissue may come either from the local tumor or distant metastasis. Fine needle aspirates and bone biopsies are not adequate.
11. At least one measurable lesion by CT scan according to RECIST 1.1. Tumors within a previously irradiated field will be designated as "non-target" lesions unless progression is documented or a biopsy is obtained to confirm persistence at least 90 days following completion of radiation therapy
12. Adequate hematological, hepatic and renal function:
    - Hemoglobin ≥ 9.0 g/dL (for phase II part 2: without packed red blood cell transfusion within the prior 3 weeks)
    - Neutrophils ≥ $1.5x10^9$/L
    - Total lymphocytes count ≥ $0.4x10^9$/L

- CD4 + ≥ 200 / µL
- Platelets count ≥ $100x10^9$/L
- Total bilirubin ≤ 1.5 x ULN
- Serum transaminases (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) ≤ 3 x ULN
- Glomerular Filtration Rate ≥ 50 mL/min (according to Modification of the Diet in Renal Disease (MDRD) formula or Cockroft & Gault formula)
- Serum albumin ≥ 30 g/L

13. Negative blood pregnancy test at screening for women of childbearing potential (Appendix II)
14. Highly effective contraception (i.e., methods with a failure rate of less than 1% per year) during the study period and for 3 months after the last study treatment administration for female patients of childbearing potential (WOCBP) and for male patients who are sexually active with WOCBP (See Appendix II for WOCBP definition and details on highly effective contraception methods). Highly effective contraception methods are defined as:
    - Hormonal methods of contraception including combined oral contraceptive pills, vaginal ring, injectables, implants, intrauterine devices (IUDs) such as Mirena and Nonhormonal IUDs such as ParaGard for WOCBP patient or male patient's WOCBP partner
    - Tubal ligation
    - Vasectomy

    In addition to highly effective contraception, participating male patients
    - must use a condom during the study period and for 3 months after the last study treatment administration when engaging in any activity that allows for exposure to ejaculate
    - must refrain from donating sperm

Exclusion criteria

1. Prior exposure to cancer immunotherapy including cancer vaccines, any antibody/drug targeting T cell co-regulatory proteins (immune checkpoints) such as anti-PD-L1, anti-PD-1, or anti-cytotoxic T-lymphocyte antigen-4 (CTLA-4) antibody
2. a) Concurrent anticancer treatment within 28 days before the start of study treatment (e.g., chemotherapy, radiotherapy or cytokine therapy except erythropoietin)
   b) Recurrent drainage procedures (once monthly or more frequently) for pleural effusion, pericardial effusion, or ascites
3. Major surgery within 28 days before the start of study treatment
4. 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 the first study treatment, 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
5. Patients with central nervous system (CNS) metastases except those meeting the following criteria:
    - Brain metastases that have been treated locally and are clinically stable during 4 weeks prior to start of study treatment
    - No ongoing neurological symptoms that are related to the brain localization of the disease (sequelae that are a consequence of the treatment of the brain metastases are acceptable)
6. Other active malignancy requiring concurrent systemic intervention
7. Patients with previous malignancies other than the target malignancy to be investigated in this trial (except non-melanoma skin cancers, and the following in situ cancers: bladder, gastric, colon, endometrial, cervical/dysplasia, melanoma, or breast) are excluded unless a complete remission was achieved at least 2 years prior to study entry AND no additional therapy is required during the study period
8. Patient with any organ transplantation, including allogeneic stem cell transplantation
9. Known severe hypersensitivity reactions to monoclonal antibodies (Grade ≥ 3 NCI-CTC V4.03 or V5.0 for phase II part 2), any history of anaphylaxis, or uncontrolled asthma

10. Any known allergy or reaction to eggs, gentamycin or attributed to compounds of similar chemical or biological composition to therapeutic vaccines/immunotherapeutic products
11. Any known allergy or reaction to any component of anti-PD-L1/PD-1 or its excipients
12. Patients with history of interstitial lung disease (phase Ib and phase II part 1)
13. Patients with known history or any evidence of active interstitial lung disease / pneumonitis (phase II part 2)
14. Administration of a live vaccine within 28 days prior to the start of the study treatment
15. Participation in a clinical study with an investigational product within 4 weeks prior to the start of the study treatment
16. Patients with active, known, or suspected auto-immune disease or immunodeficiency, except type I diabetes mellitus, hypothyroidism only requiring hormone replacement or skin disorders (such as vitiligo, psoriasis) not requiring systemic treatment
17. Significant chronic or acute infections including infection with mpox and SARS-CoV-2 (COVID-19) PCR positive testing
18. Positive serology for Human Immunodeficiency Virus (HIV) or Hepatitis C Virus (HCV) or presence in the serum of the Hepatitis B surface antigens (HBsAg), at Baseline
19. Persisting toxicity related to prior therapy of Grade ≥ 2 NCI-CTCAE v4.03 or v5.0 for phase II part 2 (except neuropathy [see exclusion criterion below] and alopecia)
20. Neuropathy ≥ Grade 3
21. Clinically significant (that is, active) cardiovascular disease: cerebral vascular accident/stroke or myocardial infarction (< 6 months prior to enrollment), unstable angina pectoris, congestive heart failure (New York Heart Association Classification Class ≥ II), or serious uncontrolled cardiac arrhythmia requiring medication/active intervention, history of myocarditis (history of myocarditis for phase II part 2)
22. Patient with any underlying medical condition that the treating physician considers might be aggravated by treatment or might impair the patient's tolerance to study treatment
23. History of uncontrolled intercurrent illness including but not limited to:
    - Hypertension uncontrolled by standard therapies (not stabilized to 150/90 mmHg or lower)
    - Uncontrolled diabetes (e.g., hemoglobin A1c ≥ 8%)
    - Uncontrolled infection (phase II part 2)
24. Patients with pulse oximetry of less than 92% on room air (phase II part 2)
25. Any psychological, familiar, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule; those conditions should be discussed with the patient before registration in the trial
26. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test (> 10 mIU/mL)

Dose, Mode of Administration

TG4001

- TG4001 is an HPV-16 targeted immunotherapy derived from a replication deficient strain of vaccinia virus (Modified Vaccinia virus Ankara, MVA), engineered to express modified forms of the HPV-16 early proteins, E6 (delE6) and E7 (delE7), as well as the full length sequence of human interleukin 2 (IL-2). TG4001 is a suspension of recombinant viral particles suspended in a formulation medium. The formulation medium is also used as diluent for reconstitution to obtain the dose of 5×10^6 PFU (DL1). The product code of the diluent is TG0008.
- TG4001 is supplied in 4-mL glass vials as a single dose for injection. The infectious titer of the active ingredient in the vial is 5×10^7 PFU in a recoverable volume of suspension of 0.5 mL. It will be administered as subcutaneous (SC) injections. TG0008 is supplied in 4-mL glass vials with a recoverable volume of solution in each vial of 0.5 mL.
- Phase Ib, Phase II part 1 and Phase II part 2 combination arm: Patients will receive SC injections of TG4001 weekly on Days 1, 8, 15, 22, and 29, then once every 2 weeks (starting on Day 36) until Month 6 (Day 204), thereafter once every 12 weeks for a maximum of 2 years or until disease

progression or unacceptable toxicity, or premature discontinuation due to any reason, whichever occurs first.

Avelumab

- Avelumab is a fully human programmed death ligand 1 (PD-L1) blocking antibody.
- Avelumab is supplied in a single-use type I glass vial for injection, containing 200 mg of the product at a concentration of 20 mg/mL.
- Phase Ib and Phase II part 1: It will be administered as an IV infusion over 60 minutes at a dose of 10 mg/kg, starting one week (Day 8) after the first injection of TG4001, then once every 2 weeks for a maximum of 2 years or until disease progression or unacceptable toxicity, or premature discontinuation due to any reason, whichever occurs first. The dose of avelumab will be calculated based on the weight of the subject determined within 72 hours prior to administration. The dose of avelumab used for the previous administration can be repeated if the change in the subject's weight is 10% or less than the weight used for the last dose calculation.
- Phase II part 2, both arms: It will be administered as an IV infusion over 60 minutes at a dose of 800 mg, starting on Day 8, then once every 2 weeks for a maximum of 2 years or until disease progression or unacceptable toxicity, or premature discontinuation due to any reason, whichever occurs first.
- For phase Ib and phase II part 1: In order to mitigate infusion-related reactions (IRRs), patients will receive pretreatment with histamine H1 receptor (H1) blockers and acetaminophen/paracetamol 30 to 60 minutes prior to every avelumab infusion. A premedication regimen of 25 to 50 mg diphenhydramine and 500 to 650 mg acetaminophen/paracetamol (IV or oral equivalent) is recommended prior to each dose of trial drug. This regimen may be modified based on local treatment standards and guidelines as appropriate.
- For phase II part 2: In order to mitigate IRRs, patients have to be premedicated with an antihistamine and with paracetamol (acetaminophen) prior to the first 4 infusions of avelumab. Premedication should be administered for subsequent avelumab doses based upon clinical judgement and presence/severity of prior infusion reactions.
- When both drugs are given on the same day, premedication for avelumab and avelumab should be administered after TG4001 (Phase Ib, phase II part 1 and phase II part 2 for the combination arm).

There will be no dose delay or dose reduction for TG4001 and avelumab in this study.

If an AE is related to only one agent (TG4001 or avelumab) and dose omission is required, the other agent continues as planned (Phase Ib, phase II part 1 and phase II part 2 for the combination arm).

Beyond 2 years of treatment and based on the clinical judgement of the investigator the patient could continue to receive study treatments according to the Study Flow-Chart (APPENDIX IIIB and D).

Reference / Associated Therapy

Permitted medicines and therapies:

- 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.
- The use of the following drugs will not be restricted during the course of the study: erythropoietin, antiemetics, amifostine, folates, vitamin B12 and vitamin D.
- The use of systemic corticosteroids during the study is restricted as follows: for short term treatment (≤7 days) of allergic reactions or for the treatment of irAEs, or for replacement for adrenal insufficiency at doses equivalent to ≤ 10 mg prednisone daily.
- Radiotherapy for pain relief (e.g., bone metastases) is permitted. If lesions are in the field of radiation they will be no longer evaluable for the tumor response, patients receiving palliative radiotherapy will be analyzed separately.

Non permitted medicines and therapies during the study treatment:

- Any live vaccine for the prevention of infectious disease (e.g., human papilloma virus vaccine).

- Growth factors (granulocyte colony stimulating factor or granulocyte macrophage colony stimulating factor), except erythropoietin and darbepoietin alpha (may be prescribed at the investigator's discretion).
- Bisphosphonate or denosumab treatment is not allowed unless it has been initiated more than 14 days prior to receiving the first administration of study treatment.

Duration of Study Treatment

The study treatments will be administered until disease progression, or unacceptable toxicity, or patient withdrawal for any reason or for a maximum of 2 years, whichever occurs first.

Beyond 2 years of treatment and based on the clinical judgement of the investigator the patient could continue to receive study treatments according to the Study Flow-Chart (APPENDIX IIIB and D).

Depending on the response, the following rules will be applied:

- Patients who achieve a confirmed complete response (CR) MAY stop the treatment earlier at the discretion of the investigator provided that they have been treated for a minimum of 12 months. After discontinuation of the study treatment, patients will be followed until disease progression or death due to any cause or the date of data cut-off, whichever occurs first.
- Patients with a response of partial response (PR) / stable disease (SD) will continue to receive TG4001 and avelumab until achievement of a confirmed CR, disease progression, development of unacceptable toxicity or until they have received a maximum of 2 years of study treatment, whichever occurs first. Beyond 2 years of treatment and based on the clinical judgement of the investigator the patient could continue to receive study treatments according to the Study Flow-Chart (APPENDIX IIIB and D).
- Patients with progressive disease (PD) based on RECIST 1.1 will stop study treatment and complete the off-treatment procedures in phase I and phase II part 1.
- In phase II part 2 at the 1st radiologic evidence of PD, clinically stable patients may continue study treatment at the Investigator's discretion while awaiting a confirmatory scan. If repeat imaging confirms PD, study treatment must be discontinued except if the patient is clinically stable or clinically improved, and there is no further increase in the target lesions, no unequivocal increase in non-target lesions, and no additional new lesions (non-worsening PD). If repeat scan shows SD, PR or CR patient continues study treatment and imaging assessment should be performed every 6 weeks.
- Patients who are withdrawn from study drug treatment for reasons other than disease progression will be followed until disease progression or death due to any cause or the date of data cut-off whichever occurs first.

Criteria for Evaluation / Endpoints

Safety assessment

- Physical examination including vital signs and body weight will be performed at each visit. Performance Status will be recorded every 2 weeks.
- AEs and Serious Adverse Events (SAEs) will be reported and graded according to NCI CTCAE, version 4.03 for phase Ib and phase II part 1 or version 5.0 for phase II part 2 at each visit, at the end of treatment visit and at the safety follow-up visit.
- Laboratory investigations will be undertaken:
  - Complete blood cells count at baseline, on Days 1 (phase Ib and phase II part 1 only), 8, 15, 22, 29 and 36, then every 2 weeks up to Month 6 (D204), thereafter every 6 weeks, at the end of treatment visit and at the safety follow-up visit
  - Biochemistry analyses (including: AST, ALT, alkaline phosphatases, total bilirubin, lipase, amylase, LDH, serum protein, serum albumin, glucose, electrolytes) and creatinine, at baseline, on Days 1 (phase Ib and phase II part 1 only), 8, 15, 22, 29 and 36, then every 2 weeks up to Month 6 (D204), thereafter every 6 weeks, at the end of treatment visit and at the safety follow-up visit
  - TSH will be performed at baseline, on Day 36, then every 6 weeks and at the end of treatment visit
  - Free T4 will be performed at baseline and at the end of treatment visit

- Blood pregnancy test at baseline, on Day 36, then every 6 weeks, at the end of treatment visit and the safety follow-up visit for women of childbearing potential

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

Efficacy assessment will be based on local evaluations using RECIST 1.1.

- Patients will have at least one measurable lesion by CT/MRI scan (minimum size not less than 10 mm). All target lesions (measurable) and non-target lesions (measurable or not) will have to be recorded. Preferably CT (or MRI) of the head and neck, chest, abdomen and all other known sites of disease (e.g. pelvis, if applicable) will be performed within 21 days prior to start of study treatment. Patients will be evaluated every 6 weeks from start of treatment until disease progression or for a period of 9 months after start of study treatment, whichever occurs first. Beyond 9 months of treatment, the evaluations will be performed every 12 weeks until disease progression.
- Overall Response Rate (ORR): proportion of patients with CR or PR.
- Disease Control Rate (DCR): proportion of patients with CR, PR or SD.
- Duration of overall Response (DoR): applies only to patients with CR or PR. The start date is the date of first documented response (CR or PR) and the end date is the date of first documented disease progression or the date of death due to underlying cancer.
- Progression Free Survival (PFS):
  Phase Ib and phase II part 1: time from the date of first study treatment administration to the date of first documented tumor progression or death due to any cause, whichever occurs first.
  Phase II part 2: time from the date of randomization to the date of first documented disease progression or death due to any cause, whichever occurs first.
- Overall Survival (OS):
  Phase Ib and phase II part 1: time from date of first study treatment administration to the date of death due to any cause. If a patient is not known to have died at the cut-off date for analysis, survival will be censored at the date of last contact.
  Phase II part 2: time from the date of randomization to the date of death due to any cause. If a patient is not known to have died at the cut-off date for analysis, survival will be censored at the date of last contact.

PFS and OS will be calculated using the Kaplan-Meier method.

Immunology and translational research

Blood and tumor samples collection:

- Blood:
  - For phase Ib and phase II part 1: blood samples (prior to drug administration, when applicable) at Baseline, on Day 1, Day 8 (except for PBMC), Day 43, Day 85 (except for PBMC), Month 6, Month 12 and Month 24.
  - For phase II part 2: blood samples (prior to drug administration, when applicable) at Baseline, on Day 1, Day 8 (except for PBMC), Day 15, Day 43, Day 85, Month 6 (D204), Month 9 (D288), and Month 12 (D372, except for PBMC). Furthermore, on D1 6 hours post-dose (except for PBMC) for patients randomized in the combination arm and treated with TG4001.
- Tumor
  - For phase Ib and phase II part 1: tumor biopsies at baseline, on Day 43 and Day 85 (unless it is unsafe or undesirable)
  - For phase II part 2: in patients with accessible lesions tumor biopsies at baseline, in patients with accessible lesions and under study treatment on Day 85 and at Month 9 (D288). In patients with accessible lesions at time of progressive disease.

Blood samples will be collected to assess the following parameters:

- [redacted]

Tumor sample(s) will be collected to assess:

- [redacted]

Statistical Methods:

Populations of analyses and statistical analysis

Safety population (SAF): all patients included and who received any amount of study treatment will be included in the SAF. Any patient who is assigned a patient number, but does not receive any study treatment will not be included in the SAF.

Evaluable patients' population for DLT determination (DLT population): For the phase Ib of the study, the purpose being to evaluate the safety of the combination, patients must complete the first 4 weeks of the combination or discontinue before the end of the 4 weeks for a DLT to be evaluable for the primary objective of the phase Ib of the study. Patients who are not evaluable for phase Ib safety analysis or are withdrawn for other reasons than toxicity, will be replaced.

Patients must receive at least one dose of both IMPs (TG4001 + avelumab) and have at least one valid post-baseline safety assessment. The statement that a patient had no AE, on the Adverse Events eCRF page, constitutes a valid safety assessment. The occurrence of death also constitutes a valid safety assessment.

Phase II part 1: Evaluable patients' population for tumor response (evaluable per protocol population, EPP): consists of all included patients who were dosed with both IMPs (TG4001 + avelumab) and have at least one baseline and one post-baseline evaluable CT-scan at week 6 after start of study treatment with a best overall response assessment different from 'Unknown' according to RECIST 1.1 evaluation criteria. However, if a patient progressed or died due to underlying cancer before scheduled scan 6 weeks after study treatment start could be performed, the patient will still be included in the evaluable population. Any patient who has a major inclusion/exclusion violation, major dosing violation, or major protocol conduct violation will be excluded from the EPP. Major dosing violation is considered when minimum exposure is not met, defined as at least 6 TG4001 injections and 3 avelumab administrations except if patient has progressed or died due to underlying disease before or at the first evaluation. Due to potential abscopal effect when associating radiotherapy and immunotherapy, patients receiving palliative radiotherapy will be analyzed separately. Whatever the reason for withdrawal, except for disease progression and death due to underlying cancer before scheduled scan 6 weeks after study treatment start could be performed, patients considered as non-evaluable for tumor response will be replaced.

Descriptive statistics will be used. For all analyses, results and graphical representation of data will be presented by dose level and phase II cohort.

No statistical analyses will be performed on safety data. Safety summary tables will include all safety assessments up to 90 days after last study treatment administration.

Phase II part 2:

Full Analysis Set (FAS) will be the primary set for efficacy analyses. It consists of all randomized patients who were administered at least one dose of IMP(s) according to the treatment allocated at randomization.
Evaluable patients' population (evaluable per protocol population, EPP): consists of all patients from the FAS without any major inclusion/exclusion violation, major dosing violation as defined for phase II part 1, or major protocol conduct violation who were dosed with IMP(s) according to the treatment allocated at randomization and have at least one baseline and one post-baseline evaluable CT-scan at week 6 after start of study treatment with a best overall response assessment different from 'Unknown' according to RECIST 1.1 evaluation criteria.

Sample size:
Phase Ib of the study: there will be no formal sample size for the phase Ib of the study. The dose escalation part of the trial follows the methodology of a 3+3 cohort design for dose-finding studies in oncology. Depending on the observed DLTs, a maximum of 12 evaluable patients will be included in this part of the study.

Phase II part 1: a Simon's two-stage design will be used. The null hypothesis for response rate H_0 is set at 10% corresponding to the response rate observed in second line patients, the alternative hypothesis of efficacy is set at H_A=25%, the type I error α is set at 5% one sided, the type II error β is set at 20% (power=80%). Under these hypotheses and applying a minimax two-stage Simon design, enough patients will be treated to obtain 22 evaluable patients as a first stage. If at least 3/22 patients are considered responders, the enrolment will be continued, otherwise it will be stopped. In the initial design and at the second stage enough patients should have been treated to obtain at least 40 evaluable patients in total. The study would have been considered positive with at least 8/40 responders. With a hierarchical strategy on the final analysis, a subgroup analysis performed in oropharyngeal SCCHN patients and with a null hypothesis for response rate (H0) set at 10% and the alternative hypothesis of efficacy set at HA = 35%, 18 oropharyngeal SCCHN patients would have been needed to reach a power of 81% and actual alpha at 2.8%. This analysis would have been considered positive with at least 5 responders among the 18 SCCHN patients. The second stage of the Simon's design has not been done following the decision to exclude oropharyngeal SCCHN and to change to a randomized controlled two-arms study (phase II part 2).

Phase II part 2:

- For the cohort of patients without liver metastases at baseline, an adaptive sample size re-estimation is applied: based on the results obtained in phase II part 1, the hypothesis for median PFS in the combination arm (TG4001 with avelumab) is set at 4.5 months. The hypothesis for median PFS in the monotreatment arm (avelumab alone) is set at 2 months. The type I error α is set at 5% one sided, the type II error β is set at 5%.
  A two-stage group sequential design will be used with logrank test and boundary for efficacy at alpha=0.00001 and Conditional Power (CP) at 10% for futility.

  At the interim analysis, a first test for efficacy is performed on 37 PFS events at a level of significance of 0.000001. A sample size of 50 patients is estimated at time of the Interim Analysis.
  Otherwise, the following decision rules are applied based on CP using CHW (Cui, Hung and Wang) approach.

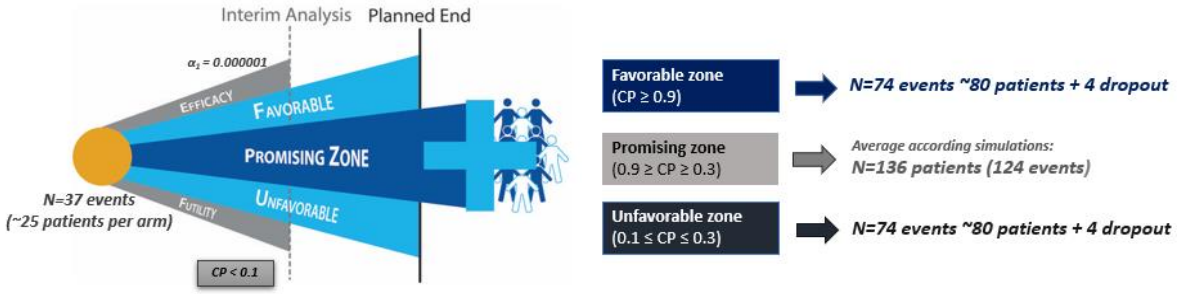
  - Favorable zone: If the interim results are sufficiently favorable corresponding to a CP of more than 90%, final analysis will be performed on 74 PFS events corresponding to an estimated sample size of 80 patients.

  - Promising zone: If the interim results are equivalent to a CP between 90% and 30%, the sample size will be recalculated according to the median PFS observed in the two arms with a cap of 2 times the initial number of events.

- Unfavorable zone: If the interim results are not favorable corresponding to a CP between 30% and 10%, the trial may continue up to the initial sample size of 80 patients or could be stopped.

- Futility zone: If the interim results are futile corresponding to a CP lower than 10%, the trial will be stopped for futility at the interim analysis.

Assuming uniform enrollment with 3 patients per month, an average of 136 patients are needed to observe 124 PFS events. Assuming a 5% lost to follow-up or withdrawal of consent rate, a total of 142 patients should be randomized to the 2 treatment arms in a 1:1 ratio (71 patients in each treatment arm). [redacted]



- For the cohort of patients with liver metastases at baseline, [redacted]

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ABBREVIATIONS / DEFINITION OF TERMS

ABBREVIATIONS	MEANING OF ABBREVIATIONS IN DOCUMENT
ADA	Anti Drug Antibody
ADCC	Antibody Dependent–Cell mediated Cytotoxicity
ADR	Adverse Drug Reaction
AE	Adverse Event
AIDS	Acquired Immune Deficiency Syndrome
ALT	Alanine amino-transferase (= SGOT)
ANA	Anti-Nuclear Antibodies
ANCA	Antineutrophil cytoplasmic antibody
AST	Aspartate amino-transferase (= SGPT)
C_{trough}	Concentration at the end of dose interval
CFR	Code of Federal Regulations
CI	Confidence Interval
CIN	Cervical Intraepithelial neoplasia
CNS	Central Nervous System
CP	Conditional Power
CR	Complete Response
CRA	Cytokine Release Assays
CRF	Case Report Form
CRO	Contract Research Organization
CRP	C-Reactive Protein
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTL	Cytotoxic T Lympocytes
CxCa	Cervix cancer
D	Day
DC	Dendritic Cells
DCR	Disease Control Rate
DL	Dose Level
DLT	Dose Limiting Toxicity
DNA	Deoxyribonucleic acid
DoR	Duration of Response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EGFR	Epidermal Growth Factor Receptor
EPP	Evaluable per Protocol Population
FACS	Fluorescence-activated cell-sorting
FDG-PET	Fluorodeoxyglucose Positron Emission Tomography
GCP	Good Clinical Practice
GMO	Genetically Modified Organism
HBV	Hepatitis B Virus
hCG	human Chorionic Gonadotropin
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HLA	Histocompatibility Leukocyte Antigen
HNC	Head and Neck Cancer
HPV	Human Papilloma Virus
HR	Hazard Ratio
IB	Investigator's brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ICMJE	International Committee of Medicinal Journal Editors
ICU	Intensive Care Unit
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IFN	Interferon

IL	Interleukin
IM	Intramuscular
IMP	Investigational Medicinal Product
IND	Investigational New Drug
IO	Immuno-Oncology
IRB	Institutional Review Board
IRR	Infusion-Related Reaction
irAE	Immune-related Adverse Event
ISH	In Situ Hibridization
IU	International Unit
IUD	Intrauterine devices
IV	Intravenous
LDH	Lactate Dehydrogenase
LLN	Lower Limit of Normal
M	Month
MAD	Maximum Administered Dose
MDRD	Modification of the Diet in Renal Disease
MoAb	Monoclonal Antibody
mL	Milliliters
MTD	Maximum Tolerated Dose
MRI	Magnetic Resonance Imaging
MVA	Modified Vaccinia virus Ankara
NCI-CTCAE	National Cancer Institute's Common Terminology Criteria for Adverse Events. Also referred as CTCAE in the text
NK	Natural Killer
NOAEL	No Observed Adverse Effect Level
NSAID	Non-Steroidal Anti-Inflammatory Drug
ORR	Overall Response Rate
OS	Overall Survival
PBMC	Peripheral Blood Mononuclear Cells
PCR	Polymerase Chain Reaction
PD	Progressive Disease
PD-1	Programmed-Death 1
PD-L1	Programmed-Death Ligand 1
PHA	Phytohemaglutinin
PFS	Progression Free Survival
PFU	Plaque Forming Unit
PR	Partial Response
PS	Performance Status
Q2W	Every two Weeks
Q4W	Every four Weeks
RECIST	Response Evaluation Criteria In Solid Tumors
RNA	Ribonucleic Acid
RP2D	Recommended Phase 2 Dose
SAE	Serious Adverse Event
SAF	Safety Population
SC	Subcutaneous
SCCHN	Squamous Cell Carcinoma of Head and Neck
Sd	standard deviation
SD	Stable Disease
SUSAR	Suspected Unexpected Serious Adverse Reaction
TAA	Tumor Associated Antigen
TCR	Tumor Cross reactivity
TEAE	Treatment Emergent Adverse Event
TIL	Tumor Infiltrating Lymphocytes
TMF	Trial Master File
TPO	Thyroid Peroxidase
TO	Target Occupancy
ULN	Upper Limit of Normal

VIN	Vulvar Intraepithelial neoplasia
WBC	White Blood Cells

ABBREVIATIONS / DEFINITION OF TERMS (Cont.)

DEFINITIONS

Consented patient	A patient who has signed the informed consent form.
Screened patient	A patient identified during the pre-screening process as a candidate for entry into the study and who has signed the Informed Consent Form (ICF) to undergo procedures required to verify the eligibility criteria before inclusion
Screen Failure	Any patient who underwent screening procedures, and who is found to be not eligible for entry into study and therefore does not receive any study treatment.
Included patient	A patient who signed the ICF, has been included in the study and has received at least one administration of study treatments (TG4001 or avelumab).
Lost of follow-up patient	An included patient for whom no further news is obtained by the Investigator before the last study assessment. The date of lost of follow-up is the date the Investigator received the last news from the patient i.e. during a visit or a telephone contact or any written means.
Protocol deviation	All non adherences to following protocol requirements: study inclusion or exclusion criteria, conduct of the study, patient management or patient assessment.
Evaluable patients	Evaluable patients for DLT determination: patients must complete the first 4 weeks of the combination or discontinue before the end of the 4 weeks for a DLT. Patients must receive at least one dose of both IMPs (TG4001 + avelumab) and have at least one valid post-baseline safety assessment. Patients who are not evaluable for phase Ib safety analysis or are withdrawn for other reasons than toxicity, will be replaced. Phase II part 1: Evaluable patients population for tumor response: patients who were dosed with both IMPs (TG4001 + avelumab) and have at least one baseline and one post-baseline evaluable CT-scan at week 6 after start of study treatment with a best overall response assessment different from 'Unknown' according to RECIST 1.1 evaluation criteria and have no major protocol violations or major dosing violations. Major dosing violation is considered when minimum exposure is not met, defined as at least 6 TG4001 injections and 3 avelumab administrations except if patient has progressed or died due to underlying disease before or at the first evaluation. Phase II part 2: Full Analysis Set (FAS) which consists of all randomized patients who were administered at least one dose of IMP(s) according to the treatment allocated at randomization.

Start of study treatment	Corresponds to date of Day 1 for phase Ib and phase II part 1 and to date of randomization for phase II part 2

1 INTRODUCTION

1.1. Background and introduction

1.1.1. Human PapillomaVirus (HPV) and related diseases

Human papillomavirus (HPV) is the most common diagnosed sexually transmitted infection. It is associated with condyloma acuminata, anogenital (cervical, vaginal, vulval, penile, anal) squamous intraepithelial lesions and malignancies, and also squamous cell carcinoma of the head and neck (SCCHN).

HPV is a small deoxyribonucleic acid (DNA) virus of approximately 7900 base pairs. The HPV genome encodes DNA sequences for six early (E) proteins associated with viral gene regulation and cell transformation, two late proteins which form the shell of the virus, and a region of regulatory DNA sequences known as the long control region or upstream regulatory region (Palefsky J.M. and Holly E.A., 1995).

HPV genotypes can be broadly split into “high-risk” (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68) and “low-risk” (6, 11, 40, 42, 43, 44, 53, 54, 61, 72, 73 and 81) based upon their malignant potential. Types 16 and 18 are the most commonly isolated HPV types in cancer with type 16 found in approximately 50 % of patients with cervical cancer for example (de Sanjose S. *et al.*, 2010). However, not all infections with HPV type 16 or 18 progress to cancer. Furthermore, within single oncogenic HPV types, variants exist that are associated with different oncogenic potential (Hildesheim A. *et al.*, 2001). Beyond causing cervical cancer, HPV is also implicated in cancer of the anus (Tilston P., 1997) and penis (Varma V.A. *et al.*, 1991). There is also an approximately 2 to 3 fold increased risk for cancers of the oral cavity and oropharynx in patients infected with high-risk (oncogenic) HPV subtypes: HPV-16 genotype but also HPV-18, 31 or 33 (de Sanjose S. *et al.*, 2010), (Hildesheim A. *et al.*, 2001). HPV associated tumors predominantly arise in the base of the tongue or the tonsillar region, although a small percentage of tumors at other sites are also HPV positive. It is unclear why the oropharynx is more susceptible to HPV transformation than other sites.

Cohort studies from the 1990s suggested that approximately 50 % of oropharyngeal cancers were attributable to HPV, while more recent studies suggest that HPV may account for as much as 70 to 80% of these malignancies (Sturgis E.M. and Ang K.K., 2011), (Chaturvedi A.K. *et al.*, 2011).

A review on the published clinical trials, both single-arm and randomized, demonstrated HPV positivity ranging from 20 to 60% of oropharyngeal cancers (Ihloff A.S. *et al.*, 2010).

These data were confirmed in 2013 by a systematic literature review that assessed for Europe a 39.7% overall prevalence of HPV oropharyngeal cancer, demonstrating also a substantial increase over the time from 35.3% before year 2000 to 73.1% after year 2005 and a 23.7% overall prevalence of HPV non-oropharyngeal cancer, demonstrating also a substantial decrease over the time from 23.6% before year 2000 to 11.7% after year 2005 (Mehanna H. *et al.*, 2013).

1.1.2. Role of HPV in the carcinogenesis of SCCHN

Tumor carcinogenesis in SCCHN involves dynamic interactions among many factors. Exposure of the upper aerodigestive tract to alcohol or tobacco is one of the preponderant risk factors for SCCHN, and exposure to both increases the risk beyond what would be expected if the agents simply had additive effects (Cann C.I. *et al.*, 1985).
Another common risk factor is alteration of the function of the p53 tumor suppressor gene, which may be caused by either gene mutation or infection with an oncogenic type of human papillomavirus (HPV) (Brachman D.G. *et al.*, 1992), (Gillison M.L. and Shah K.V., 2001).
In some patients, particularly those with oropharyngeal cancer not associated with p53 mutation or the molecular impacts of alcohol and tobacco, HPV infection can cause head and neck cancer even in the absence of other molecular alterations (Haddad R.I. and Shin D.M., 2008), (D'Souza G. *et al.*, 2007). All of these risk factors are likely to result from and contribute to suppression of the patient's immune system, as is the tumor itself (Alhamarneh O. *et al.*, 2008).
Studies show that an infection with high-risk HPV is an independent risk factor for the development of SCCHN and needs to be considered along with the traditional risk factors such as tobacco abuse or alcohol (D'Souza G. *et al.*, 2007), (Gillison M.L. *et al.*, 2000b).

HPV-16 is the far most common type detected in oropharyngeal cancer accounting for 90–95% of the HPV positive tumors (Marur S. *et al.*, 2010), (Kreimer A.R. *et al.*, 2005). High-risk HPVs produce 2 oncoproteins, E6 and E7, which are necessary for viral replication through their proliferation stimulating activity and play a key role in malignant transformation. The E6 oncoprotein binds and induces the degradation of the p53 tumor suppressor protein via an ubiquitin-mediated process disrupting the p53 pathway which leads to uncontrolled cell cycle progression (Chung C.H. and Gillison M.L., 2009), (Havre P.A. *et al.*, 1995). The HPV E7 protein binds and degrades the retinoblastoma protein (pRb), preventing it from inhibiting the transcription factor E2F resulting in loss of cell cycle control. Furthermore, the functional inactivation of Rb results in upregulation of the p16-protein. P16 is encoded by the CDKN2A tumor suppressor gene and regulates the activity of Cyclin D-CDK4/6 complexes that phosphorylate Rb leading to release of the transcription factor E2F which initiates cell cycle progression. HPV-positive tumors are characterised by high expression of high levels of p16 (Nevins J.R., 2001). The p16 protein can be detected by immunohistochemistry, and since several studies have shown a very high correlation (> 90%) to HPV-positivity in oropharyngeal tumors, it has been suggested as a clinically useful sorrogate marker (Mellin Dahlstrand H. *et al.*, 2005), (Klussmann J.P. *et al.*, 2003)

In head and neck cancer caused by the traditional risk factors, tobacco and alcohol, p53 is commonly mutated (Ahomadegbe J.C. *et al.*, 1995), (Carlos de Vicente J. *et al.*, 2004) and 9p21-22 is lost early in carcinogenesis resulting in the loss of the tumor suppressing gene p16 (Kim S.H. *et al.*, 2007). In contrast, HPV-positive head and neck tumors have decreased expression of wild-type p53 due to the inactivation and degradation by the E6 oncoprotein.

1.1.3. HPV vaccine

Many diverse vaccine platforms have been evaluated in clinical trials; including injection of peptides or proteins, injection of recombinant viruses or other recombinant micro-organisms, delivery of killed tumor cells, or delivery of protein or peptide-activated dendritic cells (DCs) to the patient. Each of them has strengths and weaknesses that can be influenced by the particular tumor-associated antigen that is targeted, the disease and disease stage, the clinical

trial endpoint, and whether the vaccine is evaluated in combination with an immune stimulant, an inhibitor of immune suppression, or another mode of cancer therapy (Schlom J., 2012).

Two prophylactic vaccines have been developed against HPV infection in females; one is a quadrivalent vaccine (Gardasil) and the other is a bivalent vaccine (Cervarix). Both are approved for the prevention of HPV-related diseases.
Vaccine efficacy is measured only by the prevention of virologic infection or related clinical events. Excellent antibody responses have been reported following immunization with both quadrivalent and bivalent vaccines (Villa L.L. *et al.*, 2006), (Harper D.M. *et al.*, 2006), (GlaxoSmithKline Vaccine H.P.V.S.G. *et al.*, 2009).

To date, few antitumor vaccines for SCCHN have been clinically evaluated. The emphasis is on dendritic cell-based vaccines, largely because of enhanced immunogenicity of epitopes presented by adoptively-transferred DC to responder T cells *in vivo.* Delivery of such antitumor vaccines in combination with conventional therapies and in the setting of a minimal residual disease to SCCHN patients takes advantage of exquisite specificity of the immune system at the time when tumor-induced suppression is reduced. Vaccine-driven generation, long-term survival and maintenance of tumor-specific immune cells are the objectives that antitumor vaccines have to realize to be clinically beneficial in SCCHN (Whiteside T.L., 2007).

Early data suggest that targeting E6 and E7 with vaccine-based approaches is feasible and efficacious. A phase I study attempted to combine HPV-16 derived peptides with the melanoma differentiation antigen MAGE-A3 into a therapeutic vaccine (Voskens C.J. *et al.*, 2012)**.** Although there were no clinical responses in this small study, immune responses directed against the HPV epitopes targeted by the vaccine were detected, including T-cell responses in 4 of 5 treated patients. An additional preclinical study demonstrated the feasibility of inserting the E7 gene within a viral plasmid in a DNA-based HPV-targeting vaccine (Peng S. *et al.*, 2010).

Vaccines targeting HPV are also being explored for a range of premalignant and malignant gynecologic diseases, and these findings could potentially be applicable to HPV-associated head and neck cancers (Kenter G.G. *et al.*, 2009). Vaccination strategies are also being tested in HPV-negative malignancies; preliminary testing of a dendritic cell vaccine targeting p53 epitopes was reported recently (Andrade P. *et al.*, 2009).

1.1.4. PD-1 and PD-L1 pathway and immune responses

PD-1 is a negative regulator of T-cell activity that limits the activity of T cells at a variety of stages of the immune response when it interacts with its two ligands, PD-L1 and PD-L2 (Ishida Y. *et al.*, 1992), (Freeman G.J. *et al.*, 2000), (Keir M.E. *et al.*, 2006). When engaged by a ligand, through phosphatase activity, PD-1 inhibits kinase-signaling pathways that normally lead to T-cell activation. A number of antibodies that disrupt the PD-1 axis have entered clinical development. PD-L1 is also believed to exert negative signals on T cells by interacting with B7 (Butte M.J. *et al.*, 2007), and PD-L1-blocking antibodies prevent this interaction. Immune checkpoint inhibitors also enhance the function of tumor-infiltrating lymphocytes (TILs), which augments antitumor immunity within the tumor microenvironment. The presence of TILs has been correlated with better prognosis in many cancer types, including bladder (Tsujihashi H. *et al.*, 1988), (Lipponen P.K. *et al.*, 1992), (Sharma P. *et al.*, 2007), lung (Geng Y. *et al.*, 2015), breast (Adams S. *et al.*, 2014), ovarian (Zhang L. et al., 2003), renal ((Li Y. *et al.*, 1998), colon

(Maby P. et al., 2015), and esophageal (Liu J.Y. *et al.*, 2015) carcinomas. Thus, PD-L1$^+$ TILs have been shown to be indicators of response to immune checkpoint blockade, and a lack of TILs may be a predictive marker for lack of response to PD-1/L1 blockade (Curran M.A. *et al.*, 2010) (Huang R.R. *et al.*, 2011), (Herbst R.S. *et al.*, 2014).

1.2. Investigational medicinal products (IMPs)

The two investigational medicinal products evaluated in the present trial are TG4001 and avelumab.

1.2.1. TG4001

TG4001 is a therapeutic recombinant vaccine/immunotherapy product based on the non-propagative highly attenuated vaccinia vector Modified Vaccinia virus Ankara (MVA) whose genome, a single linear double-stranded DNA molecule of approximately 178 kilobase pairs (Antoine G. *et al.*, 1998) contains inserted transgenes coding for three proteins: HPV antigens E6 and E7 onco-proteins modified to remove their oncogenic potential and human interleukin-2 (IL-2) as an adjuvant.

The modified forms of E6 and E7 proteins each lack the region known to interact with tumor suppressor proteins p53 and Rb, respectively (Munger K. *et al.*, 1989), (Crook T. *et al.*, 1991) and are joined to secretory signal and membrane anchoring domains in order to direct the targeting of these proteins toward the cytoplasmic membrane.

The mode of action is to activate the adaptive immune system towards cells expressing E6 and E7 and weeding out of infection through IL-2.

1.2.1.1. Summary of preclinical data

Preclinical studies have demonstrated that the recombinant MVA is a non-replicative virus and stimulates the innate immunity through IFN-gamma induction. Moreover the human cytokine IL2 is a growth factor for T lymphocytes and natural killer cells. The E6 and E7 HPV-16 genes fused to heterologous sequences encoding secretory signal and membrane-anchoring domains thus causing the elicitation of antigen specific Cytotoxic T lymphocytes (CTL) and enhancing the immunogenicity through improved antigen presentation. E6 and E7 are continuously expressed by HPV+ cancer cells and their expression is required for maintenance of the malignant phenotype. This provides higher efficacy specifically against HPV infected cells without any interaction with normal cells.

The antitumor efficacy of TG4001 was assessed in C57Bl/6 mice engrafted with TC1 tumor cells, primary lung cells from C57Bl/6 mice immortalized by expression of HPV-16 E6 and E7 (Halbert C. *et al.*, 1991) and then transformed with the activated RAS oncogene. This transformation process mimics the natural sequence in the pathogenesis of cervical cancer in which HPV-16 plays a critical role in carcinogenesis (Halbert C. *et al.*, 1991).
TG4001 was demonstrated to have CD8+ T cell-dependent anti-tumor activity and to confer immunity against TC1 tumors expressing wild-type HPV-16 E6 and E7 genes (Pecheur C. and Bizouarne N., 2000).

Preliminary data suggested also that TG4001 does cross-react with HPV-16,31,33,35, and 52 genotypes.
The mechanism by which the immune system may induce regression of HPV-induced lesions was investigated and CD8+ T-cell response was shown to be critical for anti-tumor efficacy (Paul S., 2007).

The effect of the route of administration as a function of the administered dose was studied in mice in immunotherapy experiments (Balloul J.M. and Pecheur C., 2006), (Bizouarne N., 1998a). The most efficient route was shown to be intraperitoneal, with 100% immunoprophylaxis and 82% tumor rejection. However, the intraperitoneal route is not a viable commercial option for patient administration. Further data show that intramuscular (IM) and subcutaneous (SC) administration were both also effective: SC route is more efficient than the IM route under the conditions of the study (Bizouarne N., 1998b), (Balloul J.M. and Pecheur C., 2007).

Excretion occurs through urine. Neither absorption/pharmacokinetic parameters or metabolism studies were conducted.

TG4001 safety profile was investigated for its systemic toxicity and local tolerance in mice, rats, and rabbits. Except for slight to moderate irritant effects (erythema, and/or edema) at the injection site, changes included decreased reticulocytes and lymphocytes, and an increased spleen weight that correlated with lymphoid hyperplasia. TG4001 demonstrated an acceptable safety profile in doses up to 2676-fold of the maximum human dose. (Pecheur C., 1998b), (Pecheur C., 1998a) (Kaiser S., 2007). Focal or maculate erythema, hyperkeratosis, and follicular hypertrophy/hyperplasia were observed at the application site and blue skin was observed at application site and head. (Christ M., 2001)**.** No concerns of effects on central nervous, respiratory, and cardiovascular systems. Reproductive and developmental toxicity standard genotoxicity studies were not conducted. No oncogenic potential of TG4001 was evident (Balloul J.M., 1998), (Menguy T., 2009).

1.2.1.2. Summary of TG4001 efficacy data

TG4001 was investigated in gynaecological conditions.
Three Phase I multiple ascending dose studies have been conducted and were designed to determine the maximum tolerated dose (MTD), safety, local (dysplastic cervical tissues) and systemic immune responses (TG4001.01, TG4001.02, and TG4001.03) and five phase II studies (See Table 1-1) to determine safety and efficacy (TG4001.04, TG4001.05, TG4001.06, TG4001.07 and NV25025), 3 of these studies also examined immune response.

The Phase I clinical studies were conducted in a total of 18 patients with either cervical disease including grade 3 CIN (TG4001.01) or different stages of cervical cancer (TG4001.02 and TG4001.03). Patients received repeated IM injections of TG4001 at one of the following dose levels: 5×10^5 PFU, 5×10^6 PFU, or 5×10^7 PFU.

Among the 5 phase II studies, 4 were considered as not conclusive (See Table1-1) but the fifth Phase II (**NV25025**) trial in HPV-16 associated cervical intraepithelial neoplasia (CIN) grade 2/3 demonstrated a proof of concept that TG4001 had higher activity and efficacy compared to placebo in terms of histologic resolution and response rates as well as viral clearance. The dose that was used in this phase II trial of HPV-16 associated CIN grade 2/3 patients was 5×10^7

PFU. Moreover, the therapeutic vaccine/immunotherapy product was demonstrated to be safe with no major toxicities, apart from injection site reaction (Brun J.L. *et al.*, 2011).

Among the phase II studies, **TG4001.04,** was the only evaluating the efficacy and safety of TG4001 in cervical cancer. It was a randomized, multicenter study in 30 hispanic women with HPV-16 positive locally advanced cervical cancer resistant to or relapsing after radiotherapy. Of the 16 patients included in the per protocol analysis, only two met the primary efficacy criteria, experiencing stable disease at Month 6.

Table 1-1 : Summary of Phase II clinical trials with TG4001

Study #	Study design	Selected population	Schedule of administration, dose	Number of patients	Key results
TG4001.04	Open-label phase II	Women with HPV-16 positive cervical cancer resistant to or having relapsed after radiotherapy	One SC injection on Days 1, 8, and 15 $5x10^5$ PFU (initial safety phase) and $5x10^6$ PFU (efficacy)	N=30 age 27-82 yrs	2/16 stable disease at 6 months (PP population) No clinical significant effect of $5x10^6$ PFU
TG4001.05	Open-label phase II	Women with HPV-16 positive grade 2/3 Cervical intraepithelial neoplasia (CIN2/3)	One SC injection on Days 1, 8, and 15 $5x10^5$ PFU and $5x10^7$ PFU	N=31 Age 31-48 yrs	7/17 early/partial regression of baseline lesions at 6 t 8 weeks at $5x10^7$ PFU (dose effect)
TG4001.06	Randomized, open-label, phase II	Women with HPV-16 positive grade 3 vulvar intraepithelial neoplasia (VIN) except Bowen's disease	One SC injection on Days 1, 8 and 15 $5x10^6$ PFU of TG4001 or Placebo	N=20 Age 27-58 yrs	No clinically significant effect of $5x10^6$ PFU
TG4001.07	Open–label phase II	Women with HPV-16 positive grade 2/3 Cervical intraepithelial neoplasia (CIN2/3)	One SC injection on days 1,8, and 15 of TG4001 at $5x10^7$ PFU	N=21 Age 25-44 yrs	10/21 responders at 6 months
NV 25025	Randomized double blind placebo controlled parallel group multicenter phase II	Women with histologically confirmed diagnosis of CIN2 or 3 associated with a current single or multiple high risk HPV infection	One SC injection on Days 1, 8 and 15 of TG4001 or placebo at $5x10^7$ PFU	N= 206 Age 18-60 yrs	11/55 complete responders at 6 months. Significant effect compared to placebo

1.2.1.3. Summary of TG4001 safety data

The overall safety profile of TG4001 is based on data from completed studies of a total of 313 subjects, either healthy volunteers (n=66) or patients with CIN 2/3 (n=194), cervical carcinoma (N=42) or VIN (N=11), treated with TG4001 in monotherapy or in combination with immunomodulator imiquimod.
Among those subjects, 18 (5.8%) received injections via IM route in 3 phase I studies and 295 (94.2%) received injections via SC route in one single-blind phase I study, in 4 open-label phase II studies and in one double-blind placebo-controlled phase II study.

TG4001 was well tolerated up to highest dose tested of 5 x 10^7 PFU administered to patients either weekly or every 3 weeks up to 7 weeks, with a maximum of 6 injections.

The most frequently adverse drug reactions (ADRs) reported as related to TG4001 were common vaccine-associated reactions. The most frequent ones observed in patients receiving IM administrations (18 patients, incidence ≥10%) being pain at the injection site (27.8%), fatigue (11.1%) and feeling of body temperature change (11.1%). The most frequently observed ADRs in patients receiving SC administrations (295 patients, incidence ≥5%), were injection site reaction (ISRs) (73.9%), injection site erythema (9.5%), injection site inflammation (6.4%), headache (5.4%), and lymphadenopathy (5.1%). Most of these events were of mild to moderate intensity (grade 1 or 2).
Most ISRs were reported as "mild" or "moderate", all were considered probably related to study treatment, and all resolved without sequelae.

In the indications for which TG4001 was studied, all of the serious AEs (SAEs) and deaths were considered unrelated to the study treatment, except of two:

- In study NV25025 (patients with CIN 2/3) one SAE, lymphadenopathy, was assessed by the investigator as possibly related to TG4001.
- In study TG4001.04 (patients with late-stage cervical cancer with resistance to or relapse after radiotherapy) one SAE, renal failure was assessed by the investigator as possibly related to TG4001. This SAE was as well assessed by the investigator as possibly related to the underlying disease as the patient presented at baseline cervix tumor with extended lymph nodes involvement and bilateral renal obstruction. The sponsor considered renal failure as unlikely related to TG4001 since there is a plausible and more likely relationship between CxCa and the patient's evolution, based on baseline disease.

The deaths that occurred were in patients with advanced cervical carcinoma or late-stage cervical cancer, resistant to or relapsed after radiotherapy; there were no reports of deaths in CIN2/3 patients treated with TG4001.

Long term safety data were collected from subjects enrolled from both studies NP21903 (phase I in healthy volunteers) and NV25025 (phase II in CIN 2/3 patients). Overall duration of safety follow-up extended to a maximum of 946 days and no safety concern was raised over this period.

For more details and updated information refer to TG4001 Investigator's Brochure.

1.2.2. Avelumab

Avelumab (also known as MSB0010718C) is an investigational fully human anti-PD-L1 IgG1 monoclonal antibody (MoAb).
Avelumab is currently in clinical investigation.

Avelumab has 2 main mechanisms of action for exerting its anti-tumor effects:

- PD-L1 on tumor cells can interact with PD-1 or B7-1 on activated T cells. These interactions have been shown to significantly inhibit T cell activities. Therefore, blocking PD-L1 interaction with PD-1 or B7-1 by anti-PD-L1 can release T cells from immunosuppression, and lead to elimination of tumor cells by T cells.

- Tumor cells may express high levels of PD-L1 on their surface compared with normal tissues. As a fully human IgG1 MoAb, avelumab has antibody-dependent cell-mediated cytotoxicity (ADCC) potential. Upon binding to PD-L1 on tumor cells and binding with

their Fc part to Fc-gamma receptors on leukocytes, avelumab can trigger tumor-directed ADCC.

Therefore, blocking PD-L1 inhibitory mechanisms by interactions with not only PD-1 but also the other ligand, B7-1, avelumab may offer unique therapeutic potential compared with MoAbs targeting PD-1.

1.2.2.1. Summary of preclinical data

The nonclinical pharmacology studies have shown that avelumab functionally enhances T cell activation *in vitro* and significantly inhibits the growth of PD-L1 expressing tumors *in vivo.* Avelumab binds to human PD-L1 with a high affinity of 0.7 nM and not to any other B7 family proteins, and competitively blocks the interaction of PD-L1 with PD-1. The *in vitro* study results have shown that by binding to PD-L1, avelumab effectively enhances T cell activation as measured by interleukin (IL)-2 or interferon-gamma (IFN-gamma production). In addition, as a fully human IgG1 antibody, avelumab has the potential to trigger the ADCC against target cells expressing PD-L1.

As a monotherapy, avelumab has demonstrated anti-tumor activity against murine MC38 colon carcinoma tumors that are characterized by a high level of PD-L1 expression. A dose-dependent trend was observed, and 400 µg per dose (20 mg/kg, approximately) was identified as the optimally effective dose when given every third day for 3 total doses.

The *in vivo* anti-tumor effects were found to be primarily mediated by $CD8^+$ T cells as evidenced by the observation that *in vivo* depletion of this cell type completely abrogated the anti-tumor efficacy of avelumab. The contribution of ADCC as a potential mechanism of anti-tumor activity was further demonstrated *in vivo* using a deglycosylated version of avelumab to abrogate fragment crystalline (Fc) receptor binding or via the systemic depletion of natural killer (NK) cells. In both settings, loss of *in vivo* ADCC potential significantly reduced the anti-tumor activity.

Various immunomonitoring assays were incorporated into the *in vivo* studies. Treatment with avelumab resulted in a consistent increase in the percentage of $CD8^+PD\text{-}1^+$ T cells and an increased frequency of $CD8^+$ T cells with an effector memory (T_{EM}) phenotype as determined by flow cytometry. Furthermore, these changes correlated with the anti-tumor effect. Increases in tumor antigen-specific T cell responses, as measured by enzyme-linked immunosorbent spot and pentamer immunoassays, were evident following treatment with avelumab. Hence, increases in $CD8^+PD\text{-}1^+$ T cells, $CD8^+$ T_{EM} cells, and antigen-specific T cell responses, may be leveraged as pharmacodynamics (PD) biomarkers with translational relevance to the clinical setting.

As expected for a MoAb binding to a cellular target, avelumab demonstrated pronounced non-linear pharmacokinetic (PK) characteristics in mice and monkeys in single dose studies at doses below 20 mg/kg, suggesting a combination of first order catabolic clearance and saturable target-mediated clearance. Toxicokinetic data from repeated dose toxicity studies in mice, rats, and monkeys indicated that the PK of avelumab was linear within the dose range of 20 to 140 mg/kg, suggesting that the target mediated clearance could be saturated when higher doses than 20 mg/kg are administered. Similar terminal half-lives ($t_{1/2}$) of approximately 60 to 70 hours were observed in toxicity studies in mice and monkeys.

The toxicological profile of avelumab was evaluated in repeat-dose toxicity studies of 4-week duration with once weekly IV bolus injection/infusion of avelumab in mice, rats, and cynomolgus monkeys. A repeat-dose toxicity study with intermittent once weekly IV infusion of avelumab over 13 weeks followed by an 8-week recovery period in cynomolgus monkeys was also conducted. In addition, in vitro cytokine release assays (CRA) in human and cynomolgus monkey whole blood and peripheral blood mononuclear cells (PBMCs) followed by an optimized CRA in phytohemagglutinin (PHA) pre-stimulated PBMCs from 16 human volunteers was completed. Tissue cross reactivity (TCR) studies in normal human and cynomolgus monkey tissues have also been performed.

In cynomolgus monkeys neither in the pilot 4-week IV repeat-dose toxicity study nor in the pivotal 13-week study, clinical signs of hypersensitivity have been seen after repeated treatment with avelumab at dose levels of 20, 60, and 140 mg/kg, respectively. For the pilot 4-week study as well as for the pivotal 13-week IV repeat-dose toxicity study, a no observed adverse effect level (NOAEL) of 140 mg/kg for systemic toxicity was established.

Initial CRA in human and cynomolgus monkey whole blood and PBMCs revealed no clear-cut evidence for release of pro-inflammatory cytokines. However, a subsequent, optimized CRA demonstrated evidence of potential cytokine release in PHA pre-stimulated PBMCs.

1.2.2.2. Pharmacokinetics and metabolism

Pharmacokinetics following the first 1-hour infusion and dose proportionality of avelumab have been characterized in 57 Caucasian patients treated in the dose escalation and expansion cohort of the Phase I Trial EMR100070-001 by standard non-compartmental analysis based on rich serum concentration-time data obtained over a complete dosing interval of 2 weeks (= tau). The analysis of these data revealed that the exposure parameters maximum concentration observed post-dose (C_{max}) and area under the concentration-time curve (AUC_{tau}) increased with the doses in a linear fashion.
The apparent terminal half-life ($t_{1/2}$) was 69 hours (mean) ± 21 hours (standard deviation) for 1 mg/kg, 84 ± 22 hours for the 3 mg/kg, 106 ± 29 hours for 10 mg/kg, and 134 ± 74 hours for the 20 mg/kg dose. Taking into account the variability, the $t_{1/2}$ of the 10 and 20 mg/kg doses can be regarded as similar, indicating that target mediated elimination does not increase at these doses. This implies that target occupancy is likely to be high at these 2 doses throughout the dosing interval.

Trough concentrations (C_{min}) were obtained for the majority of patients enrolled in the trial. The median C_{min} at the end of the first cycle after administration of the 10 mg/kg dose was 20 µg/mL (n=256). This median C_{min} increased during the subsequent cycles to 24 µg/mL (second cycle; n=233), 26 µg/mL (third cycle; n=167), and remained between 24 and 37 µg/mL during the subsequent cycles (n=22 to 114) indicative for no significant accumulation with the biweekly dosing scheme. Median C_{min} after the 3 mg/kg dose were 3.7µg/mL after the first dose, 3.9 µg/mL after the second dose and 8.3 µg/mL after the third dose (n=7 to 12), though some trough values below 1 µg/mL were observed, as well as antidrug antibodies in at least 1 patient in this dose group on day 85 of the treatment period, accompanied by loss of quantifiable exposure. Median trough concentrations after the 20 mg/kg dose were 44, 70, and 77 µg/mL after the first, second, and third dose, respectively (n=14 to 19).

For the 10 mg/kg dose, the volume of distribution was 55 mL/kg (mean) ± 12 mL/kg (standard deviation) and total systemic clearance was low (0.38 mL/h/kg ± 0.11 mL/h/kg).

Avelumab, as a MoAb, is not expected to have a direct drug-drug interaction (DDI) effect on other small molecule drugs. In addition, like other checkpoint inhibitors in the class, avelumab is not considered to be a cytokine modulator, which was confirmed by cytokine data collected from EMR 1000700-001.
Based on the acquired information, avelumab is unlikely to have an effect on drug metabolizing enzymes or transporters in terms of inhibition or induction. It is also not expected to have DDI with other drugs because it is primarily metabolized through catabolic pathways and is not expected to affect the expression of CYP450 enzymes.

For more details and updated information refer to the Investigator's Brochure.

1.2.2.3. Summary of safety data

The safety of avelumab was investigated in 4 currently ongoing clinical trials in more than 1400 patients with solid tumors:

- EMR 100070-001: A Phase I, open-label, multiple ascending dose trial to investigate the safety, tolerability, pharmacokinetics, biological and clinical activity of avelumab in patients with metastatic or locally advanced solid tumors and expansion to selected indications (1353 patients treated with avelumab, who received at least 1 dose and were followed up for at least 4 weeks from the first dose at the cutoff date of 05 November 2015)
- EMR 100070-002: A Phase I trial to investigate the tolerability, safety, pharmacokinetics, biological and clinical activity of avelumab in Japanese patients with metastatic or locally advanced solid tumors, with expansion part in Asian patients with gastric cancer (52 patients have been treated with avelumab at the cutoff date of 17 December 2015).
- EMR 100070-003: A Phase II, single arm, open-label, multicenter trial to investigate the clinical activity and safety of avelumab in patients with Merkel cell carcinoma (MCC) (88 patients have been treated with avelumab at the cutoff date of 17 December 2015)
- EMR 100070-004: A Phase III open-label, multicenter trial of avelumab versus docetaxel in patients with non-small cell lung cancer who progressed after a platinum-containing doublet (75 patients treated with avelumab or docetaxel at the cutoff date of 17 December 2015).

For the sake of the proposed trial, safety data of the large EMR 100070-001 phase I study in solid tumors are presented in the section below.

For more details and updated information on full safety data, please refer to the latest available version of the avelumab Investigator's Brochure and APPENDIX V Avelumab Summary of Safety Profile).

As of the safety cutoff date of 05 November 2015, 1353 patients have received at least 1 dose of avelumab at doses ranging from 1.0 to 20 mg/kg in the Phase I Trial EMR 100070-001, of which 1315 have received the proposed dose of 10 mg/kg (15 in the dose escalation part of the study and 1300 patients in the pooled expansion cohort).

- <u>In the dose escalation phase of the trial:</u>

The median avelumab treatment duration was 12.0 weeks, and the median number of avelumab infusions received was 6.0. As of 05 November 2015, all 53 patients (100%) discontinued trial treatment. The primary reason for treatment discontinuation was disease progression (38

patients; 71.7%), followed by treatement emergent adverse event (TEAE) (10 patients; 18.9%), withdrawal of consent and deaths (2 patients each; 3.8%).
There was no evidence of differences in the safety profile across all administered dose levels from 1 mg/kg to 20 mg/kg. The MTD was not reached.

The most frequently observed treatment related TEAE was fatigue reported in 21 patients (39.6%), followed by influenza-like illness in 11 patients (20.8%), and pyrexia in 8 patients (15.1%). Nine of the 53 patients (17.0%) experienced at least 1 Grade ≥ 3 treatment-related TEAE. These included event terms of autoimmune disorders (3 patients; 5.7%), aspartate aminotransferase (AST) increased and blood creatine phosphokinase (CPK) increased (each in 2 patients; 3.8%), and fatigue, abdominal pain lower, lipase increased, amylase increased, alanine aminotransferase (ALT) increased, blood alkaline phosphatase increased, and lymphocyte count decreased (each in 1 patient 1.9%). Of the 9 patients (17.0%) who had Grade ≥ 3 treatment-related TEAEs, 7 (13.2%) had Grade 3 events, 2 (3.8%) had Grade 4 events (blood CPK increased and autoimmune disorder), and no Grade 5 treatment-related TEAEs were observed.

Thirty-one patients (58.5%) died as of the data cutoff date (05 November 2015). No deaths were due to treatment-related TEAEs.

- In the pooled expansion cohort:

The 1300 patients comprising the pooled expansion cohort includes patients from 16 tumor expansion cohorts.

Treatment exposure:
As of 05 November 2015, the median avelumab treatment duration was 11.5 weeks and the median number of avelumab infusions was 5.0; 425 of the 1300 patients (32.7%) remained on trial treatment. The primary reason for treatment discontinuation was disease progression (608 patients; 46.8%), followed by TEAEs (122 patients; 9.4%). Other reasons for treatment discontinuation included deaths (58 patients; 4.5%), withdrawal of consent (40 patients; 3.1%), protocol non-compliance (7 patients; 0.5%), and lost to follow-up (3 patients; 0.2%). For 37 patients (2.8%), the reason for treatment discontinuation was labelled as “other” in the database at the time of the data cutoff.

Treatment-emergent adverse events (TEAEs):
Of the 1300 patients treated in the pooled expansion cohort, 1200 (92.3% experienced at least one TEAE. The most frequently reported TEAEs (incidence ≥ 10%) were fatigue (27.4%), followed by nausea (21.2%), infusion-related reaction (16.2%), diarrhea (15.8%), and constipation (15.7%).

Treatment-related TEAEs were observed in 813 (62.5%) patients, the most commonly observed (incidence > 2%) being fatigue (212 patients, 16.3%), infusion-related reaction (209 patients, 16.1%), nausea (108 patients, 8.3%), chills (102 patients, 7.8%), diarrhea (79 patients, 6.1%), and pyrexia (72 patients, 5.5%). Grade ≥ 3 treatment-related TEAEs were observed in 124 patients (9.5%) (See Table 1-2).

The most frequently reported Grade ≥ 3 treatment related TEAEs were gamma-glutamyl transferase increased (GGT) and infusion-related reaction (each occurred in 9 patients; 0.7%).

Infusion-related reactions including drug hypersensitivity reactions and immune-mediated adverse reactions have been identified as expected adverse drug reactions of avelumab. The safety profile of avelumab is consistent with findings reported for other anti-PD-1 or anti-PD-L1 antibodies.

Table 1-2 : Most Frequently Reported (Incidence ≥ 2% in the Pooled Expansion Cohort) Treatment-Related TEAEs in the Pooled Expansion Cohort

MedDRA PT	Pooled Expansion Cohort (n=1300) n (%)
Patients with at least 1 AE	813 (62.5)
Fatigue	212 (16.3)
Infusion-related reaction	209 (16.1)
Nausea	108 (8.3)
Chills	102 (7.8)
Diarrhoea	79 (6.1)
Pyrexia	72 (5.5)
Decreased appetite	60 (4.6)
Arthralgia	53 (4.1)
Vomiting	46 (3.5)
Hypothyroidism	45 (3.5)
Influenza like illness	42 (3.2)
Pruritus	40 (3.1)
Myalgia	37 (2.8)
Rash	36 (2.8)
Headache	34 (2.6)
Anaemia	30 (2.3)
Asthenia	29 (2.2)
Aspartate aminotransferase increased	26 (2.0)
Constipation	26 (2.0)

MedDRA: Medical Dictionary for Regulatory Activities; PT: preferred term; TEAE: treatment-emergent adverse event. Safety Population.

Serious adverse events:

As of 05 November 2015, 509 of 1300 patients (39.2%) in the pooled expansion cohort had at least 1 serious TEAE and 71 (5.5%) experienced at least one treatment-related serious TEAEs. These included infusion-related reaction (11 patients; 0.8%), pneumonitis (8 patients; 0.6%), pyrexia and dyspnea (each in 5 patients; 0.4%), autoimmune hepatitis (3 patients; 0.2%), and asthenia, blood creatine phosphokinase increased, abdominal pain, colitis, diarrhea, vomiting,

hyponatremia, adrenal insufficiency, and non-cardiac chest pain (each in 2 patients; 0.2%). All other treatment-related serious TEAEs were reported in a single patient (0.1%) only.

Deaths:
As of 05 November 2015, 466 deaths (35.8%) occurred in the pooled expansion cohort. The majority of deaths were due to progressive disease (360 patients; 27.7%). A total of 5 deaths (0.4%) due to TEAEs related to trial treatment were considered as primary reason of the death by the investigator. Two additional cases of death were reported and assessed as treatment-related, but the treatment related TEAEs were not considered as the primary reason of the death.

Potential immune related AEs (irAEs):
Table 1-3 shows incidences of the treatment-related TEAEs, considered and described as immune-mediated adverse reactions observed in the pooled expansion cohort in the ongoing trial EMR 100070-001 after 1300 subjects were treated with 10 mg/kg of avelumab once every 2 weeks (cut-off date 05 Nov 2015). Hypothyroidism was the most frequent treatment-related potential immune-mediated AE, which occurred in 45 patients (3.5%) in the pooled expansion cohort (See Table 1-3). The majority of potential immune-mediated AEs were Grade 1 or Grade 2 events.

Risk mitigation measures have been implemented and guidelines for management of irAEs are provided in the trial protocol (see Section 6.5.2.6). Of note, irAEs are considered an identified risk of avelumab.

Table 1-3 : **Incidence of Treatment-Related TEAEs of Immune-Mediated Adverse Reactions in Trial EMR 100070-001**

Category	MedDRA PT(s)	AE of Any Grade (n=1300) n (%)[b]	AE Grade ≥ 3 (n=1300) n (%)	Serious AE (n=1300) n (%)
Immune-mediated pneumonitis	Pneumonitis	13 (1.0)	4 (0.3)	8 (0.6)
Immune-mediated colitis	Colitis	4 (0.3)	3 (0.2)	2 (0.2)
Immune-mediated hepatitis	Autoimmune hepatitis	4 (0.3)	0	3 (0.3)
Immune-mediated thyroid disorders	Hyperthyroidism	7 (0.5)	0	1 (0.1)
	Hypothyroidism	45 (3.5)	0	1 (0.1)
	Thyroiditis	2 (0.2)	0	0
	Autoimmune thyroiditis	2 (0.2)	0	0

Category	MedDRA PT(s)	AE of Any Grade (n=1300) n (%)[b]	AE Grade ≥ 3 (n=1300) n (%)	Serious AE (n=1300) n (%)
Immune-mediated skin reactions	Rash	36 (2.8)	2 (0.2)	0
	Pruritus	40 (3.1)	0	0
	Rash pruritic	8 (0.6)	1 (0.1)	0
	Rash generalized	3 (0.2)	0	1 (0.1)
	Rash maculo-papular	22 (1.7)	0	0
	Erythema	6 (0.5)	0	0
	Pemphigoid	1 (0.1)	0	0
Other immune-mediated reactions	Adrenal insufficiency	5 (0.4)	1 (0.1)	2 (0.2)
	Myositis	3 (0.2)	3 (0.2)	1 (0.1)
	Myocarditis[a]	1 (0.1)	0	0

MedDRA: Medical Dictionary for Regulatory Activities; PT: preferred term.

[a] The data are from the pooled expansion cohort of the ongoing, uncontrolled Trial EMR 100070-001 (cut-off date 05 Nov 2015). There was no event reported as myocarditis, but 1 event of autoimmune disorder including myositis and myocarditis. In addition, 2 cases of fatal myocarditis have been reported from trials B9991002 and EMR 100070-004 recently. Narratives for these cases are provided in the avelumab Investigator's Brochure.

Infusion related reaction: (See Table 1-4)

Four patients (7.5%) in the dose escalation cohort reported an infusion-related reaction (all Grade 2) with an onset after the first (1 patient, 1.9%) or second (3 patients, 5.7%) infusion.
A total of 215 out of the 1300 patients (16.5%) in the pooled expansion cohort experienced at least 1 episode of infusion-related reaction. Most of the events were Grade 1 (53 patients, 4.1%) or Grade 2 (153 patients, 11.8%) in intensity, and Grade 3 (6 patients, 0.5%) or Grade 4 events (3 patients, 0.2%) were less frequent. No Grade 5 events were reported.

Most of the infusion-related reactions had an onset after the first (149 patients, 11.5%) or second (48 patients, 3.7%) avelumab infusion, and those with an onset after the third (12 patients, 0.9%) or fourth or later avelumab infusion (6 patients, 0.5%) were less frequent. In 23 patients (1.8%), avelumab treatment was discontinued because of infusion-related reaction.

One hundred and ninety-four of 1259 patients (15.4%) in the pooled expansion cohort experienced infusion-related reaction in the presence of premedication with 50 patients (4.0%)

having Grade 1, 138 patients (11.0%) having Grade 2, 4 patients (0.3%) having Grade 3, and 2 patients (0.2%) having Grade 4 events.

Table 1-4 : Summary of infusion related reaction events for Trial EMR 100070-001

	Dose Escalation Patients (n=53) n (%)	Pooled Expansion Patients (n=1300) n (%)
Number of patients with at least 1 event	4 (7.5)	215 (16.5)
Grade 1	0	53 (4.1)
Grade 2	4 (7.5)	153 (11.8)
Grade 3	0	6 (0.5)
Grade 4	0	3 (0.2)
Grade 5	0	0
Number of patients with the event leading to permanent treatment discontinuation	0	23 (1.8)
Time related to the first onset of the event		
Infusion 1	1 (1.9)	149 (11.5)
Infusion 2	3 (5.7)	48 (3.7)
Infusion 3	0	12 (0.9)
Infusion 4 or later	0	6 (0.5)

Preferred terms of 'Infusion-related reaction', 'Drug hypersensitivity', or 'Anaphylactic reaction' are summarized in this table. A patient may have more than 1 event, but the patient is counted only once by the worst grade.
An infusion-related reaction is assigned to a drug infusion if its onset is at the same date (but not before dosing) or the following day of drug infusion.

Antidrug antibody (ADA) response

Post-treatment samples for evaluation of ADA response were available for 39 patients from the dose escalation cohort and 338 patients in the pooled expansion cohort.
Anti-drug antibody (ADA) was tested positive in 1 of 39 patients in the dose escalation cohorts and in 10 of 338 patients in the pooled expansion cohort. Of the 11 ADA-positive patients, 2 patients had symptoms on the day of the infusion consistent with a possible hypersensitivity reaction (chills, fever, nausea, and vomiting) and may be ADA related. However, in the other 9 ADA-positive patients, no hypersensitivity reactions were observed.

Laboratory abnormalities:

Post-baseline laboratory data abnormalities in Trial EMR 100070-001 during the treatment expansion phase were assessed by NCI-CTCAE grade. It should be noted that interpretation of the laboratory data is limited at this point in time due to various missing laboratory assessment data as of the safety data cutoff (05 November 2015).

- Hematology

Some hematology abnormalities of any grade were reported in the pooled expansion cohort with the most frequent abnormalities of anemia (74.9%) and lymphocyte count decreased (52.3%), followed by white blood cell (WBC) count decreased (17.2%) and platelet count decreased (17.0%).
Most hematology abnormalities were mild or moderate (Grade 1 or 2). The most frequent Grade 3 or Grade 4 abnormalities were lymphocyte count decreased in 11.4% of patients, of which 0.5% had Grade 4 events; anemia in 4.5% of patients, all being Grade 3 events; and platelet count decreased in 1.1% of patients, of which 0.8% experienced a Grade 4 abnormality.

- Blood chemistry

In the pooled expansion cohort, the most frequent blood chemistry abnormalities of any grade included creatinine increased (75.5%) followed by hyponatremia (41.3%), alkaline phosphatase increased (37.8%), hypoalbuminemia (34.0%), GGT increased (32.2%), hypertriglyceridemia (32.3%), AST increased (30.4%), and cholesterol high (26.8%).
Most of the blood chemistry abnormalities were Grade 1 or Grade 2, and Grade 3 or 4 blood chemistry abnormalities occurred less frequently (usually with a single digit incidence or even lower incidence for any measurement).

In conclusion, preliminary data from EMR 100070-001 comprising the pooled expansion cohort including patients from 16 tumor expansion cohorts showed that avelumab at doses up to 20 mg/kg IV every 2 weeks was well tolerated, and the dose of 10 mg/kg IV every 2 weeks was considered to have an acceptable safety profile for further investigation in clinical studies.

Safety data obtained in the ongoing SCCHN expansion cohort including 153 patients reveals consistency in the overall safety profile (unpublished data, internal communication by Merck KGaA / EMD Serono).
Of the 153 patients treated, 143 (93.5%) experienced at least one TEAE.
Treatment-related TEAEs were observed in 79 (51.6%) patients, the most commonly observed (incidence > 5%) being fatigue (15 patients, 9.8%), pyrexia (14 patients, 9.2%), infusion-related reaction (13 patients, 8.5%), chills (9 patients, 5.9%), and diarrhoea (8 patients, 5.2%). Grade ≥ 3 treatment-related TEAEs were observed in 8 patients (5.2%).
Immune-related AEs occurred in 14 patients (9.2%), hypothyroidism (7 patients, 4.6%) and pneumonitis (2 patients, 1.3%) being the most frequent.

1.2.2.4. Summary of clinical efficacy

Currently, more than 1400 cancer patients have been treated with avelumab in the Phase Ib/II clinical program (Solid Tumors).
Single agent avelumab given at 10 mg/kg Q2W has showed an acceptable safety profile and promising clinical activity for patients with lung, breast (Dirix L.Y. *et al.*, 2015)**,** ovarian, and gastric cancers (Chung H.C. *et al.*, 2016), (Nashina T *et al.*, 2016).
Based on findings from the phase II JAVELIN Merkel 200 submission for marketing applications are planned avelumab in metastatic Merkel Cell Carcinoma. The study was conducted in 88 patients with chemotherapy-refractory metastatic Merkel cell carcinoma showing objective response rate with avelumab of 31.8%, including a 9.1% complete response rate. After a median follow-up of 10.4 months, 82% of patients continued to respond to therapy (Kaufman H.L. *et al.*, 2016)**.**

Preliminary results from the ongoing expansion cohort in SCCHN reveal a clinical benefit in this heavily pre-treated patient population.

For more details, please refer to the avelumab Investigator's Brochure.

1.3. Rationale for conducting the trial

1.3.1. Rationale for selecting SCCHN in the phase II of the study

Head and neck cancer (HNC) is the sixth most common cancer worldwide and is ranked as the eighth leading cause of cancer death (Siegel R. *et al.*, 2012). In Europe, it is estimated that there are approximately 143 000 new cases and > 68 000 deaths due to the disease each year (Globocan, 2012).

Head and neck cancer is comprised of a heterogeneous group of cancers with different anatomic locations with squamous histology representing 95% of the cases. These tumors can be found in the oral cavity, the larger pharyngeal area (including the nasopharynx, oropharynx, and hypopharynx), and the larynx. Occasionally, other anatomic sites are involved, such as the paranasal sinuses, lips, salivary glands, and other areas of the head and neck and upper aerodigestive tract.

The incidence of head and neck cancers varies widely around the world and even within populations. Oral and oropharyngeal cancer constitutes 3-5% of the malignancies in Europe, while this figure in parts of Southeast Asia and India reaches up to 40–50% (Bray F. *et al.*, 2002). In certain parts of Asia, such as India, HNC is the most common cancer type, even more common than lung cancer.

Tobacco and alcohol use are the predominant risk factors for the development of carcinomas across all subsites of the head and neck tumors. Oncogenic viruses also play a large and important role in the carcinogenesis of HNC. In the last few years, there has been a rapid rise in the incidence of human papilloma virus (HPV) positive HNC in the Western world (Shiboski C.H. *et al.*, 2005), (Marur S. *et al.*, 2010; Nasman A. *et al.*, 2009),(Chaturvedi A.K., 2012). Most of these tumors occur in the subsites of the oropharynx, including the tonsil, base of tongue, and soft palate by contrast, to HPV-negative tumors occuring throughout the entire upper aerodigestive tract.

HPV-positive oropharyngeal squamous cell carcinomas of head and neck (SCCHN) represent a growing entity in the head and neck with distinct carcinogenesis, clinico-pathological presentation and survival profile. HPV-positive tumors are usually poorly differentiated and nonkeratinizing and have a basaloid appearance in contrast to the HPV-negative that is more moderately differentiated and keratinizing (Wilczynski S.P. *et al.*, 1998),(Gillison M.L. *et al.*, 2000a). HPV-positive tumors also display significantly lower levels of chromosomal mutations than the HPV-negative tumors (Braakhuis B.J. *et al.*, 2004), (Smeets S.J. *et al.*, 2006). Furthermore, patients with HPV-positive oropharyngeal cancers in general, especially tonsillar cancers, tend to be younger at time of diagnosis (Hammarstedt L. *et al.*, 2006), (Smith E.M. *et al.*, 2004), possibly with the exception of base of tongue cancers where no age difference could be found between the HPV-positive and HPV-negative cancer patients (Attner P. *et al.*, 2010). The majority of the patients have no prior history of tobacco and/or high alcohol consumption and have generally a better performance status compared to the HPV-negative patients (Gillison M.L. *et al.*, 2008), (Lassen P. *et al.*, 2009). Moreover, HPV-positive tumors often present at a higher stage with a small T-size (T1-T2) (Lassen P. *et al.*, 2009) but frequently there is a large, often cystic, nodal involvement (N+) (Goldenberg D. *et al.*, 2008), (Lassen P., 2010) , thus, HPV-positive tumors are often diagnosed in clinical advanced stages (i.e., Stages III-IV) (Lindquist D. *et al.*, 2007).

HPV-positive patients are known to have a better prognosis than HPV-negative ones. Several studies have also shown that HPV-positive patients are more responsive to treatment and have better rates of disease-specific survival than patients with traditional risk factors such as tobacco and alcohol (Kumar B. *et al.*, 2007), (Weinberger P.M. *et al.*, 2006). The reason for the better response to oncological treatment for patients with HPV-positive tumors may be explained by the presence of an intact p53-mediated apoptotic response. Another explanation is the presence of immunological factors related to HPV infection (Spanos W.C. *et al.*, 2009). Nevertheless, there is a subgroup of the HPV-positive oropharyngeal cancers that have worse clinical outcome, that do not respond as well to given treatment, and have a higher rate of relapses and worse survival than the majority of the tumors in this group.

Despite the knowledge of the heterogeneity regarding tumor aggressiveness and response to treatment of SCCHN, the management of patients with HPV-positive and HPV-negative SCCHN is today similar. The treatment depends on primary tumor location and extension and requires generally a multidisciplinary approach. Approximately 40% of patients with SCCHN present with early-stage disease. For these patients, single-modality treatment with surgery or radiotherapy is generally recommended (Gregoire V. *et al.*, 2010).

Most patients (60%) present with locally advanced disease at diagnosis and require a multidisciplinary approach using some combination of surgery, radiotherapy, and chemotherapy (Gregoire V. *et al.*, 2010), but will eventually relapse, either locoregionally only, at distant sites only or both. A few patients with a locoregional recurrence can be salvaged by surgery or reirradiation. However, most patients with recurrent or metastatic (R/M) disease only qualify for palliative treatment. Treatment options in these patients include supportive care only, or in addition single agent chemotherapy, combination chemotherapy or targeted therapies either alone or in combination with cytotoxic agents.

The prognosis for SCCHN is generally poor in the advanced stages and there has been only a modest improvement in recent years in the treatment. Standard treatment with radiation and/or chemotherapy frequently sentences the patient to life-long sequelaes such as difficulties with swallowing, dryness of the mouth, esophageal strictures, and osteoradionecrosis.

1.3.2. Rationale for the use of checkpoint inhibitors in HPV-positive SCCHN

Because HPV-positive tumors are induced by a viral infection of HPV, these tumors have a different pathological background compared to cancer induced by traditional risk factors such as tobacco and alcohol. The viral infection can serve as a foreign antigen that might enhance the immune system's response to the tumor. Humoral immune responses against the viral antigens E6 and E7 have been found frequently in HPV-positive cancer patients and can be correlated with increased survival, implying an important role in the immunological recognition of HPV (Rotnaglova E. *et al.*, 2011). That is why HPV-associated SCCHN is considered an optimal entity for immunotherapy.

Recently, the group of Heusinkveld et al. (Heusinkveld M. *et al.*, 2012) discussed the important immunological role of HPV-16-specific systemic and local T cells. HPV-SCCHN expresses the two viral oncoproteins E6 and E7. These two oncoproteins are foreign to the body, so they are thought to have an immunogenic potential. Heusinkveld et al. evaluated the presence of systemic and local T cells reactive against these oncoproteins. The study included 50 patients

with SCCHN, 12 of which were positive for DNA of HPV-16. Almost all HPV-positive tumors were oropharyngeal cancers. The authors found circulating HPV-16- and p53-specific T cells in 17/47 and 7/45 tested patients. In 20 of these patients, T cells were isolated from tumor cultures and/or lymph nodes. Tumor-infiltrating HPV-16-specific T cells were found in six of eight HPV-positive tumors. In the 12 HPV-negative tumors, no HPV-16-specific T cells were found. In-depth analysis of the HPV16-specific T cell response revealed that this response comprised a broad repertoire of CD4 + T- helper type 1 and 2 cells, CD4+ regulatory T cells and CD8+ T cells reactive to HPV-16. The local presence of HPV-16-specific T cell immunity in HPV-16-induced SCCHN implicates a role in the antitumor response and supports the approaches for immunotherapy of HPV-positive SCCHN (Heusinkveld M. *et al.*, 2012).

A possible mechanism for tumor immune escape in HPV-positive SCCHN has been examined by Lyford-Pike et al (Lyford-Pike S. and . e.a., 2012). The authors provided evidence for an adaptive immune resistance mechanism, which is mediated trough the PD-1/PD-L1 pathway. *In vitro* studies showed that blockage of the interaction between PD-1 and PD-L1 potentiates the immune response and mediates preclinical antitumor activity (Fife B.T. *et al.*, 2009)**,** (Iwai Y. et al., 2002), (Lyford-Pike S. and . e.a., 2012) analyzed tumor infiltrating lymphocytes (TILs) for PD-1 expression and the PD-L1 expression in HPV-positive SCCHN. The authors showed that the majority of CD8+ TILs in HPV-positive SCCHN express the PD-1 co-inhibitory receptor and there was a higher PD-1 expression by CD4+ and CD8+ T cells in tonsil tissue as compared to the peripheral blood. In 20 patients with HPV-positive SCCHN, 14 (70 %) expressed PD-L1. A very interesting point is that the ligands PD-L1 on the tumor cells were predominantly located at the periphery of tumor nests, whereas only 1 of the 14 patients demonstrated diffuse PD-L1 expression. Furthermore the authors found an association between expression of ligand PD-L1 on tumor cells and tumor-associated macrophages and the presence of TILs. In the microenvironment of HPV SCCHN, a significant increase of CD8-positive TILs and interferon-c (IFN-c) mRNA in PD-L1+ compared to PD-L1- cancers was seen. This study showed that the PD-1/PD-L1 interaction creates an immune-privileged site for initial virus infection, leading to adaptive immune resistance once tumors are established. These findings suggest that the blockade of this pathway could be a new approach to treat HPV-positive tumors (Lyford-Pike S. and . e.a., 2012). These new findings are of special significance since the activity of a PD-L1 and a PD-1 antibody has been recently demontrated in two phase I trials in patients with advanced cancer (Brahmer J.R. *et al.*, 2012; Topalian S.L. *et al.*, 2012). Therefore, immunotherapy represents an attractive treatment strategy for R/M SCCHN, with promising preliminary data from studies involving immune checkpoint blockade.

Clinical activity of pembrolizumab at 10mg/kg Q2W for treatment of recurrent/metastatic SCCHN in PD-L1 positive patients was demonstrated in the phase I Keynote-012 study (Seiwert T.Y. *et al.*, 2016)**.**

In an initial cohort, the proportion of patients with ORR by central imaging review was 18% (8/45) in all patients and was 25% (4/16) in HPV-positive patients, whereas the ORR in HPV-negative patients was 14% (4/29). In the full analysis set population (n=56) median progression-free survival was 2 months, 4 months in the HPV-positive patients and 2 months in the HPV-negative patients. Median overall survival (OS) was 13 months in the intention-to-treat population (n = 61), not reached for HPV-positive patients and 8 months for HPV-negative patients.

In an expansion cohort of the Keynote-012 study 132 patients with R/M SCCHN irrespective of PD-L1 expression or human papillomavirus (HPV) status received a fixed dose of pembrolizumab 200 mg administered every 3 weeks (Chow L.Q. *et al.*, 2016). The ORR was 18% (24/132) by central imaging review in biomarker-unselected patients. Similar to the initial SCCHN cohort of the Keynote-012 trial, a higher response to pembrolizumab was observed in HPV+ patients (32%, 9/28) versus HPV-negative patients (14%, 15/104). Of note, an ORR of 14% was consistently observed in HPV-negative patients in both Keynote-012 cohorts. Treatment-related AEs of any grade occurred in 62% of patients, and treatment-related grade ≥ 3 AEs occurred in 9% of patients.
Based on the results of the Keynote-012 study, KEYTRUDA® (pembrolizumab) has been approved in the US in August 2016 at a fixed dose of 200 mg every three weeks for the treatment of patients with recurrent or metastatic SCCHN with disease progression on or after platinum-containing chemotherapy and in EU in September 2018 for the treatment of recurrent or metastatic SCCHN in adults whose tumours express PD-L1 with a ≥ 50% TPS with disease progression on or after platinum-containing chemotherapy, based on the results from the phase III Keynote-040 (Cohen E.E.W. *et al.*, 2019) with supportive data from Keynote-012 and Keynote-055.

Another study, CheckMate-141 a Phase III, open-label, randomized study investigated nivolumab versus investigator's choice of therapy in previously treated patients with SCCHN who have tumor progression on or within 6 months of platinum therapy in the primary, recurrent, or metastatic setting (Ferris R.L. *et al.*). The trial randomized 361 patients 2:1 to receive either nivolumab 3 mg/kg intravenously every two weeks or investigator's choice (cetuximab/methotrexate/docetaxel) until documented disease progression or unacceptable toxicity. The study was stopped early after an independent monitoring panel determined the primary endpoint of improvement in OS was met with a median OS of 7.5 months (95%CI: 5.5-9.1) for nivolumab and 5.1 months (95%CI: 4.0-6.0) for investigator's choice of therapy (HR, 0.70; 97.73% CI, 0.51-0.96; P =0.01). The 1-year OS rates were 36% with nivolumab compared with 16.6% for investigator's choice. The reponse rate was 13.3% in the nivolumab group versus 5.8% in the standard-therapy group (Ferris R.L. *et al.*, 2016).

Nivolumab has been approved in the US in November 2016 and in the EU in April 2017 for the treatment of patients with recurrent or metastatic SCCHN with disease progression on or after a platinum-based therapy, based on the results from CheckMate-141 (Ferris R.L. *et al.*, 2016)**.**

1.3.3. Rationale for the use of cancer vaccines in SCCHN

At the present time there is no evidence to indicate that treatment should be different according to the HPV status. However, it is well recognized that HPV+ patients do well with a better progression-free survival and overall survival compared to HPV negative patients.
The HPV status needs to be taken into account when designing all clinical trials for the treatment of oropharyngeal cancer, given the more favorable prognosis for HPV positive oropharyngeal cancer patients and the fact that this subset represents a distinct and well-defined entity. Testing patients with oropharyngeal cancer for HPV positivity is also useful prior to therapy given its prognostic implications, but there is insufficient information to alter therapy based upon HPV status. However, changes in the therapeutic approach to HPV positive oropharyngeal cancer can only be determined through prospective clinical trials and will need to be done carefully as to not compromise the excellent prognosis in these patients.

The structure of TG4001 should determine a higher efficacy specifically against HPV infected cells without any interaction with normal cells.

TG4001 has been tested in a Phase II trial in HPV-16 associated cervical intraepithelial neoplasia (CIN) grade 2/3 demonstrating activity and higher efficacy compared to placebo in histologic resolution and response rates as well as viral clearance. Moreover the therapeutic vaccine/immunotherapeutic product was demonstrated to be safe with no major toxicities, apart from injection site reaction (Brun J.L. *et al.*, 2011).

1.3.4. Rationale for combining TG4001 and immune checkpoints inhibitors

Given the well-established role of immune system dysfunction in SCCHN, immunotherapy is an attractive treatment option, potentially associated with more tolerable side effects and improved efficacy. Recent advances in identifying SCCHN tumor antigens have provided targets for novel treatment modalities.

The clinical and regulatory successes of the PD-1 and CTLA-4 checkpoint proteins are driving a resurgence of interest in immunotherapy as a mainstream form of cancer treatment, with numerous clinical studies exploring the application of these therapeutics in combination with traditional and experimental agents including therapeutic cancer vaccines and oncolytic virus immunotherapies (Melero I. *et al.*, 2015).

1.3.5. Rationale for including other HPV-16 positive malignancies in the phase II of the study

Appropriate treatment of incurable advanced disease for other HPV-16 positive cancers including cervical, anal, vulvar, vaginal and penile cancers consists mainly of platinum-based doublet chemotherapy which however has only limited efficacy in terms of response rate or median OS. Even though checkpoint blockade monotherapy has resulted in modest advances (Hollebecque A. *et al.*, 2017), (Morris V.K. *et al.*, 2017), (Frenel J.S. *et al.*, 2017), (Ott P.A. *et al.*, 2017), novel strategies of combining therapies are needed to improve the survival of recurrent and metastatic HPV-positive anogenital tract cancers.

It is hypothesized that regardless the location of a HPV-16 positive tumor the presence of viral antigens leads to an induction of HPV-specific immune response which could augment the proportion of patients benefiting from PD-1 checkpoint blockade.

1.3.6. Rationale for the exclusion of oropharyngeal SCCHN in phase II part 2

As outlined under section 1.1.8 KEYTRUDA® (pembrolizumab) has been approved in the US in August 2016 for the treatment of patients with recurrent or metastatic SCCHN with disease progression on or after platinum-containing chemotherapy and in EU in September 2018.
In addition, OPDIVO® (nivolumab) has been approved in the US in November 2016 and in the EU in April 2017 for the treatment of patients with recurrent or metastatic SCCHN with disease progression on or after a platinum-based therapy in biomarker (PD-L1) unselected patients.

This shift in standard of care has been observed during the conduct of the phase Ib and phase II part 1: while in phase Ib 5 out of 9 patients included had SCCHN, in phase II part 1 only 5 out of 32 patients included had SCCHN.

Furthermore, with the registration of KEYTRUDA® in US and EU for first-line treatment of recurrent or metastatic SCCHN either as monotherapy or in combination with platinum and 5-fluorouracil (5-FU) chemotherapy, the proportion of IO-naïve patients for second-line treatment will decrease significantly. As prior treatment with cancer immunotherapy is an exclusion criterion for this clinical study the number of eligible patients with SCCHN will be negligible. Therefore in order to be consistent with the current standard of care, patients with SCCHN will be excluded from the study population of the phase II part 2.

1.3.7. Rationale for transforming the phase II into a randomized, open-label controlled study

At the time of interim analysis of phase II part 1 a pooled efficacy analysis was performed in a population of 34 evaluable patients consisting of 6 patients of the phase Ib treated with the recommended phase II dose of TG4001 and 28 evaluable patients included at cut off for the interim analysis. Out of these 34 patients, 15 presented anal cancer, 8 oropharyngeal cancer, 6 cervical cancer and 5 vulvar/vaginal cancer. The ORR was 23.5% and the Disease Control Rate (DCR) at 12 weeks 41.2% representing a valuable anti-tumor activity in a population of patients with HPV-16+ pre-treated recurrent/metastatic (R/M) cancers and comparing positively to the ORR observed for avelumab alone. In a randomized trial evaluating avelumab alone or in combination with cetuximab in pretreated unresectable, locally advanced or metastatic squamous cell anal carcinoma, ORR was 10% (3/30) for avelumab alone vs 17% (5/30) for avelumab combined with cetuximab (Lonardi S. *et al.*, 2020). In the Javelin phase I b cohort enrolling patients with platinum-refractory/ineligible R/M SCCHN, ORR was 13.1% in the overall population. A higher response to avelumab was observed in HPV+ patients (17.9%, 7/39) versus HPV-negative patients (11.1%, 11/99, (Guigay J. *et al.*, 19-21 September 2020).
Considering other PD-L1 / PD-1 inhibitors, the largest clinical experience in HPV-related malignancies comes from KEYTRUDA® (pembrolizumab). As described under 1.3.2 in patients with R/M SCCHN with disease progression on or after platinum-containing chemotherapy unselected for biomarker, the ORR was 18% (24/132) by central imaging review and 20% by investigator review. A higher response to pembrolizumab was observed in HPV+ patients (32%, 9/28) versus HPV-negative patients (14%, 15/104, KEYNOTE-012 expansion cohort). In SCCHN patients whose tumours express PD-L1 with a ≥ 50% TPS, the ORR was 26.6% (KEYNOTE-040).
The ORR of pembrolizumab was 12.2% (12/98) evaluated in patients with R/M cervical cancer with disease progression on or after platinum-containing chemotherapy unselected for biomarker (Chung H.C. *et al.*, 2019). Based on these results pembrolizumab has been approved in PD-L1 positive cervix cancer in the US in 2018.
In the pooled analysis of KEYNOTE-28 and KEYNOTE-158 evaluating pembrolizumab as monotherapy in patients with advanced anal squamous cell carcinoma the ORR to pembrolizumab was 10.9% (15/137) (Marabelle A. *et al.*, 2020).
It has been acknowledged that combining immune checkpoint blockade with a HPV-antigen targeting immunotherapy can represent a complementary immune strategy to increase the proportion of patients benefiting from checkpoint blockers and promising results have been published. In a single arm trial evaluating ISA101, a synthetic long peptide HPV-16 vaccine targeting E6 and E7, in combination with nivolumab in patients with advanced HPV-16+ tumors, an ORR of 33% (8/24) has been observed (Massarelli E. *et al.*, 2019). MEDI0457, a DNA vaccine expressing HPV16/18 E6/E7 proteins and IL-12, was evaluated in combination with anti-PD-L1 durvalumab in patients with R/M HPV+ SCCHN. ORR was 22.2% (6/27) in

this study (Aggarwal C. *et al.*, 2020).The ORR of 23.5% observed in our study is in line with these published results.
The ultimate validation however whether adding a HPV vaccine to an anti-PD1/PD-L1 leads to an increase of the proportion of patients benefiting from checkpoint blockers needs to be done in a trial evaluating the combination of the vaccine with the anti-PD1/PD-L1 vs the anti-PD1/PD-L1 alone. This randomized phase II trial will include patients with any HPV-16 associated anogenital cancer stratified on the primary site (anal, cervix, genital).

1.3.8. Rationale for the restriction on the extent of liver metastases for eligibility in phase II part 2

Out of the 34 patients for the pooled efficacy analysis, 15 presented anal cancer, 8 oropharyngeal cancer, 6 cervical cancer and 5 vulvar/vaginal cancer. Median age was 61 years, the majority (88%) had received at least 1 prior line of chemotherapy (CT) with 32% having received ≥ 2 lines.
8 patients achieved confirmed response according to RECIST 1.1 (1 CR, 7 PR, ORR 23.5%). Responses were observed in all primary tumor types and across all lines of prior therapy. Regarding the type of organs affected, there was a positive trend for lymph nodes; conversely the presence of liver metastases had a significant negative impact on outcome: ORR was 0% and PFS 1.4 months in patients with liver metastases (n=11) versus 34.8% and PFS of 5.6 months in patients without liver metastases (n=23).
Out of the 11 patients with liver metastases at baseline, none of them had more than 3 liver metastases but 10 patients had a hepatic target disease greater than 30 mm. The single patient with hepatic target disease of 12.1 mm remained stable until week 12.
It has been repeatedly described in the literature that liver metastasis at the time of diagnosis is associated with poor prognosis. Even though immunotherapy with the most successful candidates anti-PD-L1 or anti-PD-1 have shown clinical activity, however, their efficacy remains uncertain in patients with liver metastases. Different potential mechanisms are being proposed for this finding. When exploring the association between liver metastases, tumor CD8+ T-cell count and response to the anti-PD-1 pembrolizumab it turned out that presence of liver metastases was associated with fewer infiltrating CD8+ cells at the invasive margin in distant tumors, suggesting a systemic effect of the liver metastases (Tumeh P.C. *et al.*, 2017).
Therefore, and in order to balance between the assumption that patients with important hepatic disease will not benefit from an IO-based therapy and the need to seek optimal therapy for patients with limited hepatic disease, an eligibility criterion has been introduced limiting the number of liver metastases to a maximum of 3, with a maximum size in target disease to ≤ 30 mm.

1.4. Summary of the overall benefit and risk

1.4.1. Expected benefits

TG4001 is a human papillomavirus (HPV) targeted active immunotherapy product designed for the treatment of HPV-16 related diseases. TG4001 preclinical data demonstrated that TG4001 has CD8+T cell dependent antitumor activity and confers immunity against TC1 tumors expressing wild-type HPV-16 E6 and E7 genes.

The PD-1 pathway is a key mechanism by which many cancers evade immune surveillance. Immune checkpoints inhibitors have shown promising activity in SCCHN and anogenital tract

cancers like cervical or anal cancer. It is therefore, hypothesized that the combination of a checkpoint inhibitor with TG4001 may cause additional changes in the tumor microenvironment leading to enhanced anti-tumoral activity.

1.4.2. Potential risks

With TG4001:
Experimental data derived from murine models demonstrated an acceptable safety profile and no oncogenic potential. It was highlighted a slight to moderate irritant effects (erythema, and/or edema) at the injection site, decreased reticulocytes and lymphocytes, and an increased spleen weight that correlated with lymphoid hyperplasia (potential effect of exaggerated pharmacology).
The following were the most common reported AEs in clinical trials (incidence >1%):

- Injection site reaction
- Injection site erythema
- Pyrexia
- Injection site pain
- Injection site inflammation
- Headache
- Asthenia
- Fatigue
- Lymphadenopathy
- Injection site oedema
- Injection site induration
- Nausea
- Influenza like illness
- Chills
- Injection site pruritus
- Injection site rash
- Injection site haematoma
- Injection site haemorrhage
- Pain

With avelumab:
Specific risks associated with the use of avelumab as a monoclonal antibody have been observed.
The risks of exposure to avelumab include mainly:

- Severe infusion-related reactions (grade ≥3) including drug hypersensitivity reactions
- Immune-related adverse reactions (immune-related pneumonitis, immune-related colitis, immune-related hepatitis, immune-related myocarditis, immune-related pancreatitis, immune-related endocrinopathies (thyroid disorders, adrenal insufficiency, new onset type I diabetes mellitus, pituitary disorders), immune-related nephritis and renal dysfunction and other immune-related AEs (myositis, Guillain-Barré syndrome, uveitis, and myasthenia gravis/myasthenic syndrome). Fatal outcome was reported for immune-related hepatitis, immune-related pneumonitis, immune-related myocarditis, and immune-related pancreatitis.

The safety data from patients with different tumor types treated with avelumab in the clinical trials suggest an acceptable safety profile of the compound. Most of the observed events were

either in line with those expected in patients with advanced solid tumors or with similar class effects of MoAb blocking the PD-1/PD-L1 axis. Infusion-related reactions including drug hypersensitivity reactions and immune-mediated adverse reactions have been identified as important risks for avelumab.

1.4.3. Measures taken during the study to mitigate the risks

The risk-benefit relationship has been carefully considered in the planning of the trial. Based on the pre-clinical and clinical data available to date on both IMPs, the conduct of the trial is considered justifiable using the dose(s) and dosage regimen(s) of TG4001 and the avelumab as specified in this clinical trial protocol.

Respective risk mitigation measures as regard to the expected potential drug reaction to avelumab have been implemented in the current clinical study (see **Section** 6.5.2). In addition, a safety committee is planned for the ongoing assessment of the risk-benefit ratio. The trial shall be discontinued in the event of any new findings that indicate a relevant deterioration of the risk-benefit relationship and would render continuation of the trial unjustifiable.

This clinical trial will be conducted in compliance with the clinical trial protocol, Good Clinical Practice (ICH Topic E6, Good Clinical Practice [GCP]) and the applicable national regulatory requirements.

2 OBJECTIVES

2.1. Primary objective

Phase Ib: To evaluate the safety and tolerability of the combination of TG4001 plus avelumab in patients with recurrent or metastatic HPV-16 positive advanced malignancies.

Phase II part 1: To evaluate the efficacy of TG4001 combined to avelumab in terms of Overall Response Rate (ORR) by using RECIST 1.1 in patients with recurrent or metastatic (R/M) HPV-16 positive advanced malignancies including oropharyngeal SCCHN.

Phase II part 2: To compare the PFS of TG4001 in combination with avelumab vs avelumab alone in patients with R/M HPV-16 positive advanced malignancies and without liver metastases at baseline. PFS will be evaluated based on RECIST 1.1.

2.2. Secondary objectives (Phase Ib + II)

To evaluate the combination of TG4001 and avelumab with respect to:

- Overall Response Rate (ORR) by using RECIST 1.1 (phase Ib and phase II part 2)
- Progression Free Survival (PFS, phase Ib and phase II part 1)
- Overall Survival (OS)
- Duration of Response (DoR)
- Disease control rate (DCR)
- Safety profile (phase II)
- Percentage of patients with liver metastases at baseline who have disease progression at D43 (phase II part 2)

2.3. Exploratory objectives (phase Ib +II)

- [redacted]

3 STUDY DESIGN

3.1. Overall study design and plan description

3.1.1. Overall design and treatment plan

This is a multicenter, open label phase Ib/II study evaluating the combination of TG4001 and avelumab in patients with HPV-16 positive advanced malignancies.
The phase II consists of two parts: phase II part 1 is a single arm study (TG4001 with avelumab) and phase II part 2 is a randomized, controlled two arms study (TG4001 with avelumab vs avelumab alone).
In the phase Ib: safety will be assessed in consecutive cohorts of 3 to 6 patients at increasing doses of TG4001 in combination with avelumab according to a 3+3 design (see table below). There will be no intra-patient dose escalation.
Patients will receive TG4001 on a weekly basis on Days 1, 8, 15, 22, and 29, then every 2 weeks (starting on Day 36) until Month 6 (from Day 1 of study treatment), thereafter once every 12 weeks, until disease progression, unacceptable toxicity, patient withdrawal from study for any reason or for a maximum of 2 years, whichever occurs first. Avelumab will be given once every 2 weeks starting from Day 8 (one week after the first vaccine dose), until disease progression, unacceptable toxicity, patient withdrawal from study for any reason or for a maximum of 2 years, whichever occurs first.
Beyond 2 years of treatment and based on the clinical judgement of the investigator the patient could continue to receive study treatments according to the Study Flow-Chart (APPENDIX IIIB).

Dose escalation (3+3 design)
Two dose levels are planned for TG4001: doses of 5×10^6 PFU (DL1) and 5×10^7 PFU (DL2) in combination with avelumab at 10 mg/kg. Depending on the nature of the DLTs observed at these two DLs, alternative schedule for TG4001 (Q4W) may be tested with the combination. In

that case a minimum of 6 additional patients will be included. Implementation of this alternative schedule will be subject to a substantial amendment to this clinical study protocol.
A minimum of 3 patients will be required at each dose level. If the maximal tolerated dose (MTD) is reached where 1 of 3 patients experiences a DLT, the cohort will be expanded with 3 additional patients at the same DL (a maximum of 6 patients will be enrolled at each DL).

Enrolment within a given cohort: The first patient will be monitored for 2 weeks (i.e. 7 days after the first administration of both products in combination) before the next two patients of the cohort can be enrolled simultaneously. In case the cohort must be extended by 3 additional patients for occurrence of a DLT among the first 3 treated patients, an interval of 2 weeks will be applied between the first additional patient and the 2 additional next patients.
Enrolment into the next cohort*:* Enrolment into the next cohort cannot begin until the last patient in the previous cohort has completed her/his 4 weeks (from Day 1 to Day 28) of study treatment (interval time for assessment of DLT) or experienced a DLT.

Number of DLTs / evaluable patients	Rule
0/3	Accrue 3 new patients at the next dose level
1/3	Accrue 3 additional patients at current dose level
≥ 2/3	Stop current dose = unacceptable dose MTD = dose immediately below
1/6	Accrue 3 new patients at the next dose level
≥ 2/6	Stop: current dose = unacceptable dose MTD = dose immediately below

The dose level at which unacceptable toxicity in at least 2/3 or 2/6 patients occurs will be considered as the unacceptable dose. The MTD will be considered as the dose immediately below. If no DLT in more than 1/3 or 1/6 is observed, the MTD will be considered as the recommended dose for the phase II (RP2D).

A total of 6 patients will be treated at the MTD.

If at both Dose Levels no DLT in more than 1/3 or 1/6 patients is observed, the MAD, Maximum Administered Dose (DL2), will be considered as the recommended dose for the phase II (RP2D).

Upon completion of phase Ib and for the purpose of clarification RP2D for TG4001 corresponds to DL2, i.e. 5 x 10^7 PFU.

In the phase II part 1, patients will be treated at the established RP2D for TG4001, i.e. 5 x 10^7 PFU in combination with avelumab until disease progression, death or unacceptable toxicity, or study withdrawal for any reason, or for a maximum of 2 years, whichever occurs first.
In the phase II part 2, patients will be treated at the established RP2D for TG4001, i.e. 5 x 10^7 PFU in combination with avelumab 800 mg Q2W (combination arm) or with avelumab 800 mg Q2W alone (monotreatment arm) until disease progression, death or unacceptable toxicity, or study withdrawal for any reason, or for a maximum of 2 years, whichever occurs first.
Beyond 2 years of treatment and based on the clinical judgement of the investigator the patient could continue to receive study treatments according to the Study Flow-Chart (APPENDIX IIIB and D).

In the phase II part 1, evaluation of efficacy and further evaluation of safety of the combination of TG4001 and avelumab will be performed in a single arm of patients with recurrent or metastatic HPV-16 positive advanced malignancies including HPV-16 positive oropharyngeal squamous cell carcinoma of the head and neck (SCCHN).

In the phase II part 2, evaluation of efficacy of the combination of TG4001 and avelumab will be performed in a randomized, open-label controlled study comparing TG4001 in combination with avelumab (combination arm) to avelumab alone (monotreatment arm) in patients with HPV-16 positive recurrent or metastatic malignancies.

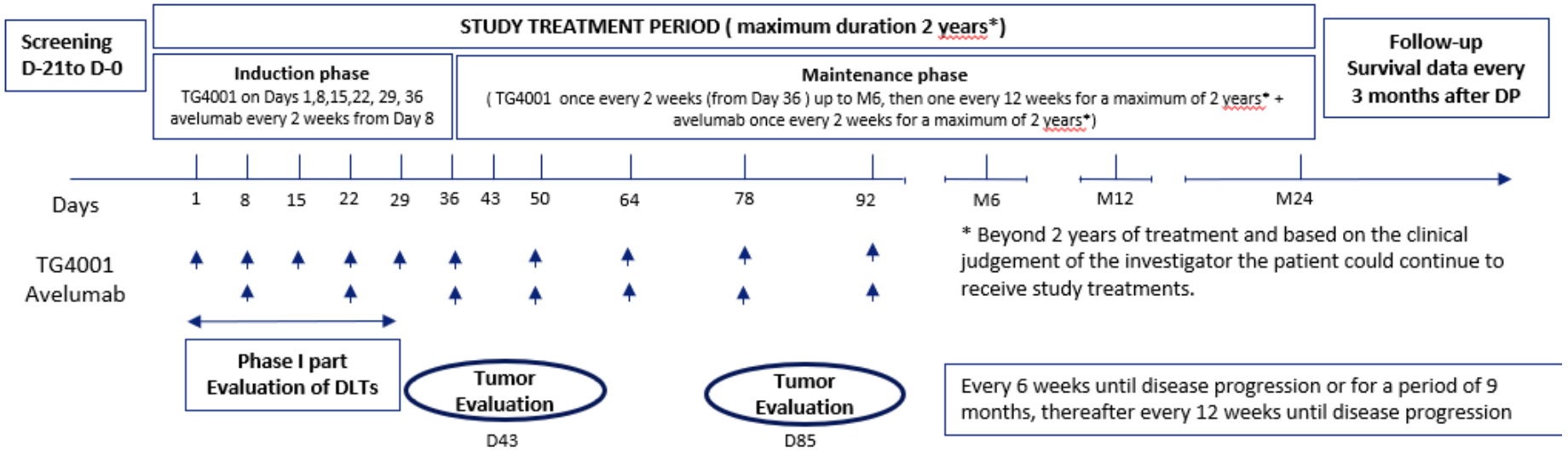
- In patients without liver metastases at baseline randomization will be conducted equally in a 1:1 ratio TG4001 with avelumab (combination arm) versus avelumab alone (monotreatment arm). A stratification will be done on primary tumor site.
- In patients with liver metastases at baseline randomization will be conducted equally in a 1:1 ratio TG4001 with avelumab versus avelumab alone, no stratification will be performed.

In both phases, tumor response will be evaluated at baseline and then every 6 weeks until disease progression. Beyond 9 months after start of treatment, tumor evaluation will be performed every 12 weeks until disease progression. Tumor evaluations will be based on local assessment using RECIST 1.1.
All patients will be followed up until disease progression or death due to any cause or the date of data cut-off, whichever occurs first.

For all patients included in the phases Ib and II of the study, blood samples and tumor samples from biopsies will be collected for immunological tests and translational research.

A schematic illustration of the trial design is shown in Figures 3-1 and 3-2 below.

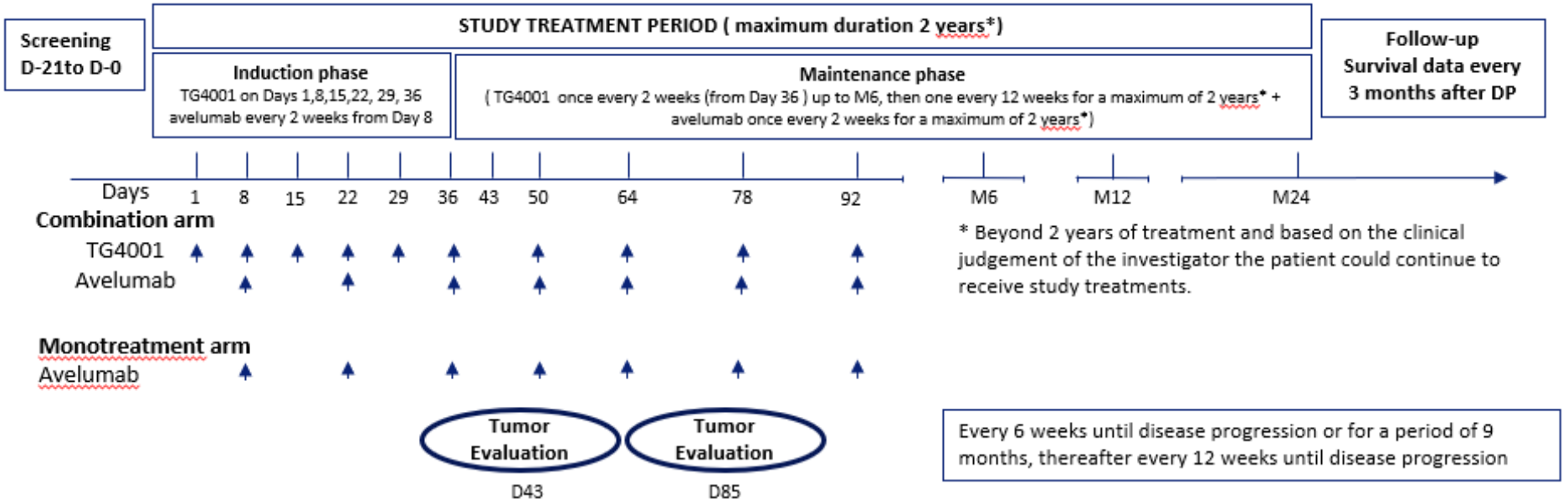
Figure 3-1 : Overall study design and investigational plan phase Ib and phase II part 1



Blood and tumor samples collection for immunological analyses

Day-21	Day 1	Day 8	Day 43	Day 85	M 6	M12	M24
Fresh tumor sample from biopsy	Blood	Blood	Blood	Blood	Blood	Blood	Blood
Day -7			Fresh tumor sample from biopsy	**Mandatory**			
Blood			**Mandatory**	Fresh tumor sample from biopsy			
Mandatory				**Unless it is unsafe or undesirable**			

Figure 3-2 : Overall study design and investigational plan phase II part 2



Blood and tumor samples collection for immunological analyses

Day-21	Day 1	Day 8	Day 15	Day 43	Day 85	M 6	M 9	M 12	At progressive disease
Fresh tumor sample from biopsy	Blood	Blood	Blood	Blood	Blood	Blood	Blood	Blood	Fresh tumor sample from biopsy
Day -3	Day 1 +6h**				Fresh tumor sample from biopsy		Fresh tumor sample from biopsy		
Blood	Blood								

** for patients in the combination arm

3.1.2. Number of centers and patients

Phase Ib: a maximum of 12 evaluable patients depending on the safety of the combination, in 3 centers
Phase II part 1: at least 22 evaluable patients until the first stage of the Simon design in up to 20 centers.
Phase II part 2 in up to 25 centers:
For patients without liver metastases a sample size of 50 patients (25 patients in each arm) is estimated to reach the number of PFS events required for Interim Analysis. Following Interim Analysis and sample size adjustment reviewed by the Independent Data Monitoring Committee (IDMC) a total of 120 patients are to be recruited until Q1 2024 to reach the number of PFS events required for Final Analysis. A 5% lost to follow-up or withdrawal of consent rate is estimated. With an actual recruitment rate of 2 patients per month, at least 80 patients will be recruited until Q1 2024.
For patients with liver metastases a sample size of [redacted] is planned.

3.1.3. Independent Data Monitoring Committee

An Independent Data Monitoring Committee (IDMC) will be set up during the study. In the phase Ib, the IDMC will be composed of 2 independent clinicians, external to the study.
In the phase II part 2, the IDMC will be composed of 2 independent clinicians and 1 independent statistician.
Representatives of Transgene (Medical monitor, Clinical Project Manager, Pharmacovigilance physician) and Merck KGaA / EMD Serono (Medical monitor) will be invited to all meetings for reporting of clinical data and to respond to any specific questions the IDMC may have on the conduct of the study.
Additional study team members may attend if deemed necessary (Clinical trial manager, Statistician). If deemed appropriate, the coordinating investigator of the study and the study investigators of the concerned centers will be invited for cases requiring specific explanation. The Sponsor can appoint any additional independent expert if needed.

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

- *In the phase Ib of the study:*

During the phase Ib of the study, the safety data of all enrolled and treated patients will be collected and evaluated by the Investigators, Transgene and Merck KGaA / EMD Serono on an ongoing basis. The IDMC will meet before each new cohort begins to analyze and review the safety data of all patients in the previous cohort. The IDMC will then recommend on continuation of accrual and whether it is possible to do the dose escalation as per the study design.
At the end of the phase Ib and depending on the nature of the toxicities observed, the safety data of all patients will be analyzed and discussed with the IDMC which will make recommendation to the sponsor on the start of accrual in the phase II of the study. DLT evaluation is performed 4 weeks after the last patient enrolled in the phase Ib had first dose of study treatments.

- *In the phase II part 1 of the study:*

During the phase II part 1 of the study the IDMC will review safety data at interim analysis. However, the IDMC may meet at any time on Sponsor request, especially in the case of unexpected toxicities or significant SAEs occurrence.

- *In the phase II part 2 of the study:*

During the phase II part 2 of the study and in addition to safety review the IDMC will evaluate efficacy results at interim analysis.

3.1.4. Patient accrual and duration of study

This study is expected to start in Q3 2017 and is expected to be completed by Q4 2024.
For safety reasons, inclusion of the patients in the phase Ib will be performed with a security interval of 2 weeks between the first patient of each cohort and the next 2 patients of the cohort.

In case of no safety concerns and for the further conduct of the study it is understood that the accrual rate is based on reasonable planning expectations. The actual accrual rate should be compared to the expected rate on an ongoing basis. If problems with recruitment are encountered this should be discussed with Transgene as early as possible in order to institute measures to meet the above timelines.

3.2. Discussion of study design

The study is designed as a phase Ib/II trial to evaluate the safety and efficacy of the combination of TG4001 with avelumab in patients with HPV-16 positive recurrent or metastatic cancer including oropharyngeal SCCHN patients.
The phase II consists of two parts: the phase II part 1 is a single arm study (TG4001 with avelumab) and the phase II part 2 is a randomized, open-label, controlled two arms study (TG4001 with avelumab vs avelumab alone).
TG4001 was studied in several clinical trials including patients with HPV-16 positive CIN2-3, HPV-16 positive cervical cancer and HPV-16 positive VIN3 at doses ranging from 5×10^5 PFU to 5×10^7 PFU administered by SC injections. The clinical data generated in CIN demonstrated that such HPV targeted active immunotherapy could eradicate HPV infected cervical cells by generating T-cell responses. In addition TG4001 displayed a good safety profile across all these studies (see Section 1.2.1).

Taking into account the fact that TG4001 has not been investigated previously in combination with avelumab, the study will be run in its first phase Ib in cohorts of 3 to 6 patients using a traditional 3+3 design to test two doses of TG4001 (5×10^6 and 5×10^7 PFU) in combination with a fixed dose of avelumab (10 mg/kg) in order to evaluate the safety profile of the combination of the two agents.
Should the data from this phase Ib of the study confirm the good tolerance of the combination, the study will be expanded (phase II of the study) to determine the efficacy of the combination in terms of overall response rate in this population of patients.

The phase II part 1 of the study is designed as an open label, single arm study evaluating the efficacy of combination of TG4001 + avelumab. The primary efficacy endpoint for the phase II of the study is ORR, this endpoint is widely accepted as directly attributable to drug effect without necessity of a control arm. It is also considered as an early endpoint allowing decision making to continue clinical development of TG4001 in combination with checkpoint inhibitors.

The phase II part 2 of the study is designed as a randomized, open label, controlled two arms study comparing the PFS of TG4001 in combination with avelumab vs avelumab alone.
For the cohort of patients without liver metastases at baseline, due to the uncertainty on the true treatment effect and data variability, and to reduce the risk of running an underpowered study, it is considered appropriate to adopt an adaptive approach to the sample. This will offer a mechanism to adjust the sample size to updated treatment effect and variability estimates seen at a planned interim analysis (Mehta C.R. and Pocock S.J., 2011).

The hypothesis for median PFS in the combination arm (TG4001 with avelumab) is set at 4.5 months and the hypothesis for median PFS in the monotreatment arm (avelumab alone) is set at 2.0 months. Interim analysis is performed after 37 PFS events and based on the conditional power observed, 120 patients should be enrolled to reach at Final Analysis a conditional power of 90% based on 104 PFS. To stick with initial timelines and with an observed enrollment of only 2 patients per month, Final Analysis will be performed based on at least 69 PFS events reaching a conditional power higher than 75% corresponding to at least 80 randomized patients.

3.3. Doses and schedule selection

3.3.1. TG4001 doses selection

The doses of TG4001 for the Phase Ib of the study were selected based on an evaluation of the toxicology data, *in-vivo* efficacy in oncology models, and clinical data in patients with cancer treated with TG4001. TG4001 was demonstrated to be safe up to the highest dose of 5×10^7 PFU in patients with gyneacological cancers. The starting dose chosen for TG4001 will be 5×10^6 PFU, in case no DLT occurs in combination with avelumab 10 mg/kg, the dose of 5×10^7 PFU used in previous clinical trials, which demonstrated to be safe will be tested in combination with avelumab 10 mg/kg. It is expected that the combination will be safe. Nevertheless, should DLTs or unexpected toxicities occur with the combination of TG4001 and avelumab, alternative dosing regimen of TG4001 and/or avelumab will be considered (See Section 3.1.1).

3.3.2. TG4001 schedule selection

TG4001 previous clinical development in gynaecological conditions was conducted according to a standard immunization regimen of 3 injections weekly (Days 1, 8, 15). The large and most recent phase II study (study NV25025) showed TG4001 activity when compared with placebo in both histologic assessments and viral clearance, even though primary efficacy endpoint for the treatment response rate of at least 60% was not achieved. One hypothesis that may explain a lower than expected response rate is that additional administrations were needed. Indeed, other large randomised phase II studies with MVA-based products developed by Transgene [i.e. TG4010 (MVA-MUC1-IL2) and TG4040 (MVA-HCV)] completed positively with schedules of immunization characterized by more administrations (weekly for 6 weeks followed by repeated boost of vaccination at regular interval).

Both animal toxicology data from TG4001 and similar viral vectored products (TG4040 and TG4010) demonstrated an acceptable safety profile of MVA-based products. The dose, the total number of injections and the intended treatment period in the proposed study with TG4001 were tested with either TG4001 or a similar construct in 3 animal species as shown in Table 3-1 below. None of these studies evidenced toxic findings up to 20 injections for 5 months other than inflammation at the injection site.

Table 3-1 : Summary of toxicology data supportive of the intended treatment regimen

Study	Number of injections	Treatment duration	Highest dose
TG4001 / Rat	8	1 month	$6x10^6$ PFU
TG4001 / Mice	4	1 month	$4x10^7$ PFU
TG4001 / Rabbit	3	1 month	$5x10^6$ PFU
TG4010 / Mice	9	3 months	$4x10^7$ PFU
TG4040 / Rabbit	20	5 months	$1x10^8$ PFU

The good tolerance in animals was further confirmed in patients. Previous human experience with TG4001 and similar products is summarized in Table 3-2. After iterative injections with MVA-based products for several months in cancer patients or chronic hepatitis C patients, the safety profile of the recombinant vector was satisfactory; the adverse events were mainly associated to the disease or the concomitant treatment.

Table 3-2 : Previous human experience with TG4001 and similar MVA-based products

Product	Number of treated patients*	Max number of injections	Highest dose (PFU)	Summary of adverse drug reactions
TG4001 (MVA-HPV-IL2)	313	3 (weekly)	$5x10^7$	injection site reactions, including erythema, pain, or reaction not otherwise specified
TG4010 (MVA-MUC1-IL2)	380	51 (weekly for the first 6 weeks then every 3 weeks up to progression)	$1x10^8$	fatigue, injection site reactions, erythema
TG4040 (MVA-HCV)	173	13 (weekly)	$1x10^8$	injection site reactions, fatigue, flu-like symptoms, headache

*as of December 2016

Based on the safety review from available animal and clinical studies conducted with our MVA-based products injected dozens of times per individual, there is no known toxicity after multiple administrations of MVA viruses. Thus, the company believes that the dose regimen of TG4001 in the proposed study is safe.

Therapeutic vaccines do not directly target the tumor but they rather aim to activate and amplify the immune reactions against the tumor. Immune responses often take time to develop and can potentially be enhanced by continued booster vaccinations. Therefore, the proposed schedule of administration of TG4001 in co-administration with avelumab in the present study uses weekly SC injections of TG4001 on Days 1, 8, 15, 22, and 29 of study treatment, then once every 2 weeks (starting on Day 36) up to Month 6, thereafter once every 12 weeks up to Month 24, fitting with the schedules of administration of the two other MVA based products and with the schedule of visits at the hospital.

3.3.3. Avelumab dose selection

The avelumab dose of 10 mg/kg was selected after review of the PK, pharmacodynamics, receptor occupancy, and preliminary clinical safety and efficacy data observed in the ongoing Phase I to III monotherapy studies of over 1700 subjects that have received this dose.
For the phase II part 2 avelumab will be administered at 800 mg flat dose every 2 weeks at the same schedule as in phase Ib and phase II part 1. This dose regimen has been approved in global markets. Avelumab was originally dosed on a mg/kg basis to reduce inter subject variability in drug exposure. However, data for mAbs, including the marketed PD-1 and PD-L1 ICIs inhibitors nivolumab, pembrolizumab and atezolizumab, reveal that body weight based dose regimens do not result in less variability in measures of exposure over fixed (i.e., body weight independent) dose regimens (Wang D.D. *et al.*, 2009), (Freshwater T. *et al.*, 2017), (Zhao X. *et al.*, 2017). Simulation showed that exposures to avelumab across the available range of body weights are less variable with 800 mg every 2 weeks compared with 10 mg/kg every 2 weeks; exposures were similar near the population median weight. Furthermore, the 800 mg every 2 weeks dose regimen is expected to result in C_{trough} > 1 mg/mL required to maintain avelumab serum concentrations at > 95% TO throughout the entire every 2 weeks dosing interval in all weight categories. Furthermore, the advantages of flat dosing are minimizing drug wastage, facilitating preparation and administration, and reducing pharmacy errors (Wang D.D. *et al.*, 2009).

4 STUDY POPULATION

4.1. Inclusion criteria

Patients must satisfy all the following inclusion criteria for entry into the study

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 (for phase II part 2: part of normal patient care can be: e.g. CT or MRI, biopsy, determination of HPV-16 positivity by specified central laboratory)
2. Female or male patients, aged at least 18 years (no upper limit of age for phase Ib and phase II part 1), 18 to 80 years of age (for phase II part 2)
3. Eastern Cooperative Oncology Group (ECOG) Performance Status 0 or 1 (Appendix I)
4. Life expectancy of at least 3 months
5. Patients with histologically or cytologically documented metastatic or refractory/recurrent HPV-16+ cancer (determined in an accredited central laboratory using a validated assay)
6. Phase Ib and Phase II part 1: Patients with HPV-16 + cancers including oropharyngeal squamous cell carcinoma of the head and neck (SCCHN), cervical, vulvar, vaginal, penile, and anal cancer
   Phase II part 2: Patients with HPV-16 + cancers including cervical, vulvar, vaginal, penile, and anal cancer
7. Disease MUST not be amenable to curative surgery resection or curative radiotherapy with documented disease progression after concertation with multidisciplinary board
8. Prior therapy:
   Phase Ib and Phase II part 1:
   - Patients MAY have received up to two prior lines of systemic chemotherapy for the management of metastatic or recurrent disease; for SCCHN, patients MUST have previously been exposed to platinum-based therapy, either as part of definitive chemo-radiation OR as first line systemic treatment for metastatic disease which

may include cetuximab. Patients with recurrence/progression within 6 months of prior multimodal therapy using platinum-based therapy are eligible. Patients with cervical cancer may have undergone surgery and/or received definitive radiation or chemo-radiation therapy for localized disease. Patients MUST have been exposed to platinum–based chemotherapy for metastatic disease which may include bevacizumab. Patients with platinum-refractory disease will be eligible

Phase II part 2:

- For recurrent/metastatic disease no more than one prior line of chemotherapy which can contain a platinum
- Prior treatment for metastatic disease is not required for:
  - Patients with recurrence/progression within 6 months after completion of prior multimodal therapy for localized or locally advanced disease not amenable to curative treatment
  - Patients who are unsuitable for platinum-based therapy
  - Patients who refuse chemotherapy or other standard therapies for the treatment of metastatic or recurrent disease. The benefit of an immunotherapy over standard therapies must be validated by the medical board and duly documented.

A minimum of 4 weeks interval should have elapsed between the completion of the last chemotherapy and study treatment start

A minimum of 4 weeks interval between palliative bone directed radiotherapy and the start of study treatment provided that radiation therapy does not affect the unique measurable lesion, if applicable

9. Phase II part 2: For patients with hepatic metastases:
   - no more than 3 hepatic lesions in total (target and non-target lesions)
   - maximum size of hepatic target disease ≤ 30 mm according to RECIST 1.1
10. Phase Ib and phase II part 1: **Availability of tumor tissue from biopsy:** at least two fresh tumor tissue samples are to be collected. Tumor tissue may come either from the local tumor or distant metastasis. Cytological material is not accepted for this analysis

    Phase II part 2:

    - Availability of archived or fresh tumor tissue for the determination of HPV-16 positivity.

    - . Patients must agree to undergo a core or excisional biopsy of a tumor lesion not previously irradiated (at least 2 fresh tissue samples to be collected). An archival sample obtained within one year prior to randomization is acceptable only if tumor is not accessible. Tumor tissue may come either from the local tumor or distant metastasis. Fine needle aspirates and bone biopsies are not adequate.
11. At least one measurable lesion by CT scan according to RECIST 1.1. Tumors within a previously irradiated field will be designated as "non-target" lesions unless progression is documented or a biopsy is obtained to confirm persistence at least 90 days following completion of radiation therapy
12. Adequate hematological, hepatic and renal function:
    - Hemoglobin ≥ 9.0 g/dL (for phase II part 2: without packed red blood cell transfusion within the prior 3 weeks)
    - Neutrophils ≥ $1.5x10^9$/L
    - Total lymphocytes count ≥ $0.4x10^9$/L
    - CD4 + ≥ 200 /µL
    - Platelets count ≥ $100x10^9$/L
    - Total bilirubin ≤ 1.5 x ULN

- Serum transaminases (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) ≤ 3 x ULN
- Glomerular Filtration Rate ≥ 50 mL/min (according to Modification of the Diet in Renal Disease (MDRD) formula or Cockroft & Gault formula)
- Serum albumin ≥ 30 g/L

13. Negative blood pregnancy test at screening for women of childbearing potential (Appendix II)
14. Highly effective contraception (i.e., methods with a failure rate of less than 1% per year) during the study period and for 3 months after the last study treatment administration for female patients of childbearing potential (WOCBP) and for male patients who are sexually active with WOCBP (See Appendix II for WOCBP definition and details on highly effective contraception methods). Highly effective contraception methods are defined as:
    - Hormonal methods of contraception including combined oral contraceptive pills, vaginal ring, injectables, implants, intrauterine devices (IUDs) such as Mirena and Nonhormonal IUDs such as ParaGard for WOCBP patient or male patient's WOCBP partner
    - Tubal ligation
    - Vasectomy

    In addition to highly effective contraception, participating male patients
    - must use a condom during the study period and for 3 months after the last study treatment administration when engaging in any activity that allows for exposure to ejaculate
    - must refrain from donating sperm

4.2. Exclusion criteria

If any of the following criteria apply, the patient must not enter into the study

1. Prior exposure to cancer immunotherapy including cancer vaccines, any antibody/drug targeting T cell co-regulatory proteins (immune checkpoints) such as anti-PD-L1, anti-PD-1, or anti-cytotoxic T-lymphocyte antigen-4 (CTLA-4) antibody
2. a) Concurrent anticancer treatment within 28 days before the start of study treatment (e.g., chemotherapy, radiotherapy or cytokine therapy except erythropoietin)
   b) Recurrent drainage procedures (once monthly or more frequently) for pleural effusion, pericardial effusion, or ascites
3. Major surgery within 28 days before the start of study treatment
4. 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 the first study treatment, 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
5. Patients with central nervous system (CNS) metastases except those meeting the following criteria:
    - Brain metastases that have been treated locally and are clinically stable during 4 weeks prior to start of study treatment
    - No ongoing neurological symptoms that are related to the brain localization of the disease (sequelae that are a consequence of the treatment of the brain metastases are acceptable)

6. Other active malignancy requiring concurrent systemic intervention
7. Patients with previous malignancies other than the target malignancy to be investigated in this trial (except non-melanoma skin cancers, and the following in situ cancers: bladder, gastric, colon, endometrial, cervical/dysplasia, melanoma, or breast) are excluded unless a complete remission was achieved at least 2 years prior to study entry AND no additional therapy is required during the study period
8. Patient with any organ transplantation, including allogeneic stem cell transplantation
9. Known severe hypersensitivity reactions to monoclonal antibodies (Grade ≥ 3 NCI-CTC V4.03 or V5.0 for phase II part 2), any history of anaphylaxis, or uncontrolled asthma
10. Any known allergy or reaction to eggs, gentamycin or attributed to compounds of similar chemical or biological composition to therapeutic vaccines/immunotherapeutic products
11. Any known allergy or reaction to any component of anti-PD-1/PD-L1 or its excipients
12. Patients with history of interstitial lung disease (phase Ib and phase II part 1)
13. Patients with known history or any evidence of active interstitial lung disease / pneumonitis (phase II part 2)
14. Administration of a live vaccine within 28 days prior to start of study treatment
15. Participation in a clinical study with an investigational product within 4 weeks prior to the start of the study treatment
16. Patients with active, known, or suspected auto-immune disease or immunodeficiency, except type I diabetes mellitus, hypothyroidism only requiring hormone replacement or skin disorders (such as vitiligo, psoriasis) not requiring systemic treatment
17. Significant chronic or acute infections including infection with mpox and SARS-CoV-2 (COVID-19) PCR positive testing
18. Positive serology for Human Immunodeficiency Virus (HIV) or Hepatitis C Virus (HCV) or presence in the serum of the Hepatitis B surface antigens (HBsAg), at Baseline
19. Persisting toxicity related to prior therapy of Grade ≥ 2 NCI-CTCAE v4.03 or v5.0 for phase II part 2 (except neuropathy [see exclusion criterion below] and alopecia).
20. Neuropathy ≥ Grade 3
21. Clinically significant (that is, active) cardiovascular disease: cerebral vascular accident/stroke or myocardial infarction (< 6 months prior to enrollment), unstable angina pectoris, congestive heart failure (New York Heart Association Classification Class ≥ II), or serious uncontrolled cardiac arrhythmia requiring medication/active intervention, history of myocarditis (history of myocarditis for phase II part 2).
22. Patient with any underlying medical condition that the treating physician considers might be aggravated by treatment or might impair the patient's tolerance to study treatment
23. History of uncontrolled intercurrent illness including but not limited to:
    - Hypertension uncontrolled by standard therapies (not stabilized to 150/90 mmHg or lower)
    - Uncontrolled diabetes (e.g., hemoglobin A1c ≥ 8%)
    - Uncontrolled infection (phase II part 2)
24. Patients with pulse oximetry of less than 92% on room air (phase II part 2)
25. Any psychological, familiar, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule; those conditions should be discussed with the patient before registration in the trial
26. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test (> 10 mIU/mL)

4.3. Criteria for patient premature withdrawal and replacement

4.3.1. Premature withdrawal from the trial

Patients are free to discontinue the trial at any time without giving reasons. Withdrawal of consent will be considered withdrawal from the trial unless the patients agree to be followed until documentation of progressive disease, if applicable and for survival, which may include verification of medical records.
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 treatment duration of this trial.

In case of premature withdrawal from the trial, the investigations scheduled for the end of treatment visit should be performed (see Section 6.8), if possible, with focus on the most relevant assessments. In any case, the appropriate case report form (eCRF) section must be completed.

4.3.2. Withdrawal from the Investigational Medicinal Products

Patients may discontinue the IMPs treatment (*i.e.*, for another reason than documented disease progression according to RECIST 1.1 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 or significant worsening of existing symptoms. However, every effort should be made to document objective progression even after discontinuation of treatment
- Adverse event(s) that according to the Investigator's evaluation unacceptably endanger the safety of the patient
- Physician's determination that patient's further participation in the study is not in the patient's best interest
- Patient's request at any time for any reason (patient's consent withdrawal)
- Protocol violation
- Lost to follow up

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

4.3.3. Replacement policy

In the phase Ib of the trial, only patients who do not complete the DLT observation period (the first 4 weeks of study treatment) for reasons other than a DLT or who are not evaluable for phase Ib safety analysis will be replaced. Patients who require discontinuation of TG4001 and/or avelumab due to a DLT will not be replaced. An evaluable patient must have received at least one dose of both IMPs (TG4001 + avelumab) and have had at least one valid post-

baseline safety assessment. The statement that a patient had no AE, on the Adverse Events eCRF page, constitutes a valid safety assessment. The occurrence of death also constitutes a valid safety assessment.
In the phase II part 1 of the trial, whatever the reason for withdrawal, except for disease progression and death due to underlying cancer before scheduled scan 6 weeks after study treatment start could be performed, patients considered as non-evaluable for tumor response will be replaced.
In the phase II part 2 of the trial, patients will not be replaced.

4.4. Definition of End of Study (EOS)

The end of the trial will be defined as the date of last patient last visit (LPLV).

5 INVESTIGATIONAL MEDICINAL PRODUCTS (IMPs)

In this study the IMPs are TG4001 and avelumab.

5.1. TG4001

TG4001 is a suspension of a recombinant attenuated Modified Vaccinia virus of Ankara (MVA strain), a significantly attenuated strain of Vaccinia virus, containing DNA sequences coding for the mutation-inactivated HPV-16 E6 and E7 antigens and for human Interleukin-2. For further information see TG4001 Investigator's Brochure.

[redacted]

In this study, the formulation medium is also used as diluent for reconstitution to obtain the dose of 5 x 10^6 PFU (DL1). The product code of the diluent is TG0008.

TG4001 and TG0008 will be supplied along with a Technical Sheet detailing their characteristics.

5.1.1. Packaging and labeling

TG4001 is supplied as a frozen suspension filled in individual 4-mL glass vials (Type I glass). Each vial is intended for single use (i.e., 1 injection to 1 patient). The recoverable volume of TG4001 in each vial is 0.5 mL with an infectious titer of 5 x 10^7 PFU. TG4001 is a colorless to whitish liquid clear or slightly turbid at room temperature (see TG4001 Investigator's Brochure and Technical Sheet).

TG0008 is supplied as a frozen solution filled in individual 4-mL glass vials (Type I glass). Each vial is intended for single use. The recoverable volume of TG0008 in each vial is 0.5 mL. TG0008 is a sterile, colorless, preservative-free suspension for injection.

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 TG4001 and TG0008 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 3373 regulations). TG4001 and TG0008 are shipped on dry-ice with the official transport designation "Biological Substance, Category B". Shipments are monitored with temperature control devices.

5.1.2. Conditions of storage and use

TG4001 and TG0008 must be stored at -20°C +/-5°C (between -15°C and -25°C) in a freezer 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.

TG4001 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 a Technical Sheet and a Preparation Procedure that are provided by Transgene detailing instructions for TG4001 handling (biosafety requirements, preparation, administration, destruction) and incident management.

During all TG4001 and TG0008 handlings, lab coat, goggles, gloves and mask must be worn. All transport of TG4001 and TG0008 (vial or syringe containing the dose to be injected) must be done using a leakproof container/bag.

5.1.3. Preparation for administration

TG4001 doses will be prepared and handled according to the instructions provided in the Preparation Procedure provided by Transgene. TG4001 will be diluted in the diluent TG0008 to obtain the dose of 5 x 10^6 PFU (DL1). No dilution will be necessary for the dose of 5 x 10^7 PFU (DL2) since it is contained in the TG4001 vials.
Upon completion of phase Ib and for the purpose of clarification RP2D for TG4001 corresponds to DL2, i.e. 5 x 10^7 PFU.

TG4001 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 TG4001 solutions.

In case of incident while handling TG4001, the actions recommended are described in the Technical Sheet. Any incident must be documented by a written report to be sent immediately upon occurrence or knowledge to Transgene Medical Department or its designee:

[redacted]

5.1.4. Disposal and destruction or return

During the course of the study based on Transgene's request and at termination of the study all unused TG4001 and TG0008 will be destroyed locally or returned to the supply provider contracted by Transgene.

For local destruction, the Investigator / Pharmacist or delegated person will ensure that destruction is performed according to written instructions for disposal of TG4001 (and TG0008) and waste generated during the TG4001 preparation and administration available in the TG4001 Investigator's Brochure and the Technical Sheet, and will not expose humans to any risks from TG4001. A certificate of destruction will be completed and provided to Transgene (copy retained by the site).

Alternatively, unused TG4001 and TG0008 may be returned to the supply provider contracted by Transgene with the appropriate documentation. The supply provider will coordinate the return of unused TG4001 and TG0008. A certificate of return will be completed and provided to the supply provider (copy retained by the site).

Upon completion or termination of the study at a site, the monitor will verify that all used TG4001 and TG0008 vials have been destroyed, all unused TG4001 and TG0008 vials have been returned or destroyed, and no TG4001 or TG0008 vial remains on site.

Accurate records of TG4001 and TG0008 received at, dispensed from, returned to and disposal of by the study site should be recorded appropriately on the drug log.

5.1.5. Supplier

TG4001 and TG0008 will be supplied by or on behalf of Transgene for this study at no cost to the study participant.

5.2. Avelumab

The active pharmaceutical ingredient in avelumab drug product is a fully human antibody of the immunoglobulin G (IgG) 1 isotype that specifically targets and blocks PD-L1, the ligand of PD-1. For further information see avelumab Investigator's Brochure.

5.2.1. Packaging and labeling

Avelumab is a sterile, clear and colorless concentrate for solution intended for intravenous (IV) administration. The drug is presented at a concentration of 20 mg/mL in Type I glass vial closed with a rubber stopper and sealed with an aluminium polypropylene flip-off seal. Each vial is intended for single use (i.e., 1 injection to 1 patient).

Each vial contains 200 mg of avelumab as a preservative free-acetate buffered solution (pH 5.2) containing Mannitol and Polysorbate 20 (Tween 20).

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.

Avelumab is shipped in suitable transport containers according to its storage and shipping conditions. Shipments are monitored with temperature control devices.

5.2.2. Conditions of storage and use

Avelumab must be stored at 2°C to 8°C in a fridge until use under the supervision of the study Pharmacist / Investigator (or his/her delegate). Avelumab must not be frozen.

Avelumab stored at room temperature (23°C to 27°C) or at elevated temperatures (38°C to 42°C) for extended periods is subject to degradation. Rough shaking of avelumab must be avoided.

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.

For further information on avelumab storage and handling see avelumab Investigator's Brochure.

5.2.3. Preparation for administration

For administration in clinical trials, avelumab must be diluted with 0.9% saline solution (sodium chloride injection), supplied in an infusion bag, alternatively a 0.45% saline solution can be used if needed. Detailed information on infusion bags and medical devices to be used for the preparation of the dilutions and subsequent administration will be provided in the Manual of Preparation.

The chemical and physical in-use stability for the infusion solution of avelumab in 0.45% or 0.9% saline solution has been demonstrated for a total of 24 hours at room temperature. However, from a microbiological point of view, the diluted solution should be used immediately and is not intended to be stored unless dilution has taken place in controlled and validated aseptic conditions. It is consequently recommended that the diluted solution of avelumab is used immediately.

No other drugs should be added to the solution for infusion containing avelumab.
For further information on avelumab preparation see the Manual of Preparation.

5.2.4. Disposal and destruction or return

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

For local destruction, the Investigator / Pharmacist or delegated person will ensure that destruction is performed according to written instructions for disposal of avelumab and waste generated during the avelumab preparation and administration, and will not expose humans to any risks from avelumab. Any unused portion of the solution or unused vial should be discarded in biohazard waste disposal with final disposal by accepted local and national standards of incineration. A certificate of destruction will be completed and provided to Transgene (copy retained by the site).

Alternatively, unused avelumab may be returned to the supply provider contracted by Transgene with the appropriate documentation. The supply provider will coordinate the return

of unused avelumab. A certificate of return will be completed and provided to the drug supply provider (copy remained by the site).

Upon completion or termination of the study at a site, the monitor will verify that all used avelumab vials have been destroyed, all unused avelumab vials have been returned or destroyed, and no avelumab vial remains on site.

Accurate records of avelumab received at, dispensed from, returned to and disposal of by the study site should be recorded appropriately on the drug log.

5.2.5. Supplier

Avelumab will be supplied by or on behalf of Merck KGaA for this study at no cost to the study participant.

6 TREATMENT PLAN

6.1. Trial medication administrations

The study treatments for all patients in the phase Ib and the phase II part 1 of the study are TG4001 with avelumab.
For the phase II part 2, study treatments are TG4001 with avelumab in the combination arm and avelumab alone in the monotreatment arm.

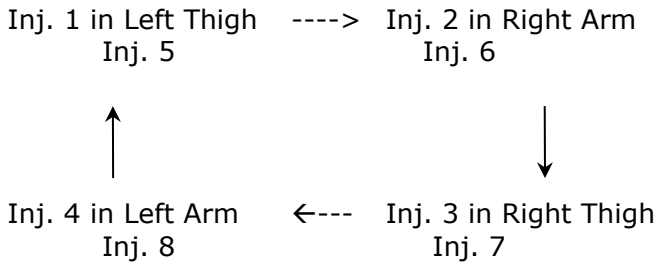
The study drugs treatment will be given on an outpatient setting, where all facilities for observation of the patients during and after study drug administrations are available and are in accordance with the local regulations laws.

6.1.1. TG4001

6.1.1.1.Administration of TG4001

Phase Ib, phase II part 1 and phase II part 2 combination arm: TG4001 will be administered weekly on Days 1, 8, 15, 22, and 29, and then once every 2 weeks (starting on Day 36) up to Month 6 (D204), then once every 12 weeks for a maximum of 2 years or until disease progression or unacceptable toxicity, or premature discontinuation due to any reason, whichever occurs first.
Beyond 2 years of treatment and based on the clinical judgement of the investigator the patient could continue to receive study treatments according to the Study Flow-Chart (APPENDIX IIIB and D). When both drugs are administered in the same day, TG4001 will be administered first (BEFORE avelumab) 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.



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

6.1.1.2.TG4001 dose administered and dose escalation scheme

- In the phase Ib of the study

Two dose levels will be tested: doses of 5 x 10^6 PFU (DL1) and 5 x 10^7 PFU (DL2) in combination with avelumab at 10 mg/kg tested in a 3+3 design (see Table 6-1).
Depending on the nature of the DLTs observed at these two DLs, alternative schedule for TG4001 (Q4W) may be tested with the combination. In that case a minimum of 6 additional patients will be included. Implementation of this alternative schedule will be subject to a substantial amendment to this clinical study protocol.

Table 6-1: Doses of TG4001 and avelumab in the phase Ib of the study

Dose level	TG4001 dose	Avelumab dose	Number of patients
DL1	5 x 10^6 PFU	10 mg/kg	3 – 6
DL2	5 x 10^7 PFU	10 mg/kg	3 – 6

Dose escalation rules and definition of MTD
All patients in the first DL (5 x 10^6 PFU) must complete the first 4 weeks treatment before dose escalation to the next dose level (DL2) will occur.
There will be no intra-patient dose escalation; each patient will stay on the dose level assigned in the trial unless study drugs need to be stopped.
Patients who experience a DLT will be withdrawn from the study treatment and followed up to disease progression or death, whichever occurs first.
Patients who are not evaluable for DLT or who are withdrawn during the first 4 weeks of study treatment for other reasons than a DLT, will be replaced.

Doses are escalated until MTD is reached as follows.

Number of DLTs / evaluable patients	Rule
0/3	Accrue 3 new patients at the next dose level
1/3	Accrue 3 additional patients at current dose level
≥ 2/3	Stop current dose = unacceptable dose MTD = dose immediately below

1/6	Accrue 3 new patients at the next dose level
≥ 2/6	Stop: current dose = unacceptable dose MTD = dose immediately below

The dose level at which unacceptable toxicity in at least 2/3 or 2/6 patients occurs will be considered as the unacceptable dose. The MTD will be considered as the dose immediately below. If no DLT in more than 1/3 or 1/6 is observed, the MTD will be considered as the recommended dose for the phase II (RP2D).
A total of 6 patients will be treated at the MTD.
If at both Dose Levels no DLT in more than 1/3 or 1/6 patients is observed, the MAD (DL2) will be considered as the recommended dose for the phase II (RP2D).

Upon completion of phase Ib and for the purpose of clarification RP2D for TG4001 corresponds to DL2, i.e. 5 x 10^7 PFU.

Dose limiting toxicity (DLT) will be assessed in each included and treated patient during the first 4 weeks [Day 1 to Day 28] of dosing (4 injections of TG4001 and 2 injections of avelumab) and includes the following toxicities:

- Grade ≥ 3 drug related adverse event. However, fatigue, nausea/vomiting adequately treated with anti-emetics, endocrinopathies adequately controlled with one physiologic hormone replacement, skin toxicity and single laboratory values out of normal range without any clinical correlate, asymptomatic grade ≥3 lipase or amylase elevation, tumor flare defined as local pain, irritation, or rash localized at sites of known or suspected tumor or a transient Grade 3 infusion adverse event are excluded.
- Liver function test abnormality:
  - AST or ALT > 5 x ULN
  - Total bilirubin > 3 x ULN
  - Concurrent AST or ALT > 3 x ULN and total bilirubin > 2 x ULN
- Drug related adverse event requiring treatment interruption for more than 2 weeks

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

All adverse events that meet DLT criteria must be reported to Transgene, within 24 hours (See Section 9.4).

- In the phase II part 1 and phase II part 2 combination arm

TG4001 will be administered at the RP2D established during the phase Ib of the study in combination with avelumab.

Upon completion of phase Ib and for the purpose of clarification RP2D for TG4001 corresponds to DL2, i.e. 5 x 10^7 PFU.

6.1.2. Avelumab

- In the phase Ib and phase II part 1

Avelumab will be administered at the dosage of 10 mg/kg as an IV infusion over 1 hour [-10 minutes / +20 minutes, i.e., 50 to 80 minutes] once every 2 weeks. The dose of avelumab will be calculated based on the weight of the patient determined within 72 hours prior to the day of drug administration. The dose of avelumab used for the previous administration can be repeated if the change in the patient's weight is 10% or less than the weight used for the last dose calculation.
Patients will be treated with avelumab once every 2 weeks, starting one week after the first vaccine dose (on Day 8), until disease progression, unacceptable toxicity, patient withdrawal from the study for any reason, or for a maximum of 2 years, whichever occurs first.
Beyond 2 years of treatment and based on the clinical judgement of the investigator the patient could continue to receive study treatments according to the Study Flow-Chart (APPENDIX IIIB).
In order to mitigate infusion-related reactions, subjects will receive pretreatment with histamine H1 receptor blockers and acetaminophen/paracetamol 30 to 60 minutes prior to **every** avelumab infusion. A premedication regimen of 25 to 50 mg diphenhydramine and 500 to 650 mg acetaminophen/paracetamol (IV or oral equivalent) is recommended prior to each dose of trial drug. This regimen may be modified based on local treatment standards and guidelines as appropriate.

PREMEDICATION FOR AVELUMAB ADMINISTRATION AND AVELUMAB SHOULD BE ADMINISTERED AFTER TG4001.

- In the phase II part 2, combination arm and monotreatment arm

Avelumab will be administered at the flat dose 800 mg as an IV infusion over 1 hour [-10 minutes / +20 minutes, i.e., 50 to 80 minutes].
Patients will be treated with avelumab once every 2 weeks starting on Day 8, until disease progression, unacceptable toxicity, patient withdrawal from the study for any reason, or for a maximum of 2 years, whichever occurs first.
Beyond 2 years of treatment and based on the clinical judgement of the investigator the patient could continue to receive study treatments according to the Study Flow-Chart (APPENDIX IIID).
In order to mitigate infusion-related reactions, a premedication regimen of 25 to 50 mg diphenhydramine and 500 to 650 mg acetaminophen/paracetamol (IV or oral equivalent) is recommended prior to the first 4 infusions of avelumab. This regimen may be modified based on local treatment standards and guidelines as appropriate. Premedication should be administered for subsequent avelumab doses based upon clinical judgement and presence/severity of prior infusion reactions.

FOR THE COMBINATION ARM PREMEDICATION FOR AVELUMAB ADMINISTRATION AND AVELUMAB SHOULD BE ADMINISTERED AFTER TG4001.

6.2. Planned study treatment duration and observation period

The trial duration for a patient is estimated to be up to 2.5 years. This includes a 21-day screening period (decision will be made in this period for patient's trial inclusion if all eligibility

criteria are met); a treatment duration which may last up to 2 years or beyond based on the investigator's clinical judgement, unless disease progression, unacceptable toxicity, withdrawal from the trial or IMP occurs for any reason, an end-of-treatment visit as soon as both IMPs are permanently discontinued; and a safety follow-up visit which must occur 30 days after the last study treatment administration (See Section 7). At 90 days after the last study treatment administration, patients will be contacted by telephone to collect information on new or ongoing SAEs and treatment-related non-serious AEs. Subjects will also be asked about any further antineoplastic therapy.

6.2.1. Planned duration of study treatment in case of related toxicity to one of the IMPs

For the phase Ib, phase II part 1, and phase II part 2 combination arm, the duration of treatment lasts from the first study drug administration (TG4001) until the last IMP dose administration (TG4001 and/or avelumab).

- In case avelumab has to be stopped for toxicity, TG4001 will be also stopped and the end of the study treatment will correspond to the last IMP dose administration.
- In case TG4001 has to be stopped for toxicity, avelumab may be continued alone at the discretion of the investigator if a clinical benefit is observed. In this case, the end of study treatment will correspond to the date when avelumab is permanently discontinued.

For the monotreatment arm in phase II part 2, the duration of treatment lasts from the first avelumab administration until the last avelumab administration.

- In case avelumab has to be stopped for toxicity, the end of the study treatment will correspond to the last avelumab administration

After the patient has been discontinued from IMP(s), he/she will be followed-up until disease progression, or death due to any cause or the date of data cut-off, whichever occurs first.

6.2.2. Planned duration of study treatment according to response

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

- Patients who achieved a confirmed CR MAY stop the treatment earlier at the discretion of the investigator provided that they have been treated for a minimum of 12 months. After discontinuation of the study treatment, patients will be followed until disease progression or death due to any cause or the date of data cut-off, whichever occurs first.
- Patients with a response of PR/SD will continue to receive TG4001 and avelumab until achievement of a confirmed CR, disease progression, development of unacceptable toxicity or until they have received a maximum of 2 years of study treatment, whichever occurs first. Beyond 2 years of treatment and based on the clinical judgement of the investigator the patient could continue to receive study treatments according to the Study Flow-Chart (APPENDIX IIIB and D).
- Patients with progressive disease (PD) based on RECIST 1.1 will stop treatment and complete the off-treatment procedures in phase I and phase II part 1. In phase II part 2 at the 1st radiologic evidence of PD, clinically stable patients may continue study treatment at the Investigator's discretion while awaiting confirmatory scan. If repeat imaging confirms PD, study treatment must be discontinued except if the patient is clinically stable or clinically improved, and there is no further increase in the target lesions, no unequivocal increase in non-target disease, and no additional new lesions (non-worsening PD). If repeat

scan shows SD, PR or CR patient continues study treatment and imaging assessment should be performed every 6 weeks.
- Patients who are withdrawn from study drug treatment for reasons other than disease progression based on RECIST 1.1 will be followed until disease progression or death due to any cause or the date of data cut-off, whichever occurs first.

For any patient, as soon study treatment is permanently discontinued, an "end of treatment visit" will be completed in the eCRF (See Section 7.4).

6.3. Concomitant therapies and medications

6.3.1. Concomitant medications

Concomitant medications are:
- Medications and/or non-drug therapies taken by the patient during the month before Day 1 of study treatment (*i.e.*, start of the study treatment), and continuing after the start of the study treatment
- All medications and non-drug therapies taken during the treatment period of the study starting from start of study treatment up to 30 days after the last study treatment administration

Concomitant medications will be reported in the eCRF with their reason for prescription, start date and end date, route of administration and dose.
Any prior medication or significant non-drug therapies ending within 1 month prior to the start of the study treatment will be reported in the eCRF in the same way.

6.3.2. Permitted medicines and therapies

- Any medications (other than those excluded by the study protocol) that are considered necessary for the patient's 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: erythropoietin, antiemetics, amifostine, folates, vitamin B12 and vitamin D.
- The use of systemic corticosteroids during the study is restricted as follows: for short term treatment (≤ 7 days) of allergic reactions or for the treatment of irAEs, or for replacement for adrenal insufficiency at doses equivalent to ≤ 10 mg prednisone daily (see **Section** 6.3.4).
- Radiotherapy for pain relief (e.g., bone metastases) is permitted. If lesions are in the field of radiation they will no longer be evaluable for the tumor response, patients receiving palliative radiotherapy will be analyzed separately.

6.3.3. Non-permitted medicines and therapies

- Any live vaccine for the prevention of infectious disease (e.g., human papilloma virus vaccine).
- Growth factors (granulocyte colony stimulating factor or granulocyte macrophage colony stimulating factor), except erythropoietin and darbepoietin alpha (may be prescribed at the investigator's discretion).

- Bisphosphonate or denosumab treatment is not allowed unless it has been initiated more than 14 days prior to receiving the first administration of study treatment.

If the administration of a non-permitted concomitant drug becomes necessary during the trial, the patient will be withdrawn from study treatment (the Sponsor may be contacted to discuss whether the study treatment must be discontinued).

6.3.4. Considerations for Steroids use during the trial

Data indicate that corticosteroids have an adverse effect on T cell function (Schleimer R.P. *et al.*, 1984) and that they inhibit and damage lymphocytes (Khan M.M., 2008). Furthermore, as with all immunotherapies intended to augment cell-mediated immunity, there is a risk that concomitant immunosuppressives such as steroids will counteract the intended benefit. However, studies with anti-CTL-A4 compounds indicate that short term use of steroids can be employed without compromising clinical outcomes (Weber J.S. *et al.*, 2012). Therefore, the use of steroids during this trial is restricted as follows:

- Therapeutic use: limited to the treatment of infusion-related reactions and for short term treatment (≤ 7 days) of allergic reactions or for the treatment of irAEs. The course of steroid treatment should be completed as soon as clinically feasible and before resuming the next cycle provided the event has resolved to a Grade 1 or less.
- Physiologic use: replacement for adrenal insufficiency at doses equivalent to ≤ 10 mg prednisone daily are acceptable.

Prophylactic use: prophylactic use, e.g. for the prevention of acute infusion-related reactions, constitutes concomitant use and is prohibited.

6.3.5. Other trial considerations

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

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

Patients should not abuse alcohol or other drugs during the study.

6.3.6. Special precautions

Patients must be observed for 1 hour post-administration of avelumab for the first four infusions, in an area with resuscitation equipment and emergency agents. Immediate emergency treatment of an infusion-related reaction or a severe hypersensitivity reaction must be assured according to institutional standards. In order to treat possible anaphylactic reactions appropriate medical therapy (including epinephrine, corticosteroids, IV antihistamines, bronchodilators, and oxygen) must be available along with equipment for assisted ventilation. For subsequent infusions and if no infusion-related reactions have been observed during/after the first 4 administrations, observation time can be reduced to at least 30 minutes after completion of each infusion.

Investigators should also monitor patients closely for potential irAEs, which may become manifest at the earliest after weeks of treatment. Such events may consist of persistent rash, diarrhea and colitis, autoimmune hepatitis, arthritis, glomerulonephritis, cardiomyopathy, or uveitis and other inflammatory eye conditions. The spectrum of hypothetical irAEs also includes formation of auto-antibodies like ANAs or ANCAs (see **Section** 6.5.2.6 for details on the management of irAEs).

6.4. Method of assigning patients to treatment groups

6.4.1. Recruitment

Upon signing the informed consent form (ICF), the patient will be assigned an identification number which is a combination of the center number and the patient number.
The center number is assigned by the Sponsor to the investigational site. At each site, the first patient screened is assigned patient number 01, and subsequent patients are assigned consecutive numbers. Once assigned to a patient, the patient number will not be reused.
The screening process will start and is defined as the baseline period. The baseline lasts at most 21 days.

If the patient fails to be included for any reason, the reason for non-inclusion (e.g. withdrawal of consent, exclusion criteria) and a minimum of other parameters will be entered in the eCRF. Under no circumstances will a patient screened and found not eligible for the study be permitted to be re-screened for a second time.

6.4.2. Randomization

Non applicable for the phase Ib and the phase II part 1.
Randomization is applicable for the phase II part 2.
Upon satisfying all inclusion and exclusion criteria, the Investigator or his/her delegate will proceed to randomization which will be done in the eCRF.

- In patients without liver metastases at baseline randomization will be conducted equally in a 1:1 ratio TG4001 with avelumab (combination arm) versus avelumab alone (monotreatment arm). A stratification will be done on primary tumor site.
- In patients with liver metastases at baseline randomization will be conducted equally in a 1:1 ratio TG4001 with avelumab versus avelumab alone, no stratification will be performed.

The patient must start the study treatment according to allocation during randomization on the day of randomization (+1 day) if randomized into the combination arm and 1 week after randomization (+/- 1 day) if randomized into the monotreatment arm.

6.5. Dose modifications

There will be no delay or dose reduction for TG4001 and avelumab in this study.
If an AE is related to only one agent (TG4001 or avelumab) and dose cancellation is required, the other agent continues as planned, if applicable.

In case of occurrence of symptoms compatible with SARS-CoV-2 (COVID-19) infection or in case of SARS-CoV-2 (COVID-19) positive testing, administration of TG4001 and avelumab will be performed based on the clinical judgement by the investigator.

6.5.1. TG4001

6.5.1.1.TG4001 dose modification

For a given patient, no dose modification of TG4001 is permitted.
Criteria for administration of TG4001 are defined as follows:
- neutrophils $\geq 0.5 \times 10^9$/L
- if a Grade 1-2 AE occurs, TG4001 should be administered as planned.
- in case ≥ Grade 3 AE possibly, probably or definitely suspected to be related to TG4001 occurs, the administration of TG4001 will be cancelled and the patient should come in for his/her next, regularly scheduled visit. The next scheduled visit should occur according to the patient's next regularly scheduled visit relative to Day 1.

In case the patient misses 2 consecutives doses of TG4001, contact the sponsor for guidance.

TG4001 does not have to be omitted for avelumab related AEs, if applicable. Contact the sponsor for guidance.

For phase Ib, phase II part 1 and phase II part 2 combination arm: In case TG4001 must be discontinued due to toxicity or other reason than disease progression, the other IMP (avelumab) may be continued as planned at the discretion of the investigator if a clinical benefit is observed.

6.5.2. Avelumab

6.5.2.1.Avelumab dose modification

No dose delay or dose reduction of avelumab will be allowed in this study.
A time window of +/- 1 day up to Day 36 and of -3/+1 days beyond Day 36 will be permitted for all trials procedures. However, the bi-weekly schedule should be strictly adhered to, and patients should return to the target date (i.e. the next regularly scheduled visit relative to the start of avelumab) even if the previous visit was off schedule.

In case the patient misses 2 consecutives doses of avelumab, contact the sponsor for guidance.

Avelumab does not have to be omitted for TG4001 related AEs, if applicable. Contact the sponsor for guidance.

For phase Ib, phase II part 1 and phase II part 2 combination arm: In case avelumab must be discontinued due to toxicity or other reason than disease progression, TG4001 will be stopped as well and the patient will be followed-up until disease progression, death, or study cut off date, whichever occurs first.
For phase II part 2 monotreatment arm: In case avelumab must be discontinued due to toxicity or other reason than disease progression, the patient will be followed-up until disease progression, death, or study cut off date, whichever occurs first.

6.5.2.2.Adverse drug reactions requiring avelumab treatment modification or discontinuation

Dosing withhold or discontinuation may be required based on individual safety and tolerability (Table 6-2 below, **Summary of Product Characteristics, 19 October 2022, or later version, if available**). Resume avelumab in patients whose adverse reactions recover to Grade 1 or resolved.

Table 6-2: Treatment Modification Recommendations for Treatment-related Adverse Reactions

Treatment-related Adverse Reaction	Severity	Treatment modification
Pneumonitis	Grade 2 pneumonitis	Withhold avelumab. Resume avelumab in patients with complete or partial resolution (Grade 0 to 1) of pneumonitis after corticosteroid taper.
	Grade 3 or Grade 4 pneumonitis or recurrent Grade 2 pneumonitis	Permanently discontinue
Hepatitis	AST or ALT more than 3 and up to 5 times ULN or total bilirubin more than 1.5 and up to 3 times ULN	Withhold avelumab. Resume avelumab in patients with complete or partial resolution (Grade 0 to 1) of hepatitis after corticosteroid taper.
	AST or ALT more than 5 times ULN or total bilirubin more than 3 times ULN	Permanently discontinue
Colitis	Grade 2 or Grade 3 diarrhoea or colitis	Withhold avelumab. Resume avelumab in patients with complete or partial resolution (Grade 0 to 1) of colitis or diarrhoea after corticosteroid taper.
	Grade 4 diarrhoea or colitis or recurrent Grade 3 diarrhoea or colitis	Permanently discontinue
Endocrinopathies (including but not limited to hypothyroidism, hyperthyroidism, adrenal insufficiency, hyperglycaemia)	Grade 3 or Grade 4	Withhold avelumab. Resume avelumab in patients with complete or partial resolution (Grade 0 to 1) of endocrinopathies after corticosteroid taper.
Nephritis and Renal dysfunction	Serum creatinine more than 1.5 and up to 6 times ULN	Withhold avelumab. Resume avelumab in patients with complete or partial resolution (Grade 0 to 1) of nephritis and renal dysfunction after corticosteroid taper.
	Serum creatinine more than 6 times ULN	Permanently discontinue
Skin reactions	Grade 3 rash	Withhold until adverse reactions recover to Grade 0-1
	Grade 4 or recurrent Grade 3 rash or confirmed Stevens–Johnson syndrome (SJS) or Toxic epidermal necrolysis (TEN)	Permanently discontinue

Treatment-related Adverse Reaction	Severity	Treatment modification
Other immune-related adverse reactions (including myositis, hypopituitarism, uveitis, myasthenia gravis, myasthenic syndrome, Guillain-Barré syndrome)	For any of the following: • Grade 2 or Grade 3 clinical signs or symptoms of an immune-related adverse reaction not described above. • Grade 3 or 4 endocrinopathies	Withhold avelumab. Resume avelumab in patients with complete or partial resolution (Grade 0 to 1) of other immune-related adverse events after corticosteroid taper.
	For any of the following: • Life threatening or Grade 4 adverse reactions (excluding endocrinopathies controlled with hormone replacement therapy) • Recurrent Grade 3 immune-related adverse reaction • Requirement for 10 mg per day or greater prednisone or equivalent for more than 12 weeks • Persistent Grade 2 or 3 immune-related adverse reactions lasting 12 weeks or longer	Permanently discontinue
Infusion-related reactions	Grade 1 infusion-related reaction	Reduce infusion rate by 50%
	Grade 2 infusion-related reaction	Withhold until adverse reactions recover to Grade 0-1; restart infusion with a 50% slower rate
	Grade 3 or Grade 4 infusion-related reaction	Permanently discontinue
Pancreatitis	Suspected pancreatitis	Withhold
	Confirmed pancreatitis	Permanently discontinue
Myocarditis	Suspected myocarditis	Withhold
	Confirmed myocarditis	Permanently discontinue

ALT: alanine aminotransferase; AST: aspartate aminotransferase; ULN: upper limit of normal.
Note: toxicity grades are in accordance with National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0 (NCI-CTCAE v4.0).

Infusion-related reactions, hypersensitivity reactions and irAEs should be handled according to guidelines as detailed in Sections 6.5.2.3, 6.5.2.4 and 6.5.2.6.

6.5.2.3.Management of infusion-related reactions

Patients are at risk of developing infusion-related reactions including drug hypersensitivity reactions, mainly mild to moderate, but which may also be life-threatening.

Immediate access to an intensive care unit or equivalent environment and appropriate medical therapy (including epinephrine, corticosteroids, IV antihistamines, bronchodilators, and oxygen) must be available for use in the treatment of infusion-related reactions. Infusion of avelumab will be stopped in case of Grade $\geq$ 2 infusion-related, allergic, or anaphylactoid reactions. Patients must be observed for 1 hour post-administration of avelumab for the first four infusions. For subsequent infusions and if no infusion-related reactions have been observed during/after the first 4 administrations, observation time can be reduced to at least 30 minutes after completion of each infusion.

For phase Ib and phase II part 1: In order to mitigate infusion-related reaction, premedication with a histamine H1 receptor blocker and with paracetamol (acetaminophen) is mandatory prior to each dose of avelumab

For phase II part 2: In order to mitigate IRRs, patients have to be premedicated with an antihistamine and with paracetamol (acetaminophen) prior to the first 4 infusions of avelumab. Monitor patients for signs and symptoms of IRRs including pyrexia, chills, flushing, hypotension, dyspnea, wheezing, back pain, abdominal pain, and urticaria. Interrupt or slow the rate of infusion for mild or moderate IRRs. Stop the infusion and permanently discontinue avelumab for severe (Grade 3) or life-threatening (Grade 4) IRRs. Premedication should be administered for subsequent avelumab doses based upon clinical judgement and presence/severity of prior infusion reactions (See Section 6.1.2).

In case of occurrence of infusion-related reaction, please follow the guidelines for the treatment modifications of avelumab described in Table 6-3 below, **Avelumab Investigator's Brochure Version 8, 16 May 2018, Section 6.1.2 or later version if available.**

Table 6-3: Treatment Modification for Symptoms of Infusion-Related Reactions Caused by Avelumab

NCI-CTCAE Grade	Treatment Modification for Avelumab
Grade 1 – mild • Mild transient reaction; infusion interruption not indicated; intervention not indicated	• Decrease the avelumab infusion rate by 50% and monitor closely for any worsening
Grade 2 – moderate • Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (for example, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤ 24h	• Temporarily discontinue avelumab infusion • Resume infusion at 50% of previous rate once infusion-related reaction has resolved or decreased to at least Grade 1 in severity, and monitor closely for any worsening
Grade 3 or Grade 4 – severe or life-threatening • Grade 3: Prolonged (for example, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae • Grade 4: Life-threatening consequences; urgent intervention indicated	• Stop the avelumab infusion immediately and disconnect infusion tubing from the subject • Subjects have to be withdrawn immediately from avelumab treatment and must not receive any further avelumab treatment

IV: intravenous; NCI-CTCAE: National Cancer Institute-Common Terminology Criteria for Adverse Event; NSAIDs: nonsteroidal anti-inflammatory drugs.

6.5.2.4.Management of severe hypersensitivity reaction and flu-like syndrome

Immediate access to an intensive care unit or equivalent environment and appropriate medical therapy (including epinephrine, corticosteroids, IV antihistamines, bronchodilators, and oxygen) must be available for use in the treatment of infusion-related reactions. Infusion of avelumab will be stopped in case of Grade ≥ 2 infusion-related, allergic, or anaphylactoid reactions. Patients must be observed for 1 hour post-administration of avelumab for the first four infusions. For subsequent infusions and if no infusion-related reactions have been observed during/after the first 4 administrations, observation time can be reduced to at least 30 minutes after completion of each infusion.
Patients should be instructed to report any delayed reactions to the investigator immediately.

Symptoms of hypersensitivity reactions include
- Impaired airway
- Decreased oxygen saturation (<92%)

- Confusion
- Lethargy
- Hypotension
- Pale/clammy skin
- Cyanosis

For prophylaxis of flu-like symptoms, 25 mg indomethacin or comparable NSAID dose (e.g., ibuprofen 600 mg, naproxen sodium 500 mg) may be administered 2 hours before and 8 hours after the start of each dose of avelumab i.v. infusion. Alternative treatments for fever (e.g., paracetamol) may be given to patients at the discretion of the investigator.

6.5.2.5.Management of tumor lysis

In addition, since avelumab can induce ADCC, there is a potential risk of tumor lysis syndrome. Should this occur, patients should be treated as per local guidelines and the management algorithm published by Howard et al (Howard S.C. *et al.*, 2011).

6.5.2.6.Management of immune related adverse events

Immune-mediated adverse reactions (immune-related pneumonitis, immune-related colitis, immune-related hepatitis, immune-related pancreatitis, immune-related myocarditis, immune-related endocrinopathies (thyroid disorders, adrenal insufficiency, new onset type I diabetes mellitus, pituitary disorders), immune-related nephritis and renal dysfunction and other immune-related AEs (myositis, Guillain-Barré syndrome, uveitis and myasthenia gravis / myasthenic syndrome) have been identified as important risks for avelumab. Such events should be recognized early and treated promptly to avoid potential major complications.
For suspected immune-related adverse reactions, adequate evaluation should be performed to confirm aetiology or exclude other causes. The administration of avelumab may be cancelled due to severe or unresolved toxicity or undercurrent AEs.

Treatment of irAEs is mainly dependent upon severity (NCI-CTCAE grade):
- Grade 1 to 2: treat symptomatically or with moderate dose steroids, more frequent monitoring
- Grade 1 to 2 (persistent): manage similar to high grade AE (Grade 3 to 4)
- Grade 3 to 4: treat with high dose corticosteroids

Treatment of irAEs should follow guidelines set forth in Table 6-4 below, **Avelumab Investigator's Brochure Version 8, 16 May 2018 Section 9.2 or later version if available**.

Table 6-4: Management of Immune-related Adverse Events

Gastrointestinal irAEs		
Severity of Diarrhea/Colitis (NCI-CTCAE v4)	**Initial Management**	**Follow-up Management**
Grade 1 Diarrhoea: < 4 stools/day over Baseline Colitis: asymptomatic	Continue avelumab therapy Symptomatic treatment (e.g. loperamide)	Close monitoring for worsening symptoms Educate subject to report worsening immediately If worsens: Treat as Grade 2, 3 or 4.
Grade 2 Diarrhoea: 4 to 6 stools per day over Baseline; IV fluids indicated < 24 hours; not interfering with ADL Colitis: abdominal pain; blood in stool	Withhold avelumab therapy Symptomatic treatment	If improves to Grade ≤ 1: Resume avelumab therapy If persists > 5-7 days or recurs: Treat as Grade 3 or 4.
Grade 3 to 4 Diarrhoea (Grade 3): ≥ 7 stools per day over Baseline; incontinence; IV fluids ≥ 24 h; interfering with ADL Colitis (Grade 3): severe abdominal pain, medical intervention indicated, peritoneal signs Grade 4: life-threatening, perforation	Withhold avelumab for Grade 3. Permanently discontinue avelumab for Grade 4 or recurrent Grade 3. 1.0 to 2.0 mg/kg/day prednisone IV or equivalent Add prophylactic antibiotics for opportunistic infections Consider lower endoscopy	If improves: Continue steroids until Grade ≤ 1, then taper over at least 1 month; resume avelumab therapy following steroids taper (for initial Grade 3). If worsens, persists > 3 to 5 days, or recurs after improvement: Add infliximab 5mg/kg (if no contraindication). Note: infliximab should not be used in cases of perforation or sepsis.
Dermatological irAEs		
Grade of Rash (NCI-CTCAE v4)	**Initial Management**	**Follow-up Management**
Grade 1 to 2 Covering ≤ 30% body surface area	Continue avelumab therapy Symptomatic therapy (for example, antihistamines, topical steroids)	If Grade 2 persists > 1 to 2 weeks or recurs: Withhold avelumab therapy Consider skin biopsy Consider 0.5-1.0 mg/kg/day prednisone or equivalent. Once improving, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume avelumab therapy following steroids taper. If worsens: Treat as Grade 3 to 4.
Grade 3 to 4 Grade 3: Covering > 30% body surface area; Grade 4: Life threatening consequences	Withhold avelumab for Grade 3. Permanently discontinue for Grade 4 or recurrent Grade 3. Consider skin biopsy Dermatology consult	If improves to Grade ≤ 1: Taper steroids over at least 1 month; resume avelumab therapy following steroids taper (for initial Grade 3)

	1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections	
Pulmonary irAEs		
Grade of Pneumonitis (NCI-CTCAE v4)	**Initial Management**	**Follow-up Management**
Grade 1 Radiographic changes only	Consider withholding avelumab therapy Monitor for symptoms every 2 to 3 days Consider Pulmonary and Infectious Disease consults	Re-assess at least every 3 weeks If worsens: Treat as Grade 2 or Grade 3 to 4.
Grade 2 Mild to moderate new symptoms	Withhold avelumab therapy Pulmonary and Infectious Disease consults Monitor symptoms daily; consider hospitalization 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections Consider bronchoscopy, lung biopsy	Re-assess every 1 to 3 days If improves: When symptoms return to Grade ≤ 1, taper steroids over at least 1 month, and then resume avelumab therapy following steroids taper If not improving after 2 weeks or worsening or for recurrent Grade 2: Treat as Grade 3 to 4.
Grade 3 to 4 Grade 3: Severe new symptoms; New/worsening hypoxia; Grade 4: Life-threatening	Permanently discontinue avelumab therapy. Hospitalize. Pulmonary and Infectious Disease consults. 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections Consider bronchoscopy, lung biopsy	If improves to Grade ≤ 1: Taper steroids over at least 1 month If not improving after 48 hours or worsening: Add additional immunosuppression (for example, infliximab, cyclophosphamide, IV immunoglobulin, or mycophenolate mofetil)
Hepatic irAEs		
Grade of Liver Test Elevation (NCI-CTCAE v4)	**Initial Management**	**Follow-up Management**
Grade 1 Grade 1 AST or ALT > ULN to 3.0 x ULN and/or Total bilirubin > ULN to 1.5 x ULN	Continue avelumab therapy	Continue liver function monitoring If worsens: Treat as Grade 2 or 3 to 4.
Grade 2 AST or ALT > 3.0 to ≤ 5 x ULN and/or total bilirubin > 1.5 to ≤ 3 x ULN	Withhold avelumab therapy Increase frequency of monitoring to every 3 days.	If returns to Grade ≤ 1: Resume routine monitoring; resume avelumab therapy. If elevation persists > 5 to 7 days or worsens: Treat as Grade 3 to 4.
Grade 3 to 4	Permanently discontinue avelumab therapy	If returns to Grade ≤ 1:

AST or ALT > 5 x ULN and/or total bilirubin > 3 x ULN	Increase frequency of monitoring to every 1 to 2 days 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections Consult gastroenterologist/ hepatologist Consider obtaining MRI/CT scan of liver and liver biopsy if clinically warranted	Taper steroids over at least 1 month If does not improve in > 3 to 5 days, worsens or rebounds: Add mycophenolate mofetil 1 gram (g) twice daily If no response within an additional 3 to 5 days, consider other immunosuppressants per local guidelines.
Renal irAEs		
Grade of Creatinine Increased (NCI-CTCAE v4)	**Initial Management**	**Follow-up Management**
Grade 1 Creatinine increased > ULN to 1.5 x ULN	Continue avelumab therapy	Continue renal function monitoring If worsens: Treat as Grade 2 to 3 or 4
Grade 2 to 3 Creatinine increased > 1.5 and ≤ 6 x ULN	Withhold avelumab therapy Increase frequency of monitoring to every 3 days 1.0 to 2.0 mg/kg/day prednisone or equivalent. Add prophylactic antibiotics for opportunistic infections Consider renal biopsy	If returns to Grade ≤1: Taper steroids over at least 1 month, and resume avelumab therapy following steroids taper. If worsens: Treat as Grade 4.
Grade 4 Creatinine increased > 6 x ULN	Permanently discontinue avelumab therapy Monitor creatinine daily 1.0 to 2.0 mg/kg/day prednisone or equivalent. Add prophylactic antibiotics for opportunistic infections Consider renal biopsy Nephrology consult	If returns to Grade ≤1: Taper steroids over at least 1 month.
Cardiac irAEs		
Myocarditis	**Initial Management**	**Follow-up Management**
New onset of cardiac signs or symptoms and / or new laboratory cardiac biomarker elevations (e.g. troponin, CK-muscle/brain, BNP) or cardiac imaging abnormalities suggestive of myocarditis.	Withhold avelumab therapy. Hospitalize. In the presence of life threatening cardiac decompensation, consider transfer to a facility experienced in advanced heart failure and arrhythmia management. Cardiology consult to establish etiology and rule-out immune-related myocarditis. Guideline based supportive treatment as per cardiology consult.* Consider myocardial biopsy if recommended per cardiology consult.	If symptoms improve and immune-related etiology is ruled out, re-start avelumab therapy. If symptoms do not improve/worsen, viral myocarditis is excluded, and immune-related etiology is suspected or confirmed following cardiology consult, manage as immune-related myocarditis.

Immune-related myocarditis	Permanently discontinue avelumab. Guideline based supportive treatment as appropriate as per cardiology consult.* 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections.	Once improving, taper steroids over at least 1 month. If no improvement or worsening, consider additional immunosuppressants (e.g. azathioprine, cyclosporine A).
*Local guidelines, or eg. European Society of Cardiology or American Heart Association guidelines European Society of Cardiology guidelines website: https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines American Heart Association guidelines website: http://professional.heart.org/professional/GuidelinesStatements/searchresults.jsp?q=&y=&t=1001		

Endocrine irAEs		
Endocrine Disorder	**Initial Management**	**Follow-up Management**
Grade 1 or Grade 2 endocrinopathies (hypothyroidism, hyperthyroidism, adrenal insufficiency, Type I diabetes mellitus)	Continue avelumab therapy Endocrinology consult if needed Start thyroid hormone replacement therapy (for hypothyroidism), anti-thyroid treatment (for hyperthyroidism), corticosteroids (for adrenal insufficiency) or insulin (for Type I diabetes mellitus) as appropriate. Rule-out secondary endocrinopathies (i.e. hypopituitarism / hypophysitis)	Continue hormone replacement/suppression and monitoring of endocrine function as appropriate.
Grade 3 or Grade 4 endocrinopathies (hypothyroidism, hyperthyroidism, adrenal insufficiency, Type I diabetes mellitus)	Withhold avelumab therapy Consider hospitalization Endocrinology consult Start thyroid hormone replacement therapy (for hypothyroidism), anti-thyroid treatment (for hyperthyroidism), corticosteroids (for adrenal insufficiency) or insulin (for Type I diabetes mellitus) as appropriate. Rule-out secondary endocrinopathies (i.e. hypopituitarism / hypophysitis)	Resume avelumab once symptoms and/or laboratory tests improve to Grade ≤ 1 (with or without hormone replacement/suppression). Continue hormone replacement/suppression and monitoring of endocrine function as appropriate.
Hypopituitarism/Hypophysitis (secondary endocrinopathies)	If secondary thyroid and/or adrenal insufficiency is confirmed (i.e. subnormal serum thyroxine with inappropriately low thyroid-stimulating hormone and/or low serum cortisol with inappropriately low adrenocorticotropic hormone): • Refer to endocrinologist for dynamic testing as indicated and measurement of other hormones (FSH, LH, GH/IGF-1, PRL, testosterone in men, estrogens in women) • Hormone replacement/suppressive therapy as appropriate	Resume avelumab once symptoms and hormone tests improve to Grade ≤ 1 (with or without hormone replacement). In addition, for hypophysitis with abnormal MRI, resume avelumab only once shrinkage of the pituitary gland on MRI/CT scan is documented. Continue hormone replacement/suppression therapy as appropriate.

	• Perform pituitary MRI and visual field examination as indicated **If hypophysitis confirmed:** • Continue avelumab if mild symptoms with normal MRI. Repeat the MRI in 1 month • Withhold avelumab if moderate, severe or life-threatening symptoms of hypophysitis and/or abnormal MRI. Consider hospitalization. Initiate corticosteroids (1 to 2 mg/kg/day prednisone or equivalent) followed by corticosteroids taper during at least 1 month. • Add prophylactic antibiotics for opportunistic infections.	
Other irAEs (not described above)		
Grade of other irAEs (NCI-CTCAE v4)	**Initial Management**	**Follow-up Management**
Grade 2 or Grade 3 clinical signs or symptoms suggestive of a potential irAE	Withhold avelumab therapy pending clinical investigation	If irAE is ruled out, manage as appropriate according to the diagnosis and consider re-starting avelumab therapy If irAE is confirmed, treat as Grade 2 or 3 irAE.
Grade 2 irAE or first occurrence of Grade 3 irAE	Withhold avelumab therapy 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections Specialty consult as appropriate	If improves to Grade ≤ 1: Taper steroids over at least 1 month and resume avelumab therapy following steroids taper.
Recurrence of same Grade 3 irAEs	Permanently discontinue avelumab therapy 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections Specialty consult as appropriate	If improves to Grade ≤ 1: Taper steroids over at least 1 month.
Grade 4	Permanently discontinue avelumab therapy 1.0 to 2.0 mg/kg/day prednisone or equivalent and/or other immunosuppressant as needed Add prophylactic antibiotics for opportunistic infections Specialty consult.	If improves to Grade ≤ 1: Taper steroids over at least 1 month
Requirement for 10 mg per day or greater prednisone or equivalent for more than 12 weeks for reasons other than hormonal replacement for adrenal insufficiency **Persistent Grade 2 or 3 irAE lasting 12 weeks or longer**	Permanently discontinue avelumab therapy Specialty consult	

Abbreviations: ADL = activities of daily living; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BNP = B-type natriuretic peptide; CK = creatine kinase; CT = computed tomography; FSH = follicle-stimulating hormone; GH = growth hormone; IGF-1 = insulin-like growth factor 1; irAE = immune-related adverse event; IV = intravenous; LH = luteinizing hormone; MRI = magnetic resonance imaging; NCI-CTCAE = National Cancer Institute-Common Terminology Criteria for Adverse Events; PRL = prolactin; ULN = upper limit of normal.

In addition, please refer to American Society of Clinical Oncology guideline for management of irAEs (November 2021).

6.5.2.7. Treatment of overdose

For an administration at a dose of 10 mg/kg an overdose is defined as any dose ≥ 10% than the calculated dose for that particular administration (phase Ib and phase II part 1). Any overdose must be recorded in the trial medication section of the eCRF.
For an administration at a flat dose of 800 mg an overdose is defined as any dose above 800 mg (phase II part 2). Any overdose must be recorded in the trial medication section of the eCRF.
There are no known symptoms of avelumab overdose to date. Treatment must be directed to symptoms.

6.6. Blinding / Unblinding

Not applicable.

6.7. Treatment compliance

6.7.1. Dispensing and accountability

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

The Investigator / Pharmacist or delegated person will maintain IMP accountability records for TG4001 as well as for avelumab, 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 visits. All used and unused IMPs will be accounted for. All unused IMP will be destroyed locally or returned to Transgene and/or its IMP supply provider, providing destruction or return certificates.

6.7.2. Assessment of compliance

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

6.8. End of treatment visit

An end of treatment visit will be performed as soon as study treatment(s) is/are stopped for whatever reason (e.g. disease progression, unacceptable toxicity, premature discontinuation due to any reason).

For any patient, as soon as one of the above situations occurs, an "end of treatment visit" will be completed in the eCRF. The Investigator will obtain all the required details and document the date and the reason for study treatment discontinuation in the eCRF "end of treatment" form.

The patient will then be followed for PFS (if applicable), safety (safety visit), subsequent therapies and survival.

6.9. 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.

6.10. Follow-up for PFS and subsequent antineoplastic therapy

In case the study treatment discontinuation is not due to progressive disease or death, the patient will be followed for PFS until progressive disease by RECIST 1.1 or until the date of last contact if the patient is lost to follow-up or withdraws consent. A CT scan or MRI of measurable and non-measurable disease must be obtained every 6 weeks until disease progression or for a period of 9 months after the start of study treatment. Beyond 9 months, the evaluations will be performed every 12 weeks until disease progression (see Section 7).
Tumor assessments will be recorded in the eCRF. All subsequent antineoplastic therapies (if applicable) must be recorded in the eCRF with start and end dates.

6.11. Safety follow-up visit

All patients (if alive) who discontinue the study treatment, will be evaluated for safety 30 days after the last study treatment administration, including those who refuse to return for a visit who will be contacted by phone. A "safety follow-up visit" will then be completed in the eCRF.
Concomitant medications and significant non-drug therapies prescribed within 30 days after the last study treatment administration will be collected.
At 90 days after the last study treatment administration, patients will be contacted by telephone to collect information on new or ongoing SAEs and treatment-related non-serious AEs. Subjects will also be asked about any further antineoplastic therapy. Corresponding pages will have to be completed in the eCRF.

6.12. Follow-up for survival and subsequent antineoplastic therapy

From the safety follow-up visit or last PFS follow-up visit, the patient will be followed every 3 months for survival until death or the date of last contact if the patient is lost to follow-up or withdraws consent. All subsequent antineoplastic therapies (if applicable) must be recorded in the eCRF with start and end dates.

7 STUDY VISITS AND PROCEDURES

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

7.1. Evaluations description

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

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

Demography
- Date of birth, gender
- Child bearing potential status
- Smoking habits
- Alcohol consumption

History of studied disease
- Date of diagnosis and stage at diagnosis
- Histology type
- HPV status
- Prior antineoplastic therapy

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

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

Clinical evaluation
- Physical examination of the major organ system, including vital signs (body temperature, pulse and blood pressure), oxygen saturation by pulse oximetry on room air (only for phase II part 2) and weight
- Height will be collected only at baseline.
- PS on ECOG scale (Appendix I)

Cardiac evaluation
- Electrocardiogram (12 leads)
- In case of potential symptoms of myocarditis / pericarditis during study treatment (such as chest pain, shortness of breath, heart palpitations, and reduced tolerance to exercise), cardiac laboratory analyses (e.g. creatinine kinase-mycardial band, troponin), ECG and

echocardiography (or MUGA scan) will be requested. If abnormal findings indicate possible myo- or pericarditis, the patient will be referred to consulting a cardiologist.

Safety assessment
- All SAEs from ICF signature
- New AEs including worsening of pre-existing medical condition or signs/symptoms (e.g. worsening of arterial hypertension, worsening of pain) from start of study treatment
- Follow-up of all ongoing AEs

Collection of concomitant medications and significant non-drug therapies

Laboratory evaluation (blood analyses)
- Hematology: complete blood count including Red Blood Cells, hemoglobin, hematocrit, WBC and differential, platelets
- Biochemistry analysis including: ALT, AST, LDH, alkaline phosphatases, total bilirubin, lipase, amylase, serum protein and serum albumin, electrolytes (Na^+, K^+, Cl^-, Ca^{++}), glucose
- Renal tests: creatinine (and calculated creatinine clearance at baseline)
- Free T4, TSH
- HIV and HCV serology, detection of antigen HBs at baseline
- Pregnancy test (for women of childbearing potential)

Immunology and translational research on blood and tumor biopsy samples
- [redacted]

Tumor evaluation:
- All measurable and non-measurable lesions as identified at baseline must be assessed using the same methods and techniques over the whole study period. Tumor evaluation will be assessed based on RECIST version 1.1. Additional CT or MRI may be performed in case of suspected new site of metastases.
- The tumor assessment must be performed every 6 weeks for the first 9 months from treatment start and every 12 weeks thereafter, with a time window allowed of +/-7 days (except for baseline). As far as possible, tumor assessment should be performed prior to the visit. The first CT scan or MRI post-baseline must be performed after at least 5 weeks of treatment.

Further antineoplastic therapies
All subsequent anti-neoplastic therapies given after the patient discontinued the study treatment period will be collected in the eCRF.

7.2. Baseline

The following evaluations must be performed within 21 days prior to the initiation of treatment:
- Inclusion/exclusion criteria check

- Physical examination of the major organ system, including vital signs, weight and height
- PS on ECOG scale
- Demography
- History of studied disease (including prior antineoplastic treatments)
- Relevant medical history / current medical conditions and signs and symptoms
- Serious adverse events reporting (from the date of signature of the ICF)
- Concomitant medications and significant non-drug therapies collection and medications administered during the month prior to start of study treatment
- Tumor sample on biopsy (mandatory for phase Ib and phase II part 1; mandatory only for patients with accessible lesions in phase II part 2)
- HPV status
- HIV and HCV serology, detection of antigen HBs for phase II part 2
- Tumor evaluation
    - by preferably CT (or MRI) of the head and neck, chest, abdomen and all other known sites of disease (e.g. pelvis, if applicable) and other established assessments of tumor burden if CT / MRI imaging is insufficient for the individual patient. In case of bone pain, an adequate radiological and/or isotopical exploration is to be performed to research metastases

The following evaluations must be performed within 7 days prior to the initiation of treatment, within 3 days prior to randomization for phase II part 2:
- Inclusion/exclusion criteria check
- 12-leads Electrocardiogram
- Pulse oximetry on room air only for phase II part 2
- Blood analyses:
    - Hematology, biochemistry, creatinine,
    - Free T4, TSH
    - HIV and HCV serology, detection of antigen HBs only for phase Ib and phase II part1
    - Pregnancy test for women of childbearing potential
    - Blood sample collection for immunomonitoring

7.3. During the study treatment period

The time windows allowed for the visits are:
- +/- 1 day from Day 1 to Day 36
- - 3/+1 days for the further study treatment visits beyond Day 36

Tumor evaluation must be performed every 6 weeks for the first 9 months after treatment start and every 12 weeks thereafter, with a time window allowed of +/-7 days.

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

From Day 1 to Day 36
- Physical examination* including vital signs and body weight on Days 1, 8, 15, 22, 29, 36

- Performance status* on Days 1, 15, 29
- Adverse events reporting on Days 1, 8, 15, 22, 29, 36
- Concomitant medications and non-drug therapies collection on Days 1, 8, 15, 22, 29, 36
- Hematology* on Days 1 (not for phase II part 2), 8, 15, 22, 29, and 36
- Biochemistry*, creatinine* on Days 1 (not for phase II part 2), 8, 15, 22, 29, and 36
- TSH on Day 36*
- Blood pregnancy test* for women of childbearing potential on Day 36
- Type I and II HLA on Day 1* (not for phase II part 2)
- Blood sample collection for immunomonitoring* on Days 1, 8 and D15 (D15 for phase II part 2 only); on Day 1, 6 hours post-dose for patients randomized in the combination arm and treated with TG4001 (for phase II part 2 only)
- Inclusion/exclusion criteria check on Day 1
- Randomization on Day 1 for phase II part 2
- TG4001 SC administration once a week on Days 1, 8, 15, 22, 29, and 36 (phase Ib, phase II part 1 and phase II part 2 combination arm)
- Avelumab IV administration once every 2 weeks starting on Day 8 (D22 and D36) for all patients

Beyond Day 36 up to Month 6, Day 204

- Physical examination* including vital signs, body weight and performance status every 2 weeks
- Adverse events reporting every 2 weeks
- Concomitant medications and non-drug therapies collection every 2 weeks
- Hematology* every 2 weeks
- Biochemistry*, creatinine* every 2 weeks
- TSH* every 6 weeks
- Blood pregnancy test* for women of childbearing potential every 6 weeks
- Tumor evaluation: The first CT scan or MRI post-baseline must be performed on Day 43, but not before 5 weeks after study treatment start, then every 6 weeks up to Month 6 (D204)
- Blood sample collection for immunomonitoring*: on Days 43 and 85 and Month 6 (D204)
- Tumor sample on biopsy: on Day 43 (mandatory) and Day 85 (unless it is unsafe or undesirable) for phase Ib and phase II part 1
- Tumor sample on biopsy on Day 85 (mandatory for patients with accessible lesions on Day 85 for phase II part 2)
- TG4001 SC administration every 2 weeks (phase Ib, phase II part 1 and phase II part 2 combination arm)
- Avelumab IV infusion every 2 weeks for all patients

From Day 204 until discontinuation of study treatment

- Physical examination* including vital signs, body weight and performance status every 2 weeks
- Adverse events reporting every 2 weeks
- Concomitant medications and non-drug therapies collection every 2 weeks
- Hematology* every 6 weeks
- Biochemistry*, creatinine* every 6 weeks
- TSH* every 6 weeks
- Blood pregnancy test* for women of childbearing potential every 6 weeks
- TG4001 SC administration every 12 weeks (phase Ib, phase II part 1 and phase II part 2 combination arm)

- Avelumab IV infusion every 2 weeks for all patients
- Tumor evaluation: every 6 weeks up to 9 months then every 12 weeks
- Blood sample collection for immunomonitoring*: at Month 12 and Month 24 for phase Ib, phase II part 1
- Blood sample collection for immunomonitoring*: at Month 9 (D288) and Month 12 (D372) for phase II part 2
- Tumor sample on biopsy at Month 9 (D288) for phase II part 2 in patients with accessible lesions at Month 9

*prior to study treatment(s) administration

Tumor sample on biopsy at the time of progressive disease for phase II part 2 in patients with accessible lesions at the time of progressive disease.

7.4. End of treatment visit

This visit should be completed as soon as the patient is discontinued from study treatment. The following evaluations will be conducted:
- Clinical evaluation, including vital signs, performance status and body weight
- 12-lead Electrocardiogram
- Adverse events reporting
- Concomitant medications and non-drug therapies collection
- Further antineoplastic therapies
- Hematology
- Biochemistry, creatinine
- Free T4, TSH
- Blood pregnancy test for women of childbearing potential
- Tumor sample on biopsy at the time of progressive disease for phase II part 2 in patients with accessible lesions at the time of progressive disease

7.5. Safety follow-up visit

This visit should occur 30 days after the last study treatment administration. The following evaluations will be conducted:
- Clinical evaluation including vital signs and body weight
- Adverse events reporting
- Concomitant medications and non-drug therapies collection administered within 30 days after the last study treatment administration
- Further antineoplastic therapies
- Hematology
- Biochemistry, creatinine
- Blood pregnancy test for women of childbearing potential

7.6. Safety follow-up phone call

At 90 days after the last administration of study treatment, patients will be contacted by telephone to collect information on new or ongoing SAEs and treatment-related non-serious AEs. Patients will also be asked about any further antineoplastic therapy.

7.7. Post-study follow-up

PFS-FU visit:
For patients who stopped the study treatment for a reason other than progressive disease based on RECIST 1.1 (e.g., AE), tumor evaluation should be obtained every 6 weeks until disease progression by RECIST 1.1 or for a period of 9 months after the start of study treatment. Beyond 9 months, the evaluations will be performed every 12 weeks until disease progression by RECIST 1.1. Tumor measurements will be recorded in the eCRF with the date and method of tumor assessment and the response evaluation in PFS-FU visit. This follow-up should be done even if patients start subsequent antineoplastic therapies.
Further antineoplastic therapies, given after end of study treatment will be reported in the eCRF with the start date and end date.
Tumor sample on biopsy at the time of progressive disease is to be performed for phase II part 2 in patients with accessible lesions at the time of progressive disease.

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

7.8. Biomarkers and Translational Research

As biomarker research is constantly evolving, the selection of markers with the highest specificity and relevance to treatment effect may change.

7.8.1. Immunomonitoring

Blood samples

Blood samples will be collected at baseline, on Day 1, Day 8, Day 43, Day 85, at Month 6, Month 12 and Month 24 (prior to study treatment administrations) for phase Ib and phase II part 1.
For phase II part 2 blood samples will be collected at baseline, on Day 1, Day 8, Day 15, Day 43, Day 85, at Month 6 (D204), Month 9 (D288) and Month 12 (D372) (prior to study treatment administrations) and for patients in the combination arm treated with TG4001 on Day 1 6 hours post-dose.
The following samples will be collected to assess:
Phase Ib and phase II part 1:

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

[redacted]

Phase II part 2:

- [redacted]

Tumor samples

For phase Ib and phase II part 1 tumor samples will be collected at baseline, on Day 43 and on Day 85 (unless it is unsafe or undesirable). Of note, availability of tumor material from fresh biopsies will be a prerequisite at baseline for all patients to be enrolled in the study.
For phase II part 2 and to ensure an adequate number of paired samples to perform meaningful analyses to support objectives of translational research patients with accessible lesions should undergo biopsy per protocol, i.e. tumor samples will be collected at baseline, and for patients under study treatment on Day 85, at Month 9 (D288) and at time of progressive disease.

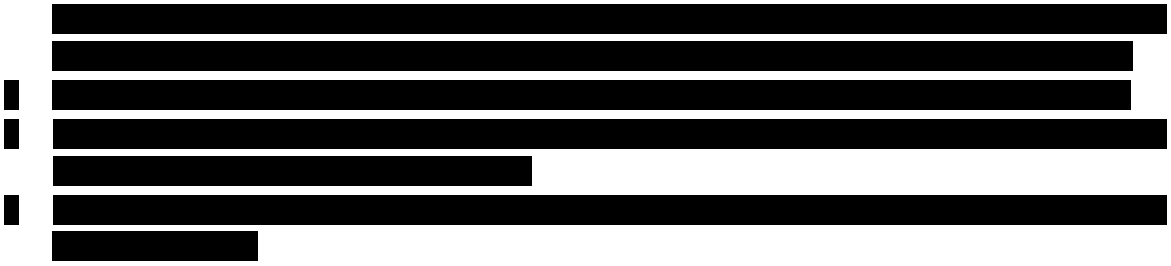
For cases when an on-treatment biopsy is required but not feasible due to complete response or not deemed safe by the investigator, these cases must be clearly documented in the medical record.

Tissue collection: Endoscopic biopsies, core needle biopsies, excisional biopsies, punch biopsies and surgical specimens are suited. Material from bone biopsies is not suited. Fine needle aspiration biopsies are not suited. The most recent biopsy or surgical specimen is required. The biopsy or surgical specimen must have been collected **within 21 days** prior to the first IMP administration at baseline, if applicable.

For each biopsy (20 mm 18G biopsies) 3 to 4 tissue fragments will be collected at each timepoint.

The following assessment will be considered:

- [redacted]



7.8.2. Handling of biological and tissue samples

Details on the calendar/procedures for handling of samples for immunological tests and tumor biomarkers are provided in a separate Manual.

8 ASSESSMENT OF EFFICACY

- Assessment of efficacy according to RECIST VERSION 1.1

The assessment of efficacy is based on Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 (Eisenhauer E.A. *et al.*, 2009).

For efficacy evaluation, patients must have at least one measurable lesion by CT/MRI scan (minimum size not less than 10 mm) at baseline and a post-baseline evaluable CT-scan at week 6 after start of study treatment with a best overall response assessment different from 'Unknown' according to RECIST evaluation criteria. However, if a patient progressed or died due to underlying cancer before scheduled scan 6 weeks after study treatment start could be performed, the patient will still be included in the evaluable population.
Tumor assessment will be performed LOCALLY according to investigator's assessment every 6 weeks from the start of study treatment until disease progression or for a period of 9 months after start of study treatment, whichever occurs first. Beyond 9 months after start of study treatment, the evaluations will be performed every 12 weeks until disease progression. The same schedule of tumor evaluation will be applied for patients who stopped the study treatment for any reason other than progressive disease.
For all patients, tumor response assessment will be performed by preferably CT (or MRI) of the head and neck, chest, abdomen and all other known sites of disease (e.g. pelvis, if applicable) and other established assessments of tumor burden if CT/MRI imaging is insufficient for the individual patient. In case of bone pain, an adequate radiological and/or isotopical exploration is to be performed to research metastases. All the scans performed at baseline and other imaging performed as clinically required (other supportive imaging) need to be repeated at subsequent visits.

Per RECIST, the imaging method used at baseline should be matched 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. However, a change in the use of contrast does not necessarily represent a change in precision since for many tumor types, the assessment can be done despite the fact that contrast has changed.

Therefore, in the calculation of overall response, the methods/modalities listed under the same bullet point will be considered the same:
- 'CT with contrast' and 'CT without contrast'
- 'Spiral CT with contrast' and 'spiral CT without contrast'
- 'MRI with contrast', 'MRI without contrast', 'Dynamic contrast – enhanced MRI' and 'GD-MRI'

In rare instances when radiological assessment is not possible to determine the progression (e.g., carcinomatous meningitis), other methods may be used (e.g., pathology, cytology).

For patients with a global deterioration of health status requiring discontinuation of study treatment without documented progression, every effort should be made to document objective progression even after discontinuation of treatment.

For phase Ib and phase II part 1 the duration of observation for efficacy lasts from the date of the first study treatment administration to the date of documented progression.

For phase II part 2 the duration of observation for efficacy lasts from the date of randomization to the date of documented progression or death whichever occurs first.

Data of locally performed tumor evaluations will be used for efficacy assessment. For phase II part 2 and to allow independent central review, anonymized copies of CT/MRI will be collected.

To assess objective response, the tumor burden at baseline will be estimated and used for comparison with subsequent measurements. At baseline, tumor lesions will be categorized in target and non-target lesions as described in Appendix IV**.**

Definitions of measurability of lesions and criteria for response are detailed in Appendix IV.
Results for these evaluations will be recorded with as much specificity as possible so that pre- and post-treatment results will provide the best opportunity for evaluating tumor response.
Any CR or PR should be confirmed as described in Appendix IV**.** In the case of a PR or CR, a confirmatory CT or MRI scan must be done no sooner than 28 days (preferably at the scheduled 6-week interval).

9 ASSESSMENT OF SAFETY

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

The safety assessments will be performed according to the schedule of assessment (refer to Appendix III).

9.1. 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 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 Event (AE)
An AE for the purposes of this protocol is a medical occurrence or deterioration of a pre-existing medical condition occurring after signing the informed consent and even if the event is not considered to be related to the study treatment(s).

Preexisting medical conditions (other than the condition being studied) judged by the investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period.

Adverse reaction (AR):
All noxious and unintended responses to a medicinal study product (TG4001 or avelumab) related to any dose or to a study specific procedure.

Laboratory abnormality
A laboratory abnormality is reported as an AE if it is out of range, considered by the Investigator as clinically significant (i.e. with clinical manifestations or requiring treatment or clinical management).

Other significant abnormalities
Any significant worsening noted during interim or final physical examinations, electrocardiograms, x-rays, and any other potential safety assessments, whether or not these procedures are required by the protocol, should also be recorded as a non serious or serious AE, as appropriate, and reported accordingly.

Other significant adverse events
Any events and any laboratory abnormalities that led to an intervention, including withdrawal / dose reduction of IMP or significant additional concomitant therapy other than those reported as SAE, and that are considered by Transgene or the Investigator to be of special interest because of clinical importance.
Serious Adverse Event (SAE) / Serious Adverse Reaction (SAR) / Suspected Unexpected Serious Adverse Reaction (SUSAR):
Any untoward medical occurrence that at any dose:
- results in death,
  The death of a patient is not per se an AE but an outcome. “Death” should be considered as a SAE only in case of “unexplained death” when no cause is identified. The event that resulted in a fatal outcome should be determined and reported as the SAE.
- is life threatening,
  This term refers to an event in which the patient was at immediate risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it was more severe.
- requires inpatient hospitalization or prolongation of existing hospitalization,
  The hospitalization is an action taken to treat the event. It should not be reported as a SAE, but the AE leading to hospitalization.
  Hospitalization for diagnosis or planned treatment procedures without AE should not be reported as a SAE.
- results in persistent or significant disability/incapacity,

The disability is a substantial disruption of a person's ability to conduct normal life functions.
- is a congenital anomaly/birth defect,
  The "congenital anomaly/birth defect" relates to events occurring to babies born after their mother and/or father have taken drug at the time of pregnancy confirmation or during pregnancy.
- is a significant medical event that may not be immediately life threatening or result in death or hospitalization, but may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above (example: intensive treatment in an emergency room or at home for bronchospasm, convulsions that do not result in hospitalization…). Medical and scientific judgement should be exercised in deciding whether some events should be considered as serious because their quick reporting to Transgene may be of interest for the overall conduct of the study.

Note:

- For SAR and SUSAR there is a reasonable relationship with an investigational medicinal product or a study procedure.

The following situations do not need to be reported as SAEs:
1. Elective hospitalization for pre-existing conditions that have not been exacerbated by trial treatment.
2. A hospitalization which was planned before the patient consented for study participation and where admission did not take longer than anticipated.
3. A hospitalization planned for protocol related treatment or protocol related procedure as per institutional standard timelines.
4. Social and/or convenience admission to a hospital.
5. Medical or surgical procedure (e.g. endoscopy, appendectomy); the condition that leads to the procedure is an (S)AE.
6. Situations where an untoward medical occurrence did not occur (palliative care, rehabilitation, overdose without occurrence of an adverse event).
7. 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.
Adverse reactions will be considered as expected, unless nature, severity, specificity, or outcome is not consistent with the one previously observed. Adverse reactions with observed fatal outcome in the avelumab clinical development programs included: immune-related pneumonitis, immune-related hepatitis, immune-related myocarditis, immune-related pancreatitis.
Expected adverse reactions are those listed or characterized in the reference document (i.e. IB).
Unexpected adverse reactions are those not listed in the reference document or not identified.
Fatal and life-threatening adverse reactions are always to be reported as unexpected.

Overdose
Avelumab:
- For an administration at a dose of 10 mg/kg an overdose is defined as any dose ≥ 10% than the calculated dose for that particular administration (phase Ib and phase II part 1).

- For an administration at a flat dose of 800 mg an overdose is defined as any dose above 800 mg (phase II part 2).

TG4001:

- an overdose is an administration at a higher dose than the highest dose already tested (i.e. 5 x 10^7 PFU) or higher than the dose planned according to the schedule of administration.

Overdose must not be considered as an AE. However, if the patient experiences an AE/SAE related to this overdose, it should be reported as such.

Verbatim

The terms or the English equivalent of the terms as reported by the Investigator on the eCRF pages and on the SAE form to describe an event.

9.2. Time period for collection

The study period during which all Aes and SAEs must be reported begins after informed consent is obtained and ends 30 days following the last administration of any study treatment (safety follow up visit). If the safety follow-up visit is performed less than 30 days after the last IMP administration, any AE / SAE occurring between the safety follow-up visit until 30 days after last study treatment administration will be considered as AE / SAE and notified to Transgene, regardless of their relationship to IMP(s).

After this period, and until day 90 after last administration of study treatment (i.e. until safety follow-up phone call) investigators should report treatment-related non-serious AE and all SAEs. Ongoing SAEs at the 90-day safety follow-up phone call must be followed up until stabilization or until the outcome is known, unless the patient is documented as "lost to follow up".

SAEs occurring more than 90 days after administration of the last dose of any study treatments, and evaluated by the investigator as related to the IMP(s) should be collected and reported to the sponsor indefinitely even after study closure. These will however not be reported in the eCRF after Database lock.

If an Adverse Event occurs during the screening period (i.e., after ICF signature and before start of study treatment), it will be recorded either on a "Medical history/ current conditions" page for an identified syndrome (e.g., pneumonia) or on a "Signs and symptoms" page for symptoms with no associated syndrome (e.g., diarrhoea).

From start of study treatment, AEs will be recorded on an "AE" page. In case of worsening of a medical condition which started before start of study treatment, an AE page will be completed using a verbatim starting by "worsening of…".

9.3. Adverse event / Serious adverse event management

9.3.1. Data collection

Reporting in eCRF

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

- nature of the event with self-explanatory and concise medical terminology (if possible indicate a diagnosis or syndrome instead of symptoms),

- date of onset and date of end (i.e. actual dates when the event starts and is resolved rather than dates when the Investigator is informed),
- intensity,
- evaluation of seriousness,
- relation to study treatment (separate evaluation for TG4001, avelumab), or to study procedures,
- action taken regarding the study treatment (separately for TG4001, avelumab),
- 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 4.03 dated 14 June 2010 for phase Ib and phase II part 1, version 5.0 dated 27 November 2017 for phase II part 2), which will be provided to the Investigators.
Should an event be missing in the CTCAE, the following 5-point scale is to be used:

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

The correspondence between the two scales is as follows:

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

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

Relationship to the IMP(s)
The relationship to the IMPs (separate evaluation for TG4001 and avelumab) of each AE/SAE will be evaluated by the Investigator with the "global introspection" method using the following levels:
● **Not related:** the temporal relationship of the clinical event to the administration of avelumab and TG4001 (separate evaluation) makes a causal relationship unlikely; and other drugs, therapeutic interventions or underlying conditions provide a sufficient explanation for the observed event.
● **Related:** the temporal relationship of the clinical event to the administration of avelumab and TG4001 (separate evaluation) makes a causal relationship possible; and other drugs, therapeutic

interventions or underlying conditions do not provide a sufficient explanation for the observed event. A clear-cut temporal association with improvement on cessation of the study drug or recurrence upon rechallenge may also be observed.

Outcome
The outcome is rated as follows:
- recovered,
- not recovered,
- recovered with sequelae,
- fatal,
- unknown.

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

Action taken regarding TG4001/avelumab
Action taken will be provided separately for each study treatment.

- None: TG4001/avelumab administration continues as planned in the protocol, or has not yet been administered and no action is planned
- Cancelled: TG4001/avelumab administration following the occurrence of the event is cancelled
- Stopped: TG4001/avelumab is definitively stopped
- Not applicable: TG4001/avelumab administration is already stopped

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)

An AE/SAE requiring therapy must be treated with recognized standards of medical care to protect the health and well-being of the patient. Any medication or non-drug therapy given will be reported on the eCRF pages dedicated to the collection of concomitant medications.

9.3.2. Follow-up

Once an AE is detected, it must be proactively followed until its resolution or 30 days after the last study treatment administration. After this visit and until day 90 after last administration of study treatment non-serious treatment-related Aes and all SAEs have to be followed. Ongoing SAEs at the 90-day safety follow-up phone call must be followed up until stabilization or until the outcome is known, unless the patient is documented as "lost to follow up".
In addition, any significant AE as recommended by Transgene must be followed until it is resolved or stable or returned to baseline status.

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) and is thought to be related to the study treatment.

9.3.3. Documentation

All Aes/SAEs will be reported in the source document with at least the nature, the date of onset and end, the causality, and the treatment (if applicable).
Copies of SAE form will be filed in the Investigator Site File along with copies of any correspondence with the Independent Ethics Committee (IEC). The Investigator Site File will also include copies of notification letters and/or faxes with forms sent to Health Authorities and Gene Therapy Bodies if appropriate.

9.4. Reporting of DLTs during the phase Ib of the study

During the phase Ib of the study, Transgene must be informed **immediately by the center** of the occurrence of any DLT occurring within the first 4 weeks of study treatments in all patients included in the phase Ib of the study.

The following action must be undertaken by the investigators on occurrence of any AE that fulfill the criteria for a DLT:

- The Investigator must inform Transgene and duly complete the appropriate eCRF form even if the data are incomplete or if it is obvious that more data will be needed.
- The following information must be present: description of the AE, intensity and relationship to study drugs, date of onset, status at the time of reporting, action taken on study treatments.
- Transgene may request any additional information (copies of reports, lab tests etc.,) to the center in order to better assess the DLT.

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

Reporting to Transgene
Any SAE occurring during the course of the study (from the signature of ICF and up to 90 days after last study treatment administration whether or not related to the IMP(s) MUST be reported to Transgene. The Investigator must complete and fax a “Serious Adverse Event Form” to Transgene within a maximum of 24 hours of occurrence or knowledge of the event.

	France
	Pharmacovigilance Physician
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

An Investigator 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 IMP(s). The signed form must be faxed to Transgene immediately.

The SAE form should be completed in English.

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

Notification to Regulatory Authorities / Gene Therapy Bodies / Ethics Committee
Transgene will be solely responsible for regulatory reporting of SUSAR and any other SAEs to Regulatory Authorities, IEC(s) / IRB(s) and Gene Therapy Bodies as per local regulations.

Transgene will also be responsible for reporting SAEs to Ethics Committees (Ecs) and Investigators in accordance with local regulations/requirements.

In case of SUSAR, Transgene will inform all investigators involved in any study with TG4001 that such an event has been reported.

The Investigator is responsible for informing IRB(s) of SUSARs, any other SAEs and any follow-up information as per local regulations.

Transgene 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).

Transgene will transmit SAEs to Merck KgaA and Pfizer for **all** initial or follow-up reports and any safety information originating from this Study within the timelines and formats specified in and in accordance with the Safety Data Exchange Agreement.

Merck KgaA / EMD Serono and Pfizer will each cross-report SUSARs from the Study associated with avelumab to national Regulatory Authorities of countries where they are Sponsors of clinical trials with avelumab and where such cross-reporting is required per applicable regulations.

9.6. Special situations

Any clinical AE with severity of Grade 4 must be reported as an SAE; however, a laboratory abnormality of Grade 4, such as anemia or neutropenia, is considered serious only if the condition meets one of the serious criteria described above (see Section 9.1).

Pregnancy
Study treatments must be discontinued immediately when a patient becomes pregnant.

The occurrence of a pregnancy must be reported to Transgene by the Investigator using a "Pregnancy form":

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

Pregnancies have to be followed up to the completion or termination of the pregnancy, collecting information about the pregnancy and knowledge of the new-born medical status. Pregnancy outcomes must be collected for the female partners of any males who took the IMP(s). Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

Pregnancy itself is not considered as an AE. However, any problem met during the pregnancy should be reported as an AE or a SAE. Spontaneous or induced abortions as well as ectopic pregnancy should be considered as serious. Similarly, any congenital anomaly/birth defect in a child born to a female patient exposed to avelumab and/or TG4001 should be reported as an SAE.
The time period for collecting new pregnancies is from the first administration of the IMP(s) up to 3 months after the last study treatment administration.

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

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

Laboratory tests results will be recorded on the laboratory results Forms of the eCRF.
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 in 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 treatments (e.g. cancellation or permanent discontinuation)
- requiring corrective treatment or clinical management

Clinically relevant abnormal laboratory or tests results will be reported by the Investigator and followed until normal or stabilization, or the safety follow-up visit if they are not related to study treatments. They should be recorded on the AE eCRF pages under the signs, symptoms, or diagnosis associated with them.

Clinically relevant abnormal findings in vital signs measurements or physical examinations or ECGs will be reported as Aes or SAEs by the Investigator.

10 STATISTICAL METHODS PLANNED AND SAMPLE SIZE

10.1. Data sets analyzed

Safety population (SAF): all patients included and who received any amount of study treatment will be included in the SAF. Any patient who is assigned a patient number, but does not receive any study treatment will not be included in the SAF.

Evaluable patients' population for DLT determination (DLT population): For the phase Ib of the study, the purpose being to evaluate the safety of the combination, patients must complete the first 4 weeks of the combination or discontinue before the end of the 4 weeks for a DLT to be evaluable for the primary objective of the phase Ib of the study. Patients who are not evaluable for phase Ib safety analysis or are withdrawn for other reasons than toxicity, will be replaced.
Patients must receive at least one dose of both IMPs (TG4001 + avelumab) and have at least one valid post-baseline safety assessment. The statement that a patient had no AE, on the Adverse Events eCRF page, constitutes a valid safety assessment. The occurrence of death also constitutes a valid safety assessment.

Phase II part 1: Evaluable patients' population for tumor response (evaluable per protocol population, EPP): consists of all included patients who were dosed with both IMPs (TG4001 + avelumab) and have at least one baseline and one post-baseline evaluable CT-scan at week 6 after start of study treatment with a best overall response assessment different from 'Unknown' according to RECIST 1.1 evaluation criteria. However, if a patient progressed or died due to underlying cancer before scheduled scan 6 weeks after study treatment start could be performed, the patient will still be included in the evaluable population. Any patient who has a major inclusion/exclusion violation, major dosing violation, or major protocol conduct violation will be excluded from the EPP. Major dosing violation is considered when minimum exposure is not met defined as at least 6 TG4001 injections and 3 avelumab administrations except if patient has progressed or died due to underlying disease before or at the first evaluation. Due to potential abscopal effect when associating radiotherapy and immunotherapy, patients receiving palliative radiotherapy will be analyzed separately. Whatever the reason for withdrawal, except for disease progression and death due to underlying cancer before scheduled scan 6 weeks after study treatment start could be performed, patients considered as non-evaluable for tumor response will be replaced.

Phase II part 2: Full Set Analysis (FAS) will be the primary set for efficacy analyses. It consists of all randomized patients who were administered at least one dose of IMP(s) according to the treatment allocated at randomization.
Evaluable patients' population per protocol (evaluable per protocol population, EPP): consists of all patients from the FAS without any major inclusion/exclusion violation, major dosing violation as defined for phase II part 1, or major protocol conduct violation who were dosed with IMP(s) according to the treatment allocated at randomization and have at least one baseline and one post-baseline evaluable CT-scan at week 6 after start of study treatment with a best overall response assessment different from 'Unknown' according to RECIST 1.1 evaluation criteria.

10.2. Determination of sample size

In the phase Ib part of the study, 3 to 6 evaluable patients will be included and treated at each selected dose level. Should the results of this first part of the study show an acceptable safety profile of the combination, accrual in the phase II part of the study will start.

Phase II part 1: A Simon's two-stage design was used. The null hypothesis for response rate (H0) is set at 10%, corresponding to the response rate observed in second line patients, the alternative hypothesis of efficacy is set at HA = 25%, the type I error α is set at 5%, the type II error β is set at 20% (power = 80%). Under these hypotheses and applying a Minimax two-stage Simon design, enough patients will be treated to obtain 22 evaluable patients in the first stage. If at least 3/22 patients are considered responders, the enrolment will be continued, otherwise it will be stopped. In the initial design and at the second stage enough patients should have been treated to obtain at least 40 evaluable patients in total. The study would have been considered positive with at least 8/40 responders. With a hierarchical strategy on the final analysis, a subgroup analysis performed in oropharyngeal SCCHN patients and with a null hypothesis for response rate (H0) set at 10% and the alternative hypothesis of efficacy set at HA = 35%, 18 oropharyngeal SCCHN patients would have been needed to reach a power of 81% and actual alpha at 2.8%. This analysis would have been considered positive with at least 5 responders among the 18 SCCHN patients. The second stage of the Simon's design has not been done following the decision to exclude oropharyngeal SCCHN and to change to a randomized controlled two-arms study (phase II part 2).
The final ORR analysis will be performed 24 weeks after last patient-in.

Phase II part 2:
The primary objective is to compare the PFS of TG4001 in combination with avelumab vs avelumab alone in patients with R/M HPV-16 positive advanced malignancies and without liver metastases at baseline. PFS will be evaluated based on RECIST 1.1.

Patients without liver metastases at baseline:
Efficacy will be evaluated by comparing the PFS between monotreatment arm (avelumab alone) and combination arm (TG4001 and avelumab) with an adaptive approach.

With an one-sided type I error α at 5%, 76 events are needed to reach a power of 95%. This should happen after around 80 patients enrolled (40 patients per arm). Assuming 5% drop-out in each arm, 84 patients will be randomized.

Due to the uncertainty on the true treatment effect and data variability, and to reduce the risk of running an underpowered study, it is considered appropriate to adopt an adaptive approach for the sample size. This will offer a mechanism to adjust the sample size in response to treatment effect and variability estimates seen at a planned interim analysis.

The interim analysis will be conducted after 37 events which will occur approximately 16 months after the inclusion of the first patient. At that time, it is estimated to have around 50 patients enrolled. Based on the results of the interim analysis, sample size re-estimation will be performed. According to simulations on CHW (Cui, Hung and Wand) approach using EAST 6.5., the proposal is as follows:

- Start with a fixed sample size calculation based on the primary endpoint.
- Based on the interim analysis result maintain or increase the sample size in order to obtain the desired power of 90%.

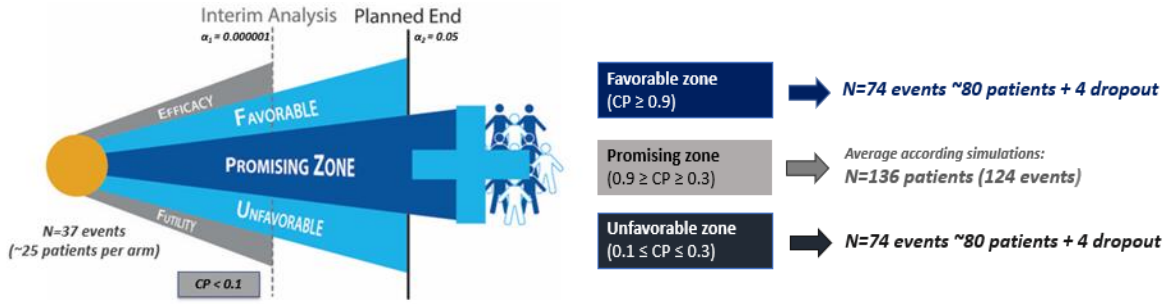
Conditional power will be calculated based on the interim results. Should the conditional power be in the favorable or unfavorable range the sample size and the number of events will not be adjusted and will remain at the initial sample size. Conditional power falling into the promising zone will have a sample and events increase. The regions and their implications on sample size are detailed below:

- **Favorable:** If the interim results are sufficiently favorable corresponding to a CP of more than 90%, final analysis will be performed on 74 PFS events corresponding to an estimated sample size of 80 evaluable patients. This will occur approximately 26 months after the inclusion of the first patient.

- **Promising zone:** If the interim results are equivalent to a CP between 90% and 30%, the sample size will be recalculated according to the median PFS observed in the two arms with a cap of 2 times the initial events.

- **Unfavorable zone:** If the interim results are not favorable corresponding to a CP between 30% and 10%, the trial may continue up to the initial sample size of 80 patients or could be stopped

- **Futility:** If the interim results are futile corresponding to a CP lower than 10%, the trial will be stopped for futility at the interim analysis.



Assuming an uniform enrollment with 3 patients per month and based on simulations, in case of sample size reassessment, an average of 124 events would be needed (corresponding to 136 patients). Assuming a 5% lost to follow-up or withdrawal of consent rate, a total of 142 patients should be randomized to the 2 treatment arms in a 1:1 ratio (71 patients in each treatment arm). Based on the aforementioned assumptions, a power of 70% is expected using an unstratified log-rank test at a 1-sided cumulative 5% level of significance. [redacted]

Full details of the adaptive method for sample size specified above will be given in the Statistical Analysis Plan (SAP).

Patients with liver metastases at baseline:

A sample size of [redacted] is planned.

[redacted]

10.3. Study endpoints

10.3.1. Primary endpoint

Phase Ib: Dose limiting toxicities defined as follows:

- Grade ≥ 3 drug related adverse event. However, fatigue, nausea/vomiting adequately treated with anti-emetics, endocrinopathies adequately controlled with one physiologic hormone replacement, skin toxicity and single laboratory values out of normal range without any clinical correlate, asymptomatic grade ≥3 lipase or amylase elevation, tumor flare defined as local pain, irritation, or rash localized at sites of known or suspected tumor or a transient Grade 3 infusion adverse event are excluded
- Liver function test abnormality:
  - AST or ALT > 5 x ULN
  - Total bilirubin > 3 x ULN
  - Concurrent AST or ALT > 3 x ULN and total bilirubin > 2 x ULN
- Drug related adverse event requiring treatment interruption for more than 2 weeks

The RP2D will be defined as the dose at which less than 33% of the patients (0 or 1 patient among 6 evaluable patients) experience a DLT.

Dose limiting toxicities will be assessed during the first 4 weeks of the combination and will be graded according to NCI CTCAE version 4.03.

To be evaluable for the primary objective of the phase Ib of the study, patients must complete the first 4 weeks of the combination or discontinue before the end of the 4 weeks for a DLT. Patients must receive at least one dose of both IMPs (TG4001 + avelumab) and have at least one valid post-baseline safety assessment. The statement that a patient had no AE, on the Adverse Events eCRF page, constitutes a valid safety assessment. The occurrence of death also constitutes a valid safety assessment. Patients who are not evaluable for phase Ib safety analysis or are withdrawn for other reasons than toxicity, will be replaced.
The DLT population will be the primary population for analyses. These analyses will be repeated on the SAF.

Phase II part 1: The primary endpoint of the phase II part 1 is the Overall Response Rate (ORR by RECIST 1.1 criteria).

The EPP will be the primary population for efficacy analyses in the phase II part 1. These analyses will be repeated on the SAF.
The best response will be recorded from the first study drug administration until documented disease progression. A PR or CR must be confirmed at a subsequent evaluation at least 4 weeks apart.

Phase II part 2: The primary endpoint of phase II part 2 is PFS by RECISIT 1.1 criteria. The FAS will be the primary population for efficacy analyses in the phase II part 2. These analyses will be repeated on the EPP.

Progression Free Survival (PFS) is defined as the time from the date of randomization to the date of first documented tumor progression or death due to any cause, whichever occurs first. If a patient has not had a PFS event at the cut-off date for analysis or at the date when a further antineoplastic therapy (other than those planned as study treatment in the protocol) is started, PFS will be censored at the date of last evaluable tumor assessment before the cut-off or start of further antineoplastic therapy.

10.3.2. Secondary endpoints

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

- Overall Response Rate (ORR) by using RECIST 1.1 (phase Ib, phase II part 2)
- Progression Free Survival (PFS) (phase Ib, Phase II part 1): time from the date of first study treatment administration to the date of first documented tumor progression or death due to any cause, whichever occurs first. If a patient has not had a PFS event at the cut-off date for analysis or at the date when a further antineoplastic therapy (other than those planned as study treatment in the protocol) is started, PFS will be censored at the date of last evaluable tumor assessment before the cut-off or start of further antineoplastic therapy.
- Overall Survival (OS):
- phase Ib and phase II part 1: time from the date of first study treatment administration to the date of death due to any cause. If a patient is not known to have died at the cut-off date for analysis, survival will be censored at the date of last contact.
- Phase II part 2: time from the date of randomization to the date of death due to any cause. If a patient is not known to have died at the cut-off date for analysis, survival will be censored at the date of last contact.
- Duration of overall Response (DoR): applies only to patients whose best overall response is CR or PR. The start date is the date of first documented response (CR or PR) and the end date is the date of first documented disease progression or death, whichever occurs first. If no progression has been observed at the cut-off date of analysis or at the date when a further antineoplastic therapy is started, DoR will be censored at the date of the last evaluable tumor assessment before the cut-off or start of further antineoplastic therapy.
- Disease control rate (DCR): proportion of patients whose best overall response is either CR, PR, or SD.
- Percentage of patients with liver metastases at baseline who have disease progression at D43 (phase II part 2)
- Safety: the assessment of safety of the combination will be based mainly on the frequency of Aes, SAEs, and on the number of laboratory values that fall outside of

predetermined ranges. Other safety data (e.g., ECG, vital signs) will be considered as appropriate.

10.3.3. Exploratory endpoints (phase Ib and II)

- To assess the following blood-based parameters and their impact on clinical outcomes (baseline and on-treatment sampling):
  - Memory and naïve T cells, regulatory T cells, CD8+ T cells, B cells, NK cells, and activation thereof
  - TG4001 and HPV-16-specific and tumor specific humoral and cellular immune responses
  - Immune related soluble factors and cytokines
- To assess tumor-based proteins and RNAs expression with potential prognostic and/or predictive value on efficacy outcomes including PD-L1 expression as well as new biomarkers identified by transcriptomic analysis (biopsies at baseline, on-treatment and at progressive disease)
- To assess the level of tumor infiltrating lymphocytes (TILs) and phenotypic characteristics thereof (biopsies at baseline, on-treatment and at progressive disease)
- To assess tumor mutation load and describe its impact on clinical outcomes (biopsies at baseline, on-treatment and at progressive disease)
- To assess viral clearance

10.4. Statistical and analytical plans

10.4.1. Safety analyses

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

Adverse Events
AE summaries will include all AEs starting on or after start of study treatment or that has worsened on or after start of study treatment and starting no later than 90 days after the date of last study treatment administration.
All Aes, significant Aes, Aes leading to discontinuation of study treatment (overall and by component: TG4001, avelumab), 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, also referred as CTCAE), relationship to study treatment (TG4001 and/or avelumab).
Separate AE summaries will be presented by SOC, PT, and CTCAE grade. In the summaries presented by grade, all Aes will be pooled. Specific tables will summarize related Aes to IMP and Aes of specific interest (injection site reactions).
The frequency of CTCAE Grade 3 and 4 Aes will be summarized separately.
Written narratives will be produced for all SAEs and unexpected or other significant Aes that are judged to be 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.

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 Informed 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 no later than 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 4.03 for phase Ib and phase II part 1, version 5.0 for phase II part 2). 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. Laboratory abnormalities 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.

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.

10.4.2. Efficacy analyses

The analysis of the efficacy endpoints will be performed on the EPP and repeated on the SAF. The analysis of efficacy will be based on RECIST 1.1.

- **Overall Response Rate (ORR)**

Overall response rate (ORR) is defined as the proportion of patients whose best overall response is either CR or PR according to RECIST version 1.1. Proportions of patients with a best overall response of CR or PR will be presented along with exact 95% confidence intervals. Patients with best overall response 'unknown' will be summarized by reason for having unknown status.
Phase II part 2: ORR will be compared between the 2 treatment arms using a (two-sided) 95% CI for the difference in proportion of patients whose best overall response is either CR or PR, stratified by indication using Cochran-Mantel-Haenszel Chi-Square test.

- **Progression Free Survival (PFS)**

Phase Ib and phase II part 1: PFS (in months) is defined as the time from the date of first study treatment administration to the date of first documented tumor progression or death due to any

cause, whichever occurs first. PFS will be censored if no progression or death is observed at the cut-off date for analysis, or at the date when a further antineoplastic therapy is started. The censoring date will be the date of the last evaluable tumor assessment before the cut-off date or start of further antineoplastic therapy.
Phase II part 2: PFS (in months) is defined as the time from the date of randomization to the date of first documented tumor progression or death due to any cause, whichever occurs first. PFS will be censored if no progression or death is observed at the cut-off date for analysis, or at the date when a further antineoplastic therapy is started. The censoring date will be the date of the last evaluable tumor assessment before the cut-off date or start of further antineoplastic therapy. The primary analysis will be a comparison of PFS between the 2 treatment arms using an unstratified log rank test at the one-sided 5% level in the FAS. A stratified log rank test stratified by indication will be also performed as supportive analysis. [redacted] HR (together with associated 95% CI) resulting from the stratified and unstratified Cox model will also be presented.

PFS will be presented descriptively using Kaplan-Meier curves. Summary statistics from the Kaplan-Meier distributions will be determined.

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

Duration of overall response in months (DoR) applies only to patients whose best overall response is CR or PR. The start date is the date of first documented response (CR or PR) and the end date is the date of event defined as first documented disease progression or death due to underlying cancer.
DoR will be censored if progression or death due to underlying cancer is not observed at the cut-off date for the analysis or start of further antineoplastic therapy. The censoring date will be the date of the last evaluable tumor assessment. Kaplan-Meier curves of DoR will be constructed. Summary statistics from the Kaplan-Meier distributions will be determined.

- **Disease Control Rate (DCR)**

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

- **Overall Survival (OS)**

Phase Ib and phase II part 1: OS is defined as the time from the date of first study treatment administration to the date of death due to any cause. If a patient is not known to have died, survival will be censored at the date of last contact.

Phase II part 2: OS is defined as the time from the date of randomization to the date of death due to any cause. If a patient is not known to have died, survival will be censored at the date of last contact. OS will be presented descriptively using Kaplan-Meier curves. Summary statistics from the Kaplan-Meier distributions will be determined. OS will be compared between the 2 treatment arms using an unstratified log rank test and log-rank stratified by indication at the one-sided 5% level in the FAS. [redacted]
HR (together with associated 95% CI) resulting from the stratified and unstratified Cox model will also be presented.

- **Phase II part 2: Percentage of patients with liver metastases at baseline who have disease progression at D43**

[redacted]

10.4.3. Biomarkers

Continuous variables may be further classified into categorical variables using quartiles, normal ranges, or limit of detection as appropriate. Student's t test or analysis of variance will be used when appropriate. Data will be transformed (*e.g.*, logarithms) prior to analysis if transformation is needed to meet the assumptions of normality and homogeneity of variances that underlie these methods. Non-parametric methods, such as the Wilcoxon-Mann-Whitney test, will be used if data fail to meet these assumptions even after transformation.
For discrete parameters, statistical analysis may include Chi square tests or Fishers Exact test as appropriate. OS and PFS will be analyzed using Cox regression model. Logistic regression models will be used to analyze overall responses. Mixed models will be used when appropriate for longitudinal analyses.
In order to explore or discover potentially important relationships between various markers, other exploratory statistical methods may be used.

10.5. Methods of analysis

10.5.1. General considerations

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

10.5.2. Disposition of patients

The number of screen failure patients and reasons for screen failure will be summarized. A patient listing will be provided with the reason of screen failure.

For phase Ib and phase II part 1:
The disposition data will be presented by patient in data listings and in a summary table on:
- Number of patients included (SAF)
- Number of patients included in each population: DLT population, EPP
- Number of patients excluded from the populations and reasons for exclusion
- Number of patients who received the combination
- Number of patients who discontinued TG4001 only and reasons for discontinuation
- Number of patients who discontinued avelumab and reasons for discontinuation

For phase II part 2:

- The disposition data will be presented by patient and treatment arm in data listings and the following items will be presented by treatment arm in a summary table on the FAS:
- Number of patients included (FAS)
- Number of patients included in each population: SAF, EPP
- Number of patients excluded from the populations and reasons for exclusion for each population
- Number of patients treated (TG4001 and/or avelumab)
- Number of patients who received TG4001 and avelumab
- Number of patients who discontinued TG4001 only and reasons for discontinuation
- Number of patients who discontinued avelumab and reasons for discontinuation

10.5.3. Demographic and baseline characteristics

Baseline demographics and patient and disease characteristics data will be listed and summarized. Qualitative data (e.g., gender, PS) will be summarized by means of contingency tables, and quantitative data (e.g., age and body weight) will be summarized by appropriate descriptive statistics (mean, standard deviation, median, minimum, and maximum).
Summaries will be provided overall for the SAF, the FAS for phase II part 2 and for key subpopulations, i.e. DLT population and EPP.

10.5.4. Treatments

10.5.4.1. Prior anti-cancer therapies

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

The SAF set and the FAS for phase II part 2 will be used for all summaries and listings of prior anti-cancer therapies.

10.5.4.2. Study treatments

Exposure to TG4001 will be provided by listing and summarizing the number of injections and the duration of treatment.
Exposure to avelumab will be provided by listing and summarizing the number of infusions, the cumulated dose and the duration of treatment.
The SAF and the FAS for phase II part 2 will be used for all summaries and listings of study treatment.
The number of patients with dose omission will be presented by study treatment component, along with reasons for the dose omission.

10.5.4.3. Concomitant medications

Medications and/or non drug therapies taken by the patient during the month prior to start of the study treatment, (continuing or not at the 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 the WHO Drug Dictionary and will be listed and summarized by active ingredient by means of frequency counts and percentages.
The SAF and the FAS for phase II part 2 will be used for all above mentioned concomitant medication tables.

10.5.4.4. Further antineoplastic therapies

All further antineoplastic therapies given after discontinuation of study will be collected with their start date and end date. They will be coded using the latest WHO Drug Dictionary and listed and summarized by active ingredient by means of frequency counts and percentages using the SAF population and the FAS for phase II part 2.

10.6. Protocol deviations

Protocol deviations impacting statistical analyses will be described in the statistical analysis plan in order to determine the EPP. A Data Review Meeting will be organized prior to final statistical analysis.

11 CHANGES IN THE CONDUCT OF THE STUDY

11.1. Protocol amendments

Changes to this protocol will be effected through amendments issued by Transgene after mutual agreement of the Investigator(s) and Transgene. Both the Investigator(s) and Transgene will sign the amendments. When applicable, amendments are submitted to Health Authorities and the Independent Ethics Committee(s) (IEC(s)) and any other committee(s) 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 committee(s) as locally required for authorisation / approval.

11.2. Premature termination or suspension of the study

The study may be suspended or terminated under any of the following circumstances:
- Sponsor’s decision
- Health Authorities’ decision
- IDMC recommendation in case of a safety concern. However, in this latter case, the final decision as to whether or not continue the study will be taken by the Sponsor

If the study needs to be terminated, Transgene and the Investigator will assure that adequate consideration is given to the protection of the patients. Transgene will notify the Health

Authorities and the IEC(s) and any other committee(s) 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.

12 ETHICAL CONSIDERATIONS

12.1. Independent Ethics Committee/Institutional Review Board

Before starting the study, the protocol, the written patient information sheet and informed consent form, and any other document specifically requested must be reviewed and approved by an IEC complying with the requirements of relevant local law.

Before enrollment of patients, Transgene must obtain from the IEC a written authorization / approval and the list of members having participated in the meeting including their qualification.

In addition, IEC written approval must be obtained by Transgene for protocol amendment as described in Section 9.1

12.2. Informed consent

The Investigator or his/her delegate will obtain a voluntary written consent from each patient after an appropriate explanation of the aims, methods, anticipated benefits, risks and any other aspect of the study relevant to the patient's decision to participate. Consent forms and all verbal study related information must be in a language fully comprehensible to the prospective patient. Patients will be informed that they are free not to participate in the study and that they may withdraw consent to participate at any time. They will be told which alternative treatments are available if they refuse to take part and that such refusal will not prejudice future treatment.
Patients will be informed that their records, including medical history, may be examined by competent authorities and authorized persons but that personal information will be treated as strictly confidential and will not be publicly available.
A written "patient information sheet" will be given to each patient to complete the verbal information. This written form should be reviewed orally with the patient. Patient must be given ample opportunity to inquire about details of the study.
The "patient information sheet" will explain that the data and images collected for this study will be stored in a computer database, with confidentiality maintained in accordance with national data legislation and the European General Data Protection Regulation for European countries. All data computer processed will be identified by patient initials depending on local laws) and number only.

Informed consent shall be documented by the use of a written consent form approved by the IEC and signed and dated by the Investigator and the patient before any exposure to a study-

related procedure, including screening tests for eligibility. Any new version of the ICF will be signed by all ongoing patients.

Should a patient start with the study treatment more than one month after having signed the informed consent form, whatever the reason, it would be ethical to ask him/her to reconfirm his/her willingness to participate to the study by signing a new consent form.

A copy of each signed informed consent form must be given to the patient and to his/her legally authorized representative. The originals are filed at the study site in the Investigator Site File.

12.3. Confidentiality of patient data

The Investigator must assure that patients' anonymity is maintained and that their identities are protected from unauthorized parties. On eCRFs or other documents collected by Transgene or its representative, patients should not be identified by their names, but by an identification code system. 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) or the HIPAA regulations.

The Investigator should keep a patient identification log showing codes, names and addresses of all patients consented. A copy of this log without names and addresses will be filed at Transgene after study completion.

13 REGULATORY CONSIDERATIONS

13.1. Regulatory considerations

This study will be conducted in accordance with:
- The updated Declaration of Helsinki adopted by the World Medical Association,
- The ICH (International Conference on Harmonization) Good Clinical Practice R2 (GCP) guidelines, and
- The local regulatory requirements.
- As per the HIPAA regulations, the individual institution may require that the Informed Consent and/or HIPAA Acknowledgement/Authorization Form be reviewed by their Privacy Board (per HIPAA guidelines). In the instance of a Privacy Board review, approval must be received on the Informed Consent Form and Subject Acknowledgment/Authorization Form prior to initiating any study related procedures.

13.2. Regulatory approval / authorization

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

13.3. Investigators' obligations

Before the study starts, the Investigator shall provide Transgene with his/her curriculum vitae (CV) 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, GCP and local regulations. Investigator must ensure that the study has been authorized / approved by all Regulatory Authorities, IEC/IRB 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.

The principal investigator, or person designated by the principal investigator, should communicate any deviation from the approved protocol to the monitor.

If the principal investigator is aware of the occurrence, or the potential occurrence of a deviation that is likely to affect, or affects, the safety and rights of a subject or the reliability and robustness of the data generated in the clinical trial (major deviation or serious breach), it should be promptly reported to TRANSGENE via the following email address, in order for TRANSGENE to meet the legal obligations:

[redacted]

13.4. Insurance

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

14 QUALITY CONTROL AND QUALITY ASSURANCE

14.1. On site monitoring

The monitor will contact and visit the Investigator periodically to evaluate study progress and protocol compliance.
On site monitoring activities are based on instructions given within the Monitoring Plan.

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

14.2. Audit and inspection

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

15 DATA HANDLING AND RECORD KEEPING

15.1. Source data and documents

Source data are all information available in original source document or certified copies of source document of any clinical findings, observations, or other activities that are necessary for the reconstruction and evaluation of the study.
The Investigator will record at least the following information in the source documents for all consented patients: date of birth, gender, medical history, reference to the study, visit dates, study treatments (TG4001, avelumab) administrations, concomitant medications, evaluation criteria and nature of adverse events with date of start and end and relationship to study treatments. The location of each source data will be identified on a dedicated form.

If computerised 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 authorised 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.

15.2. Case report forms

Electronic Data Capture (EDC) will be used for this study, meaning that all eCRF 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 or designee and signed 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 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 confirmations 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 data for archiving at the investigational site.

16 CLINICAL STUDY REPORT AND PUBLICATION

16.1. Clinical study report

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

16.2. Confidentiality of study data

Any information provided by Transgene, including non clinical data, protocols, eCRFs, verbal and written information, and results of the study will be kept strictly confidential and confined

to the clinical personnel involved in conducting this study, and no disclosure shall be made except in accordance with any right of publication granted to the Investigator by Transgene.

16.3. Publication policy

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

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

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

17 ARCHIVING

17.1. Investigator site file

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

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

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

17.2. Trial master file

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

REFERENCES

Adams S., Gray R.J., Demaria S., Goldstein L., Perez E.A., Shulman L.N., Martino S., Wang M., Jones V.E., Saphner T.J., Wolff A.C., Wood W.C., Davidson N.E., Sledge G.W., Sparano J.A. and Badve S.S. "Prognostic value of tumor-infiltrating lymphocytes in triple-negative breast cancers from two phase III randomized adjuvant breast cancer trials: ECOG 2197 and ECOG 1199." *J Clin Oncol*. (2014) 32(27): 2959-2966.

Aggarwal C., Heisler L.M., Saba N.F., Algazi A.P., Sukari A., Seiwert T., Haigentz M., Porosnicu M., Bonomi M., J. Boyer J., Durham N., Kumar R., Laubscher K., Gong M., Ceaicovscaia N. and Gascó Hernández A. *Safety and Efficacy of MEDI0457 plus Durvalumab in Patients with Human Papillomavirus Associated Recurrent/Metastatic Head and Neck Squamous Cell Carcinoma*. ESMO VIRTUAL CONGRESS.(2020).

Ahomadegbe J.C., Barrois M., Fogel S., Le Bihan M.L., Douc-Rasy S., Duvillard P., Armand J.P. and Riou G. "High incidence of p53 alterations (mutation, deletion, overexpression) in head and neck primary tumors and metastases; absence of correlation with clinical outcome. Frequent protein overexpression in normal epithelium and in early non-invasive lesions." *Oncogene*. (1995) 10(6): 1217-1227.

Alhamarneh O., Amarnath S.M., Stafford N.D. and Greenman J. "Regulatory T cells: what role do they play in antitumor immunity in patients with head and neck cancer?" *Head Neck*. (2008) 30(2): 251-261.

Andrade P., Deleo A., Visus C., Butterfield L., Argiris A. and Ferris R.L. "Phase I adjuvant trial of multi-epitope p53 vaccine for patients with squamous cell carcinoma of the head and neck (SCCHN): A preliminary report." *J Clin Oncol 27:15s, 2009 (suppl; abstr 3012)*. (2009).

Antoine G., Scheiflinger F., Dorner F. and Falkner F. "The complete genomic sequence of the modified Vaccinia Ankara Strain: Comparison with other Orthopoxviruses." *Virology*. (1998) 244: 365-396.

Attner P., Du J., Nasman A., Hammarstedt L., Ramqvist T., Lindholm J., Marklund L., Dalianis T. and Munck-Wikland E. "The role of human papillomavirus in the increased incidence of base of tongue cancer." *Int J Cancer*. (2010) 126(12): 2879-2884.

Balloul J.M. "Development of a highly -attenuated vaccinia virus co-expressing the E6 and E7 genes of Human Papillomavirus type 16 and the human IL-2 gene." Study Report (DP0037) Transgene, Strasbourg, (1998)

Balloul J.M. and Pecheur C. "Comparison of IP versus SC vaccination protocols with recombinant vaccinia viruses (MVA) expressing genes of HPV16 in a HPV + mouse tumor model." Study Report (DP0107) Strasbourg, Transgene, (2006)

Balloul J.M. and Pecheur C. "Immunotherapy experiment with a recombinant vaccinia virus expressing genes of HPV16 in a mouse model of cervical cancer: definition of the dose number for optimal immunotherapeutic effect." Study Report (DP0108) Strasbourg, Transgene, (2007)

Bizouarne N. "Comparison of recombinant vaccinia viruses expressing early genes of HPV16 in a mouse model of cervical cancer. Study of the immunization route in an immunoprophylaxis experiment." Study Report (DP0046) Transgene, Strasbourg, (1998a)

Bizouarne N. "Study of the efficiency of MVA8042 in a mouse model of cervical cancer. Dose effect in an immunoprophylaxis experiment." Study Report (DP0048) Transgene, Strasbourg, (1998b)

Braakhuis B.J., Snijders P.J., Keune W.J., Meijer C.J., Ruijter-Schippers H.J., Leemans C.R. and Brakenhoff R.H. "Genetic patterns in head and neck cancers that contain or lack transcriptionally active human papillomavirus." *J Natl Cancer Inst*. (2004) 96(13): 998-1006.

Brachman D.G., Graves D., Vokes E., Beckett M., Haraf D., Montag A., Dunphy E., Mick R., Yandell D. and Weichselbaum R.R. "Occurrence of p53 gene deletions and human papilloma virus infection in human head and neck cancer." *Cancer Res*. (1992) 52(17): 4832-4836.

Brahmer J.R., Tykodi S.S., Chow L.Q., Hwu W.J., Topalian S.L., Hwu P., Drake C.G., Camacho L.H., Kauh J., Odunsi K., Pitot H.C., Hamid O., Bhatia S., Martins R., Eaton K., Chen S., Salay T.M., Alaparthy S., Grosso J.F., Korman A.J., Parker S.M., Agrawal S., Goldberg S.M., Pardoll D.M., Gupta A. and Wigginton J.M. "Safety and activity of anti-PD-L1 antibody in patients with advanced cancer." *N Engl J Med.* (2012) 366(26): 2455-2465.

Bray F., Sankila R., Ferlay J. and Parkin D.M. "Estimates of cancer incidence and mortality in Europe in 1995." *Eur J Cancer*. (2002) 38(1): 99-166.

Brun J.L., Dalstein V., Leveque J., Mathevet P., Raulic P., Baldauf J.J., Scholl S., Huynh B., Douvier S., Riethmuller D., Clavel C., Birembaut P., Calenda V., Baudin M. and Bory J.P. "Regression of high-grade cervical intraepithelial neoplasia with TG4001 targeted immunotherapy." *Am J Obstet Gynecol*. (2011) 204(2): 169 e161-168.

Butte M.J., Keir M.E., Phamduy T.B., Sharpe A.H. and Freeman G.J. "Programmed death-1 ligand 1 interacts specifically with the B7-1 costimulatory molecule to inhibit T cell responses." *Immunity*. (2007) 27(1): 111-122.

Cann C.I., Fried M.P. and Rothman K.J. "Epidemiology of squamous cell cancer of the head and neck." *Otolaryngol Clin North Am*. (1985) 18(3): 367-388.

Carlos de Vicente J., Junquera Gutierrez L.M., Zapatero A.H., Fresno Forcelledo M.F., Hernandez-Vallejo G. and Lopez Arranz J.S. "Prognostic significance of p53 expression in oral squamous cell carcinoma without neck node metastases." *Head Neck*. (2004) 26(1): 22-30.

Chaturvedi A.K. "Epidemiology and clinical aspects of HPV in head and neck cancers." *Head Neck Pathol*. (2012) 6 Suppl 1: S16-24.

Chaturvedi A.K., Engels E.A., Pfeiffer R.M., Hernandez B.Y., Xiao W., Kim E., Jiang B., Goodman M.T., Sibug-Saber M., Cozen W., Liu L., Lynch C.F., Wentzensen N., Jordan R.C., Altekruse S., Anderson W.F., Rosenberg P.S. and Gillison M.L. "Human papillomavirus and rising oropharyngeal cancer incidence in the United States." *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. (2011) 29(32): 4294-4301.

Chow L.Q., Haddad R., Gupta S., Mahipal A., Mehra R., Tahara M., Berger R., Eder J.P., Burtness B., Lee S.H., Keam B., Kang H., Muro K., Weiss J., Geva R., Lin C.C., Chung H.C., Meister A., Dolled-Filhart M., Pathiraja K., Cheng J.D. and Seiwert T.Y. "Antitumor Activity of Pembrolizumab in Biomarker-Unselected Patients With Recurrent and/or Metastatic Head and Neck Squamous Cell Carcinoma: Results From the Phase Ib KEYNOTE-012 Expansion Cohort." *J Clin Oncol*. (2016).

Christ M. "TG4001 - Local tolerance in the female rabbit by the intramuscular, subcutaneous and intradermal routes." Study Report (921/048) L'Arbresle, France, MDS Pharma Services, (2001)

Chung C.H. and Gillison M.L. "Human papillomavirus in head and neck cancer: its role in pathogenesis and clinical implications." *Clin Cancer Res*. (2009) 15(22): 6758-6762.

Chung H.C., Arkenau H.-T., Wyrwicz L., Oh D.Y., Lee K.-W., Infante J.R., Chin K.M., Von Heydebreck A., Kang Y.K. and Safran H. "Safety, PD-L1 expression, and clinical activity of avelumab (MSB0010718C), an anti-PD-L1 antibody, in patients with advanced gastric or gastroesophageal junction cancer." *J Clin Oncol 34, 2016 (suppl 4S; abstr 167)*. (2016).

Chung H.C., Ros W., Delord J.P., Perets R., Italiano A., Shapira-Frommer R., Manzuk L., Piha-Paul S.A., Xu L., Zeigenfuss S., Pruitt S.K. and Leary A. "Efficacy and Safety of Pembrolizumab in Previously Treated Advanced Cervical Cancer: Results From the Phase II KEYNOTE-158 Study." *J Clin Oncol*. (2019) 37(17): 1470-1478.

Cohen E.E.W., Soulieres D., Le Tourneau C., Dinis J., Licitra L., Ahn M.J., Soria A., Machiels J.P., Mach N., Mehra R., Burtness B., Zhang P., Cheng J., Swaby R.F., Harrington K.J. and investigators K.-. "Pembrolizumab versus methotrexate, docetaxel, or cetuximab for recurrent or metastatic head-and-neck squamous cell carcinoma (KEYNOTE-040): a randomised, open-label, phase 3 study." *Lancet*. (2019) 393(10167): 156-167.

Crook T., Tidy J.A. and Vousden K.H. "Degradation of p53 can be targeted by HPV E6 sequences distinct from those required for p53 binding and trans-activation." *Cell*. (1991) 67: 547-556.

Curran M.A., Montalvo W., Yagita H. and Allison J.P. "PD-1 and CTLA-4 combination blockade expands infiltrating T cells and reduces regulatory T and myeloid cells within B16 melanoma tumors." *Proc Natl Acad Sci U S A*. (2010) 107(9): 4275-4280.

D'Souza G., Kreimer A.R., Viscidi R., Pawlita M., Fakhry C., Koch W.M., Westra W.H. and Gillison M.L. "Case-control study of human papillomavirus and oropharyngeal cancer." *The New England journal of medicine*. (2007) 356(19): 1944-1956.

de Sanjose S., Quint W.G., Alemany L., Geraets D.T., Klaustermeier J.E., Lloveras B., Tous S., Felix A., Bravo L.E., Shin H.R., Vallejos C.S., de Ruiz P.A., Lima M.A., Guimera N., Clavero O., Alejo M., Llombart-Bosch A., Cheng-Yang C., Tatti S.A., Kasamatsu E., Iljazovic E., Odida M., Prado R., Seoud M., Grce M., Usubutun A., Jain A., Suarez G.A., Lombardi L.E., Banjo A., Menendez C., Domingo E.J., Velasco J., Nessa A., Chichareon S.C., Qiao Y.L., Lerma E., Garland S.M., Sasagawa T., Ferrera A., Hammouda D., Mariani L., Pelayo A., Steiner I., Oliva E., Meijer C.J., Al-Jassar W.F., Cruz E., Wright T.C., Puras A., Llave C.L., Tzardi M., Agorastos T., Garcia-Barriola V., Clavel C., Ordi J., Andujar M., Castellsague X., Sanchez G.I., Nowakowski A.M., Bornstein J., Munoz N., Bosch F.X., Retrospective International S. and Group H.P.V.T.T.S. "Human papillomavirus genotype attribution in invasive cervical cancer: a retrospective cross-sectional worldwide study." *Lancet Oncol*. (2010) 11(11): 1048-1056.

Dirix L.Y., Takacs I., Nikolinakos P., Jerusalem G., Arkenau H.T., Hamilton E.P.P., VonHeydebreck A., Grote H.J., Chin K. and Lippman M.E. *Avelumab (MSB0010718C), an anti-PD-L1 antibody, in patients with locally advanced or metastatic breast cancer: A phase Ib JAVELIN solid tumor trial*. Thirty-Eighth Annual CTRC-AACR San Antonio Breast Cancer Symposium, San antonio, American Association for Cancer Research.(2015)

Eisenhauer E.A., Therasse P., Bogaerts J., Schwartz L.H., Sargent D., Ford R., Dancey J., Arbuck S., Gwyther S., Mooney M., Rubinstein L., Shankar L., Dodd L., Kaplan R., Lacombe D. and Verweij J. "New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1)." *European Journal of Cancer*. (2009) 45(2): 228-247.

Ferris R.L., Blumenschein G., Jr., Fayette J., Guigay J., Colevas A.D., Licitra L., Harrington K., Kasper S., Vokes E.E., Even C., Worden F., Saba N.F., Iglesias Docampo L.C., Haddad R., Rordorf T., Kiyota N., Tahara M., Monga M., Lynch M., Geese W.J., Kopit J., Shaw J.W. and Gillison M.L. "Nivolumab for Recurrent Squamous-Cell Carcinoma of the Head and Neck." *N Engl J Med*. (2016) 375(19): 1856-1867.

Ferris R.L., Blumenschein G.R., Fayette J., Guigay J., Colevas A.D., Licitra L.F., Harrington K.J., Kasper S., Vokes E.E., Even C., Worden F.P., Haddad R.I., Kiyota N., Tahara M., Monga M., Lynch M.J., Geese W.J., Kopit J., Shaw J.W. and Gillison M.L. "Further evaluations of nivolumab (nivo) versus investigator's choice (IC) chemotherapy for recurrent or metastatic (R/M) squamous cell carcinoma of the head and neck (SCCHN): CheckMate 141. ASCO Annual Meeting." *J Clin Oncol 34, 2016 (suppl; abstr 6009)*.

Fife B.T., Pauken K.E., Eagar T.N., Obu T., Wu J., Tang Q., Azuma M., Krummel M.F. and Bluestone J.A. "Interactions between PD-1 and PD-L1 promote tolerance by blocking the TCR-induced stop signal." *Nat Immunol*. (2009) 10(11): 1185-1192.

Freeman G.J., Long A.J., Iwai Y., Bourque K., Chernova T., Nishimura H., Fitz L.J., Malenkovich N., Okazaki T., Byrne M.C., Horton H.F., Fouser L., Carter L., Ling V., Bowman M.R., Carreno B.M., Collins M.,

Wood C.R. and Honjo T. "Engagement of the PD-1 immunoinhibitory receptor by a novel B7 family member leads to negative regulation of lymphocyte activation." *J Exp Med*. (2000) 192(7): 1027-1034.

Frenel J.S., Le Tourneau C., O'Neil B., Ott P.A., Piha-Paul S.A., Gomez-Roca C., van Brummelen E.M.J., Rugo H.S., Thomas S., Saraf S., Rangwala R. and Varga A. "Safety and Efficacy of Pembrolizumab in Advanced, Programmed Death Ligand 1-Positive Cervical Cancer: Results From the Phase Ib KEYNOTE-028 Trial." *J Clin Oncol*. (2017) 35(36): 4035-4041.

Freshwater T., Kondic A., Ahamadi M., Li C.H., de Greef R., de Alwis D. and Stone J.A. "Evaluation of dosing strategy for pembrolizumab for oncology indications." *J Immunother Cancer*. (2017) 5: 43.

Geng Y., Shao Y., He W., Hu W., Xu Y., Chen J., Wu C. and Jiang J. "Prognostic Role of Tumor-Infiltrating Lymphocytes in Lung Cancer: a Meta-Analysis." *Cell Physiol Biochem*. (2015) 37(4): 1560-1571.

Gillison M.L., D'Souza G., Westra W., Sugar E., Xiao W., Begum S. and Viscidi R. "Distinct risk factor profiles for human papillomavirus type 16-positive and human papillomavirus type 16-negative head and neck cancers." *Journal of the National Cancer Institute*. (2008) 100(6): 407-420.

Gillison M.L., Koch W.M., Capone R.B., Spafford M., Westra W.H., Wu L., Zahurak M.L., Daniel R.W., Viglione M., Symer D.E., Shah K.V. and Sidransky D. "Evidence for a causal association between human papillomavirus and a subset of head and neck cancers." *J Natl Cancer Inst*. (2000a) 92(9): 709-720.

Gillison M.L., Koch W.M., Capone R.B., Spafford M., Westra W.H., Wu L., Zahurak M.L., Daniel R.W., Viglione M., Symer D.E., Shah K.V. and Sidransky D. "Evidence for a causal association between human papillomavirus and a subset of head and neck cancers." *Journal of the National Cancer Institute*. (2000b) 92(9): 709-720.

Gillison M.L. and Shah K.V. "Human papillomavirus-associated head and neck squamous cell carcinoma: mounting evidence for an etiologic role for human papillomavirus in a subset of head and neck cancers." *Curr Opin Oncol*. (2001) 13(3): 183-188.

GlaxoSmithKline Vaccine H.P.V.S.G., Romanowski B., de Borba P.C., Naud P.S., Roteli-Martins C.M., De Carvalho N.S., Teixeira J.C., Aoki F., Ramjattan B., Shier R.M., Somani R., Barbier S., Blatter M.M., Chambers C., Ferris D., Gall S.A., Guerra F.A., Harper D.M., Hedrick J.A., Henry D.C., Korn A.P., Kroll R., Moscicki A.B., Rosenfeld W.D., Sullivan B.J., Thoming C.S., Tyring S.K., Wheeler C.M., Dubin G., Schuind A., Zahaf T., Greenacre M. and Sgriobhadair A. "Sustained efficacy and immunogenicity of the human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine: analysis of a randomised placebo-controlled trial up to 6.4 years." *Lancet*. (2009) 374(9706): 1975-1985.

Globocan. "Estimated Cancer Incidence, Mortality and Prevalence Worldwide in 2012." (2012).

Goldenberg D., Begum S., Westra W.H., Khan Z., Sciubba J., Pai S.I., Califano J.A., Tufano R.P. and Koch W.M. "Cystic lymph node metastasis in patients with head and neck cancer: An HPV-associated phenomenon." *Head Neck*. (2008) 30(7): 898-903.

Gregoire V., Lefebvre J.L., Licitra L., Felip E. and Group E.-E.-E.G.W. "Squamous cell carcinoma of the head and neck: EHNS-ESMO-ESTRO Clinical Practice Guidelines for diagnosis, treatment and follow-up." *Ann Oncol*. (2010) 21 Suppl 5: v184-186.

Guigay J., Lee K.W., Patel M., Daste A., Wong D.J., Goel S., Gordon M., Gutierrez M., Balmanoukian A., Le Tourneau C., Mita A., D. Vansteene D., U. Keilholz U., Schöffski P., H. J. Grote H., D. Zhou D., Bajars M. and Penel N. *Avelumab (anti–PD-L1) in patients with platinumrefractory/ineligible recurrent or metastatic squamous cell carcinoma of the head and neck (R/M SCCHN): results from a phase 1b cohort*. Abstract No. 4024. Presented at the ESMO Virtual Congress 2020.(19-21 September 2020).

Haddad R.I. and Shin D.M. "Recent advances in head and neck cancer." *N Engl J Med*. (2008) 359(11): 1143-1154.

Halbert C., Demers G. and Galloway D. "The E7 gene of human papillomavirus type 16 is sufficient for immortalization of human epithelial cells." *Journal of Virology*. (1991) 65: 473-478.

Hammarstedt L., Lindquist D., Dahlstrand H., Romanitan M., Dahlgren L.O., Joneberg J., Creson N., Lindholm J., Ye W., Dalianis T. and Munck-Wikland E. "Human papillomavirus as a risk factor for the increase in incidence of tonsillar cancer." *Int J Cancer*. (2006) 119(11): 2620-2623.

Harper D.M., Franco E.L., Wheeler C.M., Moscicki A.B., Romanowski B., Roteli-Martins C.M., Jenkins D., Schuind A., Costa Clemens S.A., Dubin G. and group H.P.V.V.S. "Sustained efficacy up to 4.5 years of a bivalent L1 virus-like particle vaccine against human papillomavirus types 16 and 18: follow-up from a randomised control trial." *Lancet*. (2006) 367(9518): 1247-1255.

Havre P.A., Yuan J., Hedrick L., Cho K.R. and Glazer P.M. "p53 inactivation by HPV16 E6 results in increased mutagenesis in human cells." *Cancer Res*. (1995) 55(19): 4420-4424.

Herbst R.S., Soria J.C., Kowanetz M., Fine G.D., Hamid O., Gordon M.S., Sosman J.A., McDermott D.F., Powderly J.D., Gettinger S.N., Kohrt H.E., Horn L., Lawrence D.P., Rost S., Leabman M., Xiao Y., Mokatrin A., Koeppen H., Hegde P.S., Mellman I., Chen D.S. and Hodi F.S. "Predictive correlates of response to the anti-PD-L1 antibody MPDL3280A in cancer patients." *Nature*. (2014) 515(7528): 563-567.

Heusinkveld M., Goedemans R., Briet R.J., Gelderblom H., Nortier J.W., Gorter A., Smit V.T., Langeveld A.P., Jansen J.C. and van der Burg S.H. "Systemic and local human papillomavirus 16-specific T-cell immunity in patients with head and neck cancer." *Int J Cancer*. (2012) 131(2): E74-85.

Hildesheim A., Schiffman M., Bromley C., Wacholder S., Herrero R., Rodriguez A., Bratti M.C., Sherman M.E., Scarpidis U., Lin Q.Q., Terai M., Bromley R.L., Buetow K., Apple R.J. and Burk R.D. "Human papillomavirus type 16 variants and risk of cervical cancer." *J Natl Cancer Inst*. (2001) 93(4): 315-318.

Hollebecque A., Meyer T., Moore K.N., Machiels J.P.H., De Greve J., López-Picazo J.M., Oaknin A., Kerger J.N., Boni V., Evans T.R.J., Kristeleit R.S., Rao S., Soumaoro I., Cao Z.A. and L. T.S. "An open-label, multicohort, phase I/II study of nivolumab in patients with virus-associated tumors (CheckMate 358): Efficacy and safety in recurrent or metastatic (R/M) cervical, vaginal, and vulvar cancers." *Journal of Clinical Oncology*. (2017) 35(no. 15_suppl): 5504-5504.

Howard S.C., Jones D.P. and Pui C.H. "The tumor lysis syndrome." *N Engl J Med*. (2011) 364(19): 1844-1854.

Huang R.R., Jalil J., Economou J.S., Chmielowski B., Koya R.C., Mok S., Sazegar H., Seja E., Villanueva A., Gomez-Navarro J., Glaspy J.A., Cochran A.J. and Ribas A. "CTLA4 blockade induces frequent tumor infiltration by activated lymphocytes regardless of clinical responses in humans." *Clin Cancer Res*. (2011) 17(12): 4101-4109.

Ihloff A.S., Petersen C., Hoffmann M., Knecht R. and Tribius S. "Human papilloma virus in locally advanced stage III/IV squamous cell cancer of the oropharynx and impact on choice of therapy." *Oral Oncol*. (2010) 46(10): 705-711.

Ishida Y., Agata Y., Shibahara K. and Honjo T. "Induced expression of PD-1, a novel member of the immunoglobulin gene superfamily, upon programmed cell death." *EMBO J*. (1992) 11(11): 3887-3895.

Iwai Y., Ishida M., Tanaka Y., Okazaki T., Honjo T. and Minato N. "Involvement of PD-L1 on tumor cells in the escape from host immune system and tumor immunotherapy by PD-L1 blockade." *Proc Natl Acad Sci U S A*. (2002) 99(19): 12293-12297.

Kaiser S. "TG4001 – Subcutaneous toxicity study in C57 Black 6 mice after a repeated administration followed by a 4-week recovery period." Study Report (Study Report A85386.) RCC Ltd., Itigen and Füllinsdorf, Switzerland, (2007)

Kaufman H.L., Russell J., Hamid O., Bhatia S., Terheyden P., D'Angelo S.P., Shih K.C., Lebbe C., Linette G.P., Milella M., Brownell I., Lewis K.D., Lorch J.H., Chin K., Mahnke L., von Heydebreck A., Cuillerot J.M.

and Nghiem P. "Avelumab in patients with chemotherapy-refractory metastatic Merkel cell carcinoma: a multicentre, single-group, open-label, phase 2 trial." *Lancet Oncol*. (2016) 17(10): 1374-1385.

Keir M.E., Liang S.C., Guleria I., Latchman Y.E., Qipo A., Albacker L.A., Koulmanda M., Freeman G.J., Sayegh M.H. and Sharpe A.H. "Tissue expression of PD-L1 mediates peripheral T cell tolerance." *J Exp Med*. (2006) 203(4): 883-895.

Kenter G.G., Welters M.J., Valentijn A.R., Lowik M.J., Berends-van der Meer D.M., Vloon A.P., Essahsah F., Fathers L.M., Offringa R., Drijfhout J.W., Wafelman A.R., Oostendorp J., Fleuren G.J., van der Burg S.H. and Melief C.J. "Vaccination against HPV-16 oncoproteins for vulvar intraepithelial neoplasia." *N Engl J Med*. (2009) 361(19): 1838-1847.

Khan M.M. "Immunosuppressive Agents. In: Immunopharmacology." *New York: Springer*Study Report (2008)

Kim S.H., Koo B.S. and Kang S. "HPV integration begins in the tonsillar crypt and leads to the alteration of p16, EGFR and c-myc during tumor formation." *International Journal of Cancer*. (2007) 7: 1418-1425.

Klussmann J.P., Gultekin E., Weissenborn S.J., Wieland U., Dries V., Dienes H.P., Eckel H.E., Pfister H.J. and Fuchs P.G. "Expression of p16 protein identifies a distinct entity of tonsillar carcinomas associated with human papillomavirus." *Am J Pathol*. (2003) 162(3): 747-753.

Kreimer A.R., Clifford G.M., Boyle P. and Franceschi S. "Human papillomavirus types in head and neck squamous cell carcinomas worldwide: a systematic review." *Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology*. (2005) 14(2): 467-475.

Kumar B., Cordell K.G., Lee J.S., Prince M.E., Tran H.H., Wolf G.T., Urba S.G., Worden F.P., Chepeha D.B., Teknos T.N., Eisbruch A., Tsien C.I., Taylor J.M., D'Silva N.J., Yang K., Kurnit D.M., Bradford C.R. and Carey T.E. "Response to therapy and outcomes in oropharyngeal cancer are associated with biomarkers including human papillomavirus, epidermal growth factor receptor, gender, and smoking." *Int J Radiat Oncol Biol Phys*. (2007) 69(2 Suppl): S109-111.

Lassen P. "The role of Human papillomavirus in head and neck cancer and the impact on radiotherapy outcome." *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology*. (2010) 95(3): 371-380.

Lassen P., Eriksen J.G., Hamilton-Dutoit S., Tramm T., Alsner J. and Overgaard J. "Effect of HPV-associated p16INK4A expression on response to radiotherapy and survival in squamous cell carcinoma of the head and neck." *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. (2009) 27(12): 1992-1998.

Li Y., Hou S., Zhang X., Zhang G., Zhu J. and Wang X. "[Subpopulations of TIL in renal cell carcinoma and their clinical significance]." *Zhonghua Wai Ke Za Zhi*. (1998) 36(5): 314-316.

Lindquist D., Romanitan M., Hammarstedt L., Nasman A., Dahlstrand H., Lindholm J., Onelov L., Ramqvist T., Ye W., Munck-Wikland E. and Dalianis T. "Human papillomavirus is a favourable prognostic factor in tonsillar cancer and its oncogenic role is supported by the expression of E6 and E7." *Mol Oncol*. (2007) 1(3): 350-355.

Lipponen P.K., Eskelinen M.J., Jauhiainen K., Harju E. and Terho R. "Tumour infiltrating lymphocytes as an independent prognostic factor in transitional cell bladder cancer." *Eur J Cancer*. (1992) 29A(1): 69-75.

Liu J.Y., Li F., Wang L.P., Chen X.F., Wang D., Cao L., Ping Y., Zhao S., Li B., Thorne S.H., Zhang B., Kalinski P. and Zhang Y. "CTL- vs Treg lymphocyte-attracting chemokines, CCL4 and CCL20, are strong reciprocal predictive markers for survival of patients with oesophageal squamous cell carcinoma." *Br J Cancer*. (2015) 113(5): 747-755.

Lonardi S., Pietrantonio F., Prete A.A., Messina M., Renzi N., Corsi D.C., Urbano F., Frassineti G.L., Zampino M.G., Ronzoni M., Scartozzi M., Casagrande M., Boccaccino A., Bergamo F., Prisciandaro M., Rasola

C., Corallo S., Del Bianco P., Vettore V. and Zagonel V. *Randomized phase 2 trial of avelumab alone or with cetuximab for unresectable, locally advanced or metastatic squamous cell anal carcinoma progressed to at least one line of treatment: the CARACAS study*. ASCO.(2020)

Lyford-Pike S. and . e.a. *PD-1:PD-L1(B7-H1) pathway in adaptive resistance: a novel mechanism for tumor immune escape in human papillomavirus-related head and neck cancers*. ASCO Meet Abstr 2012; 30 (15-suppl):550.(2012)

Maby P., Tougeron D., Hamieh M., Mlecnik B., Kora H., Bindea G., Angell H.K., Fredriksen T., Elie N., Fauquembergue E., Drouet A., Leprince J., Benichou J., Mauillon J., Le Pessot F., Sesboue R., Tuech J.J., Sabourin J.C., Michel P., Frebourg T., Galon J. and Latouche J.B. "Correlation between Density of CD8+ T-cell Infiltrate in Microsatellite Unstable Colorectal Cancers and Frameshift Mutations: A Rationale for Personalized Immunotherapy." *Cancer Res*. (2015) 75(17): 3446-3455.

Marabelle A., Cassier P., Fakih M., Kao S., Nielsen D., Italiano A., Guren T., Van Dongen M., Spencer K., Bariani G.M., Ascierto P., Santoro A., Hiret S., Ott P.A., Piha-Paul S.A., Liu C.C., Leiby M.A., Norwood K. and Delord J.P. *Pembrolizumab for previously treated advanced anal squamous cell carcinoma: pooled results from the keynote-028 and keynote-158 studies*. ASCO ANNUAL MEETING.(2020).

Marur S., D'Souza G., Westra W.H. and Forastiere A.A. "HPV-associated head and neck cancer: a virus-related cancer epidemic." *Lancet Oncol*. (2010) 11(8): 781-789.

Massarelli E., William W., Johnson F., Kies M., Ferrarotto R., Guo M., Feng L., Lee J.J., Tran H., Kim Y.U., Haymaker C., Bernatchez C., Curran M., Zecchini Barrese T., Rodriguez Canales J., Wistuba I., Li L., Wang J., van der Burg S.H., Melief C.J. and Glisson B. "Combining Immune Checkpoint Blockade and Tumor-Specific Vaccine for Patients With Incurable Human Papillomavirus 16-Related Cancer: A Phase 2 Clinical Trial." *JAMA Oncol*. (2019) 5(1): 67-73.

Mehanna H., Beech T., Nicholson T., El-Hariry I., McConkey C., Paleri V. and Roberts S. "Prevalence of human papillomavirus in oropharyngeal and nonoropharyngeal head and neck cancer--systematic review and meta-analysis of trends by time and region." *Head Neck.* (2013) 35(5): 747-755.

Mehta C.R. and Pocock S.J. "Adaptive increase in sample size when interim results are promising: a practical guide with examples." *Stat Med*. (2011) 30(28): 3267-3284.

Melero I., Berman D.M., Aznar M.A., Korman A.J., Perez Gracia J.L. and Haanen J. "Evolving synergistic combinations of targeted immunotherapies to combat cancer." *Nature reviews. Cancer*. (2015) 15(8): 457-472.

Mellin Dahlstrand H., Lindquist D., Bjornestal L., Ohlsson A., Dalianis T., Munck-Wikland E. and Elmberger G. "P16(INK4a) correlates to human papillomavirus presence, response to radiotherapy and clinical outcome in tonsillar carcinoma." *Anticancer Res*. (2005) 25(6C): 4375-4383.

Menguy T. "In vitro assessment of the transformation potential of mammalian cells by human papilloma virus 16 (HPV16) E6 and E7 sequences used in RO5217790." Study Report (DP0400) Strasbourg, Transgene, (2009)

Morris V.K., Salem M.E., Nimeiri H., Iqbal S., Singh P., Ciombor K., Polite B., Deming D., Chan E., Wade J.L., Xiao L., Bekaii-Saab T., Vence L., Blando J., Mahvash A., Foo W.C., Ohaji C., Pasia M., Bland G., Ohinata A., Rogers J., Mehdizadeh A., Banks K., Lanman R., Wolff R.A., Streicher H., Allison J., Sharma P. and Eng C. "Nivolumab for previously treated unresectable metastatic anal cancer (NCI9673): a multicentre, single-arm, phase 2 study." *Lancet Oncol*. (2017) 18(4): 446-453.

Munger K., Werness B.A., Dyson N., Phelps W.C., Harlow E. and Howley P.M. "Complex formation of human papillomavirus E7 proteins with the retinoblastoma tumor suppressor gene product." *The EMBO journal*. (1989) 8(13): 4099-4105.

Nashina T, Shitara K, Iwasa S and al e. "Safety, PD-L1 expression, and clinical activity of avelumab (MSB0010718C), an anti-PD-L1 antibody, in Japanese patients with advanced gastric or gastroesophageal junction cancer." *J Clin Oncol 34 (suppl 4S; abstr 168)*. (2016).

Nasman A., Attner P., Hammarstedt L., Du J., Eriksson M., Giraud G., Ahrlund-Richter S., Marklund L., Romanitan M., Lindquist D., Ramqvist T., Lindholm J., Sparen P., Ye W., Dahlstrand H., Munck-Wikland E. and Dalianis T. "Incidence of human papillomavirus (HPV) positive tonsillar carcinoma in Stockholm, Sweden: an epidemic of viral-induced carcinoma?" *Int J Cancer*. (2009) 125(2): 362-366.

Nevins J.R. "The Rb/E2F pathway and cancer." *Hum Mol Genet*. (2001) 10(7): 699-703.

Ott P.A., Piha-Paul S.A., Munster P., Pishvaian M.J., van Brummelen E.M.J., Cohen R.B., Gomez-Roca C., Ejadi S., Stein M., Chan E., Simonelli M., Morosky A., Saraf S., Emancipator K., Koshiji M. and Bennouna J. "Safety and antitumor activity of the anti-PD-1 antibody pembrolizumab in patients with recurrent carcinoma of the anal canal." *Ann Oncol*. (2017) 28(5): 1036-1041.

Palefsky J.M. and Holly E.A. "Molecular virology and epidemiology of human papillomavirus and cervical cancer." *Cancer Epidemiol Biomarkers Prev*. (1995) 4(4): 415-428.

Paul S. "Evaluation of the adjuvant effect of topical administration of Aldara on the therapeutic efficacy of MVATG8042." Study Report (DP0339) Transgene, Strasbourg, (2007)

Pecheur C. "TG4001 - Four week intramuscular toxicity study in the rat (2 administrations per week)." Study Report (921/025) Chrysalis S.A., L'Arbresle, France, (1998a)

Pecheur C. "TG4001 - Single dose intravenous (bolus) toxicity study in the rat followed by a 14-day observation period." Study Report (921/026) Chrysalis S.A., L'Arbresle, France, (1998b)

Pecheur C. and Bizouarne N. "Mechanisms of tumour rejection : Effect of CD4 or CD8 depletion before immunization with MVATG8042 -Immunoprophylaxis experiment in a mouse model of cervical cancer." Study Report (DP0068) Transgene, Strasbourg, (2000)

Peng S., Best S.R., Hung C.F., Loyo M., Lyford-Pike S., Flint P.W., Tunkel D.E., Saunders J.R., Wu T.C. and Pai S.I. "Characterization of human papillomavirus type 11-specific immune responses in a preclinical model." *Laryngoscope*. (2010) 120(3): 504-510.

Rotnaglova E., Tachezy R., Salakova M., Prochazka B., Kosl'abova E., Vesela E., Ludvikova V., Hamsikova E. and Klozar J. "HPV involvement in tonsillar cancer: prognostic significance and clinically relevant markers." *Int J Cancer*. (2011) 129(1): 101-110.

Schleimer R.P., Jacques A., Shin H.S., Lichtenstein L.M. and Plaut M. "Inhibition of T cell-mediated cytotoxicity by anti-inflammatory steroids." *J Immunol*. (1984) 132(1): 266-271.

Schlom J. "Therapeutic cancer vaccines: current status and moving forward." *J Natl Cancer Inst*. (2012) 104(8): 599-613.

Seiwert T.Y., Burtness B., Mehra R., Weiss J., Berger R., Eder J.P., Heath K., McClanahan T., Lunceford J., Gause C., Cheng J.D. and Chow L.Q. "Safety and clinical activity of pembrolizumab for treatment of recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-012): an open-label, multicentre, phase 1b trial." *Lancet Oncol*. (2016) 17(7): 956-965.

Sharma P., Shen Y., Wen S., Yamada S., Jungbluth A.A., Gnjatic S., Bajorin D.F., Reuter V.E., Herr H., Old L.J. and Sato E. "CD8 tumor-infiltrating lymphocytes are predictive of survival in muscle-invasive urothelial carcinoma." *Proc Natl Acad Sci U S A*. (2007) 104(10): 3967-3972.

Shiboski C.H., Schmidt B.L. and Jordan R.C. "Tongue and tonsil carcinoma: increasing trends in the U.S. population ages 20-44 years." *Cancer*. (2005) 103(9): 1843-1849.

Siegel R., Naishadham D. and Jemal A. "Cancer statistics, 2012." *CA Cancer J Clin*. (2012) 62(1): 10-29.

Smeets S.J., Braakhuis B.J., Abbas S., Snijders P.J., Ylstra B., van de Wiel M.A., Meijer G.A., Leemans C.R. and Brakenhoff R.H. "Genome-wide DNA copy number alterations in head and neck squamous cell carcinomas with or without oncogene-expressing human papillomavirus." *Oncogene*. (2006) 25(17): 2558-2564.

Smith E.M., Ritchie J.M., Summersgill K.F., Klussmann J.P., Lee J.H., Wang D., Haugen T.H. and Turek L.P. "Age, sexual behavior and human papillomavirus infection in oral cavity and oropharyngeal cancers." *International journal of cancer. Journal international du cancer*. (2004) 108(5): 766-772.

Spanos W.C., Nowicki P., Lee D.W., Hoover A., Hostager B., Gupta A., Anderson M.E. and Lee J.H. "Immune response during therapy with cisplatin or radiation for human papillomavirus-related head and neck cancer." *Arch Otolaryngol Head Neck Surg*. (2009) 135(11): 1137-1146.

Sturgis E.M. and Ang K.K. "The epidemic of HPV-associated oropharyngeal cancer is here: is it time to change our treatment paradigms?" *J Natl Compr Canc Netw*. (2011) 9(6): 665-673.

Tilston P. "Anal human papillomavirus and anal cancer." *J Clin Pathol*. (1997) 50(8): 625-634.

Topalian S.L., Hodi F.S., Brahmer J.R., Gettinger S.N., Smith D.C., McDermott D.F., Powderly J.D., Carvajal R.D., Sosman J.A., Atkins M.B., Leming P.D., Spigel D.R., Antonia S.J., Horn L., Drake C.G., Pardoll D.M., Chen L., Sharfman W.H., Anders R.A., Taube J.M., McMiller T.L., Xu H., Korman A.J., Jure-Kunkel M., Agrawal S., McDonald D., Kollia G.D., Gupta A., Wigginton J.M. and Sznol M. "Safety, activity, and immune correlates of anti-PD-1 antibody in cancer." *The New England journal of medicine*. (2012) 366(26): 2443-2454.

Tsujihashi H., Matsuda H., Uejima S., Akiyama T. and Kurita T. "Immunocompetence of tissue infiltrating lymphocytes in bladder tumors." *J Urol*. (1988) 140(4): 890-894.

Tumeh P.C., Hellmann M.D., Hamid O., Tsai K.K., Loo K.L., Gubens M.A., Rosenblum M., Harview C.L., Taube J.M., Handley N., Khurana N., Nosrati A., Krummel M.F., Tucker A., Sosa E.V., Sanchez P.J., Banayan N., Osorio J.C., Nguyen-Kim D.L., Chang J., Shintaku I.P., Boasberg P.D., Taylor E.J., Munster P.N., Algazi A.P., Chmielowski B., Dummer R., Grogan T.R., Elashoff D., Hwang J., Goldinger S.M., Garon E.B., Pierce R.H. and Daud A. "Liver Metastasis and Treatment Outcome with Anti-PD-1 Monoclonal Antibody in Patients with Melanoma and NSCLC." *Cancer Immunol Res*. (2017) 5(5): 417-424.

Varma V.A., Sanchez-Lanier M., Unger E.R., Clark C., Tickman R., Hewan-Lowe K., Chenggis M.L. and Swan D.C. "Association of human papillomavirus with penile carcinoma: a study using polymerase chain reaction and in situ hybridization." *Hum Pathol*. (1991) 22(9): 908-913.

Villa L.L., Ault K.A., Giuliano A.R., Costa R.L., Petta C.A., Andrade R.P., Brown D.R., Ferenczy A., Harper D.M., Koutsky L.A., Kurman R.J., Lehtinen M., Malm C., Olsson S.E., Ronnett B.M., Skjeldestad F.E., Steinwall M., Stoler M.H., Wheeler C.M., Taddeo F.J., Yu J., Lupinacci L., Railkar R., Marchese R., Esser M.T., Bryan J., Jansen K.U., Sings H.L., Tamms G.M., Saah A.J. and Barr E. "Immunologic responses following administration of a vaccine targeting human papillomavirus Types 6, 11, 16, and 18." *Vaccine*. (2006) 24(27-28): 5571-5583.

Voskens C.J., Sewell D., Hertzano R., DeSanto J., Rollins S., Lee M., Taylor R., Wolf J., Suntharalingam M., Gastman B., Papadimitriou J.C., Lu C., Tan M., Morales R., Cullen K., Celis E., Mann D. and Strome S.E. "Induction of MAGE-A3 and HPV-16 immunity by Trojan vaccines in patients with head and neck carcinoma." *Head Neck*. (2012) 34(12): 1734-1746.

Wang D.D., Zhang S., Zhao H., Men A.Y. and Parivar K. "Fixed dosing versus body size-based dosing of monoclonal antibodies in adult clinical trials." *J Clin Pharmacol*. (2009) 49(9): 1012-1024.

Weber J.S., Kahler K.C. and Hauschild A. "Management of immune-related adverse events and kinetics of response with ipilimumab." *J Clin Oncol*. (2012) 30(21): 2691-2697.

Weinberger P.M., Yu Z., Haffty B.G., Kowalski D., Harigopal M., Brandsma J., Sasaki C., Joe J., Camp R.L., Rimm D.L. and Psyrri A. "Molecular classification identifies a subset of human papillomavirus--associated oropharyngeal cancers with favorable prognosis." *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. (2006) 24(5): 736-747.

Whiteside T.L. "Anti-tumor vaccines in head and neck cancer: targeting immune responses to the tumor." *Curr Cancer Drug Targets*. (2007) 7(7): 633-642.

Wilczynski S.P., Lin B.T., Xie Y. and Paz I.B. "Detection of human papillomavirus DNA and oncoprotein overexpression are associated with distinct morphological patterns of tonsillar squamous cell carcinoma." *Am J Pathol*. (1998) 152(1): 145-156.

Zhang L., Conejo-Garcia J.R., Katsaros D., Gimotty P.A., Massobrio M., Regnani G., Makrigiannakis A., Gray H., Schlienger K., Liebman M.N., Rubin S.C. and Coukos G. "Intratumoral T cells, recurrence, and survival in epithelial ovarian cancer." *N Engl J Med*. (2003) 348(3): 203-213.

Zhao X., Suryawanshi S., Hruska M., Feng Y., Wang X., Shen J., Vezina H.E., McHenry M.B., Waxman I.M., Achanta A., Bello A., Roy A. and Agrawal S. "Assessment of nivolumab benefit-risk profile of a 240-mg flat dose relative to a 3-mg/kg dosing regimen in patients with advanced tumors." *Ann Oncol*. (2017) 28(8): 2002-2008.

APPENDICES

APPENDIX I	PERFORMANCE STATUS (ECOG) SCALE
APPENDIX II	CONTRACEPTIVE GUIDANCE AND WOMAN OF CHILDBEARING POTENTIAL
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APPENDIX IIIB	STUDY FLOW-CHART Phase Ib and phase II part 1 From [Day 204 to end of study]
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APPENDIX IIID	STUDY FLOW-CHART Phase II part 2 From [Day 204 to end of study]
APPENDIX IV	ASSESSMENT OF EFFICACY ACCORDING TO RECIST
APPENDIX V	AVELUMAB SUMMARY OF SAFETY PROFILE

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 all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours.

3. Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours.

4. Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.

APPENDIX II: Contraceptive Guidance and Woman of Childbearing Potential

Birth control methods considered as highly effective

According to the Clinical Trials Facilitation Group (CTFG) "Recommendations related to contraception and pregnancy testing in clinical trials" methods that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered as highly effective birth control methods, such as:

- combined (estrogen and progesterone containing) hormonal contraception associated with inhibition of ovulation[1] (oral, intravaginal, transdermal)
- progesterone-only hormonal contraception associated with inhibition of ovulation[1] (oral, injectable, implantable[2])
- intrauterine device (IUD)[2]
- intrauterine hormone-releasing system (IUS)[2]
- bilateral tubal occlusion[2]
- vasectomized partner[2,3]

[1] Hormonal contraception may be susceptible to interaction with the IMP, which may reduce the efficacy of the contraception method

[2] Contraception methods in the context of this guidance are considered to have low user dependency

[3] Vasectomised partner is a highly effective birth control method provided that the partner is the sole sexual partner of the woman of childbearing potential trial participant and that the vasectomized partner has received medical assessment of the surgical success. If not, an additional highly effective method of contraception should be used.

Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

Women in the following categories are not considered WOCBP

1. Premenopausal female with 1 of the following:
    - Documented hysterectomy
    - Documented bilateral salpingectomy
    - Documented bilateral oophorectomy

    Note: Documentation can come from the site personnel's: review of participant's medical records, medical examination, or medical history interview.

2. Premenarchal

3. Postmenopausal female
    - Postmenopausal state is defined as ≥ 12 months of non-therapy-induced amenorrhea (A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal

contraception or hormonal replacement therapy). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

- Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Postmenopausal female or who have undergone hysterectomy or bilateral oophorectomy are exempt from pregnancy testing.

Contraceptive Guidance

Highly Effective Contraceptive Methods That Are User Dependent
Failure rate of <1% per year when used consistently and correctly.
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b] oral intravaginal transdermal
Progestogen-only hormonal contraception associated with inhibition of ovulation[b] oral injectable
Highly Effective Methods That Are User Independent
Implantable progestogen-only hormonal contraception associated with inhibition of ovulation[b] Intrauterine device (IUD) Intrauterine hormone-releasing system (IUS) bilateral tubal occlusion
Vasectomized partner (A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
NOTES: a) Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies. b) Hormonal contraception may be susceptible to interaction with the study drug, which may reduce the efficacy of the contraceptive method. In this case two highly effective methods of contraception should be utilized during the treatment period and for at least 3 months after the last dose of study treatment

APPENDIX IIIA: Phase Ib and phase II part 1 Study Flow-Chart [Baseline to Month 6 Day 204]

	Baseline		Study treatment period from [Baseline to Month 6 Day 204]																														
			Day					Day					Day					Day					Day					Day					
Study days*	-21/ 0	-7/ 0	1	8	15	22	29	36	43	50	57	64	71	78	85	92	99	106	113	120	127	134	141	148	155	162	169	176	183	190	197	204
Injection TG4001[a]			💉	💉	💉	💉	💉	💉		💉		💉		💉		💉		💉		💉		💉		💉		💉		💉		💉		💉
Avelumab administration[b]				X		X		X		X		X		X		X		X		X		X		X		X		X		X		X
Demography, history of studied disease, HPV status, relevant medical history / current medical conditions and signs and symptoms[c]	X																															
Inclusion/exclusion criteria check	X	X																														
Clinical evaluation and body weight[e]	X[d]		X	X	X	X	X	X		X		X		X		X		X		X		X		X		X		X		X		X
Performance status[e]	X		X		X		X			X		X		X		X		X		X		X		X		X		X		X		X
Cardiac evaluation (12-lead ECG)[f]		X																														
Adverse events reporting	X[g]		X	X	X	X	X	X		X		X		X		X		X		X		X		X		X		X		X		X
Concomitant medications and significant non-drug therapies collection	X[h]		X	X	X	X	X	X		X		X		X		X		X		X		X		X		X		X		X		X
Tumor evaluation[i]	X								X[j]						X[j]						X[j]						X[j]					
Further antineoplastic therapies																																
Hematology[e,k]		X	X	X	X	X	X	X		X		X		X		X		X		X		X		X		X		X		X		X
Biochemistry, creatinine[e,k]		X	X	X	X	X	X	X		X		X		X		X		X		X		X		X		X		X		X		X
Free T4		X																														
TSH[e,k]		X						X						X						X						X						X
HIV and HCV serology; detection of antigen HBs		X																														
Pregnancy test[l,e,k]		X						X						X						X						X						X
HLA typing[e]			X																													

	Baseline		Study treatment period from [Baseline to Month 6 Day 204]																														
			Day					Day					Day					Day					Day					Day						
Study days*	**-21/ 0**	**-7/ 0**	**1**	**8**	**15**	**22**	**29**	**36**	**43**	**50**	**57**	**64**	**71**	**78**	**85**	**92**	**99**	**106**	**113**	**120**	**127**	**134**	**141**	**148**	**155**	**162**	**169**	**176**	**183**	**190**	**197**	**204**
Tumor samples (repeated biopsy)	X[m]								X[m]						X[n]																		
Immunological tests[e]		X[q]	X[o]	X[p]					X[q]						X[p]																		X[q]

*** The time windows allowed for the visits are: +/- 1 day from Day 1 to Day 36; - 3 / + 1 days for the further study treatments visits beyond Day 36**

a TG4001 will be administered SC on a weekly basis on Days 1, 8, 15, 22 and 29 then once every 2 weeks (starting from Day 36) up to Month 6, thereafter every 12 weeks until disease progression, unacceptabe toxicity, patient withdrawal from study for any reason or for a maximum of 2 years, whichever occurs first.**

b Avelumab will be administered as an IV infusion once every 2 weeks starting on Day 8 (one week after the first dose of TG4001) until disease progression, unacceptabe toxicity, patient withdrawal from study for any reason or for a maximum of 2 years, whichever occurs first.** The bi-weekly 14-day schedule should be strictly adhered to, and patients should return to the target date (i.e. the next regularly scheduled visit relative to the start of avelumab) even if the previous visit was off schedule.

c From the date of signature of the ICF and before first study treatment administration for medical history, current medical conditions, signs and symptoms

d Height will be collected only at baseline.

e If during visits with study treatment administration, to be performed prior to study treatment administration.

f Repeated during study treatment as clinically indicated (see Section 7.3).

g From start of study treatment except for SAE which must be collected from signature date of ICF

h Since 1 month prior to study treatment start.

i Includes the following: preferably CT (or MRI) of the head and neck, chest, abdomen and all other known sites of disease (e.g. pelvis, if applicable); and an adequate radiological and/or isotopical exploration in case of bone pain. Tumor evaluation will be assessed locally using RECIST 1.1 at baseline and during the study. The same technique (CT/MRI) used at baseline should be utilized throughout the study.

j Tumor evaluation must be performed every 6 weeks for the first 9 months from treatment start and every 12 weeks thereafter, with a time window allowed of +/- 7 days .

k During the study, hematology and serum chemistry (and pregnancy test, if applicable) will be evaluated by local laboratories. The results of hematology and chemistry (and pregnancy test, if applicable) **must be reviewed before study treatment administration.** Local labs may be drawn up to 2 days before study treatment administration to meet this requirement.

l For women of childbearing potential

m Tumor biopsy; mandatory at baseline and on Day 43.

n Tumor biopsy on Day 85 unless it is unsafe or undesirable.

o One blood collection of 29 ml.

p Does not include blood collection for PBMC, blood collection is limited to 11.5 ml.

q One blood collection of 49 ml.

APPENDIX IIIB: Phase Ib and phase II part 1 STUDY FLOW-CHART From [Day 204 to end of study]

	Study treatment Period from [Day 204 to end of treatment]					End of treatment visit[r]	Safety follow-up visits		PFS-FU visit[j]	OS-FU[u]
Study days*	**Every 2 Weeks**	**Every 6 weeks**	**Every 12 weeks**	**Month 12**	**Month 24**		**30 days after last study treatment[s]**	**90 days after last dose (phone call)[t]**		
Injection TG4001[a]										
Avelumab administration[b]	X									
Clinical evaluation and body weight[e]	X					X	X			
Performance status[e]	X					X				
Cardiac evaluation (12-lead ECG)[f]						X				
Adverse events reporting	X					X	X	X		
Concomitant medications and significant non-drug therapies collection	X					X	X			
Tumor evaluation [i]		X[j]	X[j]						X	
Further antineoplastic therapies						X	X	X	X	X
Hematology[e,k]		X				X	X			
Biochemistry, creatinine[e,k]		X				X	X			
Pregnancy test[l,e,k]		X				X	X			
Free T4						X				
TSH[e,k]		X				X				
Immunological tests[e]				X[q]	X[q]					

*** The time windows allowed for these visits is - 3 / + 1 days**

a TG4001 will be administered SC every 12 weeks until disease progression, unacceptabe toxicity, patient withdrawal from study for any reason or for a maximum of 2 years, whichever occurs first.**

b Avelumab will be administered as an IV infusion once every 2 weeks until disease progression, unacceptabe toxicity, patient withdrawal from study for any reason or for a maximum of 2 years, whichever occurs first.** The bi-weekly 14-day schedule should be strictly adhered to, and patients should return to the target date (i.e. the next regularly scheduled visit relative to the start of avelumab) even if the previous visit was off schedule.

e If during visits with study treatment administration, to be performed prior to study treatment administration.

f Repeated during study treatment as clinically indicated (see Section 7.3).

i Includes the following: preferably CT (or MRI) of the head and neck, chest, abdomen and all other known sites of disease (e.g. pelvis, if applicable); and an adequate radiological and/or isotopical exploration in case of bone pain . Tumor evaluation will be assessed locally using RECIST 1.1 at baseline and during the study. The same technique (CT/MRI) used at baseline should be utilized throughout the study.

j Tumor evaluation must be performed every 6 weeks for the first 9 months from treatment start and every 12 weeks thereafter, with a time window allowed of +/- 7 days .

k During the study, hematology and serum chemistry (and pregnancy test, if applicable) will be evaluated by local laboratories. The results of hematology and chemistry (and pregnancy test, if applicable) **must be reviewed before study treatment administration.** Local labs may be drawn up to 2 days before study treatment administration to meet this requirement.

l For women of childbearing potential

q One blood collection of 49 ml.

r For each patient, an end of treatment visit (EOT) will be scheduled once the patient is discontinued from all study treatments.

s Must occur 30 days after the last study treatment administration. All AEs and SAEs will be documented until this visit.

t Must occur 90 days after the last study treatment administration. Patients will be contacted by telephone to collect information on new or ongoing SAEs and treatment-related non-serious AEs. Any SAE assessed as related to IMPs must be reported whenever it occurs, irrespective of the time elapsed since the last administration of IMPs. Patients with an ongoing SAE at the 90-day Safety Follow-up Phone Call must be monitored and followed by the Investigator until stabilization or until the outcome is known, unless the subject is documented as “lost to follow-up”.

u Long-term follow-up for survival, every 3 months after the safety follow-up visit or last PFS follow-up visit (may be performed by phone contact).

** Beyond 2 years of treatment and based on the clinical judgement of the investigator the patient could continue to receive study treatments.

APPENDIX IIIC: Phase II part 2 Study Flow-Chart [Baseline to Month 6 Day 204]

	Baseline		Study treatment period from [Baseline to Month 6 Day 204]																														
			Day						Day					Day					Day					Day					Day				
Study days*	**-21/ 0**	**-3/ 0**	**1**	**1 + 6h**	**8**	**15**	**22**	**29**	**36**	**43**	**50**	**57**	**64**	**71**	**78**	**85**	**92**	**99**	**106**	**113**	**120**	**127**	**134**	**141**	**148**	**155**	**162**	**169**	**176**	**183**	**190**	**197**	**204**
In the combination arm Injection TG4001[a]																																		
In both arms Avelumab administration[b]					X		X		X		X		X		X		X		X		X		X		X		X		X		X		X
Randomization			X																														
Demography, history of studied disease, HPV status, relevant medical history / current medical conditions and signs and symptoms[c]	X																																
Inclusion/exclusion criteria check	X	X	X																														
Clinical evaluation and body weight[e]	X[d]		X		X	X	X	X	X		X		X		X		X		X		X		X		X		X		X		X		X
Pulse oximetry on room air		X																															
Performance status[e]	X		X			X		X			X		X		X		X		X		X		X		X		X		X		X		X
Cardiac evaluation (12-lead ECG)[f]		X																															
Adverse events reporting	X[g]		X		X	X	X	X	X		X		X		X		X		X		X		X		X		X		X		X		X
Concomitant medications and significant non-drug therapies collection	X[h]		X		X	X	X	X	X		X		X		X		X		X		X		X		X		X		X		X		X
Tumor evaluation[i]	X									X[j]						X[j]						X[j]						X[j]						
Further antineoplastic therapies																																	
Hematology[e,k]		X			X	X	X	X	X		X		X		X		X		X		X		X		X		X		X		X		X
Biochemistry, creatinine[e,k]		X			X	X	X	X	X		X		X		X		X		X		X		X		X		X		X		X		X

	Baseline		Study treatment period from [Baseline to Month 6 Day 204]																														
			Day						Day					Day					Day					Day					Day				
Study days*	**-21/ 0**	**-3/ 0**	**1**	**1 + 6h**	**8**	**15**	**22**	**29**	**36**	**43**	**50**	**57**	**64**	**71**	**78**	**85**	**92**	**99**	**106**	**113**	**120**	**127**	**134**	**141**	**148**	**155**	**162**	**169**	**176**	**183**	**190**	**197**	**204**
Free T4		X																															
TSH[e,k]		X							X						X						X						X						X
HIV and HCV serology; detection of antigen HBs	X																																
Pregnancy test[l,e,k]		X							X						X						X						X						X
Tumor samples (repeated biopsy)	X[m]															X[m]																	
Immunological tests[e]		X[q]	X[o]	X[r]	X[p]	X[q]				X[q]						X[q]																	X[q]

*** The time windows allowed for the visits are: +/- 1 day from Day 1 to Day 36; - 3 / + 1 days for the further study treatments visits beyond Day 36**

a TG4001 will be administered SC on a weekly basis on Days 1, 8, 15, 22 and 29 then once every 2 weeks (starting from Day 36) up to Month 6 (Day 204) , thereafter every 12 weeks until disease progression, unacceptable toxicity, patient withdrawal from study for any reason or for a maximum of 2 years, whichever occurs first.**

b Avelumab will be administered as an IV infusion once every 2 weeks starting on Day 8 until disease progression, unacceptable toxicity, patient withdrawal from study for any reason or for a maximum of 2 years, whichever occurs first.** The bi-weekly 14-day schedule should be strictly adhered to, and patients should return to the target date (i.e. the next regularly scheduled visit relative to the start of avelumab) even if the previous visit was off schedule.

c From the date of signature of the ICF and before first study treatment administration for medical history, current medical conditions, signs and symptoms

d Height will be collected only at baseline.

e If during visits with study treatment administration, to be performed prior to study treatment administration.

f Repeated during study treatment as clinically indicated (see Section 7.3).

g From start of study treatment except for SAE which must be collected from signature date of ICF

h Since 1 month prior to study treatment start.

i Includes the following: preferably CT (or MRI) of the head and neck, chest, abdomen and all other known sites of disease (e.g. pelvis, if applicable); and an adequate radiological and/or isotopical exploration in case of bone pain. Tumor evaluation will be assessed locally using RECIST 1.1 at baseline and during the study. The same technique (CT/MRI) used at baseline should be utilized throughout the study.

j Tumor evaluation must be performed every 6 weeks for the first 9 months from treatment start and every 12 weeks thereafter, with a time window allowed of +/- 7 days .

k During the study, hematology and serum chemistry (and pregnancy test, if applicable) will be evaluated by local laboratories. The results of hematology and chemistry (and pregnancy test, if applicable) **must be reviewed before study treatment administration.** Local labs may be drawn up to 2 days before study treatment administration to meet this requirement.

l For women of childbearing potential

m Tumor biopsy; mandatory at baseline and on Day 85 for patients with accessible lesions. For patients without accessible lesions at baseline, archived tumor tissue must be available at baseline for determination of HPV-16 positivity and an archival sample obtained within one year prior to randomization must be available for translational analysis.

o Blood collection of 24 ml.

p Does not include blood collection for PBMC, blood collection is limited to 9 ml.

q Blood collection of 59 ml.

r One blood collection of 9 ml. Only for patients in combination arm treated with TG4001. Time window allowed is +/- 30min.

APPENDIX IIID: Phase II part 2 STUDY FLOW-CHART From [Day 204 to end of study]

	Study treatment Period from [Day 204 to end of treatment]					End of treatment visit[r]	Safety follow-up visits		PFS-FU visit[j]	OS-FU[u]
Study days*	**Every 2 Weeks**	**Every 6 weeks**	**Every 12 weeks**	**Month 9 Day 288**	**Month 12 Day 372**		**30 days after last study treatment[s]**	**90 days after last dose (phone call)[t]**		
In the combination arm Injection TG4001[a]										
In both arms Avelumab administration[b]	X									
Clinical evaluation and body weight[e]	X					X	X			
Performance status[e]	X					X				
Cardiac evaluation (12-lead ECG)[f]						X				
Adverse events reporting	X					X	X	X		
Concomitant medications and significant non-drug therapies collection	X					X	X			
Tumor evaluation [i]		X[j]	X[j]						X	
Further antineoplastic therapies						X	X	X	X	X
Hematology[e,k]		X				X	X			
Biochemistry, creatinine[e,k]		X				X	X			
Pregnancy test[l,e,k]		X				X	X			
Free T4						X				
TSH[e,k]		X				X				
Tumor samples (repeated biopsy)				X		X[v]			X[v]	
Immunological tests[e]				X[q]	X[p]					

*** The time windows allowed for these visits is - 3 / + 1 days**

a TG4001 will be administered SC every 12 weeks until disease progression, unacceptable toxicity, patient withdrawal from study for any reason or for a maximum of 2 years, whichever occurs first.**

b Avelumab will be administered as an IV infusion once every 2 weeks until disease progression, unacceptable toxicity, patient withdrawal from study for any reason or for a maximum of 2 years, whichever occurs first.** The bi-weekly 14-day schedule should be strictly adhered to, and patients should return to the target date (i.e. the next regularly scheduled visit relative to the start of avelumab) even if the previous visit was off schedule.

e If during visits with study treatment administration, to be performed prior to study treatment administration.

f Repeated during study treatment as clinically indicated (see Section 7.3).

i Includes the following: preferably CT (or MRI) of the head and neck, chest, abdomen and all other known sites of disease (e.g. pelvis, if applicable); and an adequate radiological and/or isotopical exploration in case of bone pain. Tumor evaluation will be assessed locally using RECIST 1.1 at baseline and during the study. The same technique (CT/MRI) used at baseline should be utilized throughout the study.

j Tumor evaluation must be performed every 6 weeks for the first 9 months from treatment start and every 12 weeks thereafter, with a time window allowed of +/- 7 days.

k During the study, hematology and serum chemistry (and pregnancy test, if applicable) will be evaluated by local laboratories. The results of hematology and chemistry (and pregnancy test, if applicable) **must be reviewed before study treatment administration.** Local labs may be drawn up to 2 days before study treatment administration to meet this requirement.

l For women of childbearing potential

p Does not include blood collection for PBMC, blood collection is limited to 9 ml.

q Blood collection of 59 ml.

r For each patient, an end of treatment visit (EOT) will be scheduled once the patient is discontinued from all study treatments.

s Must occur 30 days after the last study treatment administration. All AEs and SAEs will be documented until this visit.

t Must occur 90 days after the last study treatment administration. Patients will be contacted by telephone to collect information on new or ongoing SAEs and treatment-related non-serious AEs. Any SAE assessed as related to IMPs must be reported whenever it occurs, irrespective of the time elapsed since the last administration of IMPs. Patients with an ongoing SAE at the 90-day Safety Follow-up Phone Call must be monitored and followed by the Investigator until stabilization or until the outcome is known, unless the subject is documented as “lost to follow-up”.

u Long-term follow-up for survival, every 3 months after the safety follow-up visit or last PFS follow-up visit (may be performed by phone contact).

v For patients with accessible lesions tumor sample on biopsy at the time of progressive disease

** Beyond 2 years of treatment and based on the clinical judgement of the investigator the patient could continue to receive study treatments.

APPENDIX IV: Assessment of Efficacy According to RECIST 1.1

The assessment of efficacy is based on RECIST (version 1.1) {**Eisenhauer E.A., 2009**}
Tumor response will be evaluated by preferably CT (or MRI) of the head and neck, chest, abdomen and all other known sites of disease (e.g. pelvis, if applicable) every 6 weeks until documented progression or for a period of 9 months after start of study treatment, whichever occurs first. Beyond 9 months of treatment, the evaluations will be performed every 12 weeks until documented progression.
The same schedule of tumor evaluation will be applied for patients who stopped the study treatment for any reason other than progressive disease.

All patients will be followed off treatment for further antineoplastic therapies, and for survival on a 3-monthly basis until death, lost to follow-up or withdrawal of consent.

Same definitions and rules apply for method of assessment, measurability of tumor and baseline documentation of target and non-target lesions with RECIST 1.1.

1 Measurability of tumor

All measurements should be recorded in metric notation (mm).
At baseline, tumor lesions/lymph nodes will be categorized as measurable or non-measurable.
Lymph nodes that have a short axis <10mm at baseline are considered non-pathological and should not be recorded or followed.

If no measurable lesions are identified at baseline, the patient will not be allowed to enter the study.

1.1. Measurable

For tumor lesions: the longest diameter in the plane of measurement has to be recorded with a minimum size of 10mm by CT scan when CT scan slice thickness is no greater than 5mm.

For nodal lesions: at baseline and in the follow-up, only the short axis of lymph node will be measured and followed. To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed at baseline.

1.2. Non measurable

Non measurable lesions are defined as all other lesions present at baseline, including small lesions (longest diameter < 10 mm or pathological lymph node with ≥ 10 mm to < 15 mm short axis) as well as truly non measurable lesions (i.e., pleural effusion).

2 Baseline documentation of target and non-target lesions

At baseline, preferably CT (or MRI) of the head and neck, chest, abdomen and all other known sites of disease (e.g. pelvis, if applicable) are required. In case of bone pain, an adequate radiological and/or isotopic exploration is to be performed to research bone metastases.

All baseline evaluations should be performed as closely as possible and never more than 21 days before starting the study treatment. Each lesion reported must be uniquely and sequentially numbered on the eCRF, even if it resides in the same organ, from baseline and throughout the study.
For the evaluation of lesions at baseline and throughout the study, the lesions are classified as target and non-target lesions.

2.1. Target lesions

All measurable lesions (nodal or non-nodal) up to a maximum of 5 lesions in total (and a maximum of 2 per organ), should be identified as target lesions and will be recorded and measured at baseline. Target lesions should be selected on the basis of their size, be representative of all organs involved and should be those that lend themselves to reproducible and repeated measurements (clinical lesions should be avoided for target lesion evaluation).

2.2. Non-target lesions

All other lesions, including pathological lymph nodes, are considered non-target lesions. Measurements of these lesions are not required and these lesions should be followed as "present", "absent" or "worsening" throughout the study. Multiple non-target lesions involving the same organ can be assessed as a group and recorded as a single item (i.e., multiple liver metastases). Each non-target lesion identified at baseline should be assessed at each subsequent evaluation and be recorded in the eCRF.

Tumor markers will not be used as non-target lesions.

3 Tumor evaluation according to RECIST 1.1

To assess tumor response, the sum of the longest diameters for all target lesions (and short axis for nodal lesions) will be calculated at baseline and throughout the study. At each assessment, response is evaluated first separately for the target lesions and non-target lesions identified at baseline. These evaluations are then used to calculate the overall lesion response considering the target and non-target lesions as well as the presence or absence of new lesions.

3.1 Determination of target lesions response

- **Complete Response (CR)**: Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.
- **Partial Response (PR)**: Decrease of at least 30% in the sum of the diameters of target lesions, taking as reference the baseline sum of diameters.
- **Progressive Disease (PD)**: Increase of at least 20% in the sum of diameters of target lesions and new lesions, taking as reference the smallest sum on study (including baseline evaluation). In addition to the relative increase of 20%, the sum must also demonstrate an

absolute increase of at least 5 mm. The appearance of one or more new lesions is also considered as progression.
- **Stable Disease (SD):** Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.
- **Not Evaluated (NE):** Progression has not been documented and one or more target lesions have not been assessed or have been assessed using a different method than baseline. The only exception is if the SLD of the evaluable target lesions already qualifies for PD. In this case, the Target Response will be PD.

Notes for lymph nodes as target lesions

Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as baseline), even if the nodes regress to below 10mm on study (defined as a normal lymph node). The actual short axis measurement of the nodes is to be included in the sum of target lesions.
This means also that when lymph nodes are included as target lesions, the sum of lesions may not be zero even if CR criteria are met, since a normal lymph node is defined as having a short axis < 10 mm.
Following a CR, a PD can subsequently only be assigned for target lesion response if either a non-nodal lesion reappears or if the absolute sum of the remaining nodal target lesions increases by at least 5mm and at least one of those remaining lesions are at least 10mm in size.

Target lesions that become too small to measure

While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even very small (e.g., 2 mm). However, if it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present but too small to measure a default value of 5 mm according to the slice thickness should be assigned. However, if the radiologist is able to provide an actual measure, that should be recorded even if it is below 5 mm.

Lesions that split or coalesce

In some circumstances, disease that is measurable as a target lesion at baseline and appears to be one mass can split and become two or more smaller sub-lesions. When this occurs, the diameters (long axis for non-nodal lesions; short axis for nodal lesions) of the two split lesions should be added together and the sum recorded in the diameter field on the eCRF under the original lesion number. This value will be included in the sum of diameters when deriving target lesion response. The individual split lesions will not be considered as new lesions, and will not automatically trigger a PD designation.
Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesions. If the lesions have truly coalesced such that they are no longer separable, the maximal diameter (long axis for non-nodal lesions; short axis for nodal lesions) for “merged lesion” should be used when calculating the sum of diameters for target lesions. On the eCRF, the diameter of the “merged lesion” should be recorded for the size of one of the original lesions while a size of 0 mm should be entered for the remaining lesion numbers which have coalesced.

Reappearance of lesions

If the lesion appears at the same anatomical location where a target lesion had previously disappeared, it is advised that the time point lesion disappearance be re-evaluated to make sure that the lesion was not actually present and/or not visualized for technical reasons in this previous assessment. If it is not possible to change the 0 value, then the investigator/radiologist has to decide between the following possibilities:

- The lesion is a new lesion, in which case the overall assessment will be considered as PD.
- The lesion is clearly a reappearance of a previously disappeared lesion, in which case the lesion has to be entered in the eCRF with the same numbering as baseline and the tumor assessment will remain based on the sum of tumor measurements as presented above. Proper documentation should be available to support this decision.

For those patients who have only one target lesion at baseline, the reappearance of the target lesion which disappeared previously, even if still small, is considered a PD.

Missing measurements

In cases where measurements are missing for one or more target lesions, it is sometimes still possible to assign PD if the sum of the diameters of the remaining lesions qualifies already for a PD. However, in other cases where a PD cannot definitely be attributed, the target lesion response would be NE.

3.2 Determination of non-target lesions response

- **Complete Response (CR)**: Disappearance of all non-target lesions. In addition, all lymph nodes assigned as non-target lesions at baseline must be non-pathological in size (<10mm in short axis).
- **Incomplete Response/Stable Disease (SD)**: neither CR nor PD.
- **Progressive disease (PD): Unequivocal progression** of existing non-target lesions.
- **Not All Evaluated (NE):** Progression has not been documented and one or more non-target lesions have not been assessed or have been assessed using a different method than baseline not allowing a reliable comparison.

To achieve "**unequivocal progression**" on the basis of the non-target disease, there must be an overall level of substantially worsening in non-target disease such that, even in the presence of CR, PR or SD in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A "modest" increase in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of progression solely on the basis of change in non-target disease in the face of CR, PR or SD of target disease will therefore be extremely rare.

3.3 New lesions

The appearance of a new lesion is not always associated with PD. A lesion identified on a follow-up assessment in an anatomical location that was not scanned at baseline is also considered a new lesion.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If at the next scheduled assessment, PD is confirmed, the date of progression would be the earlier date when PD was suspected.

3.4 Evaluation of overall lesion response according to RECIST 1.1

The evaluation of overall response at each assessment is a composite of the target lesions response, non-target lesions response and presence of new lesions as shown below.

Overall response by time point (RECIST 1.1)

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR[1]
CR	Incomplete response/Stable disease Or not all evaluated (NE)	No	PR
PR	Non-PD **or** not all evaluated (NE)	No	PR[1]
SD	Non-PD **or** not all evaluated (NE)	No	SD[1, 2]
Not all evaluated (NE)	Non-PD or not all evaluated (NE)	No	Not evaluable[1] (NE)
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

[1] this overall lesion response also applies when there are no non-target lesions identified at baseline.
[2]once confirmed PR is achieved, all these assessments are considered PR.

If no non-target lesions are identified at baseline, the non-target lesion response at each assessment will be considered “not applicable” (NA).

In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of CR depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate / biopsy) to confirm CR. It may be sometimes reasonable to incorporate Fluorodeoxyglucose Positron Emission Tomography (FDG-PET) scanning to complement CT in assessment of progression (especially in case of possible “new” lesion) or in case where a residual radiographic abnormality is thought to represent fibrosis or scarring.

For equivocal findings of PD (e.g., very small and uncertain new lesions, cystic changes or necrosis in existing lesions) treatment may continue until the next scheduled assessment.

3.5 Best overall response according to RECIST 1.1

The best overall response is the best response recorded from the inclusion/ randomization until disease progression/recurrence (taking as reference for PD the smallest sum on study including baseline evaluation).

The best overall response for each patient is determined from the sequence of overall lesion responses by time point according to the following rules:

Best overall response when confirmation of CR and PR required.		
Overall response First Time	Overall response Subsequent time	Best Overall Response
CR	CR	CR
CR	PR	SD, PD or PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise NE
PR	PR	PR
PR	CR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise NE
NE	NE	NE
CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable. a If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR		

- CR: at least two determinations of CR at least 4 weeks apart before progression.
- PR: at least two determinations of PR (or better) at least 4 weeks apart before progression.
- SD: at least one SD assessment (or better) > after a minimum exposure of 5 weeks.

APPENDIX V: Avelumab Summary of Safety Profile

Extract of the Bavencio Summary of Product Characteristics (SmPC) dated 19 October 2022

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

4.8 Undesirable effects

Summary of the safety profile
Avelumab is associated with immune-related adverse reactions. Most of these, including severe reactions, resolved following initiation of appropriate medical therapy or withdrawal of avelumab (see "Description of selected adverse reactions" below).

The most common adverse reactions with avelumab were fatigue (30.0%), nausea (23.6%), diarrhoea (18.5%), constipation (18.1%), decreased appetite (17.6%), infusion-related reactions (15.9%), vomiting (15.6%), and weight decreased (14.5%).

The most common Grade ≥ 3 adverse reactions were anaemia (5.6%), hypertension (3.9%), hyponatraemia (3.6%), dyspnoea (3.5%), and abdominal pain (2.6%). Serious adverse reactions were immune-related adverse reactions and infusion-related reaction (see section 4.4).

Tabulated list of adverse reactions
The safety of avelumab as monotherapy has been evaluated in 2,082 patients with solid tumours including metastatic MCC or locally advanced or metastatic UC receiving 10 mg/kg every 2 weeks of avelumab in clinical studies (see Table 2).

These reactions are presented by system organ class and frequency. Frequencies are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Table 2: Adverse reactions in patients treated with avelumab as monotherapy

Frequency	Adverse reactions
Blood and lymphatic system disorders	
Very common	Anaemia
Common	Lymphopenia, thrombocytopenia
Uncommon	Eosinophilia§
Immune system disorders	
Uncommon	Hypersensitivity, drug hypersensitivity
Rare	Anaphylactic reaction, Type I hypersensitivity
Endocrine disorders	
Common	Hypothyroidism*, hyperthyroidism*
Uncommon	Adrenal insufficiency*, autoimmune thyroiditis*, thyroiditis*, autoimmune hypothyroidism*
Rare	Adrenocortical insufficiency acute*, hypopituitarism*
Metabolism and nutrition disorders	
Very common	Decreased appetite
Common	Hyponatraemia
Uncommon	Hyperglycaemia*
Rare	Diabetes mellitus*, Type 1 diabetes mellitus*
Nervous system disorders	
Common	Headache, dizziness, neuropathy peripheral
Uncommon	Myasthenia gravis†, myasthenic syndrome†
Rare	Guillain-Barré Syndrome*, Miller Fisher syndrome*
Eye disorders	
Rare	Uveitis*
Cardiac disorders	
Rare	Myocarditis*
Vascular disorders	
Common	Hypertension
Uncommon	Hypotension, flushing
Respiratory, thoracic and mediastinal disorders	
Very common	Cough, dyspnoea
Common	Pneumonitis*
Rare	Interstitial lung disease*
Gastrointestinal disorders	
Very common	Nausea, diarrhoea, constipation, vomiting, abdominal pain
Common	Dry mouth
Uncommon	Ileus, colitis*
Rare	Pancreatitis*, autoimmune colitis*, enterocolitis*, autoimmune pancreatitis*, enteritis*, proctitis*
Hepatobiliary disorders	
Uncommon	Autoimmune hepatitis*
Rare	Acute hepatic failure*, hepatic failure*, hepatitis*, hepatotoxicity*
Skin and subcutaneous tissue disorders	
Common	Pruritus*, rash*, dry skin, rash maculo-papular*
Uncommon	Eczema, dermatitis, rash pruritic*, psoriasis*, erythema*, rash erythematous*, rash generalised*, rash macular*, rash papular*
Rare	Erythema multiforme*, purpura*, vitiligo*, pruritus generalised*, dermatitis exfoliative*, pemphigoid*, dermatitis psoriasiform*, drug eruption*, lichen planus*
Musculoskeletal and connective tissue disorders	
Very common	Back pain, arthralgia
Common	Myalgia
Uncommon	Myositis*, rheumatoid arthritis*

Frequency	Adverse reactions
Rare	Arthritis*, polyarthritis*, oligoarthritis*
Renal and urinary disorders	
Uncommon	Renal failure*, nephritis*
Rare	Tubulo-interstitial nephritis*
General disorders and administrative site conditions	
Very common	Fatigue, pyrexia, oedema peripheral
Common	Asthenia, chills, influenza like illness
Rare	Systemic inflammatory response syndrome*
Investigations	
Very common	Weight decreased
Common	Blood creatinine increased, blood alkaline phosphatase increased, lipase increased, gamma-glutamyltransferase increased, amylase increased
Uncommon	Alanine aminotransferase (ALT) increased*, aspartate aminotransferase (AST) increased*, blood creatine phosphokinase increased*
Rare	Transaminases increased*, thyroxine free decreased*, blood thyroid stimulating hormone increased*
Injury, poisoning and procedural complications	
Very common	Infusion related reaction

* Immune-related adverse reaction based on medical review
† Adverse reactions occurred in estimated 4,000 patients exposed to avelumab monotherapy beyond the pooled analysis.
§ Reaction only observed from study EMR 100070-003 (Part B) after the data cut-off of the pooled analysis, hence frequency estimated

Renal cell carcinoma

Summary of the safety profile
The safety of avelumab in combination with axitinib has been evaluated in 489 patients with advanced RCC receiving 10 mg/kg avelumab every 2 weeks and axitinib 5 mg orally twice daily in two clinical studies.

In this patient population, the most common adverse reactions were diarrhoea (62.8%), hypertension (49.3%), fatigue (42.9%), nausea (33.5%), dysphonia (32.7%), decreased appetite (26.0%), hypothyroidism (25.2%), cough (23.7%), headache (21.3%), dyspnoea (20.9%), and arthralgia (20.9%).

Tabulated list of adverse reactions
Adverse reactions reported for 489 patients with advanced RCC treated in two clinical studies with avelumab in combination with axitinib are presented in Table 3.

These reactions are presented by system organ class and frequency. Frequencies are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Table 3: Adverse reactions in patients treated with avelumab in combination with axitinib in clinical studies B9991002 and B9991003

Frequency	Adverse reactions
Infections and infestations	
Uncommon	Rash pustular
Blood and lymphatic system disorders	
Common	Anaemia, thrombocytopenia
Uncommon	Lymphopenia, eosinophilia

Frequency	Adverse reactions
Immune system disorders	
Common	Hypersensitivity
Endocrine disorders	
Very common	Hypothyroidism
Common	Hyperthyroidism, adrenal insufficiency, thyroiditis
Uncommon	Autoimmune thyroiditis, hypophysitis
Metabolism and nutrition disorders	
Very common	Decreased appetite
Common	Hyperglycaemia
Uncommon	Diabetes mellitus, Type 1 diabetes mellitus
Nervous system disorders	
Very common	Headache, dizziness
Common	Neuropathy peripheral
Uncommon	Myasthenia gravis, myasthenic syndrome
Cardiac disorders	
Uncommon	Myocarditis
Vascular disorders	
Very common	Hypertension
Common	Hypotension, flushing
Respiratory, thoracic and mediastinal disorders	
Very common	Dysphonia, cough, dyspnoea
Common	Pneumonitis
Gastrointestinal disorders	
Very common	Diarrhoea, nausea, constipation, vomiting, abdominal pain
Common	Dry mouth, colitis
Uncommon	Autoimmune colitis, autoimmune pancreatitis, enterocolitis, ileus, pancreatitis necrotizing
Hepatobiliary disorders	
Common	Hepatic function abnormal
Uncommon	Hepatitis, hepatotoxicity, immune-mediated hepatitis, liver disorder
Skin and subcutaneous tissue disorders	
Very common	Rash, pruritus
Common	Rash pruritic, rash maculo-papular, pruritus generalized, dermatitis acneiform, erythema, rash macular, rash papular, rash erythematous, dermatitis, eczema, rash generalized
Uncommon	Drug eruption, erythema multiforme, psoriasis
Musculoskeletal and connective tissue disorders	
Very common	Arthralgia, back pain, myalgia
Renal and urinary disorders	
Common	Acute kidney injury
General disorders and administrative site conditions	
Very common	Fatigue, chills, asthenia, pyrexia
Common	Oedema peripheral, influenza like illness
Investigations	
Very common	Weight decreased, alanine aminotransferase (ALT) increased, aspartate aminotransferase (AST) increased
Common	Blood creatinine increased, amylase increased, lipase increased, gamma-glutamyltransferase increased, blood alkaline phosphatase increased, blood creatine phosphokinase increased, blood thyroid stimulating hormone decreased, transaminases increased
Uncommon	Liver function test increased
Injury, poisoning and procedural complications	
Very common	Infusion related reaction

Description of selected adverse reactions
Data for immune-related adverse reactions for avelumab as a monotherapy are based on 2,082 patients including 1,650 patients in the phase I study EMR100070-001 in solid tumours, 88 patients in study EMR100070-003 in MCC, and 344 patients in study B9991001 in UC, and for avelumab in combination with axitinib are based on 489 patients in studies B9991002 and B9991003 in RCC (see section 5.1).

The management guidelines for these adverse reactions are described in section 4.4.

Immune-related pneumonitis
In patients treated with avelumab as monotherapy, 1.3% (28/2,082) of patients developed immune-related pneumonitis. Of these patients, there was 1 (less than 0.1%) patient with a fatal outcome, 1 (less than 0.1%) patient with Grade 4, and 6 (0.3%) patients with Grade 3 immune-related pneumonitis.

The median time to onset of immune-related pneumonitis was 2.5 months (range: 3 days to 13.8 months). The median duration was 8.1 weeks (range: 4 days to more than 4.9 months).

Avelumab was discontinued in 0.4% (9/2,082) of patients due to immune-related pneumonitis. All 28 patients with immune-related pneumonitis were treated with corticosteroids and 21 (75%) of the 28 patients were treated with high-dose corticosteroids for a median of 9 days (range: 1 day to 2.3 months). Immune-related pneumonitis resolved in 18 (64.3%) of the 28 patients at the time of data cut-off.

In patients treated with avelumab in combination with axitinib, 0.6% (3/489) of patients developed immune-related pneumonitis. Of these patients, none experienced immune-related pneumonitis Grade $\geq$ 3.

The median time to onset of immune-related pneumonitis was 3.7 months (range: 2.7 months to 8.6 months). The median duration was 2.6 months (range: 3.3 weeks to more than 7.9 months).

Immune-related pneumonitis did not lead to discontinuation of avelumab in any patient. All 3 patients with immune-related pneumonitis were treated with high-dose corticosteroids for a median of 3.3 months (range: 3 weeks to 22.3 months). Immune-related pneumonitis resolved in 2 (66.7%) of the 3 patients at the time of data cut-off.

Immune-related hepatitis
In patients treated with avelumab as monotherapy, 1.0% (21/2,082) of patients developed immune-related hepatitis. Of these patients, there were 2 (0.1%) patients with a fatal outcome, and 16 (0.8%) patients with Grade 3 immune-related hepatitis.

The median time to onset of immune-related hepatitis was 3.3 months (range: 9 days to 14.8 months). The median duration was 2.5 months (range: 1 day to more than 7.4 months).

Avelumab was discontinued in 0.6% (13/2,082) of patients due to immune-related hepatitis. All 21 patients with immune-related hepatitis were treated with corticosteroids and 20 (95.2%) of the 21 patients received high-dose corticosteroids for a median of 17 days (range: 1 day to 4.1 months). Immune-related hepatitis resolved in 12 (57.1%) of the 21 patients at the time of data cut-off.

In patients treated with avelumab in combination with axitinib, 6.3% (31/489) of patients developed immune-related hepatitis. Of these patients, there were 18 (3.7%) patients with Grade 3 and 3 (0.6%) patients with Grade 4 immune-related hepatitis.

The median time to onset of immune-related hepatitis was 2.3 months (range: 2.1 weeks to 14.5 months). The median duration was 2.1 weeks (range: 2 days to 8.9 months).

Avelumab was discontinued in 4.7% (23/489) of patients due to immune-related hepatitis. All 31 patients with immune-related hepatitis were treated for hepatitis including 30 (96.8%) patients treated with corticosteroids and 1 patient with a non-steroidal immunosuppressant. Twenty-eight (90.3%) of the 31 patients received high dose corticosteroids for a median of 2.4 weeks (range: 1 day to 10.2 months). Immune-related hepatitis resolved in 27 (87.1%) of the 31 patients at the time of data cut-off.

Immune-related colitis
In patients treated with avelumab as monotherapy, 1.5% (31/2,082) of patients developed immune-related colitis. Of these patients, there were 10 (0.5%) patients with Grade 3 immune-related colitis.

The median time to onset of immune-related colitis was 2.0 months (range: 2 days to 11.5 months). The median duration was 5.9 weeks (range: 1 day to more than 14 months).

Avelumab was discontinued in 0.5% (11/2,082) of patients due to immune-related colitis. All 31 patients with immune-related colitis were treated with corticosteroids and 19 (61.3%) of the 31 patients received high-dose corticosteroids for a median of 19 days (range: 1 day to 2.3 months). Immune-related colitis resolved in 22 (71%) of 31 patients at the time of data cut-off.

In patients treated with avelumab in combination with axitinib, 2.7% (13/489) of patients developed immune-related colitis. Of these patients, there were 9 (1.8%) patients with Grade 3 immune-related colitis.

The median time to onset of immune-related colitis was 5.1 months (range: 2.3 weeks to 14 months). The median duration was 1.6 weeks (range: 1 day to more than 9 months).

Avelumab was discontinued in 0.4% (2/489) of patients due to immune-related colitis. All 13 patients with immune-related colitis were treated with corticosteroids and 12 (92.3%) of the 13 patients received high-dose corticosteroids for a median of 2.3 weeks (range: 5 days to 4.6 months). Immune-related colitis resolved in 10 (76.9%) of 13 patients at the time of data cut-off.

Immune-related pancreatitis
In patients treated with avelumab as monotherapy, immune-related pancreatitis occurred in less than 1% (1/4,000) of patients across clinical trials in multiple tumour types and in 0.6% (3/489) of patients receiving avelumab in combination with axitinib including 2 (0.4%) patients with fatal outcome.

Immune-related myocarditis
In patients treated with avelumab as monotherapy, immune-related myocarditis occurred in less than 1% (5/4,000) of patients across clinical trials in multiple tumour types and in 0.6% (3/489) of patients receiving avelumab in combination with axitinib including 2 (0.4%) patients with fatal outcome.

Immune-related endocrinopathies
Thyroid disorders
In patients treated with avelumab as monotherapy, 6.7% (140/2,082) of patients developed immune-related thyroid disorders, including 127 (6.1%) patients with hypothyroidism, 23 (1.1%) with hyperthyroidism, and 7 (0.3%) with thyroiditis. Of these patients, there were 4 (0.2%) patients with Grade 3 immune-related thyroid disorders.

The median time to onset of thyroid disorders was 2.8 months (range: 2 weeks to 12.8 months). The median duration was not estimable (range: 3 days to more than 27.6 months).

Avelumab was discontinued in 0.2% (4/2,082) of patients due to immune-related thyroid disorders. Thyroid disorders resolved in 14 (10%) of the 140 patients at the time of data cut-off.

In patients treated with avelumab in combination with axitinib, 24.7% (121/489) of patients developed immune-related thyroid disorders, including 111 (22.7%) patients with hypothyroidism, 17 (3.5%)

with hyperthyroidism, and 7 (1.4%) with thyroiditis. Of these patients, there were 2 (0.4%) patients with Grade 3 immune-related thyroid disorders.

The median time to onset of thyroid disorders was 2.8 months (range: 3.6 weeks to 19.3 months). The median duration was not estimable (range: 8 days to more than 23.9 months).

Avelumab was discontinued in 0.2% (1/489) of patients due to immune-related thyroid disorders. Thyroid disorders resolved in 15 (12.4%) of the 121 patients at the time of data cut-off.

Adrenal insufficiency
In patients treated with avelumab as monotherapy, 0.5% (11/2,082) of patients developed immune-related adrenal insufficiency. Of these patients, there was 1 (less than 0.1%) patient with Grade 3 immune-related adrenal insufficiency.

The median time to onset of immune-related adrenal insufficiency was 3.3 months (range: 1 day to 7.6 months). The median duration was not estimable (range: 2 days to more than 10.4 months).

Avelumab was discontinued in 0.1% (2/2,082) of patients due to immune-related adrenal insufficiency. All 11 patients with immune-related adrenal insufficiency were treated with corticosteroids, and 5 (45.5%) of the 11 patients received high-dose systemic corticosteroids (≥ 40 mg prednisone or equivalent) for a median of 2 days (range: 1 day to 24 days). Adrenal insufficiency resolved in 3 (27.3%) of patients at the time of data cut-off.

In patients treated with avelumab in combination with axitinib, 1.8% (9/489) of patients developed immune-related adrenal insufficiency. Of these patients, there were 2 (0.4%) patients with Grade 3 immune-related adrenal insufficiency.

The median time to onset of immune-related adrenal insufficiency was 5.5 months (range: 3.6 weeks to 8.7 months). The median duration was 2.8 months (range: 3 days to more than 15.5 months).

Immune-related adrenal insufficiency did not lead to discontinuation of avelumab in any patient. Eight (88.9%) patients with immune-related adrenal insufficiency were treated with corticosteroids and 2 (25%) of the 8 patients received high-dose corticosteroids (≥ 40 mg prednisone or equivalent) for a median of 8 days (range: 5 days to 11 days). Adrenal insufficiency resolved in 4 (44.4%) of the 9 patients at the time of data cut-off.

Type 1 diabetes mellitus
In patients treated with avelumab as monotherapy, Type 1 diabetes mellitus without an alternative aetiology occurred in 0.2% (5/2,082) of patients. All 5 patients experienced Grade 3 Type 1 diabetes mellitus.

The median time to onset of Type 1 diabetes mellitus was 3.3 months (range: 1 day to 18.7 months). The median duration was not estimable (range: 14 days to more than 4.8 months).

Avelumab was discontinued in 0.1% (2/2,082) of patients due to Type 1 diabetes mellitus. Type 1 diabetes mellitus resolved in 2 (40%) patients at the time of data cut-off.

In patients treated with avelumab in combination with axitinib, Type 1 diabetes mellitus without an alternative aetiology occurred in 1.0% (5/489) of patients. Of these patients, there was 1 (0.2%) patient with Grade 3 Type 1 diabetes mellitus.

The median time to onset of Type 1 diabetes mellitus was 1.9 months (range: 1.1 months to 7.3 months).

Avelumab was discontinued in 0.2% (1/489) of patients due to Type 1 diabetes mellitus. All 5 patients with Type 1 diabetes mellitus were treated with insulin. Type 1 diabetes mellitus did not resolve in any of the patients at the time of data cut-off.

Immune-related nephritis and renal dysfunction
In patients treated with avelumab as monotherapy, immune-related nephritis occurred in 0.3% (7/2 082) of patients. There was 1 (less than 0.1%) patient with Grade 3 immune-related nephritis.

The median time to onset of immune-related nephritis was 2.4 months (range: 7.1 weeks to 21.9 months). The median duration was 6.1 months (range: 9 days to 6.1 months).

Avelumab was discontinued in 0.2% (4/2 082) of patients due to immune-related nephritis. All 7 patients with immune-related nephritis were treated with corticosteroids. 6 (85.7%) of those 7 patients with immune-related nephritis were treated with high-dose corticosteroids for a median of 2.5 weeks (range: 6 days to 2.8 months). Immune-related nephritis resolved in 4 (57.1%) patients at the time of data cut-off.

In patients treated with avelumab in combination with axitinib, immune-related nephritis occurred in 0.4% (2/489) of patients. Of these patients, there were 2 (0.4%) patients with Grade 3 immune-related nephritis.

The median time to onset of immune-related nephritis was 1.2 months (range: 2.9 weeks to 1.8 months). The median duration was 1.3 weeks (range: more than 4 days to 1.3 weeks).

Immune-related nephritis did not lead to discontinuation of avelumab in any patient. All 2 patients with immune-related nephritis were treated with high-dose corticosteroids for a median of 1.1 weeks (range: 3 days to 1.9 weeks). Immune-related nephritis resolved in 1 (50%) of the 2 patients at the time of data cut-off.

Hepatotoxicity (in combination with axitinib)
In patients treated with avelumab in combination with axitinib, Grades 3 and Grade 4 increased ALT and increased AST were reported in 9% and 7% of patients, respectively.

In patients with ALT $\geq$ 3 times ULN (Grades 2-4, n=82), ALT resolved to Grades 0-1 in 92%.

Among the 73 patients who were rechallenged with either avelumab (59%) or axitinib (85%) monotherapy or with both (55%), 66% had no recurrence of ALT $\geq$ 3 times ULN.

Immunogenicity
For study EMR107000-003 in the MCC population, out of 204 patients (88 from Part A and 116 from Part B) with at least one valid anti-drug antibodies (ADA) result at any time point treated with avelumab 10 mg/kg as an intravenous infusion every 2 weeks, 189 (79 from Part A and 110 from Part B) were evaluable for treatment-emergent ADA and 16 (8.5%) (7 from Part A and 9 from Part B) tested positive.

For study B9991001 in the UC population, out of 344 patients with at least one valid ADA result at any time point treated with avelumab 10 mg/kg as an intravenous infusion every 2 weeks plus BSC, 325 were evaluable for treatment-emergent ADA and 62 (19.1%) tested positive.

For study B9991002 and study B9991003 in the RCC population, out of 480 patients with at least one valid ADA result at any time point treated with avelumab 10 mg/kg as an intravenous infusion every 2 weeks in combination with axitinib 5 mg twice daily, 453 were evaluable for treatment-emergent ADA and 66 (14.6%) tested positive.

Overall, there was no evidence of altered pharmacokinetic profile, increased incidence of infusion reactions or effects on efficacy with anti-avelumab antibody development. The impact of neutralizing antibodies (nAb) is unknown.