transgene

Clinical Study Protocol

A phase I/IIa trial to evaluate the safety and efficacy of the combination of the oncolytic immunotherapy Pexa-Vec with the PD-1 receptor blocking antibody nivolumab in the first-line treatment of advanced hepatocellular carcinoma (HCC)

Study phase: I/IIa

PROTOCOL N° TG6006.01
Amended Version: March 20, 2019

EUDRACT N° 2016-000085-32
IND N° 17439
NCT03071094

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CONFIDENTIAL

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COORDINATING INVESTIGATOR: [redacted]

SPONSOR:

Transgene S.A.
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INVESTIGATORS / STUDY ADMINISTRATIVE STRUCTURE

NAMES AND CONTACT DETAILS

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

[redacted]

Statistician [redacted]

A complete list of details for the Independent Safety Committee 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)

[redacted]

Signature Date

[redacted]

Signature Date

COORDINATING INVESTIGATOR

[redacted]

Signature Date

STATISTICIAN

[redacted]

Signature Date

SYNOPSIS

Sponsor: Transgene - IMP1 (Investigational Medicinal Product): Nivolumab, programmed death receptor-1 (PD-1) blocking antibody (Opdivo® - BMS) - IMP2: Pexastimogene devacirepvec, Vaccinia GMCSF Thymidine Kinase-Deactivated Virus (Pexa-Vec-, JX594, TG6006 - Transgene)	Clinical Protocol: TG6006.01 EudraCT N° 2016-000085-32 IND N° 17439
Study Title: A phase I/IIa trial to evaluate the safety and efficacy of the combination of the oncolytic immunotherapy Pexa-Vec with the PD-1 receptor blocking antibody nivolumab in the first-line treatment of advanced hepatocellular carcinoma (HCC)	
Coordinating Investigator: [redacted]	
Investigational Centers: [redacted]	
Study Period: Q4 2016 – Q4 2018	**Clinical Phase:** Phase I/IIa

Objectives

Primary objective

Phase I part: To evaluate the safety profile of intratumoral (IT) Pexa-Vec combined with intravenous (IV) nivolumab in patients with advanced HCC.

Phase IIa part: To evaluate the anti-tumor activity and efficacy of IT Pexa-Vec combined with IV nivolumab in patients with advanced HCC with respect to Overall Response Rate (ORR) (RECIST 1.1).

Secondary objectives

To evaluate the efficacy of Pexa-Vec combined with nivolumab in patients with advanced HCC with respect to the following endpoints (imaging endpoints evaluated by RECIST 1.1):

- Safety (Phase IIa)
- Disease Control Rate (DCR) at 4 months
- Disease Control Rate (DCR), percent non-progressors over time
- Time to Progression (TTP)
- Duration of Response (DoR)
- Progression Free Survival (PFS), median and proportion of non progressor patients over time
- Overall Survival (OS), median and percent survivors over time
- Blood viral load (HCV, HBV when appropriate)

Exploratory objectives

[redacted]

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[redacted]

Rationale

HCC is an inflammation-associated cancer that can be considered as an immunogenic tumor for several reasons including the high rate of spontaneous regression for which antitumor immunity has been recognized as a leading mechanism (*Oquinena et al. 2009*), the observations that patients whose tumors contain lymphocytic infiltrates show longer survival and lower risk of recurrence (*Prieto J et al. 2015, Wada et al. 1998*) or more recently the encouraging results of clinical trials with check-point blocker antibodies as tremelimumab and nivolumab (*Sangro et al. 2013, El-Khoueiry et al. ASCO 2015*).

In addition, there is rising evidence for the PD-1 / PD-L1 pathways involvement in HCC (*Makarova-Rusher et al. 2015*). It was demonstrated that PD-L1 is constitutively expressed in HCC cells in vitro and moreover in tumor specimens in vivo, and elevated PD-L1 expression in HCC is significantly associated with tumor aggressiveness, suggesting that PD-L1 may represent a target for HCC immunotherapy (*Umemoto et al. 2015, Gao et al. 2009*).

These findings have encouraged several clinical studies with PD-1 blockers in HCC. In an ongoing Phase I / II trial (NCT01658878) treatment of mostly 2nd line HCC patients resulted in durable long lasting responses and promising OS at 12 months. The observed response rate in a first set of 42 evaluable patients was 19% which is substantially higher than the 2% observed with sorafenib (*Llovet et al. 2008, Cheng et al. 2009*) and half of the patients (48%) exhibited a disease stabilization (*El-Khoueiry et al. ASCO 2015*). In an ongoing Phase III trial (NCT02576509, Checkmate 459), the efficacy of nivolumab is compared to sorafenib. Another PD-1 blocker, pembrolizumab is currently investigated in 2nd line HCC in Phase II (NCT02702414) and Phase III (NCT02702401) trials. Furthermore, in an ongoing Phase II trial (NCT02519348) in 2nd line HCC, the PD-L1 blocking antibody durvalumab is investigated in combination with the Tremelimumab (anti-CTLA4)

Pexa-Vec is an oncolytic immunotherapy product based on an oncolytic poxvirus expressing granulocyte-macrophage colony-stimulating factor (GM-CSF) which has shown activity in HCC in a dose-finding clinical trial (*Heo et al. 2013*); objective intrahepatic Modified Response Evaluation Criteria in Solid Tumors (mRECIST) (15%) and Choi (62%) response rates and intrahepatic disease control (50%) were equivalent in injected and distant non-injected tumors at both tested doses, i.e. 1 x 10^8 and 1 x 10^9 pfu. Pexa-Vec treatment also improved OS in a dose dependent manner (median

survival of 14.1 months compared to 6.7 months on the high and low dose, respectively; hazard ratio 0.39; P=0.020).

In light of the numerous regulatory mechanisms that HCC tumors employ to evade an immune attack and to overcome the dual liver and tumor immune tolerance phenomena, the use of combination of several immunotherapies offers a great promise and may increase the percentage of patients that respond to immunotherapy.

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The goal of this study is to assess if the combination of these two immunotherapies with different mechanisms of action is feasible, safe and active. Other combinations of oncolytic viruses and immune check-point blockers are under way in other indications.

In this study, a prime injection of Pexa-Vec will be performed before co-administrations of nivolumab and Pexa-Vec; the application of oncolytic virus is expected to induce strong infiltration of innate immune cells to the tumor microenvironment, to trigger molecular changes likely to result in potentiation of Nivolumab (increase in the expression of PD-L1) and to promote the development of an anti-tumoral adaptive immune response.
The present study is conducted in first-line HCC patients with advanced disease but at a moment when their immune responsiveness is still considered adequate. At completion of their participation in the study, all measures will be put in place in order that patients with neither response nor stabilization nor clinical benefit will start Standard of Care without any delay.

Methodology

This is a multicenter, open label Phase I/IIa study evaluating the safety and the efficacy of the combination of Pexa-Vec with nivolumab in the first-line treatment of patients with advanced HCC.
The Investigational Medicinal Products are Pexa-Vec and nivolumab; patients will be receiving intratumoral (IT) injections of Pexa-Vec in combination with nivolumab intravenous (IV) infusions (Figure 1: IMP administration scheme).

IT Pexa-Vec injections will be performed on D1, D15 and D29. Additional Pexa-Vec boosts may be performed after discussion on a case by case basis between the investigator and Transgene.
Pexa-Vec will be injected into 1 to 5 intrahepatic tumors by a qualified and trained Interventional Radiologist or other trained physician using imaging-guidance (ultrasound and/or CT). As many as possible viable, safely injectable tumors ≥1 cm LD must be treated with a maximum of 5 tumors treated on a given treatment day. Different tumors may be treated on consecutive treatment days. The total prepared injection volume will be divided between 1 to 5 tumors, proportionally to individual tumor volumes. Patients will be monitored closely (e.g., vital signs and clinical observation) the night prior and for 24 hours after the first Pexa-Vec injection as described in the study flow chart (Appendix 1). Hence, hospital admission is required for the first administration of Pexa-Vec. Patients will be monitored the night prior and for at least 8 hours following subsequent Pexa-Vec injections. Longer hospitalization for second, third and additional (boost) administrations of Pexa-Vec is permitted based on Investigator decision.
Nivolumab will be given from D15, by IV route every 2 weeks until progression or unacceptable toxicity. Owing to the possible biphasic evolution of tumor burden often seen with immunotherapeutic products, patients may be treated beyond radiologic progression, under the condition of maintenance of clinical benefit, i.e. stable general status, absence of symptoms and stable hepatic function.
Nivolumab will be administered prior to Pexa-Vec on Days 15 and 29 ± 1 day. Owing to the perception by the investigator of the safety of the administration of the two treatments for a peculiar patient or for logistical reasons, the investigator could distribute the treatment administrations over two consecutive days.

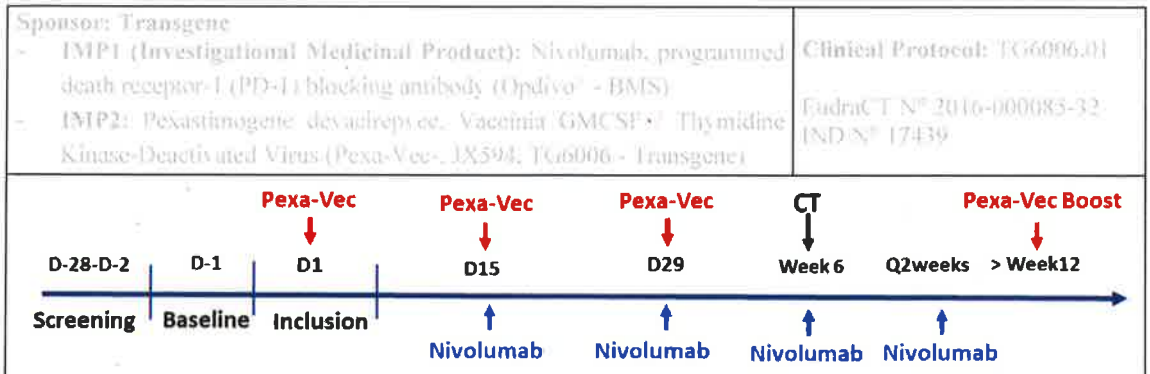

Figure 1: IMP administration scheme

The study is composed of 2 parts:

Phase I part: safety and efficacy will be assessed in 6 patients.

Given the favorable safety profile of both agents, their non-overlapping metabolism, and based on the recently completed study for nivolumab, standard doses will be used for dose level 1 as 3 bi-weekly IT injections of $1x10^9$ pfu for Pexa-Vec and 240 mg IV q2weeks for nivolumab.
The first patient will be monitored for safety after completion of 3 Pexa-Vec IT injections and 2 nivolumab infusions, scheduled on D29 (i.e. week 4), before the second patient can be enrolled. A security interval of 2 weeks between enrolments of each consecutive patients will be applied. In case of a Dose-Limiting Toxicity (DLT) is observed in no more than one patient out of 6 patients and no occurrence of any landmark AE (anticipated effect of the combination), defined as neither increase in severity of hepatic cytolysis, nor significant deterioration of hepatic function (INR, bilirubin, Child-Pugh score), nor increase in number or severity of Pexa-Vec-related skin lesions, nor increase in incidence and severity of immune-related AEs, then accrual in the Phase IIa part of the study will start at the same dose level without security intervals. The initiation of the Phase IIa part of the study will be determined following an analysis by the Independent Safety Committee (ISC) of the safety results in Phase I.

In case of a DLT is observed in more than one patient out of the first 6 patients, or of the occurrence of a landmark AE, one de-escalation regimen is planned:

- Level -1: 3 bi-weekly IT injections of $3x10^8$ pfu for Pexa-Vec and 240 mg q2 weeks for nivolumab OR 3 bi-weekly IT injections of 10^9 pfu for Pexa-Vec and 240 mg q3 weeks for nivolumab, depending on the DLT profile relative to the known toxicity of each component of the combination, as judged by the ISC

Phase IIa part: further evaluation of safety and efficacy, continuation of enrolment up to 30 evaluable patients.

Patients will be further included and treated with Pexa-Vec and nivolumab based on the doses defined in the first part.

Of note, should unexpected toxicities or increased numbers of DLTs in an expanded number of patients occur, de-escalation dose level will also apply.

In both parts, radiological assessments will be performed at Screening and repeated every 6 weeks until documented progression or discontinuation of treatment beyond progression.
Data of locally performed tumor evaluations based on RECIST 1.1 will be used for efficacy assessment. irRC will be assessed centrally for exploratory purposes.

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Beyond 12 months of treatment, the evaluations will be performed every 12 weeks until documented progression or discontinuation of treatment beyond progression. If study treatments are stopped before documented radiological progression, PFS visits will be performed every 6 weeks to continue radiological assessment until documented progression.

Number of Patients

Phase I part: 6 patients (up to 12 patients in case of dose de-escalation)
Phase IIa part: Continue enrolment up to 30 evaluable patients

Main Inclusion/Exclusion Criteria

Inclusion Criteria

1. Male or female patients, age ≥18 years old
2. Histological/cytological diagnosis of primary HCC, excluding cholangiocarcinoma, hepatocholangiocarcinoma, fibrolamellar carcinoma and hepatoblastoma. Note: if no previous pathological report is available, a tumor diagnostic biopsy should be performed
3. Advanced stage HCC per EASL-EORTC (European Association for the Study of the Liver-European Organisation for Research and Treatment of Cancer) guidelines, i.e. patients who are not candidates for curative interventions and not candidates for locoregional modalities
4. Patients naïve to systemic therapy for HCC
5. Tumor status (as determined by radiology evaluation): At least one measurable viable tumor in the liver, ≥1 cm longest diameter (LD), using a dynamic imaging technique (arterial phase of triphasic computerized tomography [CT] scan, or dynamic contrast-enhanced magnetic resonance imaging [MRI]), and injectable under imaging-guidance (CT or ultrasound)
6. At least one tumor that has not received prior local-regional treatment, or that has exhibited definitive growth of viable tumor since prior local-regional treatment of HCC undertaken at least 4 weeks prior to enrolment or 3 months prior to enrolment for radioembolization
7. Child-Pugh Class A. Note: paracentesis, albumin infusion or diuretic treatment cannot be used to downgrade Child-Pugh score (e.g., to improve from severe to moderate/mild or from moderate to mild ascites)
8. Performance status 0 or 1 on the Eastern Cooperative Oncology Group (ECOG) scale
9. Adequate hematological, hepatic, and renal function:
   a. Hemoglobin ≥9 g/dL
   b. Platelet count ≥60 10^9/L
   c. International normalized ratio (INR) ≤1.7
   d. White blood cell (WBC) count ≥2 10^9/L
   e. Absolute neutrophil count (ANC) ≥1 10^9/L
   f. Albumin ≥28 g/L, total bilirubin ≤1.5 times upper limit of normal (ULN); alanine aminotransferase (ALT), aspartate transaminase (AST) ≤5 times ULN
   g. Serum creatinine <20 mg/L or creatinine clearance >60 mL/min according to Cockroft-Gault formula

10. For patients who are sexually active: willing to use adequate barrier contraception method during Pexa-Vec and nivolumab treatment period, for at least 6 weeks after last Pexa-Vec injection and for at least 5 months after last nivolumab administration
11. Life expectancy of at least 3 months
12. Patient should agree to undergo a pre-treatment tumor biopsy, if necessary for diagnostic purposes; a post-treatment tumor biopsy is optional for translational research purposes
13. Written informed consent
14. Patients with active hepatitis B infection should be on adequate antiviral therapy
15. Cardiology consultation and clearance obtained for study participation. Baseline cardiologic investigations should include troponin T or I blood level measurement, electrocardiogram (ECG) and cardiac echography (ECHO) with measurement of left ventricular ejection fraction (LVEF). Ability to temporarily suspend treatment with anti-hypertensive medications should also be assessed.

Exclusion Criteria

1. Major surgery within 4 weeks of study treatments (minor surgical procedures are allowed e.g., intravascular access line or Port-a-Cath®)
2. Local-regional therapy of HCC within 4 weeks or radioembolization within 3 months prior to enrolment
3. Histological diagnosis of cholangiocarcinoma, hepatocholangiocarcinoma, fibrolamellar carcinoma and hepatoblastoma
4. History of moderate or severe ascites, bleeding esophageal varices, hepatic encephalopathy or pleural effusions related to liver insufficiency within 6 months of screening; patients with adequately treated esophageal varices (banding, sclerotherapy) are allowed
5. Clinically significant ascites, e.g., requiring a paracentesis or aggressive inpatient diuresis, pericardial and/or pleural effusions. Minimal, medically controlled ascites detectable on imaging studies only and not precluding a safe IT injection of Pexa-Vec- is allowed.
6. Active, known or suspected significant immunodeficiency due to underlying illness including HIV/AIDS, autoimmune diseases, and/or immune-suppressive medication including high-dose corticosteroids (defined as ≥20 mg/day prednisone or equivalent which is ongoing at the time of randomization and/or was taken for more than 4 weeks within the preceding 2 months of study treatment)
7. Any prior or planned organ transplant (e.g., liver transplant)
8. History of severe eczema and/or ongoing severe inflammatory skin condition (as determined by the Investigator) requiring medical treatment
9. Patients who experienced a severe systemic reaction or side-effect as a result of a previous vaccination with vaccinia
10. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation. Child-bearing potential patients with a positive hCG laboratory test (>10 mIU/mL) at screening and/or a urinary pregnancy test at Baseline will perform an ultrasound to confirm the pregnancy.

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11. Prior malignancy except for the following: adequately treated basal or squamous cell skin cancer, in situ cervical cancer, adequately treated cancer from which the patient has been disease-free for at least 3 years
12. Tumor(s) invading a major vascular structure (e.g., carotid artery) or other key anatomical structure (e.g., pulmonary airway) in the event of post-injection tumor swelling and/or necrosis (hepatic and portal vein involvement allowed)
13. Viable central nervous system malignancy
14. Symptomatic cardiovascular disease, including but not limited to significant coronary artery disease (e.g., requiring angioplasty or stenting) or congestive heart failure within the preceding 12 months
15. Current or past history of cardiovascular disease (e.g., past history of myocardial infarction, ischemic cardiomyopathy) unless cardiology consultation and clearance has been obtained for study participation
16. Medical conditions, per the investigator's judgment, that would contra-indicate volume loading (e.g., intravenous [[IV] fluid bolus infusion) or increase the risk of severe hypotension following treatment with Pexa-Vec (e.g., dehydration, hypovolemia).
17. Other medical condition or laboratory abnormality or active infection that in the judgment of the Principal Investigator may increase the risk associated with study participation or may interfere with interpretation of study results and/or otherwise make the patient inappropriate for entry into this study
18. Significant bleeding event due to abnormal blood clotting within the last 3 months that places the patient at risk for intrahepatic IT injection procedure based on Investigator assessment
19. Anticoagulant or anti-platelet medication that cannot be interrupted prior to Pexa-Vec- IT injections, including:
    - Aspirin that cannot be discontinued for 7 days prior to Pexa-Vec- IT injections
    - Coumadin that cannot be discontinued for 7 days prior to Pexa-Vec- IT injections
    - Low molecular weight heparin (LMWH) that cannot be discontinued >24 hours prior to Pexa-Vec- IT injections
    - Unfractionated heparin (UFH) that cannot be discontinued >4 hours prior to Pexa-Vec- IT injection
    - Oral direct thrombin inhibitor (dabigatran) or direct Factor Xa inhibitor (rivaroxaban, apixiban, and endoxaban) that cannot be discontinued for 4 days prior to Pexa-Vec- IT injection

NOTE: LMWH or UFH may be used to transition patients on and off of the above anti-coagulants (if deemed appropriate by the treating physician) prior to Pexa-Vec- treatments as long as the last dose of LMWH is administered >24 hours prior to treatments and last dose of UFH is administered >4 hours prior to treatments.

20. Hepatitis C virus therapy including interferon/pegylated interferon or ribavirin that cannot be discontinued within 14 days prior to any Pexa-Vec injection. Medical Monitor should be consulted if the patient is taking any other antiviral medications to determine eligibility, on the grounds of interference with Pexa-Vec replication properties.
21. Inability to suspend treatment with anti-hypertensive medication (including but not limited to: diuretics, beta-blockers, angiotensin converting enzyme [ACE] inhibitors, aldosterone

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antagonists, etc.) for 48 hours prior to and 48 hours after each Pexa-Vec injection, as assessed at the screening cardiology consultation.

22. Any known allergy or reaction to any component of nivolumab formulation or its excipients
23. Prior exposure to cancer immunotherapy including any immune checkpoint inhibitor, cancer vaccine and/or oncolytic virus
24. Participation in a clinical study and treatment with an active IMP within 4 weeks prior to randomization
25. Pulse oximetry O_2 saturation <90% at rest on room air
26. Patient unable or unwilling to comply with the protocol requirements.

Investigational Medicinal Products (IMPs), Dose, Mode of Administration

Pexa-Vec

Pexa-Vec (pexastimogene devacirepvec; investigational product code: JX-594, TG6006) is a replication-competent, transgene-expressing therapeutic vaccinia virus derived from the Wyeth vaccine strain (Dryvax-®, Wyeth Laboratories). Three genetic modifications are included:

1. thymidine kinase (TK) gene deactivation,
2. granulocyte macrophage colony stimulating factor (GM-CSF) gene insertion under control of the synthetic early-late promoter, and
3. lac-Z gene insertion under control of the p7.5 promoter.

Pexa-Vec- viral suspension will be supplied in individual 4-mL glass vials with a recoverable volume of 2 mL per vial and an infectious titer of 1×10^9 pfu (9.0 Log10 plaque-forming units (pfu)). Each vial is intended for single use (i.e., one injection to one patient).
Patients will receive three IT injections of Pexa-Vec at the dose of 1×10^9 pfu per treatment, every 2 weeks.
Additional Pexa-Vec boosts may be performed from Week 12 in patients based on a case by case discussion between the investigator and Transgene.

Nivolumab

Nivolumab is a programmed death receptor-1 (PD-1) blocking antibody. It will be supplied in 40 and/or 100 mg vials (10 mg/mL).

Patients will be administered as an IV infusion over 60 minutes every 2 weeks, with the targeted dose of 240 mg.
Accounting for the immunotherapeutic effect of both drugs and for the peculiar kinetics of clinical efficacy of these treatments, guidance is provided to continue treatment beyond evidence of radiologic progression.

Associated Therapies

The use of antiemetics, antipyretics, antidepressants, biphosphonates, vitamin B12 and vitamin D will not be restricted during the course of the study.

Thrombopoietin, erythropoietin and G-CSF will not be allowed throughout DLT period.

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Oral or parenteral corticosteroids may attenuate potential beneficial immunologic effects of treatment with nivolumab and Pexa-Vec and should not be used but may be administered at the discretion of the treating physician if needed. Alternatives to corticosteroids should be considered if feasible. The use of inhaled corticosteroids and mineralocorticoids (e.g. fludrocortisone) is allowed.

Antihypertensives (including diuretics) must be discontinued at least 48 hours prior to each Pexa-Vec- injection and restarted no earlier than 48 hours after the injection.

Unless contraindicated, all patients will be pre-medicated with acetaminophen (paracetamol) , ibuprofen and esomeprazole on each Pexa-Vec treatment day according to the following scheme:

- acetaminophen 1000 mg at 2 hours pre-injection, 6 hours, 14 hours and 22 hours post-injection,
- ibuprofen 400 mg at 2 hours, 10 hours and 18 hours post-injection,
- esomeprazole 40 mg, or equivalent.

In case of contra-indication to the prescription of ibuprofen, due to underlying advanced cirrhosis, the investigator may alternatively use the following regimen based on acetaminophen (paracetamol) or equivalent antipyretics, (unless contraindicated):

- 500–1000 mg at 2 hours pre-infusion/injection,
- 500–1000 mg at 4 hours post-procedure,
- 500–1000 mg every 6 hours thereafter, as needed (the total acetaminophen dose should be carefully assessed to avoid cumulative toxicity).

Any treatment may be continued if deemed necessary.

Fevers may be associated with onset of rigors. Meperidine or equivalent may be used for severe rigors.

Unless contra-indicated, patients should also be pre-hydrated with approximately 1 L of solute-containing fluids IV or orally within 12 hours of treatment initiation. In addition, during the post-treatment observation period, patients should receive IV solute-containing fluids or other appropriate treatment as needed for blood pressure support.

Duration of Treatment

The duration of treatment lasts from the first IMP administration until the last IMP administration.

Criteria for Evaluation / Study Endpoints

Efficacy assessments

Imaging

Patients will undergo imaging of the chest, abdomen and pelvis using helical/spiral contrast-enhanced CT scanning or MRI with non-contrast CT of the chest at Screening, at Week 6 and every 6 weeks thereafter. Tri-phasic contrast-enhanced imaging of the liver will include pre-contrast, arterial, and portal venous phases. For MRI Scan, either a 1.5T or a 3T MRI scanner should be used with a body array coil and gadolinium administered as an IV bolus. All target lesions (measurable) and non-target lesions (measurable or not) will have to be recorded. Radiographic assessments will be completed locally as per current practice according to RECIST 1.1. All radiographic images will also be reviewed centrally according to irRC, as exploratory endpoint.

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CT or MRI scans will be performed within 28 days prior to start of study treatment and patients will then be evaluated every 6 weeks from start of treatment until documented progression or discontinuation of treatment beyond progression or for a period of 12 months after start of study treatment, whichever occurs first. Beyond 12 months of treatment, the evaluations will be performed every 12 weeks until documented progression or discontinuation of treatment beyond progression. If study treatments are stopped before documented radiological progression, PFS visits will be performed every 6 weeks to continue radiological assessment until documented progression.

Definition of radiological endpoints:

- Overall response rate (ORR): proportion of patients, whose best overall response is either CR or PR, confirmed at least 4 weeks after initial documentation.
- Time to Progression (TTP): time from D1 to the date of first documented radiographic tumor progression; TTP does not include deaths. If a patient has not had a TTP event at the cut-off date for analysis, TTP will be censored at the date of last evaluable tumor assessment before the cut-off.
- 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 the date of death due to underlying cancer. DoR will be censored if progression or death due to underlying cancer is not observed at the cut-off date for the analysis or start of further antineoplastic therapy. The censoring date will be the date of the last evaluable tumor assessment.
- Disease control rate (DCR): proportion of patients whose best overall response during their participation in the study is either CR, PR, or stable disease (SD).
- 4-month (18-week) DCR: proportion of patients whose best overall response in the study is either CR, PR, or stable disease (SD) 4 months after D1.
- Relative change from baseline in tumor size over time. Tumor size is defined as the sum of the diameters recorded for all target lesions as identified at baseline.
- Progression Free Survival (PFS): time from D1 to the date of first of second 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, PFS will be censored at the date of last evaluable tumor assessment before the cut-off.

TTP and PFS will be assessed using the Kaplan-Meier method with the inclusion date (D1) as reference date.

- PFS over time: proportion of patients having not progressed at specified time points

Tumor blood flow (DCE/DW-MRI) and metabolic response (^{18}FDG-PET): could be optionally implemented in targeted patients for assessment of activity on tumors.

Overall Survival:

- Overall Survival (OS): time from date of D1 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.

OS will be assessed using the Kaplan-Meier method with the inclusion date (D1) as reference date.

- OS over time: proportion of patients alive at specified time points

Safety and clinical assessments

- Physical examination including vital signs, body weight and Performance Status measurements will be performed at each visit.
- Adverse Events and Serious Adverse Events (SAEs) will be reported and graded according to National Cancer Institute's Common Toxicity Criteria for Adverse Events (NCI CTCAE), version 4.03
- Safety laboratory investigations will be undertaken at baseline, every 2 weeks during the 6 first weeks and then every 6 weeks, at the end of treatment visit and at the safety follow-up visit:
  - Complete blood cells count
  - Biochemistry analyses (including: AST, ALT, alkaline phosphatases, total bilirubin, LDH, serum protein, serum albumin, electrolytes), CRP and creatinine
- Monitoring for cardiac toxicity will include for both phases of the study:
  - Cardiac echography (ECHO) with measurement of left ventricular ejection fraction (LVEF), if necessary, in addition to baseline measurement,
  - Measurement of troponin T or I blood level 3 and 8 days (± 1) after each Pexa-Vec administration,
  - ECG (12 leads), 8 days (± 1) after each Pexa-Vec administration,
  - ECG (12 leads), 3 days (± 1) after each Pexa-Vec administration, in case of detection of a clinically significant increase in troponin blood level,
  - In the Phase I section, measurement of troponin T or I level will be performed at D29 (end of DLT period), then starting from week 8, ECHO, ECG and troponin T or I level will be performed every 4 weeks (i.e. on every second nivolumab infusion) up to the 28-day safety follow-up visit.

Further examination(s) will be performed if deemed necessary by the investigator.

- Antinuclear and anti-TPO antibodies at baseline and at the end of treatment visit
- Thyroid blood tests will be performed at baseline and every 6 weeks, at the end of treatment visit and at the safety follow-up visit
- Alpha-feto protein (AFP) blood concentration at baseline and at the end of treatment visit
- In the Phase I part, **Dose-Limiting Toxicities (DLTs)** are defined as the occurrence of any of the following events evaluated as related to study drugs and occurring during the first 4 weeks (up to D29), which is defined as the DLT period:

1. All Grade 3-4 non-hematologic toxicity that represents a 2-grade increase over baseline, excluding:
   - Untreated or inadequately treated nausea, vomiting and diarrhea,
   - Untreated or inadequately treated fever > 40.0°C lasting less than 24 hours (Grade 3); only fever > 40.0°C lasting more than 24 hours (Grade 4) qualifies for DLT,
   - Alopecia,
   - Grade 3 fatigue that returns to grade 2 or less within 7 days,
   - Grade 3 laboratory/metabolic abnormalities, other than ALT or AST, that are not considered clinically significant and that return to grade 2 or less within 72 hours.
2. Any Grade ≥ 3 treatment-related acute immune-related AE involving major organs, such as: immune-related pneumonitis, colitis, nephritis, hepatitis, endocrinopathies, immune-related rash and other rare but severe immune-related reactions.
3. Grade ≥ 3 injection site reaction.
4. AST or ALT ≥ 10xULN, even if asymptomatic, unless it is related to a definite progression of liver metastases or another clearly identifiable etiology; doubling of AST or ALT that is concurrent with a doubling of the total bilirubin.
5. Any toxicity at least possibly related to study therapy that results in a delay in treatment of 2 or more weeks.

Sponsor: Transgene - IMP1 (Investigational Medicinal Product): Nivolumab, programmed death receptor-1 (PD-1) blocking antibody (Opdivo® - BMS) - IMP2: Pexastimogene devacirepvec, Vaccinia GM(CSF)- Thymidine Kinase-Deactivated Virus (Pexa-Vec-; JX594, TG6006 - Transgene)	Clinical Protocol: TG6006.01 EudraCT N° 2016-000085-32 IND N° 17439

6. Hematological:
   - Grade ≥ 3 or ≥ 2-grade increase over baseline of neutropenia lasting for more than 7 days.
   - Neutropenic fever.
   - Grade 4 thrombocytopenia or grade 3 thrombocytopenia with clinically significant bleeding.
7. Cardiac: association of the 3 following cardiac abnormalities
   - Left ventricular ejection fraction (LVEF) less than the lower limit of normal (LLN), as assessed by echocardiography and symptomatic due to drop in ejection fraction, responsive to intervention,
   - Increase of blood troponin T or I above the upper limit of normal (ULN),
   - Any ECG abnormality consistent with a Grade 3 cardiac disorder.

- In the Phase IIa part, should unexpected toxicities or increased number of DLTs in an expanded number of patients be seen, the ISC will be consulted to decide upon dose de-escalation.

[redacted]

[redacted]

Statistical Methods applicable for analysis of efficacy

As the patient survival benefit may be correlated with either radiological response of tumors or/and prolonged stabilization of the disease, the analysis of efficacy will consider ORR as primary endpoint. Sample size justification will use available data on ORR, as such: in a Phase I/II trial, 8/42 (19%) patients with previously treated HCC experienced an objective response when treated with single-agent nivolumab (El-Khoueiry et al., ASCO 2015). Therefore, a response rate of 15%-20% with the combination of Pexa-Vec + nivolumab in these patients would be considered disappointing, while a response rate of 35% or more would be promising and would encourage further study of the regimen in these patients. The null hypothesis for response rate H_0 is set at 15%, the alternate hypothesis of efficacy is set at H_A=35%, the type I error α is set at 5% one sided and the power is set at 80%.

Under these hypotheses a two-stage group sequential design using alpha and beta spending function approach with Lan DeMets spending function (O'Brien-Fleming efficacy boundaries and non-binding Pocock futility boundaries) will be used leading to a maximum sample size of 30 evaluable patients and an interim analysis based on 15 evaluable patients (implemented in EAST® 6.3) with a test proportion with normal approximation to the binomial distribution.

In the first stage 15 evaluable patients will be accrued. If there are 3 or fewer responses in these 15 patients (20% of responders or less), the study could be stopped for futility. If there are 6 or more responses in these 15 patients (40% of responders or more), the null hypothesis will be rejected and the study could be stopped. Otherwise 15 more additional evaluable patients will be accrued for a total of 30.

At the final analysis, the null hypothesis will be rejected if 8 or more responses are observed in the 30 evaluable patients (26.7% of responders or more) with a power of 80% and a type I error of 5%. It should nevertheless be reminded that given the mechanism of action of the drugs involved and the effects of immunotherapy on tumor behavior, ORR may not be the best measure of anti-tumor activity. For this reason, consideration will be given to DCR, TTP and survival parameters prior to deciding that the combination does not warrant further exploration.

At interim and final analysis, enough patients will be treated to obtain a total of 15 and 30 evaluable patients, respectively including comparable patients of the Phase I part (population, treatment regimen) still evaluable for Phase II part.

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TABLE OF CONTENTS

ABBREVIATIONS / DEFINITION OF TERMS

ABBREVIATIONS	MEANING OF ABBREVIATIONS IN DOCUMENT
ADR	Adverse Drug Reaction
AE(s)	Adverse Event(s)
AFP	Alfa-Fetoprotein
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
ANSM	Agence Nationale de Sécurité des Médicaments et des produits de santé
AST	Aspartate Transaminase
AUC	Area under the concentration-time curve
BCLC	Barcelona Clinic Liver Cancer
BID	Twice daily (bis in die)
BSC	Best Supportive Care
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CDC	Centers for Disease Control and Prevention (United States)
CFR	Code of Federal Regulations (United States)
CI(s)	Confidence Interval(s)
Cmax	Peak concentration
CL	Clearance
COREB	Coordination Opérationnelle du Risque Epidémique et Biologique
CPP	Comité de protection des personnes
CR	Complete Response
CRO	Contract Research Organization
CRP	C-reactive protein
CT	Computerized Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA4	Cytotoxic T-lymphocyte-associated protein 4
CV	Coefficient of variation
DCE MRI	Dynamic Contrast-Enhanced Magnetic Resonance Imaging
DCR	Disease Control Rate
DILI	Drug-induced liver injury
DLT(s)	Dose Limiting Toxicity(ies)
DoR	Duration of Response
EASL	European Association for the Study of the Liver
ECG	Electrocardiogram
ECHO	Cardiac echography
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
ELISA	Enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EORTC	European Organization for Research and Treatment of Cancer
FDA	Food and Drug Administration (United States)
FDG-PET	Fluorodeoxyglucose Positron Emission Tomography
GCP	Good Clinical Practice

ABBREVIATIONS	MEANING OF ABBREVIATIONS IN DOCUMENT
G-CSF	Granulocyte Colony Stimulating Factor
GLP	Good Laboratory Practices
GM-CSF	Granulocyte-Macrophage Colony Stimulating Factor
GMO	Genetically-modified organism
HCC	Hepatocellular Carcinoma
HBV	Hepatitis B virus
HCV	Hepatitis C virus
hGM-CSF	Human Granulocyte-Macrophage Colony Stimulating Factor
HIPAA	Health Insurance Portability and Accountability Act
HLA	Human Leukocyte Antigen
HR	Hazard Ratio
IATA	International Air Transportation Association
IB	Investigators' Brochure
IBC	Institutional Biosafety Committee
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Institutional Ethics Committee
IHC	Immunohistochemistry
IMP	Investigational medicinal product
INN	International Nonproprietary Name
INR	International Normalized Ratio
IRB	Institutional Review Board
irRC	immune-related Response Criteria
ISC	Independent Safety Committee
IT	Intratumoral
ITT	Intent-To-Treat
IV	Intravenous
LD	Longest Diameter
LDH	Lactate Dehydrogenase
LFTs	Liver function tests
LLN	Lower Limit of Normal
LMWH	Low Molecular Weight Heparin
LVEF	Left Ventricular Ejection Fraction
MDSC	Myeloid-derived suppressor cells
MedDRA	Medical Dictionary for Regulatory Activities
MFD	Maximum Feasible Dose
mRECIST	Modified RECIST
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute (United States)
NIH	National Institutes of Health (United States)
NK cells	Natural Killer cells
NSCLC	Non-Small Cell Lung Cancer
ORR	Overall Response Rate
OS	Overall Survival
PBMC	Peripheral Blood Mononuclear Cells
PCR	Polymerase Chain Reaction
PD	Progressive Disease
PDEs	Pre-drug events

ABBREVIATIONS	MEANING OF ABBREVIATIONS IN DOCUMENT
PD-1	Programmed death 1 receptor
PD-L1	Programmed death 1 receptor ligand
PEG-IFN	Pegylated Interferon
PEIT	Percutaneous Ethanol Injection Therapy
PET	Positron Emission Tomography
PET-CT	Positron Emission Tomography-Computerized Tomography
Pexa-Vec	Pexastimogene Devacirepvec, JX-594
PFS	Progression Free Survival
pfu	Plaque Forming Units
PK	Pharmacokinetics
PP	Per Protocol
PPE	Personal Protective Equipment
PR	Partial Response
PT/INR	Prothrombin Time/International Normalized Ratio
PTT	Partial Thromboplastin Time
QoL	Quality of Life
RCC	Renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
RFA	Radiofrequency Ablation
RP2D	Recommended Phase II Dose
SAE(s)	Serious Adverse Event(s)
SAP	Statistical Analysis Plan
SAR	Serious adverse reaction
SD	Stable Disease
SLD	Sum of Longest Diameters
SmPC	Summary of Product Characteristics
SOC	Standard of Care
SPILF	Société de Pathologie Infectieuse de Langue Française
SUSAR	Suspected Unexpected Serious Adverse Reaction
SUV	Standardized Uptake Value
TACE	Transcatheter Arterial Chemoembolization
TK	Thymidine Kinase
Tregs	Regulatory T cells
TNF-α	Tumor necrosis factor alpha
TPO	Thyroid peroxydase
TTP	Time To Progression
UFH	Unfractionated Heparin
ULN	Upper Limit of Normal
US	United States
USPI	US Prescribing Information
VIG	Vaccinia Immune Globulin
WBC	White Blood Cell
WNL	Within Normal Limits
WOCBP	Women of childbearing potential

DEFINITIONS

Screened patient	A patient identified during the screening process achieved by the Investigator as a candidate to the study and invited to sign the informed consent form.
Consented patient	A patient who has signed the informed consent form.
Not included patient	A consented patient who did not receive the Investigational Medicinal Product.
Eligible patient	A consented patient fulfilling all inclusion and exclusion criteria
Included patient	A patient having received the first Investigational Medicinal Product administration.
Treated patient	A patient having received at least the first Investigational Medicinal Product administration as planned by the protocol.
Ongoing patient	A patient included, presently treated according to the protocol requirements.
Withdrawn patient (= drop-out patient)	An included patient who leaves the study between the inclusion date and the end of study visit whatever the reason.
Completed patient	A patient who has completed all procedures up to the "end of study visit" as planned by the study protocol.
Evaluable patient	Phase I section: a patient having completed the Dose-Limiting Toxicity period (scheduled on Day 29) and having received all 3 Pexa-Vec intra-tumoral treatments and 2 nivolumab infusions. Phase IIa section: a patient having received at least 2 administrations of Pexa-Vec and 2 administrations of nivolumab and undertaken at least one post-baseline radiological assessment or exhibited any evidence of disease progression other than radiological.
Lost to follow-up patient	An included patient for whom no further news is obtained by the Investigator before the "end of study visit" has been performed. The date of lost to 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.
End of study	The date of the last visit of the last patient undergoing the study.
Protocol deviation	All non-adherences to following protocol requirements: study inclusion or exclusion criteria, conduct of the study, patient management or patient assessment.

1 INTRODUCTION

1.1 Background

1.1.1 Hepatocellular Carcinoma

Hepatocellular carcinoma (HCC) is estimated to be the third most common cause of cancer-related deaths world-wide (*Ferlay 2010; Hoos 2012*), the 5th most common cancer diagnosis in men worldwide and the 7th most common cancer in women (*El-Serag 2012*).

Approximately 750,000 people develop HCC world-wide each year with ~80% of cases reported in developing countries which have a high prevalence of hepatitis (*El-Serag 2012*). However, HCC is one of the only cancers whose incidence is increasing in developed countries (*Siegel 2014; El-Serag 2001; Goodgame 2003; Deuffic 1998*). Approximately 25,000 new cases of HCC are diagnosed annually in the United States (US) (*Siegel 2014*). The incidence of HCC is 1,550 new cases in Canada (*Canadian Cancer Society 2008*) and approximately 50,000 in Europe (*Ferlay 2013*).

Most HCC cases (approximately 90%) develop in the context of liver disease, in particular hepatocellular cirrhosis (*Simonetti 1991; Bosch 1999*). The most common causes of cirrhosis include chronic hepatitis B or C, and chemical substances such as excessive alcohol or aflatoxins (*Chen 2003*). Nonalcoholic steatohepatitis, a liver disease triggered by enhanced fat deposition in the liver, may also be a risk factor for the development of HCC (*Hashimoto 2009; Mori 2004*). The risk of death from HCC is increased both in males and females with increasing body mass index class, linking obesity to development of HCC (*Calle 2003)*.

Patients with HCC generally present with advanced disease with a poor prognosis of 6 to 9-month median survival (*Yoo 2003*). Therefore, development of effective methods for the prevention and early diagnosis of HCC methods are critical. In addition, there exists a continued need for new therapies that will further improve survival of patients with HCC.

1.1.2 Current treatment for HCC

Surgical resection and liver transplant are the only curative treatments for HCC. Small HCC tumor(s) (less than 3 cm in diameter) can be resected by hepatectomy, the most effective treatment. Surgery is associated with a reported 50–60% five-year survival rate, but unfortunately is feasible in only 10–15% of cases; most patients present with disease that is either too advanced or disease is accompanied by extensive cirrhosis that precludes surgery (*Gondolesi 2004)*. Resection in cirrhotic patients carries high morbidity and mortality.

For patients with unresectable HCC and who cannot receive liver transplantation, a large array of local-regional therapies is available including percutaneous ethanol injection therapy (PEIT), radiofrequency ablation (RFA), transarterial chemoembolization (TACE), Yttrium-90 and/or radio-embolization. The choice of local-regional therapy depends on the size and location of the intrahepatic tumors and on the underlying liver function (*Bruix 2005)*.

Sorafenib is the only systemic therapy approved for the treatment of patients with advanced HCC.

Sorafenib is a small molecule which inhibits growth signaling and pro-angiogenic pathways (*Wilhelm 2004; Chang 2007)* by targeting the serine/threonine kinases Raf-1 and B-Raf as well as receptor tyrosine kinases platelet-derived growth factor receptor β (PDGFR-β) and vascular endothelial growth factor receptors 1, 2, and 3 (VEGFR1, 2, 3) (*Wilhelm 2004; Chang 2004).* These sorafenib targets have been shown to be involved in the pathogenesis of HCC (*Ito 1998; Villanueva 2007; Calvisi 2006; Semela 2004; Llovet 2008b).* A subsequent Phase III randomized trial with sorafenib was completed in sites in Asia (n = 226 patients; Asia-Pacific Trial). Results demonstrated a statistically significant survival advantage for sorafenib (n = 150 patients) over placebo (n = 76 patients) (median 6.5 months versus 4.2 months, respectively; p = 0.014) (*Cheng 2009).* The disease control rate (DCR) with sorafenib was 35% (confirmed at 12 weeks after treatment initiation); disease control was defined as an objective response (partial or complete) or stable disease (SD) that lasted at least 4 weeks. The objective response rate (by RECIST criteria) was only 3% on sorafenib. Sorafenib is now approved in multiple countries for patients with unresectable HCC. Nevertheless, despite a 2–3month survival benefit in the front-line setting, sorafenib has significant toxicities and dose-reductions or treatment discontinuation is often required. However, disease stabilization is transient and tumor progression occurs in all patients (*Cheng 2009; Llovet 2008a).*

The survival benefit of sorafenib has been confirmed in the global non interventional GIDEON trial (Global Investigation of therapeutic DEcisions in hepatocellular carcinoma and Of its treatment with sorafeNib) (*Lencioni 2012).*

Several other systemic therapeutic agents have been tested in advanced HCC patients. In the 1st line setting, 3 receptor tyrosine kinase inhibitors – sunitinib, brivanib, linifanib – have been compared directly against sorafenib (*Cainap 2012; Cheng 2013; Johnson 2013).* In a fourth 1st line Phase III trial of a tyrosine kinase inhibitor (SEARCH), the combination of erlotinib plus sorafenib was compared to placebo plus sorafenib (*Zhu 2014a*). In these trials sorafenib had a consistent performance, demonstrating a median overall survival of 8.5–10 months. None of the investigational therapies were however able to demonstrate superiority to sorafenib, or, in the case of brivanib and sunitinib, not even non-inferiority. Most trials also showed a worse safety profile of experimental agents compared to sorafenib.

1.1.3 HCC Immunotherapy

1.1.3.1 Oncolytic Immunotherapy

Oncolytic viruses kill cancer cells through a novel mechanism of action, "oncolysis", or virus replication-associated necrosis (*Kirn 2009)* and can be targeted to cancer cells with activated genetic pathways and/or loss of tumor suppressor function (*Heise 1997; Stojdl 2000; Martuza 1991*). Selective intratumoral (IT) replication of the virus leads to lysis of the infected cancer cell and spread to adjacent cancer cells. In addition, these viruses can kill through other mechanisms, including induction or amplification of a tumor-specific cytotoxic T-lymphocyte response. Oncolytic immunotherapies can also be armed for expression of therapeutic transgenes (*Chase 1998; Todo 2001; Hermiston 2002; Hermiston 2005*).

The latter can lead to bystander cell killing via enhanced immune response to the tumor (e.g., expression of cytokines such as GM-CSF). Oncolytic immunotherapies expressing additional therapeutic transgenes have the potential to effectively treat cancers that have become refractory to currently-approved treatments.

Following the first description of a virus engineered to replicate selectively in cancer cells over 20 years ago, the field of oncolytic immunotherapy has expanded dramatically (*Lichty 2014*). Over 10 different viral species have entered clinical trials (*Miest 2014*) but as of today, Pexa-Vec is the only oncolytic immunotherapy that has demonstrated efficacy in HCC patients (see Section 1.2 for further information). The first oncolytic virus-based product approved for use is an adenovirus named H101 (approved by Chinese State Food and Drug Administration in November 2005), used in combination with chemotherapy as a treatment for head and neck cancer. More recently, a Phase III pivotal trial of *talimogene laherparepvec* (T-VEC, Imlygic), an oncolytic herpes virus expressing granulocyte-macrophage colony stimulating factor (GM-CSF) in patients with advanced melanoma met its primary endpoint. The overall response rate and the median OS were higher in the T-VEC arm compared to the GM-CSF arm (ORR: 26.4% *versus* 5.7%; OS: 23.3 months versus 18.9 months; hazard ratio, 0.79 and p = .051) (*Andtbacka et al. 2015*). This led to the U.S. Food and Drug Administration (FDA) approved Imlygic, end of October 2015, the first FDA-approved oncolytic virus therapy, for the treatment of melanoma lesions in the skin and lymph nodes, and subsequently to the EMA approval.

1.1.3.2 Checkpoint Inhibitors

The balance between co-stimulatory and co-inhibitory signals determines the cytotoxic T-cell activation and intensity of the immune response (*Chen 2013*). Immune checkpoint receptors are often upregulated in tumor tissue and promote tumor evasion from host immunosurveillance. As receptors, they readily emerged as a novel class of potential targets to be modulated in order to stimulate the immune response.

CTLA-4 has been the first immune checkpoint receptor to be clinically targeted. It is expressed exclusively on T cells where it primarily regulates the amplitude of the early stages of T cell activation (*Pardoll 2012*). The most important molecular function of CTLA-4 is the inhibition of CD28 co-stimulation, as evidenced by the CD28-dependent uncontrolled lymphoproliferative and autoimmune syndrome observed in CTLA-4 null mice. CD28 and CTLA4 share identical ligands: CD80 and CD86. The first anti-CTLA4 blocking antibody approved by FDA in 2011 is ipilimumab (BMS) for previously treated advanced melanoma patients. The specific signalling pathways of ipilimumab are not all known but one main effect is the blocking of CTLA4 interaction with its ligands CD80 and CD86, thereby promoting T cell activation. In melanoma patients, ipilimumab improved median OS by almost 4 months and resulted in long term disease control in a significant minority (*Hodi 2011*). Based on these encouraging results tremelimumab a different anti-CTLA4 antibody was tested in a pilot clinical trial in twenty patients with advanced HCC and HCV infection (*Sangro 2013*). Tremelimumab (15 mg/kg every 90 days i.v.) was tolerated well and 3 out of 17 evaluable patients (17.6%) developed confirmed partial responses and 10 patients had stable disease as the best response to treatment with 45% of the patients experiencing SD for more than 6 months. HCV-specific T cell responses were studied in these patients as a surrogate marker for the anti-CTLA4-induced immune responses. HCV-specific T cell responses were noted in a number of patients and a decline in viral load was observed in most patients followed for at least 3 months. Three patients had a complete viral response. Interestingly, tumor response was greater in patients with stable levels of IFN-γ during the treatment compared to those with lower levels. It was proposed that more active antitumor immunity occurred in these patients in response to the therapy. A Phase I clinical trial combining tremelimumab with RFA or TACE is ongoing.

Other immune checkpoint inhibitors such as anti-PD-1 are currently under clinical investigation in advanced HCC (NCT01658878). PD-1 is a CD28 superfamily member that transmits co-

inhibitory signals for the TCR receptor and is expressed not only on activated T and B cells, but also Tregs and MDSCs (*Francisco 2009*). PD-1 mediates the differentiation and proliferation of Tregs and therefore regulates peripheral tolerance and autoimmunity (*Nikolova 2009*).

1.1.3.3 Checkpoint blockade and Combination of Immunotherapies in HCC

HCC is an inflammation-associated cancer that can be considered as an immunogenic tumor for several reasons including the high rate of spontaneous regression for which antitumor immunity has been recognized as a leading mechanism (*Oquinena et al. 2009*), the observations that patients whose tumors contain lymphocytic infiltrates show longer survival and lower risk of recurrence (*Prieto et al. 2015, Wada et al. 1998*) or more recently the encouraging results of clinical trials with check-point blocker antibodies as tremelimumab and nivolumab (Sangro et al. 2013, El-Khoueiry AB et al. ASCO 2015).

In addition, there is rising evidence for the PD-1 / PD-L1 pathways involvement in HCC (*Makarova-Rusher et al. 2015*). It was demonstrated that PD-L1 is constitutively expressed in HCC cells in vitro and moreover in tumor specimens in vivo, and elevated PD-L1 expression in HCC is significantly associated with tumor aggressiveness, suggesting that PD-L1 may represent a target for HCC immunotherapy (*Umemoto et al. 2015, Gao et al. 2009*).

These findings have encouraged several clinical studies with PD-1 blockers in HCC. In an ongoing Phase I / II trial (NCT01658878) treatment of mostly second-line HCC patients resulted in durable long lasting responses and promising OS data (70% at 9 months, 62% at 12 months). The observed response rate in a first set of 42 evaluable patients was 19% which is substantially higher than the 2% observed with sorafenib (*Llovet et al. 2008, Cheng et al. 2009*) and half of the patients (48%) exhibited a disease stabilization (*El-Khoueiry et al. ASCO 2015*). Based on these encouraging results, in an ongoing Phase III trial (NCT02576509, Checkmate 459), the efficacy of nivolumab is compared to sorafenib in advanced first-line HCC patients. Another PD-1 blocker, pembrolizumab is currently investigated in second-line HCC in Phase II (NCT02702414) and Phase III (NCT02702401) trials. Furthermore, in an ongoing Phase II trial (NCT02519348) in second-line HCC, the PD-L1 blocking antibody durvalumab is investigated in combination with Tremelimumab (anti-CTLA4).

The concept of adaptive immune resistance — whereby immune-checkpoint ligands such as PDL-1 are induced in tumors in response to an endogenous antitumor immune response — suggests that PD-1-pathway blockade as a monotherapy might be enhanced in combination with other targeted therapies, such as cancer vaccines and oncolytic immunotherapy owing to the overlapping mechanisms of action (*Melero et al; 2015*) We hypothesize that expanded efficacy might be achieved when PD-1-pathway blockade is combined with an oncolytic immunotherapy, that induces *de novo* antitumor immune responses and immunogenic cell death.

By combining oncolytic therapy with checkpoint blockade, multiple immune pathways including immune tolerance during cancer progression can be circumvented. Oncolytic virus infection could induce the up-regulation of CTLA-4 or PD-L1 through activation of IFNg producing cytotoxic CD8 T cells, thereby allowing antibodies targeting CTLA-4 and PD-1/PD-L1 pathways to reach their maximum therapeutic potential.

Promising results were reported after combining an immune checkpoint inhibitor and viral-based products in preclinical and clinical studies. As anticipated, selective blockade of co-inhibitory molecules within the tumour microenvironment favors the intratumour effector functions of tumour-specific T cells primed and expanded by the vaccine. In preclinical studies, the study published by Zamarin et al. (2012) was the first to support clinical exploration of the use of checkpoint antibodies with oncolytic Newcastle disease virus (NDV). In a pre-clinical model of metastatic tumor, the combination therapy of NDV and CTLA-4 checkpoint blockade controlled both local and distant tumors better than either anti-CTLA-4 or NDV treatment alone. The combination therapy also led to long-term survival of mice (up to 100 days), elicited inflammatory recruitment of CD8 T cells, and led to overall enhancement of effector to Tregs ratio. In addition, synergies in term of anti-tumor response and demonstration that therapy is dependent on immune effectors were also seen when combining anti-CTLA-4 or anti-PD-1 antibody with on oncolytic vaccinia virus (*Rojas 2015*), with a Vesicular stomatitis virus (*Gao 2009*) or with a reovirus (Reolysin) (*Rajani 2015*). Finally, another strategy is now explored with oncolytic viruses engineered to encode antibodies against immune checkpoint. The first plublished study was done using an oncolytic measles virus engineered to locally express anti-PD-1 or anti-CTLA-4 and showed improved antitumour efficacy of these recombinant vectors compared with the parental measles virus (*Engeland 2014*).

In human, ipilimumab was combined with a GM-CSF cell-based vaccine (G-VAX) in patients with pancreatic cancer showing an improvement of OS associated with clinical activity in the combination arm (*Le 2013*). Also, the oncolytic virus T-VEC is currently tested in combination with both ipilimumab (NCT01740297) and pembrolizumab (NCT02263508) in melanoma with a doubling of the ORR communicated after an interim analysis of the NCT01740297 trial (ASCO 2014). Interestingly, in HCC, a pilot study explored the safety and feasibility of tremelimumab in combination with locoregional therapies directed to promote immunogenic tumour cell death, comparable to the one observed by oncolysis, in patients with advanced-stage HCC exposed to sorafenib (*Duffy, poster - ASCO 2015*). This combined therapy was proved to be safe with 4 out of 10 patients achieving confirmed partial objective response and tumour biopsies showing immune cell infiltration in all evaluable patients.

All these data support the clinical development of strategies based on combinations of virotherapy with checkpoint inhibitors.

1.2 IMP 1: Pexa-Vec

1.2.1 Pexa-Vec Description

Pexa-Vec (pexastimogene devacirepvec, JX-594) is an oncolytic and immunotherapeutic vaccinia virus engineered to express GM-CSF.

Pexa-Vec mechanisms-of-actions include tumor-cell infection and lysis (*Breitbach 2011; Kim 2006; Park 2008*), anti-tumor immune response induction (*Heo 2013; Kim 2013*) as well as acute vascular disruption (*Breitbach 2013*). Pexa-Vec is derived from the commonly used Wyeth vaccine strain (-Dryvax®, Wyeth laboratories).

Three genetic modifications are included in Pexa-Vec:
1. thymidine kinase (TK) gene deactivation,
2. GM-CSF gene insertion under the control of the synthetic early-late promoter, and
3. lac-Z gene insertion under control of the p7.5 promoter.

Selective targeting of tumor cells by Pexa-Vec is attributed to both engineered mechanisms as well as to inherent vaccinia selectivity for cancers (*Parato 2012*). TK gene inactivation renders viral replication dependent on the high cellular TK activity that is a hallmark of cancer cells (*Hengstschlager 1998*). Vaccinia vaccine strains have been shown to be inherently tumor targeting (*Thorne 2007; Yu 2004*). This may be attributable to the fact that many of the hallmarks of cancer (*Hanahan 2000*) (e.g., blocks in apoptotic pathways, dysregulation of cell cycle control and immune evasion) are also optimal cellular conditions for successful vaccinia virus replication. Furthermore, vaccinia replication and spread is dependent on epidermal growth factor receptor (EGFR) signaling (*Katsafanas 2004*), a pathway that is activated in most cancers (*Hanahan 2000*).

GM-CSF is reportedly an effective cytokine for stimulating tumor-specific anti-tumoral immunity (*Dranoff 1993*). Furthermore, the combination of vaccinia infection with GM-CSF production has been shown to result in enhanced efficacy in preclinical models, presumably due to additional immune stimulation due to GM-CSF expression within the tumor microenvironment (*Thorne 2007*). GM-CSF is also expressed by other oncolytic viruses like T-Vec (*Andtbacka 2015*) or Oncos-102 with efficacy demonstrated respectively in Phase III and in Phase I.

Protective anti-tumor immunity has been demonstrated following vaccinia infection of murine tumors *in vivo* (*Kirn 2007*). Pexa-Vec has also been shown to function as an immunotherapeutic in patients. GM-CSF expression was associated with increased neutrophil, monocyte and eosinophil production in Pexa-Vec treated patients (*Breitbach 2011; Park 2008*). Furthermore, inflammatory cell infiltration into tumors was also demonstrated with Pexa-Vec treatment (*Hwang 2011; Mastrangelo 1999*). Finally, functional anti-tumor antibodies mediating complement dependent cytotoxicity were induced after Pexa-Vec treatment of patients with liver tumors- (*Heo 2013; Kim 2013*).

Further information about the Investigational Medicinal Product (IMP) is available in the Investigator Brochure.

1.2.2 Previous Pexa-Vec Non-Clinical Results

1.2.2.1 Efficacy of Pexa-Vec in Rabbit VX-2 Carcinoma Model and Rat Carcinogen-Induced Primary Liver Tumors

Efficacy of Pexa-Vec- as a single agent was studied in 2 liver cancer models.

hGM-CSF, expressed by Pexa-Vec is biologically active in rabbits, a species in which vaccinia virus replicates.

Accordingly, the virus was tested in the transplantable orthotopic rabbit carcinoma VX-2 model in which cells are implanted under the liver capsule forming liver tumors and metastases in liver and lung (*Kim 2006*). Tumor-bearing rabbits were treated with a single dose of 10^9 plaque forming units (pfu) of Pexa-Vec via IT or intravenous (IV) injection. Seven weeks post therapy, mean tumor volume in both Pexa-Vec treated groups was significantly smaller when compared to the phosphate buffered saline (PBS) control group. Furthermore, Pexa-Vec treatment prevented formation of metastases. Median survival time of rabbits in the PBS control group was 50 days while median survival was not reached in either Pexa-Vec treated group at 70 days

(*Kim 2006*). Rabbits treated with Pexa-Vec exhibited weight gain while control rabbits lost weight over the course of the study, presumably due to tumor progression. The dose response of the effects of Pexa-Vec treatment was determined by comparing the efficacy of a single IV dose of 10^8 pfu used in a subsequent study with the results discussed above with application of 10^9 pfu. Whereas a dose of 10^9 pfu resulted in 88% inhibition of primary tumor growth and 100% inhibition of metastases at 7 weeks, the lower dose of 10^8 pfu inhibited primary growth by only 10%, while inhibiting the incidence of metastases by 48%.

Pexa-Vec efficacy against primary liver tumors was investigated in an orthotopic primary liver tumor model. Cirrhosis and liver cancers were induced in rats by chronic oral administration of N-nitrosodiethylamine and N-nitrosomorpholine (*Kim 2006*). Tumor-bearing rats received 3 IV infusions of Pexa-Vec every 2 weeks. Over 10 weeks, 5 of 6 animals treated with Pexa-Vec exhibited complete responses by ultrasound while tumors in all PBS control animals increased in size.

These preclinical studies provide rationale for the use of Pexa-Vec as a novel therapy for HCC (refer to the IB for further details).

[redacted]

1.2.3 Previous Pexa-Vec Clinical Results

As of February 2015, 1281 doses of Pexa-Vec have been administered by IT injection and/or IV infusion to more than 306 patients in 13 clinical research trials.

[redacted]

[redacted]

Overall, the clinical information available to date suggests that Pexa-Vec is safe at the clinical dose of 10^9 pfu when injected IT (*Kim 2006, Park 2008, Heo 2013*) and has not spread to caregivers in contact with the treated patients. For the previous clinical trials performed in France with Pexa-Vec as well as for the proposed study, the French Biosafety authority "Haut Conseil des Biotechnologies" classified Pexa-Vec for therapeutic use as a **GMO of Risk Level I** thus requiring specific rules and recommendations to be followed by caregivers. Preparation of viral solutions should be performed under a microbiological safety cabinet of type II using waterproof gloves, gown, surgical/procedure mask and safety goggles. All transfers of the preparation must be done within a sealed plastic transport bag or other sealed, leak-proof secondary container displaying a clearly marked biohazard symbol. All materials in contact with Pexa-Vec will be decontaminated and/or destroyed using hospital-grade chemical disinfectants active on vaccinia viruses.

1.2.3.3 Efficacy

Despite initial and potential transient tumor swelling due to edema and/or inflammation (termed as "oncolytic flare response" or "pseudoprogression"), Pexa-Vec has demonstrated antitumor activity as evidenced by decreased tumor enhancement and/or size on dynamic contrast-enhanced magnetic resonance imaging (MRI) or computed tomography (CT) based on RECIST 1.1 and/or mChoi and/or mRECIST for HCC criteria depending on the studies. Main activity / efficacy results from completed trials (n=12 trials) are summarized in the Table 3. Interestingly, distant tumor responses have been observed in distant, not injected, tumor lesions and this effect has been proved to be immune mediated (*Kim 2006, Heo 2013*).

In a randomized Phase II study (HEP007, NCT00554372) in advanced first line HCC a significant improvement of OS was observed with Pexa-Vec at 10^9 pfu (14.1 m) versus 10^8 pf (6.7 m) with a hazard ratio of 0.39 p = 0.020 (Heo 2013).

Pexa-Vec has now entered into a randomized, controlled Phase III trial in advanced first line HCC (NCT02562755), comparing the administration of Pexa-Vec and sorafenib to sorafenib alone with OS as primary endpoint.

[redacted]

[redacted]

Further information about the IMP is available in the Investigator Brochure.

1.3 IMP 2: Nivolumab (Opdivo®)

Nivolumab (Opdivo®) (also referred to as BMS-936558 or MDX1106) is a human monoclonal antibody (HuMAb; immunoglobulin G4 [IgG4]-S228P) that targets the programmed death-1 (PD-1) cluster of differentiation 279 (CD279) cell surface membrane receptor. PD-1 is a negative regulatory molecule expressed by activated T and B lymphocytes. Binding of PD-1 to its ligands, programmed death–ligands 1 (PD-L1) and 2 (PD-L2), results in the down-regulation of lymphocyte activation. Inhibition of the interaction between PD-1 and its ligands promotes immune responses and antigen-specific T-cell responses to both foreign antigens as well as self-antigens.

Nivolumab (Opdivo®) is approved in multiple countries including the US and Europe for the treatment of unresectable or metastatic melanoma in combination with ipilimumab (only in US) or alone for previously treated patients, and for the treatment of previously treated, metastatic non-small cell lung cancer (NSCLC) (only squamous form at present in the EU), for the treatment of previously treated advanced renal cell carcinoma (only in the US), for the treatment of advanced 2nd line squamous cell carcinoma of the head and neck (SCCHN) (US & Europe), for previously treated urothelial bladder cancer, and for classical Hodgins lymphoma. US nivolumab Prescribing Information (USPI) and EU nivolumab Summary of Product Characteristics (SmPC) are available on FDA and EMA websites, respectively.

1.3.1 Nonclinical Studies

In addition, a comprehensive preclinical characterization of nivolumab was published in 2014 by *Wang et al.* Nivolumab binds to PD-1 with high affinity and specificity, and effectively inhibits the interaction between PD-1 and its ligands, PD-L1 and PD-L2, but not to related members of the CD28 family. In vitro assays demonstrated the ability of nivolumab to potently enhance T-cell responses, proliferation and cytokine production in the mixed lymphocyte reaction and superantigen or cytomegalovirus stimulation assays. No in vitro antibody-dependent cell-mediated or complement-dependent cytotoxicity was observed with the use of nivolumab and activated T cells as targets. Nivolumab treatment did not induce adverse immune-related events when given to cynomolgus macaques at high concentrations, independent of circulating anti-nivolumab antibodies where observed.

No studies have been performed to assess the potential of nivolumab for carcinogenicity or genotoxicity. Fertility studies have not been performed with nivolumab. In 1-month and 3-month repeat-dose toxicology studies in monkeys, there were no notable effects in the male and female reproductive organs; however, most animals in these studies were not sexually mature.

1.3.2 Effects in Humans

1.3.2.1 Pharmacokinetics

As further detailed in the SmPC, the PK of nivolumab was studied in patients over a dose range of 0.1 to 20 mg/kg administered as a single dose or as multiple doses of OPDIVO every 2 or 3 weeks. Based on a population pharmacokinetic (PK) analysis using data from 909 patients, the geometric mean (% coefficient of variation [CV%]) clearance (CL) is 9.5 mL/h (49.7%), geometric mean volume of distribution at steady state (Vss) is 8.0 L (30.4%), and geometric mean elimination half-life (t1/2) is 26.7 days (101%). Steady-state concentrations of nivolumab were reached by 12 weeks when administered at 3 mg/kg every 2 weeks, and systemic

accumulation was approximately 3-fold. The exposure to nivolumab increased dose proportionally over the dose range of to 10 mg/kg administered every 2 weeks.

1.3.2.2 Efficacy

Opdivo® has been approved for and is indicated for the treatment of patients with:

- BRAF V600E mutation-negative unresectable or metastatic melanoma, as a single agent.
- BRAF V600E mutation-positive unresectable or metastatic melanoma, as a single agent. This indication is approved under accelerated approval based on progression-free survival. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.
- Unresectable or metastatic melanoma, in combination with ipilimumab. This indication is approved under accelerated approval based on progression-free survival. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.
- Metastatic NSCLC and progression on or after platinum-based chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving Opdivo®.
- Advanced RCC who have received prior anti-angiogenic therapy.

Nivolumab is currently in late stage development in numerous indications either as monotherapy or in combination with other agents: in advanced HCC Phase I / II and Phase III trials are ongoing: checkmate 459 (NCT02576509) and NCT01658878.

1.3.2.3 Clinical Safety

The overall safety experience with nivolumab, as a monotherapy or in combination with other therapeutics, is based on experience in approximately 8,600 subjects treated to date.

For monotherapy, the safety profile is similar across tumor types. There is no pattern in the incidence, severity, or causality of AEs to nivolumab dose level. In Phase III controlled studies, the safety profile of nivolumab monotherapy is acceptable in the context of the observed clinical efficacy, and manageable using established safety guidelines. Clinically relevant AEs typical of stimulation of the immune system were infrequent and manageable by delaying or stopping nivolumab treatment and timely immunosuppressive therapy or other supportive care.

In several ongoing clinical trials, the safety of nivolumab in combination with other therapeutics such as ipilimumab, cytotoxic chemotherapy, anti-angiogenics, and targeted therapies is being explored. Most studies are ongoing and, as such, the safety profile of nivolumab combinations continues to evolve.

For additional nivolumab safety information, please refer to US Prescribing Information (USPI) and EU Summary of Product Characteristics (SmPC), available on FDA and EMA websites, respectively.

1.4 Rationale for conducting the study

Novel therapies are desperately needed for patients with advanced, unresectable HCC. The only approved agent for advanced HCC, sorafenib, prolongs survival by only a few months, is not curative, and is generally cytostatic. Furthermore, several agents with similar mechanisms-of-action to sorafenib (including brivanib, sunitinib and linifanib) have failed to demonstrate improved outcome for advanced HCC patients when compared to sorafenib (*Llovet 2013*).

There is rising evidence for the PD-1 / PD-L1 pathways involvement in HCC (*Makarova-Rusher et al. 2015; Tsuchiya et al.*). It was demonstrated that PD-L1 is constitutively expressed in HCC cells in vitro and moreover in tumor specimens in vivo, and elevated PD-L1 expression in HCC is significantly associated with tumor aggressiveness, suggesting that PD-L1 may represent a target for HCC immunotherapy (*Umemoto Y et al. 2015, Gao Q et al. 2009*).

These findings have encouraged several clinical studies with PD-1 blockers in HCC. In an ongoing Phase I / II trial (NCT01658878) treatment of mostly 2nd line HCC patients resulted in durable long lasting responses and promising OS data (70% at 9 months, 62% at 12 months). The observed response rate in a first set of 42 evaluable patients was 19% which is substantially higher than the 2% observed with sorafenib (*Llovet et al. 2008, Cheng et al. 2009*) and half of the patients (48%) exhibited a disease stabilization (*El-Khoueiry et al. ASCO 2015*). Based on these encouraging results, in an ongoing Phase III trial (NCT02576509, Checkmate 459), the efficacy of nivolumab is compared to sorafenib in advanced 1st line HCC patients. Another PD-1 blocker, pembrolizumab is currently investigated in 2nd line HCC in Phase II (NCT02702414) and Phase III (NCT02702401) trials. Furthermore, in an ongoing Phase II trial (NCT02519348) in 2nd line HCC, the PD-L1 blocking antibody durvalumab is investigated in combination with Tremelimumab (anti-CTLA4).

Pexa-Vec exhibits multiple different and complementary mechanisms-of-action to nivolumab. By exploiting novel, alternative mechanisms-of-action of Pexa-Vec relative to other investigational agents, Pexa-Vec administration in combination with nivolumab may provide additional clinical benefit to nivolumab therapy alone. The concept of adaptive immune resistance — whereby immune-checkpoint ligands such as PDL-1 are induced in tumors in response to an endogenous antitumor immune response — suggests that PD-1-pathway blockade as a monotherapy might be enhanced in combination with other targeted therapies, such as cancer vaccines and oncolytic immunotherapy owing to the overlapping mechanisms of action (*Melero et al; 2015*). We hypothesize that expanded efficacy might be achieved when PD-1-pathway blockade is combined with an oncolytic immunotherapy, that induces long lasting tumor-specific responses without autoimmunity (*Melero et al. 2015*).

The rationale for combining immunotherapies in various cancer indications including HCC is based on several preclinical and clinical data to date:

Promising results were reported after combining an immune checkpoint inhibitor and viral-based products in preclinical and clinical studies. As anticipated, selective blockade of co-inhibitory molecules within the tumor microenvironment favors the intratumor effector functions of tumor-specific T cells primed and expanded by the vaccine. In preclinical studies, the study published by Zamarin et al. (2012) was the first to support clinical exploration of the use of checkpoint antibodies with oncolytic Newcastle disease virus (NDV). In a pre-clinical model of metastatic tumor, the combination therapy of NDV and CTLA-4 checkpoint blockade controlled both local and distant tumors better than either anti-CTLA-4 or NDV treatment alone. The combination therapy also led to long-term survival of mice (up to 100 days), elicited inflammatory recruitment of CD8 T cells, and led to overall enhancement of effector to Tregs

ratio. In addition, synergies in term of anti-tumor response and demonstration that therapy is dependent on immune effectors were also seen when combining anti-CTLA-4 or anti-PD-1 antibody with on oncolytic vaccinia virus (*Rojas 2015*), with a Vesicular stomatitis virus (*Gao 2009*) or with a reovirus (Reolysin) (*Rajani 2015*). Finally, another strategy is now explored with oncolytic viruses engineered to encode antibodies against immune checkpoint. The first published study was done using an oncolytic measles virus engineered to locally express anti-PD-1 or anti-CTLA-4 and showed improved antitumor efficacy of these recombinant vectors compared with the parental measles virus (*Engeland 2014*).

In human, ipilimumab was combined with a GM-CSF cell-based vaccine (G-VAX) in patients with pancreatic cancer showing an improvement of OS associated with clinical activity in the combination arm (*Le 2013*). Also, the oncolytic virus T-VEC is currently tested in combination with both ipilimumab (NCT01740297) and pembrolizumab (NCT02263508) in melanoma with a doubling of the ORR communicated after an interim analysis of the NCT01740297 trial (ASCO 2014). Interestingly, in HCC, a pilot study explored the safety and feasibility of tremelimumab in combination with loco-regional therapies directed to promote immunogenic tumor cell death, comparable to the one observed by oncolysis, in patients with advanced-stage HCC exposed to sorafenib (*Duffy, poster - ASCO 2015*). This combined therapy was proved to be safe with 4 out of 10 patients achieving confirmed partial objective response and tumor biopsies showing immune cell infiltration in all evaluable patients.

All these data support the clinical development of strategies based on combinations of virotherapy with checkpoint inhibitors.

In light of the numerous regulatory pathways that HCC tumors employ to evade an immune attack and to overcome the dual liver and tumor immune tolerance phenomena, the use of combination of several immunotherapies offers a great promise and may increase the percentage of patients that respond to immunotherapy.

1.4.1.1 Dose and Route of Administration of IMPs

1.4.1.1.1 Pexa-Vec

Due to the high rate of accessible tumors and clinical relevance of locoregional therapy in HCC, IT treatment is well established in all locoregional therapies.

IT injection of Pexa-Vec into liver tumors was well-tolerated at both the 1×10^8 pfu and the 1×10^9 pfu dose (equivalent to 9.0 Log pfu) in HCC patients treated in the JX594-IT-HEP007 protocol regimen (3 IT injections, each 2 weeks apart) (Heo 2013). Of interest, overall survival was significantly longer in the high-dose arm compared with the low-dose arm (median 14.1 months versus 6.7 months, HR 0.39; p-value 0.020, Gehan-Breslow-Wilcoxon test; 1-sided test for superiority of high-dose).

Therefore, the 1×10^9 pfu dose level administered 3 times every 2 weeks appears to have the highest likelihood of benefiting patients with advanced HCC while maintaining a tolerable safety profile of Pexa-Vec.

1.4.1.1.2 Nivolumab

Interim data of a study exploring the safety and preliminary efficacy of nivolumab in HCC support the continued exploration of nivolumab in HCC (NCT016585578) (*El-Khoueiry et al. ASCO 2015*).

A total of 47 HCC patients, who progressed on at least one prior line of systemic therapy, including sorafenib, or were intolerant to or refused sorafenib treatment were exposed to escalating doses of nivolumab, from 0.1 to 10 mg/kg q2weeks. In this Phase I clinical trial, one DLT occurred at 10mg/kg (hepatic decompensation), no MTD has been identified and the 3mg/kg dose has been selected for further expansion of the trial. However, in current studies with nivolumab, 240 mg "flat" dose, corresponding to a 3mg/kg dose for a 80 kg individual, is being used as a standard by BMS, as no additional toxicity was observed previously with 10mg/kg, as compared with 3mg/kg. Complexity and time of preparation of nivolumab infusions is then decreased, as well as involved preparation risks.

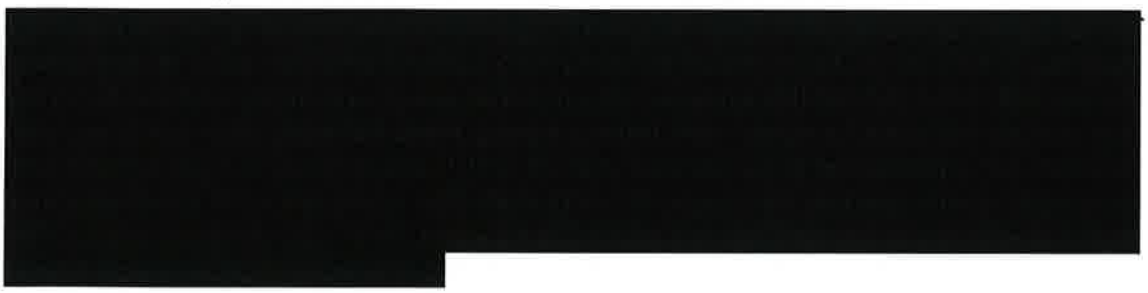
Most frequent nivolumab-related Grade 3 adverse events were hepatic cytolysis (AST increase, 11%, ALT increase, 9%) and lipase increase (6%). Investigator-assessed best overall response rate (ORR) was 19%, including 5% complete response rate. Disease stabilization as best response was seen in 48% of patients. Most interestingly, duration of responses and of stabilizations appeared to be prolonged, i.e. 1.4 to 12.5 months and 1.1 to 17.3 months, respectively. This may have been translated into 62% of patients being still alive one year after initiation of nivolumab treatment. These preliminary data are used for sample size calculation in the present combination study with Pexa-Vec.

1.4.1.1.3 Sequential Therapy

IT Pexa-Vec injections will be performed on D1, D15 and D29. Additional Pexa-Vec boosts may be performed from Week 12 after discussion on a case by case basis between the investigator and Transgene.

Nivolumab will be given from D15, by IV route every 2 weeks until progression or unacceptable toxicity.

The rationale for the sequential administration of Pexa-Vec followed by nivolumab is based on preclinical studies. Rojas et al. (2015) provided the first preclinical data to support the use of oncolytic vaccinia virus in combination with anti-CTLA-4 antibody. In these studies, it was shown that one systemic dose of vaccinia virus followed by three intra-peritoneal doses of anti-CTLA4 therapy could establish significant tumor growth control and increased OS in mice models of renal carcinoma. When the anti-CTLA-4 was administered concurrently with the vaccinia virus, no efficacy was observed.



1.5 Potential risks and benefits associated with Pexa-Vec

The risks associated with Pexa-Vec administration, as described in the patient informed consent form (ICF), are related to: 1/ the occurrence of side-effects observed in previous studies, 2/ the potential occurrence of side effects related to the parent vaccine and not observed in previous studies, i.e., infectious vaccinia complications or peri-/myocarditis 3/ the risks related to the intratumoral procedure described below and 4/ risks for third parties, who may enter into contact with the patient treated with Pexa-Vec (See section 1.2.3.2, ICF and IB).

1.5.1 Potential risks associated with Pexa-Vec intratumoral injections

The potential risks involved by the intra-tumoral procedure itself are mainly the risk of hemorrhage and the risk of infection. The risk of hemorrhage appears to be minimal, as only one hemorrhagic event has been reported in 180 patients, who each underwent several sessions of intra-tumoral injections (Development Safety Update Report, DSUR). This risk may be lower than that incurred after liver tumor biopsy, as no tissue and its blood vessels are sampled in the procedure. The risk of infection is that of every surgical procedure and is proportional to its complexity and duration.

The potential risks involved by the intra-tumoral injection of Pexa-Vec are that of tumor swelling due to the inflammatory reaction to the virus. The swelling of the tumor resulted in biliary duct compression and transitory jaundice in 2 patients after intra-tumoral injection of a high dose of Pexa-Vec (3×10^9 pfu) in the setting of the Phase 1 study; these events defined the Maximal Tolerated Dose as being 1×10^9 pfu. Tumor swelling may also result in transitory abdominal pain, especially when liver tumors are located close to the liver capsule. Leakage of injected viral suspension outside of the tumor may occur but is generally limited, as, on the one hand, the suspension is echogenic and hence the injection is controlled in real time, and, in the other hand, Pexa-Vec does not affect surrounding non-cancer tissue and does not induce hepatic cytolysis.

1.6 Potential risks and benefits associated with nivolumab

The overall safety experience with nivolumab is based on experience in approximately 8,600 subjects as either monotherapy or in combination with other therapeutics. In general, for the monotherapy, the safety profile is similar across tumor types. The most frequently reported treatment-related AE is fatigue, which is almost always of low grade. Most related AEs are thought to be due to the effects of inflammatory cells on specific tissues.

In several ongoing clinical trials, the safety of nivolumab in combination with other therapeutics such as ipilimumab, cytotoxic chemotherapy, anti-angiogenics, and targeted therapies is being explored. Most studies are ongoing and, as such, the safety profile of nivolumab combinations continues to evolve.

Hepatic AEs, including elevated liver function tests (LFTs) and, infrequently, drug-induced liver injury (DILI), have been observed following treatment with nivolumab. Most cases were of low or moderate grade. Higher-grade hepatic AEs, including DILI, were managed with corticosteroids (with or without mycophenolate mofetil) and, in almost all cases, the events resolved. The recommended management of hepatic AEs is provided in Appendix 3. Early recognition and treatment of elevated LFTs and DILI are critical to their management. Subjects should be advised to seek medical evaluation if they notice jaundice (yellow appearance of skin

or sclera) or if they develop bruising, bleeding, or right-sided abdominal pain. Physicians should monitor LFTs prior to each nivolumab treatment. As LFT abnormalities are common in subjects with HCC, it is important that an evaluation/work-up distinguishes between non-drug-related causes (e.g., infection, progression of disease, concomitant medications, or alcohol) and a possible drug-related AE as the management can be quite different. The principal treatment for high-grade hepatic AEs is corticosteroids. Consultation with Transgene medical monitor should be sought for all moderate- and high-grade hepatic AEs.

The anticipated benefits of nivolumab in HCC are stemming from the interim data presented at the 2015 ASCO annual meeting by Anthony El-Khoueiry. The benefits consisted in a best overall response rate (ORR) of 19%, including 5% complete response rate, to which a disease stabilization rate of 48% of patients could be added to obtain a 67% Disease Control Rate (DCR). Most interestingly, duration of responses and of stabilizations appeared to be prolonged that may have been translated into 62% of patients being still alive one year after initiation of nivolumab treatment.

1.7 Potential risks and benefits associated with Pexa-Vec-nivolumab combination

For suspected nivolumab-related AEs, based on the severity of the event, management with immunosuppressants may be necessary. In general, dose delays and observation are adequate when low-grade AEs are experienced. For moderate- and high-grade AEs, immunosuppression with corticosteroids should be utilized.

Once the AE has begun to resolve, corticosteroids can be tapered over approximately 3 weeks to 6 weeks (depending on the severity of the AE). Subjects with inflammatory events of any organ category expected to require more than 4 weeks of corticosteroid or other immunosuppressive agents to manage the AE should be considered, especially in the setting of the combination with Pexa-Vec treatment that is contra-indicated in patients with immunosuppression. In such an event, consultation with Transgene Medical Monitor should be sought and Pexa-Vec treatment discontinued.

Combination therapy of nivolumab with Pexa-Vec may result in "landmark" events that are the anticipated addition of events of the same type or involving the same organs. Among these "landmark" events, the most likely ones are flu-like symptoms that may occur usually at a moderate intensity with exposure to each of these compounds. Flu-like symptoms (fever, chills, myalgia, and gastrointestinal symptoms) may then be aggravated by the combination. In addition, the risk of myocarditis rarely occurring with the parent vaccinia virus may be increased by the combination with nivolumab.

It is anticipated that a treatment with the combination may also result in hepatic cytolysis (increase in liver enzymes, AST and ALT) and/or in interference with liver function, especially in patients with cirrhosis. AST and ALT elevations, as well as increases in bilirubin, prothrombin time (INR) translated into Child-Pugh score aggravation are deemed "landmark" events. In addition, increase in incidence or severity of immune-related AEs are also deemed "landmark" events. Severity of immune-related AEs is related to the need for steroid treatment. These events are monitored for dose-escalation in the phase I part of the study. Appendix 3 is summarizing the guidance to the Investigator in case of immune-realted AEs including immune-realted hepatic AEs and may be supplemented by discussions with Transgene Medical Monitor.

Pexa-Vec administration in combination with nivolumab may provide additional clinical benefit to nivolumab therapy alone by exploiting novel, complementary mechanisms-of-action to nivolumab. In this study, a prime injection of Pexa-Vec will be performed before co-administrations of nivolumab and Pexa-Vec; the application of oncolytic virus is expected to induce strong infiltration of innate immune cells to the tumor microenvironment, to trigger molecular changes likely to results in potentiation of nivolumab (increase in the expression of PD-L1) and to promote the development of an anti-tumoral adaptive immune response.

2 OBJECTIVES

The TG6006.01 study comprises two parts: Phase I and Phase IIa.

2.1 Primary objective

The primary objective of this study is:

Phase I part: To evaluate the safety profile of intratumoral (IT) Pexa-Vec combined with intravenous (IV) nivolumab in patients with advanced HCC.

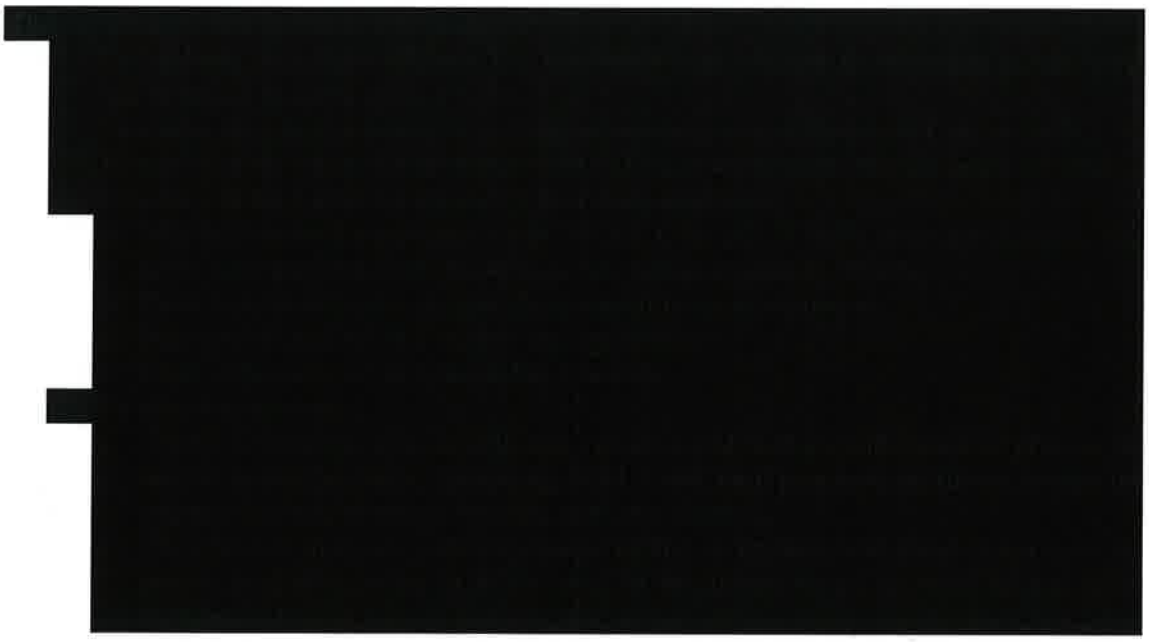
Phase IIa part: To evaluate the anti-tumor activity and efficacy of IT Pexa-Vec combined with IV nivolumab in patients with advanced HCC with respect to Overall Response Rate (ORR) (RECIST 1.1).

2.2 Secondary objectives

The secondary objectives of this study are to evaluate the efficacy of Pexa-Vec combined with nivolumab in patients with advanced HCC with respect to the following endpoints:

- Imaging endpoints evaluated by RECIST 1.1: Disease Control Rate (DCR) at 4 months and over time, Time to Progression (TTP), Duration of Response (DoR), Progression Free Survival (median PFS and percent of patients having not progressed over time) and Overall Response Rate (ORR, Phase I)
- Safety (Phase IIa)
- Overall Survival (OS), median and percent survivors over time
- Blood viral load (HCV, HBV and viral antigens (HBsAg, HBeAg) when appropriate)

2.3 Exploratory objectives



3 STUDY DESIGN

3.1 Overall study design and plan description

3.1.1 Overall design and primary / secondary endpoints

This is an open-label single-arm 2-part Phase I/IIa study.

The Phase I part is a single cohort enrolling six patients at standard Pexa-Vec and nivolumab dose, ie $1x10^9$ pfu and 240 mg, respectively. The study provides dose-limiting toxicity (DLT) and landmark AE-driven dose de-escalation patient cohort. A landmark AE is an anticipated effect of the combination, defined as an increase in severity of hepatic cytolysis (doubling of AST – ALT baseline blood concentrations), or significant deterioration of hepatic function (INR, bilirubin), or increase in incidence or severity of immune-related AEs, or increase in number or severity of Pexa-Vec-related skin lesions. In case of a DLT is observed in more than one patient out of the first 6 patients, or in case of the occurrence of a landmark AE, one de-escalation dose regimen is planned that will be consecutively applied on cohorts of 6 other patients, if needed:

- Dose level -1: $3x10^8$ pfu for Pexa-Vec and 240 mg q2 weeks for nivolumab OR 10^9 pfu for Pexa-Vec and 240 mg q3 weeks for nivolumab, depending on the DLT profile relative to the known toxicity of each component of the combination,

The first patient will be monitored for safety after 3 Pexa-Vec IT injections and 2 nivolumab infusions, scheduled on D29, corresponding to the completion of the DLT monitoring period (i.e. week 4), before the second patient can be enrolled. In addition, a security interval of 2 weeks between enrolments of each consecutive patients will be applied. These intervals and their duration are appropriate to prevent additional patients to be exposed in case acute or subacute toxic events are observed in the first patients. It has been shown that Pexa-Vec-related events usually resolve within days of evolution.

In case of a DLT is observed in **more than one patient** out of the first 6 patients or of occurrence of any landmark AE, dose de-escalation level -1 will apply on up to 6 additional patients, upon the decision of the Independent Safety Committee (ISC, see section 13.4) on the dose reduction on either component of the combination, based on the AEs recorded in the first patients. The time needed for collection of the safety data from the first patient together with the organization of the ISC meeting will introduce a time interval of at least one month after the completion of the DLT period of the last patient exposed to the first dose level that will extend the period of observation of possible late-occurring AEs.

In case of a DLT is observed in **no more than one patient** out of 6 patients of any Phase I dose level and of no occurrence of any landmark AE, then accrual in the Phase IIa part of the study will start at the same dose level without security intervals. The initiation of the Phase IIa part of the study and the dose level to be applied in this part will also be determined following an analysis by the ISC of all safety results collected in Phase I.

The primary endpoint of the Phase I part is the determination of the safety profile of Pexa-Vec combined with nivolumab in patients with advanced HCC, after NCI-CTCAE version 4.03 grading system.

The secondary endpoints to assess signals of efficacy, in terms of radiological endpoints (all imaging endpoints evaluated by RECIST 1.1), survival and viral load are:

- Disease Control Rate (DCR) at 4 months and over time
- Time to Progression (TTP)
- Duration of Response (DoR)
- Progression Free Survival (PFS), median and percent of patients having not progressed over time
- Overall Survival (OS), median and percent survivors over time
- Blood viral load (HCV, HBV when appropriate)

The Phase IIa part involves a single patient cohort. The primary endpoint of the Phase IIa part is to evaluate the anti-tumor activity and efficacy of Pexa-Vec combined with nivolumab in patients with advanced HCC with respect to Overall Response Rate (ORR) (RECIST 1.1).

The secondary endpoints to assess safety and signals of efficacy, in terms of additional radiological endpoints (all imaging endpoints evaluated by RECIST 1.1), survival and viral load are:

- Safety, after NCI-CTCAE version 4.03 grading system.
- Disease Control Rate (DCR) at 4 months
- Disease Control Rate (DCR), percent non-progressors over time
- Time to Progression (TTP)
- Duration of Response (DoR)
- Progression Free Survival (PFS), median and percent of patients having not progressed over time
- Overall Survival (OS), median and percent survivors over time
- Blood viral load (HCV, HBV when appropriate).

3.1.2 Number of centers and patients

The Phase I part of the study will be conducted in about 2 sites not located in the USA. This part would enroll between 6 and 12 evaluable patients, should none or one dose de-escalation level be applied, respectively.

In the Phase IIa part of the study, the number of participating countries and of participating sites will be expanded to about 10 sites, overall, in order to enroll a total of 30 evaluable patients, including evaluable Phase II patients and comparable Phase I patients still evaluable for Phase II, in terms of population and treatment regimen.

The maximal overall number of patients to be enrolled may then be of 42 evaluable patients; taking into account a 10% rate of non-evaluable patients, who will have to be replaced for the implementation of principal per protocol analyses, the final total and maximal patient enrolment in this study would involve 47 patients.

3.1.3 Patient accrual and duration of study

This study is expected to start in June 2017 with recruitment of the Phase I part to be completed by January 2018. Recruitment in the Phase IIa part is expected to be completed by March 2019 and the study to be completed by August 2019.

It is understood that these accrual rates are based on reasonable planning expectations. The actual accrual rates should be compared to the expected rates 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 design of the Phase I part of the study is derived from a classic 3+3 dose-escalation design, after which safety is assessed on 6 patients treated at the same dose level. Given the favorable safety profile of both agents, their non-overlapping metabolism, and based on Pexa-Vec safety data and on nivolumab safety data in HCC from the recently completed study, standard doses will be used for initial dose level as 3 bi-weekly IT injections of $1x10^9$ pfu for Pexa-Vec and 240 mg IV q2weeks for nivolumab.

Despite of the exploratory nature of this study, an approach to the calculation of an appropriate sample size is based on the ORR observed in the Phase I study performed with nivolumab in HCC, in an intent to detect an increased anti-tumor activity brought by the combination with Pexa-Vec.

Considering a type I error of 5% and a power of 80%, a two-stage group sequential design using alpha and beta spending function approach with Lan DeMets spending function (O'Brien-Fleming efficacy boundaries and non-binding Pocock futility boundaries) was used leading to a maximum sample size of 30 evaluable patients and an interim analysis based on 15 evaluable patients with a test proportion with normal approximation to the binomial distribution.

4 STUDY POPULATION

The study population will include patients with advanced stage HCC per EASL-EORTC (European Association for the Study of the Liver-European Organisation for Research and Treatment of Cancer) guidelines, i.e. patients who are not candidates for curative interventions and not candidates for locoregional modalities; in addition, patients shall not have been previously treated with a systemic therapy for HCC (first-line patients).

4.1 Inclusion criteria

Patients must satisfy all of the following criteria for entry into the protocol:

1. Male or female patients, age ≥18 years old,

2. Histological/cytological diagnosis of primary HCC, excluding cholangiocarcinoma, hepatocholangiocarcinoma, fibrolamellar carcinoma and hepatoblastoma. Note: if no previous pathological report is available, a tumor diagnostic biopsy should be performed,

3. Advanced stage HCC per EASL-EORTC (European Association for the Study of the Liver-European Organisation for Research and Treatment of Cancer) guidelines, i.e. patients who are not candidates for curative interventions and not candidates for locoregional modalities,

4. Patients naïve to systemic therapy for HCC,

5. Tumor status (as determined by radiology evaluation): At least one measurable viable tumor in the liver, ≥1 cm longest diameter (LD), using a dynamic imaging technique (arterial phase of triphasic computerized tomography [CT] scan, or dynamic contrast-enhanced magnetic resonance imaging [MRI]), and injectable under imaging-guidance (CT or ultrasound),

6. At least one tumor that has not received prior local-regional treatment, or that has exhibited definitive growth of viable tumor since prior local-regional treatment of HCC undertaken at least 4 weeks prior to enrolment or 3 months prior to enrolment for radioembolization,

7. Child-Pugh Class A. Note: paracentesis, albumin infusion or diuretic treatment cannot be used to downgrade Child-Pugh score (e.g., to improve from severe to moderate/mild or from moderate to mild ascites),

8. Performance status 0 or 1 on the Eastern Cooperative Oncology Group (ECOG) scale,

9. Adequate hematological, hepatic, and renal function:
   a. Hemoglobin ≥9 g/dL
   b. Platelet count ≥60 10^9/L
   c. International normalized ratio (INR) ≤1.7
   d. White blood cell (WBC) count ≥2 10^9/L
   e. Absolute neutrophil count (ANC) ≥1 10^9/L
   f. Albumin ≥28 g/L, total bilirubin ≤1.5 times upper limit of normal (ULN); alanine aminotransferase (ALT), aspartate transaminase (AST) ≤5 ULN

g. Serum creatinine <20 mg/L or creatinine clearance >60 mL/min according to Cockroft-Gault formula,

10. For patients who are sexually active: willing to use adequate barrier contraception method during Pexa-Vec and nivolumab treatment period, for at least 6 weeks after last Pexa-Vec injection and for at least 5 months after last nivolumab administration,

11. Life expectancy of at least 3 months,

12. Patient should agree to undergo a pre-treatment tumor biopsy, if necessary for diagnostic purposes; a post-treatment tumor biopsy is optional for translational research purposes,

13. Written informed consent,

14. Patients with active hepatitis B infection should be on adequate antiviral therapy,

15. Cardiology consultation and clearance obtained for study participation. Baseline cardiologic investigations should include troponin T or I blood level measurement, electrocardiogram (ECG) and cardiac echography (ECHO) with measurement of left ventricular ejection fraction (LVEF). Ability to temporarily suspend treatment with anti-hypertensive medications should also be assessed.

4.2 Exclusion criteria

Patients will not be included in the study for any of the following reasons:

1. Major surgery within 4 weeks of study treatments (minor surgical procedures are allowed e.g., intravascular access line or Port-a-Cath®),

2. Local-regional therapy of HCC within 4 weeks or radioembolization within 3 months prior to enrolment,

3. Histological diagnosis of cholangiocarcinoma, hepatocholangiocarcinoma, fibrolamellar carcinoma and hepatoblastoma,

4. History of moderate or severe ascites, bleeding esophageal varices, hepatic encephalopathy or pleural effusions related to liver insufficiency within 6 months of screening; patients with adequately treated esophageal varices (banding, sclerotherapy) are allowed,

5. Clinically significant ascites, e.g., requiring a paracentesis or aggressive inpatient diuresis, pericardial and/or pleural effusions. Minimal, medically controlled ascites detectable on imaging studies only and not precluding a safe IT injection of Pexa-Vec- is allowed,

6. Active, known or suspected significant immunodeficiency due to underlying illness including HIV/AIDS, autoimmune diseases, and/or immune-suppressive medication including high-dose corticosteroids (defined as ≥20 mg/day prednisone or equivalent

which is ongoing at the time of randomization and/or was taken for more than 4 weeks within the preceding 2 months of study treatment),

7. Any prior or planned organ transplant (e.g., liver transplant),

8. History of severe eczema and/or ongoing severe inflammatory skin condition (as determined by the Investigator) requiring medical treatment,

9. Patients who experienced a severe systemic reaction or side-effect as a result of a previous vaccination with vaccinia,

10. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation. Child-bearing potential patients with a positive hCG laboratory test (>10 mIU/mL) at screening and/or a urinary pregnancy test at Baseline will perform an ultrasound to confirm the pregnancy,

11. Prior malignancy except for the following: adequately treated basal or squamous cell skin cancer, in situ cervical cancer, adequately treated cancer from which the patient has been disease-free for at least 3 years,

12. Tumor(s) invading a major vascular structure (e.g. carotid artery) or other key anatomical structure (e.g. pulmonary airway) in the event of post-injection tumor swelling and/or necrosis (hepatic and portal vein involvement allowed),

13. Viable central nervous system malignancy

14. Symptomatic cardiovascular disease, including but not limited to significant coronary artery disease (e.g., requiring angioplasty or stenting) or congestive heart failure within the preceding 12 months,

15. Current or past history of cardiovascular disease (e.g., past history of myocardial infarction, ischemic cardiomyopathy) unless cardiology consultation and clearance has been obtained for study participation,

16. Medical conditions, per the investigator's judgment, that would contra-indicate volume loading (e.g., intravenous |[IV] fluid bolus infusion) or increase the risk of severe hypotension following treatment with Pexa-Vec (e.g., dehydration, hypovolemia),

17. Other medical condition or laboratory abnormality or active infection that in the judgment of the Principal Investigator may increase the risk associated with study participation or may interfere with interpretation of study results and/or otherwise make the patient inappropriate for entry into this study,

18. Significant bleeding event due to abnormal blood clotting within the last 3 months that places the patient at risk for intrahepatic IT injection procedure based on Investigator assessment,

19. Anticoagulant or anti-platelet medication that cannot be interrupted prior to Pexa-Vec- IT injections, including:
    a. Aspirin that cannot be discontinued for 7 days prior to Pexa-Vec- IT injections

b. Coumadin that cannot be discontinued for 7 days prior to Pexa-Vec- IT injections
c. Low molecular weight heparin (LMWH) that cannot be discontinued >24 hours prior to Pexa-Vec- IT injections
d. Unfractionated heparin (UFH) that cannot be discontinued >4 hours prior to Pexa-Vec- IT injection
e. Oral direct thrombin inhibitor (dabigatran) or direct Factor Xa inhibitor (rivaroxaban, apixiban, and endoxaban) that cannot be discontinued for 4 days prior to Pexa-Vec- IT injection,

NOTE: LMWH or UFH may be used to transition patients on and off of the above anti-coagulants (if deemed appropriate by the treating physician) prior to Pexa-Vec- treatments as long as the last dose of LMWH is administered >24 hours prior to treatments and last dose of UFH is administered >4 hours prior to treatments,

20. Hepatitis C virus therapy including interferon/pegylated interferon or ribavirin that cannot be discontinued within 14 days prior to any Pexa-Vec injection. Transgene Medical Monitor should be consulted if the patient is taking any other antiviral medications to determine eligibility, on the grounds of interference with Pexa-Vec replication properties,

21. Inability to suspend treatment with anti-hypertensive medication (including but not limited to: diuretics, beta-blockers, angiotensin converting enzyme [ACE] inhibitors, aldosterone antagonists, etc.) for 48 hours prior to and 48 hours after each Pexa-Vec injection, as assessed at the screening cardiology consultation,

22. Any known allergy or reaction to any component of nivolumab formulation or its excipients

23. Prior exposure to cancer immunotherapy including any immune checkpoint inhibitor, cancer vaccine and/or oncolytic virus,

24. Participation in a clinical study and treatment with an active IMP within 4 weeks prior to randomization,

25. Pulse oximetry O_2 saturation <90% at rest on room air,

26. Patient unable or unwilling to comply with the protocol requirements.

4.3 Concomitant diseases

Concomitant diseases are diseases present at the baseline visit and not listed in the exclusion criteria.

Concomitant diseases will be reported in the electronic case report form (eCRF) with their treatments. Whenever possible, the treatments for associated diseases should not be changed during the course of the study. If this occurs, changes should be reported on the eCRF.

4.4 Concomitant therapy

4.4.1 Concomitant medications

Concomitant medications are treatments (medications and/or non-drug therapies) taken by the patient during the month before baseline and ongoing at the baseline visit. They are reported in the eCRF with their reasons for prescription, start and end dates, route of administration and dose.

4.4.2 Therapy restrictions

Thrombopoietin, erythropoietin and G-CSF will not be allowed throughout DLT period.

Oral or parenteral corticosteroids may attenuate potential beneficial immunologic effects of treatment with nivolumab and Pexa-Vec and should not be used but may be administered at the discretion of the treating physician if needed. Alternatives to corticosteroids should be considered if feasible. The use of inhaled corticosteroids and mineralocorticoids (e.g. fludrocortisone) is allowed.

Antihypertensives (including diuretics) must be discontinued at least 48 hours prior to each Pexa-Vec injection and resumed no earlier than 48 hours after the injection.

The use of antiemetics, antipyretics, antidepressants, biphosphonates, vitamin B12 and vitamin D will not be restricted during the course of the study.

5 INVESTIGATIONAL MEDICINAL PRODUCTS

Pexa-Vec is in development for an advanced HCC patient population in combination with nivolumab. Therefore, in this study Pexa-Vec and nivolumab are considered as Investigational Medicinal Products (IMPs).

Pexa-Vec and nivolumab are provided free of charge by Transgene. The Investigator/Pharmacist will not supply IMP to any patient not included in the study, nor to any physicians or scientists who are not designated as sub-Investigators. The Investigator must ensure that patients receive IMP only from personnel who fully understand the procedures for dosing and administering the drugs.

5.1 Pexa-Vec

5.1.1 Characteristics and supply

Pexa-Vec (pexastimogene devacirepvec-; investigational product code: JX-594/ TG6006) is a replication-competent, transgene-expressing therapeutic vaccinia virus derived from the Wyeth vaccine strain (Dryvax®, Wyeth Laboratories). Three genetic modifications are included:

1. thymidine kinase (TK) gene deactivation,
2. granulocyte macrophage colony stimulating factor (GM-CSF) gene insertion under control of the synthetic early-late promoter, and
3. lac-Z gene insertion under control of the p7.5 promoter.

Pexa-Vec viral suspension will be supplied in individual 4-mL glass vials with a recoverable volume of 2 mL per vial and an infectious titer of 1×10^9 pfu (9.0 Log10 plaque-forming units (pfu)). Each vial contains Pexa-Vec diluted in 30 mM Tris 10% Sucrose buffer. Each vial is intended for single use (i.e., one injection to one patient). Pexa-Vec suspension is a sterile, frozen liquid; white to off-white; clear to opalescent when thawed.

5.1.2 Packaging and labeling

Each vial is packed in a cardboard box (secondary packaging) which constitutes a Pexa-Vec treatment kit (1-vial treatment kit).

The primary labels on the vials as well as the secondary labels on the cardboard boxes are in the language of countries where the study is to be performed. Labels are compliant with local regulatory requirements and contain information including, but not limited to: Transgene name, product code, lot number, concentration, volume, storage conditions, route of administration and a cautionary statement in proper language.

Examples of the primary and secondary labels which are used are displayed in the Product Handling Manual.

5.1.3 Biosafety/Containment Level Classification of Pexa-Vec

Depending on the country, Pexa-Vec is classified as a Biosafety/Containment Level 1 or Level 2 infectious substance. All applicable infection control policies should be consulted and followed.

Refer to the current Pexa-Vec Investigator's Brochure (IB) and Pexa-Vec Guidelines (Appendix B of the IB) for recommendations on handling Pexa-Vec and for management of patients treated with Pexa-Vec, as well as for any patients who develop Pexa-Vec-related pustules.

5.1.4 Transport of Pexa-Vec

5.1.4.1 Interstate and International Transport

Pexa-Vec is shipped on dry-ice with the official transport designation: "Biological Substance, Category B", in compliance with Good Distribution Practices and IATA (International Air Transportation Association) and ADR (International Carriage of Dangerous Goods by Road) regulations for air and road transport of infectious substances (UN 3373 regulations).

5.1.4.1.1 Drug Receipt and Approval of Shipment

The supply of Pexa-Vec is managed by Transgene based on Pexa-Vec inventory of sites and patient treatment prospects.

Detailed information on Pexa-Vec receipt instructions and approval of shipment process is provided in the Product Handling Manual.

5.1.4.2 Transport within the Institution

All transport of Pexa-Vec (in vial, or syringe containing the dose to be administered) within the institution must be done using a leak-proof container/bag clearly-marked with a biohazard symbol.

5.1.5 Conditions of storage, dispensing and handling

Pexa-Vec must be stored at or below –60°C in an alarmed, temperature-monitored, secure freezer with restricted access. Detailed information on drug storage requirements and temperature excursions management are provided in the Product Handling Manual.

Pexa-Vec will be dispensed only with the written authorization of the Investigator or a sub-Investigator to staff that have been specifically designated and trained for this study. Please refer to the Product Handling Manual for detailed instructions.

All applicable institutional policies for preparation, transport, and disposal of viral vectors should be consulted and followed. During all Pexa-Vec manipulations personal protective equipment (PPE) must be worn: gloves, gown, surgical mask and goggles (or safety glasses with side shields). Headgear and overshoes are not mandatory.

In addition, refer to the Pexa-Vec IB, Pexa-Vec Guidelines (Appendix B to the IB), and supplemental information (as available) for recommendations regarding proper handling during preparation, administration, and disposal of Pexa-Vec.

In case of an incident while handling Pexa-Vec, the recommended actions are described in the IB and in the Technical Sheet. Any incident must be documented by a written report and must be immediately sent to Transgene Medical Department or its designee:

Emergency 24-hour telephone number (international):
Fax: [redacted]

5.1.6 Preparation for administration

Pexa-Vec is a Genetically Modified Organism (GMO). As such, preparation of Pexa-Vec will be carried out in accordance with local regulatory requirements for Biosafety/Containment level (Level 1 or Level 2 depending on countries) in a pharmacy or laboratory, according to site's standard operating procedures (SOPs) and all applicable laws and regulations.

During Pexa-Vec preparation PPE must be worn: gloves, gown, surgical mask and goggles (or safety glasses with side shields). Headgear and overshoes are not mandatory.

Pexa-Vec is suspended in sterile normal saline buffered with sodium bicarbonate. All transfers of Pexa-Vec must be done using a closed container. Detailed information on drug preparation is provided in the Pexa-Vec IT Injection Preparation Worksheet.

5.1.7 Administration of Pexa-Vec

[redacted] Tumor numbers and measurements will be documented at baseline and before each IT re-treatment and transmitted to the pharmacy for drug preparation purposes and to the study coordinator for eCRF completion. Calculation and preparation instructions are provided in the Pexa-Vec IT Injection Preparation Worksheet.

During Pexa-Vec administration, PPE must be worn: gloves, gown, surgical mask and goggles (or safety glasses with side shields). Headgear and overshoes are not mandatory.

5.1.8 Cleaning / disinfection and disposal

Standard institutional policies should be followed for cleaning and decontamination while handling vaccinia virus-based products. Hospital-grade chemical disinfectants containing: bleach (with at least 0.6% of active chlorine), alcohols (≥60%), aldehydes, hydrogen peroxide (3%), iodophor (75 ppm), phenols or quaternary ammonium compounds are adequate for routine cleaning and disinfection of work areas after Pexa-Vec handling. The manufacturer's instructions should be followed to ensure adequate contact time and confirm the ability of the equipment to withstand the disinfectant used.

All disposable contaminated material (e.g., syringes, catheters, needles, tubing, gloves, used or unused vials, containers, bandages, etc.) should be disposed of in a clearly-marked biomedical waste container and discarded according to country-specific requirements and/or hospital procedures for infectious waste, i.e.: autoclaving, treatment with sodium hypochlorite solution and/or incineration.

Textiles and fabrics can be cleaned/treated according to hospital procedures for infectious material (i.e., hot water 71°C washing with detergent and hot air drying).

Recommendations for the decontamination and the destruction of the material used for Pexa-Vec preparation and administration are available in the IB and the Technical Sheet.

5.1.9 Spills or environmental contamination

In the event of a spill, people in the immediate area will be alerted and other institutional personnel will be notified as required by institutional policies. Refer to the current Pexa-Vec IB and Pexa-Vec Guidelines (Appendix B of the IB) and the Technical Sheet, for detailed instructions.

Spills and accidents that result in overt exposures to infectious material will be reported as required by institutional policies. Refer to Section 5.1.8 above.

5.1.10 Unused Pexa-Vec destruction or return

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

For local destruction, the Investigator/Pharmacist or delegated person will ensure that destruction is performed according to written instructions available in the Pexa-Vec IB and the Technical Sheet and will not expose humans to any risks from Pexa-Vec. A certificate of destruction will be completed and provided to Transgene (copy retained by the site).

The IMP supply provider contracted by Transgene will coordinate the return of all unused Pexa-Vec patient kits. A certificate of return will be completed and provided to the IMP supply provider (copy retained by the site).

Upon completion or termination of the study at a site, the monitor will verify that all used Pexa-Vec patient kits have been decontaminated (if applicable) and disposed, all unused Pexa-Vec patient kits have been returned or destroyed, and no IMP remains on site.

5.1.11 Pexa-Vec accountability

Pexa-Vec will only be dispensed, according to Investigator's prescription, to patients who meet all selection criteria. The Investigator/Pharmacist, or delegated person, will maintain a Pexa-Vec accountability log detailing the dates and quantities dispensed for each patient along with kit and vial numbers. -Pexa-Vec- accountability records will be verified by the monitor during site visits.

All documentation related to Pexa-Vec- shipment, receipt, authorization for use, dispensing, destruction, temperature monitoring, etc., must be filed in the Pharmacy file and must be available for monitor verification, audit and inspection. A copy of all drug accountability records will be returned to Transgene at the end of the study.

5.2 Nivolumab

5.2.1 Characteristics, supply, packaging and labelling

Nivolumab is a programmed death receptor-1 (PD-1) blocking antibody marketed by Bristol-Myers Squibb Pharma EEIG. It will be supplied in 40 and/or 100 mg vials (10 mg/mL) in its commercial packaging with brand name "OPDIVO 10 mg/mL concentrate for solution for infusion" (pack size of one 10 mL vial (Type I glass) with a stopper (coated butyl rubber) and a flip-off seal (aluminium), and labelled appropriately as investigational material for this study. Nivolumab concentrate is a clear to opalescent, colourless to pale yellow liquid that may contain few light particles. (See also Summary of Product Characteristics (SmPC).

5.2.2 Transport of nivolumab

5.2.2.1 Interstate and International Transport

Nivolumab is shipped per manufacturer's instructions.

5.2.2.1.1 Drug Receipt and Approval of Shipment

The supply of nivolumab is managed by Transgene based on nivolumab inventory of sites and patient's treatment prospects.

Detailed information on nivolumab receipt instructions and approval of shipment process is provided in the Product Handling Manual.

5.2.2.2 Transport within the Institution

No specific instructions.

5.2.3 Conditions of storage and use

In accordance with its USPI/ EU SmPC, nivolumab vials must be stored in the refrigerator at 2-8°C in the original package in order to protect from light.

From a microbiological point of view, once opened, nivolumab should be used immediately. If not used immediately, nivolumab infusions should be stored at room temperature (20-25°C) and room light for no more than 4 hours from time of preparation. This includes room temperature storage of infusion in IV container and time for administration of infusion. Alternatively, nivolumab infusion can be stored under refrigeration at 2 to 8°C (36-46°F) for no more than 24 hours from the time of infusion preparation and protected from light. The infusion should not be frozen.

5.2.4 Preparation for administration

Preparation of nivolumab should be performed by trained personnel in accordance with USPI/ EU SmPC and good practices rules, especially with respect to asepsis.

The required volume of nivolumab should be withdrawn using an appropriate sterile syringe and transferred into a sterile, evacuated glass bottle or an intravenous container (PVC or

polyolefin). Nivolumab should be used directly or be diluted with either 9 mg/mL (0.9%) sodium chloride solution for injection, USP or 50 mg/mL (5%) glucose solution for injection, USP, to prepare an infusion with a final concentration ranging from 1 mg/mL to 10 mg/mL. Diluted solution should be mixed by gentle inversion, but should not be shaken. Partially used or empty vials of nivolumab should be discarded.

5.2.5 Unused nivolumab destruction or return

Any unused portion of the infusion solution must not be stored for reused. Any unused nivolumab or waste material will be disposed of in accordance with local requirements. A certificate of destruction will be completed and provided to Transgene (copy retained by the site).

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

5.2.6 Nivolumab accountability

Nivolumab will only be dispensed, according to the Investigator's prescription, to patients who meet all selection criteria. The Investigator/Pharmacist, or delegated person, will maintain a nivolumab accountability log detailing the dates and quantities dispensed for each patient along with kit numbers.

Nivolumab accountability records will be verified by the monitor during site visits.

All documentation related to nivolumab shipment, receipt, dispensing, destruction, temperature monitoring, etc., must be filed in the Pharmacy file and must be available for monitor verification, audit and inspection. A copy of all drug accountability records will be returned to Transgene at the end of the study.

6 TREATMENT PLAN

6.1 Treatment administered

6.1.1 Treatment regimens

6.1.1.1 Phase I part:

Safety and efficacy will be assessed in 6 patients, using a standard regimen for dose level 1 as 3 bi-weekly IT injections of $1x10^9$ pfu for Pexa-Vec and 240 mg IV q2weeks for nivolumab (Figure 1: IMP administration scheme).

In case of a Dose-Limiting Toxicity (DLT) is observed in more than one patient out of the first 6 patients, or in the occurrence of a landmark AE, one de-escalation regimen is planned:

- Dose level -1: 3 bi-weekly IT injections of $3x10^8$ pfu for Pexa-Vec and 240 mg q2weeks for nivolumab OR 3 bi-weekly IT injections of 10^9 pfu for Pexa-Vec and 240 mg q3 weeks for nivolumab, depending on the DLT profile relative to the known toxicity of each component of the combination, as judged by the Independent Safety Committee (ISC).

A landmark AE is an anticipated effect of the combination, defined as either increase in severity of hepatic cytolysis (doubling of AST – ALT baseline blood concentrations), or significant deterioration of hepatic function (INR, bilirubin), or increase in number or severity of immune-related AEs, or increase in number or severity of Pexa-Vec-related skin lesions.

6.1.1.2 Phase IIa part:

The regimen applied in Phase IIa will be that with occurrence of a DLT at most in one patient out of 6 patients in the Phase I part and upon final recommendation of the ISC that will prevail. However, should unexpected toxicities or increased numbers of DLTs in an expanded number of patients occur, de-escalation dose levels will also apply in the Phase II part of the study.

6.1.2 Administration of the IMPs

Patients will be receiving intratumoral (IT) injections of Pexa-Vec in combination with nivolumab intravenous (IV) infusions.

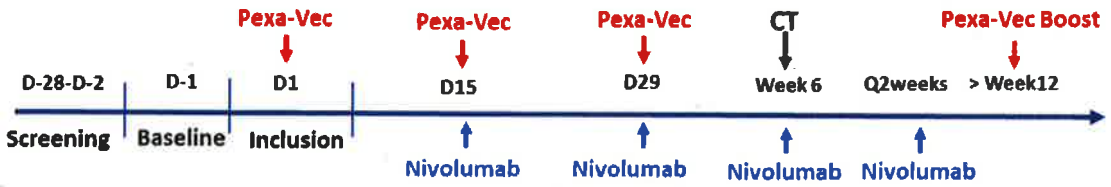


Figure 1: IMP administration scheme

6.1.2.1 Administration of Pexa-Vec

IT Pexa-Vec injections will be performed on D1, D15 and D29. Additional Pexa-Vec boosts may be performed from Week 12 after discussion on a case by case basis between the investigator and Transgene.

Unless contraindicated, all patients will be pre-medicated with acetaminophen (paracetamol), ibuprofen and esomeprazole on each Pexa-Vec treatment day according to the following scheme:

- acetaminophene 1000 mg at 2 hours pre-injection, 6 hours, 14 hours and 22 hours post-injection,
- ibuprofen 400 mg at 2 hours, 10 hours and 18 hours post-injection,
- esomeprazole 40mg, or equivalent.

In case of contra-indication to the prescription of ibuprofen, due to underlying advanced cirrhosis, the investigator may alternatively use the following regimen based on acetaminophen (paracetamol) or equivalent antipyretics, (unless contraindicated):

- 500–1000 mg at 2 hours pre-infusion/injection,
- 500–1000 mg at 4 hours post-procedure,
- 500–1000 mg every 6 hours thereafter, as needed (the total acetaminophen dose should be carefully assessed to avoid cumulative toxicity).

Any treatment may be continued if deemed necessary.

Fevers may be associated with onset of rigors. Meperidine or equivalent may be used for severe rigors.

Unless contra-indicated, patients should also be pre-hydrated with approximately 1 L of solute-containing fluids IV or orally within 12 hours of treatment initiation. In addition, during the post-treatment observation period, patients should receive IV solute-containing fluids or other appropriate treatment as needed for blood pressure support.

Pexa-Vec will be injected into 1 to 5 intrahepatic tumors by a qualified and trained Interventional Radiologist or other trained physician using imaging-guidance (ultrasound and/or CT). As many as possible viable, safely injectable tumors ≥1 cm LD must be treated with a maximum of 5 tumors treated on a given treatment day. Different tumors may be treated on consecutive treatment sessions. [redacted]

Patients will be monitored closely (e.g., vital signs and clinical observation) the night prior and for 24 hours after the first Pexa-Vec injection as described in the study flow chart (Appendix 1). Hence, hospital admission is required for the first administration of Pexa-Vec. Patients will be monitored the night prior and for at least 8 hours following subsequent Pexa-Vec injections. Longer hospitalization for second, third and additional (boost) administrations of Pexa-Vec is permitted based on Investigator decision.

Pexa-Vec is to be administered after nivolumab on Days 15 and 29 ± 1 day.

6.1.2.2 Administration of nivolumab

Nivolumab will be given from D15, by IV route every 2 weeks until progression or unacceptable toxicity. Owing to the possible biphasic evolution of tumor burden often seen with immunotherapeutic products, patients may be treated beyond first evidence of radiologic progression, under specified conditions, as such:

1. Patients with a consecutive evidence of radiologic progression and who do not benefit clinically from nivolumab treatment, as assessed by the investigator, should discontinue nivolumab treatment and be treated with another systemic therapy, e.g. sorafenib,
2. Patients with a consecutive evidence of radiologic progression and who do benefit clinically from nivolumab treatment could continue nivolumab treatment upon decision of the investigator and after discussion with Transgene Medical Monitor. Clinical benefit is defined as:
    a. Maintenance of general status
    b. Absence of disease-related symptoms
    c. Stability of hepatic function,
3. Patients without evidence of progression at a consecutive radiologic assessment with maintenance of clinical benefit are deemed pseudo-progressors and could continue nivolumab treatment.

Nivolumab infusion must not be administered as an intravenous push or bolus injection. Use an infusion set and an in-line, sterile, non-pyrogenic, low protein binding filter (pore size of 0.2 µm to 1.2 µm). Nivolumab infusion is compatible with PVC and polyolefin containers, glass bottles, PVC infusion sets and in-line filters with polyethersulfone membranes with pore sizes of 0.2 µm to 1.2 µm.

Patients should be administered nivolumab 240mg as an in intravenous infusion over 60 minutes every 2 weeks (± 1 day for cycles 1 to 3 and ± 3 days for subsequent cycles). For the first infusion, the patient's vital signs (heart rate, respiratory rate, blood pressures, and temperature) should be determined within 60 minutes before, during (every 15 [±5] minutes), and 30 (±10) minutes after the infusion. For subsequent infusions, vital signs will be collected within 60 minutes before infusion. Patients will be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop acute symptoms.

Nivolumab will be administered prior to Pexa-Vec on Days 15 and 29 ± 1 day. Owing to the perception by the investigator of the safety of the administration of the two treatments for a peculiar patient or for logistical reasons, the investigator could distribute the treatment administrations over two consecutive days.

6.1.3 Duration of treatment and observation period

The expected treatment duration of Phase I and Phase IIa patients depends on the occurrence of unacceptable toxicity events or progression, or on the decision to continue treatment beyond progression, under protocol-specified conditions.

The expected study duration for Phase I and Phase IIa patients depends on CT or MRI scans for efficacy assessment that will be performed every 6 weeks from start of treatment until documented progression or discontinuation of treatment beyond progression or for a period of 12 months after start of study treatment, whichever occurs first.

Beyond 12 months of treatment, the evaluations will be performed every 12 weeks until documented progression or discontinuation of treatment beyond progression. If study treatments are stopped before documented radiological progression, PFS visits will be performed every 6 weeks to continue radiological assessment until documented progression.

6.2 Recommended Phase II dose (RP2D)

In the Phase I part, all patients will be monitored up to D29 for the occurrence of DLTs that defines the DLT period. The RP2D is defined as the maximum dose level (1 or -1) at which a DLT attributable to the IMPs is observed at most in one patient out of 6 patients in the DLT period and upon final recommendation of the ISC that will prevail.

The **DLTs**, applicable for the Phase I part of the study, are defined as such:

1. All Grade 3-4 non-hematologic toxicity that represents a 2-grade increase over baseline, excluding:
   - Untreated or inadequately treated nausea, vomiting and diarrhea,
   - Untreated or inadequately treated fever > 40.0°C lasting less than 24 hours (Grade 3); only fever > 40.0°C lasting more than 24 hours (Grade 4) qualifies for DLT,
   - Alopecia,
   - Grade 3 fatigue that returns to grade 2 or less within 7 days,
   - Grade 3 laboratory/metabolic abnormalities, other than ALT or AST, that are not considered clinically significant and that return to grade 2 or less within 72 hours.

2. Any Grade ≥ 3 treatment-related acute immune-related AE involving major organs, such as: immune-related pneumonitis, colitis, nephritis, hepatitis, endocrinopathies, immune-related rash and other rare but severe immune-related reactions.

3. Grade ≥ 3 injection site reaction.

4. AST or ALT ≥ 10xULN, even if asymptomatic, unless it is related to a definite progression of liver metastases or another clearly identifiable etiology; doubling of AST or ALT that is concurrent with a doubling of the total bilirubin.

5. Any toxicity at least possibly related to study therapy that results in a delay in treatment of 2 or more weeks.

6. Hematological:
   - Grade ≥ 3 or ≥ 2-grade increase over baseline of neutropenia lasting for more than 7 days.
   - Neutropenic fever.
   - Grade 4 thrombocytopenia or grade 3 thrombocytopenia with clinically significant bleeding.

7. Cardiac: association of the 3 following cardiac abnormalities
   - Left ventricular ejection fraction (LVEF) less than the lower limit of normal (LLN), as assessed by echocardiography and symptomatic due to drop in ejection fraction, responsive to intervention,
   - Increase of blood troponin T or I above the upper limit of normal (ULN),
   - Any ECG abnormality consistent with a Grade 3 cardiac disorder.

In the Phase IIa part, should unexpected toxicities or increased number of DLTs in an expanded number of patients be seen, the ISC will be consulted to decide upon dose de-escalation that would re-define the RP2D.

6.3 Method of assigning patients to treatment groups

6.3.1 Recruitment

The study involves one group of patients, distributed in consecutive cohorts, Phase I dose-level 1 and -1, and Phase IIa.

The Investigator will be asked to complete a "screening log" in which each potential patient (i.e. screened patient) will be listed. After having signed the informed consent form, a screened patient is considered as a "consented patient".

Upon satisfaction of all of the inclusion and exclusion criteria for a "consented patient", the patient will be considered as an "eligible patient" for the study. This process is fully documented on the "screening log" should a patient be included or not in the study.

In Phase I, the first enrolled patient will be monitored for safety up to the completion of 3 Pexa-Vec IT injections and 2 nivolumab infusions, scheduled on D29 (i.e. week 4), before the second patient can be enrolled. A security interval of 2 weeks between enrolments of each consecutive patients will be applied. In case of occurrence of a DLT in more than one patient in the first cohort of 6 patients treated at Dose-Level 1, another cohort of 6 patients will be enrolled, who will be treated at the dose de-escalation level (-1).

In Phase IIa, patients will be enrolled without security intervals between consecutive patients.

Under no circumstances will a patient enrolled in the study be permitted to re-enroll for a second time in the study.

6.3.2 Randomization

Not applicable. No randomization is used for this study.

6.3.3 Stratification / Minimizations

Not applicable. Non-viral, viral hepatitis B and C etiologies for HCC will be recorded without stratification on this factor.

6.3.4 Dose modifications

No dose modifications for Pexa-Vec or nivolumab are permitted outside protocol-specified conditions for dose de-escalation in Phase I and in Phase IIa detailed in sections 6.1 and 6.2.

6.3.4.1 Management of nivolumab-specific Adverse Events

Toxicities associated or possibly associated with nivolumab treatment should be managed according to standard medical practice. Additional tests, such as autoimmune serology or biopsies, may be used to determine a possible immunogenic etiology.

Although most immune-related adverse events observed with immunomodulatory agents have been mild and self-limiting, such events should be recognized early and treated promptly to avoid potential major complications.

Discontinuation of nivolumab may not have an immediate therapeutic effect and in severe cases, immune-related toxicities may require acute management with topical corticosteroids, systemic corticosteroids, mycophenolate, or TNF-α inhibitors.

The primary approach to Grade 1-2 immune-related adverse events is supportive and symptomatic care with continued treatment with nivolumab; for higher grade immune-related adverse events, nivolumab should be held and oral/parental steroids administered. Recurrent Grade 2 immune-related adverse events may also mandate holding nivolumab or the use of steroids. Consideration for benefit/risk balance should be made by the investigator, with consideration of the totality of information as it pertains to the nature of the toxicity and the degree of clinical benefit a given patient may be experiencing prior to further administration of nivolumab. Nivolumab should be permanently discontinued in patients with lifethreatening irAEs.

6.3.4.2 Guidelines for Treatment Interruption or Discontinuation

Nivolumab treatment will be given as long as the patient continues to experience clinical benefit in the opinion of the investigator, and discontinued in case of unacceptable toxicity, symptomatic deterioration attributed to disease progression, or any of the other reasons for treatment discontinuation.

Patients may temporarily suspend study treatment for up to 42 days from the last dose if they experience toxicity that is considered related to the study drug and requires a dose to be held. If nivolumab is held because of adverse events for >42 days beyond the last dose, then the patient will be discontinued from nivolumab.

If a patient must be tapered off steroids used to treat adverse events, nivolumab may be held for additional time beyond 42 days from the last dose until steroids are discontinued or reduced to prednisone dose (or dose equivalent) ≤10 mg/day. The acceptable length of interruption will depend on an agreement between the investigator and the Coordinating Investigator.

Dose interruptions for reason(s) other than toxicity, such as surgical procedures, may be allowed with Coordinating Investigator approval. The acceptable length of interruption will depend on agreement between the investigator and the Coordinating Investigator.

Although most irAEs observed with immunomodulatory agents have been mild and self-limiting, such events should be recognized early and treated promptly to avoid potential major complications. Discontinuation of nivolumab may not have an immediate therapeutic effect, and there is no available antidote for nivolumab. In severe cases, -immune-related- toxicities may be acutely managed with topical corticosteroids, systemic corticosteroids, mycophenolate, or TNFα inhibitors.

Patients should be assessed clinically (including review of laboratory values) for toxicity prior to, during, and after each infusion. If unmanageable toxicity due to nivolumab occurs at any time during the study, treatment with nivolumab should be discontinued.

Discontinuation Criteria

Treatment should be permanently discontinued for the following (applicable for Phase I and Phase II parts of the study):

- Any Grade 2 drug-related uveitis or eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within the re-treatment period OR requires systemic treatment

- Any Grade 3 non-skin, drug-related adverse event lasting > 7 days, with the following exceptions for drug-related laboratory abnormalities, uveitis, pneumonitis, bronchospasm, hypersensitivity reactions, and infusion reactions, and endocrinopathies:
  - Grade 3 drug-related uveitis, pneumonitis, bronchospasm, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation
  - Grade 3 drug-related endocrinopathies adequately controlled with only physiologic hormone replacement do not require discontinuation
  - Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except those noted below

- Grade 3 drug-related thrombocytopenia > 7 days or associated with bleeding requires discontinuation

- Any drug-related liver function test (LFT) abnormality that meets the following criteria require discontinuation:
  - AST or ALT > 8 x ULN
  - Total bilirubin > 5 x ULN
  - Concurrent AST or ALT > 3 x ULN and total bilirubin > 2 x ULN

- Any Grade 4 drug-related adverse event or laboratory abnormality, except for the following events which do not require discontinuation:
  - Isolated Grade 4 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis and decrease to < Grade 4 within 1 week of onset.
  - Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset
  - Grade 4 lymphopenia or leucopenia
  - Grade 4 drug-related endocrinopathy adverse events, such as adrenal insufficiency, ACTH deficiency, hyper- or hypothyroidism, or glucose intolerance, which resolve or are adequately controlled with physiologic hormone replacement (corticosteroids, thyroid hormones) or glucose-controlling agents, respectively, may not require discontinuation after discussion with and approval from the Coordinating Investigator [as allowed by protocol].
  - Any dosing interruption lasting > 6 weeks with the following exceptions:
  - Dosing delays or interruptions to allow for prolonged steroid tapers to manage drug-related adverse events are allowed. Prior to re-initiating treatment in a

subject with a dosing interruption lasting > 6 weeks, the Investigator must be consulted. Tumor assessments should continue as per protocol even if dosing is interrupted or delayed

- Dosing interruptions or delays lasting > 6 weeks that occur for non-drug-related reasons may be allowed if approved by the Investigator. Prior to re-initiating treatment in a subject with a dosing interruption lasting > 6 weeks, the Investigator must be consulted. Tumor assessments should continue as per protocol even if dosing is interrupted
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the subject with continued nivolumab dosing

Management of potentially immune related AEs are described in Appendix 3.

6.4 Blinding / Unblinding

Not applicable: the study is single-arm open-label.

6.5 Treatment compliance

6.5.1 Dispensing and accountability

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

The Pharmacist will maintain an IMP accountability log detailing the dates and quantities dispensed for each patient along with ampoule / vial's numbers and lots numbers. IMP accountability records will be verified by the monitor during site visits. All used and unused IMP will be accounted for. All unused IMP will be returned to Transgene or destroyed locally at the end of the study. The Pharmacist will ensure that this alternative disposition is performed according to Transgene's written instructions and will not expose human to risks from the IMP. Moreover, a "certificate of destruction" will be established and provided to Transgene.

6.5.2 Assessment of compliance

The compliance will be monitored with the IMP accountability log and information reported on the eCRF pages.

6.6 Premature withdrawal of patients

6.6.1 Circumstances

The patient's participation in the protocol may terminate under any of the following circumstances:

- Patient's request at any time for any reason,
- Physician's determination that patient's further participation in the protocol is not in the patient's best interest,
- Need to treat the patient with a prohibited medication,
- Transgene's decision (for example in case of new fact or toxicity issue regarding the IMP),
- Health Authorities' decision,
- Unacceptable toxicity associated with any IMP,

- Progressive disease after consideration of possible treatment continuation.

For any discontinuation, the Investigator will obtain all the required details and document the date of and the reason for the discontinuation in the eCRF. In any case of treatment cessation not related to disease progression the patient will be followed per protocol until documentation of progressive disease (PFS visits).

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 study visit.

6.6.2 Replacement policy

In Phase I, the patient cohort on which the combination safety is evaluated comprises 6 evaluable patients; a Phase I evaluable patient is the patient who has completed the DLT period, ie undergone all 3 Pexa-Vec IT injections and 2 nivolumab IV infusions or exhibited a DLT. A not evaluable patient in Phase I should be replaced.

In Phase IIa, the patient cohort on which the combination efficacy is evaluated comprises 30 evaluable patients, including comparable patients of the Phase I part (population, treatment regimen); a Phase IIa evaluable patient is a patient having received at least 2 administrations of Pexa-Vec and 2 administrations of nivolumab and undertaken at least one post-baseline radiological assessment or exhibited any evidence of disease progression other than radiological. A not evaluable patient in Phase IIa should be replaced.

6.6.3 Subsequent therapy

Recommended therapy for patients with advanced HCC is sorafenib. Sorafenib treatment will be implemented as soon as the combination therapy will be terminated.

6.7 Premature study discontinuation

The study may terminate under any of the following circumstances:

- Transgene's decision,
- ISC's decision,
- IRB's decision,
- Health Authorities' decision,
- Further to - for example - unacceptable toxicity associated with any IMP.

In case of study discontinuation, the Investigator will document the date of and the reason for discontinuation in the eCRF. In case of associated treatment cessation, the patients will be followed per protocol until documentation of progressive disease (PFS visits).

As far as possible, the Investigator will make thorough efforts to organize end of study visits for ongoing patients.

7 NON-INVESTIGATIONAL MEDICINAL PRODUCT

7.1 Vaccinia Immune Globulin (VIG)

Vaccinia Immune Globulin (VIG) can be used as a rescue medication in case of a serious complication following Pexa-Vec injections. For the description of serious complications, please refer to paragraph 10. VIG is to be ordered using the Notification of VIG Medication Request Form. The circuit of VIG is summarized in Appendix 5 and must be administered as per its summary of product characteristics. French sites can consult the Procédure SPILF-COREB – Vaccine in Appendix 4.

8 STUDY VISITS AND PROCEDURES

A flow-chart shown in appendix 1 summarizes the evaluations to be performed and their time points.

8.1 Evaluations description

Clinical evaluation:

Medical history and physical examination of the major organ systems, including vital signs (body temperature, systolic and diastolic blood pressure, heart rate, respiratory rate), body weight and Performance Status measurements will be performed at each visit. Patients will be monitored closely (e.g., vital signs and clinical observation) the night prior and for 24 hours after the first Pexa-Vec injection as described in the study flow chart (Appendix 1). Patients will be monitored the night prior and for at least 8 hours following subsequent Pexa-Vec injections. Actual duration of monitoring after 2nd and 3rd Pexa-Vec injections will be determined by the investigator on the grounds of the events recorded after 1st injection and anticipated decrease of intensity of such events at consecutive injections. Overall and specifically, patients will be monitored hourly for the first 8 hours post Pexa-Vec infusion after which monitoring will be performed every 6 hours up to 24 hours or patient's release from hospital.

At each visit, subjects will be asked about their state of health and use of any concomitant medication since the previous study visit. They will also be questioned about their adherence with study restrictions.

Safety assessment:

The assessment and follow-up of all Serious Adverse Reactions (SARs), Adverse Events (AEs) and Serious Adverse Events (SAEs) will be reported and graded according to National Cancer Institute's Common Toxicity Criteria for Adverse Events (NCI CTCAE), version 4.03, and will be documented in the eCRF.

Laboratory evaluation:

- Blood analysis (to be performed locally):
  - Hematology

  - Complete blood count including RBC, hemoglobin, hematocrit, WBC and differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils), and platelets.
- Biochemistry
  - Liver tests: total bilirubin, ALT, AST, LDH and alkaline phosphatase.
  - Renal tests: creatinine, calculated creatinine clearance (Cockroft-Gault method) and blood urea nitrogen (BUN).
  - Electrolytes: sodium, potassium, phosphorus, calcium, magnesium, bicarbonate, and chloride.
  - Serum protein, serum albumin.
  - Glucose
- Coagulation parameters:
  - INR and aPTT (activated partial thromboplastin time).
- Inflammatory parameters: CRP.
- Women of childbearing potential (WOCBP) will undergo a pregnancy test at screening (blood test), then at baseline, on Day 15, Day 29, Pexa-Vec boost, week 6 and every 6 weeks and end of study-safety visit (urine tests). If positive, an ultrasound scan will be performed to confirm pregnancy.
- Other:
  - HIV serology
  - Antinuclear and anti TPO antibodies
  - Thyroid blood tests
  - AFP

- Urinalysis (to be performed locally):
  - Blood, bilirubin, glucose, ketones, nitrite, pH, protein, specific gravity, urobilinogen, and leukocyte esterase; microscopic if leukocyte esterase is abnormal: bacteria, casts, crystals, epithelial cells, mucous, RBC and WBC counts.

Tumor evaluation:

Patients will undergo imaging of the chest, abdomen and pelvis using helical/spiral contrast-enhanced CT scanning or MRI with non-contrast CT of the chest at Screening, at Week 6 and every 6 weeks thereafter. Tri-phasic contrast-enhanced imaging of the liver will include pre-contrast, arterial, and portal venous phases. For MRI Scan, either a 1.5T or a 3T MRI scanner should be used with a body array coil and gadolinium administered as an IV bolus. All target lesions (measurable) and non-target lesions (measurable or not) will have to be recorded. Radiographic assessments will be completed locally as per current practice according to RECIST 1.1. All radiographic images will also be reviewed centrally according to irRC, as exploratory endpoint.

CT or MRI scans will be performed within 28 days prior to start of study treatment and patients will then be evaluated every 6 weeks from start of treatment until documented progression or discontinuation of treatment beyond progression or for a period of 12 months after start of study treatment, whichever occurs first. Beyond 12 months of treatment, the evaluations will be performed every 12 weeks until documented progression or discontinuation of treatment beyond progression. If study treatments are stopped before documented radiological progression, PFS visits will be performed every 6 weeks to continue radiological assessment until documented and confirmed progression.

Definition of radiological endpoints:

- Overall response rate (ORR): proportion of patients, whose best overall response is either CR or PR, confirmed at least 4 weeks after initial documentation.
- Time to Progression (TTP): time from D1 to the date of first documented radiographic tumor progression; TTP does not include deaths. If a patient has not had a TTP event at the cut-off date for analysis, TTP will be censored at the date of last evaluable tumor assessment before the cut-off.
- 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 the date of death due to underlying cancer. DoR will be censored if progression or death due to underlying cancer is not observed at the cut-off date for the analysis or start of further antineoplastic therapy. The censoring date will be the date of the last evaluable tumor assessment.
- Disease control rate (DCR): proportion of patients whose best overall response during their participation in the study is either CR, PR, or stable disease (SD).
- 4-month (18-week) DCR: proportion of patients whose best overall response in the study is either CR, PR, or stable disease (SD) 4 months after D1.
- Relative change from baseline in tumor size over time. Tumor size is defined as the sum of the diameters recorded for all target lesions as identified at baseline.
- Progression Free Survival (PFS): time from D1 to the date of first of second 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, PFS will be censored at the date of last evaluable tumor assessment before the cut-off.
- *PFS over time, milestone PFS: proportion of patients having not progressed at* specified *time points.*

Tumor blood flow (DCE/DW-MRI) and metabolic response (^{18}FDG-PET): could be optionally implemented in targeted patients for assessment of activity on tumors.

Overall Survival:

Overall survival (OS) will be analyzed by both estimation of median survival on the population exposed to the combination and by the proportion of patients alive at specified time points after the initiation of treatment:

- OS: time from date of D1 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. OS and median OS will be assessed using the Kaplan-Meier method with the inclusion date (D1) as reference date.
- OS over time, milestone OS: proportion of patients alive at specified time points.

[redacted]

[redacted]

[redacted]

Cardiac evaluation:

- Monitoring for cardiac toxicity will include for both phases of the study:
  - Cardiac echography (ECHO) with measurement of left ventricular ejection fraction (LVEF), if necessary, in addition to baseline measurement,
  - Measurement of troponin T or I blood level 3 and 8 days (± 1) after each Pexa-Vec administration,
  - ECG (12 leads), 8 days (± 1) after each Pexa-Vec administration,
  - ECG (12 leads), 3 days (± 1) after each Pexa-Vec administration, in case of detection of a clinically significant increase in troponin blood level,
  - In the Phase I section, measurement of troponin T or I level will be performed at D29 (end of DLT period), then starting from week 8, ECHO, ECG and troponin T or I level will be performed every 4 weeks (i.e. on every second nivolumab infusion) up to the 28-day safety follow-up visit.

Further examination(s) will be performed if deemed necessary by the investigator.

8.2 Screening visit (-28 days, D-2)

Screening assessments will begin after the signature of the informed consent form (ICF). A Patient study identification numbers will be assigned chronologically. The patient study identification number is unique and remains with the patient for the entirety of the trial.

Patient eligibility for the study will be determined up to 28 days before Day 1, date of first Pexa-vec injection. Screening procedures may be completed in less than 28 days, which is preferred. The 28-day screening window starts when the first protocol-required screening procedure is performed, and does not include the ICF signature date. If Day 1 does not occur within 28 days of the first screening procedure, the patient must be screen failed.

Laboratory results must be obtained prior to D1 and used for eligibility determination and for receiving Day 1 IT injection.

At the Screening visit, the following will occur:

- Signature of the ICF
- Collection of detailed medical, surgical, and cancer history
- Prior and Concomitant medications reporting
- Review of Clinical inclusion and exclusion criteria
- Complete physical examination including weight and height
- Vital signs (blood pressure, temperature, heart and respiratory rates)
- ECOG performance status (PS)
- Blood sample collection for laboratory eligibility/safety assessment including:
  - Hematology, chemistry, coagulation and CRP
  - HIV, Hepatitis B and C testing
  - AFP
  - Pregnancy test for women of child-bearing potential (WOCBP) (if positive, an ultrasound will be performed to confirm pregnancy)
- Standard urinalysis
- Tumor assessment: CT (preferred) or MRI (if CT not possible): tumors are numbered with unique number and identified as Target or Non-Target tumors. Tumors should be assigned the next available chronological number wherever possible.
- Histological HCC diagnosis. If no pathology reports available, perform biopsy
- Child-Pugh scoring
- European Association for the Study of the Liver (EASL) / European Organization for Research and Treatment of Cancer (EORTC) criteria
- From the date of signature of the ICF and up to initiation of study treatments, only SAEs caused by a protocol-required procedure will be collected and reported to Transgene

8.3 Baseline visit (-4 days, D-1)

At the Baseline visit, up to 4 days before Day 1, the following will occur:

- Concomitant medications reporting
- Complete physical examination, including weight
- Vital signs (blood pressure, temperature, heart and respiratory rate)
- ECOG performance status (PS)

- Blood sample collection for the following testing:
  - Hematology, chemistry, coagulation and CRP
  - Antinuclear and anti TPO antibodies
  - Thyroid blood tests
  - HBV and HCV viral load
  - Immune related soluble factors and cytokines
  - Antibodies against vaccinia and Pexa-Vec expressed transgenes in serum
  - HLA typing

- Pregnancy test (urine) for WOCBP (if positive, an ultrasound will be performed to confirm pregnancy)
- From the date of signature of the ICF and up to initiation of study treatments, only SAEs caused by a protocol-required procedure will be collected and reported to Transgene
- Final eligibility assessment (clinical, laboratory, imaging); an ultrasound scan may be optionally performed to assess suitability of IT injection within selected liver lesions and to select lesions for injection; or to rule out pregnancy for patients with a positive hCG laboratory test (>10 mIU/mL).
- 12-lead Electrocardiogram (ECG)
- Cardiac echography (ECHO) with measurement of left ventricular ejection fraction (LVEF)
- Measurement of troponin T or I level
- Cardiology consultation clearance

8.4 Day 1 visit: Pexa-Vec injection 1

Before Day 1 intratumoral injection of Pexa-Vec, patients will undergo:

- Complete physical examination, including weight, vital signs and ECOG PS
- Medical, and surgical history update with any event that would have occurred from the signature of the ICF. NB: Any SAE caused by a protocol-related procedure must be collected and reported to Transgene.

Pexa-Vec intratumoral injection:

- A qualified and trained Interventional Radiologist will identify up to 5 intrahepatic tumors, each ≥1 cm LD, for injection. As noted at baseline visit above, a pre-treatment ultrasound may be performed if needed to confirm ability to inject tumors under imaging guidance.
- The Interventional Radiologist can select tumors for injection that were identified as target or non-target tumors and numbered with a unique number at screening.
- The Interventional Radiologist will measure and document the LD of the tumors (with appropriate tumor numbers) selected for injection. Tumor numbers and measurements will be documented by the Interventional Radiologist/physician performing the injection on the Pexa-Vec IT Injection Preparation Worksheet.

- The number(s) of the tumor(s) injected and the volume of solution injected into each tumor (among other data points) will be recorded in the eCRF.
- Intratumoral procedure is shortly described in section 5.1.7 and in the IT injection of Pexa-Vec Procedure Manual, for details.

[redacted]

Patients will be monitored closely (e.g., vital signs and clinical observation) the night prior and for 24 hours after the first Pexa-Vec injection as described in the study flow chart (Appendix 1). After injection, the following procedures will be implemented:

- Reporting of AEs/SAEs (that occurred during or after IT) and concomitant medications
- Vital signs (blood pressure, temperature, heart and respiratory rates) within 60 minutes prior to injection to establish baseline, 15 minutes (±5 minutes) after injection completion and then every hour (±15 minutes) for at least 8 hours after treatment, after which monitoring will be performed every 6 hours up to 24 hours or patient's release from hospital.

Patients will be monitored for troponin T or I blood level 3 and 8 days (± 1) after Pexa-Vec administration.
Patients will undergo an ECG 8 days (± 1) after Pexa-Vec administration.
Patients will undergo an ECG 3 days (± 1) after Pexa-Vec administration, in case of troponin clinically significant increase.

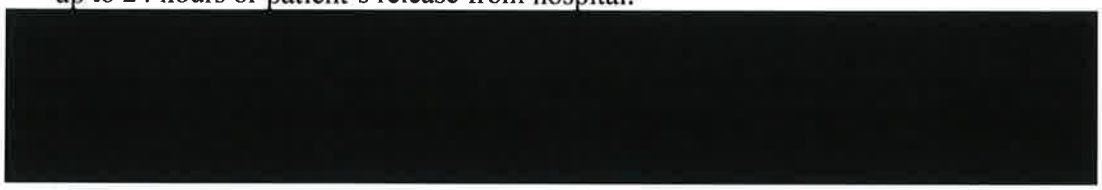
8.5 Day 15 visit (± 1 day): nivolumab infusion 1 - Pexa-Vec injection 2

Before Day 15 nivolumab infusion and intratumoral injection of Pexa-Vec, patients will undergo:

- Complete physical examination, including weight, vital signs, and ECOG PS
- Skin and mucosal examination; AEs and concomitant medications reporting
- Blood sample collection for the following testing: hematology, chemistry, coagulation and CRP
- Pregnancy test (urine) for WOCBP (if positive, an ultrasound will be performed to confirm pregnancy)
- Ultrasound scan may be optionally performed to assess suitability of IT injection within selected liver lesions and to select lesions for injection
- Nivolumab infusion 1
- Pexa-Vec intratumoral injection 2
- In case the administrations are distributed over 2 consecutive days, patients will undergo another complete physical examination and recording of vital signs prior to Pexa-Vec administration on the second treatment day.

Patients will be observed in the clinic or hospital for a minimum of 8 hours after IT Pexa-Vec treatment. After injection, the following procedures will be implemented:

- Reporting of AEs (that occurred during or after either drug administration) and concomitant medications.
- Vital signs (blood pressure, temperature, heart and respiratory rates) 15 minutes (±5 minutes) after injection completion and then every hour (±15 minutes) for at least 8 hours after Pexa-Vec treatment, after which monitoring will be performed every 6 hours up to 24 hours or patient's release from hospital.



Patients will be monitored for troponin T or I blood level 3 and 8 days (± 1) after Pexa-Vec administration.
Patients will undergo an ECG 8 days (± 1) after Pexa-Vec administration.
Patients will undergo an ECG 3 days (± 1) after Pexa-Vec administration, in case of troponin clinically significant increase.

8.6 Day 29 visit (± 1 day): nivolumab infusion 2 - Pexa-Vec injection 3

Before Day 29 nivolumab infusion and intratumoral injection of Pexa-Vec, patients will undergo:

- Complete physical examination, including weight, vital signs, and ECOG PS
- Skin and mucosal examination; AEs and concomitant medications reporting
- Blood sample collection for the following testing: hematology, chemistry, coagulation and CRP
- Pregnancy test (urine) for WOCBP (if positive, an ultrasound will be performed to confirm pregnancy)
- Ultrasound scan may be optionally performed to assess suitability of IT injection within selected liver lesions and to select lesions for injection
- Nivolumab infusion 2
- Pexa-Vec intratumoral injection 3
- In case the administrations are distributed over 2 consecutive days, patients will undergo another complete physical examination and recording of vital signs prior to Pexa-Vec administration on the second treatment day.

In addition, in the **phase I** part of the study, the following assessments will be performed:

- Cardiac echography (ECHO) with measurement of LVEF
- Measurement of troponin T or I level
- 12-lead ECG.

Patients will be observed in the clinic or hospital for a minimum of 8 hours after IT Pexa-Vec treatment. After injection, the following procedures will be implemented:

- Reporting of AEs (that occurred during or after either drug administration) and concomitant medications
- Vital signs (blood pressure, temperature, heart and respiratory rates) 15 minutes (±5 minutes) after injection completion and then every hour (±15 minutes) for at least 8

hours after Pexa-Vec treatment, after which monitoring will be performed every 6 hours up to 24 hours or patient's release from hospital

[redacted]

Patients will be monitored for troponin T or I blood level 3 and 8 days (± 1) after Pexa-Vec administration.
Patients will undergo an ECG 8 days (± 1) after Pexa-Vec administration.
Patients will undergo an ECG 3 days (± 1) after Pexa-Vec administration, in case of troponin clinically significant increase.

8.7 Radiographic Status Visits: Week 6 ±2 Days and every 6 weeks ±4 Days

At Week 6, radiographic status will be evaluated and then every 6 weeks ±4 days up to the End of Treatment Visit.

Beyond 12 months of treatment, the evaluations will be performed every 12 ± 2 weeks until documented progression or discontinuation of treatment beyond progression. If study treatments are stopped before documented radiological progression, PFS visits will be performed every 6 weeks to continue radiological assessment until documented progression. Patients will complete the following procedures:

- Complete physical examination, including weight, vital signs, and ECOG PS
- Skin and mucosal examination; AEs and concomitant medications reporting
- Blood sample collection for the following testing: hematology, chemistry, coagulation, CRP and thyroid blood tests
- Pregnancy test (urine) for WOCBP (if positive, an ultrasound will be performed to confirm pregnancy)
- Tumor assessment: CT or MRI, according to screening assessment
- Patient contact log update
- Week 6 only:
  - HBV and HCV viral load

[redacted]

8.8 Nivolumab infusion Visits: Week 6 ±2 Days and every 2 weeks ±4 Days

Nivolumab infusion visits will be planned every 2 weeks (± 2 days), at which patients will complete the following procedures:

- Complete physical examination, including weight, vital signs, and ECOG PS
- Skin and mucosal examination; AEs and concomitant medications reporting.

In addition, in the **phase I** part of the study, the following assessments will be performed every 4 weeks starting on Week 8:

- 12-lead ECG
- Cardiac echography (ECHO) with measurement of LVEF
- Measurement of troponin T or I level.

At week 6 and after Week 6, radiographic status visits (q6 weeks) will be combined with nivolumab infusion visits (q2 weeks), should nivolumab treatment continuation be appropriate.

8.9 Pexa-Vec injection boost Visits

Additional Pexa-Vec boosts may be performed in patients based on a case by case discussion between the investigator and Transgene, on the grounds of individual patient benefit. In any case, Pexa-Vec boosts will be performed no sooner than Week 12 and will be combined with a nivolumab infusion session. At such visits, patients will complete the following procedures:

- Complete physical examination, including weight, vital signs, and ECOG PS
- Skin and mucosal examination; AEs and concomitant medications reporting
- Blood sample collection for the following testing: hematology, chemistry, coagulation and CRP.
- Pregnancy test (urine) for WOCBP (if positive, an ultrasound will be performed to confirm pregnancy).

Patients will be monitored for troponin T or I blood level 3 and 8 days (± 1) after Pexa-Vec administration.
Patients will undergo an ECG 8 days (± 1) after Pexa-Vec administration.
Patients will undergo an ECG 3 days (± 1) after Pexa-Vec administration, in case of troponin clinically significant increase.

8.10 End of treatment visit

Accounting for the immunotherapeutic effect of both drugs and for the peculiar kinetics of clinical efficacy of these treatments, guidance is provided to continue treatment beyond

evidence of radiologic progression. The end of treatment visit is organized after last IMP administration. On end of treatment visit, patients will undergo:

- Complete physical examination, including weight, vital signs, and ECOG PS
- Skin and mucosal examination; AEs and concomitant medications reporting
- Blood sample collection for the following testing: hematology, chemistry, coagulation and CRP, AFP, antinuclear and anti TPO antibodies, thyroid blood tests
- Standard urinalysis
- Patient contact log update

8.11 Progression-free survival (PFS) follow-up visits

For patients who discontinue the study treatment prior to documented radiographic progression, radiological evaluation should be obtained every 6 weeks ± 2 weeks (until documented progression). Beyond 12 months, the evaluations will be performed every 12 weeks ± 2 weeks until documented progression. NOTE: patients undergoing follow-up visits for PFS are still on the active study participation phase and may not receive other anti-cancer treatments. End of study visit will only occur after disease progression.

8.12 28-day safety follow-up and end of study visit

The 28-day safety follow-up visit will be organized at least 28 days after the last treatment intake. In case of prior disease progression, this visit will be merged with the end of study visit. In case of treatment discontinuation without disease progression, the 28-day safety follow-up visit will be distinct from the end of study visit that will only occur after disease progression. In this case, patients will undergo in the meantime 6-weekly PFS follow-up visits. On both 28-day safety follow-up visit and end of study visit, patients will undergo:

- Complete physical examination, including weight, vital signs, and ECOG PS
- Skin and mucosal examination; reporting of AEs that occurred within 28 days of last study treatment administration and of concomitant medications, including potential anti-cancer therapies and significant non-drug therapies
- Blood sample collection for the following testing: hematology, chemistry, coagulation, CRP and thyroid blood tests
- Pregnancy test (urine) for WOCBP (if positive, an ultrasound will be performed to confirm pregnancy)

In addition, in the **phase I** part of the study, the following assessments will be performed:

- Cardiac echography (ECHO)
- Measurement of troponin levels
- 12-lead electrocardiogram (ECG).

8.13 Overall Survival follow-up

After the end of study/safety follow-up visit, all patients will be monitored every 8 weeks for:

- Survival information
- Reporting of any anti-cancer therapies

Patient consent for survival follow-up contacts is implicit when patients consent to study participation. If a patient withdraws consent from study procedures (discontinues), they will continue to be contacted for the protocol-specified survival follow-up unless the patient explicitly withdraws consent for survival follow-up.

Due diligence should be used in contact efforts including:

- At least 3 documented direct patient contact attempts and certified letter sent
- If a patient cannot be directly contacted, utilize all contact information provided by the patient on the patient contact log
- If all contact attempts are unsuccessful, death registries should be reviewed
- These patient contact procedures should be followed for at least 3 months before the patient can be considered lost to follow-up. Death registry data should be accessed for all patients until the study is completed.
- If a patient explicitly withdraws consent for survival follow-up, or if the site is unable to contact the patient, other methods to determine survival may be used, including referencing death registries, clinic/hospital visit records, primary oncologist or physician records, and/or newspaper obituaries, in compliance with local regulations.

8.14 Long-term follow-up

As per the guideline on follow-up of patients administered with gene therapy medicinal products (reference EMEA/CHMP/GTWP/60436/2007), long-term follow-up observations have been implemented in this trial. These observations are performed yearly after the last study visit (i.e. end of study visit) for a duration of five years and consist of a clinical history and a physical examination. In case of a detection/suspicion of an adverse event related to Pexa-Vec, the Sponsor is to be informed and further investigations can be performed as appropriate such as blood sampling for viral genome detection.

8.15 Handling of biological samples

[redacted]

[redacted]

9 ASSESSMENT OF EFFICACY

The assessment of the efficacy of the Pexa-Vec – nivolumab combination on HCC will involve radiological endpoints, overall survival and biological endpoints.

9.1 Primary variables

The primary variable to assess efficacy of the combination is ORR, using imaging data.

9.1.1 Imaging Data Acquisition

All patients will undergo CT (preferred) or MRI (if CT not possible) at Screening (up to 28 days before Day 1). Tumors will be numbered with a unique number and identified as Target or Non-Target tumors (refer to the next paragraph for definitions). Tumors should be assigned the next available chronological number wherever possible.

Collection of radiographic imaging scans will then occur at Week 6 (±2 days) and continue thereafter every 6 weeks (±4 days).

Beyond 12 months of treatment, the evaluations will be performed every 12 weeks.

If a patient discontinues the treatment phase prior to documented radiographic progression (e.g. permanently stops taking the study medication), PFS Follow-up Visits will be performed every 6 weeks for radiology evaluation until confirmed radiographic progression or until premature study discontinuation.

Specific imaging acquisition instructions are provided in the Imaging Manual provided by the core imaging laboratory.

Preferred Modality: Triphasic helical/spiral CT of the abdomen (pre-contrast, arterial phase, and portal venous phase; delayed imaging of the abdomen is optional) and post-contrast helical/spiral CT of the chest and pelvis. All follow-up scans must also be CT. If a CT IV contrast allergy (toxicity) develops after the patient has been randomized, then a DCE MRI of the abdomen and pelvis with gadolinium contrast will be required along with a non-contrast CT of the chest.

Alternative Modality: While triphasic CT remains the preferred modality for the abdomen, if a patient is unable to undergo triphasic CT due to iodinated contrast allergy, then Dynamic Contrast Enhanced Magnetic Resonance Imaging (DCE MRI) of the abdomen and pelvis with gadolinium contrast will be required along with a non-contrast CT of the chest. The abdominal MRI will be triphasic in nature, and the pelvic MRI will be performed following MRI of the abdomen. If an MRI is performed at screening, all follow-up scans must also be DCE MRI of the abdomen and pelvis with gadolinium contrast with a non-contrast CT of the chest.

The same method of assessment and the same technique should be used to assess each identified and reported lesion for the radiological baseline (screening CT/MRI) and each follow up scan collected during the study.

9.1.2 Imaging Data Evaluations

The management of patients is based on RECIST version 1.1 (*Eisenhauer 2009*). If the site reader determines that radiographic PD has occurred, the patient will be considered to have progressed radiographically. Definitions and methodology indicated hereafter and within the Imaging Charter are based on RECIST 1.1.

9.1.3 Measurability of Tumor

All measurements should be recorded in metric notation (mm). The radiological baseline will be defined according to the screening CT/MRI and tumor lesions/lymph nodes will be categorized as measurable (Target lesions) or non-measurable (Non-Target lesions). Lymph nodes that have a short axis <10 mm at Baseline are considered nonpathological- 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.

For tumor lesions: the LD in the plane of measurement has to be recorded with a minimum size of 10 mm by CT scan when CT scan slice thickness is no greater than 5 mm.

For nodal lesions: at Baseline and in the followup-, 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.

9.1.4 Non-Measurable Lesions

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.

9.1.5 Target / Non Target Tumors

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 nontarget- lesions.

Target Tumors: Target tumors should be selected on the basis of their size (tumors with the LD which are able to be reproducibly measured across time points) and are preferred to be within the liver. However, target tumors may be selected outside of the liver. Up to a maximum of 5 tumors total, and a maximum of 2 tumors per organ (except for the liver where 5 tumors can be selected as non-target for the purpose of this trial), representative of all involved organs will be identified as target tumors and will be recorded and measured at baseline by the site reader.

Selection of tumors outside the liver is subject to Transgene's approval.

All post-baseline measurements must be performed using the same tumors and methods as the baseline assessment.

Response assessments for target tumors are defined as:

- Complete Response (CR): Disappearance of all target tumors. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
- Partial Response (PR): At least 30% decrease in the SLD of target tumors, taking as reference the baseline SLD of target tumors.
- Progressive Disease (PD): Radiographic tumor progression for target tumors requires an increases in the SLD of target tumors of at least 20% taking as reference the smallest sum of diameters of target tumors recorded since the treatment started (this includes the baseline sum if that is the smallest on study). PD should be confirmed with a second radiological assessment performed at least 4 weeks after the first evidence of PD.
- Stable Disease (SD): Neither sufficient shrinkage to qualify for PR, nor sufficient increase to qualify for PD, taking as reference the smallest SLD while on study (including Baseline). Contingent upon minimum duration of 6 weeks from enrollment.
- Non-Evaluable (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. Rules for selecting non-evaluable include the following:
  1. All target tumors are not evaluable.
  2. Or, if at least 1 target tumor is not evaluable, the target tumor SLD is still calculated using the remaining evaluable/measureable target tumors. The only acceptable assessment in this situation is progressive disease or non-evaluable. If the SLD of target tumor has increased at least 20% from nadir (including Baseline if it is the nadir) then the response is PD. Any other calculated result gives an assessment of non-evaluable.

NOTE: SLD = sum of the LDs of viable enhancing hepatic target tumors plus LDs of any non-nodal extrahepatic target tumors plus the short axis diameters of any nodal target tumors will be calculated.

Non-Target Tumors: 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", "worsening" or in rare cases "unequivocal progression" (as defined in the below note) 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 enlarged pelvic lymph nodes). Each nontarget lesion identified at Baseline should be assessed at each subsequent evaluation and be recorded in the eCRF-.

Furthermore, for the purposes of this trial, special assessments are recommended for the following:

- Malignant portal vein thrombosis should be considered a non-measurable tumor due to the difficulty of performing reliable repeat measurements of a malignant thrombus.
- Porta hepatis lymph node can be considered as malignant if the lymph node short axis is at least 20 mm.
- Ascites, pleural effusion, and pericardial effusion: these may not be used to assess response as non-target tumors, nor may they be selected as evidence of new disease as radiographic progression. They may not be used due to the incidence of therapeutic fluid removal and benign occurrence of these fluid collections which makes them unreliable as a marker of disease evolution.

Response assessments for non-target tumors are defined as:

- Complete Response (CR): Disappearance of all non-target tumors. All lymph nodes must be non-pathological in size (<10 mm short axis).
- Incomplete Response / Stable Disease (SD): Neither CR nor PD
- Progressive Disease (PD): Unequivocal progression of existing non-target tumors
- Non-Evaluable (NE): Progression has not been documented and one or more nontarget- lesions have not been assessed or have been assessed using a different method than baseline not allowing a reliable comparison.

Rules for selecting non-evaluable for non-target tumors include the following:

1. All non-target tumors are not evaluable.
2. Or, if at least 1 non-target tumor is not evaluable and no other non-target tumor demonstrates unequivocal progression, the assessment is "NE"
3. If at least 1 non-target tumor is not evaluable and at least 1 other non-target tumor demonstrates unequivocal progression, the assessment is "unequivocal progression."

NOTE: To achieve "unequivocal progression" on the basis of the nontarget disease, there must be an overall level of substantially worsening in nontarget 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 -nontarget- lesions is usually not sufficient to qualify for unequivocal progression status. The designation of progression solely on the basis of change in -nontarget- disease in the face of CR, PR, or SD of target disease will therefore be extremely rare.

9.1.6 New Tumors

The appearance of new lesion is always associated with PD. A lesion identified on a followup 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 -followup- 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.

New Tumor Progressive Disease (PD): If a newly detected lesion is obviously a tumor, progression criteria is met at the current time point. 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.

If no nontarget lesions are identified at baseline, the -nontarget- 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.

Table 2:
Overall Response Assessment in RECIST 1.1[1]

Target Tumors	Non-Target Tumors	New Tumors	Overall Response
CR	CR	No	CR[2]
CR	Non-CR/non-PD	No	PR
CR	Non-PD or not all evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR[2]
SD	Non-PD or not all evaluated	No	SD[2,3]
Not all evaluated	Non-PD	No	NE[1]
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

1 Responses for all possible combinations of tumor responses in target and non-target lesions with or without the appearance of new lesions
2 this overall lesion response also applies when there are no nontarget- lesions identified at baseline.
3 once confirmed PR is achieved, all these assessments are considered PR.
CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease; NE = non evaluable

9.2 Secondary variable(s)

To evaluate the efficacy of Pexa-Vec combined with nivolumab in patients with advanced HCC, the following secondary endpoints will be assessed, of which imaging endpoints have been described above and will be evaluated by RECIST 1.1:

- Disease Control Rate (DCR), percent non-progressors over time
- 4-month DCR
- Time to Progression (TTP)
- Duration of Response (DoR)
- Progression Free Survival (PFS), median and percent of patients having not progressed.

Overall Survival (OS), median and percent survivors over time as reflective of final patient benefit will be recorded and possible correlations with ORR and/or DCR established.

Blood viral load (HCV, HBV) will be measured over time, as previous data showed a possible influence of Pexa-Vec treatment.

In addition, the safety will be assessed in the Phase IIa part of the study.

9.3 Biodistribution

In this trial, blood pharmacokinetic (PK) parameters of nivolumab and Pexa-Vec (viral genomes) will be assessed, including concentration in serum, peak concentration (Cmax), area under the concentration-time curve (AUC), clearance (CL), and elimination half-life (t½) (see Chapter 10).

10 ASSESSMENT OF SAFETY

The condition of the patient will be monitored throughout the study.

10.1 Definitions

- Adverse Event (AE): An AE for the purposes of this study is defined as any medical occurrence or deterioration of a pre-existing medical condition occurring in a patient after signing the informed consent, regardless of its relationship to the study treatment(s). An AE can therefore be any signs, symptoms, abnormal laboratory finding, abnormal imaging finding, or a disease temporarily associated with the use of the protocol treatment(s), whether or not considered related to the investigational medicinal product

- Adverse Reaction (AR): An AR of an investigational medicinal product is defined as "any noxious and unintended response to a medicinal product related to any dose administered or to a study-specific procedure". All AEs judged by either the reporting investigator or Transgene as having a reasonable causal relationship to a medicinal product qualify as AR.

- Unexpected Adverse Reaction (UAR): An UAR is "any adverse reaction, the nature, or severity of which is not consistent with the applicable product information" (*e.g.* investigator's brochure for an unapproved investigational product or summary of product characteristics (SmPC) for a marketed product). When the outcome of the AR is not consistent with the applicable product information this adverse reaction should be considered as unexpected.

- Severity: The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate or severe, or as described in CTC grades); the event itself, however, may be of relative minor medical significance (such as severe headache). This is not the same as "serious," which is based on patient/event outcome or action criteria usually associated with events that pose a threat to patient's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

- Serious Adverse Event (SAE): is defined as any untoward medical occurrence or effect in a patient, whether or not considered related to the protocol treatment, that at any dose: (i) results in death, (ii) is life-threatening (*i.e.* an event in which the subject was at risk of death at the time of event; it does not refer to an event which hypothetically might have caused death if it were more severe), (iii) requires inpatient's hospitalization or prolongation of existing inpatients' hospitalization, (iv) results in persistent or significant disability or incapacity, (v) is a congenital anomaly or birth defect, (vi) results in any other medically important condition (*i.e.* important adverse reactions that are not immediately life threatening or do not result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed above), e.g. secondary malignancy, AE as a result of an overdose.

- SAR: A Serious Adverse Event (SAE) which is considered related to the IMP or study-specific procedure is defined as a Serious Adverse Reaction.

- SUSAR: An unexpected Serious Adverse Event (SAE) which is considered related to the protocol treatment (IMP or study-specific procedure) is defined as a Suspected Unexpected Serious Adverse Reaction. SUSARs occurring in clinical investigations qualify for expedited reporting to the appropriate Regulatory Authorities within the following timeframes: (i) Fatal or life-threatening SUSARs within 7 calendar days, (ii) Non-fatal or non-life-threatening SUSARs within 15 calendar days.

- Vaccinia infectious complications: Complications that are related to vaccinia infection, such as:

  - Pustular rash of Grade ≥ 3
  - Post-vaccinal encephalitis
  - Eczema vaccinatum
  - Generalized vaccinia
  - Progressive vaccinia
  - Fetal vaccinia
  - Ocular vaccinia

  Vaccinia infectious complications occurring in clinical investigations qualify for expedited reporting to the French Competent Authority, ANSM within the timeline of SUSAR.

- Grade ≥ 3 cardiotoxicity events (including but not limited to NCI CTCAE v.4.03 cardiac disorders)

- Inpatient or in-patient's hospitalization: A patient who is admitted to a hospital or clinic for at least one overnight stay.

- Dose-limiting toxicity (DLT): Any of the following treatment-related adverse events (AEs) and is evaluated and reported from Baseline through Day 29 in the Phase I section of the study; grades are referring to NCI CTCAE v. 4.03:

  1. All Grade 3-4 non-hematologic toxicity that represent a 2 grade increase over baseline, excluding:
     - Untreated or inadequately treated nausea, vomiting and diarrhea,
     - Untreated or inadequately treated fever > 40.0°C lasting less than 24 hours (Grade 3); only fever > 40.0°C lasting more than 24 hours (Grade 4) qualifies for DLT,
     - Alopecia,
     - Grade 3 fatigue that returns to grade 2 or less within 7 days,
     - Grade 3 laboratory/metabolic abnormalities, other than ALT or AST, that are not considered clinically significant and that return to grade 2 or less within 72 hours.

  2. Any Grade ≥ 3 treatment-related acute immune-related AE involving major organs, such as: immune-related pneumonitis, colitis, nephritis, hepatitis, endocrinopathies, immune-related rash and other rare but severe immune-related reactions.

  3. Grade ≥ 3 injection site reaction.

4. AST or ALT ≥ 10xULN, even if asymptomatic, unless it is related to a definite progression of liver metastases or another clearly identifiable etiology; doubling of AST or ALT that is concurrent with a doubling of the total bilirubin.

5. Any toxicity at least possibly related to study therapy that results in a delay in treatment of 2 or more weeks.

6. Hematological:
- Grade ≥ 3 or ≥ 2-grade increase over baseline of neutropenia lasting for more than 7 days.
- Neutropenic fever.
- Grade 4 thrombocytopenia or grade 3 thrombocytopenia with clinically significant bleeding.

7. Cardiac: association of the 3 following cardiac abnormalities
- Left ventricular ejection fraction (LVEF) less than the lower limit of normal (LLN), as assessed by echocardiography and symptomatic due to drop in ejection fraction, responsive to intervention,
- Increase of blood troponin T or I above the upper limit of normal (ULN),
- Any ECG abnormality consistent with a Grade 3 cardiac disorder.

- DLT Period: The DLT period is the period during which the DLTs are recorded in a patient eligible for safety assessment within the Phase I section of the study, defined as the interval between the 1st Pexa-Vec administration (Day 1) and 3rd Pexa-Vec administration concomitant to the 2nd nivolumab infusion (Day 29 in evaluable patients, who have received all three Pexa-Vec IT injections and 2 nivolumab IV infusions in Phase I). In the event that a patient does not complete the DLT period and withdraws for other reasons than toxicity, then the patient will not be considered evaluable for Phase I and will have to be replaced.

10.2 Intensity, relationship and outcome evaluation

Intensity

The intensity of AEs/SAEs will be graded according to the NCI-CTCAE version 4.03 (dated June 14, 2010).

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	Death

Relationship to the IMP

The relationship to either IMP (either Pexa-Vec or nivolumab) for each AE/SAE will be evaluated by the Investigator with the "global introspection" method using the following levels:

- Related: The temporal relationship of the clinical event to the administration of either IMP/other study treatment 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 any study drug or recurrence upon rechallenge may also be observed.

- Not Related: The temporal relationship of the clinical event to the administration of either IMP makes a causal relationship unlikely; and other drugs, therapeutic interventions or underlying conditions provide a sufficient explanation for the observed event.

Outcome

The outcome is rated as follows:

- Recovered,
- Not recovered,
- Recovered with *sequelae* (to be specified on comment page),
- 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".

10.3 Time Period for Collection of AEs and SAEs

From the date of signature of ICF and up to first IMP administration (i.e. before the patient receives any IMP) only SARs caused by a protocol-required procedure (e.g., related to invasive procedures such as blood sampling) will be collected and reported (See sections 9.4 and 9.5). AEs, SAEs, or procedure related ARs that occur during this period, and that are considered by the investigator as relevant to the patient condition, will be collected as a current medical history.

After the initiation of either IMP and up to 28 days after the last dose of IMP, all AEs and SAEs should be collected and recorded on the eCRF. SAEs should also be reported to Transgene.

SAEs occurring more than 28 days after the last dose of IMP, and evaluated by the Investigator as related to the IMP should be collected and reported to Transgene indefinitely even after end of study. Only SAEs occurring prior to end of study will be reported in the eCRF.

10.4 Adverse Event Management

Reporting in eCRFs

Any AE/SAE directly observed (physical examination, laboratory test, or other assessments), mentioned by the patient or reported by the patient upon nondirective questioning at each visit during the study, will be reported by the Investigator on the page "Adverse Events" of the eCRF (= AE page). The following items must be documented:

- AE term (*i.e.*, the nature of the event with self-explanatory and concise medical terminology indicating 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),
- outcome,
- intensity,
- relation to IMP,
- relation to study procedure,
- action taken regarding each IMP,
- action taken regarding the event,
- evaluation of seriousness.

AE 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.

Specifications for the management of Grade 3 or 4 AEs, and Grade 3 or 4 laboratory abnormalities that are considered related to Pexa-Vec are displayed in section 10.9.

Follow-up

AE/SAE must be followed until resolution or the last visit planned by the protocol, i.e. end of study visit, occurring 28 days after last study treatment administration or after disease progression, whichever is the latest.

However, the AE listed below must be followed until they are resolved or stable or returned to Baseline status, which may occur after the last visit planned by the protocol:

- AE evaluated as related to the IMP,
- SAEs,
- Any other significant AE as recommended by Transgene i.e. formation of skin pustules.

In addition to the collection in the eCRF, follow-up information about the development of skin pustules will be reported to Transgene in an expedited manner within 24 hours of knowledge by the Investigator as indicated in the eCRF.

Documentation

AE will be reported in the source document with at least the nature of the event, the start and end date, the relationship to the treatment (any IMP or procedure) of the event.

Information about the Pexa-Vec IMP common side effects can be found in the Investigator Brochure. New information between Investigator Brochure updates will be communicated in the form of an Investigator Brochure attachment or letter. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed.

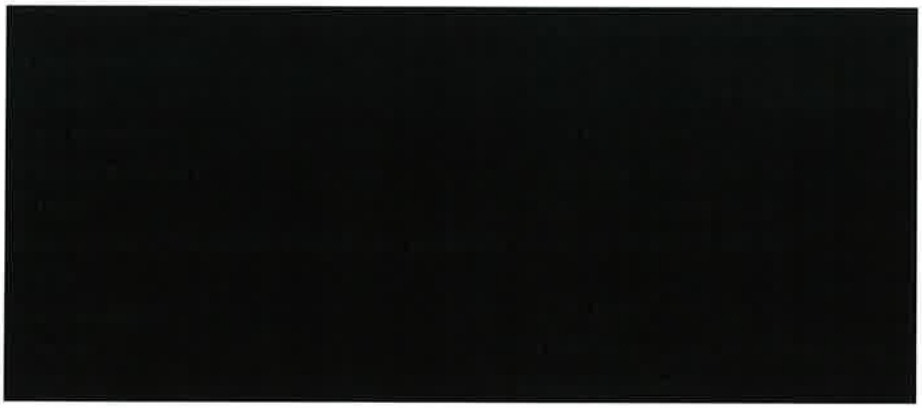
The Investigator Brochure and SmPC for nivoluamb (Opdivo®) are available in the Investigator site files.

10.5 Serious Adverse Event Management

Reporting

Any SAE occurring in a patient during the course of a study MUST be reported by the Investigator to Transgene or its representative (**PPD**).

The Investigator will complete the "Serious Adverse Event Form" in English, and send the completed, signed form by fax or email to Transgene and its representative without delay from the day of occurrence or knowledge of the event.



The original copy of the "SAE Form" and the fax confirmation sheet (if faxed) must be kept at the study site in the Investigator Site File (ISF).

Follow up

Follow-up information (e.g. complications or progression of the initial SAE) must be reported without delay to Transgene and its representative using a new SAE form with the box "follow-up" ticked. New information must be sent to Transgene and its representative without delay from the day of occurrence or knowledge. Transgene or its representative may request further information as needed.

All SAEs will be followed until the final outcome is known.

Any case of vaccinia of grade ≥ 3, any case of pustular rash of grade ≥ 3 and any case of grade ≥ 3 cardiotoxicity occurring in a patient during the course of a study MUST be reported by the Investigator to Transgene and its representative by using the Serious Adverse Event Form without delay from the day of occurrence or knowledge of the event.
The Investigator will tick the box: "**Event subject to immediate reporting**"

Follow-up information must be reported without delay to Transgene and its representative using a new SAE form with the box "follow-up" ticked. New information must be sent to Transgene and its representative without delay from the day of occurrence or knowledge. Transgene or its representative may request further information as needed.

These events will be followed until the final outcome is known.

Notifications

Transgene or its representative will be responsible for reporting SUSARs and any follow-up information to Regulatory Authorities and to Central Ethics Committees as per local regulation. In case of a SUSAR, Transgene or its representative will inform all investigators involved in any study with the same IMP that such an event has been reported.

[redacted]

The Investigator is responsible for informing local Ethics Committee of SUSARs, any other SAEs, and any follow-up information as per local regulations.

The Investigator Site File will include copies of notification letters and/or faxes with forms sent to Ethics Committee/Health Authorities if appropriate.

10.6 Special situations

Pregnancy

The occurrence of a pregnancy must be reported to Transgene and Transgene's representative 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 immediately
- 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

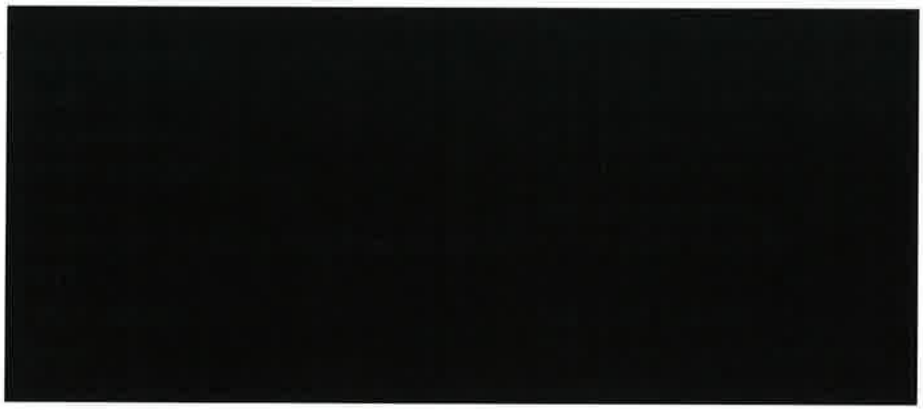
[redacted]

Pregnancies have to be followed up to the completion or termination of the pregnancy, collecting information about the pregnancy and knowledge of the newborn medical status. Pregnancy outcomes must be collected for the female partners of any males who took any IMP. 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.
All pregnancies starting from the first IMP administration and up to 3 months after the last IMP administration must be reported.

Overdose

Any overdose should be reported to Transgene and Transgene's representative within 24 hours of occurrence or knowledge of the overdose, and documented and followed-up using an "Overdose form". In addition, any associated symptoms should be reported as an AE or SAE.



10.7 Laboratory values, vital signs, physical findings and other safety data

Clinically relevant abnormal laboratory results will be repeated immediately (if relevant) and followed until return to normal unless an adequate explanation is determined, or 28 days after last IMP administration if not related to IMP.

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

10.8 Viral safety and nivolumab safety assessed by blood pharmacokinetics

In Phase I, blood samples for pharmacokinetic analyses will be collected in all patients. Analyses will be performed in all patients within the Recommended Phase II Dose (RP2D) and

RP2D-1 cohorts, and will evaluate the change over time in viral genomes and/or viral infectious units (pfu), and of nivolumab in patient blood samples.

In Phase IIa, blood samples for pharmacokinetic analyses will be collected in all patients. Analyses will be performed in all samples collected. Change over time in viral genomes and/or viral infectious units (pfu), and of nivolumab in patient blood samples will be assessed.

Unscheduled sampling and analyses will be performed only if there is the occurrence of clinical events for which measurement of viral genomes and/or viral infectious units (pfu), and/or nivolumab would be needed for event evaluation.

10.9 Toxicity Management

All patients should have blood drawn for laboratory abnormalities assessment before any administration of IMP. Blood draws prior to IMP administration should be tested in the local laboratory.

Management of patients with a DLT within a given dose-escalation cohort: Patients who experience a DLT within a given cohort will be monitored by the Investigator until resolution and the Investigator will report the occurrence of a DLT without any delay or within 24 hours of knowledge or occurrence of the event to Transgene and Transgene representative.

If a patient death occurs within 28 days of the last Pexa-Vec or nivolumab administration due to a serious and unexpected Adverse Drug Reaction (ADR) that is determined by the Investigator or Transgene Medical Monitor to be possibly or probably related to Pexa-Vec and/or nivolumab, further administration of Pexa-Vec /nivolumab will be suspended for ongoing patients. Additionally, further patient enrolment into the study will be suspended and ISC, Ethics Committees (ECs) and Regulatory Authorities will be notified as regards further study handling.

- Management of Adverse Events (other than the formation of pustules)

  Patient Management: in case of grade 3 or 4 adverse events considered as related to Pexa-Vec and/or nivolumab, the Investigator should contact Transgene Medical Monitor regarding the management of the patient and to determine if the next administration of Pexa-Vec or nivolumab should be postponed until resolution within an acceptable timeframe (*i.e.* within 30 days) otherwise the Pexa-Vec and/or nivolumab treatment will be stopped (*i.e.* no subsequent injection or infusion, respectively).

- Overall Management in the event of Pustule Formation

  Pustule Management: specific precautions should be applied to patients treated with Pexa-Vec, in whom the occurrence of pustules is observed, to prevent contamination from spread of the virus in the environment:

  - The infusion sites and any skin lesions should be covered loosely with a non-occlusive bandage (*e.g.*, gauze) held in place with first-aid tape for at least 1 week after treatment. If a blister forms, bandaging of the infusion sites or skin lesions should be continued either until healed or the scab falls off.

- Non-occlusive bandage should be changed at least every 3 days or every time the bandage becomes wet.
- Infectious wastes should be disposed of according to the Institution or local procedures.
- Contaminated linen should be managed according to the Institution or local procedures.
- Recommendation to wear personal protective equipment when changing the bandage on the injection/infusion sites and skin lesions, to remove the gloves and clean hands immediately after changing the bandage and before touching any other part of the patient's body, another person, or objects in the environment.

Patient Management: in the event that the AE is due to skin lesions ≥ than 10 pustules corresponding to infection that is possibly or probably related to the administration of Pexa-Vec, the Investigator will contact Transgene and a patient monitoring plan will be implemented to fully document the occurrence and evolution of the pustules (*e.g.* photographs of skin lesions). Specific details and instructions will be provided to Investigators as part of a patient monitoring plan and other site-specific study documentation. Transgene must be notified immediately and the ISC may be consulted as needed.

- Management in the event of suspected infectious complication related to Pexa-Vec

In case of occurrence of symptoms compatible with the development of an infectious complication that may be related to Pexa-Vec, such as described in paragraph 10.1, please contact Transgene Medical Monitor.

For France, management guidelines have been established by the Société de Pathologie Infectieuse de Langue Française (SPILF), Coordination Opérationnelle du Risque Epidémique et Biologique (COREB) and are described in Appendix 4: Procédure SPILF – COREB – Vaccine.

- Management in the event of accidental exposure to Pexa-Vec

Any accidental exposure should be reported to Transgene's representative within 24 hours of occurrence or knowledge of occurrence, and documented and followed-up using an "Report of Exposure to Infectious Material", faxed to the below number.

[redacted]

For France, the SPILF-COREB has established management guidelines which are to be followed by French sites (Appendix 4).

- Management of Laboratory Abnormalities

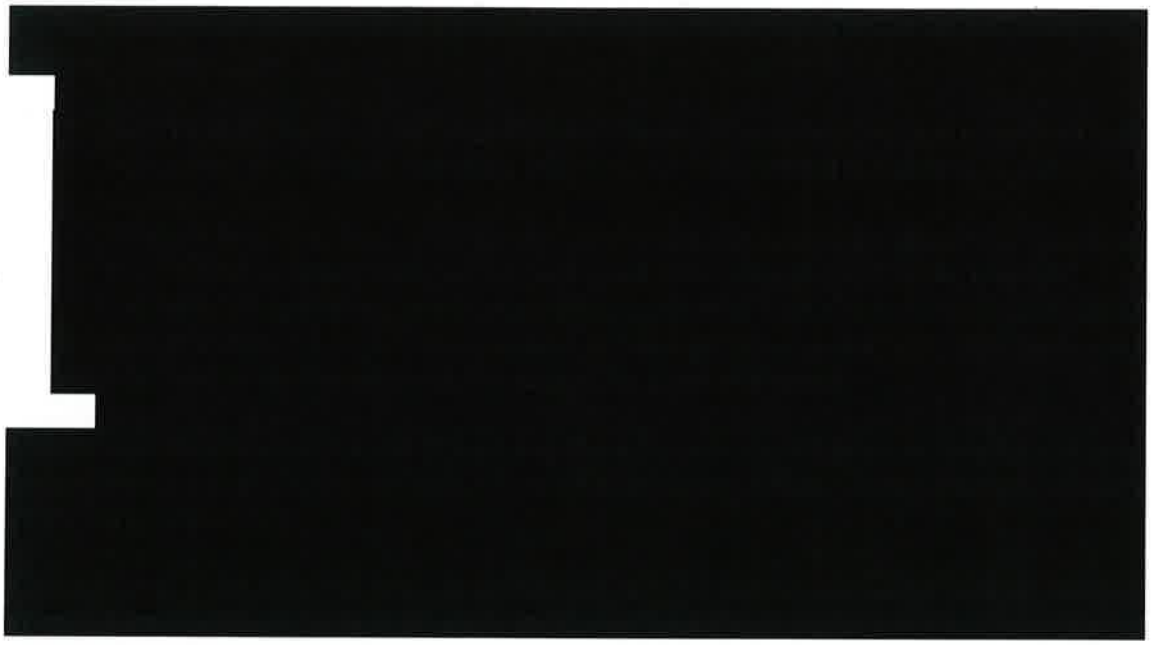
All clinically significant laboratory abnormalities of Grade 3 or 4 and regardless of the relationship to the IMP should be confirmed by repeat testing within up to 5 days of

receipt of results. If the laboratory abnormality is confirmed and considered at least possibly related to Pexa-Vec and/or nivolumab, the Investigator should contact the Coordinating Investigator (SC) regarding the management of the patient and to determine if the treatment regimen can be reinitiated once the laboratory abnormality has resolved.

If the laboratory abnormality considered at least possibly related to Pexa-Vec and/or nivolumab has not resolved, the next administration should be postponed until resolution within an acceptable timeframe (*i.e.* within 30 days) otherwise the Pexa-Vec and/or nivolumab treatment will be stopped (*i.e.* no subsequent dosing).

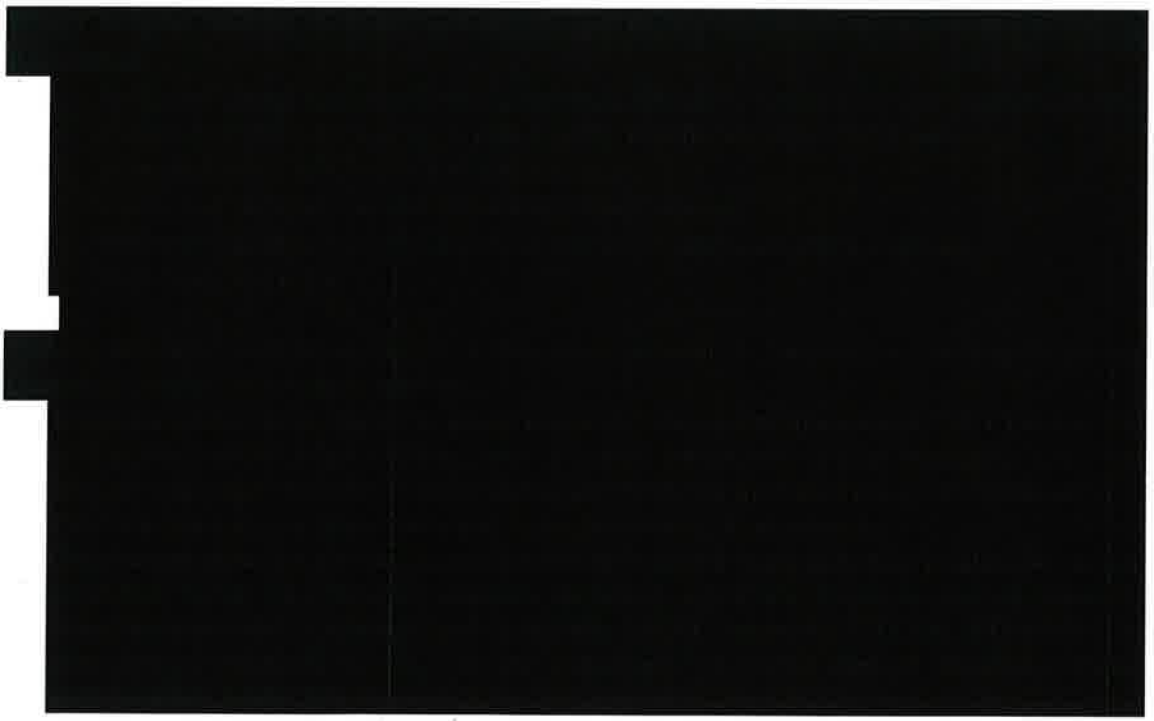
11 PHARMACOKINETICS AND LABORATORY ANALYSES

11.1 Blood pharmacokinetics of Pexa-Vec



11.2 Blood pharmacokinetics of nivolumab

11.3 Other laboratory analyses



12 STATISTICAL METHODS PLANNED AND SAMPLE SIZE

12.1 Determination of sample size

Hypothesis

As the patient survival benefit may be correlated with either radiological response of tumors or/and prolonged stabilization of the disease, the analysis of efficacy will consider ORR as primary endpoint. Sample size justification will use available data on ORR, as such: in a Phase I/II trial, 8/42 (19%) patients with previously treated HCC experienced an objective response when treated with single-agent nivolumab (El-Khoueiry et al., ASCO 2015). Therefore, a response rate of 15%-20% with the combination of Pexa-Vec + nivolumab in these patients would be considered disappointing, while a response rate of 35% or more would be promising and would encourage further study of the regimen in these patients. The null hypothesis for response rate H0 is set at 15%, the alternate hypothesis of efficacy is set at HA=35%, the type I error α is set at 5% one sided and the power is set at 80%.

Statistical Design

Under these hypotheses a two-stage group sequential design using alpha and beta spending function approach with Lan DeMets spending function (O'Brien-Fleming efficacy boundaries and non-binding Pocock futility boundaries) will be used leading to a maximum sample size of 30 evaluable patients and an interim analysis based on 15 evaluable patients (implemented in EAST® 6.3) with a test proportion with normal approximation to the binomial distribution.
In the first stage 15 evaluable patients will be accrued. If there are 3 or fewer responses in these 15 patients (20% of responders or less), the study could be stopped for futility. If there are 6 or more responses in these 15 patients (40% of responders or more), the null hypothesis will be rejected and the study could be stopped. Otherwise 15 more additional evaluable patients will be accrued for a total of 30.
At the final analysis, the null hypothesis will be rejected if 8 or more responses are observed in the 30 evaluable patients (26.7% of responders or more) with a power of 80% and a type I error of 5%. It should nevertheless be reminded that given the mechanism of action of the drugs involved and the effects of immunotherapy on tumor behavior, ORR may not be the best measure of anti-tumor activity. For this reason, consideration will be given to DCR, TTP and survival parameters prior to deciding that the combination does not warrant further exploration.
At interim and final analysis, enough patients will be treated to obtain a total of 15 and 30 evaluable patients, respectively including comparable patients of the Phase I part (population, treatment regimen) still evaluable for Phase II part.

12.2 Study endpoints

- **Primary endpoints**

  Phase I part: The primary objective is to evaluate the safety profile of intratumoral (IT) Pexa-Vec combined with intravenous (IV) nivolumab in patients with advanced HCC.

  Phase IIa part: The primary objective is to evaluate the anti-tumor activity and efficacy of IT Pexa-Vec combined with IV nivolumab in patients with advanced HCC with respect to the following endpoint: Overall Response Rate (ORR) (RECIST 1.1).

- **Secondary endpoints**

The secondary objectives of this study are to evaluate the efficacy of Pexa-Vec combined with nivolumab in patients with advanced HCC with respect to the following endpoints (imaging endpoints evaluated by RECIST 1.1):

- Safety (Phase IIa)
- Disease Control Rate (DCR) at 4 months
- Disease Control Rate (DCR) (proportion of non-progressing patients over time)
- Time to Progression (TTP)
- Duration of Response (DoR)
- Progression Free Survival (PFS) (median and proportion of non-progressing patients over time)
- Overall Survival (OS)(median and proportion of survivors over time)
- Blood viral load (HCV, HBV when appropriate)

12.3 Statistical and analytical plans

12.3.1 Demographic and baseline characteristics

Baseline demographics and characteristics will be listed and summarized for each phase and presented by dose.

Qualitative data (eg. Gender, Country) will be summarized by percentages and quantitative data (e.g., age and body weight) will be summarized by appropriate descriptive statistics (mean, standard deviation, median, minimum and maximum).

12.3.2 Safety Data

Safety data are primary endpoint for Phase I and secondary endpoint for Phase IIa. The primary dataset for safety evaluation is the safety population.

The safety data will be classified according to their intensity and relationship to the IMP. The more common AEs, laboratory test changes, etc. will be identified, classified and analyzed, as appropriate, for factors that may affect the frequency of AEs, such as time dependence, relation to demographic characteristics or relation to dose. The number of patients with each AE will be displayed by decreasing frequency of occurrence and body system classes and by SOC and preferred Term.

From the date of signature of the informed consent form and up to prior to initiation of either IMP administration, AEs, SAEs, or procedure related ARs that occur during this period, and that are considered by the investigator as relevant to the patient condition, will be collected as a current medical history and reported as such in eCRF.

All AEs occurring after the initiation of the study treatments, including events likely to be related to the underlying disease or likely to represent concomitant illness should be reported, including events present at baseline which worsened during the study. Written narratives will be provided for all serious, unexpected or other important AEs that are judged to be of special interest because of their clinical importance.

12.3.3 Efficacy data

The primary dataset for efficacy evaluation is the Per Protocol population.

Primary objectives for Phase IIa

Overall response rate (ORR) is the proportion of patients, whose best overall response is either CR or PR, confirmed at least 4 weeks after initial documentation.

Secondary objectives for Phase I and Phase IIa

Disease control rate (DCR) is the proportion of patients whose best overall response during their participation in the study is either CR, PR, or SD. It will be presented using percentage and exact 95% confidence interval. 4-month (18-week) DCR is proportion of patients whose best overall response in the study is either CR, PR, or SD 4 months after D1.

The Time to Progression (TTP) is the time from Day 1 to the date of first documented radiographic tumor progression. TTP does not include deaths. If a patient has not had a TTP event at the cut-off date for analysis, TTP will be censored at the date of last evaluable tumor assessment before the cut-off.

Progression Free Survival (PFS) is the time from Day 1 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, PFS will be censored at the date of last evaluable tumor assessment before the cut-off.

Overall Survival (OS) is the time from Day 1 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 the date of death due to underlying cancer. DoR will be censored if progression or death due to underlying cancer is not observed at the cut-off date for the analysis or start of further antineoplastic therapy. The censoring date will be the date of the last evaluable tumor assessment.

TTP, PFS, OS and DoR will be presented using the number of events, number of censored patients, quartiles TTP/PFS/OS/DoR (Q1, median and Q3) and the associated confidence interval. A graphical representation will be done for these four outcomes using a Kaplan-Meier curve with 95% confidence interval.

For OS, the percent survivors over time will also be presented considering the proportions of patients alive at 6, 9, 12, 18, and 24 months, along with corresponding 95% CIs.

For PFS, the percent non-progressors over time will also be presented considering the proportions of patients having not progressed at 6, 9, 12, 18, and 24 months, along with corresponding 95% CIs.

Tumor size is defined as the sum of the diameters recorded for all target lesions as identified at baseline. Relative change from baseline in tumor size over time will be analyzed using a repeated measurements analysis model.

Immunology data

Blood viral load (HCV, HBV when appropriate) evolution over time will be studied by considering a parametric or non-parametric (as appropriate) paired test to compare baseline value at Day 1 and value measured at Week 6.

Exploratory efficacy analyses

12.4 Disposition of patients

The number of patients screened and not included will be presented with the main reason for their non-inclusion. All patients who failed to meet inclusion criteria after informed consent signature will be considered as screening failure and reported in the study report.

All patients enrolled and who completed each phase of the study will be considered in the study report. All post-inclusion discontinuations will be summarized by main reason for discontinuation.

12.5 Protocol deviations

Any protocol deviation will be discussed with the Investigator on a case by case basis, and characterized as minor or major. Patients with deviations deemed major cannot be included in per protocol analyzes and should be replaced. Anticipated but not limited major deviations are:

- Failure to complete all 3 IT Pexa-Vec injections and 2 nivolumab IV infusions in the Phase I part, 2 IT Pexa-Vec injections and 2 nivolumab IV infusions in the Phase IIa part,
- No histological confirmation of HCC,
- Previous systemic therapy for HCC,
- Child-Pugh score beyond A, or deteriorated hepatic function beyond score, or advanced cirrhosis diagnosis based on albuminemia, INR, bilirubin blood levels and clinical symptoms: uncontrolled ascites or esophageal varices, etc.
- ECOG PS > 1,
- Prohibited concomitant medications or no withdrawal of anti-hypertensive, anticoagulant or anti-platelet medications within protocol-specified conditions,
- Immunologic deficiency,
- Pregnancy and breast-feeding.

12.6 Data sets analyzed

Safety population

All patients entered into the study who received at least one dose of either IMP will be included in the safety analysis. The patients will be analyzed according to the treatment actually received and this population will be the primary dataset for safety evaluation.

DLT Population

All patients entered into the study who received at least one dose of either IMP and who are evaluable for Phase I will be included in DLT population. The patients will be analyzed according to the treatment actually received and this dataset will be used for safety evaluation.

Per protocol population

The main analyses will be based on a per protocol population, only including evaluable patients for Phase II and excluding all patients with major protocol deviations like eligibility deviations or deviations from protocol. Evaluable patients from Phase I who are comparable (same inclusion/exclusion criteria and same treatment regimen), still evaluable for Phase II and without major deviation will be included in the PP population. The patients will be analyzed according to the treatment planned and this dataset will be the primary dataset for efficacy evaluation.

Intent to treat population

In addition, there will be intent to treat population, i.e. on all patients treated with at least one administration of either drugs, irrespective of the time of stopping the treatment. The patients will be included according to the treatment planned and this dataset will be used for efficacy evaluation.

A patient evaluable for Phase I assessments is an eligible patient, who completed the DLT period up to D29, including all three intratumoral injections of Pexa-vec and two infusions of nivolumab. A patient evaluable for Phase IIa assessments is an eligible patient having received at least 2 administrations of Pexa-Vec and 2 administrations of nivolumab and undertaken at least one post-baseline radiological assessment or exhibited any evidence of disease progression other than radiological. Per protocol analysis for the Phase I section should include at least 6 evaluable patients treated with the same dose level; per protocol analysis for the Phase IIa section should include at least 30 evaluable patients that may include comparable Phase I patients (population, regimen), who are evaluable for Phase IIa analysis.

12.7 Interim analysis

At interim analysis, enough patients will be treated to obtain a total of 15 evaluable patients, including comparable (population, treatment regimen) patients of the Phase I part still evaluable for Phase II.

At interim analysis, if there are 3 or fewer responses in these 15 patients (20% of responders or less), the study could be stopped for futility. If there are 6 or more responses in these 15 patients

(40% of responders or more), the null hypothesis will be rejected and the study could be stopped. Otherwise 15 more additional evaluable patients will be accrued for a total of 30.

12.8 Final analysis

At final analysis, enough patients will be treated to obtain a total of 30 evaluable patients, including comparable (population, treatment regimen) patients of the Phase I part still evaluable for Phase II.

At the final analysis, the null hypothesis will be rejected if 8 or more responses are observed in the 30 evaluable patients (26.7% of responders or more) with a power of 80% and a type I error of 5%.

It should nevertheless be reminded that given the mechanism of action of the drugs involved and the effects of immunotherapy on tumor behavior, ORR may not be the best measure of anti-tumor activity. For this reason, consideration will be given to DCR, TTP and survival parameters prior to deciding that the combination does not warrant further exploration.

13 CHANGES IN THE CONDUCT OF THE STUDY

13.1 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/Institutional Review Board (IEC(s)/ IRB(s)) and any other committees by Transgene or the sub-contractor or the Coordinating / Principal Investigator according to local regulations.

Authorization / approval will be required before implementation of any change to the protocol which could significantly affect the safety of patients, the scope of the investigation, the scientific quality of the study or any other aspect of the study. Other changes will be provided when required by local laws to IEC(s)/IRB(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 without any delay to Regulatory Authorities IEC(s)/IRB(s) and any other committees as locally required for authorisation / approval.

13.2 Premature study termination

Both the Investigator and Transgene reserve the right to terminate the study at any time. Should this become necessary, the procedures will be agreed upon after consultation between the two parties. 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 / IRB and any other committees of the premature study termination according to local regulations.

Should the study be prematurely stopped or put "on-hold" upon Health Authorities' decision, Transgene will inform immediately the Investigators in written including measures to be implemented.

14 ETHICAL CONSIDERATIONS

14.1 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/IRB complying with the requirements of relevant local law.

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

In addition, IEC/IRB written approval must be obtained by Transgene / the Investigator for protocol amendment as described in §11.1.

14.2 Informed consent

The Investigator 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.

The "patient information sheet" will explain that the data collected for this study will be stored in a computer database, with confidentiality maintained in accordance with national data legislation. All data computer processed will be identified by patient initials and number only.

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.

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

A copy of each signed informed consent form must be given to the patient. The originals are filed at the study site in the Investigator Site File.

14.3 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 consisting of a x-digit number.

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.

For US only:
Confidentiality of patients' medical records will be maintained in accordance with the HIPAA regulations. As a part of the regulatory approval process at the site, the study coordinator will consult with the local hospital administration regarding the language that the site should use.

14.4 Independent Safety Committee (ISC)

An Independent Safety Committee (ISC) is organized in the setting of this phase I/IIa study:

- Role: to control and to preserve patient safety. Its systematic role will be to analyze after each completed Phase I cohorts the safety events collected in patients exposed to the same dose level of the combination. It will then recommend either dose, or any modification thereof for consecutive patients, planned (dose de-escalation level –1), or unplanned, the definition of the recommended Phase II dose (RP2D), the continuation of the trial in its Phase IIa part at a specified treatment regimen, or study termination, should it estimate that observed safety events are incompatible with continued exposure of patients to the combination. No new patient cohort could be started without advice of the ISC. In addition, should unexpected safety events occur, the ISC will be consulted for their interpretation and any consecutive advice concerning the affected patient and the study.

- Membership: considering the expected safety events from the compounds used in this trial, the ISC will comprise at least three clinicians with respective expertise in hepatology, immunology and virology, independent from the study investigators and Transgene.

- Meetings: the ISC will meet prior to study initiation to refine its organization and to designate its Chairman, and consecutively at least twice a year, regardless of study events. Meetings will be organized after study events: within days after the completion of the DLT period of the first patient to analyze the observed AE profile, within 2 weeks of Phase I study cohort(s) completion and within days after the occurrence of an IMP-related severe or serious adverse event that may require a decision on further study conduct prior to any further patient enrolment.

- Reporting: recommendations issued by the ISC will appear in a report signed by the ISC Chairman and forwarded to the Sponsor.

15 REGULATORY CONSIDERATIONS

15.1 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 (GCP) guidelines, and
- The local regulatory requirements.

For US only:
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.

15.2 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.

15.3 Investigators' obligations

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

The Investigator also provides to the site staff appropriate training. The staff training will be documented in the Investigator Site File.

The Investigator ensures the quality of the study through strict observance of the protocol, Good Clinical Practice and local regulations. Investigator must ensure that the study has been authorized / approved by all Regulatory Authorities, IEC/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.

15.4 Insurance

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

16 QUALITY CONTROL AND QUALITY ASSURANCE

16.1 Periodic monitoring

The monitor will contact and visit the Investigator periodically to evaluate study progress and protocol compliance. For this study, the average frequency of the monitoring visits is intended to be approximately every 6 to 8 weeks with the first visit occurring without any delay after the first patient inclusion. Intervals may be adjusted according to patient accruals, protocol changes or site performance.

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

16.2 Audit and inspection

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. 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.

17 DATA HANDLING AND RECORD KEEPING

17.1 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: patient name, date of birth, sex, medical history, reference to the study, visit dates, IMP administration, concomitant medications, evaluation criteria, nature of adverse events with date of start and related treatment.

Data for which the eCRF is considered as source document (i.e. no prior written or electronic record of data has been produced) are the following: none.

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

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

17.2 Electronic Case report forms

Electronic Data Capture (EDC) will be used for this study. For each patient included (screen failure and enrolled), data will be entered in an eCRF that must be completed in English, by the Investigator or designee and signed by the Investigator.

The eCRF should always reflect the latest observations on the patients participating in the study. Therefore, the eCRF are to be completed without any delay after the patient's visit.

Data reported in the eCRF will be verified against source documents by the Monitor. The extent of source data verification performed by the Monitor is 100% for all items.

All entries, corrections, and alterations are to be made by the Investigator or his/her delegate. Role and rights of the site personnel responsible for entereing data in eCRF will be determined in advance and documented in the "Delegation Form". The monitor(s) cannot enter data in the eCRF.

Once clinical data of the eCRF have been saved on EDC system, corrections to the data fields will be audit trailed, meaning that the reason for change with the name of the person who performed the change, together with the date and time, will be recorded. If additional

corrections and/or confirmations are needed, the Monitor(s) and/or Data Manager(s) will raise a query in the EDC system. The appropriate investigational site staff will answer queries and this will be audit-trailed by the EDC application, meaning that the name of the person who answered and the date and time stamp are captured.

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

18 CLINICAL STUDY REPORT AND PUBLICATION

18.1 Clinical study report

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

18.2 Confidentiality of study data

Any confidential information relating to the IMP or the study, including any data and results from the study is the property of Transgene. Documents are supplied to the Investigators under conditions of strict confidentiality. Neither the Investigator nor any person working on his/her behalf may disclosure any of the information therein without having obtained prior written authorization from Transgene.

18.3 Publication policy

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

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

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

19 ARCHIVING

19.1 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.

19.2 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.

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21 APPENDICES

Appendix 1: Study flow-chart
Appendix 2: Performance status criteria (ECOG)
Appendix 3: Guidance to the Investigator in case of immune-related AEs
Appendix 4: Procédure SPILF – COREB - Vaccine
Appendix 5: Country specific instructions for VIG medication ordering and shipment

APPENDIX 1

FLOW-CHART

Schedule of Activities	**Screening**	**Baseline**	**Pexa-Vec IT 1**	**Pexa-Vec IT 2 Nivo IV 1**	**Pexa-Vec IT 3 Nivo IV 2**	**Radio-graphic Status Visit 1**	**Subsequent Nivolumab Cycles**	**Radio-graphic Status Visits**	**Pexa-Vec Boost Visit**	**End of treatment Visit**	**PFS follow-up Visit**	**28-day safety follow-up End of study Visit[m]**	**OS follow up**	**Long-term follow up (up to 5 years)**
Day/Week (Window)	**Days -28 to -2[a]**	**Days -4 to -1**	**Day 1**	**Day 15 (± 1 D)**	**Day 29 (± 1 D)**	**W6 (± 2 D)**	**q2 weeks (± 4 Days)**	**q6 weeks (± 4 D)**	**≥ W12**	**After treatment discont. with or w/o PD**	**q6 weeks until PD**	**≥28 days after last IMP intake and PD**	**q8 weeks (± 7 days)**	**Yearly after last study visit**
Signature of ICF	X													
Medical, surgical and cancer histories and demographic information	X													
Medical history update		X	X											X
Prior and Concomitant medications	X	X	X	X	X	X	X	X	X	X		X		
Review of inclusion and exclusion criteria	X	X[b]												
Complete physical examination, including weight	X	X	X	X[n]	X[n]	X	X	X	X	X	X	X		X
Height	X													
Vital signs[c]	X	X	X	X[n]	X[n]	X	X	X	X	X	X	X		
ECOG performance status	X	X	X	X	X	X	X	X	X	X	X	X		
Hematology	X	X		X	X	X		X	X	X		X		
Serum chemistry[d]	X	X		X	X	X		X	X	X		X		
Coagulation (aPTT, INR)	X	X		X	X	X		X	X	X		X		
C-reactive protein	X	X		X	X	X		X	X	X		X		
Thyroid blood tests		X				X		X		X		X		
HIV/HBV/HCV	X													

Schedule of Activities	**Screening**	**Baseline**	**Pexa-Vec IT 1**	**Pexa-Vec IT 2 Nivo IV 1**	**Pexa-Vec IT 3 Nivo IV 2**	**Radio-graphic Status Visit 1**	**Subsequent Nivolumab Cycles**	**Radio-graphic Status Visits**	**Pexa-Vec Boost Visit**	**End of treatment Visit**	**PFS follow-up Visit**	**28-day safety follow-up End of study Visit[m]**	**OS follow up**	**Long-term follow up (up to 5 years)**
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Urinalysis[e]	X									X				
AFP	X									X				
Anti-nuclear and anti-TPO antibodies		X								X				
HLA typing		X												
HBV and HCV viral load		X				X								
Anti-Vaccinia and Pexa-Vec expressed transgenes Antibodies		X				X								
Serum pregnancy test[f]	X													
Urine pregnancy test[f]		X		X	X	X		X	X			X		
Archival histological HCC diagnosis/biopsy	X													
Child-Pugh scoring	X													
Adverse events	X		X	X	X	X	X	X	X	X				
12-lead electrocardiogram		X	(D9) (± 1 D)	(D23) (± 1 D)	D29 & D37 (± 1 D)		X[o]					X		
12-lead electrocardiogram if troponin increased			(D4) (± 1 D)	(D18) (± 1 D)	(D32) (± 1 D)									
Cardiac echography with measurement of left ventricular ejection fraction (phase I only)		X			X		X[o]					X		
Cardiac echography with measurement of left ventricular ejection		X												

Schedule of Activities	**Screening**	**Baseline**	**Pexa-Vec IT 1**	**Pexa-Vec IT 2 Nivo IV 1**	**Pexa-Vec IT 3 Nivo IV 2**	**Radio-graphic Status Visit 1**	**Subsequent Nivolumab Cycles**	**Radio-graphic Status Visits**	**Pexa-Vec Boost Visit**	**End of treatment Visit**	**PFS follow-up Visit**	**28-day safety follow-up End of study Visit[m]**	**OS follow up**	**Long-term follow up (up to 5 years)**
Day/Week (Window)	**Days -28 to -2[a]**	**Days -4 to -1**	**Day 1**	**Day 15 (± 1 D)**	**Day 29 (± 1 D)**	**W6 (± 2 D)**	**q2 weeks (± 4 Days)**	**q6 weeks (± 4 D)**	**≥ W12**	**After treatment discont. with or w/o PD**	**q6 weeks until PD**	**≥28 days after last IMP intake and PD**	**q8 weeks (± 7 days)**	**Yearly after last study visit**
fraction (phase IIa) + if needed														
Troponin T or I level		X	D4 & D9 (± 1 D)	D18 & D23 (± 1 D)	D29, D32 & D37 (± 1 D)		X[o]					X		
[redacted]														
Tumor biopsy[j]	X					X								
Patient contact log update						X		X		X				
Survival													X	
Treatment & Assessments														
Pexa-Vec IT injection			X	X	X				X[k]					
Nivolumab infusion				X	X	X	X							
Tumor assessment: CT or MRI[l]	X					X		X			X			

[a] Screening procedures should be completed in less than 28 days before Day 1, date of first Pexa-vec injection. If Day 1 does not occur within 28 days of the first screening procedure, the patient must be screen failed.

[b] Final eligibility assessment (clinical, laboratory, imaging); an ultrasound scan may be optionally performed to assess suitability of IT injection within selected liver lesions and to select lesions for injection; or to rule out pregnancy for patients with a positive hCG laboratory test (>10 mIU/mL).

[c] Vital signs include heart rate, respiratory rate, blood pressures, and temperature. For Pexa-Vec injections, vital signs will be collected prior to injection, then 15 ± 5 minutes after injection and then every hour [± 15] minutes after injection completion for at least 8 hours, after which monitoring will be performed every 6 hours up to 24 hours or patient's release from hospital. For the first infusion of nivolumab, vital signs will be collected within 60 minutes prior to the infusion, and then every 15 [± 5] minutes) and 30 [± 10] after the infusion until clinically appropriate. For subsequent nivolumab infusions, vital signs will be collected within 60 minutes prior to the infusion and should be collected during or after the infusion if clinically indicated or if symptoms occurred in the prior infusion.

[d] Serum chemistry includes BUN, creatinine, creatinine clearance (Cockcroft-Gault formula), sodium, potassium, magnesium, chloride, bicarbonate, calcium, phosphorus, glucose, total bilirubin, ALT, AST, alkaline phosphatase, LDH, total protein, and albumin.

[e] Urinalysis: Blood, bilirubin, glucose, ketones, nitrite, pH, protein, specific gravity, urobilinogen, and leukocyte esterase; microscopic if leukocyte esterase is abnormal: bacteria, casts, crystals, epithelial cells, mucous, RBC and WBC counts

[f] If positive pregnancy test for women of child-bearing potential (WOCBP) an ultrasound will be performed to confirm pregnancy.

[g] [redacted]

[h] [redacted]

[i] [redacted]

[j] Baseline biopsy should be performed if no archival tumor sample is available to establish HCC diagnosis; optional on-trial biopsy scheduled at the discretion of the investigator for translational research purposes can be performed up to Week 8.

[k] Additional Pexa-Vec boosts may be performed in patients based on a case by case discussion between the investigator and Transgene, on the grounds of individual patient benefit. In any case, Pexa-Vec boosts will be performed no sooner than Week 12 and will be combined with a nivolumab infusion.

[l] Beyond 12 months of treatment, the evaluations will be performed every 12 weeks until documented progression or discontinuation of treatment beyond progression. If study treatments are stopped before documented radiological progression, PFS visits will be performed every 6 weeks to continue radiological assessment until documented progression.

[m] The 28-day safety follow-up visit will be organized at least 28 days after the last treatment intake. In case of prior disease progression, this visit will be merged with the end of study visit. In case of treatment discontinuation without disease progression, the 28-day safety follow-up visit will be distinct from the end of study visit that will only occur after disease progression. In this case, patients will undergo in the meantime PFS follow-up visits.

[n] In case the administrations are distributed over 2 consecutive days, patients will undergo another complete physical examination and recording of vital signs prior to Pexa-Vec administration on the second treatment day.

[o] Every 4 weeks starting at W8

APPENDIX 2

PERFORMANCE STATUS (ECOG) SCALE

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

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

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

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

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

APPENDIX 3

GUIDANCE TO THE INVESTIGATOR IN CASE OF IMMUNE-RELATED AEs

Gastrointestinal Toxicity

Immune-mediated colitis has been associated with the administration of nivolumab. Diarrhea or colitis was reported in 21% of patients in two trials of nivolumab. Immune-mediated colitis occurred in 2.2% of patients in one trial- of these one patient had Grade 2 colitis, and five had Grade 3 colitis. In the other trial, Grade 3 immune-mediated colitis occurred in 0.9% of patients.

Patients should be advised to inform the investigator if any diarrhea occurs, even if it is mild. Range for time to onset of symptoms of colitis has been 1-6 months.

If the event is of significant duration or magnitude or is associated with signs of systemic inflammation or acute phase reactants (e.g. increased CRP or platelet count or bandemia), it is recommended that sigmoidoscopy (or colonoscopy, if appropriate) with colonic biopsy with three to five specimens for standard paraffin block be performed. If possible, one or two biopsy specimens should be snap frozen and stored.

Treatment may be restarted following the resolution of colitis. In addition, if the patient is being managed with corticosteroids, treatment should not be restarted until the steroids have been tapered down to a prednisone dose $\leq$ 10 mg/day. Patients who resume treatment should be monitored closely for signs of renewed diarrhea.

Table on next page provides a summary of dose modification guidelines for gastrointestinal toxicities.

Dosing Guidelines for Gastrointestinal Toxicity

GI Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue I-O therapy. Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.

Grade of Diarrhea/ Colitis (NCI CTCAE v4)	Management	Follow-up
Grade 1 Diarrhea: < 4 stools/day over baseline; Colitis: asymptomatic	• Continue I-O therapy per protocol • Symptomatic treatment	• Close monitoring for worsening symptoms. • Educate patient to report worsening immediately If worsens: • Treat as Grade (G) 2 or 3/4
Grade 2 Diarrhea: 4-6 stools per day over baseline; IV fluids indicated <24 hours (hrs); not interfering with ADL Colitis: abdominal pain; blood in stool	• Delay I-O therapy per protocol • Symptomatic treatment	If improves to grade 1: • Resume I-O therapy per protocol If persists > 5-7 days or recur: • 0.5-1.0 mg/kg/day methylprednisolone or oral equivalent • When symptoms improve to grade 1, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy per protocol. If worsens or persists > 3-5 days with oral steroids: • Treat as grade 3/4
Grade 3-4 Diarrhea (G3): ≥7 stools per day over baseline; incontinence; IV fluids ≥24 hrs; interfering with activities of daily living (ADL) Colitis (G3): severe abdominal pain, medical intervention indicated, peritoneal signs G4: life-threatening, perforation	• Discontinue I-O therapy per protocol • 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections • Consider lower endoscopy	If improves: • Continue steroids until grade 1, then taper over at least 1 month If persists > 3-5 days, or recurs after improvement: • Add infliximab 5 mg/kg (if no contraindication). Note: Infliximab should not be used in cases of perforation or sepsis

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Hepatotoxicity

Immune-mediated hepatitis has occurred with the administration of nivolumab.

Patients should be monitored for abnormal liver tests prior to and periodically during treatment. While on this study, patients presenting with right upper-quadrant abdominal pain and/or unexplained nausea or vomiting should have LFTs performed immediately and LFTs should be reviewed before administration of the next dose of study drug.

If LFTs increase, neoplastic, concurrent medications, viral hepatitis, and toxic etiologies should be considered and addressed, as appropriate. Imaging of the liver, gall bladder, and biliary tree should be performed to rule out neoplastic or other causes for the increased LFTs. Anti-nuclear antibody, perinuclear anti-neutrophil cytoplasmic antibody, anti-liver-kidney microsomal antibodies, and anti-smooth muscle antibody tests should be performed in an autoimmune etiology is considered.

Patients with LFT abnormalities should be managed according to the guidelines in Table below.

Dosing Guidelines for Hepatotoxicity

Hepatic Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider imaging for obstruction.

Grade of Liver Test Elevation (NCI CTCAE v4)	Management	Follow-up
Grade 1 AST or ALT > ULN to 3.0 x ULN and/or T. bili > ULN - 1.5 x ULN	• Continue I-O therapy per protocol	• Continue LFT monitoring per protocol If worsens: • Treat as Grade 2 or 3-4
Grade 2 AST or ALT > 3.0 to ≤ 5 x ULN and/or T. bili > 1.5 to ≤ 3 x ULN	• Delay I-O therapy per protocol • Increase frequency of monitoring to every 3 days	If returns to baseline: •Resume routine monitoring, resume I-O therapy per protocol If elevations persist > 5-7 days or worsen : • 0.5-1 mg/kg/day methylprednisolone or oral equivalent and when LFT returns to grade 1 or baseline, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy per protocol
Grade 3-4 AST or ALT > 5 x ULN and /or T.bili >3 x ULN	• Discontinue I-O therapy* • Increase frequency of monitoring to every 1-2 days • 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent** • Add prophylactic antibiotics for opportunistic infections • Consult gastroenterologist	If returns to grade 2: • Taper steroids over at least 1 month If does not improve in >3-5 days, worsens or rebounds: • Add mycophenolate mofetil 1 g BID • If no response within an additional 3-5 days, consider other immunosuppressants per local guidelines

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.
*I-O therapy may be delayed rather than discontinued if AST/ALT ≤ 8 x ULN and T.bili ≤ 5 x ULN.
**The recommended starting dose for grade 4 hepatitis is 2 mg/kg/day methylprednisolone IV.

Renal Toxicity

Immune-mediated nephritis or renal dysfunction occurred with nivolumab treatment. Patients should be monitored for elevated serum creatinine prior to and periodically during treatment and clinically monitored for symptoms of decreased volume of urination, hematuria, peripheral edema, loss of appetite.

In one trial, there was increased incidence of elevated creatinine in the nivolumab-treated group as compared to chemotherapy (13% v 9%). Grade 2 or 3 immune-mediated nephritis or renal dysfunction occurred in 0.7% (2/268) of patients. In another trial, the incidence of elevated creatinine was 22%, with Grade 2 immune-mediated renal dysfunction occurring in 0.9% (1/117) patients.

Renal toxicity should be managed according to the guidelines in Table below.

Dosing Guidelines for Renal Toxicity

Renal Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy

Grade of Creatinine Elevation (NCI CTCAE v4)	Management	Follow-up
Grade 1 Creatinine > ULN and > than baseline but ≤ 1.5x baseline	• Continue I-O therapy per protocol • Monitor creatinine weekly	If returns to baseline: -Resume routine creatinine monitoring per protocol If worsens: -Treat as Grade 2 or 3/4
Grade 2-3 Creatinine > 1.5x baseline to ≤ 6x ULN	• Delay I-O therapy per protocol • Monitor creatinine every 2-3 days • 0.5 to 1.0 mg/kg/day methylprednisolone IV or oral equivalent • Consider renal biopsy	If returns to Grade 1: -Taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy and routine creatinine monitoring per protocol If elevations persist > 7 days or worsen: -Treat as Grade 4
Grade 4 Creatinine > 6x ULN	• Discontinue I-O therapy per protocol • Monitor creatinine daily • 1.0-2.0 mg/kg/day methylprednisolone IV or IV equivalent • Consult nephrologist • Consider renal biopsy	If returns to Grade 1: Taper steroids over at least 1 month and add prophylactic antibiotics for opportunistic infections

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

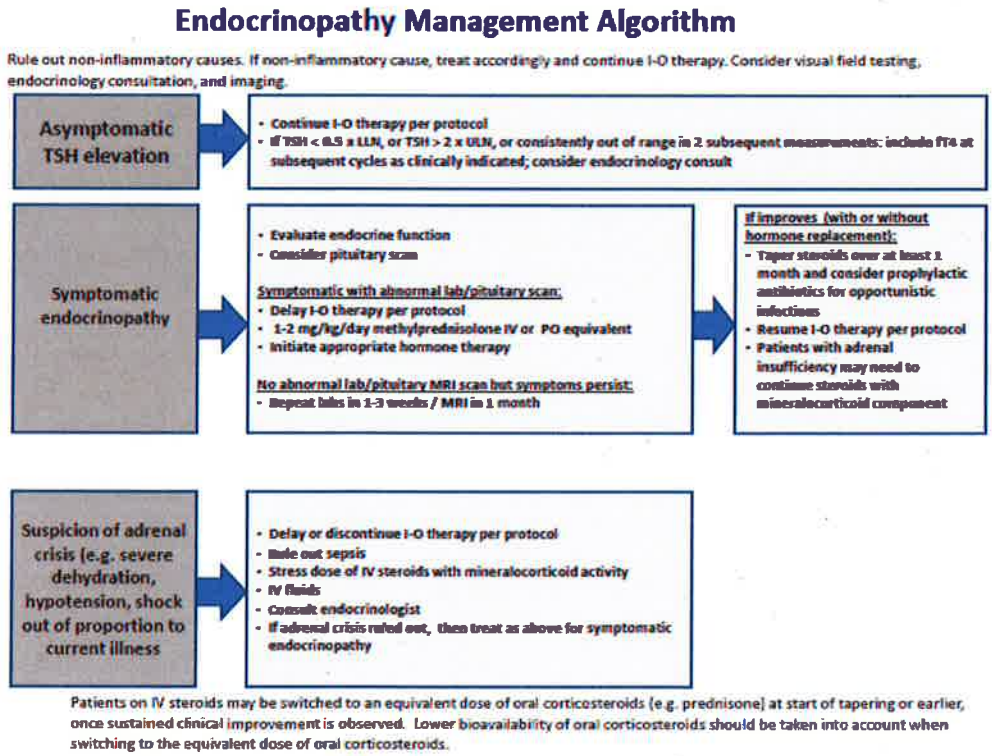
Endocrine Toxicity

Immune-mediated hypothyroidism and hyperthyroidism has been associated with the administration of nivolumab. In one trial, Grade 1 or 2 hypothyroidism occurred in 8% (21/268) of patients receiving nivolumab. Grade 1 or 2 hyperthyroidism occurred in 3% (8/268) of patients on nivolumab on that trial, and in 1% (1/102) patients receiving chemotherapy. In another trial, hypothyroidism occurred in 4.3% (5/117) of patients. Hyperthyroidism occurred in 1.7% (2/117) of patients. One patient experienced Grade 2 hyperthyroidism.

Patients with unexplained symptoms such as fatigue, headaches, myalgias, impotence, mental status changes, or constipation should be investigated for the presence of thyroid, pituitary, or adrenal endocrinopathies, as well as for hyponatremia or hyperkalemia. An endocrinologist should be consulted if an endocrinopathy is suspected. TSH and free T4 levels should be obtained to determine if thyroid abnormalities are present. TSH, prolactin, and a morning cortisol level will help to differentiate primary adrenal insufficiency from primary pituitary insufficiency.

Hypothyroidism should be managed according to the guidelines in Table below.

Dosing Guidelines for Endocrine Toxicity

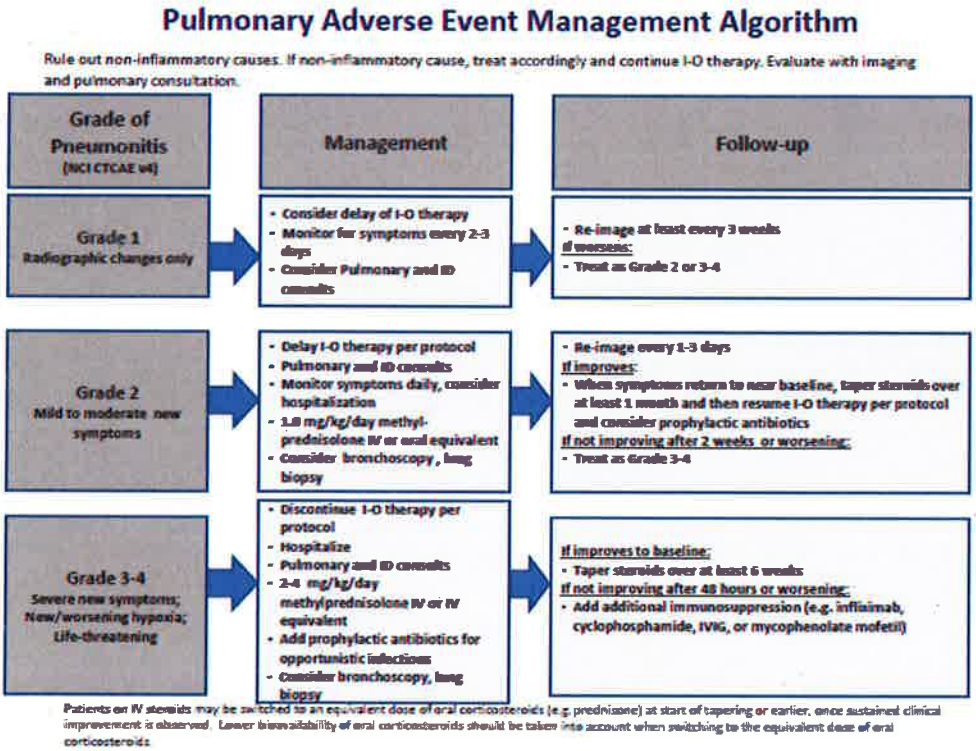


Pulmonary Toxicity

Severe pneumonitis or interstitial lung disease, including fatal cases, have occurred with nivolumab treatment. As such, patients must be monitored for signs and symptoms of pneumonitis. Across clinical trial experience in 691 patients with solid tumors, fatal immune mediated pneumonitis occurred in 0.7% (5/691) of patients receiving nivolumab. In one trial 2.2% (6/268) of patients receiving nivolumab developed immune-mediated pneumonitis, one with Grade 3 and vie with Grade 2 cases. In another trial, immune-mediated pneumonitis occurred in 6% (7/117) of patients receiving nivolumab including five Grade 3 and two Grade 2 cases.

Pulmonary toxicity should be managed according to the guidelines in Table below.

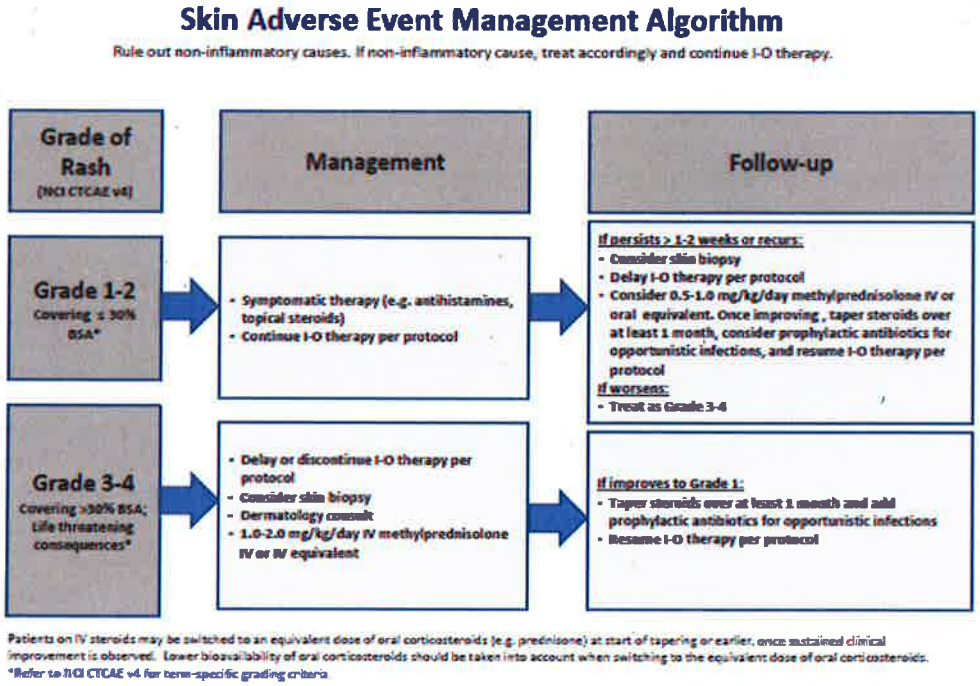
Dosing Guidelines for Pulmonary Toxicity



Pericardial and Pleural Effusions

Pericardial and pleural involvement with associated effusions is common in patients with NSCLC and have the theoretical potential to be exacerbated by inflammation associated with antitumor immunity following PD-L1 blockade. Patients presenting with dyspnea, chest pain, or unexplained tachycardia should be evaluated for the presence of a pericardial effusion. Patients with preexisting pericardial effusion should be followed closely for pericardial fluid volume measurements and impact on cardiac function. When intervention is required for pericardial or pleural effusions, appropriate workup includes cytology, LDH, glucose, cholesterol, protein concentrations (with pleural effusions), and cell count. For patients with a pericardial effusion causing end-diastolic right ventricular collapse, treatment may be restarted following the placement of a pericardial window, demonstrations of hemodynamic stability, and resolution of right ventricular dysfunction.

Skin



Nervous system

Neurological Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.

Grade of Neurological Toxicity (NCI CTCAE v4)	Management	Follow-up
Grade 1 Asymptomatic or mild symptoms; intervention not indicated	• Continue I-O therapy per protocol	Continue to monitor the patient. If worsens: - Treat as Grade 2 or 3-4
Grade 2 Moderate symptoms; Limiting instrumental ADL	• Delay I-O therapy per protocol • Treat symptoms per local guidelines • Consider 0.5 to 1.0 mg/kg/day methylprednisolone IV or PO equivalent	If improves to baseline: •Resume I-O therapy per protocol when improved to baseline If worsens: - Treat as Grade 3-4
Grade 3-4 Severe symptoms; Limiting self-care ADL; Life-threatening	• Discontinue I-O therapy per protocol • Obtain neurology consult • Treat symptoms per local guidelines • 1.0-2.0 mg/kg/day IV methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections	If improves to Grade 2: - Taper steroids over at least 1 month If worsens or atypical presentation: - Consider IVIG or other immunosuppressive therapies per local guidelines

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

APPENDIX 4
Procédure SPILF – COREB – Vaccine

For French sites: The infectious disease unit of the hospital/infectious reference site must be involved in case of suspicion of a VV-related serious complication. [redacted]

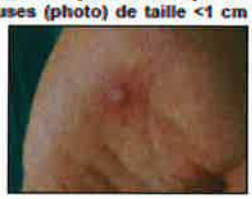
[redacted]

Procédure SPILF - COREB - Vaccine

Comment prendre en charge un patient suspect d'infection par le virus de la vaccine ?

En contexte d'utilisation de thérapies oncolytiques ayant pour support un virus de la vaccine génétiquement modifié, cette procédure résumée est destinée aux soignants de 1ère ligne prenant en charge un patient suspect de vaccine. A ce jour sur 300 patients traités, 20% ont présenté une éruption cutanée pustuleuse limitée en taille (< 1 cm) ou muqueuse dans les 7 jours après injection, résolutive sans complications en 3 semaines.
Compte-tenu des complications possibles de ces traitements, de la potentielle transmission par contact, il est essentiel que les cancérologues référents de ces patients qui dépistent un patient suspect de vaccine 1) appellent rapidement l'expertise infectiologique, et 2) qu'une protection adaptée soit proposée au patient et aux soignants.

1- DEPISTER - Patient suspect = Tableau clinique, 7 à 14 jours après exposition ET Exposition compatibles.
Tableau clinique le plus évocateur : éruption de lésions cutanées pustuleuses (photo) de taille <1 cm en nombre limité < à 5, voire érosions muqueuses buccales, ayant évolué d'un aspect de papules érythémateuses, à celui de vésicules à liquide trouble, puis pustules, **puis croutes**



- Fièvre possible - Aspects atypiques à ne pas exclure sans analyse experte, si exposition caractérisée.

Exposition : injection intra-lésionnelle ou parentérale de virus de la vaccine modifié à visée oncolytique (Pexa vec ou TG 6002) ; ou contact proche avec un patient cas possible ou documenté, ou accident d'exposition au produit oncolytique.

☞ **Analyse clinique experte pour estimer la probabilité diagnostique** après exposition
- Patient suspect : manifestations non évocatrices, diagnostic alternatif possible à documenter, PCR en attente
- Cas possible : manifestations évocatrices, PCR en attente
- Cas confirmé : manifestations compatibles, PCR positive dans le sang ou prélèvement local
- Cas exclu : manifestations non évocatrices et PCR négative dans le sang et prélèvement local.

☞ **Diagnostic alternatif** : évoquer et documenter (PCR à partir des lésions) une autre infection virale à Herpes virus (HSV, varicelle–zona) ou autres (pox) virus, pouvant prendre des aspects atypiques chez ces patients ayant reçu des chimiothérapies possiblement immunosuppressives. Dermite ou eczéma de contact, érythème polymorphe, toxidermies bulleuses, autres dermatoses vésiculo-pustuleuses.

2- PROTEGER, dès la suspicion, et jusqu'à infirmation du diagnostic.
> Patient : isolement en chambre seule, SHA, port de masque chirurgical (si lésions buccales), lésions cutanées couvertes (pansement non compressif) jusqu'à la chute des croutes.
> Soignant : **Application stricte des précautions standard et complémentaires de type contact avec surblouse** usage unique, port de gants (masque chirurgical si lésion buccale chez le patient).
- **Gestion des déchets de soins** : prévoir une filière spécifique risque infectieux avec incinération (DASRI).
- **Identification (précoce) des personnes contact.** Prévention AES : soignants informés.

3- PRENDRE EN CHARGE
- **Recherche de signes et facteurs de gravité :**

Signes de gravité spécifiques (extension de l'éruption, sepsis, manifestations neurologiques ont été décrits après vaccination antivariolique, non décrits à ce jour dans le contexte de thérapies oncolytiques. Prise en compte d'éventuelles co-morbidités (eczéma et autre dermatose inflammatoire chronique).
- **Traitement au plus tôt,** au minimum symptomatique. Contre-indication : aux AINS, et aux anticoagulants.

***Indications* traitements spécifiques** : dépendent du type, nombre, extension des lésions, signes systémiques, et évolutivité des manifestations. ***Avec expertise clinique infectiologique, et RCP, associant les industriels responsables de leur délivrance* autant que de besoin.**
Modalités traitements spécifiques : durée à titre indicatif, 14j, adaptée selon évolution
- Immunoglobulines spécifiques anti-virus vaccine : 6000 à 9000 UI/kg en une perfusion lente (2 ml/minute) sur une voie d'abord spécifique ; à renouveler selon évolution clinique.
- Brincidofovir: 4 mg/kg chez les patients de moins de 50 kg, et 200 mg si plus de 50 kg, PO, une fois par semaine Surveillance de la tolérance gastro-intestinale (diarrhées graves décrites) et rénale.
- **Alerte et Orientation du patient : Dès la suspicion de vaccine, appel de l'infectiologue référent pré-identifié** (cf infra) pour expertise en vue de prise en charge ; et, si cas confirmé, pharmacovigilance, ANSM
- si patient cas possible ou confirmé : transfert en service MIT, structure de traitement dédié
- si patient suspect : discussion /expertise clinique et prise en compte des diagnostics alternatifs.
- **Confirmation virologique dès que possible,** par le laboratoire référent. Mesures d'hygiène et biosécurité (guide OMS) pour prélèvements, leur transport et manipulations à visée diagnostic, y compris alternatif. PCR **vaccine sur prélèvement cutanéo-muqueux et sanguin.**

☞ Infectiologue référent / ESR à joindre : Nom :.....Téléphone :.....

Fiche COREB PeC pt suspect vaccine – / document de travail, vf corrigée au 29 août 2017 actualisations prévues

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APPENDIX 5

Instructions for VIG medication ordering and shipment

Vaccinia Immune Globulin (VIG) will be provided to the Investigator and Pharmacist through the process described hereafter.

The site should contact immediately:

Emergency 24/7 telephone number (any country):

[redacted]

and will complete and send a "Notification of VIG Medication Request Form" [redacted]

VIG will be shipped as soon as possible from the central depot to the patient's treating facility.

Upon reception of VIG, follow the instructions in VIG Summary of Product Characteristics.

For France, the instructions of the SPILF-COREB Vaccine procedure for the dosage treatment (see APPENDIX 4) should be followed.