

A Phase 1b/2a Dose-escalation and Safety/Efficacy Evaluation Study of Pexa-Vec (Thymidine Kinase-Deactivated Vaccinia Virus plus GM-CSF) in Combination with Cemiplimab (REGN2810; anti-PD-1) in Patients with Metastatic or Unresectable Renal Cell Carcinoma (RCC)

STUDY PROTOCOL NUMBER:	JX594-REN026
INVESTIGATIONAL PRODUCT:	Pexastimogene Devacirepvec (Pexa-Vec)
PHASE:	1b/2a
IND NUMBER:	17713
SPONSOR:	SillaJen Inc. 475 Sansome St, Suite 740 San Francisco, CA 94111 - USA
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PROTOCOL DATE:	11 October 2017
AMENDMENT 1:	16 November 2017
AMENDMENT 2:	13 December 2017
AMENDMENT 3:	07 February 2018
AMENDMENT 4 – Ex-US:	08 May 2018
AMENDMENT 5 – Ex-US:	29 October 2018
AMENDMENT 6 – Ex-US:	25 September 2019
AMENDMENT 7 – EX-US:	08 January 2020
AMENDMENT 8 – Ex-US:	12 August 2020
AMENDMENT 9 – Ex-US:	24 November 2020

Confidentiality Statement

This document contains confidential information. It is intended solely for the use of the principal investigator, co-investigators, staff, appropriate institutional review boards or ethical committees, and other required regulatory bodies.

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SPONSOR SIGNATURE PAGE

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KHa

Kyoungsoo Ha, MD PhD
Medical Monitor

26 NOV 2020

Date

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INVESTIGATOR SIGNATURE PAGE

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I have read and understand the protocol and I agree that it contains all the ethical, legal and scientific information necessary to conduct this study. I will conduct this study as outlined herein and will make a reasonable effort to complete the study within the time designated. I will work according to the principles of Good Clinical Practice (GCP) as described (for the US) in the Code of Federal Regulations (CFR) Section 21, Parts 11, 50, 54, 56, and 312, The Declaration of Helsinki (2008), and GCP as described in the International Conference on Harmonization (ICH) document "Guidance for Industry – E6 Good Clinical Practice: Consolidated Guidance". Further, I will conduct the study in keeping with local and regulatory requirements.

I will provide copies of the protocol and access to all relevant information to study personnel under my supervision. I will discuss this material with them to ensure that they are fully informed about the drug and the study.

Principal Investigator Signature	Date
Principal Investigator Name (Printed)	

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ACE	Angiotensin Converting Enzyme
ADR	Adverse Drug Reaction
AE(s)	Adverse Event(s)
AESI	Adverse Events of Special Interest
AIDS	Acquired Immune Deficiency Syndrome
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
anti-PDL1	Anti-Programmed Death Cell Receptor Ligand
AST	Aspartate Transaminase
BSC	Best Supportive Care
BSL-2	Biosafety Level 2
BUN	Blood Urea Nitrogen
CAFs	Cancer-Associated Fibroblasts
CBC	Complete Blood Count
CEV	Cell-Associated Enveloped Virion
CI(s)	Confident Interval(s)
CPI	Checkpoint Inhibitors
CR	Complete Response
CRC	Colorectal Carcinoma
CRFs	Case Report Forms
CT	Computerized Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DLT(s)	Dose Limiting Toxicity(ies)
EC	Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EEV	Extracellular Enveloped Virion
EGFR	Epidermal Growth Factor Receptor
EOI	End of Infusion
FDA	Food and Drug Administration (United States)
FDG-PET	Fluorodeoxyglucose Positron Emission Tomography
GCP	Good Clinical Practice

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Abbreviation	Definition
GM-CSF	Granulocyte-Macrophage Colony Stimulating Factor
HCC	Hepatocellular Carcinoma
hGM-CSF	Human GM-CSF
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
IB	Investigators' Brochure
IBC	Institutional Biosafety Committee
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Institutional Ethics Committee
INR	International Normalized Ratio
IP	Investigational Product
irAE	Immune-Related Adverse Event
IRB	Institutional Review Board
irRECIST	Immune-Related Response Evaluation Criteria in Solid Tumors
IT	Intratumoral
ITT	Intent-To-Treat
IV	Intravenous
LD	Longest Diameter
LDH	Lactate Dehydrogenase
LMWH	Low Molecular Weight Heparin
mChoi	Modified Choi
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)
NCI-CTC	National Cancer Institute – Common Toxicity Criteria
NIH	National Institutes of Health (United States)
NK	Natural Killer
ORR	Overall Response Rate
PBS	Phosphate Buffered Saline

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Abbreviation	Definition
PD	Progressive Disease
PD-1	Programmed-cell Death protein-1
PEG-IFN	Pegylated Interferon
Pexa-Vec	Pexastimogene Devacirepvec, JX-594
pfu	Plaque Forming Units
PI 3-K	Phosphatidylinositol 3-kinase
PR	Partial Response
PT/INR	Prothrombin Time/International Normalized Ratio
PTT	Partial Thromboplastin Time
Q3W	Every 3 Weeks
qPCR	Quantitative Polymerase Chain Reaction
RCC	Renal Cell Carcinoma
REB	Research Ethics Board
RECIST	Response Evaluation Criteria in Solid Tumors
SAE(s)	Serious Adverse Event(s)
SD	Stable Disease
SLD	Sum of Longest Diameters
SUSAR	Suspected Unexpected Serious Adverse Reaction
TK	Thymidine Kinase
T-Vec	Talimogene Laherparepvec
UFH	Unfractionated Heparin
ULN	Upper Limit of Normal
US	United States
VEGFR 1, 2, 3	Vascular Endothelial Growth Factor Receptor 1, 2, 3
WBC	White Blood Cell
WHO	World Health Organization
WNL	Within Normal Limits

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1 PROTOCOL SYNOPSIS

Title:	A Phase 1b/2a, Dose-escalation and Safety/Efficacy Evaluation Study of Pexa-Vec (Thymidine Kinase-Deactivated Vaccinia Virus plus GM-CSF) in Combination with Cemiplimab (REGN2810, anti-PD-1) in Patients with Metastatic or Unresectable Renal Cell Carcinoma (RCC)
Sponsor:	SillaJen, Inc.
Investigational Products:	Pexastimogene Devacirepvec (Pexa-Vec) is a replication-competent, transgene-expressing therapeutic vaccinia virus 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. granulocyte macrophage colony stimulating factor (GM-CSF) gene insertion under control of the synthetic early-late promoter 3. lac-Z gene insertion under control of the p7.5 promoter Pexa-Vec is shipped and handled as a Biosafety Level 2 (BSL-2) infectious substance. Cemiplimab has been developed by Regeneron, and is a hinge stabilized human IgG4 monoclonal antibody that binds with high affinity to programmed cell death 1 (PD-1) and blocks this pathway of inhibitory T-cell signaling. Cemiplimab has an approximate molecular weight of 143 kDa based on the primary sequence.
Phase:	1b/2a
Study Location:	South Korea, United States, and Australia
Objectives:	**Primary Objective:** • *Part 1*: Determine the maximum-tolerated dose (MTD) or maximum feasible dose (MFD) of Pexa-Vec administered by intravenous (IV) infusion in combination with IV-administered Cemiplimab • *Part 1 and 2:* Determine the safety of Pexa-Vec administered by IV infusion or intratumoral (IT) injection in combination with IV-administered Cemiplimab by assessing severity and frequency of adverse events (AEs) and laboratory toxicity using Common Terminology Criteria for Adverse Events [CTCAE] v5. • Part 2: Evaluate anti-tumor activity and efficacy of IV or IT Pexa-Vec combined with IV Cemiplimab with respect to overall response rate (ORR) per Response Evaluation Criteria in Solid Tumors (RECIST 1.1) **Secondary Objectives:** • Determine progression free survival according to RECIST 1.1 • Determine the disease control rate (complete response [CR] + partial response [PR] + stable disease [SD]) by RECIST 1.1 • Determine best radiographic response (based on RECIST 1.1) • Evaluate anti-tumor activity and efficacy of IV or IT Pexa-Vec combined with IV Cemiplimab with respect to overall response rate (ORR) per immune-related Response Evaluation Criteria in Solid Tumors (irRECIST)

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	• Determine the disease control rate (complete response [CR] + partial response [PR] + stable disease [SD]) by irRECIST • Best radiographic response (based on irRECIST) • Estimate overall survival **<u>Exploratory Objectives:</u>** • To assess in the blood, the following immune parameters at Baseline, and on study Day 1 (excluding Arm B, Cemiplimab monotherapy), Day 22 (Day 43 in Arm D), End of Treatment, and Post Progression on PD-1 monotherapy at Baseline, 2 weeks, and 4 weeks (Arm B only): o Tumor specific and Pexa-Vec specific cellular immune responses (including but not limited to assessment of B-cells, T-cells, activated T-cells, natural killer [NK] cells, regulatory T-cells, myeloid derived suppressor cells [MDSC]) o Pexa-Vec and Cemiplimab specific humoral responses o Immune-related cytokines • To assess in previously archived tumor biopsies (if available) and/or biopsied tumors at Baseline, and on study Day 8 (excluding Arm B, Cemiplimab monotherapy) and Day 57 (Arm B patients will undergo repeat biopsy at disease progression and 2 weeks after first Pexa-Vec): o Tumor microenvironment including T-cell, B-cell, NK cell, monocytes, macrophages, and other relevant immune cell subtypes of interest o Immune modulating proteins that may have predictive or prognostic value, including, but not limited to PD-L1, PD-1, and CTLA-4 o Pexa-Vec infection and transgene expression • Measure Cemiplimab and Pexa-Vec concentrations in serum and plasma, respectively
Study Design:	This is a Phase 1b/2a, open-label, dose-escalation and safety/efficacy evaluation trial of Pexa-Vec administration plus Cemiplimab in patients with metastatic renal cell carcinoma (RCC). Up to 12 patients will be enrolled in Part 1 dose escalation and up to a further 101 patients will be enrolled in Part 2. ***Part 1:*** Patients will be treated with Cemiplimab at a dose of 350 mg and Pexa-Vec at one of 2 dose levels: • Dose Level 1: 3×10^8 plaque forming units (pfu) • Dose Level 2: 1×10^9 pfu Pexa-Vec will be administered IV every 7 days beginning on study Day –7 for a total of 4 treatments (Days –7, 1, 8, and 15; –1/+7 days). Cemiplimab will be administered at a dose of 350 mg via IV infusion every 3 weeks starting on Day 1 for up to 12 months or until progressive disease (PD), unacceptable toxicity, or study discontinuation. Three patients will be treated in each of Dose Levels 1 and 2, unless a dose limiting toxicity (DLT) is observed. Patients will be observed for a DLT through study Day 29. Enrollment will proceed to the next dose cohort if 0 out of 3 patients experiences a DLT. If 1 of the 3 patients experiences a DLT, additional patients will be enrolled until a second patient experiences a DLT (which defines the MTD as the dose below this level) or until 6 patients have been treated at that dose, whichever

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	comes first. If a second DLT is not experienced within this cohort, the next Dose Level may be initiated. The MFD for this study is 1×10^9 pfu. ***Part 2:*** There will be 4 arms in Part 2 of the study. Patients naive to anti-PD-1 or anti-PD-L1 with tumors that are accessible for injection will be randomized into Arm A or Arm B at a ratio of 1:1, stratified according to number of prior systemic therapies for RCC, prior to the first study treatment. Patients naive to anti-PD-1 or anti-PD-L1 who do not have accessible tumors will be placed on to Arm C. Patients with prior treatment with anti-PD-1 or anti-PD-L1 will be placed on Arm D. ***Arm A: IT Pexa-Vec + IV Cemiplimab*** Patients will receive Pexa-Vec at the MTD/MFD defined in Part 1, administered via IT injection every 14 days, beginning on study Day –7 for a total of 3 treatments (Days –7, 8, and 22) Starting at Day 1 (one week following initial Pexa-Vec administration), patients will also receive Cemiplimab at a dose of 350 mg, administered via IV infusion every 3 weeks for 12 months, or until confirmed progressive disease (PD) or discontinuation from study. Patients may continue to receive Cemiplimab past radiographic progressive disease (PD) if, in the opinion of the Investigator, the patient is deriving clinical benefit from treatment. If further progressive disease (PD) (defined as an additional 20% increase in tumor burden from the time of initial progressive disease) is confirmed, Cemiplimab must be discontinued and other anti-cancer therapy considered, if appropriate. Treatment past progressive disease (PD) must be approved by the study sponsor. ***Arm B: IV Cemiplimab (+ IT Pexa-Vec if Progressive Disease [PD])*** Patients in Arm B will receive Cemiplimab, starting at Day 1, at a dose of 350 mg, administered via IV infusion every 3 weeks until progressive disease (PD), or removal from trial. Patients with confirmed progressive disease (PD) via irRECIST on single-agent Cemiplimab will then be eligible to receive IT Pexa-Vec at the MTD/MFD defined in Part 1, administered via IT injection every 14 days for a total of 3 doses. Cemiplimab will continue. Patients may continue to receive Cemiplimab past radiographic progressive disease (PD) if, in the opinion of the Investigator, the patient is deriving clinical benefit from treatment. If further progressive disease (PD) (defined as an additional 20% increase in tumor burden from the time of initial progressive disease [PD]) is confirmed, Cemiplimab must be discontinued and other anti-cancer therapy considered, if appropriate. Treatment past progressive disease (PD) must be approved by the study sponsor. ***Arm C and Arm D: IV Pexa-Vec + IV Cemiplimab*** Patients in Arm C and Arm D will receive Pexa-Vec at the MTD/MFD defined in Part 1, administered via IV infusion every 7 days, beginning on study Day –7 for a total of 4 treatments (Days –7, 1, 8, and 15) Patients in Arm C and Arm D will also receive Cemiplimab at a dose of 350 mg, beginning at Day 1, administered via IV infusion every 3 weeks for 12 months, or until confirmed progressive disease (PD), or discontinuation from study. Patients may continue to receive Cemiplimab past radiographic progressive disease (PD) if, in the opinion of the Investigator, the patient is deriving clinical benefit from treatment. If further progressive disease (PD) (defined as an additional 20% increase in tumor burden from the time of initial progressive disease [PD]) is confirmed, Cemiplimab must be discontinued and other anti-cancer therapy considered, if

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	appropriate. Treatment past progressive disease (PD) must be approved by the study Sponsor. ***All Arms:*** Pexa-Vec Boosters Patients on all arms of the study treated with Pexa-Vec found to have confirmed stable disease (SD) or partial response (PR) at Week 27 or later (or 26 weeks post initial Pexa-Vec treatment in Part 2 – Arm B) are eligible to receive "booster" Pexa-Vec treatments every 9 weeks assuming the patient is fit for treatment, continues to meet core eligibility criteria and the Investigator believes there is a potential for clinical benefit. Up to a maximum of 3 boosters will be given. Patients will be treated via the same modality by which they originally received Pexa-Vec, if possible. Patients who no longer have an accessible lesion, but are otherwise eligible for Pexa-Vec, may receive IV Pexa-Vec boosters. Patients will be assessed for response every 9 weeks until confirmed progressive disease (PD) (via irRECIST) or study discontinuation. Biopsies Mandatory core or excisional biopsies will be performed in patients with lesions amenable to biopsy before and after Pexa-Vec treatment. Part 1, Arm A, Arm C, and Arm D: at Baseline (Day –7 [up to 14 days prior]), an early biopsy (Day 8 [up to 4 days prior]) and a late biopsy (Day 57 [±5 days]). Biopsy immediately prior to the IT injection procedure is allowable. Patients in Part 2, Arm B will be biopsied at Baseline (Day 1 [up to 14 days prior]) and at a late time point (Day 57 [±5 days]) as well as at the time of progression on Cemiplimab (prior to initiation of Pexa-Vec) and early biopsy relative to first day of Pexa-Vec treatment (Day 1 and Day 15). Patients with a response or clinical course of interest may undergo further biopsies for research purposes. Imaging Patients will be assessed for response every 9 weeks until confirmed progressive disease (PD) (and further PD, if needed See Section 6.F.16) via irRECIST or study discontinuation. For details on irRECIST assessment, please see the Site Reader Manual.
Study Population:	**Inclusion Criteria:** 1. Histologically or cytologically confirmed metastatic or unresectable clear cell RCC 2. Naive to systemic therapy for RCC or have progressed after, or were intolerant of, prior systemic therapy. ***Part 2 Arm D ONLY***: Patients must be refractory to anti PD-1 or anti-PD-L1 (either as monotherapy or in-combination with other approved checkpoint inhibitors or targeted therapies according to their approved label) and patients must meet all of the following criteria: a. Received treatment of approved anti PD-1 or anti-PD-L1 (dosed per label of the country providing the clinical site) for at least 6 weeks. b. Progressive disease after anti PD-1 or anti-PD-L1 will be defined according to RECIST 1.1. The initial evidence of progressive disease is to be confirmed by a second assessment, no less than 4 weeks from the date of the first documented progressive disease, in the absence of rapid

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	clinical progression. (This determination is made by the Investigator; the Sponsor will collect imaging scans for retrospective analysis. Once progressive disease is confirmed, the initial date of progressive disease documentation will be considered the date of disease progression). c. Documented disease progression within 12 weeks of the last dose of anti PD-1 or anti-PD-L1. Patients who were re-treated or on maintenance with anti-PD-1 or anti-PD-L1 will be allowed to enter the study as long as there is documented progressive disease within 12 weeks of the last treatment date. 3. Have measurable disease based on RECIST 1.1/irRECIST criteria as determined by the site study team. Tumor lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions. 4. At least one lesion, ≥1 cm longest diameter, injectable under imaging-guidance (except Part 1, Arm C, and Arm D – where lesions for injection are not required) 5. Expected survival of approximately 18 weeks or longer 6. Karnofsky performance status of 70–100 7. Aged ≥20 years old (or appropriate age of consent for the region) 8. White blood cell (WBC) count ≥2,000 cells/mm^3 and ≤50,000 cells/mm^3 9. Absolute neutrophil count (ANC) ≥1,000 cells/mm^3 10. Hemoglobin ≥8 g/dL 11. Platelet count ≥75,000 platelets/mm^3 12. Partial thromboplastin time (PTT) within allowable institutional limits for biopsy or injection procedures (patients with non-accessible lesions or patients on anticoagulation therapy are exempt from this criteria) 13. International Normalized Ratio (INR) <1.5 (patients with non-accessible lesions or patients on anticoagulation therapy are exempt from this criteria) 14. Adequate liver function (albumin ≥2.8 g/dL, total; total bilirubin ≤3 mg/dL [51.3 µmol/L]) 15. Alanine aminotransferase (ALT) and aspartate transaminase (AST) ≤2.5 times upper limit of normal (ULN) (in case of liver metastasis: ALT, AST ≤5 times ULN) 16. Serum chemistries sodium, potassium, and calcium within normal limits (WNL) or Grade 1 17. Serum creatinine ≤1.5 × ULN or estimated glomerular filtration rate >50 mL/min/1.73m^2 18. For patients who are sexually active: willing to use double barrier contraception method for at least 6 weeks after each treatment of Pexa-Vec, and, for patients who are of child bearing potential, for 6 months after each Cemiplimab treatment 19. Written informed consent obtained from the patient **Exclusion Criteria:** 1. Known significant immunodeficiency due to underlying illness (e.g., human immunodeficiency virus [HIV] / acquired immune deficiency syndrome

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	[AIDS]) and/or immune-suppressive medication including high-dose corticosteroids (defined as >10 mg/day prednisone or equivalent within 4 weeks prior to the initiation of study treatment). Inhaled steroids and adrenal replacement steroid doses ≤10 mg daily prednisone or equivalent are permitted in the absence of active autoimmune disease. 2. ***Part 2 Arm A, Arm B, and Arm C ONLY:*** Prior treatment with anti-PD-1 or anti-PD-L1 (prior IL-2 or interferon allowed). ***For Part 1 ONLY:*** patients are excluded if they were intolerant to anti-PD-1, anti-PD-L1, or anti-CTLA-4 targeted therapies. 3. Major surgery within 4 weeks of study treatment (minor surgical procedures are allowed [e.g., intravascular access line or port-a-cath]) 4. Local-regional therapy within 4 weeks prior to study treatment. 5. Systemic therapy for RCC within 4 weeks prior to study treatment, with the exception of: a. TKI and mTOR inhibitors which can be administered up until 2 weeks prior to study treatment. b. ***Part 2 Arm D ONLY:*** anti-PD-1 or anti-PD-L1 agents which can be administered up until 3 weeks prior to study treatment. Anti-CTLA-4 which can be administered up until 60 days prior to study treatment. ***NOTE***: Any toxicities attributed to prior anti-cancer therapy, other than alopecia, must resolve to Grade 1 (National Cancer Institute [NCI] CTCAE v5) or Baseline before randomization. ***Part 2 Arm D ONLY:*** Resolution/improvement of immune related AEs (irAEs) back to Grade 0, 1, and ≤10 mg/day prednisone (or equivalent dose) for irAEs for at least 2 weeks prior to the first dose of study drug. Patients must have a. No history of common toxicity criteria adverse events (CTCAE) Grade 4 irAEs from anti PD-1 or anti-PD-L1. b. No history of CTCAE Grade 3 requiring steroid treatment (>10 mg/day prednisone or equivalent dose) for >12 weeks or CTCAE Grade 2 pneumonitis regardless of steroid treatment. 6. Ongoing severe inflammatory skin condition requiring medical treatment 7. History of severe eczema requiring prior medical treatment 8. 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-treatment tumor swelling and/or necrosis. 9. Clinically significant and/or rapidly accumulating ascites, pericardial and/or pleural effusions. 10. Symptomatic cardiovascular disease, including but not limited to significant coronary artery disease (e.g., myocardial infarction or other coronary artery disease requiring angioplasty or stenting) or congestive heart failure within the preceding 12 months. 11. Asymptomatic cardiovascular disease (current or past history) unless cardiology consultation and clearance has been obtained for study participation.

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	12. Medical conditions that place the patient at risk should tachycardia, hypotension or volume loading occur during or following treatment with Pexa-Vec 13. Viable central nervous system malignancy (history of completely resected or irradiated brain metastases allowed) 14. Participation in any other research protocol involving an investigational product (IP) within 4 weeks prior to first treatment 15. 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 16. Prior malignancy except for cancer from which the patient has been disease-free for 3 years, or the following: adequately treated basal or squamous cell skin cancer, *in situ* carcinoma (including cervical, prostate or breast cancer, superficial bladder cancer), adequately treated Stage 1 or Stage 2 cancer from which the patient is currently in complete remission. 17. Prior or planned organ transplant (e.g., kidney transplant) 18. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation. 19. Experienced a severe systemic reaction or side-effect, as a result of a previous vaccinia vaccination 20. Patient unable or unwilling to comply with the protocol requirements 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 all Pexa-Vec treatments. 22. Previous treatment with Pexa-Vec or other vaccinia vector-based treatment 23. Pulse oximetry O2 saturation <90% at rest on room air 24. Use of interferon/pegylated interferon (PEG-IFN) or ribavirin that cannot be discontinued within 14 days prior to any Pexa-Vec dose. ***NOTE***: Please consult the Medical Monitor if patient is taking any other anti-viral medications to determine eligibility 25. Inability to receive IV contrast agents for computerized tomography (CT) OR magnetic resonance imaging (MRI) scanning due to documented history of contrast allergy unless controlled by medical intervention (e.g., premedication with steroids, diphenhydramine, or other anti-allergic medications) 26. For patients with accessible tumors for IT injection or biopsy: the use of anti-platelet or anti-coagulant therapy that cannot be safely suspended for per protocol biopsies as per standard of care or IT injections as per the following guidance: a. Aspirin that cannot be discontinued for 7 days prior to Pexa-Vec IT injection b. Coumadin that cannot be discontinued for 7 days prior to Pexa-Vec IT injection c. Low molecular weight heparin (LMWH) that cannot be discontinued >24 hours prior to Pexa-Vec IT injection

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	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, apixaban, 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 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 Please contact the Sponsor for questions regarding the management of other anticoagulants prior to treatments. 27. Active autoimmune disease that has required systemic treatment in past 2 years (i.e., with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered an excluded form of systemic treatment. 28. History of non-infectious pneumonitis. 29. History of interstitial lung disease. 30. Known active Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative] is detected). 31. Prior treatment with idelalisib 32. Patients must not receive live vaccines, other than Pexa-Vec, within 30 days of planned start of study investigational product, during the study, and for a minimum of 15 weeks after the last dose of investigational product. 33. Documented allergic or acute hypersensitivity reaction attributed to antibody treatments 34. Known allergy to doxycycline or other tetracycline antibiotics 35. ***AUSTRALIA ONLY:*** Patients with no accessible tumors: For the period from first study treatment to 2 weeks following last infusion of Pexa-Vec. Patients likely to come in to contact with: • Children under 12 months of age; • Women who are known to be pregnant, or who are breastfeeding; • Persons with known significant immunodeficiency due to underlying illness (e.g. HIV/AIDS) and/or immunosuppressive medication; • Persons with an ongoing severe inflammatory skin condition requiring medical treatment; and • Persons with a history of severe eczema requiring prior medical treatment ***NOTE:*** This must be documented in writing
DLT Definition:	A DLT is defined as any of the following treatment-related AEs that are evaluated and reported through Day 29 of the dose-escalation (Part 1) phase of the study: 1. Grade 4 hematologic toxicity lasting ≥7 days except:

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	• Grade 4 lymphopenia without clinically relevant sequelae • Grade 4 thrombocytopenia not associated with a clinically significant bleeding event 2. All Grade 3 and Grade 4 non-hematologic toxicity that represent a 2-grade increase over baseline except: • Grade 3 flu-like symptoms (specifically fatigue, malaise, headache, and myalgia) lasting <14 days • Grade 3–4 fever lasting <3 days • Grade 3 hypotension lasting <24 hours • Grade 3–4 alopecia, hair or skin discoloration • Grade 3–4 nausea, vomiting and diarrhea lasting <7days • Grade 3–4 hypothyroidism responsive to hormone therapy • Grade 3 hyponatremia without clinical significance • Grade 3–4 non-hematologic toxicity without clinical significance (e.g., transient, asymptomatic elevation of amylase or lipase) 3. Any Grade 3 or Grade 4 non-hematologic laboratory value if: • The abnormality leads to hospitalization 4. Grade 3 or greater cardiac toxicity that does not decrease to a Grade 1 event 72 hours after initiation of maximal supportive care 5. Grade 3 and Grade 4 thrombocytopenia with clinically-significant bleeding associated with Pexa-Vec 6. Grade ≥3 febrile neutropenia • If Grade 3, the event must (in the judgement of both the Investigator and Sponsor) A) be clinically significant and B) require intervention (e.g. G-CSF, antibiotic therapy) for resolution of the event 7. Grade ≥3 myocarditis of any duration 8. Grade 5 toxicity The frequency, time to onset, and severity of toxicities, as well as the success of standard medical management and dosing interruptions/delays will be analyzed to determine if a given toxicity should be considered a DLT for dose escalation purposes. AEs that appear to meet the DLT definition, as described above, will be discussed between the Sponsor and the Investigator. The decision of whether or not the AE meets the DLT definition will be based on a review of all relevant data by the Sponsor, with input from the Investigator.
Drug Dosage:	**<u>Part 1</u>:** ***Pexa-Vec*** Dose Levels per IV infusion: • Dose Level 1: 3×10^8 pfu • Dose Level 2: 1×10^9 pfu Pexa-Vec IV Infusion will be administered weekly × 4 treatments starting on study Day –7 (Days –7, 1, 8, and 15).

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	Cemiplimab (IV) • 350 mg Cemiplimab will be administered at a dose of 350 mg IV every 3 weeks, starting at Day 1 for up to 1 year, or until progressive disease (PD), unacceptable toxicity, or complete remission. **Part 2 (Arm A):** ***Pexa-Vec (IT)*** • MTD/MFD as per Part 1 Pexa-Vec IT injection will be administered every 2 weeks for 3 treatments, starting on Day –7 (Days –7, 8, and 22) ***Cemiplimab (IV)*** • 350 mg Cemiplimab will be administered at a dose of 350 mg IV every 3 weeks, starting at Day 1 for up to 1 year, or until progressive disease (PD), unacceptable toxicity or complete remission. **Part 2 (Arm B):** ***Cemiplimab (IV)*** • 350 mg Cemiplimab will be administered at a dose of 350 mg IV every 3 weeks, starting at Day 1 for up to 1 year, or until progressive disase (PD) following Pexa-Vec treatment, unacceptable toxicity or complete remission. ***Pexa-Vec (IT)*** • MTD/MFD as per Part 1 Pexa-Vec IT injection will be administered every 2 weeks for 3 treatments, starting following progressive disease (PD) following Cemiplimab therapy. **Part 2 (Arm C and Arm D):** ***Pexa-Vec (IV)*** • MTD/ MFD as per Part 1 Pexa-Vec IV Infusion will be administered weekly × 4 treatments starting on study Day –7 (Days –7, 1, 8, and 15). ***Cemiplimab (IV)*** • 350 mg Cemiplimab will be administered at a dose of 350 mg IV every 3 weeks starting at Day 1 for up to 1 year, or until progressive disease (PD), unacceptable toxicity or complete remission.
Treatment Plan:	**Part 1:** ***Pexa-Vec IV Infusions: Day –7, 1, 8, and 15*** Patients will receive an IV infusion of Pexa-Vec in approximately 250 mL buffered saline over 60 minutes ± 5 minutes. The dose will depend on what dose level (1 or 2) the patient has been assigned (see above). Refer to the *Infusion Preparation*

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	Worksheet for details. Patients will be observed in the clinic and/or hospital for a minimum of 20 hours after the infusion. Treatments 2–4 will be administered at weekly 7-day intervals (Day 1, Day 8, and Day 15). The allowable window is –1 to +7 days. If a treatment is not given within the window, it will be considered missed (e.g., the patient will not receive the infusion, but future protocol specified treatments will be administered as originally scheduled per protocol). Pexa-Vec treatments must minimally be at least 6 days apart. ***Cemiplimab IV Infusions: Beginning Day 1, Every 3 Weeks*** Cemiplimab will be administered every 3 weeks (± 3 days) beginning on Day 1. Patients will receive the infusion over 30 minutes (± 10 minutes). On days in which both Cemiplimab and Pexa-Vec are given, Cemiplimab will be given first and the treatments will be separated by at least one hour of observation. **Part 2:** ***Pexa-Vec IT Injections: Day –7, 8, 22 (Arm A), PD, PD+2 Weeks, PD+4 Weeks (Arm B)*** Patients will receive an IT injection of Pexa-Vec, prepared in buffered saline. Refer to the *IT Injection Preparation Worksheet* for details. Patients will be observed in the clinic and/or hospital for a minimum of 8 hours after the injection. Treatments 2 and 3 will be administered in 14-day intervals (window: –4 days to +7 days). If a treatment is not given within the +7 day window, it will be considered missed (e.g., the patient will not receive the injection, but future protocol specified treatments will be administered as originally scheduled per protocol). ***Pexa-Vec IV Infusions: Day –7, 1, 8, and 15 (Arm C and Arm D)*** Patients will receive an IV infusion of Pexa-Vec in approximately 250 mL buffered saline over 60 minutes ± 5 minutes. The dose will depend on what dose level (1 or 2) the patient has been assigned (refer above). Refer to the *Infusion Preparation Worksheet* for details. Patients will be observed in the clinic and/or hospital for a minimum of 20 hours after the infusion. Treatments 2–4 will be administered at weekly 7-day intervals (Day 1, Day 8, and Day 15). The allowable window is –1 to +7 days. If a treatment is not given within the window, it will be considered missed (e.g., the patient will not receive the infusion, but future protocol specified treatments will be administered as originally scheduled per protocol). Pexa-Vec treatments must minimally be at least 6 days apart. ***Cemiplimab IV Infusions: Beginning Day 1, Every 3 Weeks (All Arms)*** Cemiplimab will be administered every 3 weeks (± 3 days) beginning on Day 1. Patients will receive the infusion over 30 minutes (± 10 minutes). On days in which both Cemiplimab and Pexa-Vec are given, Cemiplimab will be given first and the treatments will be separated by at least one hour of observation. **Premedication and Post-Treatment Symptom Management on all Treatment Days** The use of the following drugs will not be restricted during the course of the study: antiemetics, antipyretics, antidepressants, bisphosphonates, vitamin B12, and vitamin D. Oral or parenteral corticosteriods may attenuate potential beneficial immunologic effects of treatment with Pexa-Vec and Cemiplimab and should not be used but may be administered at the discretion of the physician if clinically indicated treatment of

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	an AE. Alternatives to corticosteroids should be considered if feasible. The use of inhaled corticosteriods and mineralocorticosteriods (e.g., fludrocortisone) is allowed. Antihypertensives (including diuretics) should be discontinued at least 48 hours prior to treatment with Pexa-Vec and restarted no earlier than 48 hours after completion of therapy. All patients should be pre-medicated with acetaminophen (paracetamol) or equivalent antipyretics, (unless contraindicated) on each Pexa-Vec treatment day. For example, the following regimen may be used: • 650 mg 2 hours pre-infusion, • 650 mg at 4 hours post-procedure, • 650 mg every 6 hours thereafter, as needed, for up to 22 hours total post-treatment (the total acetaminophen dose should be carefully assessed to avoid cumulative toxicity). Fevers may be associated with onset of rigors. Meperidine or equivalent may be used for rigors. Patients must 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.
Imaging & Follow-up Schedule:	***Safety:*** Starting from the initial treatment and continuing through 28 days after the last treatment with Pexa-Vec and Cemiplimab patients will be evaluated for safety. ***Histologic:*** For patients with accessible lesions, mandatory core or excisional biopsies will be performed. Part 1, Arm A, Arm C, and Arm D: at Baseline (Day –7 [up to 14 days prior]), early Day 8 (up to 4 days prior), and late time point (Day 57 [± 5 days]). Part 2, Arm B: at Baseline (Day 1 [up to 14 days prior]), late time point (Day 57 [± 5 days]), as well as at the time of progression on Cemiplimab (prior to initiation of Pexa-Vec) and an early biopy relative to first day of Pexa-Vec treatment (Day 1 and Day 15). The biopsy should be obtained prior to Pexa-Vec treatment where applicable, and is permissible immediately prior to IT Pexa-Vec treatment, during the same treatment session. ***Radiographic:*** Imaging studies will be evaluated by the site radiologist Investigator and/or Principal Investigator. All scans described below will also be submitted for independent central review. Patients will be assessed radiologically (CT) at Screening and every 9 weeks until documented progression is confirmed per irRECIST. After 1 year, patients will be assessed every 12 weeks from End of Treatment (EOT) visit. Detailed instruction on irRECIST response assessment will be provided in the Site Reader Manual. ***CT Scan:*** A detailed imaging acquisition protocol will be provided to the sites in the Imaging Manual. Briefly, a contrast-enhanced helical/spiral CT of the abdomen from the dome of the liver through both kidneys will be performed. Post-contrast CT of the chest and pelvis will also be performed. ***NOTE***: In patients unable to receive iodinated contrast material for CT scanning, triphasic dynamic MRI of the abdomen should be performed. Post-

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	contrast MRI of the pelvis should also be performed, along with non-contrast CT of the chest. ***Follow-Up:*** Patients will be followed up weekly for clinical assessment for the first 6 weeks then every 3 weeks while on Cemiplimab. Patients may remain on Cemiplimab for up to 1 year as long as they continue to receive clinical benefit and do not demonstrate confirmed progression per irRECIST (refer to Site Reader Manual). Thereafter, Cemiplimab will be discontinued but patients will continue to be followed radiographically every 12 weeks from EOT visit until confirmed radiographic progression and subsequent study completion. ***Survival:*** Patients will be followed for survival during and after study participation. After discontinuation from the study treatment, patients, and/or their specified contacts will continue to be contacted approximately every 12 weeks from EOT visit for survival and information on subsequent anti-cancer therapy, including dose duration, significant associated toxicities and efficacy. Radiology assessments may be reviewed for patients who have gone onto subsequent therapies.
Endpoints:	**<u>Primary Endpoints</u>:** • MTD/MFD of Pexa-Vec administered by IV infusion in combination with Cemiplimab • Safety of Pexa-Vec administered by IV infusions or IT injections in combination with IV Cemiplimab as evaluated by incidence of all AEs, Grade 3 or greater AEs, serious adverse events (SAEs), AEs requiring discontinuation of study agent(s), and deaths according to National Cancer Institute – Common Toxicity Criteria (NCI-CTC) version 5 • Overall response rate (ORR) according to RECIST 1.1 - This endpoint is primary for efficacy in Part 2 of the trial **<u>Secondary Endpoints</u>:** • Progression free survival according to RECIST 1.1 • Disease control rate (complete response [CR] + partial response [PR] + stable disease [SD]) based on RECIST 1.1 • Best radiographic response (based on RECIST 1.1) • ORR according to irRECIST • Best radiographic response (based on irRECIST) • Disease control rate (complete response [CR] + partial response [PR] + stable disease [SD]) by irRECIST • Overall survival **<u>Exploratory Endpoints:</u>** • To assess in the blood, the following immune parameters at Baseline, and on Study Days 1 (excluding Arm B, Cemiplimab monotherapy), Day 22 (Day 43 in Arm D), End of Treatment and Post Progression on anti-PD-1 monotherapy at Baseline, 2 weeks, and 4 weeks (Arm B only): o Tumor specific and Pexa-Vec specific cellular immune responses (including but not limited to assessment of B-cells, T-cells, activated T-cells, NK cells, regulatory T-cells, MDSC). o Pexa-Vec and Cemiplimab specific humoral responses o Immune related cytokines

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	• To assess in previously archived tumor biopsies (if available) and/or biopsied tumors at Baseline and on Study Day 8 (excluding Arm B, Cemiplimab monotherapy) and Day 57 (Arm B patients will undergo repeat biopsy at disease progression and 2 weeks after first Pexa-Vec): o Tumor microenvironment including T-cell, B-cell, NK cell, monocytes, macrophages, and other relevant immune cell subtypes of interest o Immune modulating proteins that may have predictive or prognostic value, including, but not limited to PD-L1, PD-1, and CTLA-4 o Global changes in gene expression based on genome wide RNAseq analysis o Tumor mutational load based on whole exome sequencing of tumor and the matched germline blood DNA samples o Pexa-Vec infection and transgene expression • Concentration of Cemiplimab and Pexa-Vec in serum and plasma, respectively, after Pexa-Vec IV and IT (at pre-dose, end-of-infusion/injection and Day 8) with Cemiplimab IV (pre-dose and end-of-Day 1 infusion, Day 8, as well as C_{trough} and C_{eoi} throughout therapy)
Statistical Rationale and Analysis:	**Sample Size:** The estimated sample size for both Part 1 and 2 combined will be 116 patients. In the dose escalation Part 1 portion of the study 3–12 patients will be enrolled. ***Arm C Expansion:*** For this dose-expansion cohort, the sample size is determined for a Simon 2-stage Minimax design with 1-sided alpha of 0.12 and power of 80% to test an H0 21.5% vs H1 43%. Eleven patients will be enrolled at the MTD/MFD established in the initial dose escalation portion of the study. If a sufficient radiographic response signal is seen at the futility interim analysis for the Simon design and enrollment is feasible, a further 9 evaluable patients (for 80% power on the Simon design) may be enrolled at the discretion of the Sponsor on to this arm. ***Arm D Expansion:*** For this dose-expansion cohort, the sample size is determined using a 2-stage design based on testing a null hypothesis ORR rate ≤5% versus alternative hypothesis ORR rate ≥20% with a probability of early termination of 75.5%, satisfying the 1-sided alpha of 5% and power of 80% constraints. Nineteen patients will be enrolled in the first stage. If 2 or more patients experience a response, a further 8 patients will be enrolled and assessed for efficacy. The null and alternative ORR rates (5% and 20%) are designed to test for a clinically meaningful treatment effect of the 2nd line RCC treatment assuming an ineffective response rate of 5%. Because there is no response data of 2nd line check point blocker treatment available from RCC patient population refractory to 1st line check point blocker treatment, ORR of 20%, pooled from studies (*Eichelberg 2008, Dudek 2009, Sablin 2009, Zama 2010, Porta 2011, Zimmerman 2009, Eichelberg 2015, Rini 2008*) where standard of care (sunitinib) in the 2nd line setting, was used. ***Arm A and B Comparison:*** The sample size is based on historical data from clinical trials investigating nivolumab (anti-PD-1 antibody). In a study of 821 patients with previously treated advanced renal cell carcinoma, the objective response rate of nivolumab was 21.5% (Nivolumab package insert, 2015). Based on this rate in the control arm, 27 patients in each arm (Arm A vs B) will provide 75% power to test for equal ORR rates (null hypothesis) at 1-sided alpha = 0.15, when the actual ORR on Arm B is 43%. Total planned n = 54 patients for both Arm A and Arm B).

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	Safety and Toxicity ***Part 1:*** The dose-finding plan is designed to ensure that no more than 2 out of 6 patients experience a DLT at the MTD. All patients receiving at least 3 Pexa-Vec infusions and one Cemiplimab infusion prior to Day 29 are eligible for DLT assessment (patients who do not receive this minimum exposure will not count for the purposes of DLT assessment and additional patients will be enrolled to complete the DLT cohort enrollment and assessment). All patients receiving at least one treatment of Pexa-Vec will be included in the overall safety analyses. ***Part 1 and 2:*** All AEs will be coded and tabulated using the Medical Dictionary for Regulatory Activities (MedDRA) classification scheme based a standard set of terms (NCI CTCAE, Version 5). The incidence of treatment-emergent AEs will be tabulated; in addition, the data will be stratified by severity and relationship to Pexa-Vec, Cemiplimab, or both. **Immunologic Endpoints** The immune response to the tumor following Pexa-Vec treatment will be evaluated and summarized. **Efficacy Endpoints** Response assessment will be conducted by central, expert reader evaluation of CT scans. Tumor response will be evaluated on CT by RECIST 1.1 and irRECIST criteria. Descriptive statistics will be presented for all endpoints. The results of the primary hypothesis tests and confidence intervals will be reported for the primary endpoint. Progression free survival and overall survival will be estimated using Kaplan-Meier methods. Response rates will be reported (and confidence intervals provided) for: • Complete response (CR) • Partial response (PR) • Objective response (OR) = CR + PR • Stable disease (SD) • Disease control rate = SD + PR + CR • Progressive disease (PD) Exploratory subgroup analyses may be performed.

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2 BACKGROUND

2.A RENAL CELL CARCINOMA

Renal cell carcinoma (RCC) accounts for 90% of kidney cancer, the 12th most common cancer in the world (*WHO 2012*). Globally, 338,000 new cases of kidney cancer are diagnosed, accounting for approximately 4% of total cancer diagnoses. (*Znaor 2015*). In the United States (US), there are approximately 63,000 individuals diagnosed with RCC and almost 14,000 patients succumbed to the disease (*Siegel 2016)*. RCC is composed of 5 major subtypes (based on genetics and molecular biology): clear cell, papillary (type I and type II), chromophobe, collecting duct, and unclassified RCC (*Klatte 2007*). Though novel therapies have been approved for patients with metastatic RCC in recent years, patients will ultimately progress on these therapies. Therefore, additional treatment options are needed, in an effort to extend life, and improve quality of life in RCC. To this end, this study will explore the combination of Pexa-Vec in combination with Cemiplimab, in an effort to improve upon the activity of either agent alone for the treatment patients with metastatic RCC.

2.A.1 Current Treatment for Renal Cell Carcinoma

The past decade has experienced an increased understanding of RCC biology as well as unprecedented advances in the treatment of RCC. Systemic therapy for patients with metastatic RCC was long limited to the very marginal activity of cytokine therapies (interleukin-2 and interferon) as RCC has proven to be resistant to traditional chemotherapeutic treatments *(Oudard 2007)*. The understanding that aberrant angiogenic signaling often underpins disease progression gave rise to several treatments targeting vascular endothelial growth factor (VEGF) signaling, namely: sunitinib, pazopanib, axitinib, sorafenib, bevacizumab, cabozantanib, and lenvatinib (*Motzer 2016*). In addition, the mTOR inhibitors, temsirolimus and everolimus have also shown activity and are approved for the treatment of RCC.

A recent addition to the arsenal of cytokines, antiangiogenics, and mTOR inhibitors, is the immunotherapeutic checkpoint inhibitor, nivolumab. A study of nivolumab for the treatment of patients with clear cell variant (~90% of RCC) RCC following initial first line therapy demonstrated significant activity, leading to its approval by the US Food and Drug Administration (FDA). In a randomized Phase 3 trial targeting patients with RCC who had received previous treatment, a marked improvement in anti-tumor activity was demonstrated across clinical endpoints for nivolumab vs everolimus, including overall survival (25 vs. 19.6 months, respectively) and response rate (25 vs. 5%) (*Motzer 2015a*). Notably, the safety profile also

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favored nivolumab over everolimus in this study with 19 vs. 37%, respectively, of patients experiencing Grade 3/4 treatment related adverse events (AE). The most common AE of any grade reported for patients classified as related to nivolumab with frequency of 10% or more included: fatigue (33%), nausea (14%), pruritus (14%), diarrhea (12%), decreased appetite (12%), and rash (10%). Notable Grade 3/4 AE for nivolumab included: fatigue and anemia (2% each); and nausea, diarrhea, decreased appetite, rash, dyspnea, pneumonitis, and hyperglycemia (1% or less for each) (*Motzer 2016*).

Despite recent advances, the 5-year survival for metastatic RCC is less than 30% (*Chittoria 2013*). Collectively, these agents are not curative and therapies with novel mechanisms-of-action are needed for patients with metastatic RCC having failed the available treatment options.

2.B ONCOLYTIC IMMUNOTHERAPY

Oncolytic immunotherapy employs viruses that are designed to preferentially replicate in and lyse cancer cells and in this process trigger anti-tumor immunity. 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. Over 10 different viral species have entered clinical trials. One oncolytic virus-based product (Onyx-015 adenovirus) entered a Phase 3 clinical trial in the US, and a similar virus, H101, was approved for use in combination with chemotherapy as a treatment for head and neck cancer by the Chinese State Food and Drug Administration in November 2005. More recently, a Phase 3 pivotal trial of *talimogene laherparepvec* (T-VEC), an oncolytic herpes virus expressing granulocyte-macrophage colony stimulating factor (GM-CSF) was approved for use in patients with advanced melanoma (*Andtbacka 2016)*.

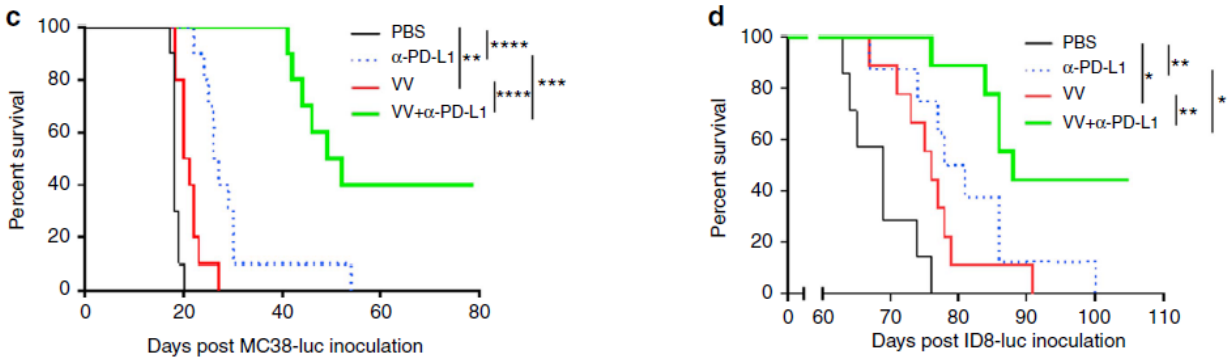
Oncolytic immunotherapies kill cancer cells through a novel mechanism of action ("oncolysis"), or virus replication-associated necrosis (*Parato 2005; Kirn 2009)* and can be targeted to cancer cells with activated genetic pathways and/or loss of tumor suppressor function (*Heise 1997; Stojdl 2000; Martuza 1991*). Selective intratumoral (IT) replication of the virus leads to lysis of the infected cancer cell and viral 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.

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2.B.1 Assessment of Oncolytic Vaccinia Infection in Combination With Checkpoint Inhibitors

Combination therapy of oncolytic vaccinia virus with a CTLA-4 inhibitor was assessed in mouse models of renal and colorectal cancer. Mice that were treated with oncolytic vaccinia followed by a CTLA-4 inhibitor had increased acute cytotoxic T lymphocyte (CTL) responses and improved survival, when compared to control arms. Furthermore, increasing the immunotherapeutic properties of the virus improved the synergistic efficacy of vaccinia virus in combination with checkpoint blockade (*Thorne 2007*). In another study, oncolytic vaccinia upregulated PD-L1 on cancer cells and attracted effector T-cells into the tumor microenvironment. Combining vaccinia with a PD-L1 antibody resulted in increased anti-tumor immune responses and improved survival (Figure 1) (*Liu 2017*). Taken together, these data demonstrate that oncolytic vaccinia is capable of boosting the immunotherapeutic effects of checkpoint inhibitors.

Figure 1: Vaccinia Virus and PD-L1 Blockade Synergistically Elicit Anti-Tumor Effects in Mouse Models of Colon and Ovarian Cancer



(*Liu 2017*)

2.B.2 Assessment of Oncolytic Vaccinia Infection in the RCC Tumor Microenvironment

Two studies were completed to assess the effects of oncolytic vaccinia in the human RCC xenograft. In a set of *in vitro* experiments, an RCC cell line (786-0) and cancer-associated fibroblasts (CAFs) were found to secrete paracrine factors that promoted oncolytic vaccinia infection of both CAFs and renal cancer cells. These CAFs were found to inhibit antiviral signaling, thereby promoting vaccinia infection and spread (*Ilkow 2015*). In a second study, human RCC cells (Caki-1) were found to sensitize human endothelial cells to oncolytic vaccinia infection. This model recapitulates aberrant VEGF signaling in hypervascular RCC. VEGF

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signaling promoted the ability of oncolytic vaccinia to infect tumor vasculature, facilitating vaccinia delivery and spread within tumors (*Arulanandam 2015*). These studies demonstrate that oncolytic vaccinia is able to capitalize on the features of the RCC tumor microenvironment to exert therapeutic effects.

2.B.3 Pexa-Vec: Selective Tumor Infection and Active Immunotherapy

Pexa-Vec (Pexastimogene Devacirepvec) is an oncolytic and immunotherapeutic vaccinia virus engineered to express GM-CSF. Pexa-Vec mechanisms-of-actions include tumor cell infection and lysis (*Breitbach 2011b; Kim 2006; Park 2008*), anti-tumor immune response induction (*Heo 2013; Kim 2014*) 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 (*Hengstschläger 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 or Oncos-102. In addition, in melanoma patients GM-CSF when added to ipilimumab led to an improved outcome (*Hodi 2013*).

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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 2011b; 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 2014*).

2.C PRECLINICAL EXPERIENCE WITH PEXA-VEC

2.C.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. The transgene product expressed by Pexa-Vec, human GM-CSF, is biologically active in rabbits, a species in which vaccinia virus replicates. Accordingly, the virus was tested versus 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. Median survival was improved (50 days in control group vs not reached in Pexa-Vec treated at 70 days), metastases were prevented and rabbits treated with Pexa-Vec exhibited weight gain. Dose-responses were seen. 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 (*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. (Refer to the Investigator's Brochure [IB] for further details).

2.C.2 Toxicity and Biodistribution of Single or Repeated IV Doses of Pexa-Vec in the Rabbit

An exploratory study in New Zealand White rabbits was conducted. Animals in this study received one (n = 1M, 1F) or 3 (n = 3M, 3F) weekly IV doses of Pexa-Vec (10^{10} pfu/dose; approximately 4×10^9 pfu/kg). The treatments were well-tolerated: no overt clinical signs were observed

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throughout the 92 days of the study, with the following exception: Animals receiving multiple doses lost approximately 5% of their body weight by Day 6. Thereafter, body weight rose intermittently until the end of measurements on Day 33. Histological and hematological findings are consistent with vaccinia virus infection. Reversible lymphoid depletion in the thymus and lymphoid hyperplasia with red pulp expansion in the spleen were also considered physiopathological adaptations. All of these findings appeared to be resolved by Day 92 and none are considered to be of toxicological significance (refer to the IB for further details).

In another study, 9 groups of 5 rabbits/sex/group received IV administrations of a clinical lot (Lot No. C173-3) at doses of 3×10^6 and 3×10^7 pfu/kg (~0.2 and 2-fold the 10^9 pfu/patient dose on a pfu/kg basis). Rabbits were assigned to groups that received 3 weekly infusions of low dose or high dose Pexa-Vec or a single high dose Pexa-Vec. Rabbits in a vehicle control group received 3 infusions. Pexa-Vec triggered treatment-related inappetence, and dose-related, reversible, early loss of body weight at both dose levels. There were some mild, dose–related, reversible changes in hematology and clinical chemistry parameters. Mild anemia was considered secondary to spleen enlargement. At the high dose only, abscesses were observed in the testes. All of the observed changes appear to be reversible (refer to the IB for further details).

2.D ONCOLYTIC VACCINIA AND ANTI-PD-1 IN MOUSE MODELS

2.D.1 Evidence of Oncolytic Vaccinia Efficacy and Immune Activation in a RIP-Tag2 Transgenic Mouse Model of Pancreatic Cancer

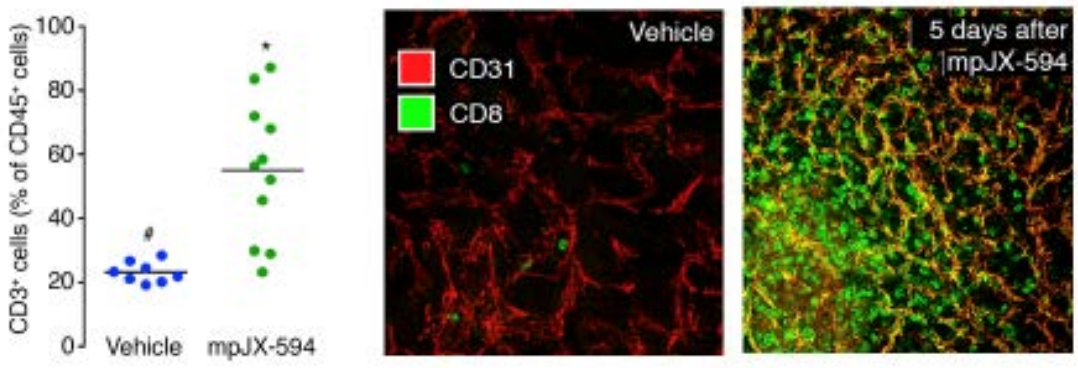
Anti-tumor as well as immune effects following IV oncolytic vaccinia treatment was interrogated in RIP-Tag2 mice, a transgenic model in which mice develop pancreatic neuroendocrine tumors. These tumors are VEGF driven, therefore are also representative of several angiogenic tumors, such as RCC. Experimental models such as this, represent human cancer more accurately than do the commonly used xenograft models, in which human tumors are transplanted into nude mice. This is because xenografts do not develop in their normal tissue environment, the tumor-stroma interactions that support tumor growth are absent and contributions of adaptive immunity to efficacy cannot be interrogated.

Oncolytic vaccinia injected IV into RIP-Tag mice bearing tumors, selectively infects tumors, replicates, and causes tumor cell death by apoptosis. Virus spread can be monitored by anti-vaccinia antibody staining, and tumor cell death by staining for activated caspase-3 in sections of excised tumors. Immunofluorescence based staining of the vasculature (anti-CD31) and lymphocyte infiltrate (CD45), in control and treated tumors, revealed a significant increase in both numbers and distribution of CD45+ leukocytes in vaccinia treated mice. T-cell recruitment to

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tumors was demonstrated 5 days post IV vaccinia administration (Figure 2). CD8 T-cells recruited to tumors were also shown to be activated (as evidenced by granzyme B positivity, data not shown). When CD8 cells were depleted, vaccinia-mediated cytotoxicity was reduced, indicating oncolytic vaccinia recruits CD8 T-cells that contribute to its anti-tumor activity of PV (Figure 3).

Figure 2: FACS Analysis and Immunohistofluorescence Base Staining with anti CD8 Antibodies

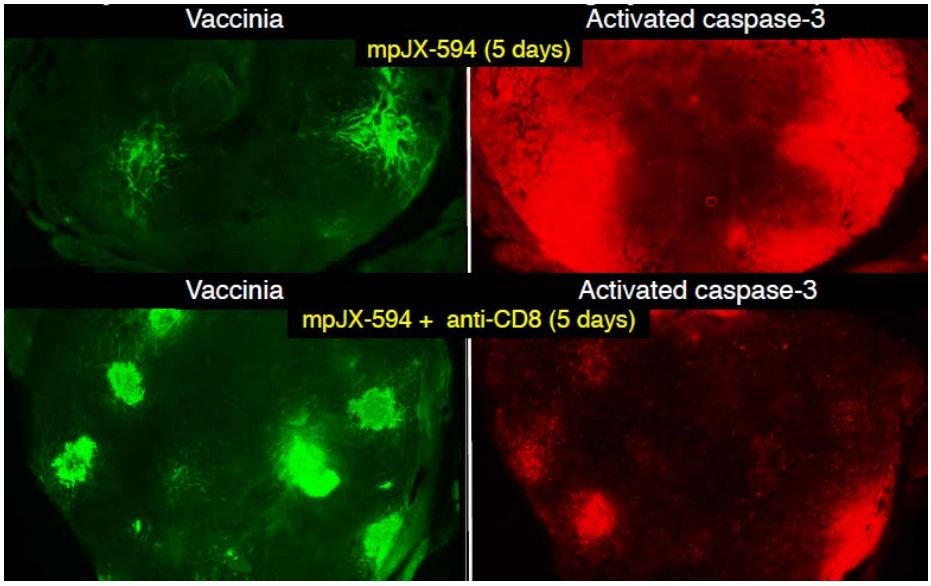


McDonald laboratory, UCSF: Unpublished data

RIP-Tag2 mice were treated with *mouse prototype JX-594* (also referred to as mpJX-594 or WR TK- hGMCSF), an oncolytic vaccinia virus designed to replicate in mice while retaining the oncolytic properties of Pexa-Vec. A) Quantification of CD3+ cells from tumors, 5 days following virus administration. B) Immunofluorescent staining for CD8+ cells (green) and CD31 cells (red) in histological tumor sections, 5 days following treatment.

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Figure 3: Reduced Tumor Cell Killing in CD8 Cell Depleted Mice



RIP-Tag2 mice were depleted of CD8 cells, and treated with oncolytic vaccinia. Immunofluorescence analysis of tumors for vaccinia virus (green) and apoptosis (red), 5 days following IV administration.

These data support a model in which oncolytic vaccinia virus treatment induces tumor lysis that secondarily leads to infiltration and activation of immune cells in the tumor micro-environment. We then explored whether this immune response could be further activated by combining treatment with vaccinia virus with an immune checkpoint blocking antibody targeting the protein PD-1.

2.D.2 Combination of Oncolytic Vaccinia Virus with anti-PD-1 Antibody in RIP-Tag2 Mice

Anti-tumor activity of the combination of oncolytic vaccinia and anti-PD-1 antibody was evaluated in RIP-Tag2 mice by quantification of activated caspase 3 (marker of apoptosis).

Virus alone induced cell death; however, the addition of anti-PD-1 antibody significantly enhanced tumor cell death, when used in combination (analysis performed at Day 5 and Day 10 [Figure 4 and Figure 5, respectively]). Combination treatment also resulted in reductions in tumor volume (Figure 6). No significant effect of the anti-PD-1 antibody alone were seen in this experiment.

These results provide for a rational basis for combining Pexa-Vec and an anti-programmed death receptor (anti-PD-1) antibody in clinical trials of a combination treatment for RCC.

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Figure 4: Enhanced Tumor Cell Death Induced By Combination Oncolytic Vaccinia and anti-PD-1 Treatment As Compared with anti-PD-1 Alone or Oncolytic Vaccinia Alone

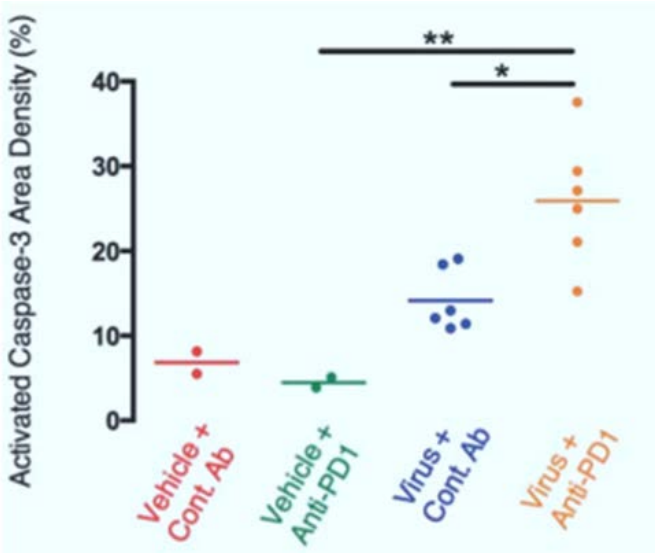
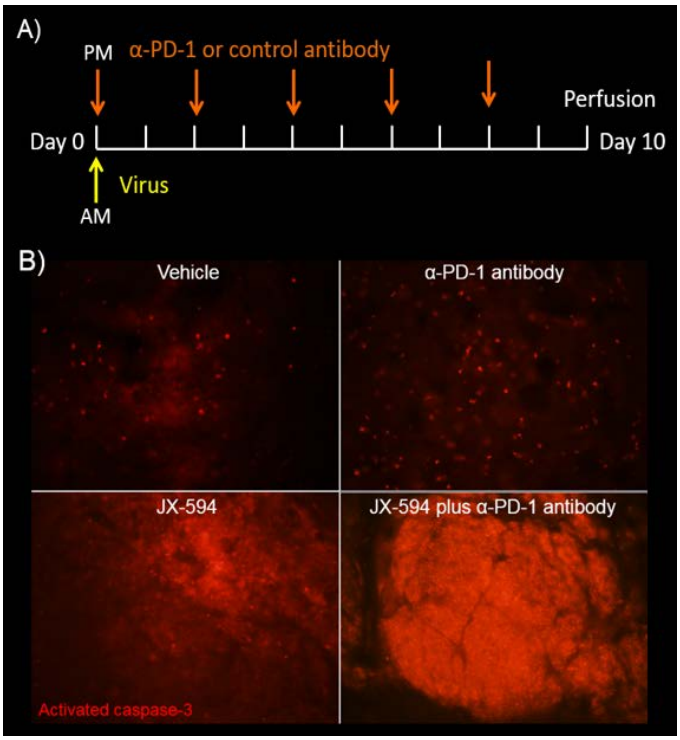


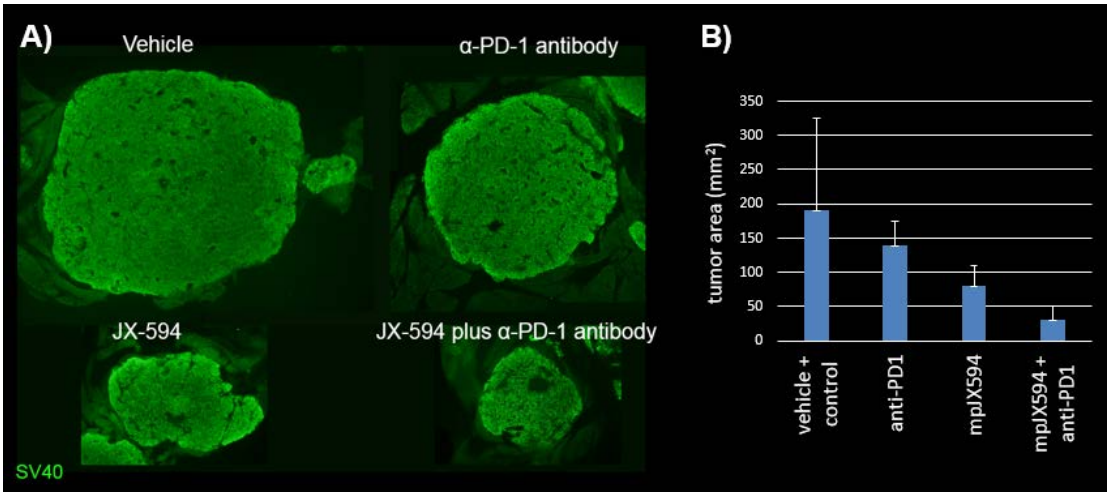
Figure 5: Combination Treatment of Oncolytic Vaccinia and anti-PD-1 Antibody Increases Tumor Apoptosis, 10 Days After Treatment



Rip-Tag2 mice were treated with anti-PD-1 in combination with mpJX-594. A) Schematic of dosing regimen. B) Tumors were stained for activated caspase-3 staining (red). Representative images are shown.

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Figure 6: Combination Treatment of Oncolytic Vaccinia and anti-PD-1 Leads to Reductions in Tumor Volume, 10 Days Post Treatment



A) Staining for tumor cells (SV40 T antigen, green). B) Quantification of total tumor area.

2.E CLINICAL EXPERIENCE

2.E.1 Overview of Clinical Experience with Pexa-Vec

Pexa-Vec has been evaluated in 21 completed and ongoing clinical trials to date (refer to the IB for trial details and status).

As of March 2020, there have been 1923 doses of Pexa-Vec administered by IT injection and/or IV infusion to approximately 553 patients. Pexa-Vec therapy has been well-tolerated to date at doses up to and exceeding 1×10^9 pfu. The most common side effects related to Pexa-Vec reported include: pyrexia (79%), chills (49%), nausea (24%), hypotension (21%), vomiting (19%), rash pustular (21%), headache (16%), and influenza like illness (18%). Transient, hypotension responsive to fluid administration was also noted in a subset of patients within 24 hours of treatment. The most common Grade 3 or greater AEs were: pyrexia (6%), hypertension (3%), hypotension (2%), chills (2%), fatigue (10%), nausea (1%) and vomiting (1%). Pexa-Vec related skin pustules were observed in approximately 21% of patients receiving Pexa-Vec IT injections (4.5% of all IT treatments). The pustules were self-limited and resolved without sequela within 2–4 weeks of treatment, consistent with the timeline for pustule resolution utilizing wild-type vaccinia vaccine. Anti-tumor activity was suggested in patients treated across all studies with Pexa-Vec as determined by Choi and Response Evaluation Criteria in Solid Tumors (RECIST)

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response criteria. Please refer below to the summary of key company-sponsored Pexa-Vec studies, as well as the IB, for more information on activity and toxicity of Pexa-Vec.

Table 1:
Pexa-Vec Summary of Clinical Trials

Study	Indication / Administration	Phase	Status	Patients Enrolled as of 31 March 2020[a]
	Melanoma Mastrangelo, investigator initiated / IT	1	Completed	7
HEP001	Liver metastases: dose escalation / up to 8 doses IT	1	Completed	14
IV011	Solid tumors / 1 dose IV	1	Enrollment completed, data analysis ongoing	23
MEL005	Melanoma / 6 doses IT	1/2	Completed	10
P009	Pediatric tumors / 1 dose IT	1	Stopped	6
HEP012	CRC: neoadjuvant therapy / 1 dose IT or IV	2a	Stopped	2
HEP007	HCC primarily 1st line: 2 dose levels / 3 doses IT	2a	Completed	30
HEP016	HCC 2nd line: 1 dose IV + 2 doses IT f/b Sorafenib	2	Enrollment completed, data analysis ongoing	25
HEP021	HCC 1st line: 5 doses IV	2	Completed	16
HEP018	HCC 2nd line / TRAVERSE (RCT): 1 dose IV + 5 doses IT (randomized 2:1) Arm A: Pexa-Vec + BSC Arm B: BSC	2b	Completed	129 Arm A: 86[b]
CRC014	CRC: dose escalation / 4 doses IV	1	Completed	15
CRC019	CRC: single agent & combo (irinotecan) / 5 doses IV + 3 doses IT	1/2a	Completed	52[b]
REN022	RCC / 5 doses IV	1/2	Completed	17
OBS023	HCC / RCC post Pexa-Vec observational study	2	Completed	5
HEP024	HCC 1St Line / Pexa-Vec 3 doses IT 3 doses IT followed by sorafenib vs. sorafenib alone	3	Stopped	459 (234 enrolled for Pexa-Vec) 217 dosed with Pexa-Vec

[a] 7 compassionate use patients

[b] 2 patients enrolled however not treated

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2.E.2 Phase 2 Study of Metastatic Refractory Renal Cell Carcinoma (RCC) Patients Treated Intravenously (IV) with JX-594 (JX594-IV-REN022)

Preliminary data on JX594-IV-REN022, an Investigator-initiated Phase 2 single-arm trial in patients with advanced RCC refractory to standard therapy, showed that Pexa-Vec (formerly JX-594) was generally safe and was associated with anti-tumor activity. Patients received Pexa-Vec at a dose of 1×10^9 pfu in up to 5 weekly IV infusions, with an option for IV treatment extensions every 3 weeks if patients exhibited disease control.

Pexa-Vec was well-tolerated with most AEs being mild-to-moderate in severity. The AE profile generally reflected that observed to date across the clinical program. The most common Pexa-Vec treatment related AEs identified as a percent of total patients treated included generally mild-to-moderate: influenza like illness (100%), nausea (24%), vomiting (24%), and chills (24%).

Grade 3 AEs reported as related to Pexa-Vec included: platelet count decreased (1), hyperglycaemia (1), haematuria (1), and hypertension (1). No Grade 4 or Grade 5 AEs related to treatment were reported. All patients were evaluable radiographically at Week 6. The mRECIST objective response rate was 6% (1 partial response which evolved into a complete response by Week 36). The mRECIST disease control rate was 70.6% at Week 6.

2.E.3 IV Treatment of Other Solid Tumors with Pexa-Vec

2.E.3.a Phase 1 Study of Single-Dose IV Pexa-Vec in Patients with Advanced Solid Tumors (JX594-IV-011)

A Phase 1 IV dose-escalation trial of Pexa-Vec in patients with solid tumors has been completed and the results published (*Breitbach 2011a*). A total of 23 patients were included in a Phase 1 dose escalation study of Pexa-Vec delivered IV in patients with refractory solid tumors. Patients received a single IV infusion of Pexa-Vec at 1 of 5 dose levels followed by an expansion cohort.

Pexa-Vec was well-tolerated in study patients with most AEs being mild-to-moderate in severity. The most common Pexa-Vec treatment related AEs identified as a percent of total patients treated included generally mild-to-moderate: pyrexia (78%), chills (57%), fatigue (26%), nausea (22%), headache (22%), and hypotension (22%). Vital sign changes included fever, tachycardia and hypotension for up to 24 hours after treatment. In general, these changes in vital signs required no significant medical intervention other than hydration for transient mild-moderate, asymptomatic hypotension. Based on this observation, pre-hydration was instituted as a precaution prior to Pexa-Vec treatment. Laboratory assessment revealed, generally, transient, mild-to-moderate

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changes from baseline laboratory values in a minority of patients. No dose limiting toxicities (DLTs) or serious adverse events (SAEs) related to Pexa-Vec were reported during the dose escalation phase of the trial. Grade 3 AEs reported as related to Pexa-Vec included: lymphocytes decreased (91), partial thromboplastin time prolonged (1), and hypoxia (1). No Grade 4 or Grade 5 AEs related to treatment were reported. Although no formal DLT was reached on this trial, SillaJen designated the maximum tolerated dose (MTD) as 10^9 pfu (total dose) based on the onset of mild hypotension, tachycardia, and cytokine induction in patients treated at the highest dose level (3×10^7 pfu/kg). All patients in the expansion cohort (n = 5) were thereafter treated at an MTD of 10^9 pfu total dose per patient.

Quantitative polymerase chain reaction (qPCR) was used to measure the Pexa-Vec genome concentration in the blood. For patients treated at doses of $\geq 1 \times 10^7$ pfu/kg ($\geq 5 \times 10^8$ pfu/dose), genomes were still detectable in the blood at 4 hours. Peak genome concentrations and the area under the curve in blood were both dose-related. Pexa-Vec infectious units were also detected during IV infusion in most patients, and up to 4 hours in some patients in higher dose cohorts.

Cancer-selective Pexa-Vec delivery and replication in tumors were assessed by PCR analysis and immunohistochemistry of tumor biopsies obtained 8–10 days following infusion. Dose-related delivery and replication were both demonstrated. Of patients treated at approximately $\geq 1.5 \times 10^7$ pfu/kg ($\geq 1 \times 10^9$ pfu/dose) and evaluable for biopsy analysis, 87% exhibited Pexa-Vec positivity by qPCR and/or immunohistochemistry analysis, whereas Pexa-Vec was not detected in biopsies collected from patients treated at lower doses. Of note, delivery and replication were demonstrated in a high dose patient who had baseline antibodies to Pexa-Vec/vaccinia. Immunohistochemistry staining for the Pexa-Vec transgene β-galactosidase revealed the transgene was expressed in Pexa-Vec infected tumor cells. The induction of antibodies to β-galactosidase was demonstrated in a dose-related fashion, with 100% of high-dose patients developing a positive response. Finally, expression of the second Pexa-Vec transgene (human GM-CSF [hGM-CSF]) was assessed. After IV infusion of Pexa-Vec on this study, 3 patients exhibited hGM-CSF at multiple time points between Day 4 and Day 15. All 3 patients had evidence of β-galactosidase expression, tumor infection, and/or tumor response (modified Choi [mChoi] criteria and/or fluorodeoxyglucose positron emission tomography [FDG-PET] criteria).

Twenty-one of 23 patients were evaluable for independent radiographic assessment of response at Day 29. Based on computerized tomography (CT) scan evaluation at Day 29, using standard RECIST criteria, 12 of 22 patients had stable disease (SD) of their overall disease burden. Six of 8 (75%) evaluable patients receiving a total dose $\geq 1 \times 10^9$ pfu had stable disease (SD) at Day 29

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while 6 of 13 (46.2%) evaluable patients who received $<1 \times 10^9$ pfu total dose had stable disease (SD) (range: 29 days to 16+ weeks).

2.E.3.b Phase 1 Study of Biweekly IV Dosing of Pexa-Vec in Patients with Advanced Colorectal Cancer (JX594-CRC014)

A Phase 1 dose-escalation study of stable disease administered IV every 2 weeks × 4 in patients with Stage 4, chemotherapy refractory colorectal carcinoma (CRC) has been completed. Pexa-Vec was administered via IV every 14 days to a total of 15 patients for up to 4 cycles, at dose levels of 1×10^6, 1×10^7, or 3×10^7 pfu/kg. Enrolled patients were heavily pretreated (mean 4.5 prior lines of therapy). All patients received at least 2 Pexa-Vec doses (median = 4; range = 2–4). Pexa-Vec was well tolerated in study patients with all AEs being mild-to-moderate in severity. The most common Pexa-Vec treatment related AEs identified as a percent of total patients treated included generally mild-to-moderate: pyrexia (93%), chills (93%), tachycardia (73%), headache (60%), nausea (53%), rash papulopustular (40%), hypotension (40%), decreased appetite (33%), rash (27%), stomatitis (20%), pain (20%), and vomiting (20%). No Grade 3, 4, or 5 AEs related to treatment were reported. No DLTs were reported, and the MTD was not reached. Dose dependent skin pustules (Grade 1) developed on Days 3–7 of cycle one in 7 of 9 patients at high dose, and 0 of 6 at lower dose. During the first and last cycles, genome pharmacokinetics were unchanged. In addition, infectious pfu could be detected in plasma up to 2 hours after Cycle 1 and up to 30 minutes after Cycle 4 (when anti-vaccinia antibody titers are known to have peaked). Ten patients (67%) had radiographically stable disease. There were no objective radiographic responses at Day 29, but 10 patients (67%) had stable disease. Interestingly, among patients with a total Pexa-Vec dose $<3 \times 10^9$ pfu/kg (n = 6), two (33%) had stable disease (SD); whereas 8 out of 9 patients (89%) with a total dose $\geq 3 \times 10^9$ pfu/kg achieved stable disease (SD) ($p = 0.09$; Fisher's exact test).

2.E.3.c Phase 1 Study of Weekly IV Dosing of Pexa-Vec in Patients with Advanced Colorectal Cancer (JX594-CRC019)

A Phase 1/2a dose-escalation study of Pexa-Vec administered weekly IV × 5 alone or in combination with irinotecan in patients with Stage 4, chemotherapy refractory CRC has been completed and data analysis is ongoing. A total of 52 patients received up to 5 IV doses of Pexa-Vec weekly at doses of 3×10^8 pfu to 1×10^9 pfu alone or in combination with irinotecan. Pexa-Vec alone and in combination with irinotecan was generally well-tolerated with no dose-limiting toxicities experienced.

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Preliminary data reveals that Pexa-Vec was well-tolerated in study patients with most AEs being mild-to-moderate in severity. The most common Pexa-Vec treatment related AEs identified as a percent of total patients treated included generally mild-to-moderate: pyrexia (94%), chills (84%), hypotension (62%), nausea (46%), and rash pustular (42%). The following Grade 3 AEs related to Pexa-Vec single-agent treatment were experienced by 3.6% (n = 1) of patients: chills, hypotension, fatigue, hypertension, abdominal pain, blood bilirubin increased, cytokine release syndrome, hypoxia, alanine aminotransferase (ALT) increased, aspartate transaminase (AST) increased, somnolence, and troponin increased. No Grade 4 or Grade 5 AEs related to Pexa-Vec were reported.

Patients receiving single-agent Pexa-Vec at a dose of 1×10^9 pfu had a RECIST disease control rate of 12% (2 of 17 evaluable patients). Patients receiving Pexa-Vec at a dose of 1×10^9 pfu in combination with irinotecan exhibited a disease control rate of 69% (9 of 13 evaluable patients). Final efficacy and safety data are pending at this time.

2.E.4 Other Key Clinical Studies with Pexa-Vec in Hepatocellular Carcinoma (HCC)

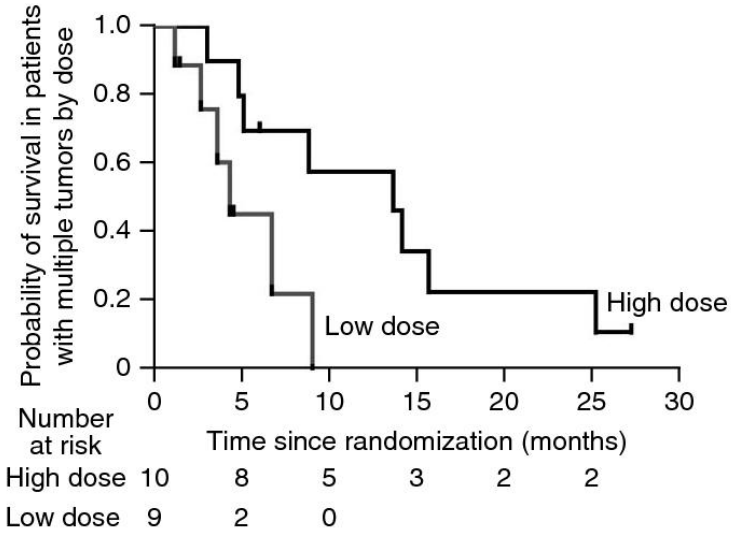
2.E.4.a Phase 2 Liver Cancer (HCC) Trial (JX594-IT-HEP007)

A Phase 2 randomized dose-finding trial of Pexa-Vec in patients with liver cancer (hepatocellular carcinoma [HCC]) (JX594-IT-HEP007) has been completed and the results published (*Heo 2013*). Pexa-Vec was administered by IT injection every 2 weeks for 3 total doses in patients with injectable tumors within the liver. Study dose levels were 1×10^8 pfu (Arm A) and 1×10^9 pfu (Arm B). Thirty patients were treated (16 patients in Arm A, 14 patients in Arm B). Twenty-nine patients received all 3 planned injections; one low-dose patient received 2 Pexa-Vec treatments. IT injection was well-tolerated at both dose levels in this population of patients with HCC. One treatment-related SAE was reported in the high-dose group (nausea and vomiting requiring prolonged hospitalization). Flu-like symptoms (Grade 1–2) occurred in all patients over the first 12–24 hours after treatment, including fever, rigors, nausea or vomiting. In the low dose cohort, Grade 3 AEs related to treatment included: hypertension, asthenia, dyspnea, hyperbilirubinemia, lymphopenia (2), aspartate aminotransferase increased (2), and white blood cell count (WBC) decreased. In the high dose cohort, Grade 3 AEs related to treatment included: pyrexia (3), hyperbilirubinemia, dehydration, hyponatremia, hypophosphatasia, and lymphocyte count decreased. No Grade 4 or Grade 5 AEs related to treatment were reported in both cohorts. Four patients responded to treatment based on modified RECIST (mRECIST) criteria (1 complete response [CR]; 3 partial responses [PR]). Responses were observed in injected and non-injected tumors. Further, overall survival was significantly longer in the high-dose arm compared with the

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low-dose arm (median 14.1 months versus 6.7 months, hazard ratio [HR] 0.39; p-value 0.020, Gehan-Breslow-Wilcoxon test; 1-sided test for superiority of high-dose) (Figure 7). The median overall survival was 9.0 months for the entire population.

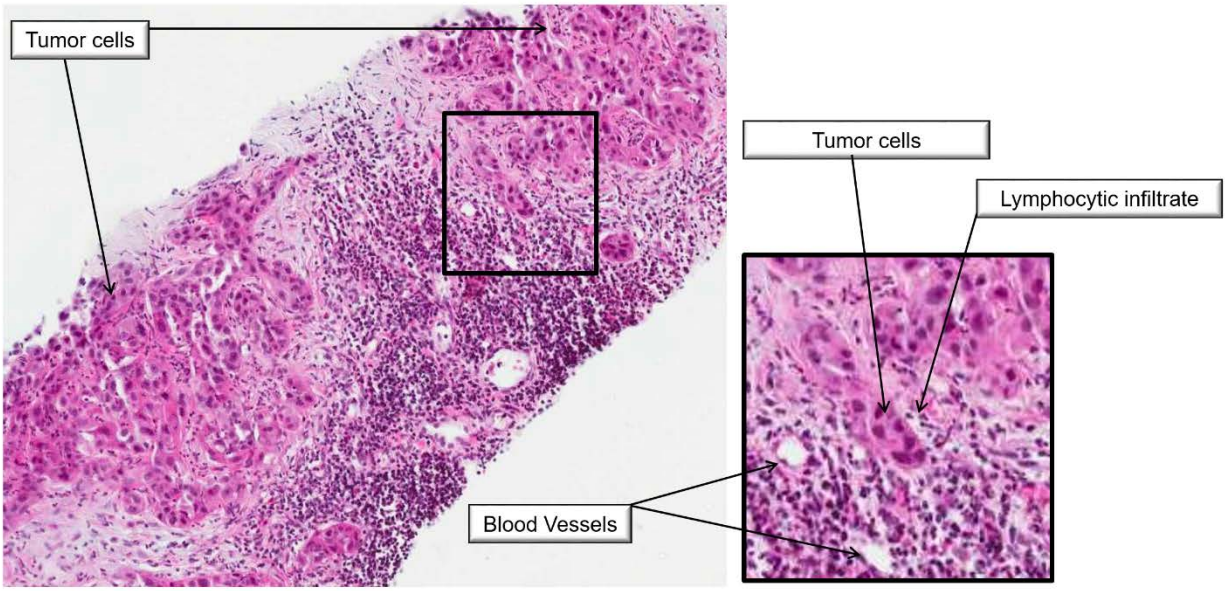
Figure 7: Kaplan-Meier Plot of Overall Survival by Dose



In this study, tumor lymphocytic infiltration was observed in a patient with HCC 1.5 years after Pexa-Vec therapy, demonstrating that tumor related inflammation may also occur in patients after treatment with Pexa-Vec. (Figure 8)

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Figure 8: Lymphocytic Infiltration of Non-Injected Tumor ~1.5 Years after Last Pexa-Vec Dose



Heo 2013

2.E.4.b Phase 2b Randomized Trial of Pexa-Vec Plus Best Supportive Care Versus Best Supportive Care in Patients with Advanced Hepatocellular Carcinoma Who Have Failed Sorafenib Treatment (JX594-HEP018/TRAVERSE)

One hundred and twenty-nine patients having failed previous sorafenib therapy were enrolled on this Phase 2b study and randomized 2:1 to receive either Pexa-Vec plus best supportive care (BSC) (Arm A) or BSC alone (Arm B). Eighty-six patients were assigned to the Pexa-Vec arm and were to receive one IV dose followed by up to 5 IT injections (1, 3, 6, 12, and 18 weeks after the IV infusion), and 43 to BSC-only arm.

The most common AEs related to Pexa-Vec experienced by patients in Arm A included: pyrexia (78.6%), chills (50.0%), pustular rash (28.6%), hypotension (26.2%), and nausea (25%). These AEs were generally mild-to-moderate in severity and tolerability, with the exception of hypotension, which was more severe than previously observed in other trials of Pexa-Vec.

The most frequent Pexa-Vec-related SAE, which occurred in 6 patients (8 SAEs) was severe hypotension defined as a systolic blood pressure <90 mmHg, lasting and requiring a medical treatment for at least 24 hours after Pexa-Vec administration. Notably, anti-hypertensive medication was on-going at the time of treatment with Pexa-Vec prior to the development of

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hypotension in the majority of these patients, thereby possibly exacerbating the potential for hypotension.

Treatment with Pexa-Vec did not improve overall survival or other efficacy measures, compared with BSC, in patients with advanced HCC in this open-label study. No significant improvement of overall survival was shown in Arm A compared to Arm B (p = 0.426, stratified log-rank test) for the Intent-to-Treat (ITT) population. Median overall survival was 4.2 (95% confidence interval [CI]: 3.3 to 5.4 months) vs 4.4 months (95% CI: 3.2 to 6.0 months) for Arm A vs Arm B, respectively. The hazard ratio observed was 1.19 (95% CI: 0.78 to 1.80).

The limited number of patients completing treatment on Arm A in conjunction with the significantly shorter median overall survival (~4.2 vs 4.4 months on Arms A and B, respectively) observed in this study versus studies of other agents for second line HCC (~7–9 months) suggests a relatively more advanced HCC patient population was included in TRAVERSE (*Llovet 2013; Zhu 2014*).

2.E.5 Other Studies of Pexa-Vec

Please refer to the IB for details on the remaining the clinical studies conducted with Pexa-Vec.

2.F OVERVIEW OF CLINICAL EXPERIENCE WITH CHECKPOINT INHIBITORS

Recent advances in tumor immunotherapy have centered on immunomodulation via antibodies targeting key ligand-receptor interactions between tumor specific T-cells and tumor cells or other immune cells. Most prominently anti-PD-1, anti-programmed death receptor ligand (anti-PD-L1), and anti-CTLA-4 antibodies (or "checkpoint inhibitors or CPI") have led to substantial clinical activity across multiple tumor types including drug approval in melanoma, non-small cell lung cancer, RCC, and bladder cancer. Further, CPI's have been relatively well-tolerated especially as compared to cytotoxic chemotherapy, although auto-immune events are observed across tumor types studied thus far. Despite breakthrough anti-tumor activity and manageable toxicity, single agent response rates across tumor types are generally only ~20% although a subset of responses appear to be durable. Similarly, for previously treated metastatic RCC the response rate is 25% as demonstrated in a Phase 3 randomized trial of nivolumab vs everolimus (refer above Section 2.A.1 for details). Therefore, although clearly representing a leap forward in the treatment of many incurable solid tumors, augmentation of single agent CPI activity through combination with novel therapies that may further boost anti-tumor immunity is being pursued.

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2.F.1 Clinical Studies

2.F.1.a Single Agent Experience

The first generation of check point blocker antibodies targeting CTLA-4, PD-1, PD-L1 were successful in generating responses in sub-sets of patients when used as single agent. Durable responses were seen in some melanoma, Hodgkin lymphoma, non-small cell lung cancer, bladder cancer, and renal cancer patients *(Hodi 2010; Powles 2014; Hamid 2013; Brahmer 2010)*. Use of predictive markers such as PDL1 status *(Herbst 2014; Garon 2015)* and mismatch repair enzyme status, *(Le 2015),* proved to be successful in identifying responders in certain indications. However, while these clinical outcomes were very encouraging, the limited response prompted a significant effort to enhance the frequency of responses by combination with chemotherapy, radiotherapy, targeted therapy, vaccines, and oncolytic viruses.

2.F.1.b Combination Studies

Combination studies using anti-PD-1 or anti-PD-L1 as a foundation have suggested improved efficacy with higher (but acceptable) toxicity. Combination studies with 2 checkpoint inhibitors, anti-PD-1 and anti-CTLA4, demonstrated a reduction in the risk of death versus anti-PD-1 monotherapy (nivolumab) in treatment-naïve advanced melanoma (*Larkin 2015*).

Combination studies with 2 checkpoint blocking antibodies, anti-PD-1, and anti-CTLA-4, demonstrated improved clinical benefit over the approved anti-CTLA-4 drug (Ipilimumab) when used alone in treating melanoma. While the improvement in overall survival is striking, it remains to be seen whether the durable benefit seen with Ipilimumab alone (up to 10 years), is also seen with the combination *(Robert 2015; Larkin 2015)*. Although combining anti-PD-1 and anti-CTLA-4 improved response rates, this particular combination also significantly increased toxicity *(Postow 2015)*. Improved response rates were also demonstrated when the anti-PD-1 / anti-CTLA-4 combination was used in treating non-small cell lung cancer. Numerous clinical studies of combinations of check point inhibitors are underway in a variety of indications (*ClinicalTrials.gov*). The combination of nivolumab and ipilimumab is approved for unresectable or metastatic melanoma. Further combinations are now in late stage clinical studies for multiple indications.

Chemotherapy and targeted therapy plus check point inhibitors have also been evaluated in preclinical models and in clinical settings. Synergy has been seen in several models, for example 5, fluorouracil, gemcitabine, and taxanes can cause a depletion of myeloid derived suppressor cells (MDSC's), priming an immune response that can better respond to check point blockade

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(Vincent 2010; Sevko 2013). Other chemotherapeutic agents that have demonstrated success in preclinical studies include epigenetic modifiers (e.g., histone deacetylase inhibitors) that synergize with CTLA-4 or PD-1 blockers to eradicate primary and metastatic tumors in murine models of relatively poor immunogenic tumors *(Kim 2014)*. The first combination of checkpoint inhibitor and chemotherapy was approved by the FDA in May 2017. Pembrolizumab in combination with pemetrexed and carboplatin is approved for first-line use in metastatic nonsquamous non-small cell lung cancer.

Targeted drugs directed to BRAF mutations or vascular endothelial growth factor receptor (VEGFR) angiogenic targets have been extensively studied preclinically and clinical trials evaluating combinations PD-1 inhibitors and BRAF inhibitors as well as MEK inhibitors are underway in melanoma trials.

Tumor cell vaccine combinations with check point inhibitors have also been evaluated. Among the studies reported, are combination GM-CSF based tumor vaccines with anti-CTLA-4 antibodies in murine models of glioma, where significant synergy was observed with combination over treatment with the tumor cell vaccine alone *(Agarwalla 2012)*. Similar synergy was seen with a GM-CSF expressing prostate cancer vaccine when combined with anti-CTLA-4 (*Wada 2013)*. The combination of Ipilimumab with an allogenic pancreatic tumor cell vaccine expressing GM-CSF was evaluated in a Phase 1 trial of 30 pancreatic cancer patients *(Jaffee 1998)*. Evidence of an enhanced effect of the combination over Ipilimumab alone in terms of disease progression markers was reported. These results are seen as a supporting model where vaccine priming can initiate an immune response that can be amplified by removal of a check point block.

Therapeutic interventions to improve the responsiveness of refractory "cold tumors" to immune check point blockers are being investigated with various combinational therapies in clinical trials. Effects of oncolytic viruses have been tested and it was reported that the replication and spread of oncolytic viruses was more active in cold tumors where there are few immune cells to eliminate the virus whereas hot tumors with ample resident tumor infiltrating lymphocytes can induce premature clearance of virus and attenuate its therapeutic effects *(Bell 2017)*. Oncolytic vaccina virus makes the tumor microenvironment more immunogenic by inducing intratumoral inflammatory responses: induction of T-cell responses along with activation and recruitment, and upregulation of PD-L1 *(Chon 2019, Kim 2018)*.

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2.G Cemiplimab

Cemiplimab is a hinge-stabilized IgG4P anti-PD-1 monoclonal antibody that has demonstrated encouraging efficacy and favorable tolerability in a Phase 1 study that is now enrolling patients in multiple expansion cohorts (*Papadopoulos 2016*) (NCT02383212). Cemiplimab is also being evaluated in a pivotal Phase 2 study for patients with unresectable locally advanced or metastatic cutaneous squamous cell carcinoma (NCT02760498). PD-1 is expressed on activated T-cells, and binding of PD-1 to its ligands, PD-L1 and PD-L2, imparts inhibition of cytotoxic T-cell activity (*Francisco 2010*). Upregulated expression of PD-1/PD-L1 checkpoint signaling in the tumor microenvironment plays a role in resistance to antitumor immune responses (*Zou 2008*).

2.G.1 Key Cemiplimab Preclinical Studies

A number of *in vitro* and *in vivo* studies have been performed to characterize the activity of Cemiplimab. Additionally, to compare the activity of Cemiplimab to the most clinically advanced anti-PD-1 antibodies, REGN1672 (primary sequence identical to nivolumab) and REGN2626 (primary sequence identical to pembrolizumab), were produced in-house based on publicly available sequences and included in the nonclinical pharmacology studies. A summary of the findings from *in vitro* and *in vivo* pharmacology studies is provided in Section 4.1 of the Cemiplimab Investigator's Brochure. Key findings are as follows:

- Cemiplimab, REGN1672, and REGN2626 bound monomeric human (KD = 5.61–11.9 nM) and monkey (KD = 3.38–9.02 nM) PD-1 with similar affinities
- Cemiplimab blocked the binding of both human PD-1 and cynomolgus monkey PD-1 to human PD-L1 and PD-L2 by ELISA with IC_{50} values below 1 nM for each, similar to the IC_{50} for inhibition by the comparator antibodies
- Cemiplimab blocked PD-1/PD-L1 signaling in a cell-based assay with an EC50 of 1.37 nM subsequently restoring T-cell receptor stimulation and downstream events. REGN1672 and REGN2626 blocked PD-1/PD-L1 signaling with EC50 values of 1.58 nM and 0.60 nM, respectively.
- Cemiplimab, REGN1672, and REGN2626 demonstrated robust inhibition of MC38.Ova tumor growth in PD-1 humanized mice. Mice that received 2.5 or 5 mg/kg Cemiplimab, REGN1672 and REGN2626 showed complete tumor regression in 6 of 7 (85.7%) mice during the course of treatment.

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2.G.2 Cemiplimab Use in Renal Cell Carcinoma (RCC)

In the Cemiplimab (anti-PD-1) first in human study (R2810-ONC-1423), patients received Cemiplimab alone or in combination with radiation therapy, GM-CSF, cyclophosphamide or cytotoxic chemotherapy. Only 2 patients have been treated with RCC, one with clear cell RCC and one with sarcomatoid RCC. The patient with clear cell RCC had previously progressed on MEDI0680, an experimental anti-PD-1 antibody. The patient tolerated therapy with 3 mg/kg Cemiplimab, radiation therapy, cyclophosphamide and GM-CSF without any SAEs or Grade 3–4 AEs, had stable disease (SD) on Day 56, and was removed from study on Day 121 after disease progression. The patient with sarcomatoid RCC tolerated therapy with Cemiplimab and low dose cyclophosphamide (200 mg/m^2 IV) without any SAEs or Grade 3–4 AEs, had an unconfirmed partial response on Day 113, and was removed from study for disease progression on Day 142.

2.G.3 Cemiplimab Pharmacokinetics

Cemiplimab pharmacokinetics in humans is discussed in Section 5.1.1 of the Cemiplimab IB.

2.G.4 Cemiplimab Animal Toxicology and Pharmacology

Cemiplimab animal toxicology and animal pharmacology are discussed in Section 4.3 and Section 4.2, respectively, of the Cemiplimab IB.

2.H RATIONALE

2.H.1 Rationale for Treatment of Renal Cell Carcinoma

2.H.1.a Rationale for Combination Therapy of Pexa-Vec and Cemiplimab

Significant evidence supports the concept that oncolytic virus mediated cell lysis induces an immune response that is at least partially responsible for anti-tumor efficacy. This has been reported for oncolytic adenovirus (*Kleijn 2014*), parvovirus (*Grekova 2012*), vaccinia (*Parviainen 2015*), herpes simplex virus (*Todo 1999*), Newcastle disease virus (*Zamarin 2014)*, vesicular stomatitis virus (*Diaz 2007*), and polio virus (*Toyoda 2011*). Preclinical studies of Pexa-Vec administered to a murine transgenic pancreatic tumor model demonstrates significant immune infiltration at the tumor site following IV viral delivery (refer to Section 2.D.1). The lysis of tumor cells by these viruses likely creates an "immunogenic meal" that is phagocytosed by antigen presenting cells, priming an immune response. This mechanism of action is immunologically distinct from the mechanism of check point blocker action, prompting the

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possibility that oncolytic viruses might synergize with a PD-1 pathway blocker. There are reports that PD-1 blockade can enhance the effects of vaccinia based oncolytic anti-tumor action in murine models *(Rojas 2015)*. Additionally, Quetglas et al. *(Quetglas 2015)* have demonstrated that a Semiliki Forest Virus based vector encoding IL12 synergizes with PD-1/PD-L1 blockade. A study of Reovirus treatment of B16 melanoma also demonstrated that PD-1 blockade significantly enhanced survival of mice as compared with Reovirus treatment or anti-PD-1 treatment alone. *In vitro* immune analysis demonstrated that check point inhibition improved the ability of natural killer (NK) cells to kill Reovirus infected tumor cells, reduced T(reg) activity and increased the adaptive CD8 (+) T-cell dependent anti-tumor response *(Rajani 2016)*.

The preclinical studies, reported by Zamarin et al. *(Zamarin 2014)* was the first to support clinical exploration of the use of checkpoint antibodies with oncolytic Newcastle disease virus. In a preclinical model of metastatic tumor, the combination therapy of Newcastle disease virus and CTLA-4 checkpoint blockade controlled both local and distant tumors better than either anti-CTLA-4 or Newcastle disease virus 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.

Clinically, the oncolytic herpes simplex virus, T-Vec, that has demonstrated efficacy in treatment of melanoma is being evaluated in combination with the check point blockers, Ipilimumab (CTLA-4), and Pembrolizumab (PD-1) delivered 2 weeks following virus delivery. Preliminary, interim analysis of the clinical data supports an enhancing effect of check point blocker on anti-tumor effect in this indication with the sequential administration of oncolytic virus and drug *(Puzanov 2016)*.

In summary, numerous preclinical studies, as well as limited clinical experience, support a clinical development strategy of Pexa-Vec administration in combination with checkpoint inhibition.

The rationale for the treatment of advanced RCC with Pexa-Vec and Cemiplimab is further supported by the following:

1. Clinical data indicating preliminary safety and activity of Pexa-Vec monotherapy for RCC (refer to Section 2.E.2 and Section 2.E.3 for details)

2. Preclinical evidence of Pexa-Vec anti-tumor activity in preclinical studies. Pexa-Vec was shown to infect and destroy all RCC cell lines tested (n = 8) *(Parato 2012)*.

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3. Initial preclinical data with Pexa-Vec revealing increased inflammation in tumors after Pexa-Vec treatment (refer to the preclinical Section 2.B.1) which may increase the anti-tumor activity of the combination vs single agent treatment

Despite the approval of check point blockers for first and second line therapy for RCC based on anti-tumor activity and a tolerable safety profile (*Motzer 2015b, Motzer 2018, Rini 2019, Motzer 2019*), there is a continued need for more effective treatments for advanced RCC which remains generally an incurable malignancy. Though numerous therapies, such as nivolumab, have become available for patients with metastatic RCC, a significant proportion of patients, do not respond to or progress on these therapies. Therefore, this population has a major unmet medical need for effective novel therapies.

2.H.2 Rationale for IV Administration

As of March 2020, over 750 doses of Pexa-Vec have been administered IV and generally well-tolerated in studies of multiple different advanced solid tumors across the Pexa-Vec clinical development program (refer to Section 2.E.1). In RCC specifically, weekly IV doses of Pexa-Vec were well-tolerated and associated with preliminary evidence of anti-RCC activity in an initial Phase 2 study of previously treated RCC patients (refer to Section 2.E.2 above).

Furthermore, biopsy-proven Pexa-Vec delivery to tumors following IV administration of a single Pexa-Vec dose has now been demonstrated in 7 patients with advanced, metastatic tumors (*Breitbach 2011a*). This finding is likely based on the fact that vaccinia biology is adapted to IV stability and delivery, even in the face of neutralizing antibodies, and Pexa-Vec is therefore designed for effective repeat IV dosing. Studies have demonstrated that vaccinia virus can spread locally by cell-to-cell infection and systemically by release into the blood stream and lymphatic system, using 2 variants of the virus' infective particles *(Smith 2002)*. Local, cell-to-cell infection is primarily accomplished by the cell-associated enveloped virion (CEV), a particle which becomes tethered to the host cell membrane, allowing for contact with, and subsequent infection of, neighboring cancer cells. CEV are motile and are actively "injected" into neighboring cancer cells. The second mechanism of spread utilizes the extracellular enveloped virion (EEV), which may be released into the blood stream and lymphatic system. The host cell derived outer envelope of this particle helps EEV to elude the host's immune system, permitting the particle to infect distant tissues and cells even in the face of neutralizing antibodies *(Vanderplasschen 1997)* and complement *(Vanderplasschen 1998)*. The final infectious form of the virus, the intracellular mature virus is released upon lysis of the infected cell. As vaccinia virus has evolved for systemic spread it may be a suitable oncolytic virus platform for repeat IV administration.

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2.H.3 Rationale for IT Administration

IT injection of Pexa-Vec into solid tumors has been well established. Phase 3 study of Pexa-Vec in first-line HCC utilized IT injection at a dose of 1×10^9 pfu with no new significant safety risks identified in over 160 patients treated with Pexa-Vec IT. This route of administration and dose was developed from the Phase 2 study, JX594-IT-HEP007, in which patients were assigned to receive either high-dose (1×10^9 pfu) or low-dose (1×10^8 pfu) Pexa-Vec (3 IT injections, each 2 weeks apart). Overall survival was significantly longer in the high-dose arm compared with low-dose (median 14.1 months versus 6.7 months).

Local administration of vaccinia virus is thought to have favorable efficacy for various reasons. IT administration reduces the systemic distribution of the virus in the bloodstream and therefore the exposure to neutralizing antibodies. Neutralizing antibodies are a part of the humoral response and should theoretically reduce the ability for subsequent virus particles to infect tumor cells. There is evidence to suggest that these neutralizing antibodies do not effectively penetrate tumor cells and so would not impede the infective and replicative ability of locally-administered virus (*Ganly 2000*).

IT administration of other oncolytic viruses are well-defined in the clinic. T-Vec was approved in 2015 for the treatment of metastatic melanoma and is administered for IT injection. In the Phase 3 study, responses were seen in un-injected skin and soft tissue sites and visceral tissues, evidence of an abscopal effect.

2.H.4 Rationale for Dose Selection

2.H.4.a Pexa-Vec

In studies to date, tolerability, delivery, replication and biological activity were consistently demonstrated at the top dose targeted in this proposed study, 1×10^9 pfu IV.

In a Phase 2 study of advanced RCC, repeated IV doses of 1×10^9 pfu IV resulted in a tolerable safety profile and preliminary evidence of anti-tumor activity (refer to Section 2.E.2).

In a pilot Phase 1 study of single agent Pexa-Vec, tumor responses (by mRECIST for mesothelioma and/or mChoi), disease control (by RECIST and/or mChoi), and suppression of new tumor outgrowth were also observed more frequently in higher dose cohorts than in patients receiving lower systemic doses of Pexa-Vec *(Breitbach 2011a)*. Furthermore, Pexa-Vec delivery to tumors following IV infusion was detected in tumor biopsies by qPCR as well as IHC staining

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only in patients treated at an absolute dose of 1×10^9 pfu or higher. Therefore, since biopsy-proven IV delivery and objective tumor response (mRECIST criteria) in patients with metastatic solid tumors were found to be feasible at 1×10^9 pfu, repeat dosing at 1×10^9 pfu was selected in order to further assess safety and efficacy in this trial. Lower doses would not be ethical or indicated since previously lower doses were shown not to result in tumor infection *(Breitbach 2011a)*. No DLTs were observed upon biweekly (every 2 weeks) IV dosing of Pexa-Vec in patients with advanced CRC (refer to Section 2.E.3.b). The safety of multiple IV infusions at this dose level is also currently being evaluated on an ongoing study (weekly IV dosing) in CRC (refer to Section 2.E.3.c). Most common AEs following IV infusion of Pexa-Vec were flu-like symptoms (fever, chills, nausea), generally resolving within 24 hours of treatment. In addition, mild, asymptomatic hypotension was observed acutely after IV treatment patients treated at 1×10^9 pfu and above (3/3 patients treated at approximately 3×10^9 pfu and 1/6 patients treated in the expansion cohort at a dose of 1×10^9 pfu).

2.H.4.b Cemiplimab

Cemiplimab monotherapy at a dose of 350 mg every 3 weeks (Q3W) is being utilized across its development program. This Cemiplimab dose of 350 mg Q3W was chosen based on the safety and preliminary anti-tumor activity observed in the ongoing first in human study R2810-ONC-1423 (NCT02383212), and was supported by modeling of Cemiplimab exposure in serum based on data collected in the first in human study.

Simulations of Cemiplimab exposure in 1000 patients using population pharmacokinetic analyses indicated that the variability in Cemiplimab exposure (CV%) was similar with body-weight adjusted as compared to fixed doses, therefore supporting the fixed dose selection, and that a 350 mg Q3W dose resulted in similar (≤20% difference) C_{trough}, AUC_{12W}, and C_{max} as compared to a 3 mg/kg Q2W dose, used in the first in human study. Cemiplimab concentrations exceeded those observed at 1 mg/kg Q2W dose, which demonstrated clinical efficacy in the first in human study and C_{trough} values exceeded concentrations of approximately 5 mg/L to 20 mg/L above which saturation of PD-1 target occupancy is expected to occur, based on animal data. The 350 mg Q3W dose of Cemiplimab has therefore been chosen as the optimal dose across the Cemiplimab program.

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2.H.5 Rationale for Schedule

This study is designed to provide preliminary data on the combination of Pexa-Vec and Cemiplimab, with Pexa-Vec delivered via IT or IV injection (e.g., in those patients without an injectable tumor).

Repeat systemic exposures from IT injections of liver tumors, as well as weekly IV infusions has been demonstrated safe and well-tolerated in previous trials (refer to Section 2.E.1). In those patients receiving IT Pexa-Vec (Arm A and a subset of patients in Arm B who progress on Cemiplimab therapy), doses will be administered once every 2 weeks. This is the most feasible dosing frequency for IT administration with supportive safety data.

Patients in Part 1 and Part 2, Arm C and Arm D will receive weekly IV doses of Pexa-Vec. As previously noted, in a Phase 2 study of advanced RCC, repeated weekly IV dosing at 1×10^9 pfu IV resulted in a tolerable safety profile and preliminary evidence of anti-tumor activity (refer to Section 2.E.2).

Repeat dose IV efficacy is superior to single dose efficacy in animal models. For example, 3 weekly doses of 1×10^9 pfu (4×10^8 pfu per kg) were superior to a single IV dose in rabbits bearing subcutaneous VX2 tumors (unpublished data). In addition, animal weight gain was significantly superior in IV weekly repeat dose treated animals compared with either saline treatment or a single IV administration (20% weight gain versus 1% versus 12%); this is likely due to tumor growth control. In addition, biweekly repeat IV dosing at 10^8 pfu (4.8×10^8 pfu/kg) resulted in significant efficacy (5/6 animals with complete responses) in a rat carcinogen induced liver cancer model *(Kim 2006)*. Finally, IV repeat dose Pexa-Vec was also safe and efficacious in a VX2 rabbit model with tumors in the liver or in widespread lung metastases (10^8 pfu [4×10^7 pfu/kg] were administered weekly IV). This regimen was safe, well-tolerated and exhibited significant efficacy versus phosphate buffer saline (PBS) control both in the liver tumors as well as lung metastases. Of note, this was also associated with significant increase in survival (80% vs. 0% at Day 65). Finally, animal weight gain was significantly superior with IV Pexa-Vec vs. PBS control (25% weight gain versus 20% weight loss by day 40; $p < 0.01$ [*Kim 2006*]).

Weekly doses are indicated for the following reasons. First, preclinical pharmacology and toxicology studies support the safety and efficacy of this regimen (refer to Section 2.E.3). Second, clinical data supports the safety of repeat IV exposure of Pexa-Vec at a weekly interval. Both after IV and IT administration, re-emergence of Pexa-Vec in systemic circulation within one week of dosing has been observed. However, the concentration of Pexa-Vec one week or more after IV dosing in patients with metastatic tumors is undetectable (or orders of magnitude less [≤1%] than

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the safe concentrations associated with acute dosing IV or IT) thereby reducing the risk of reaching a cumulative systemic dose of Pexa-Vec that could be toxic and supports the rationale and safety of weekly IV dosing. Finally, it is desirable to administer doses prior to development to neutralizing antibodies (shown to occur within 1–2 months) (*Park 2008*).

2.H.5.a Rationale of Sequence of Administration of Combination Therapy

Arm A, Arm C, and Arm D:

The rationale for the initial sequential administration of Pexa-Vec followed by Cemiplimab is based on preclinical studies. Rojas et al. *(Rojas 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 3 intraperitoneal doses of anti-CTLA-4 therapy could establish significant tumor growth control and increased overall survival in mice models of renal carcinoma. When the anti-CTLA-4 was administered concurrently with the vaccinia virus, no efficacy was observed.

The rationale for the combination treatment of Pexa-Vec plus Cemiplimab in tumors refractory to immune checkpoint blockers is based on recent preclinical data with therapeutic interventions to improve the responsiveness of "cold tumors". The replication and spread of oncolytic viruses was more active in cold tumors where there are few immune cells to eliminate the virus than in hot tumors *(Bell 2017)*. Oncolytic vaccinia virus makes the tumor microenvironment more immunogenic by inducing intratumoral inflammatory responses in Renca kidney tumor model and Rip-Tag2 pancreatic tumor model *(Chon 2019, Kim 2018)*.

Similar conclusions were reached in GM-CSF based vaccine combination treatments with anti-CTLA-4 in a prostate cancer model. Combined vaccine and anti-CTLA-4 treatment led to a dramatic increase in effector CD8 T-cells in the prostate gland and enhanced tumor antigen directed lytic function (*Wada 2013)*. These effects were seen when the ant-CTLA-4 blocking antibody was given after the vaccine treatment but not before. GM-CSF expressing glioma cells administered as a vaccine in combination with anti-CTLA-4 also were effective in treating murine intracranial tumors with optimal results being seen with sequential delivery of vaccine, followed by anti-CTLA-4 targeted antibodies rather than simultaneous delivery of both agents *(Agarwalla 2012)*.

T-Vec combination studies with checkpoint blocking antibodies are being carried out with sequential delivery of oncolytic virus and blocking antibodies, and promising responses have been

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reported *(Puzanov 2016)*. In another clinical context, patients with melanoma or ovarian cancer responded in a clinically meaningful way to later administration of CTLA-4 blocking antibodies.

Arm B:

Patients in Arm B will initially receive PD-1 therapy alone, followed by IT Pexa-Vec at the time of disease progression. The rationale for the design of this arm is two-fold. Firstly, it will provide a comparator of single-agent anti-PD-1 therapy against the combination arm (Arm A) when examining response rate. Secondly, enrollment in this arm will provide data on the ability of Pexa-Vec to sensitize tumors following anti-PD-1 therapy. Anti-PD-1 therapy will continue beyond initial progression alongside Pexa-Vec therapy.

2.H.6 Rationale for IV only Dose Escalation

As per the protocol, the Part 1 dose escalation comprises of a dose-escalation phase with IV administration only. In Part 2, Arm A and Arm B, who progress on Cemiplimab monotherapy, patients will be treated with the MTD/MFD determined in Part 1 via IT administration.

Based on previous studies, the AE profile for Pexa-Vec after IV and IT administration is similar (*internal SillaJen data*). The distribution of Pexa-Vec systemically after local IT administration has been found to be significantly less than that following IV administration. Pharmacokinetic studies of Pexa-Vec have shown that roughly half of the dose administered via IT injection distributes into the systemic circulation (*Park 2008*). Due to the higher systemic exposure to Pexa-Vec after IV compared to IT route of administration, and the similar AE profile observed following IT or IV, establishing the MTD in Part 1 of the study utilizing IV administration is a rational and efficient approach.

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3 OBJECTIVES

3.A PRIMARY OBJECTIVE

- *Part 1:* Determine the maximum tolerated dose (MTD) or maximum feasible dose (MFD) of Pexa-Vec administered by IV infusion in combination with IV-administered Cemiplimab
- *Part 1 and 2:* Determine the safety of Pexa-Vec administered by IV infusion or IT injection in combination with IV-administered Cemiplimab by assessing severity and frequency of AEs and laboratory toxicity using Common Terminology Criteria for Adverse Events (CTCAE) v5.
- *Part 2:* Evaluate anti-tumor activity and efficacy of IV or IT Pexa-Vec combined with IV Cemiplimab with respect to overall response rate (ORR) per Response Evaluation Criteria in Solid Tumors (RECIST 1.1)

3.B SECONDARY OBJECTIVES

- Determine progression free survival according to RECIST 1.1
- Determine the disease control rate (complete response [CR] + partial response [PR] + stable disease [SD]) by RECIST 1.1
- Determine best radiographic response (based on RECIST 1.1)
- Evaluate anti-tumor activity and efficacy of IV or IT Pexa-Vec combined with IV Cemiplimab with respect to overall response rate (ORR) per immune-related Response Evaluation Criteria in Solid Tumors (irRECIST)
- Determine the disease control rate (complete response [CR] + partial response [PR] + stable disease [SD]) by irRECIST
- Best radiographic response (based on irRECIST)
- Estimate overall survival

3.C EXPLORATORY OBJECTIVES

- To assess in the blood, the following immune parameters at Baseline, and on study Day 1 (excluding Arm B, Cemiplimab monotherapy), Day 22 (Day 43 in Arm D), End of

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Treatment, and Post Progression on anti-PD-1 monotherapy at Baseline, 2 weeks, and 4 weeks (Arm B only):

- Tumor specific and Pexa-Vec specific cellular immune responses (including but not limited to assessment of B-cells, T-cells, activated T-cells, NK cells, regulatory T-cells, MDSC)
- Pexa-Vec and Cemiplimab specific humoral responses
- Immune-related cytokines

- To assess in previously archived tumor biopsies (if available) and/or biopsied tumors at Baseline and on Study Day 8 (excluding Arm B, Cemiplimab monotherapy) and Day 57 (Arm B patients will undergo repeat biopsy at disease progression and 2 weeks after first Pexa-Vec):
  - Tumor microenvironment including T-cell, B-cells, NK cell, monocytes, macrophages, and other relevant immune cell subtypes of interest
  - Immune modulating proteins that may have predictive or prognostic value, including, but not limited to PD-L1, PD-1, and CTLA-4
  - Global changes in gene expression based on genome wide RNAseq analysis
  - Tumor mutational load based on whole exome sequencing of tumor and the matched germline blood DNA samples
  - Pexa-Vec infection and transgene expression
- Measure Cemiplimab and Pexa-Vec concentrations in serum and plasma, respectively

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4 STUDY DESIGN

4.A STUDY OVERVIEW

This is a Phase 1b, open-label, dose-escalation trial of Pexa-Vec administration plus Cemiplimab in patients with metastatic RCC (clear cell). It is estimated that approximately107 patients will be enrolled on the trial. Three to 12 patients may be enrolled in the Part 1 dose escalation and up to 101 patients will be enrolled in Part 2. Patients may be required to be replaced in the dose-escalation period due to insufficient exposure to the treatment regime. Up to a maximum of 3 patients will be replaced. The maximum number of patients to be enrolled in the study is 116.

4.A.1 Part 1 Enrollment

Patients will be treated with Pexa-Vec at one of 2 dose levels (Dose Level 1 at 3×10^8 pfu or Dose Level 2 at 1×10^9 pfu). Pexa-Vec will be administered via IV infusion weekly for 4 doses, beginning on Day –7.

Cemiplimab will be administered at a dose of 350 mg IV infusion every 3 weeks as previously established, beginning on Day 1. Three patients will be treated at Dose Level 1 unless a DLT, as defined within this protocol, is observed. Patients will be observed for a DLT during the IV treatment phase through Day 29, which includes all 4 Pexa-Vec IV infusions and 2 treatments of Cemiplimab. If a DLT does not occur in the first 3 patients, enrollment will proceed to Dose Level 2 where an additional 3 patients will be enrolled. However, if at any dose level one of the first 3 patients experiences a DLT, additional patients will be enrolled until a second patient experiences a DLT or until 6 total patients have been treated at that dose level, whichever comes first. If a second DLT is not experienced within the dose level, the next dose level or Part 2 may be initiated. If 2 patients in a dose level experience a DLT, enrollment will cease and the MTD will be defined for Part 2. To ensure that no more than 2 patients experience a DLT within a dose level, enrollment will proceed with the first 2 patients, then once the first patient has completed the DLT period (e.g., Day 29), the third patient may be enrolled. Enrollment into Dose Level 2 or Part 2 cannot proceed until all 3, or 6 patients, in the previous dose level have completed the DLT period. If one of the first 3 patients experiences a DLT, additional patients will be enrolled one at a time with the next patient entered into the study only after the preceding patient has completed the DLT period.

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4.A.2 Part 2 Enrollment

Up to an additional 101 patients will be enrolled in Part 2 of the study. There will be 4 treatment arms in Part 2: Arm A, Arm B, Arm C, and Arm D. Patients naïve to anti-PD-1 or anti-PD-L1 with lesions accessible for biopsy and injection will be randomized into Arm A or Arm B and will receive IT Pexa-Vec the MTD/MFD defined in Part 1. Patients naïve to anti-PD-1 or anti-PD-L1 with no accessible lesions for IT injection will be placed into Arm C and will receive IV Pexa-Vec at the established MTD or MFD determined in the Part 1 portion of the study to assess the safety and tolerability of treatment with Pexa-Vec in combination with Cemiplimab. Patients with prior treatment with anti-PD-1 or anti-PD-L1 will be placed on Arm D. Biopsies may be collected in patients with lesions amenable to biopsy in Arm C and Arm D.

Patients will be assessed radiologically (CT), at Screening and every 9 weeks until documented progression or discontinuation beyond documented progression. After 1 year, patients will be assessed every 12 weeks from EOT visit.

4.B STUDY ENDPOINTS

4.B.1 Primary Endpoints

- MTD or MFD of Pexa-Vec administered by IV infusions in combination with Cemiplimab
- Safety of Pexa-Vec administered by IV infusions or IT injections in combination with Cemiplimab as evaluated by incidence of all AEs, Grade 3 or greater AEs, SAEs, AEs requiring discontinuation of study agent(s), and deaths according to National Cancer Institute – Common Toxicity Criteria (NCI-CTC) version 5
- ORR according to RECIST 1.1
    - This is the primary efficacy endpoint for Part 2 and the basis for the power calculations

4.B.2 Secondary Endpoints

- Progression free survival according to RECIST 1.1
- Disease control rate (complete response [CR] + partial response [PR] + stable disease [SD]) by RECIST 1.1
- Best radiographic response (based on RECIST 1.1)

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- ORR according to irRECIST
- Best radiographic response (based on irRECIST)
- Disease control rate (complete response [CR] + partial response [PR] + stable disease [SD]) by irRECIST
- Overall survival

4.B.3 Exploratory Endpoints

- To assess in the blood, the following immune parameters at Baseline and on Study Days 1 (excluding Arm B, Cemiplimab monotherapy), Day 22 (Day 43 in Arm D) End of Treatment, and Post Progression on anti-PD-1 monotherapy at Baseline, 2 weeks, and 4 weeks (Arm B only):
    - Tumor specific and Pexa-Vec specific cellular immune responses (including but not limited to assessment of B-cells, T-cells, activated T-cells, NK cells, regulatory T-cells, MDSC)
    - Pexa-Vec and Cemiplimab specific humoral responses
    - Immune-related cytokines
- To assess in previously archived tumor biopsies (if available) and/or biopsied tumors at Baseline and on Study Day 8 (excluding Arm B, Cemiplimab monotherapy) and Day 57 (Arm B patients will undergo repeat biopsy at disease progression and 2 weeks after first Pexa-Vec):
    - Tumor microenvironment including T-cell, B-cell, NK cell, monocytes, macrophages, and other relevant immune cell subtypes of interest
    - Immune modulating proteins that may have predictive or prognostic value, including, but not limited to PD-L1, PD-1, CTLA-4
    - Global changes in gene expression based on genome wide RNAseq analysis
    - Tumor mutational load based on whole exome sequencing of tumor and the matched germline blood DNA samples
    - Pexa-Vec infection and transgene expression

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- Concentration of Cemiplimab and Pexa-Vec in serum and plasma, respectively, after Pexa-Vec IV and IT (pre-dose, end-of-infusion/injection and Day 8) with Cemiplimab IV (pre-dose and end-of-Day 1 infusion, Day 8, as well as C_{trough}, and C_{eoi} throughout therapy)

4.C STUDY COHORTS

4.C.1 Part 1

Part 1 will determine the MTD/MFD of Pexa-Vec, when given in combination with Cemiplimab at a dose of 350 mg.

Dosage cohorts per IV infusion:

- Dose Level 1: 3×10^8 pfu
- Dose Level 2: 1×10^9 pfu

Pexa-Vec IV Infusion will be administered weekly × 4 treatments starting on study Day –7 (Days –7, 1, 8, and 15 [Window: –1/+7 days]).

Cemiplimab IV infusion will be administered every 3 weeks, at a dose of 350 mg, starting on study Day 1 (Day 1, 22, 43…) [Window: ±3 days]

If patient has partial response (PR) or stable disease (SD), they may be eligible to receive Pexa-Vec boosters beyond Week 27 at the same dose.

4.C.2 Part 2 (Arm A)

Pexa-Vec will be given via IT injection, at the MTD/MFD as defined in part 1, administered every 2 weeks for 3 treatments, starting on Day –7 (Days –7, 8, 22 [Window: –4/+7 days])

Cemiplimab IV infusion will be administered every 3 weeks, at a dose of 350 mg, starting on study Day 1 (Day 1, 22, 43…) [Window: ±3 days] until disease progression, unacceptable toxicity, or a maximum treatment course of 1 year.

If patient has partial response (PR) or stable disease (SD), they may be eligible to receive Pexa-Vec boosters beyond Week 27.

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4.C.3 Part 2 (Arm B)

Cemiplimab IV infusion will be administered every 3 weeks, at a dose of 350 mg, starting on study Day 1 (Day 1, 22, 43…) [Window: ±3 days] until disease progression, unacceptable toxicity or a maximum treatment course of 1 year.

Pexa-Vec IT injection will be administered, at the MTD/MFD as defined in Part 1, every 2 weeks for 3 treatments, following progressive disease on Cemiplimab monotherapy. Please discuss with the Medical Monitor of the Sponsor prior for any questions.

If patient has partial response (PR) or stable disease (SD), after Pexa-Vec IT injection, they may be eligible to receive Pexa-Vec boosters 26 weeks after their initial Pexa-Vec treatment. See Section 6.F.17. Pexa-Vec Boosters.

4.C.4 Part 2 (Arm C and Arm D)

Pexa-Vec IV Infusion will be administered, at the MTD/MFD defined in Part 1, weekly × 4 treatments starting on study Day –7 (Days –7, 1, 8, and 15 [Window: –1/+7 days]).

Cemiplimab IV infusion will be administered every 3 weeks, at a dose of 350 mg, starting on study Day 1 (Day 1, 22, 43…) [Window: ±3 days] until disease progression, unacceptable toxicity or a maximum treatment course of 1 year.

If patient has partial response (PR) or stable disease (SD), they may be eligible to receive Pexa-Vec boosters beyond Week 27 at the same dose.

4.C.5 Dose Modifications

4.C.5.a Pexa-Vec

No intra-patient modification in the dose of Pexa-Vec is permitted. If a treatment is not given within the specified window (–1/+7 days for IV, –4/+7 for IT) then the treatment will be missed, but future protocol specified treatments will be administered as originally scheduled per protocol.

4.C.5.b Cemiplimab

No intra-patient modification in the dose of Cemiplimab is permitted. The specified window is ±3 days. Cemiplimab dosing can be delayed or temporarily interrupted up to 28 days or longer for

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management of immune-mediated adverse reactions (Appendix A). Doses may be administered outside the window after Sponsor approval.

4.D DOSE-LIMITING TOXICITY (DLT)

4.D.1 DLT Definition

A DLT is defined as any of the following Pexa-Vec or Cemiplimab treatment-related AEs that are evaluated and reported through Day 29 of the dose-escalation (Part 1) phase of the study. The DLTs described below are selected based on previous experience with Pexa-Vec, Cemiplimab, and other immunotherapies. Based on this determination, any of the following events observed in the dose-escalation phase would suggest significant clinical toxicity, at the specific dose level being tested or above.

Exceptions to the DLT definition include events that have been previously observed in prior Pexa-Vec and Cemiplimab clinical trials that were self-limiting and/or non-serious. Exclusion of these adverse events will reduce the risk of a premature MTD arising from events with a previously observed association, in both severity and frequency, to Pexa-Vec or Cemiplimab. Both DLTs and exceptions are listed below:

- Grade 4 hematologic toxicity lasting ≥7 days **except**:
  - Grade 4 lymphopenia without clinically relevant sequelae
  - Grade 4 thrombocytopenia not associated with a clinically significant bleeding event
- All Grade 3 and Grade 4 non-hematologic toxicity that represent a 2-grade increase over baseline **except**:
  - Grade 3 flu-like symptoms (specifically fatigue, malaise, headache, and myalgia) lasting <14 days.
  - Grade 3–4 fever lasting <3 days
  - Grade 3 hypotension lasting <24 hours
  - Grade 3–4 alopecia, hair or skin discoloration
  - Grade 3–4 nausea, vomiting and diarrhea lasting <7 days
  - Grade 3–4 hypothyroidism responsive to hormone therapy
  - Grade 3 hyponatremia without clinical significance

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- Grade 3–4 non-hematologic laboratory abnormalities without clinical significance (e.g., transient, asymptomatic elevation of amylase or lipase)

- Any Grade 3 or Grade 4 non-hematologic laboratory value if:
  - the abnormality leads to hospitalization
- Grade 3 or greater cardiac toxicity that does not decrease to a Grade 1 event 72 hours after initiation of maximal supportive care
- Grade 3 and Grade 4 thrombocytopenia with clinically-significant bleeding associated with Pexa-Vec
- Grade ≥3 febrile neutropenia
  - If Grade 3, the event must (in the judgement of both the Investigator and Sponsor)

    be clinically significant, and

    require intervention (e.g. G-CSF, antibiotic therapy) for resolution of the event
- Grade ≥3 myocarditis of any duration
- Grade 5 toxicity

The frequency, time to onset, and severity of toxicities, as well as the success of standard medical management and dosing interruptions/delays will be analyzed to determine if a given toxicity should be considered a DLT for dose escalation purposes.

AEs that appear to meet the DLT definition as described above will be discussed between the Sponsor and the Investigator. The decision of whether the AE meets the DLT definition, or not, will be based on a review of all relevant data by the Sponsor, with input from the Investigator.

4.D.2 DLT Reporting

DLTs will be evaluated and reported through the Day 29 evaluation period. To qualify for the DLT portion, patients must have suitable exposure to the regimen to assess for a DLT. Therefore, unless the patient discontinues the trial due to a DLT, patients will need to complete all 29 days of the evaluation period. In addition, patients will only be assessed if they have received at least 3 Pexa-Vec treatments and 1 Cemiplimab prior to Day 29. If the patient does not meet this criteria, the patient will be replaced.

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4.D.3 Timing of Cohort

4.D.3.a Part 1: Dose Escalation Sequence

Three patients will be treated at Dose Level 1 unless a DLT, as defined within this protocol, is observed. If a DLT does not occur in the first 3 patients, enrollment will proceed to Dose Level 2 where an additional 3 patients will be enrolled. However, if at any dose level one of the first 3 patients experiences a DLT, additional patients will be enrolled until a second patient experiences a DLT or until 6 total patients have been treated at that dose level, whichever comes first. If a second DLT is not experienced within the dose level, the next dose level or Part 2 may be initiated.

If 2 patients in a dose level experience a DLT, enrollment will cease and the MTD will be defined for Part 2.

To ensure that no more than 2 patients experience a DLT within a dose level, enrollment will proceed with the first 2 patients, then once the first patient has completed the DLT period (e.g., Day 29), the third patient may be enrolled. Enrollment into Dose Level 2 or Part 2 cannot proceed until all 3, or 6 patients, in the previous dose level have completed the DLT period. If one of the first 3 patients experiences a DLT, additional patients will be enrolled one at a time with the next patient entered into the study only after the preceding patient has completed the DLT period.

4.D.3.b Part 2 Patient Enrollment Sequence

Once the MTD or MFD has been established in Part 1, enrollment in Part 2 will begin.

Patients naïve to anti-PD-1 or anti-PD-L1 who have a lesion accessible for injection and biopsy will be randomized into Arm A or Arm B prior to the first study treatment. Patients in Arm A will receive the MTD/MFD dose of Pexa-Vec directly injected into accessible tumor(s) and IV Cemiplimab. Patients in Arm B will receive IV Cemiplimab until confirmed disease progression, when they will also receive Pexa-Vec (at the MTD/MFD dose established in Part 1) directly injected into accessible tumor(s). Twenty-seven patients will be enrolled into each of Arm A and Arm B. Randomization will be stratified by number of previous systemic therapies for RCC.

Patients naïve to anti-PD-1 or anti-PD-L1 who do not have an injectable lesion will be enrolled in to Arm C and will be treated at the MTD or MFD determined in the Part 1 portion of the study. An initial 11 patients will be enrolled into Arm C. If the response criteria is met (refer to Section 11.A.3), and further enrollment into this Arm is feasible, a further 9 patients may be enrolled at the discretion of the Sponsor to further determine efficacy and safety of this regimen.

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Patients with prior anti-PD-1 or anti-PD-L1 will be enrolled in to Arm D and will be treated at the MTD or MFD determined in the Part 1 portion of the study. An initial 19 patients will be enrolled into Arm D. If the response criteria is met (refer to Section 11.A.4), and further enrollment into Arm D is feasible, a further 8 patients may be enrolled at the discretion of the Sponsor to further determine efficacy and safety of this regimen. Patients will be assessed radiologically (CT), at Screening, Day 64/Week 9, and every 9 weeks until documented progression is confirmed (refer to Section 7.C.2). After 1 year, patients will be assessed every 12 weeks.

4.D.4 Monitoring of Patients Who Experience a DLT

Patients who experience a DLT will continue to be monitored post-treatment according to the Schedule of Events (refer to Section 6.D). If a DLT occurs during one of the infusions, Pexa-Vec administration will be stopped, and no further investigational product (IP) will be administered to that patient.

4.D.5 Patient/Study Stopping Rules

If 2 DLTs are observed within a cohort, enrollment into the cohort will cease. If any patient dies within 36 days of Pexa-Vec or Cemiplimab administration due to a serious and unexpected adverse drug reaction (ADR) that is determined to be possibly- or probably-related to Pexa-Vec or Cemiplimab, the study will be stopped and Regulatory Authorities and Institutional Review Boards (IRB) / Independent Ethics Committees (IECs) / Research Ethics Boards (REBs) will be notified.

4.E OVERALL STUDY DURATION AND FOLLOW UP

4.E.1 Study Participation

Patients will be on study from enrollment until a maximum treatment course of 1 year, confirmed disease progression, unacceptable toxicity, beginning other cancer therapy, patient withdrawal, or death, whichever comes first during the treatment period. Safety follow up will start 28 days after last dose of study treatment and survival will be followed up every 12 weeks from End of Treatment visit. Imaging follow up will be continued until confirmed radiographic progression.

4.E.2 End of Treatment Visit

When patients go off-study due to maximum treatment course reached, confirmed disease progression, beginning other cancer therapy, or early withdrawal, an End of Treatment Visit should

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be conducted depending on the timing of discontinuation. The End of Treatment Visit should be conducted as soon as possible, and within 4 weeks of going off study treatment. Patients will subsequently enter into the Survival Follow-Up Phase (refer to Section 4.E.3).

4.E.3 Survival Follow-Up Phase

Patients and/or their specified contacts will continue to be contacted approximately every 12 weeks from EOT visit for survival and information on subsequent anti-cancer therapy and their general safety and efficacy.

Once patients go off study and enter survival follow-up, other anti-cancer therapy, and other contraindicated medications are no longer prohibited. Additional images may be requested and independently reviewed for patients who have gone onto subsequent therapies.

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5 SELECTION OF PATIENTS

5.A INCLUSION CRITERIA

1. Histologically or cytologically confirmed metastatic or unresectable clear cell RCC

2. Naive to systemic therapy for RCC or have progressed after, or were intolerant of, prior systemic therapy.

   Part 2 Arm D ONLY: Patients must be refractory to anti PD-1 or anti-PD-L1 (either as monotherapy or in combination with other approved checkpoint inhibitors or targeted therapies according to their approved label) and patients must meet all of the following criteria:

   a. Received treatment of approved anti PD-1 or anti-PD-L1 (dosed per label of the country providing the clinical site) for at least 6 weeks.

   b. Progressive disease after anti PD-1 or anti-PD-L1 will be defined according to RECIST 1.1. The initial evidence of progressive disease is to be confirmed by a second assessment, no less than 4 weeks from the date of the first documented progressive disease, in the absence of rapid clinical progression. (This determination is made by the Investigator; the Sponsor will collect imaging scans for retrospective analysis. Once progressive disease is confirmed, the initial date of progressive disease documentation will be considered the date of disease progression).

   c. Documented disease progression within 12 weeks of the last dose of anti PD-1 or anti-PD-L1. Patients who were re-treated or on maintenance with anti-PD-1 or anti-PD-L1 will be allowed to enter the study as long as there is documented progressive disease within 12 weeks of the last treatment date.

3. Have measurable disease based on RECIST v1.1/irRECIST criteria as determined by the site study team. Tumor lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions.

4. At least one lesion, ≥1 cm longest diameter, injectable under imaging-guidance (except Part 1, Arm C, and Arm D, where lesions for injection are not required)

5. Expected survival of approximately 18 weeks or longer

6. Karnofsky performance status of 70–100 (refer to Appendix B)

7. Aged ≥20 years old (or appropriate age of consent for the region)

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8. WBC count ≥2,000 cells/mm^3 and ≤50,000 cells/mm^3
9. Absolute neutrophil count (ANC) ≥1,000 cells/mm^3
10. Hemoglobin ≥8 g/dL
11. Platelet count ≥75,000 platelets/mm^3
12. Partial thromboplastin time (PTT) within allowable institutional limits for biopsy or injection procedures (patients with non-accessible lesions or patients on anticoagulation therapy are exempt from this criteria)
13. International Normalized Ratio (INR) ≤1.5 (patients with non-accessible lesions or patients on anticoagulation therapy are exempt from this criteria)
14. Adequate liver function (albumin ≥2.8 g/dL, total; total bilirubin ≤3 mg/dL [51.3 µmol/L])
15. ALT and AST ≤2.5 times upper limit of normal (ULN) (in case of liver metastasis: ALT, AST ≤5 times ULN)
16. Serum chemistries sodium, potassium, and calcium within normal limits (WNL) or Grade 1
17. Serum creatinine <1.5 × ULN or estimated glomerular filtration rate >50 mL/min/1.73 m^2
18. For patients who are sexually active: willing to use double barrier contraception method for at least 6 weeks after each treatment of Pexa-Vec and, for patients who are of child bearing potential, for 6 months after each Cemiplimab treatment
19. Written informed consent obtained from the patient

5.B EXCLUSION CRITERIA

1. Known significant immunodeficiency due to underlying illness (e.g., human immunodeficiency virus [HIV] / acquired immune deficiency syndrome [AIDS]) and/or immune-suppressive medication including high-dose corticosteroids (defined as >10 mg/day prednisone or equivalent within 4 weeks prior to the initiation of study treatment). Inhaled steroids and adrenal replacement steroid doses ≤10 mg daily prednisone or equivalent are permitted in the absence of active autoimmune disease.
2. ***Part 2 Arm A, Arm B, and Arm C ONLY:*** Prior treatment with anti-PD-1 or anti-PD-L1 (prior IL-2 or interferon allowed). ***For Part 1 ONLY:*** patients are excluded if they were intolerant to anti-PD-1, anti-PD-L1, or anti-CTLA4 targeted therapies.

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3. Major surgery within 4 weeks of study treatment (minor surgical procedures are allowed [e.g., intravascular access line or port-a-cath])

4. Local-regional therapy within 4 weeks prior to study treatment.

5. Systemic therapy for RCC within 4 weeks prior to study treatment, with the exception of:

    a. TKI and mTOR inhibitors which can be administered up until 2 weeks prior to study treatment.

    b. ***Arm D ONLY:*** anti-PD-1 or anti-PD-L1 agents which can be administered up until 3 weeks prior to study treatment. Anti-CTLA-4 which can be administered up until 60 days prior to study treatment.

    NOTE: Any toxicities attributed to prior anti-cancer therapy, other than alopecia, must resolve to Grade 1 (National Cancer Institute [NCI] CTCAE v5) or baseline before randomization.

    Part 2 Arm D ONLY: Resolution/improvement of immune related AEs (irAEs) back to Grade 0, 1, and ≤10 mg/day prednisone (or equivalent dose) for irAEs for at least 2 weeks prior to the first dose of study drug. Patients must have:

        a. No history of common toxicity criteria adverse events (CTCAE) Grade 4 irAEs from anti PD-1 or anti-PD-L1.

        b. No history of CTCAE Grade 3 requiring steroid treatment (>10 mg/day prednisone or equivalent dose) for >12 weeks or CTCAE Grade 2 pneumonitis regardless of steroid treatment.

6. Ongoing severe inflammatory skin condition requiring medical treatment

7. History of severe eczema requiring prior medical treatment

8. 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-treatment tumor swelling and/or necrosis.

9. Clinically significant and/or rapidly accumulating ascites, pericardial and/or pleural effusions.

10. 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.

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11. Asymptomatic cardiovascular disease (current or past history) unless cardiology consultation and clearance has been obtained for study participation.

12. Medical conditions that place the patient at risk should tachycardia, hypotension or volume loading occur during or following treatment with Pexa-Vec

13. Viable central nervous system malignancy (history of completely resected or irradiated brain metastases allowed)

14. Participation in any other research protocol involving an IP within 4 weeks prior to first treatment

15. 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

16. Prior malignancy except for cancer from which the patient has been disease-free for 3 years, or the following: adequately treated basal or squamous cell skin cancer, *in situ* carcinoma (including cervical, prostate or breast cancer, superficial bladder cancer), adequately treated Stage 1 or Stage 2 cancer from which the patient is currently in complete remission.

17. Prior or planned organ transplant (e.g., kidney transplant)

18. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation.

19. Experienced a severe systemic reaction or side-effect as a result of a previous vaccinia vaccination

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

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 all Pexa-Vec treatments.

22. Previous treatment with Pexa-Vec or other vaccinia vector based treatment

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

24. Use of PEG-IFN or ribavirin that cannot be discontinued within 14 days prior to any Pexa-Vec dose.

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***NOTE*:** Please consult the Medical Monitor if patient is taking any other anti-viral medications to determine eligibility

25. Inability to receive IV contrast agents for CT or magnetic resonance imaging (MRI) scanning due to documented history of contrast allergy unless controlled by medical intervention (e.g., premedication with steroids, diphenhydramine, or other anti-allergic medications)

26. *For patients with accessible tumors:* The use of anti-platelet or anti-coagulant therapy that cannot be safely suspended for per protocol biopsies as per standard of care or IT injections as per the following guidance:

    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 injections

    e. Oral direct thrombin inhibitor (dabigatran) or direct Factor Xa inhibitor (rivaroxaban, apixaban 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 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

Please contact the Sponsor for questions regarding the management of other anticoagulants prior to treatments.

27. Active autoimmune disease that has required systemic treatment in past 2 years (i.e., with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered an excluded form of systemic treatment.

28. History of non-infectious pneumonitis.

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29. History of interstitial lung disease.

30. Known active Hepatitis B (e.g., HbsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative] is detected).

31. Patients must not receive live vaccines, other than Pexa-Vec, within 30 days of planned start of study investigational product, during the study, and for a minimum of 15 weeks after the last dose of investigational product

32. Documented allergic or acute hypersensitivity reaction attributed to antibody treatments

33. Known allergy to doxycycline or other tetracycline antibiotics

34. ***AUSTRALIA ONLY:*** *Patients with no accessible tumors*:

    - For the period from first study treatment to two weeks following last infusion of Pexa-Vec. Patients likely to come in to contact with:
    - Children under 12 months of age;
    - Women who are known to be pregnant, or who are breastfeeding;
    - Persons with known significant immunodeficiency due to underlying illness (e.g., HIV/AIDS) and/or immunosuppressive medication;
    - Persons with an ongoing severe inflammatory skin condition requiring medical treatment; and
    - Persons with a history of severe eczema requiring prior medical treatment

      NOTE: This must be documented in writing.

5.C PATIENT ENROLLMENT PROCEDURES

5.C.1 Ensuring Eligibility

The Principal Investigator is ultimately responsible for ensuring that patient(s) meet all eligibility criteria prior to enrollment. Once the Investigator conducts the screening evaluations and confirms a patient's eligibility, the SillaJen Medical Monitor will review screening and eligibility information and provide written approval to the Investigator for each patient's enrollment.

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5.C.2 Screen Failures

Patients ineligible for any of the aforementioned reasons may be re-screened for participation if their eligibility characteristics change. A new study screening identification number will be assigned if a patient is re-screened, and a new informed consent form (ICF) will be signed.

5.C.3 Obtaining Detailed Contact Information

At Baseline visit, a Patient Contact Log will be completed. The log will include detailed contact information for the patient and family/caregivers and will be updated periodically throughout study participation to ensure current contact information is on file. This log will remain on site and will not be collected by the Sponsor.

5.D PATIENT WITHDRAWAL CRITERIA

Patients may be discontinued (withdrawn) from active study participation (i.e., prior to radiographic disease progression or maximum treatment course) by the site Principal Investigator or Medical Monitor for any of the following reasons:

- An intercurrent illness develops that precludes objective clinical assessments
- Prohibited concomitant medications are required or used
- The incidence or severity of AEs in this study denotes potential untoward health risks
- Consent for study participation is withdrawn
- Any other situation where, in the opinion of the Investigator or the Medical Monitor, continued participation in the study would not be in the best interest of the patient
- Termination of the study by SillaJen, Inc.
- Request by a Health Authority or IRB/IEC/REB

5.D.1 Data Collection for Withdrawn Patients

If patient is withdrawn from active study participation prior to confirmation of tumor progression by site, an End of Treatment Visit should be performed as soon as possible. The reason(s) for withdrawal should be reported on case report forms (CRFs). Subsequently, all patients should continue to be followed for survival provided consent for continued monitoring has been provided

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by the patient. AEs should be documented as soon as possible, but at least 28 days after the most recent treatment allow for collection and assessment of AEs and Concomitant Medications.

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6 STUDY PROCEDURES AND TREATMENT

6.A ADMINISTRATION OF PEXA-VEC

6.A.1 Pexa-Vec IV Infusions (Part 1 / Part 2: Arm C and Arm D): Day –7, 1, 8, and 15

Patients allocated to Part 1 or Part 2: Arm C or Arm D will receive an IV infusion of Pexa-Vec in approximately 250 mL buffered saline. Refer to the *Infusion Preparation Worksheets* for details. Patients will be observed in the clinic and/or hospital for a minimum of 20 hours after the infusion.

Treatments 2–4 may be administered at weekly 7-day intervals (–1/+7 days). If a treatment is not given within the window, it will be considered missed (e.g., the patient will not receive the infusion, but future protocol specified treatments will be administered as originally scheduled per protocol). Pexa-Vec treatments must be at least 6 days apart.

6.A.2 Pexa-Vec IT Injections (Part 2 Arm A + Arm B)

Patients in Part 2, Arm A (and those in Arm B who progress on Cemiplimab monotherapy) will receive an IT injection of Pexa-Vec in a volume of buffered saline dependent on size of tumor(s). Patients will be observed in the clinic and/or hospital for a minimum of 8 hours after the injection.

Treatments are administered at 14-day intervals (–4/+7 days). If a treatment is not given within the window, it will be considered missed (e.g., the patient will not receive the injection, but future protocol specified treatments will be administered as originally scheduled per protocol). IT Pexa-Vec treatments must be at least 10 days apart.

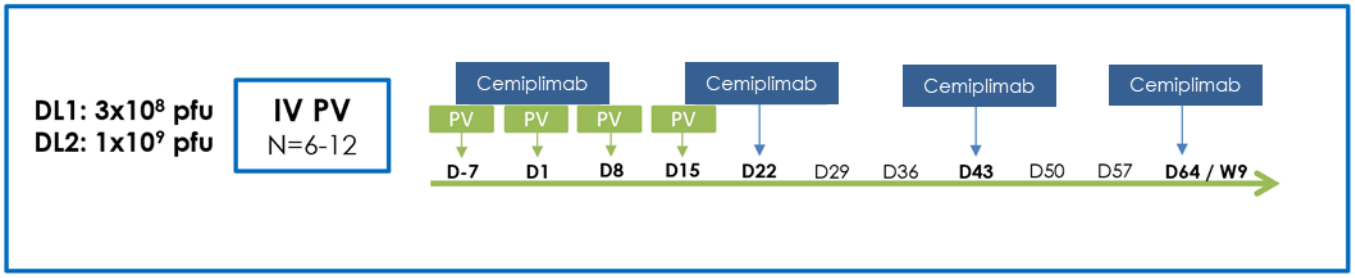
6.B ADMINISTRATION OF CEMIPLIMAB

Cemiplimab will be administered at a dose of 350 mg IV infusion over 30 minutes (±10 minutes) every 3 weeks per manufactures guidelines. Starting at Day 1, treatments will be administered at 21-day intervals (±3 days). If Cemiplimab and Pexa-Vec are given on the same day, Cemiplimab will be completed prior to the start of the Pexa-Vec infusion/injection by at least 1 hour. In the event of Pexa-Vec treatment is delayed, the Cemiplimab should be administered per protocol. Cemiplimab dosing may be delayed or temporarily interrupted by up to 28 days or longer for management of immune-mediated adverse reactions (refer to Appendix A for details) upon Sponsor's approval.

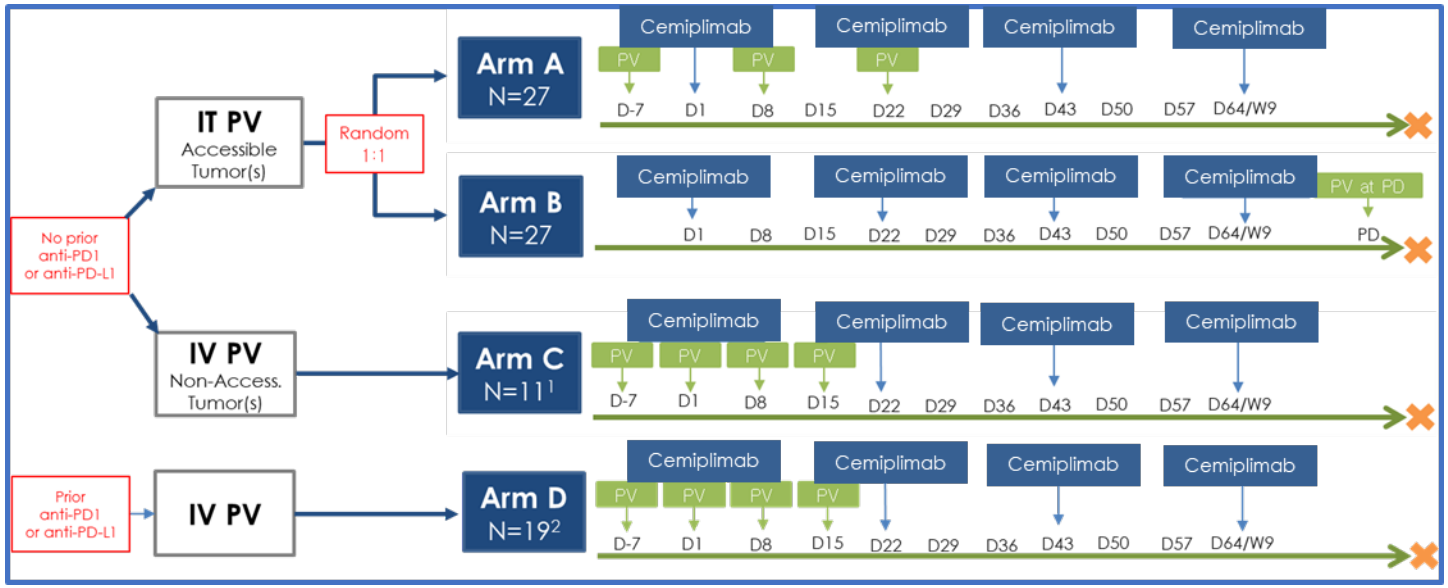
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6.C STUDY SCHEMATIC

6.C.1 Part 1



6.C.2 Part 2



[1] N to be expanded to 20, pending clinical efficacy
[2] N to be expanded to 27, pending clinical efficacy

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6.D SCHEDULE OF EVENTS

6.D.1 Part 1 / Part 2 - Arm C and Arm D

PART 1 / Part 2 - Arm C and Arm D Schedule of Events	Screen	Baseline	Cycle 1								Anti-PD-1 Maintenance[19] + Pexa-Vec Booster[14]			End of Treatment	Overall Survival Visit[17]	Safety Follow-up
Visit Day/Week[1]	Screen	Baseline	D-7	D1	D8	D15	D22	D43	D57[10]	D64	Q 3 Week	Q 9 Weeks (From W27)	Q 9 weeks[15]	After Last Treatment	Q 12 weeks	End of Study
Window (days)	–35 to –7	–11 to –7	n/a	–1/+7	–1/+7	–1/+7	±3	±3	±5	±3	±3	±7	±7	Within 28	±14	28–60 days after last dose
Informed Consent	X															
IWRS	X	X	X	X	X	X	X	X		X	X	X		X		
Medical history	X	X[9]	X[9]													
Physical exam (including weight)[2]	X	X	X	X[22]	X[22]	X[22]	X[22]	X[22]		X[22]	X[22]	X[22]		X		X
Height	X															
KPS	X	X								X			X	X		
Vital signs	X	X	X[11]	X[11]	X[11]	X[11]	X[11]	X[11]	X	X[11]	X[11]	X[11]		X		X
Pulse Oximetry	X	X	X[11]	X[11]	X[11]	X[11]	X[11]	X[11]	X	X[11]	X[11]	X[11]		X		X
Cardiac function (ECG and Echo)	X													X		
Pexa-Vec Re-Treatment Eligibility[3]				X	X	X						X				
Cemiplimab Re-Treatment Eligibility[3]				X			X	X		X	X					
TREATMENTS																
Pexa-Vec IV infusion			X	X[12]	X[12]	X[12]						X[12]				
Cemiplimab IV infusion				X[12]			X[12]	X[12]		X[12]	X[12]					
LABORATORY TESTS																
Hematology	X	X		X[22]	X[22]	X[22]	X[22]	X[22]	X	X[22]	X[22]	X[22]		X		X
Chemistry Panel	X	X		X[22]	X[22]	X[22]	X[22]	X[22]	X	X[22]	X[22]	X[22]		X		X
Coagulation	X	X[10]			X[10]				X							
Thyroid Function	X									X			X[18]	X		X
Troponin	X						X	X		X	X[21]					

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PART 1 / Part 2 - Arm C and Arm D Schedule of Events	**Screen**	**Baseline**	**Cycle 1**								**Anti-PD-1 Maintenance[19] + Pexa-Vec Booster[14]**			**End of Treatment**	**Overall Survival Visit[17]**	**Safety Follow-up**
Visit Day/Week[1]	**Screen**	**Baseline**	**D-7**	**D1**	**D8**	**D15**	**D22**	**D43**	**D57[10]**	**D64**	**Q 3 Week**	**Q 9 Weeks (From W27)**	**Q 9 weeks[15]**	**After Last Treatment**	**Q 12 weeks**	**End of Study**
Window (days)	–35 to –7	–11 to –7	n/a	–1/+7	–1/+7	–1/+7	±3	±3	±5	±3	±3	±7	±7	Within 28	±14	28–60 days after last dose
Amylase and Lipase	X	X														
Hepatitis B and C	X															
HIV Test	X															
Pregnancy test[4]	X	X														
Urinalysis	X															
SAMPLES ARCHIVING FOR ANALYSIS																
Pexa-Vec PK			X[20]	X[20]	X[20]	X[20]										
Cemiplimab PK				X[20]	X		X[20]	X[20]		X[20]	X[20]					
Blood – Immune Corr.		X		X			X	X[24]						X		
Biopsy – Immune Corr.[23]		X[10]			X[10, 13]				X							
IMAGING STUDIES																
CT / MRI	X									X			X	X		
Nuclear Bone Scan	X									X[7]			X[7]	X[7]		
MRI/CT Head	X[7]									X[7]			X[7]	X[7]		
OTHER																
irRECIST Tumor Assessment[16]	X									X			X	X		
IT injection eligibility review by IR	X															
AE collection[5]	X[8]	X[8]	X[8]	X	X	X	X	X	X	X	X	X	X	X		X
Concomitant medications[6]	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Anti-cancer therapies															X	
Patient Contact Log		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Survival															X	

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Part 1 / Part 2 – Arm C and Arm D Footnotes

1. All visit dates will be counted from the treatment initiation date per each group such as "Day 1" for Arm B and "Day –7" for Part 1, Arms A, C, and D.
2. Complete physical exam should include assessment for presence of skin pustules. At screening, height will be collected.
3. Assessment for Pexa-Vec and/or Cemiplimab re-treatment eligibility can occur up to 3 days prior to treatment visit (refer to Section 6.F.14 for more details).
4. If positive, an ultrasound for pregnancy confirmation can be performed prior to screen failing the patient.
5. AEs will continue to be collected and recorded through 28 days after last study treatment, Pexa-Vec and/or Cemiplimab
6. Concomitant medications will continue to be collected through 28 days after last study treatment, Pexa-Vec and/or Cemiplimab
7. If applicable, refer to Section 6.F.15 for details
8. From the date of signature of the ICF and up to initiation of IP, Pexa-Vec and/or Cemiplimab, only SAEs caused by a protocol-required procedure will be collected and reported to the Sponsor.
9. Medical and surgical history should be updated with any AEs/SAEs that would have occurred from the signature of the informed consent form (before study treatment).
10. In patients with tumors accessible for core biopsy, visit/procedure only to be performed if biopsy taken
11. Please refer to the *Study Procedures* section (Section 6.F.3) for timing of vital signs before and after Cemiplimab or Pexa-Vec IV infusion. If Pexa-Vec or Cemiplimab is missed, only baseline vitals should be taken as part of the pre-visit assessment.
12. Patients must meet re-treatment eligibility to be re-treated. If eligibility is initially not met, the patient may be re-evaluated and treated if eligible, so long as the treatment occurs within the specified window (e.g. until Day 8 for IV Pexa-Vec #2). It should be noted that IV Pexa-Vec cannot be given less than 6 days from previous Pexa-Vec infusions, and the last date for IV Pexa-Vec, unless approved by Sponsor, is Day 22. If a treatment is not given within the window, it is missed. Subsequent treatments may still be given if patient is eligible and within the treatment window.
13. Up to 4 days prior to Day 8 Pexa-Vec IV Infusion
14. "Booster" Pexa-Vec infusions to be given only to patients beyond Week 27 up to 1 year from the initial treatment with stable disease (SD) or partial response (PR) at latest imaging
15. Imaging every 9 weeks (or every 12 weeks after 12 months), will continue until confirmed progressive disease (PD) (and further PD, if needed. See Section 6.F.16) regardless of IP dispensation status.
16. As per irRECIST criteria, a response (PR or CR) or progressive disease (PD) should be confirmed at least 4 weeks following initial finding on imaging. Please see Section 6.F.16 and Site Reader Manual for more details.
17. Patient survival and anti-cancer therapy reporting to be performed in patients who have discontinued from study treatment.
18. Only collected if Cemiplimab treatment is ongoing
19. Cemiplimab to continue for no longer than 12 months
20. Pre-dose and at end of infusion (within 15 minutes of end of infusion)
21. Collected every 6 weeks only
22. Performed or collected within 72 hours prior to infusion
23. Previously archived tumor biopsy prior to enrollment may be collected if available.
24. Sampling at D43 instead of D22 in Arm D patients.

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6.D.2 Part 2 – Arm A

Arm A Schedule of Events	**Screen**	**Baseline**	**Cycle 1**							**Anti-PD-1 Maintenance[14] + Pexa-Vec Booster[15]**			**End of Treatment**	**Overall Survival Visit[19]**	**Safety Follow-up**
Visit Day/Week[1]	**Screen**	**Baseline**	**D–7**	**D1**	**D8**	**D22**	**D43**	**D57[23]**	**D64**	**Q 3 Week**	**Q 9 Weeks (From W27)**	**Q 9 weeks[17]**	**After Last Treatment**	**Q 12 weeks**	**End of Study**
Window (days)	–35 to –7	–11 to –7	n/a	±3	-4/+7	–4/+7	±3	±5	±3	±3	±7	±7	Within 28	±14	28–60 days after last dose
Informed Consent	X														
IWRS	X	X	X	X	X	X	X		X	X	X		X		
Medical history	X	X[10]	X[10]												
Physical exam (including weight)[2]	X	X	X	X[22]	X[22]	X[22]	X[22]		X[22]	X[22]	X[22]		X		X
Height	X														
KPS	X	X							X			X	X		
Vital signs	X	X	X[11]	X[11]	X[11]	X[11]	X[11]	X	X[11]	X[11]	X[11]		X		X
Pulse Oximetry	X	X	X[11]	X[11]	X[11]	X[11]	X[11]	X	X[11]	X[11]	X[11]		X		X
Cardiac function (ECG and Echo)	X												X		
Pexa-Vec Re-Treatment Eligibility[3]					X	X					X				
Cemiplimab Re-Treatment Eligibility[3]				X		X	X		X	X					
TREATMENTS															
Pexa-Vec IT injection			X		X[12]	X[12]					X[12]				
Cemiplimab IV infusion				X		X[12]	X[12]		X[12]	X[12]					
LABORATORY TESTS															
Hematology	X	X	X[22]	X[22]	X[22]	X[22]	X[22]	X	X[22]	X[22]	X[22]		X		X
Chemistry Panel	X	X	X[22]	X[22]	X[22]	X[22]	X[22]	X	X[22]	X[22]	X[22]		X		X
Coagulation	X	X	X[22]		X[22]	X[22]		X			X[22]				
Thyroid Function	X								X			X[16]	X		X
Amylase and Lipase	X	X													
Troponin	X					X	X		X	X[21]					
Hepatitis B and C	X														

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Arm A Schedule of Events	**Screen**	**Baseline**	**Cycle 1**							**Anti-PD-1 Maintenance[14] + Pexa-Vec Booster[15]**			**End of Treatment**	**Overall Survival Visit[19]**	**Safety Follow-up**
Visit Day/Week[1]	**Screen**	**Baseline**	**D–7**	**D1**	**D8**	**D22**	**D43**	**D57[23]**	**D64**	**Q 3 Week**	**Q 9 Weeks (From W27)**	**Q 9 weeks[17]**	**After Last Treatment**	**Q 12 weeks**	**End of Study**
Window (days)	–35 to –7	–11 to –7	n/a	±3	-4/+7	–4/+7	±3	±5	±3	±3	±7	±7	Within 28	±14	28–60 days after last dose
HIV Test	X														
Pregnancy test[4]	X	X													
Urinalysis	X														
SAMPLES ARCHIVING FOR ANALYSIS															
Pexa-Vec PK			X[20]		X[20]	X[20]									
Cemiplimab PK				X[20]	X	X[20]	X[20]		X[20]	X[20]					
Blood – Immune Corr.		X		X		X							X		
Biopsy – Immune Corr.[24]		X[9]			X[13]			X[13]							
IMAGING STUDIES															
CT / MRI	X								X			X	X		
Nuclear Bone Scan	X								X[7]			X[7]	X[7]		
MRI/CT Head	X[7]								X[7]			X[7]	X[7]		
OTHER															
irRECIST Tumor Assessment[18]	X								X			X	X		
IT injection eligibility review by IR	X										X				
AE collection[5]	X[8]	X[8]	X[8]	X	X	X	X	X	X	X	X	X	X		X
Concomitant medications[6]	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Anti-cancer therapies														X	
Patient Contact Log		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Survival														X	

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Part 2 – Arm A Footnotes

1. All visit dates will be counted from the treatment initiation date per each group such as "Day 1" for Arm B and "Day –7" for Part 1, Arms A, C, and D.
2. Complete physical exam should include assessment for presence of skin pustules. At Screening, height will be collected.
3. Assessment for Pexa-Vec and/or Cemiplimab re-treatment eligibility can occur up to 3 days prior to treatment visit. Refer to Section 6.F.14 for more details.
4. If positive, an ultrasound for pregnancy confirmation can be performed prior to screen failing the patient
5. AEs will continue to be collected and recorded through 28 days after last study treatment, Pexa-Vec and/or Cemiplimab.
6. Concomitant medications will continue to be collected through 28 days after last study treatment, Pexa-Vec and/or Cemiplimab.
7. If applicable, see Section 6.F.15 for details
8. From the date of signature of the ICF and up to initiation of IPs, Pexa-Vec and/or Cemiplimab, only SAEs caused by a protocol-required procedure will be collected and reported to the Sponsor.
9. First biopsy to be taken up to 14 days prior to Pexa-Vec treatment, inclusive of treatment day
10. Medical and surgical history should be updated with any AEs/SAEs that would have occurred from the signature of the informed consent form (before study treatment)
11. Please refer to the *Study Procedures* section (Section 6.F.3) for timing of vital signs before and after Cemiplimab IV infusion or Pexa-Vec IT administration. If Pexa-Vec or CEMIPLIMAB is missed, only baseline vitals should be taken as part of the pre-visit assessment.
12. Patients must meet re-treatment eligibility to be re-treated. If eligibility is initially not met, the patient may be re-evaluated and if eligible treated, so long as the treatment occurs within the specified window (e.g., until Day 15 for IT Pexa-Vec #2). It should be noted that IT Pexa-Vec cannot be given less than 10 days from previous Pexa-Vec injections (excluding "Boosters"), and the last date for IT Pexa-Vec, unless approved by Sponsor, is Day 29. If a treatment is not given within the window, it is missed. Subsequent treatments may still be given if patient is eligible and within window.
13. Second and 3rd biopsy to be taken up to 4 days prior to visit day
14. Cemiplimab to continue for no longer than 12 months
15. "Booster" Pexa-Vec injections to be given only to patients beyond Week 27 up to 1 year from the initial treatment with stable disease (SD) or partial response (PR) at latest imaging
16. Only collected if Cemiplimab treatment is ongoing
17. Imaging every 9 weeks (or every 12 weeks after 12 months), will continue until confirmed progressive disease (PD) (and further PD, if needed. See Section 6.F.16) regardless of IP dispensation status.
18. As per irRECIST criteria, a response (PR or CR) or progressive disease (PD) should be confirmed at least 4 weeks following initial finding on imaging. Please see Section 6.F.16 and Site Reader Manual for more details.
19. Overall survival and anti-cancer therapy reporting to be performed in patients who have discontinued from study treatment.
20. Pre-dose and at end of injection/infusion (within 15 minutes at end of infusion/injection)
21. Collected every 6 weeks only
22. Performed or collected within 72 hours prior to injection/infusion
23. Visit performed only if biopsy to be taken
24. Previously archived tumor biopsy prior to enrollment may be collected if available.

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6.D.3 Part 2 – Arm B

Arm B Schedule of Events	**Screen**	**Baseline**	**Cycle 1**					**Anti-PD-1 Maintenance[13]**		**Confirmed Progressive Disease[15, 25]**			**Pexa-Vec Booster[16]**	**End of Treatment**	**OS Visit[19]**	**Safety Follow-Up**
Visit Day/Week[1]	**Screen**	**Baseline**	**D1**	**D22**	**D43**	**D57[24]**	**D64**	**Q 3 Week**	**Q 9 Weeks[1] [7]**	**Post PD**	**Post PD + 2W**	**Post PD + 4W**	**Q 9 weeks (26 weeks after 1st PV)**	**After Last Treatment**	**Q 12 weeks**	
Window (days)	–28 to 1	–4 to 1	N/A	±3	±3	±5	±3	±3	±7	Within 14 days of PD	–4/+7	–4/+7	±7 days	Within 28	±14	28–60 days after last dose
Informed Consent	X															
IWRS	X	X	X	X	X		X	X		X	X	X	X	X		
Medical history	X	X[9]	X[9]													
Physical Exam (including weight)[2]	X	X	X	X[23]	X[23]		X[23]	X[23]		X[23]	X[23]	X[23]	X[23]	X		X
Height	X															
KPS	X	X					X		X					X		
Vital signs	X	X	X[11]	X[11]	X[11]	X	X[11]	X[11]		X[11]	X[11]	X[11]	X[11]	X		X
Pulse Oximetry	X	X	X[11]	X[11]	X[11]	X	X[11]	X[11]		X[11]	X[11]	X[11]	X[11]	X		X
Cardiac function (ECG and Echo)	X													X		
Pexa-Vec Re-Treatment Eligibility[3]										X	X	X	X			
R2810 Re-Treatment Eligibility[3]				X	X		X	X								
TREATMENTS																
Pexa-Vec IT injection										X[12]	X[12]	X[12]	X[12]			
Cemiplimab IV infusion			X	X[12]	X[12]		X[12]	X[12]								
LABORATORY TESTS																
Hematology	X	X		X[23]	X[23]	X	X[23]	X[23]		X[23]	X[23]	X[23]	X[23]	X		X
Chemistry Panel	X	X		X[23]	X[23]	X	X[23]	X[23]		X[23]	X[23]	X[23]	X[23]	X		X
Coagulation	X	X				X				X[23]	X[23]	X[23]	X[23]			
Thyroid Function	X						X		X[14]					X		X
Amylase and Lipase	X	X														

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Arm B Schedule of Events	**Screen**	**Baseline**	**Cycle 1**					**Anti-PD-1 Maintenance[13]**		**Confirmed Progressive Disease[15, 25]**			**Pexa-Vec Booster[16]**	**End of Treatment**	**OS Visit[19]**	**Safety Follow-Up**
Visit Day/Week[1]	**Screen**	**Baseline**	**D1**	**D22**	**D43**	**D57[24]**	**D64**	**Q 3 Week**	**Q 9 Weeks[1] [7]**	**Post PD**	**Post PD + 2W**	**Post PD + 4W**	**Q 9 weeks (26 weeks after 1st PV)**	**After Last Treatment**	**Q 12 weeks**	
Window (days)	–28 to 1	–4 to 1	N/A	±3	±3	±5	±3	±3	±7	Within 14 days of PD	–4/+7	–4/+7	±7 days	Within 28	±14	28–60 days after last dose
Troponin	X			X	X		X	X[21]								
Hepatitis B and C	X															
HIV Test	X															
Pregnancy test[4]	X	X														
Urinalysis	X															
SAMPLES ARCHIVING FOR ANALYSIS																
Pexa-Vec PK										X[20]	X[20]	X[20]				
Cemiplimab PK			X[20]	X[20]	X[20]		X[20]	X[20]								
Blood – Immune Corr.		X		X						X	X	X		X		
Biopsy – Immune Corr. [26]		X[10]				X				X[22]	X					
IMAGING STUDIES																
CT / MRI	X						X		X					X		
Nuclear Bone Scan	X						X[7]		X[7]					X[7]		
MRI/CT Head	X[7]						X[7]		X[7]					X[7]		
OTHER																
irRECIST tumor measurement[18]	X						X		X					X		
IT injection eligibility review by IR	X									X						
AE collection[5]	X[8]	X[8]	X	X	X	X	X	X	X	X	X	X	X	X		X
Concomitant medications[6]	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Anti-cancer therapies															X	
Patient Contact Log		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Survival															X	

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Part 2 – Arm B Footnotes

1. All visit dates will be counted from the treatment initiation date per each group such as "Day 1" for Arm B and "Day –7" for Part 1, Arms A, C, and D.
2. Complete physical exam should include assessment for presence of skin pustules. At screening, height will be collected.
3. Assessment for Pexa-Vec and/or Cemiplimab re-treatment eligibility can occur up to 3 days prior to treatment visit. Please refer to Section 6.F.14 for more details.
4. If positive, an ultrasound for pregnancy confirmation can be performed before screen failing the patient
5. AEs will continue to be collected and recorded through 28 days after last study treatment, Pexa-Vec and/or Cemiplimab.
6. Concomitant medications will continue to be collected through 28 days after last study treatment, Pexa-Vec and/or Cemiplimab.
7. If applicable, refer to Section 6.F.15 for details
8. From the date of signature of the ICF and up to initiation of IPs, Pexa-Vec and/or Cemiplimab, only SAEs caused by a protocol-required procedure will be collected and reported to the sponsor.
9. Medical and surgical history should be updated with any AEs/SAEs that would have occurred from the signature of the informed consent form (before study treatment)
10. Initial biopsy can be taken up to 14 days prior to Cemiplimab treatment, inclusive of treatment day
11. Please refer to the *Study Procedures,* Section 6.F.3, for timing of vital signs before and after Cemiplimab infusion or Pexa-Vec IT administration. If Pexa-Vec or Cemiplimab is missed, only baseline vitals should be taken as part of the pre-visit assessment.
12. Patients must meet re-treatment eligibility to be re-treated. If eligibility is initially not met, the patient may be re-evaluated and if eligible treated, so long as the treatment occurs within the specified window (e.g., until Day 15 post IT#1 for IT#2). It should be noted that IT Pexa-Vec cannot be given less than 10 days from previous Pexa-Vec injections, and the last date for IT Pexa-Vec, unless approved by Sponsor, is Week 5/Day 29 post IT#1. If a treatment is not given within the window, it is missed. Subsequent treatments may still be given if patient is eligible and within window.
13. Cemiplimab treatment to continue for no longer than 12 months
14. Only collected if Cemiplimab treatment is ongoing
15. Cemiplimab to continue every 3 weeks during Pexa-Vec treatment but for no longer than 12 months from initial Cemiplimab treatment
16. "Booster" Pexa-Vec injections only to be given in patients with partial response (PR) or stable disease (SD) at least 26 weeks after their first Pexa-Vec injection at progressive disease (PD) up to 1 year. Patients who did not receive an initial Pexa-Vec course are not eligible for booster injections.
17. Beyond Month 12, this should be performed every 12 weeks.
18. As per irRECIST criteria, a response (PR or CR) or progressive disease (PD) should be confirmed at least 4 weeks following initial finding on imaging. Please see Section 6.F.16and Site Reader Manual for more details.
19. Overall survival and anti-cancer therapy reporting to be performed in patients who have discontinued from study treatment.
20. Pre-dose and at end of infusion/ injection (within 15 minutes of end of infusion / injection)
21. Collected every 6 weeks only
22. Only collected if patient did not undergo Day 57 biopsy within last 8 weeks
23. Performed or collected within 72 hours prior to injection/infusion

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24. Visit performed only if biopsy to be taken

25. Pexa-Vec must be initiated within 2 weeks of confirmation of progressive disease (PD) and be completed up to 1 year. Pexa-Vec will be given for 3 doses, 2 weeks apart. The first visit of IT Pexa-Vec after confirmation of progression is named "Post PD". The second dose visit is named "Post PD + 2W". The third dose visit is named "Post PD +4W".

26. Previously archived tumor biopsy prior to enrollment may be collected if available.

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6.E STUDY PROCEDURES

Patients will be assessed at study visits according to the *Schedule of Events* (Section 6.D). Descriptions of all study procedures are described in this section.

6.E.1 Screening Visit (All Patients; 28 Days Prior to First Treatment)

Screening assessments will begin **after** signature of the ICF.

Patient eligibility for the study will be determined up to 28 days prior to treatment initiation. 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 first treatment does not occur within 28 days of the first screening procedure, some procedures may be required to be repeated. Please contact the Sponsor to determine if the patient may need to be screen failed. Patients who previously screen failed may be re-screened at a later date if their eligibility characteristics are favorable for study entry.

At the Screening visit, the following will occur:

- Collection of detailed medical, surgical, and cancer history
- Complete physical exam including weight, height, and vital signs (blood pressure, pulse, temperature)
- Pulse oximetry reading
- Spiral abdominal CT and post-contrast CT chest and pelvis (preferred) or dynamic MRI abdomen and pelvis with non-contrast chest CT (if contrast CT is contraindicated) (refer to Section 7.C.2).
- Review of abdominal imaging by Interventional Radiologist and/or Principal Investigator to assess for safely injectable tumors. Presence of injectable tumors is not required for study enrollment but will affect treatment arm assignment in Part 2.
- Nuclear Bone Scan
- Head MRI/CT
- Electrocardiogram (ECG)
- Echocardiogram (All patient but not required if patient had echocardiogram within last 6 months, and result is available, unless there is a suspicion of an interim cardiac event)

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- Karnofsky Performance Status
- Concomitant medications review and where applicable, documentation

  NOTE: 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 the Sponsor

- Blood sample collection for eligibility assessment by the site Principal Investigator and Sponsor's Medical Monitor including:

  - Hematology/ CBC with differential which includes: WBC count, hemoglobin, hematocrit, RBC, MCH, MCHC, MCV, MPV, platelet count, absolute neutrophil count, absolute lymphocyte count, absolute basophil count, absolute eosinophil count, and absolute monocyte count
  - Complete metabolic panel which includes: glucose, calcium, magnesium, albumin, total protein, sodium, potassium, bicarbonate, chloride, lactate dehydrogenase (LDH), blood urea nitrogen (BUN), creatinine, alkaline phosphatase (ALP), AST, ALT, total bilirubin, amylase and lipase
  - Thyroid function testing (TSH, free T3 (or T3), free T4)
  - Troponin (I or T)
  - Coagulation which includes: INR, prothrombin time (PT), activated partial thromboplastin time (APTT)
  - HIV, Hepatitis B (HBV surface antibody [HBsAb/anti-HBs], HBV core antibody [HBcAb], and HBV surface antigen [HBsAg]), and C (HCV antibody, EIA [HCVAb]) testing
  - Serum pregnancy test for women of child-bearing potential (if positive, an ultrasound will be performed to confirm pregnancy)

- Standard urinalysis

  - Glucose, Protein, Bilirubin, Urobilinogen, pH, Blood, Ketone, Nitrite, Leukocyte Esterase, Specific Gravity

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6.E.1.a Dose Level Assignment and Randomization

Upon completion of all Screening activities, if it is determined that the patient is eligible, a Patient Eligibility Approval Form must be completed and sent to the SillaJen Medical Monitor for review and approval. During Part 1 of the study, the first patients enrolled will be assigned to Dose Level 1 until this has been deemed safe. Following this, patients will then be enrolled into Dose Level 2 until the MTD/MFD has been reached.

In Part 2 of the study, after Medical Monitor approval, patients naïve to anti-PD-1 or anti-PD-L1 with tumors safely accessible for IT injection will be randomized, prior to initiation of study treatment, 1:1 to either Arm A or Arm B. It is imperative that the number, size, and location of any injectable lesions are noted on the form as determined by the treating physician. Those who do not have safely accessible tumors for injection will be placed in to Arm C (naïve to anti-PD-1 or anti-PD-L1) or Arm D (with prior anti-PD-1 or anti-PD-L1).

It should be noted that the Principal Investigator is ultimately responsible for ensuring and endorsing that the patient(s) meet the inclusion and exclusion criteria.

6.E.2 Baseline Visit (4 Days Prior to First Treatment Visit)

At the Baseline visit, up to and including 4 days before first treatment, the following will occur:

- Medical and surgical history updated with any AEs/SAEs that have occurred from signing of informed consent and are not related to a protocol procedure
- Complete physical exam including weight and vital signs (blood pressure, pulse, and temperature)
- Pulse oximetry
- Karnofsky Performance Status
- Patients with lesions accessible for biopsy: Core or excisional biopsy (within –14 days of first treatment) of an accessible lesion and processing in accordance with the Specimen Handling and Processing Manual. Biopsy **can** be performed immediately prior to the first Pexa-Vec injection (i.e., during the same procedure).
- Confirm eligibility for Pexa-Vec / Cemiplimab treatment (refer to Section 6.F.14).
- Blood sample collection for the following testing:

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- Hematology / complete blood count (CBC), complete metabolic panel plus amylase and lipase (refer to Section 6.F.8, for specific analysis variables)
- Serum pregnancy test for women of child-bearing potential
- Immune correlate and archival blood samples (refer to Specimen Handling and Processing Manual)
- Cytokines profile (refer to Specimen Handling and Processing Manual)

Screening, baseline and survival follow-up procedures are uniform across all patient groups. However, study procedures following these visits vary depending on assigned patient group. Please refer to the *Schedule of Events* and Section 6.F for study procedures.

6.F STUDY PROCEDURES

6.F.1 Medical History

A medical, surgical and cancer history will be taken and updated with any AEs or SAEs that have occurred prior to the first treatment dose per the CRF completion guidelines. The Investigator will also be responsible for evaluating the medical history to ensure that the patient continues to be fit enough for treatment.

6.F.2 Physical Examination

A complete physical examination, including weight, will be performed at the visits specified in the *Schedule of Events*. This will include examination of the heart, lungs, abdomen, skin and other organ systems as necessary, including injection sites, if applicable.

6.F.3 Vital Signs

Vital signs to be collected at various time points in the study include: blood pressure, heart rate, body temperature and pulse oximetry. For more specific details on collection timepoints on the day of treatment administration, please refer to Section 6.F.11 (IV Pexa-Vec), Section 6.F.12 (IT Pexa-Vec) and Section 6.F.13 (IV Cemiplimab).

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6.F.4 Karnofsky Performance Status

At various time points during the study, the patient's Karnofsky Performance Status will be assessed. Please refer to Appendix B for further details on the assessment.

6.F.5 Concomitant Medications

Concomitant medications or significant non-drug therapies (therapeutic intervention [e.g., surgery, blood transfusion]) will be reported within 28 days before start of study treatment and up to 28 days after the last dose of Pexa-Vec or Cemiplimab.

All medications (International Nonproprietary Names [INN] or generic name), dosage, route of administration, frequency, duration of administration, and the indication will be recorded in the appropriate sections of the CRF.

Concomitant medications or non-drug therapy used or performed to treat a SAE, an AE related to study treatments or any other significant AE as recommended by the Sponsor, should be recorded beyond the AE reporting period as described in Section 10.D.1.

Each time a frequency, dosage, or an indication changes, a new entry must be made in the appropriate section of the electronic CRF (eCRF).

6.F.6 Adverse Event (AE) Collection

For the purposes of this protocol, an AE is a medical occurrence or deterioration of a pre-existing medical condition occurring after the initiation of study treatment (e.g. treatment exposure) and even if the event is not considered to be related to the study treatment(s). At various time points through the study, as specific in the *Schedule of Events*, these events will need to be collected and recorded, up until 28 days after last study treatment. Further detail on the definition, collection and reporting of AEs is found in Section 10.

From the date of signature of the ICF and up to initiation of IPs, only SAEs caused by a protocol-required procedure will be collected and reported to the Sponsor.

6.F.7 Cardiac Monitoring

The following cardiac investigations are taken at baseline and/or at regular intervals until the end of study treatment. The investigations should also be performed at any point during the trial if clinically indicated in the case of chest pain, shortness of breath etc.

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6.F.7.a Electrocardiogram

At Screening, an electrocardiogram should be performed in all patients. The patient should be at rest for at least 5 minutes before recording an ECG. The ECG will be reviewed by the Investigator. Any abnormality in the ECG, if clinically significant, may prompt a need for cardiac clearance prior to enrollment of the patient on to the study.

6.F.7.b Echocardiogram

At Screening, an echocardiogram should be performed in all patients except patient having available echocardiogram result within last 6 months, unless there is a suspicion of an interim cardiac event. This is to ensure patient has no significant underlying cardiac disease and to record the patient's estimated cardiac function. Any abnormality in the echocardiogram, if clinically significant, may prompt a need for cardiac clearance prior to enrollment of the patient on to the study.

6.F.7.c Troponin

Troponin (I or T) will be taken at Screening and at regular intervals throughout the study. It will be tested every 3 weeks until Day 64 / Week 9, then it will be monitored every 6 weeks. Any abnormality should be assessed by a Cardiologist and may prompt further investigation.

6.F.8 Laboratory Testing

The following laboratory tests will be taken at various time points through the study:

- Hematology:
    - WBC count, hemoglobin, hematocrit, RBC, MCH, MCHC, MCV, MPV, platelet count, absolute neutrophil count, absolute lymphocyte count, absolute basophil count, absolute eosinophil count, and absolute monocyte count. Proportion (%) value is allowed for WBC differential.
- Chemistry Panel:
    - Glucose, calcium, magnesium, albumin, total protein, sodium, potassium, bicarbonate (CO2), chloride, lactate dehydrogenase (LDH), blood urea nitrogen (BUN), creatinine, alkaline phosphatase (ALP), AST, ALT, total bilirubin

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- Amylase and lipase
- Coagulation:
  - INR, prothrombin time (PT), activated partial thromboplastin time (APTT)
- Thyroid function testing
  - TSH, Free T3 (or T3), Free T4
- Troponin
  - Troponin I **or** Troponin T
- Hepatitis B and C panels:
  - HBV surface antibody [HBsAb/anti-HBs], HBV core antibody [HBcAb], and HBV surface antigen [HBsAg]
  - HCV antibody, EIA [HCVAb]
- HIV test
- Serum pregnancy test (for women of childbearing potential)
- Urinalysis
  - Glucose, Protein, Bilirubin, Urobilinogen, pH, Blood, Ketone, Nitrite, Leukocyte Esterase, Specific Gravity

For specific timing of safety laboratory tests prior to treatment with an Investigational agent, please refer to Section 6.F.14 for more details.

6.F.9 Samples for Immune Analysis

Samples for immune analysis will consist of blood and tissue samples per schedule of event. The samples will be analyzed and reported at study completion.

6.F.9.a Blood Samples

Blood samples should be collected at various time points. These samples should be taken within the visit description window, **before** administration of study agent. Samples should be collected and processed as per instructions in the Specimen Handling and Processing Manual.

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6.F.9.b Biopsy Samples

Biopsy samples will be collected at multiple time points as indicated in the *Schedule of Events*. If the visit window allows, certain biopsy samples can be taken either at a separate clinic visit or immediately prior to a Pexa-Vec injection. For specific guidance on equipment, tumor selection, technique, please refer to the Specimen Handling and Processing Manual and institutional guideline.

Biopsies are mandatory for patients in Part 2 Arm A and Arm B, providing that they can be safely collected in the opinion of the Investigator and/or Interventional Radiologist.

Patients in Part 1, Arm C, and Arm D, with lesions safely accessible for biopsy, should also undergo biopsy at the time points detailed in the *Schedule of Events*.

6.F.10 Samples for Pharmacokinetic Testing

6.F.10.a Pexa-Vec

At each indicated time point, samples for Pexa-Vec pharmacokinetic testing should be collected, as per the Specimen Handling and Processing Manual, pre-dose and at the end of infusion/injection (within 15 minutes of end of infusion/ injection).

6.F.10.b Cemiplimab

At each indicated time point, samples for Cemiplimab pharmacokinetic testing should be collected pre-dose and at the end of infusion (within 15 minutes of end of infusion). For collection at time points not associated with a Cemiplimab infusion, only a single sample is required to be collected at the latest pre-dose sampling time point.

6.F.11 IV Pexa-Vec Infusion

- Pre-treatment hydration: patients will receive at least 1 L of solute containing fluid, orally or IV, within 12 hours prior to the infusion.
- Pre-Medication: All patients should be pre-medicated with acetaminophen (or equivalent, unless contraindicated) on each treatment day. For acetaminophen, the following regimen may be used:

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- 500–1000 mg at 2 hours pre-treatment
- 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)

- Vital Signs: Blood pressure, heart rate, body temperature and pulse oximetry will be collected at the following time points:
  - up to 60 minutes prior to infusion
  - 30 minutes (±10 minutes) into the infusion
  - end of infusion (±10 minutes),
  - every 30 minutes (±10 minutes) for the first 2 hours
  - 3 hours and 4 hours (±30 minutes) after the end of infusion
  - every 2 hours thereafter (±30 minutes) until 20 hours post infusion.
- IV Pexa-Vec Infusion: Patients will receive an IV infusion of Pexa-Vec in approximately 250 mL buffered saline over 60 minutes (±5 minutes) at a dose level assigned by the Sponsor at the time of randomization. They will then be observed in the clinic for a minimum of 20 hours following infusion.

6.F.12 IT Pexa-Vec Injection

- Pre-treatment hydration: patients will receive at least 1 L of solute containing fluid, orally or IV, within 12 hours prior to the infusion.
- Pre-Medication: All patients should be pre-medicated with acetaminophen (or equivalent, unless contraindicated) on each treatment day. For acetaminophen, the following regimen may be used:
  - 500–1000 mg at 2 hours pre-treatment
  - 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)

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- Vital Signs: Blood pressure, heart rate, body temperature and pulse oximetry will be collected at the following time points:
  - up to 60 minutes prior to injection
  - 15 minutes (±10 minutes) after injection completion
  - every hour thereafter (±15 minutes) until 8 hours post injection.
- Ultrasound (optional): may be completed if deemed appropriate by the treating Investigator
- The total Pexa-Vec dose for IT injection is the MTD/MFD as determined in Part 1, diluted in sterile buffered normal saline. The volume of saline used for dilution will vary according to the size of the tumor to be injected. Each tumor will be injected with Pexa-Vec diluted in buffered normal saline solution in a volume that is approximately 25% of that tumor's volume (percentage dependent on the size of the tumor), but will not exceed a specified upper limit. After an appropriate pre-hydration (refer to the Pre-Dose Section), the injection will be performed by the Interventional Radiologist or other trained physician using imaging-guidance (ultrasound and/or CT). Different tumors may be treated on each treatment day, including new tumors that have developed since screening evaluation.
- Injection needles designed for percutaneous insertion into tissues will be used. Depending on Investigator's judgement (tumor size, tumor location, patient safety, etc.), either multi-pronged injection needles (provided by the Sponsor), or straight needles, preferably with multiple side ports (not provided by the Sponsor), will be used.
- Refer to the "***Pexa-Vec IT Injection: Procedure Manual***" and to the "***Pexa-Vec IT Injection: Preparation Worksheet***" for more information about the specific calculation and preparation instructions and for the detailed injection procedure guidelines and needle use recommendations.

6.F.13 IV Cemiplimab Infusion

- Vital signs: Blood pressure, heart rate, body temperature and pulse oximetry will be collected at the following time points:
  - Up to 60 minutes prior to infusion
  - End of infusion (EOI) (+5 minutes)
  - EOI + 30 minutes (±5 minutes)

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- EOI + 2 hours (±10 minutes) (first Cemiplimab infusion only)
- EOI + 3 hours (±30 minutes) (first Cemiplimab infusion only)
- EOI + 4 hours (±30 minutes) (first Cemiplimab infusion only)
- EOI + 6 hours (±30 minutes) (first Cemiplimab infusion only)
- EOI + 8 hours (±30 minutes) (first Cemiplimab infusion only)

- IV CEMIPLIMAB Infusion: A 350 mg dose of Cemiplimab will be administered over 30 minutes (±10 minutes).

  ***NOTE*:** If Pexa-Vec and Cemiplimab are to be given the same day, CEMIPLIMAB should be given first. Pexa-Vec should be given at **least one hour** following the end of CEMIPLIMAB infusion.

6.F.14 Re-Treatment Criteria

Patients will need to continue to meet specific eligibility criteria in order to safely receive Pexa-Vec and Cemiplimab treatments. The visit will be performed up to 3 days prior to the treatments (inclusive). This visit must occur regardless of whether the treatments will be given. The visit may be repeated if Pexa-Vec or Cemiplimab treatment is delayed.

The Principal Investigator is ultimately responsible for ensuring and endorsing that the patient(s) meet the required clinical and laboratory criteria in order to receive treatment.

Re-treatment eligibility assessments may be repeated until the patient becomes eligible for treatment within the specified window, but all eligibility criteria must be ultimately confirmed prior to treatment (visit not to occur earlier than 3 days prior to treatment). If eligibility is not met within the treatment window, the visit will be considered missed.

6.F.14.a <u>IV Pexa-Vec Infusion</u>

To be eligible for doses of IV Pexa-Vec infusion, patients will undergo the following assessments:

- Physical examination (including skin infection)
- Weight
- Vital Signs: Blood pressure, heart rate, body temperature, and pulse oximetry

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- Safety Blood Sample collection: Hematology (including differential) and Chemistry
- AEs and concomitant medications review and reporting

Patients will be eligible for re-treatment with **IV Pexa-Vec** if all of the following laboratory criteria are met:

- Adequate liver function (total bilirubin ≤3.0 mg/dL [51.3 µmol/L]; ALT and AST ≤5 × ULN)
- Platelet count ≥50,000 platelets/mm^3 (correction with transfusion or thrombopoietin based therapy allowed to meet re-treatment criteria)
- Hemoglobin ≥8 g/dL (correction with transfusion or erythropoietin based therapy allowed to meet re-treatment criteria)

6.F.14.b IT Pexa-Vec Injection

To be eligible for doses of IT Pexa-Vec injection, patients will undergo the following assessments:

- Physical examination (including skin infection)
- Weight
- Vital Signs: Blood pressure, heart rate, body temperature, and pulse oximetry
- Safety Blood Sample collection: Hematology (including differential), Chemistry and coagulation
- AEs and concomitant medications review and reporting

Patients will be eligible for each of the 3 Pexa-Vec IT injections if all of the following clinical and laboratory criteria are met prior to each Pexa-Vec IT treatment:

- Adequate liver function (total bilirubin ≤3.0 mg/dL [51.3 µmol/L]; ALT and AST <5 × ULN)
- Platelets ≥75×10^9/L (correction with transfusion or thrombopoietin based therapy allowed to meet re-treatment eligibility criteria)

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- Hemoglobin ≥8 g/dL (correction with transfusion or erythropoietin based therapy allowed to meet re-treatment eligibility criteria)
- INR ≤1.5 (correction with plasma protein support allowed to meet re-treatment eligibility criteria [e.g., fresh frozen plasma])
- PTT within normal limits
- Patient is still expected to have at least one viable, injectable tumor ≥1 cm longest diameter (LD)
- No clinical significant and/or rapidly accumulating ascites, pericardial and/or pleural effusions. Minimal ascites that does not preclude safe IT injection of Pexa-Vec as allowed at the discretion of the treating physician and Interventional Radiologist.

Patients in Part 2, Arm B will need to meet the above criteria prior to their first Pexa-Vec IT injection as well.

6.F.14.c IV Cemiplimab Infusion

To be eligible for doses of intravenous Cemiplimab infusion, patients will undergo the following assessments:

- Physical examination (including skin infection)
- Weight
- Vital Signs: Blood pressure, heart rate, body temperature, and pulse oximetry
- Safety Blood Sample collection: Hematology (including differential) and Chemistry
- AEs and concomitant medications review and reporting

In order to continue treatment with Cemiplimab or resume treatment with Cemiplimab after a treatment interruption, patients must be safe for further treatments per Cemiplimab specified management criteria (refer to Appendix A)

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6.F.15 Radiographic Imaging

6.F.15.a CT and MRI

Radiographic imaging is required at Screening, every 9 weeks during the study, and at the end of treatment visit (if more than 4 weeks since the last radiographic assessment). Beyond 12 months of treatment, imaging is performed every 12 weeks.

Tri-phasic (pre-contrast, arterial, and portal venous phases) contrast enhanced helical/spiral CT of the abdomen from the dome of the liver through both kidneys will be performed. Post-contrast CT of the chest and pelvis will also be performed.

NOTE: In patients unable to receive iodinated contrast material for CT scanning, triphasic dynamic MRI of the abdomen should be performed. Post-contrast MRI of the pelvis should also be performed, along 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.

6.F.15.b Nuclear Bone Scan

A nuclear whole body bone scan will be performed at Screening. It will also be performed throughout the trial in patients who present with documented bone metastases, symptoms or laboratory findings suspicious for the presence of bone metastases. It may also be performed to confirm a complete response (CR) in patients with absent disease on CT or MRI.

6.F.15.c MRI/CT Head

An MRI or CT of the head will be performed for all patients at Screening. In those patients with a clinical history or patients who present with clinical symptoms of brain metastasis, brain imaging will be performed at Screening, every 9 weeks during the study, and at the end of treatment visit (if more than 4 weeks since the last radiographic assessment). Beyond 12 months of treatment, imaging is performed every 12 weeks.

6.F.15.d Ultrasound

Ultrasound can be performed as an optional modality at the time of injection of Pexa-Vec or biopsy collection as required by the treating physician.

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6.F.16 Imaging and Response Assessment

Local reads of imaging is recommended to be performed within 5 days of the imaging date.

Patients will be assessed by irRECIST by the site. Please see the Site Reader Manual for detailed description of this assessment criteria. The management of patients, and determination whether patients will continue to receive therapy, will be based on irRECIST by local reads whereas the primary efficacy endpoint, overall response rate (ORR) utilizing RECST 1.1, will be determined by independent central review. irRECIST requires an additional scan at least 4 weeks later in patients with progressive disease (PD), partial response (PR) or complete response (CR). Please refer to Site Reader Manual for more details. For patients in Arm B, who require progressive disease (PD) before treatment with Pexa-Vec, this **must** also be confirmed on a repeat scan at least 4 weeks following PD via irRECIST. Treatment can continue while waiting for the confirmatory scan.

If the site reader determines that radiographic progressive disease (PD) has occurred on the repeat scan, the patient will be considered to have radiographic progression (as of the date of initial progressive disease [PD]). In addition, independent central efficacy reads of the images will be performed throughout the study.

Patients with stable disease (SD) or better can continue the treatment regimen until progressive disease (PD) or unacceptable toxicity for up to 1 years.

Based on local reads, patients may continue to receive Cemiplimab past confirmed radiographic progressive disease (PD) upon Sponsor's approval if, in the opinion of the Investigator, the patient is deriving clinical benefit from treatment. If further progressive disease (PD) (defined as an additional 20% increase in tumor burden from the time of initial progressive disease [PD]) is confirmed, Cemiplimab must be discontinued and other anti-cancer therapy considered, if appropriate.

6.F.17 Pexa-Vec Boosters

Certain patients may be eligible to receive "boosters" of Pexa-Vec. Boosters are a repeat dose of Pexa-Vec, given **once every 9 weeks**, in the same modality that the patient originally received. To be eligible for **each** booster, patients must meet the following criteria:

- No earlier than 26 weeks post initial Pexa-Vec treatment

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- After Week 27 for Part 1, Arm A, Arm C, and Arm D (Week 27 is chosen since administration of Pexa-Vec immediately prior to an imaging timepoint may confound assessment [e.g., transient tumor swelling]).
- At least 26 weeks post Pexa-Vec at progressive disease for Arm B

- Partial response (PR) or stable disease (SD) on most recent imaging
- Continue to meet re-treatment criteria for each booster as described in Section 6.F.14

Patients will receive a maximum of 3 doses of Pexa-Vec boosters OR given up to Month 12 of the study calendar, whichever comes earlier.

Patients who no longer have an accessible lesion, but are otherwise eligible for Pexa-Vec, may receive IV Pexa-Vec boosters.

6.F.18 End of Treatment

Upon confirmation of progressive disease (PD), patient withdrawal, or commencement of other anti-cancer therapy, the patient must complete a safety visit to evaluate their end of treatment. This visit should occur as soon as possible, but not to exceed 28 days from the last study treatment.

- Complete physical examination
- Weight
- Vital signs including pulse, blood pressure, and temperature
- Karnofsky Performance Status
- Safety Blood Sample collection: Hematology (including differential), Chemistry, and Thyroid (TSH, Free T3, Free T4)
- Immune Correlate Blood Sample collection (refer to the Specimen Handling and Processing Manual)
- Imaging (if more than 4 weeks since previous imaging) and irRECIST
- AE collection and concomitant medication review
- Patient Contact Log: Confirm accuracy of contact information for the patient and/or caregiver(s)

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6.G SURVIVAL FOLLOW-UP

Patients will be followed for survival during and after study participation. From the EOT visit, patients, and/or their specified contacts will continue to be contacted approximately every 12 weeks for survival and information on subsequent anti-cancer therapy, including dose, duration, significant associated toxicities and efficacy. Radiology assessments may be reviewed for patients who have gone onto subsequent 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) (refer to Section 5.D, *Patient Withdrawal Criteria*), they will continue to be contacted for the protocol-specified survival follow-up unless the patient explicitly withdraws consent for survival follow-up. This consent withdrawal will be documented in the source documents.

Every effort should be made to obtain complete survival data. Due diligence should be used in contact efforts including:

- At least 3 documented direct patient contact attempts and certified letter
- 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, the site will not contact the patient or their caregiver(s) to collect survival or subsequent anti-cancer therapy data; however, the site may use other means to determine the patient's survival status (e.g., referencing death registries, newspaper obituaries, etc.).

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7 PATIENT MANAGEMENT

7.A TREATMENTS

7.A.1 Expected Toxicities of Pexa-Vec Treatment

7.A.1.a Flu-Like Symptoms

(mild-to-severe fever, rigors, anorexia, aches/pain, fatigue, headache, and/or nausea)

These flu-like symptoms typically peak during the first 12 hours after Pexa-Vec treatment. Acute fever is expected within 4–12 hours post-treatment and has a typical duration of 18–24 hours, although these can last up to 72 hours.

7.A.1.b Hypotension

Across clinical trials and indications, mild-to-moderate transient hypotension can be observed within 24 hours following treatment with Pexa-Vec (approximately 21% of all patients as of March 2020). Severe (grade 3) events were reported in 2% of patients. However, in the TRAVERSE trial for patients with advanced 2nd line HCC, 6 patients (8 total SAEs) have experienced severe hypotension following Pexa-Vec treatment, requiring >24 hours of medical treatment, intensive care unit care, and vasopressor treatment. Notably, anti-hypertensive medication was ongoing at the time of treatment with Pexa-Vec prior to the development of hypotension in the majority of these patients, thereby potentially exacerbating the potential for hypotension. As of March 2020, there was one additional severe hypotension SAE in the PHOCUS trial (Phase 3, first-line HCC), bringing the total number of affected patients to 7 (9 total SAEs). This event occurred post-procedurally after the patient's first dose of Pexa-Vec and was associated with acute hypoxic respiratory failure partly attributed to pulmonary edema due to volume overload vs. underlying previously undiagnosed interstitial lung disease vs. Pexa-Vec associated lung injury. The patient required IV fluid therapy and vasopressor treatment for 36 hours.

To mitigate risk of hypotension following Pexa-Vec treatment, the following are required:

- Pre-hydration with 1 liter of solute-containing fluid (p.o. or IV) prior to each treatment
- Suspension of anti-hypertensive medication (including diuretics, beta-blockers, ACE inhibitors, aldosterone antagonists, etc.) for 48 hours prior to and 48 hours after each Pexa-Vec treatment
- Observation of patients for at least 8 hours following each IT Pexa-Vec injection and 20 hours after each IV Pexa-Vec infusion

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- For patients with a history of cardiovascular disease, cardiology consultation and cardiology clearance must be obtained prior to enrollment.

NOTE: Patients with active cardiac disease within 12 months of study entry are excluded from study participation.

7.A.1.c Hematological Events

Transient decreases in WBC counts (including neutrophils and lymphocytes), platelets and hematocrit can occur. Transient thrombocytopenia (including reduced platelet count) occurred within days of treatment with Pexa-Vec and resolved within 1 week of treatment without medical intervention. Transient leukopenia (including reduced neutrophil and lymphocyte counts), has been observed with resolution generally occurring within 7 days of treatment. Leukopenia is a common finding associated with viral infection in general. Conversely, transient leukocytosis (including neutrophil, eosinophil, and monocyte subsets) has also been observed. An elevated WBC count is expected based on a GM-CSF mediated effect by Pexa-Vec and the infusion of an attenuated vaccinia virus.

7.A.1.d Chemistry Changes

Transient chemistry changes including dose-related direct hyperbilirubinemia (due to tumor swelling and occlusion of biliary tract drainage) has been noted in patients treated with Pexa-Vec. In this instance, the patients had liver tumors which were adjacent to or impeding the biliary tract at baseline. Biliary tract drainage should be considered as clinically indicated if biliary occlusion does not resolve quickly enough clinically. Acute post-treatment tumor swelling can result in hyperbilirubinemia within approximately one week following treatment.

7.A.1.e Tumor Swelling

In addition to the above, acute respiratory distress secondary to airway obstruction was observed following treatment in one patient with metastases in the lung. Therefore, patients with tumors in a location that would potentially result in significant clinical adverse effects if post-treatment tumor swelling were to occur, should not be included as per Exclusion Criteria 8. Tumor swelling may resolve over time.

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7.A.1.f Rashes

Rashes related to latent virus reactivation have been reported, both with Varicella-Zoster (i.e., "shingles") and herpes simplex virus; whether these rashes are related to Pexa-Vec itself, or due to the fever induced, is unknown.

Small (<1 cm) superficial skin or oral mucous membrane pustules containing Pexa-Vec may develop after Pexa-Vec treatment. If they develop, it is typically within 1 week after the first IV infusion only. These pustules generally resolve within approximately the following 2–3 weeks, a time course that is consistent with the usual course following intentional vaccination with wild-type [non-attenuated] vaccinia vaccine. All pustules to date have been self-limited and resolved without complications or the need for specific anti-viral treatment.

7.A.2 Risks Associated with IT Injection

At the tumor or injection sites, the following toxicities are possible: pain, swelling, necrosis, ulceration, bleeding, and inflammation. For the majority of cases, no significant treatment other than local wound therapy and analgesia has been required. Differentiation of local skin reactions from Pexa-Vec related skin pustules should be made and testing performed as clinically indicated.

Overall, 3 patients have experienced a total of 3 clinically significant bleeding SAEs including Grade 5 post-IT injection procedure bleeding, Grade 3 hepatic hemorrhage, and Grade 2 intercostal bleeding, related to the IT injection procedure or the IP. Management of anti-coagulation while receiving Pexa-Vec should follow the protocol-specified recommendations and caution exercised in determining the optimal time to re-initiate anti-coagulation following injection. Baseline coagulation parameters should be evaluated carefully prior to treatment and factored into assessment of procedure safety and pre-/post-treatment management plan. The treating physician should consider pre-treatment with FFP or other blood products in patients judged at a potentially increased risk of procedure related bleeding. In all cases, supportive blood products should be readily available and early intervention with these products implemented should bleeding occur.

Further, clinical judgment must be used to ensure safe tumor access - injection into tumor should be avoided if in the judgment of the Interventional Radiologist, the characteristics of the target tumor (e.g., high vascularity) or its location (e.g., close proximity to critical structures that could be inadvertently damaged during IT injection procedure) may increase the risk of procedure-related complications. The use of CT guided injection for lesions identified as high risk based on

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increased vascularity should be considered. Such tumors should not be injected if image guidance does not allow a safe approach to the tumor, in the judgment of the Interventional Radiologist.

7.A.3 Cemiplimab Toxicity Management

Please refer to Appendix A for detailed overview of Cemiplimab side effect profile and guidance on managing toxicity.

7.A.3.a Cemiplimab Dose Limiting Toxicities (DLT) Management

Patients who experience protocol-defined DLTs, or Grade ≥3 treatment-related toxicity (excluding exceptions outlined in Section 4.D.1, such as laboratory abnormalities that are considered clinically insignificant) that are not otherwise specified in the protocol will be required to temporarily discontinue treatment with study therapy. Such patients may be considered for resumption of treatment once the toxicity resolves to Grade 1 or Baseline, or when the toxicity is stable and manageable through supportive/medical therapy (e.g., Grade 3 hypertension that can be controlled with addition of a second anti-hypertensive agent).

Upon occurrence of a DLT or other study treatment-related event at any dose level and at any time on the study, resumption of treatment after resolution or stabilization of the condition is allowed at the discretion of the Investigator and Sponsor if resuming treatment is thought to be in the best interest of the patient, with the exception of the following categories requiring permanent discontinuation of Cemiplimab:

- Patients with AEs that require all study therapy to be stopped for more than 84 days
- Patients with DLTs of Grade ≥2 uveitis
- Patients with DLTs of hepatic abnormalities consistent with Hy's Law

Resumption of treatment may be at the treatment dose, based upon the discretion of the Investigator and the Sponsor. A repeat occurrence of the same AE at the same grade after resumption of treatment will require permanent discontinuation of study treatment.

If either study drug is discontinued (either permanently or temporarily) for an AE, if the patient receiving combination therapy, the patient will generally discontinue the combination therapy treatment as well. If, however, a patient experiences an AE (such as an infusion reaction) that in

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the opinion of the Investigator is *SOLELY* related to 1 drug, the other study drug may be continued, and the responsible therapy may be discontinued.

Any patient currently receiving Cemiplimab who was previously treated with a phosphatidylinositol 3-kinase (PI 3-K) inhibitor and who develops stomatitis or mucositis should temporarily suspend study treatment. If this or any other irAE occurs among these patients, the Sponsor should be informed as soon as possible to discuss further management of the patient. An irAE of any grade in a patient previously treated with a PI 3-K inhibitor should be reported as an Adverse Event of Special Interest (AESI).

Guidelines for study treatment temporary discontinuations, including delays and interruptions, and permanent discontinuations for study drug-related toxicity are outlined in Section 7.A.3.b, Section 7.A.3.c, and Appendix A.

7.A.3.b Immune-Related Adverse Event (irAE)

CRFs for this study are designed to capture AEs that may be suggestive of potential irAEs. Attribution of AEs in the CRFs will require not only the Investigator's assessment regarding whether the AE was related to Cemiplimab, but also whether the AE was an irAE. Please refer to the CRF completion guidelines for information about attribution of irAEs.

Investigators must be extremely vigilant and be ready to intervene early in the management of irAEs, as the onset of symptoms of irAEs (e.g., pneumonitis) may be subtle. Detailed guidance of management of irAEs is provided in Appendix A. In the event of irAEs that are not addressed in Appendix A, general guidance is provided in Table 2. The recommendations in Table 2 and Appendix A should be seen as guidelines, and the treating physician should exercise clinical judgment based on the symptoms and condition of the individual patient.

Table 2:
General Treatment Hold Guidelines for Immune-Related AEs (irAEs)

Severity	Withhold/Discontinue Treatment?	Resume / Discontinuation?
Grade 1	Continue study treatment with close monitoring and provide symptomatic management	
Grade 2	Consider withholding study treatment	

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Severity	Withhold/Discontinue Treatment?	Resume / Discontinuation?
Grade 3 Grade 4	Withhold study treatment Discontinue study treatment	Except as described for select irAEs, if Cemiplimab is withheld for ≤Grade 3 irAE, consider resuming when symptoms and/or laboratory values the irAE revert improves to Grade 0 or 1 after corticosteroid taper to ≤prednisone 10 mg/day or equivalent. Except as described for select irAEs, give an initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper and permanently discontinue study treatment for: • Grade 4 adverse reactions (excluding endocrinopathies) • Recurrent Grade 3 irAEs • Grade 2 or 3 irAEs persistent for ≥12 weeks after the last study treatment • Requirement for ≥10 mg per day prednisone or equivalent lasting ≥12 weeks after the last study treatment.

NOTE: These recommendations should be seen as guidelines, and the treating physician should exercise clinical judgment based on the symptoms and condition of the individual patient. Refer to regional irAE management guidance such as the National Comprehensive Cancer Network (NCCN) or European Society for Medical Oncology (ESMO) guidance.

NOTE Regarding irAEs: For any AE that is of a type known to be potentially immune-related (e.g., rash, colitis, elevated transaminases, endocrine), but is deemed not to be an irAE by the Investigator, the Sponsor may request additional information.

7.A.3.c Permanent Discontinuation of Cemiplimab

In the event of an infusion reaction of Grade ≥3 severity during or directly following Cemiplimab infusion, dosing should be stopped and the patient must permanently discontinue Cemiplimab treatment.

Study treatment will be permanently stopped in the event of evidence of pregnancy.

In addition, study treatment for any patient may be discontinued for other safety reasons or compliance issues at the discretion of the Investigator or Sponsor. A patient may choose to discontinue study treatment or study participation at any time for any reason.

A patient who permanently discontinues Cemiplimab treatment should continue follow-up in the study without additional treatment until progression of disease, completion of all study assessments, or closure of the study (Section 6.G).

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7.A.3.d Management of Infusion/Allergic/Hypersensitivity Reactions

Acute infusion reactions are defined as any AE that occurs during the infusion or within 2 hours after the infusion is completed. Emergency equipment and medication for the treatment of these potential adverse effects (e.g., antihistamines, bronchodilators, IV saline, corticosteroids, acetaminophen, and/or epinephrine) must be available for immediate use. Infusion reactions must be reported as AEs (refer to Section 10.D.1), or AESI (refer to Section 10.A) and graded according to the NCI-CTCAE version 5 grading scale (refer to Section 10.B.1)

In the event of an infusion reaction of Grade 3 or greater severity during or directly following Cemiplimab infusion, dosing should be stopped and the patient must be permanently discontinued from Cemiplimab treatment.

7.A.3.d.1 Interruption of the Infusion

The infusion should be interrupted if any of the following AEs are observed:

- Cough
- Rigors/Chills
- Rash, pruritis (itching)
- Urticaria (hives, welts, wheals)
- Diaphoresis (sweating)
- Hypotension
- Dyspnea (shortness of breath)
- Vomiting
- Flushing

The reaction(s) should be treated symptomatically, and the infusion may be restarted at 50% of the original rate.

If Investigators feel there is a medical need for treatment or discontinuation of the infusion other than described above, they should use clinical judgment to provide the appropriate response according to typical clinical practice.

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For patients who experience infusion-related hypersensitivity reactions that are less than Grade 3 and who plan to continue treatment, premedication will be required for re-treatment

For **Grade 1 symptoms** (mild reaction; infusion interruption not indicated; intervention not indicated), the following prophylactic medications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 325 mg to 1000 mg at least 30 minutes prior to subsequent Cemiplimab infusions

For **Grade 2 symptoms** (moderate reaction that requires therapy or infusion interruption, but for which symptoms resolve promptly with appropriate treatment such as antihistamines, nonsteroidal anti-inflammatory drugs, narcotics, corticosteroids, and/or IV fluids; prophylactic medications indicated ≤24 hours), the following prophylactic medications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 325 mg to 1000 mg at least 30 minutes prior to subsequent Cemiplimab infusions. If necessary, corticosteroids (up to 25 mg of hydrocortisone or equivalent) may be used.

7.A.3.d.2 Termination of the Infusion

The infusion should be terminated and NOT restarted if any of the following AEs occur:

- Anaphylaxis
- Laryngeal/pharyngeal edema
- Severe bronchospasm
- Seizure
- Severe hypotension

7.A.4 Concomitant Authorized and Contraindicated Treatments

7.A.4.a Definitions and Reporting of Concomitant Medication and Non-Drug Therapy

Concomitant medications or significant non-drug therapies (therapeutic intervention [e.g., surgery, blood transfusion]) will be reported within 28 days before start of study treatment and up to 28 days after the last dose of Pexa-Vec or Cemiplimab.

Concomitant medications or non-drug therapy used or performed to treat a SAE, an AE related to study treatments, or any other significant AE as recommended by the Sponsor, should be recorded beyond the AE reporting period as described in Section 10.D.1.

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Each time a frequency, dosage, or an indication changes, a new entry must be made in the appropriate section of the eCRF.

7.A.4.b Concomitant Authorized & Contraindicated Treatments

7.A.4.b.1 Recommended Medications Related to Flu-like Symptoms (mild-to-severe fever, rigors, anorexia, aches/pain, fatigue, headache, and/or nausea)

Pre-Medication for Treatment Day

Patients should receive approximately 1 liter of solute-containing fluids (e.g., normal saline) IV or orally within 12 hours of treatment initiation.

All patients should be pre-medicated with acetaminophen (or equivalent, unless contraindicated) on each treatment day. For acetaminophen, the following regimen may be used:

- 500–1000 mg 2 hours pre-treatment
- 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)

Acute Post-Treatment Symptom Management

During the observation period post-Pexa-Vec treatment, patients should receive IV solute-containing fluid and other measures (e.g., vasopressor therapy) per standard of care, as needed for blood pressure support. Anti-rigor medication (e.g., meperidine) or support medications may be used as needed.

Anti-emetics may be used at the Investigator's discretion for treatment of nausea or vomiting; it is noted, however, that corticosteroids should not be used.

Analgesics, anti-pyretics (e.g., prophylactic acetaminophen), antidepressants, bisphosphonates, erythropoietin growth factors and other supportive care measures may be used at the Investigator's discretion.

7.A.4.b.2 Management of Hypotension and Contraindicated Treatments

To mitigate risk of hypotension following Pexa-Vec treatment, the following are required:

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- Prehydration with 1 liter of solute-containing fluid (p.o. or IV) prior to each treatment
- Suspension of anti-hypertensive medication for 48 hours prior to and 48 hours after all Pexa-Vec treatments
    - Following Pexa-Vec administration, in immediate post-dose period anti-hypertensive medication(s) can be used for management of adverse event of hypertension; however, preference should be given to short-acting agents in view of the risk of Pexa-Vec-induced hypotension.
- Anti-hypertensive medications include, but are not limited to, the following:
    - Diuretics
    - Beta-blockers
    - ACE inhibitors
    - Aldosterone agonists

7.A.4.b.3 Agents with Potential Inhibitory Activity Against Vaccinia Viruses

In the extremely unlikely case of severe or recurrent generalized vaccinia virus infection, progressive vaccinia, or eczema vaccinatum, or another clinically-significant toxicity that, in the opinion of the Investigator could be related to Pexa-Vec replication, Investigators may consider the use of agents with vaccinia inhibitory activity, if available in their country for such clinical use. Such agents may include anti-vaccinia immune globulin (VIG), cidofovir, and/or Arestvyr (USAN tecovirimat; ST-246). For clarity, none of these agents have been used or approved for this purpose to date. Clinical judgement should be used when determining the optimal regimen and duration of treatment.

The availability of these antiviral products is country-dependent; options will be investigated and a plan for a response to infection-related toxicities will be documented and communicated to study staff prior to initiation of the clinical trial (refer to the IB for additional information).

7.A.4.b.4 Other Contraindicated Treatments

- Interferon/PEG-interferon, ribavirin or antiviral agents shown to inhibit vaccinia replication
- Anti-cancer therapy once a patient has been randomized

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- ***NOTE:*** Radiotherapy may be considered for pain palliation or treatment of oligo-progressive disease, if patients are deriving benefit (e.g., treatment of known bone metastases). Study drug administration may be continued during radiotherapy. Please contact the Sponsor before starting palliative radiotherapy.

- High dose systemic corticosteroids (defined as ≥10 mg/day prednisone or equivalent which is ongoing at the time of arm allocation and/or was taken for more than 4 weeks within the preceding 2 months of randomization) or other immunosuppressive medications. Pre-medication with steroids is not permitted.

- Anti-coagulation or anti-platelet medication that cannot be interrupted prior to biopsy or IT injection, including:

  - Aspirin that cannot be discontinued for 7 days prior to treatment

  - Coumadin that cannot be discontinued for 7 days prior to treatment

  - Low molecular weight heparin that cannot be discontinued >24 hours prior to treatment and unfractionated heparin that cannot be discontinued >4 hours prior to treatment (low molecular weight heparin or unfractionated heparin may be used to transition patients on and off the above anti-coagulants, if deemed appropriate by the treating physician) prior to Pexa-Vec treatments as long as the last dose of low molecular weight heparin is administered 24 hours prior to treatments and the last dose of unfractionated heparin is administered >4 hours prior to treatments.

  - Oral direct thrombin inhibitor (dabigatran) or direct Factor Xa inhibitor (rivaroxaban, apixiban, and endoxaban) that cannot be discontinued for 4 days prior to treatments

  - Any other anti-coagulant or anti-platelet therapy that cannot be safely suspended for per protocol biopsies or IT injections as per standard of care

7.A.4.b.5 Other Authorized Concomitant Treatments

- thrombopoietin, erythropoietin, G-CSF

- antidepressants

- steroids (***NOTE:*** oral or parenteral steroids are not allowed during the Pexa-Vec treatment period, and for 1 week prior to and 2 weeks after Pexa-Vec treatment unless clinically indicated for management of an AE, following consultation and approval from SillaJen Medical Monitor)

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- biphosphonates, vitamin B12 and vitamin D
- Hepatitis B antivirals are ALLOWED as DO NOT inhibit vaccinia virus replication: lamivudine, adefovir (and adefovir dipivoxil prodrug), telbivudine, tenofovir, emtricitabine, clevudine and entecavir. The ability of combinations of these agents to inhibit vaccinia virus replication has however not been evaluated. Therefore, combination therapy with anti-viral agents should be avoided if at all possible.

NOTE: Please contact the Sponsor for any questions regarding management of immunosuppressive, anticoagulant, antihypertensive, or antiviral medications prior to treatments.

NOTE: Sites will be notified as additional information regarding allowed and contraindicated antivirals becomes available

7.A.5 Potential Mechanisms of Pexa-Vec Shedding to the Environment, Biodissemination and Prevention of Transmission

7.A.5.a Superficial Skin Pustules

As mentioned in Section 7.A.1, small (<1 cm) superficial skin or oral mucous membrane pustules containing Pexa-Vec may develop after Pexa-Vec treatment. If pustules develop, they do so typically within 1 week after the first administration. These pustules generally resolve within approximately the following 2–3 weeks, a time course that is consistent with the usual course following intentional vaccination with wild-type (non-attenuated) vaccinia vaccine. All pustules to date have been self-limited and resolved without complications or the need for specific anti-viral treatment.

Since these pustules contain Pexa-Vec they should be managed as per the "***Recommendations for Pexa-Vec Handling and Patient Management***" (Appendix B of the Pexa-Vec IB).

The following steps should be carried out in the event of skin or oral mucosa pustule identification (patient or patient contact, which is unexpected):

1. Record the AE (event term for Pexa-Vec related pustules must be recorded as "papulopustular rash").
2. Instruct the patient/contact to cover the pustule with non-occlusive dressing (or wear a mask when around other people if oral lesions are present). Refer to the "***Recommendations for***

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Pexa-Vec Handling and Patient Management" (Appendix B of the Pexa-Vec IB) for further instructions.

7.A.5.b Urine, Feces, Blood, Throat and/or Saliva

Testing for the presence of Pexa-Vec after patient treatment has been conducted in several clinical studies in throat swabs, urine, feces, and blood samples.

Refer to the current Pexa-Vec IB for available data on shedding and to the "Pexa-Vec Guidelines" for recommendations on the care of Pexa-Vec treated patients. No person-to-person transmission of Pexa-Vec has been reported.

7.B SAFETY, CLINICAL, DEMOGRAPHY, AND DIAGNOSIS ASSESSMENTS

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

- Inclusion/Exclusion criteria: patient eligibility by the Investigator by confirming all inclusion/exclusion criteria. Violation of any entry criterion excludes a patient from enrollment into the study. If violation is discovered after enrollment, the patient may be discontinued.
- Demography: Year of birth (in countries where complete date of birth is not permitted, this will be de-identified as required), gender, race, ethnicity, child bearing potential status
- Occurrence of AEs/SAEs (refer to Section 10, *Safety Reporting*)
- Concomitant medications and significant non-drug therapies collection
- Clinical laboratory evaluations:
    - HIV and HBV/HCV tests to rule out exclusion criteria
    - Complete Metabolic panel: sodium, potassium, magnesium, chloride, CO^2 content, BUN, creatinine, random glucose, total bilirubin, ALT, AST, calcium, ALP, LDH, total protein, albumin, plus lipase and amylase.
    - TSH, Free T4, T3 (or Free T3)
    - Hematology: CBC with differential and platelet count
    - Coagulation: PTT, PT/INR

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- Blood pregnancy test at screening and urinary pregnancy test at Baseline (for women of childbearing potential)

- Standard urinalysis (Screening only)
  - Glucose, Protein, Bilirubin, Urobilinogen, pH, Blood, Ketone, Nitrite, Leukocyte Esterase, Specific Gravity

- Physical examinations of the major organ system including skin assessment (after Pexa-Vec treatment has been initiated), weight and vital signs (blood pressure, pulse and temperature). Height will be collected at Screening.

- Performance status on the Karnofsky Performance Status (KPS) scale

7.C EFFICACY ASSESSMENTS

7.C.1 Biomarker/Immune Assessments

Correlative exploratory studies of immune response to treatment will generally be as specified below. Please refer to the Specimen Handling and Processing for details.

To assess in the blood, the following immune parameters at Baseline and on Study Days 1 (excluding Arm B, Cemiplimab monotherapy), and 22 (D43 in Arm D), End of Treatment and Post Progression on PD-1 monotherapy at Baseline, 2 weeks, and 4 weeks (Arm B only):

- Tumor specific and Pexa-Vec specific cellular immune responses (including but not limited to assessment of B-cells, T-cells, activated T-cells, NK cells, regulatory T-cells, MDSC)

- Pexa-Vec and Cemiplimab specific humoral responses

- Immune related cytokines

To assess in previously archived tumor biopsies (if available) and/or biopsied tumors at Baseline and on Study Day 8 (excluding Arm B, Cemiplimab monotherapy) and Day 57 (Arm B patients will undergo repeat biopsy at disease progression and 2 weeks after first Pexa-Vec):

- Tumor microenvironment including T-cell, B-cell, NK cell, monocytes, macrophages, and other relevant immune cell subtypes of interest

- Immune modulating proteins that may have predictive or prognostic value, including, but not limited to PD-L1, PD-1, CTLA-4

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- Global changes in gene expression based on genome wide RNAseq analysis
- Tumor mutational load based on whole exome sequencing of tumor and the matched germline blood DNA samples
- Pexa-Vec infection and transgene expression

7.C.2 Imaging Data Acquisition and Evaluations

7.C.2.a Imaging Data Acquisition

All scans described below will be submitted for Independent Central Review. A separate detailed imaging acquisition protocol will be provided in the Imaging Manual. Please refer to the manual, Section 6.F.15, and the *Schedule of Events* (Section 6.D) for a description of the required imaging collection time points.

7.C.2.b Imaging Data Evaluations

Patients will be assessed by irRECIST by the site as described in the Site Reader Manual.

Patients will be assessed by irRECIST and RECIST 1.1 by an independent central reader.

The management of patients, and determination whether patients will continue to receive therapy, will be based on irRECIST, as determined by the site.

The same imaging modality should be used throughout the study. Response (PR or CR) or progressive disease should be confirmed with a repeat scan at least 4 weeks after the finding. Please refer to the Imaging Manual and Site Reader Manual for details.

If the site reader determines that radiographic progressive disease (PD) has occurred on the repeat scan, the patient will be considered to have progressed radiographically (as of the date of **initial** progressive disease [PD]). In addition, independent central efficacy reads of the images will be performed.

7.C.2.c Measurability of Tumor

Please see the Site Reader Manual for details. 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 Target Lesions or Non-Target. Lymph nodes that have a short axis <10 mm at Baseline are considered non-pathological and should not be

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recorded or followed. If no measurable lesions are identified at Baseline, the patient will not be allowed to enter the study.

7.C.2.d Response Assessment

For details on irRECIST response criteria assessment, please refer to the Site Reader Manual.

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8 MANAGEMENT OF NON-PATIENT EXPOSURE TO PEXA-VEC

Transmission to patient contact or caregivers has not been documented to date. Nevertheless, the following guidelines should be considered as also noted in the current Pexa-Vec IB and Pexa-Vec Guidelines (Appendix B of the IB), to minimize the risk of potential transmission and to manage infected individuals should an unexpected transmission occur.

8.A EXPOSURE TO PEXA-VEC

If an accidental human exposure to Pexa-Vec occurs, no specific interventions other than local wound care, as needed, and close observation are indicated. Specifically, the following is recommended:

1. Implementation of local, institutional needle stick, or other exposure guidelines.
2. Wash area thoroughly with soap and water.
3. Cover area with non-occlusive dressing until complete resolution.
4. Report the event to the Principal Investigator, the institution's Biosafety Specialist, and/or physician knowledgeable in the care of individuals experienced with vaccinia infection. Record and report the event to the Sponsor by completing and submitting a *Report of Exposure to Infectious Material* form as indicated on the report form.

8.B CONTACTS EXHIBITING SYMPTOMS OF VIRAL INFECTION

If a contact of a patient treated with Pexa-Vec reports symptoms of a possible Pexa-Vec related toxicity:

1. Immediately notify the institution's Biosafety Specialist
2. The individual should be referred to and medically monitored by a physician knowledgeable in the care and treatment of patients with vaccinia infections
3. Report the event to the Sponsor by completing and submitting a *Report of Possible Pexa-Vec Toxicity* form. Follow all instructions on the form regarding avoidance of excluded individuals, consideration (in conjunction with consultation with infectious diseases expert and the Sponsor) of antiviral treatment if warranted (refer to the IB), obtaining clinical samples if applicable, monitoring the individual for response to treatment (if any), and resolution of symptoms.

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9 INVESTIGATIONAL PRODUCTS (IPs)

Pexa-Vec is in development for an advanced RCC patient population. Cemiplimab is in development for a multitude of malignancies. Therefore, in this study Pexa-Vec and Cemiplimab are considered as Investigational Products (IPs).

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

9.A PEXA-VEC

9.A.1 Nomenclature of Pexa-Vec

- Sponsor Designation: Pexa-Vec; VACC-6.25.1
- Synonyms: Recombinant Vaccinia/GM-CSF (VAC-6.25.1 [GM-CSF1]),
  VAC GM-CSF
  Vaccinia/GM-CSF (Pexa-Vec)
- Generic Name: Recombinant Vaccinia GM-CSF; RAC VAC GM-CSF (thymidine kinase-deactivated plus GM-CSF)

Pexa-Vec is provided with a technical sheet detailing its characteristics.

9.A.2 Pharmaceutical Form

9.A.2.a Pexa-Vec

Pexa-Vec is a viral suspension supplied in individual 4-mL glass vials. Each vial contains Pexa-Vec diluted in 30 mM Tris 10% Sucrose buffer. The recoverable volume of Pexa-Vec in each vial is 2 mL with an infectious titer of 1×10^9 pfu (9.0 Log pfu). Each vial is intended for single use (i.e., 1 infusion preparation to 1 patient).

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9.A.3 Packaging and Labeling

9.A.3.a Pexa-Vec

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: Sponsor name, product code, lot number, concentration, volume, storage conditions, route of administration and a cautionary statement in proper language.

9.A.4 Biosafety/Containment Level Classification

9.A.4.a Pexa-Vec

Depending on the country, Pexa-Vec is classified 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 IB and Pexa-Vec Guidelines (Appendix B of the IB) for recommendations on handling Pexa-Vec and for management of Arm A patients treated with Pexa-Vec, as well as for any Arm A patients who develop Pexa-Vec-related pustules.

9.A.5 Transport of Pexa-Vec

9.A.5.a Interstate and International Transport

Pexa-Vec is shipped on dry-ice with the official transport designation as a "Biological Substance, Category B" in compliance with International Air Transportation Association and Department of Transportation regulations and other local regulations for air and road transport of infectious substances (UN 3373 regulations).

9.A.5.b Drug Receipt and Approval of Shipment

Detailed information on drug receipt instructions and approval of shipment process are provided in the Product Handling Manual (located in Pharmacy Binder).

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9.A.5.c Transport within the Institution

All transport of Pexa-Vec (in vial, IV bag 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.

9.A.6 Storage of Pexa-Vec

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 (located in Pharmacy Binder).

9.A.7 Dispensing of Pexa-Vec

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 (located in Pharmacy Binder) for detailed instructions.

9.A.8 Handling of Pexa-Vec

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

In addition, refer to the 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.

9.A.8.a Preparation of Pexa-Vec

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.

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Pexa-Vec is suspended in sterile normal saline buffered with sodium bicarbonate. Detailed information on drug preparation is provided in the Pexa-Vec IV Preparation Worksheet.

9.A.8.b Administration of Pexa-Vec

9.A.8.b.1 IV Administration

Pexa-Vec will be diluted in sodium bicarbonate buffered sterile normal saline to a volume of approximately 250 mL. Preparation instructions are provided in the *IV Preparation Worksheet* (templates in the Pharmacy Binder and Investigator Site File).

9.A.8.b.2 IT Administration

The injection volume (Pexa-Vec and sodium bicarbonate buffered sterile normal saline, when needed) will be equivalent to 25–100% of the size of the tumor to be injected (percentage dependent on the size [LD] of the tumor – refer to the *IT Injection of Pexa-Vec: Procedure Manual* for details), not to exceed a specified upper limit (60 mL). 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*.

9.A.8.c 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 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 regular institution procedure for infectious waste i.e., autoclaving, incineration, or treatment with sodium hypochlorite solution. Biomedical waste will not be left unattended in a public area; autoclaved medical waste must not be disposed of as regular trash.

Textiles and fabrics can be laundered in hot water (71°C) with detergent and hot air drying.

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9.A.8.d 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 (Pexa-Vec) will be reported as required by institutional policies.

9.A.8.e Unused Drug Return or Destruction

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

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

9.B CEMIPLIMAB

9.B.1 Pharmaceutical Form of Cemiplimab

Cemiplimab is manufactured by Regeneron Pharmaceuticals, Inc.

Cemiplimab (50 mg/mL) is manufactured with Cell Line 2 Process 1 (C2P1), and formulated in an aqueous buffered solution at pH 6.0 containing 10 mM histidine, 5% (w/v) sucrose, 1.5% (w/v) L proline, and 0.2% (w/v) polysorbate 80.

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9.B.2 Packaging and Labeling of Cemiplimab

Open-label Cemiplimab will be supplied as a liquid in sterile, single-use vials that will display the product lot number on the label. Each vial will contain a withdrawable volume of 5 mL or 7 mL of Cemiplimab at a concentration of 50 mg/mL.

9.B.3 Storage of Cemiplimab

A pharmacist, or other qualified individual, will be identified at each site to prepare Cemiplimab for administration. The prepared infusion bag should be kept no more than 6 hours at controlled room temperature (15–25°C), or no more than 24 hours at 2–8°C. Detailed preparation and administration instructions will be provided to the sites in the Pharmacy Binder.

9.B.4 Dispensing of Cemiplimab

Cemiplimab 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* (located in Pharmacy Binder) for detailed instructions.

9.B.5 Unused Drug Return or Destruction

During the course of the study, based on the Sponsor's request, and at termination of the study, all unused Cemiplimab patient kits will be destroyed locally or returned to the drug supply provider contracted by the Sponsor.

For local destruction, the Investigator/Pharmacist or delegated person will ensure that destruction is performed according to written instructions available in the Cemiplimab IB and the Technical Sheet and will not expose humans to any risks from Cemiplimab. A certificate of destruction will be completed and provided to the Sponsor (copy retained by the site). The drug supply provider contracted by the Sponsor will coordinate the return of all unused Cemiplimab patient kits. A certificate of return will be completed and provided to the drug supply provider (copy retained by the site).

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

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9.B.6 Drug Accountability

The Investigator/Pharmacist, or delegated person, will maintain drug accountability for Pexa-Vec and Cemiplimab products including the date of vial receipt, date of product preparation, vial quantities dispensed, dose dispensed, and destruction of product (used and/or used with Sponsor permission). A drug accountability log with kit and/or vial numbers will be provided by the Sponsor. If the site has an institutional specific accountability log, this will need to be reviewed by the Sponsor and approved prior to use. Drug accountability records will be verified by the monitor during site visits. All documentation related to IP (e.g., Pexa-Vec or Cemiplimab) shipment, receipt, authorization for use, dispensing, destruction, temperature monitoring, etc., must be filed in the Pharmacy Binder and must be available for inspection. A copy of all drug accountability records will be returned to the Sponsor at the end of the study.

Cemiplimab storage, preparation, and administration will be performed per standard practices as specified per manufacturer guidance.

Any unused Cemiplimab and Pexa-Vec will be returned to the Sponsor depot for destruction.

In addition to the above, the site will be responsible for documenting storage conditions of the product until administration into the patient.

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10 SAFETY REPORTING

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

10.A DEFINITIONS

Adverse Event (AE): An AE for the purposes of this protocol is a medical occurrence or deterioration of a pre-existing medical condition occurring after initiation of study treatment (e.g. treatment emergent) and even if the event is not considered to be related to the study treatment(s).

Examples of AEs include:

1. Pre-existing conditions (any sign, symptom, physical examination finding or laboratory result) that worsens in nature, severity, or frequency compared to Day 1, before the first administration of the IP. A pre-existing condition is one that is present prior to the first administration of the IP and is reported at Baseline or Day 1.
2. Clinical laboratory abnormality, vital signs measurements, physical examinations or ECG findings should be reported as an AE only if it is considered clinically significant (i.e., with clinical manifestations or receiving treatment or clinical management) by the Investigator.
3 All Grade 3 and Grade 4 clinical laboratory results that represent an increase in severity from Baseline will be reported as AEs.
4. Leukocytosis will not be reported as an AE; however, any clinical signs or symptoms resulting from leukocytosis will be recorded as an AE.
5. All reactions from IP, including those occurring as a result of an overdose, abuse, withdrawal phenomena, sensitivity, or toxicity to the IP.
6. Concurrent illness.
7. Injury or accident.

Adverse Event of Special Interest (AESI): All AESI, serious and non-serious, must be reported within 24 hours of identification using the same reporting process as for SAE reporting, per Section 10.E.1. AESIs for this study include the following:

- Any AE that meets DLT criteria
- Grade 2 or greater infusion-related reactions

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- Grade 2 or greater allergic/hypersensitivity reactions
- Myocarditis of any grade.
- Grade 3 or greater irAE (refer to Section 7.A.3.b), or Grade 2 or greater Uveitis (refer to Section 7.A.3.a)
- An irAE of any grade in a patient previously treated with a PI 3-K inhibitor

NOTE: An irAE can occur shortly after the first dose or several months after the last dose of treatment. All AEs of unknown etiology associated with drug exposure should be evaluated to determine possible immune etiology. If an irAE is suspected, efforts should be made to rule out neoplastic, infectious, metabolic, toxin or other etiologic causes prior to labeling an AE as an irAE.

Adverse Drug Reaction (ADR): All noxious and unintended responses to the IP related to any dose or to a study specific procedure as determined by the Investigator or the Sponsor.

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

Other Significant AEs: Any AE and any laboratory abnormality, other than those reported as SAEs, that are considered by the Investigator or the Sponsor to be of special interest because of clinical importance whether or not they lead to an intervention, including:

- withdrawal,
- modification of the schedule of administration of Pexa-Vec,
- modification of the schedule of administration or the dose of Cemiplimab,
- addition of significant concomitant therapy.

Disease progression of underlying malignancy will not be considered an AE if it is consistent with the typical progression pattern of the underlying cancer, as determined by the Investigator. Clinical symptoms may be reported as adverse events if it is unclear if the event is exclusively a result of disease progression or it does not fit the expected pattern of disease progression of the cancer under study. If there is any uncertainty about reportability of an AE, it should be reported as an AE or SAE.

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Serious Adverse Event (SAE): Any untoward medical occurrence that at any dose fulfills one or more of the following criteria:

- Results in death; the death of a patient is not per se an AE but an outcome. "Death" should be considered as a SAE only in case of "unexplained death" when no cause is identified. The event that resulted in a fatal outcome should be determined and reported as a SAE.
- Is life threatening; this term refers to an event in which the patient was at immediate risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it was more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization; the hospitalization is an action taken to treat the event. It should not be reported as a SAE, but the AE leading to hospitalization.
- Results in persistent or significant disability/incapacity; the disability is a substantial disruption of a person's ability to conduct normal life functions.
- Is a congenital anomaly/birth defect; a "congenital anomaly/birth defect" relates to events occurring to babies born after their mother and/or father have taken the IP at the time of pregnancy confirmation or during pregnancy.
- Is a medically significant defined as an event that may not be immediately life threatening or result in death or hospitalization, but may jeopardize the patient or may require medical or surgical intervention to prevent one of the outcomes listed above.

NOTE: Medical and scientific judgment should be exercised in deciding whether some events should be considered as serious because their quick reporting to the Sponsor or its representative may be of interest for the overall conduct of the study.

NOTES About Hospitalization:

- Planned hospitalization for the purpose of administering the study treatment and monitoring the patient per protocol will not be considered a SAE.
- It will not be considered an SAE if patients are hospitalized or their hospitalization is prolonged post-treatment for observation of Grade 1 or 2 flu-like symptoms, provided the time from initial treatment to discharge does not last longer than 48 hours.

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NOTES About Hospitalization (continued):

- Hospitalization planned before or during the study should not be considered as a SAE in case it occurs for:
  - Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition;
  - Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened in an unexpected way since signing informed consent;
  - Treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission;
  - Social reasons and respite care in the absence of any deterioration in the patient's general condition.

Suspected Unexpected Serious Adverse Drug Reaction (SUSAR): Any unexpected SAE considered as related to the IP or to a study specific procedure.

Overdose: An overdose is an administration of the IP at a higher dose than the highest dose already tested in clinical studies or higher than known therapeutic doses or higher than the dose planned according to the schedule of administration.

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

10.B INTENSITY, RELATIONSHIP AND OUTCOME EVALUATION

10.B.1 Intensity

The intensity of AEs/SAEs will be graded according to the NCI-CTCAE version 5 (dated November 27, 2017).

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

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- ***Life-threatening:*** Risk of death at the time of the event
- ***Fatal:*** The patient died

The correspondence between the 2 scales is as follows:

CTCAE	5-Point Scale
1	Mild
2	Moderate
3	Severe
4	Life threatening
5	Death

10.B.2 Relationship to the Investigational Product

The relationship to the IP of each AE/SAE will be evaluated by the Investigator with the "global introspection" method using the following levels:

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

10.B.3 Relationship to the IT Injection Procedure

IT injection of Pexa-Vec into tumors requires a complex and invasive procedure that carries risk, distinct to that of the study agent. The relationship to the IT injection procedure of each AE/SAE will be evaluated with the "global introspection" method using the following levels:

- ***Not related:*** The temporal relationship of the clinical event to the IT injection procedure makes a causal relationship unlikely; and other drugs, therapeutic interventions or underlying conditions provide a sufficient explanation for the observed event.

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- ***Related:*** The temporal relationship of the clinical event to the IT injection procedure makes a causal relationship possible; and other drugs, therapeutic interventions or underlying conditions do not provide a sufficient explanation for the observed event. A clear-cut temporal association with improvement on cessation of the study drug or recurrence upon rechallenge may also be observed.

10.B.4 Outcome

The outcome is rated as follows:

- recovered,
- not recovered,
- recovered with sequelae,
- fatal,
- unknown.

NOTE ON "FATAL": this outcome is to be used only for the event leading to death. The outcome of all other events at the time of the death must be reported; if ongoing at the time of death, the outcome of those other events should be reported as "not recovered".

10.C TIME PERIOD FOR COLLECTION

From the date of signature of the informed consent form and up to prior to initiation of IP administration, only SAEs caused by a protocol-required procedure (e.g., SAEs related to invasive procedures such as biopsies) will be collected and reported to the Sponsor as specified in Section 10.E.

After the initiation of IP and up to 28 days after the last dose of IP, all AEs and SAEs should be collected and recorded on the eCRFs as described in Section 10.D and SAE reported to the Sponsor as specified in Section 10.E.

Post-study SAEs (i.e., occurring more than 28 days after the last dose of IP), and evaluated by the Investigator as related to the IP should be collected and reported to the Sponsor indefinitely even after study closure as specified in Section 10.E. These would however not be reported in the eCRF.

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10.D ADVERSE EVENT MANAGEMENT

10.D.1 Reporting

Any AE/SAE directly observed (physical examination, laboratory test, or other assessments), mentioned by the patient or reported by the patient upon non-directive questioning at each visit during the study, will be reported by the Investigator on the "Adverse Events" page of the eCRF as follows:

- AE term (i.e., the nature of the event with self-explanatory and concise medical terminology [indicate a diagnosis or syndrome instead of symptoms]),
- date of onset and date of end (i.e., actual dates when the event starts and is resolved rather than dates when the Investigator is informed),
- outcome,
- intensity,
- relation to Pexa-Vec, Cemiplimab, or study procedure (e.g., infusion)
- action taken regarding Pexa-Vec, Cemiplimab
- 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 wellbeing of the patient. Any treatment given will be reported on the page "Concomitant Medication" of the CRF.

The Sponsor or its representative reserves the right to ask for further information on any AE/SAE that may be considered of interest or when the event is not previously documented in the IB (new occurrence) and is thought to be related to Pexa-Vec, Cemiplimab, the combination or a study specific procedure.

10.D.2 Follow-up

AE must be followed until resolution or the last visit planned by the protocol.

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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 Pexa-Vec and/or Cemiplimab or to a study specific procedure,
- SAEs,
- any other significant AE as recommended by the Sponsor.

10.D.3 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 IP and the treatment (if applicable) of the event.

10.E SERIOUS ADVERSE EVENT MANAGEMENT

10.E.1 Reporting

SAE occurring during the course of a study, irrespective of the treatment received by the patient MUST be reported by the Investigator to the Sponsor or its representative within 24 hours of occurrence or knowledge of the event. The Investigator will also complete the "SAE Form" to be provided to the Sponsor or its representative as per SAE reporting guidelines. SAE related documentation, if any, must be kept at the study site in the Investigator site file.

10.E.2 Follow-Up

Follow-up information (e.g., complications or progression of the initial SAE) must be notified as soon as possible to the Sponsor or its representative using a new SAE form with the box "follow-up" ticked. New information must be sent to the Sponsor or its representative within 24 hours of knowledge as specified in the Investigator site file. The Sponsor or its representative may request further information as needed.

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

10.E.3 Notifications

The Sponsor or its representative will be responsible for reporting SUSARs and any follow-up information to Regulatory Authorities and to central Ethics Committees (ECs) as per local

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regulation. In case of a SUSAR, the Sponsor or its representative will inform all Investigators involved in any study with Pexa-Vec that such an event occurred.

The Sponsor or its representatives will provide copies of all safety reports submitted to regulatory authorities to the Investigator for inclusion in the Investigator site file.

The Investigator is responsible for informing local IRB/IEC/REBs, Institutional Biosafety Committees (IBCs), and other required institutional committees of SUSARs and any follow-up information as per local regulations.

10.F SPECIAL SITUATIONS

10.F.1 Post-Study SAE

Any SAE occurring more than 28 days after the last IP administration **and** that is considered by the Investigator to be related to the IP must be reported to the Sponsor or its representative, documented and followed-up as described in Section 10.E.

10.F.2 Pregnancy

Patient treatment (Pexa-Vec or Cemiplimab) must be discontinued immediately if the patient, or the patient's partner, becomes pregnant.

If a patient or their partner becomes pregnant during the active study participation phase and up to 6-weeks of last Pexa-Vec dose or Cemiplimab dose, the Investigator must report the pregnancy to the Sponsor or its representative, using a "Pregnancy form" within 24 hours of the site's awareness of the pregnancy.

NOTE: If a patient's partner becomes pregnant, the Sponsor or its representatives will make every effort to obtain consent from the partner to collect data on the pregnancy.

Pregnancies have to be followed by the Investigator up to the completion or termination of the pregnancy, collecting information about the pregnancy, the new-born medical status follow up on the status of the infant until 8–12 weeks of age.

Pregnancy itself is not considered as an AE. However, any problem met during the pregnancy and its outcome should be reported as an AE or a SAE. Spontaneous or induced abortions as well as ectopic pregnancy should be considered as serious. Any problem concerning the newborn should also be reported as an AE or SAE.

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All pregnancies starting from the first IP administration and up to 6 months after the last IP administration must be reported.

10.F.3 Overdose

Any overdose should be reported to the Sponsor's representative and documented and followed-up using an "Overdose" form. In addition, any associated symptoms should be reported as an AE or SAE as per instructions in Section 10.D and Section 10.E, respectively.

10.F.4 Death

Death of a study patient occurring during the active study participation phase must be reported to the Sponsor or its representative by phone and email or fax within 24 hours of the site's awareness of the event.

Deaths that occur outside of this reporting period but that are the outcome of an unresolved AE or SAE will also be reported to the Sponsor or its representative on a dedicated eCRF page.

In addition, if the patient's death occurred within 28 days of the most recent dose of Pexa-Vec, or death was >28 days after the most recent dose of Pexa-Vec but was due to an unresolved potentially related AE or SAE, the Sponsor may also request formalin-fixed and flash frozen tissue specimens from normal organs examined as well as from as many tumor site(s) as possible to assess the biodistribution and safety of Pexa-Vec in humans. Special histopathology stains for Pexa-Vec replication and gene expression, virus-induced cytopathic effects, and inflammatory infiltration (characterize immune cells in tissues) may be performed. Tissue specimens may be retained by the sponsor for up to 2 years after sampling for these purposes.

A copy of the death certificate should be obtained, if the local regulation / law allows.

If an autopsy is performed, a copy of the autopsy report should be obtained by the site and provided to the Sponsor or its representative, if the local regulation / law allows.

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11 STATISTICAL CONSIDERATIONS

11.A DOSE ESCALATION AND SAMPLE SIZE

11.A.1 Part 1, Dose Escalation Phase

Up to 12 DLT-evaluable patients are planned based on a 3+3 design. The actual sample size will depend on DLT occurrences. Dose Level 1 and 2, three patients will be treated at each dose level unless a DLT is observed. Patients will be observed for a DLT through Day 29. Enrollment will proceed to the next dose level if 0 of 3 patients experiences a DLT. If one of the first 3 patients experiences a DLT, additional patients will be enrolled until a second patient experiences a DLT (which defines the toxic dose; the dose level immediately preceding this toxic dose level will be determined as the MTD) or until 6 total patients have been treated, whichever comes first. If a second DLT is not experienced within that cohort, dose-escalation may continue.

11.A.2 Part 2, Arm A vs Arm B

Efficacy will be evaluated comparing the objective response rate in the combination arm (Arm A) with the anti-PD-1 arm (Arm B). Patients with injectable lesions will be randomized to either Arm A or Arm B, stratified by number of prior therapies. The hypothesis test is powered based on a control rate of 21.5%, derived from nivolumab data, the anti-PD-1 agent approved for use in advanced RCC (Nivolumab package insert). A treatment effect corresponding to ORR of 43% (double the ORR of anti-PD-1 monotherapy) in Arm A (treatment difference of 21.5%) from a randomized comparison, would be encouraging for further study of the combination of Pexa-Vec and Cemiplimab in this patient population. The randomized design will provide support for the estimated effect size on ORR in spite of the unknown variability of the control estimate and effects of potential confounding factors. Notably, the ORR endpoint is selected in this randomized trial instead of progression free survival due to historical data with anti-PD-1 antibodies demonstrating that progression free survival may not be a reliable surrogate for anti-tumor activity or overall survival in RCC and other solid tumors (*Motzer 2015, Borghaei 2015, Herbst 2016*). To reject the null hypothesis that the combination (Arm A) will have no greater effect than the anti-PD1 alone (Arm B) with a power of 75% when the actual combination ORR in the population is 43% and a 1-sided alpha of 0.15, 27 patients will be enrolled in to each Arm A and Arm B (n = 54).

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11.A.3 Part 2, Arm C

For this dose-expansion cohort, the sample size is determined using a Simon 2-stage Minimax design with 1-sided alpha of 0.12 and power of 80%. Eleven patients will be enrolled in the first stage. If 3 or more patients experience a response, a further 9 patients will be enrolled and assessed for efficacy.

The null and alternative ORR rates (21.5% and 43%) are designed to test for a clinically meaningful treatment effect when compared to an estimated control arm response rate derived from a historical control, potentially worth pursuing further in clinical development.

11.A.4 Part 2, Arm D

For this dose-expansion cohort, the sample size is determined using a 2-stage design based on testing a null hypothesis ORR rate ≤5% versus alternative hypothesis ORR rate ≥20% with a probability of early termination of 75.5%, satisfying the 1-sided alpha of 5% and power of 80% constraints. Nineteen patients will be enrolled in the first stage. If 2 or more patients experience a response, a further 8 patients will be enrolled and assessed for efficacy.

The null and alternative ORR rates (5% and 20%) are designed to test for a clinically meaningful treatment effect of the 2nd line RCC treatment assuming an ineffective response rate of 5%. Because there is no response data of 2nd line check point blocker treatment available from RCC patient population refractory to 1st line check point blocker treatment, ORR of 20%, pooled from studies *(Eichelberg 2008, Dudek 2009, Sablin 2009, Zama 2010, Porta 2011, Zimmerman 2009, Eichelberg 2015, Rini 2008)* where standard of care (sunitinib) in the 2nd line setting was used.

11.B ANALYSIS POPULATIONS

The ITT population will comprise all enrolled patients.

The safety population will comprise all patients who receive at least one dose of any one component of the study treatment (Pexa-Vec or Cemiplimab). The occurrence of death also constituted a valid safety assessment. Patients will be analyzed according to the treatment they actually received. The safety population will be the population for safety and drug exposure analyses.

The per protocol population will comprise all patients from the ITT population without any protocol deviations who have completed a minimum exposure requirement. The minimum

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exposure requirement is dependent on Arm enrolled. From Arm A, the minimum exposure is at least one Pexa-Vec injection and at least one Cemiplimab infusion. For Arm B, the minimum exposure is at least one Cemiplimab infusion. For Arm C and Arm D, the minimum exposure is at least one Pexa-Vec infusion and at least one Cemiplimab infusion. However, if a patient was discontinued for AE, or died before the required exposure could be met, that patient will still be included in per protocol population.

11.C METHODS OF ANALYSIS

11.C.1 Safety: Methods of Analysis

All analyses will be descriptive. None are powered to be comparative.

11.C.2 Efficacy: Methods of Analysis

For the primary efficacy analysis, the ORR will be defined as by RECIST 1.1 criteria (*Eisenhauer 2009*). Both assessments will be applied by the central imaging vendor as a measure for assessment of tumor response and date of disease progression. irRECIST will be used for patient management at the clinical study site and also retrospectively assessed by central imaging vendor.

Tumor response by irRECIST over time and ORR, based on the best observed response at any time, will be summarized descriptively. Time-to-event distributions for the overall survival and progression free survival will be estimated using the Kaplan-Meier method.

The primary analysis for Arm C and Arm D respectively, the hypothesis test for a 2-stage design described in Section 11.A.4 above, will be a one-sided single proportion, single sample test with the parameters described above. This will be supplemented/supported by descriptive assessments (95% confidence intervals [CIs] and other descriptive statistics) for the primary endpoint and related endpoints (such as complete response [CR] rate and partial response [PR] rate, etc.).

The primary analysis comparing Arm A and Arm B, described above in Section 11.A.2, will be a two sample, 1-sided test of difference of proportions (as per Simon's "randomized Phase 2.5 design") (*Simon 2001*) with the parameters specified above. This will be supported by descriptive analyses per arm and comparatively across arms. The data from the treatment cohort(s) may be split or combined for the ad-hoc analyses, which will be exploratory in nature and hypothesis-generating only.

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11.C.3 Treatments (Study Treatment, Concomitant Therapies)

The safety population will be used for all summaries and listings about treatments.

11.C.3.a Study Treatments (Pexa-Vec and Cemiplimab)

Exposure to Pexa-Vec and Cemiplimab will be provided by summarizing the dose received during each treatment session (in pfu, corrected if not complete) and the cumulative dose (sum of doses received during each treatment). In addition, number of Pexa-Vec and Cemiplimab doses received (partial doses will be counted as one dose) will be categorized and summarized.

In addition, total duration of study treatment (including Pexa-Vec and Cemiplimab) will be listed and summarized.

11.C.3.b Concomitant Medications

Medications and/or non-drug therapies will be collected as described in Section 7.A.4.

The concomitant medications (i.e., ongoing at the start of study treatment or taken during the course of the study) will be coded using the World Health Organization (WHO) Drug Dictionary and will be listed and summarized by active ingredient by means of frequency counts and percentages.

Any prior medications or significant non-drug therapies starting and ending within the month before start of study treatment will be listed.

11.C.4 Efficacy

11.C.4.a Overall Response Rate (ORR)

Overall response rate (ORR) is defined as the proportion of patients whose best overall response is either complete response (CR) or partial response (PR). The best overall response is the best response recorded from the randomization until disease progression.

Proportions of patients with a best overall response of complete response (CR) or partial response (PR) will be presented by treatment arm along with exact 95% CIs.

Analyses will be performed based on central assessments using RECIST 1.1,

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Analyses will also be performed on central assessments using irRECIST and will be repeated using both local and central readings.

11.C.4.b Progression Free Survival

Progression free survival is defined as the date of the first study treatment to the date of first documented radiographic tumor progression or death due to any cause, whichever occurs first. If a patient has not had a progression free survival event at the cut-off date for analysis, progression free survival will be censored at the date of last evaluable tumor assessment before the cut-off.

If a progression is observed after 2 or more missing or non-evaluable tumor assessments, then the date of progression will be censored at the latest occurring evaluable tumor assessment before missing; for a progression observed after a single missing or non-evaluable tumor assessment, the actual date of disease progression will be used.

Progression free survival will be presented descriptively using Kaplan-Meier curves. Summary statistics from the Kaplan-Meier distributions will be determined, including median progression free survival and 25% and 75% quartiles with corresponding 95% CIs. The proportions of patients remaining progression-free at 3, 6, and 9 months, along with 95% CIs will also be provided.

Analyses will be performed based on central assessments using RECIST 1.1 and irRECIST. irRECIST will also be performed by a local reader.

11.C.4.c Disease Control Rate

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

Proportions of patients with a best overall response of complete response (CR), partial response (PR), or stable disease (SD) will be presented.

Analyses will be performed based on central assessments using RECIST 1.1 and irRECIST. irRECIST will also be performed by a local reader.

11.C.4.d Overall Survival

Overall survival is defined as the time from first study treatment until death from any cause. For patients not known to have died at the time of the analysis, overall survival will be censored on the date they were last known to be alive. If a patient withdraws early, overall survival will not be

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censored at the date of withdrawal unless this is the date they were last known to be alive. Date of death will be obtained from the death certificate (preferable) or from a written statement from the primary care or attending physician, or from death registry data.

Overall survival will be presented descriptively using Kaplan-Meier curves. Summary statistics from the Kaplan-Meier distribution will be determined, including median overall survival with corresponding 95% CIs. The proportions of patients alive at 6, 12, 18, and 24 months, along with corresponding 95% CIs, will also be provided.

11.C.4.e Exploratory Efficacy Analysis

Immune, biomarker, and other correlative endpoints will be summarized descriptively.

11.C.5 Safety

Safety is the primary endpoint of the study.

Analyses will be based on the safety population. The safety summary tables will include all safety assessments collected from the start of treatment with Pexa-Vec or Cemiplimab up to 28 days after the last treatment dose of Pexa-Vec or Cemiplimab.

The assessment of safety will be based mainly on the frequency of AEs and on the number of laboratory values that fall outside of predetermined ranges. Other safety data (e.g., ECG, vital signs) will be considered as well and reported as AEs.

Overall incidence of AEs and SAEs will be evaluated.

AEs will be coded and tabulated using the Medical Dictionary for Regulatory Activities (MedDRA) classification scheme and based on NCI CTCAE v5: 27 November 2017. All AEs, AEs leading to discontinuation, and SAEs recorded during the study will be listed and summarized by body system organ class and preferred terms, severity (grade), relationship to each study treatment component (Pexa-Vec and Cemiplimab). AEs related to study procedure will be also listed.

AEs will be summarized by presenting the number and percentage of patients having at least one AE. Data will be presented by system organ class, preferred term and maximum grade. A patient with multiple occurrence of an AE will be counted only once in the AE category.

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11.C.5.a Laboratory Abnormalities

The summaries will include all laboratory assessments collected no later than 28 days after study treatment discontinuation. All laboratory assessments will be listed and those collected during 28 days after study treatment discontinuation will be flagged in the listings.

All laboratory values will be converted into SI units and the severity grade calculated using appropriate common terminology criteria for AEs (NCI CTCAE, version 5). A listing of laboratory values will be provided by laboratory parameter, patient, and treatment arm. A separate listing will display notable laboratory abnormalities (i.e., newly occurring CTCAE Grade 3 or Grade 4 laboratory toxicities). The frequency of laboratory abnormalities will be displayed.

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12 ETHICAL REQUIREMENTS

All parties involved with this clinical trial, including Sponsor, representatives of the Sponsor, and the Investigators, will conduct the study in compliance with the protocol and according to the International Conference on Harmonisation (ICH) Guidelines for Good Clinical Practices (E6), the Declaration of Helsinki, and all regulatory and institutional requirements, including those for patient privacy, informed consent, IRB/IEC/REB review and approval, source documentation, and record retention and including any local regulation.

12.A PATIENT PRIVACY

Patient medical information obtained for the purposes of this trial will be considered confidential and will not be disclosed to anyone not directly concerned with the trial prior written permission. Upon the patient's request and written permission, medical information may be given to his/her personal physician or other appropriate medical personnel responsible for the patient's welfare.

Patient confidentiality requirements of the region(s) where the trial is conducted will be met.

However, data generated for this study, with full access, must be available for inspection upon request to representatives of the FDA or other national or local health authorities; the Sponsor or its representatives; the associated IRB/IEC/REB and other institutional committees, as required; and/or as required by law.

Patients will be identified only by unique patient's number. However, release of research results or data that reveal patient names or other identifiers, such as photographs, audio or videotapes, must be carried out in accordance with the Department of Health and Human Services proposed Standards for Privacy of Individual Health information, 45 CFR 164.508, and all applicable laws or other country-specific regulations. Written authorization must be obtained from the patient and IRB/IEC/REB (or other institutional committee delegated to represent patient privacy considerations) prior to the release of such information. Identifiable patient data may not be used for purposes of promoting the IP.

In the US, a written Health Insurance Portability and Accountability Act (HIPAA) authorization must be signed by the study participant before participating in the study to permit the use and disclosure of his/her personal health information as stated in the written authorization. Any other applicable laws and other country-specific regulations must also be followed.

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12.B IRB/IEC/REB

This study must have the approval of a properly-constituted IRB/IEC/REB. Before the IP may be used to treat patients, the Investigator will provide the Sponsor or its representatives with a copy of the IRB/IEC/REB approval letter stating that the study protocol and ICF have been reviewed and approved. A copy of the approved ICF and other documents, as requested, will be provided to the Sponsor or its representatives.

12.C INSTITUTIONAL BIOSAFETY COMMITTEE (IBC)

In the US, this study must have the approval of an IBC, which has been created under the guidance of the National Institutes of Health (NIH) to ensure proper monitoring and conduct of gene transfer protocols. In other countries, other requirements for biosafety or infection control may apply and will be followed, as applicable.

12.D INFORMED CONSENT

Written consent will be obtained from the patient before he/she can participate in the study. The content and process of obtaining informed consent will be in accordance with all applicable regulatory requirements.

Prior to the initiation of any procedures relating to the study, a patient's consent shall be documented by the use of a consent form written in the patient's native language that has been approved by the IRB/IEC/REB and that is signed and personally dated by the patient at the time of consent. The person who conducted the informed consent discussion shall sign and personally date the consent form. A copy of the signed and dated informed consent will be given to the patient. The Investigator must keep each patient's original, signed and dated consent form on file for inspection by a regulatory authority or authorized party at any time.

Depending on national regulations, an authorized person other than the Investigator may inform the patient, sign and date the consent form.

During the patient's participation in the trial, whenever important new information becomes available that may be relevant to the patient's consent, the consent form will be updated accordingly for IRB/IEC/REB approval. The patient should be informed in a timely manner if new information becomes available that may be relevant to the patient's willingness to continue participation in the trial. The communication of this information should be documented. The approved revised consent form will be signed and dated by the patient.

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13 STUDY ADMINISTRATION

13.A DOCUMENTS

13.A.1 Investigator's Brochure

The Investigator will review the current version of the Cemiplimab IB and Pexa-Vec IB, including Appendix B: Pexa-Vec Guidelines, which contains detailed information regarding warnings, precautions, contraindications, AEs, recommendations for managing the potential for virus transmission to health care workers and patient contacts, and other significant data pertaining to the IP. It is obligatory that the Investigator be familiar with all sections of this document, and ensures adequate training of relevant study personnel, prior to initiation of the study. New information between Cemiplimab and/or Pexa-Vec IB updates will be communicated in the form of an IB Attachment or letter.

13.A.2 Protocol Amendments

The Sponsor will initiate any significant changes to this protocol in writing as a protocol amendment. The amendment must be submitted to National Health Authorities and the IRB/IEC/REB with a revised ICF, if necessary and as locally requested. Written documentation of IRB/IEC/REB approval must be received before the amendment may take effect.

13.A.3 Case Report Forms

Clinical data will be recorded on eCRFs provided by the Sponsor or its representatives. All data recorded in the eCRFs must be substantiated by data contained within the patients' original source documents. The electronic system should allow all corrections to the eCRFs to be dated and traceable to the individual making the correction. The Investigator will ensure that all eCRFs are completed accurately. A copy (electronic or paper) of all eCRFs will be retained by the site as part of the study documents.

13.B QUALITY CONTROL AND QUALITY ASSURANCE

13.B.1 Study Monitoring

The Sponsor or its representatives will monitor the site at appropriate intervals to ensure protocol and Good Clinical Practice (GCP) compliance and accurate data recording. The frequency of monitoring may vary depending on enrollment rate and the quality of data collected. The

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Investigator and staff are expected to cooperate and provide all relevant study documentation upon request. Each site will also be routinely monitored by phone or email to keep abreast of patient status and to answer questions.

In addition to routine monitoring visits, direct access to all study-related records must also be granted at any time for inspection by FDA or other national or local health authorities, the Sponsor or its representatives, the associated IRB/IEC/REB and other institutional committees, as required, and/or as required by law.

13.B.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 the Sponsor or legal representative, 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 study have been processed and reported in compliance with GCP and applicable regulatory requirements.

13.C RECORD RETENTION

The Investigator must retain the following: protocols; amendments; IRB/IEC/REB approvals; IBC approvals (if applicable); copies of the Form FDA 1572; completed, signed, dated consent forms; patient medical records and original source documents; eCRFs; drug accountability records; all study-related correspondence; and any other documents pertaining to the conduct of the study.

According to ICH (E6), essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the IP. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the Investigator/Institution as to when these documents no longer need to be retained.

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13.D STUDY TERMINATION

The Sponsor retains the right to terminate the study or terminate a study site and remove all the study materials from the study site at any time. Specific instances that may precipitate such termination are as follows:

- Completion of the study at an investigational site
- Unanticipated adverse medical experiences in this or other studies indicating a potential health hazard caused by the IP
- Significant protocol deviation and/or lack of compliance and cooperation on the part of the Investigator, including but not limited to: failure to obtain signed ICF prior to initiating study related procedures; unsatisfactory patient enrollment with regard to quality or quantity; deviation from protocol requirements without prior approval from the Sponsor; or inaccurate and/or incomplete data recording on a recurrent basis
- Investigator withdrawal from participation in study
- Lack of patient recruitment at an investigational site
- Withdrawal of IP from investigational use
- Termination of this study by the Sponsor or Health Authority
- In the event of premature termination of the study or a site, the Sponsor will work with the Investigator(s) to arrange safety follow-up for all patients exposed to IP. The Follow-Up plan will be communicated to the IRB/IEC/REB, IBC (as applicable), and Regulatory authorities.

13.E PUBLICATION AND PRESENTATION POLICY

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

Consistent with Good Publication Practices (*Graf 2009*), authorship is to follow the criteria outlined by the International Committee of Medical Journal Editors, and/or follow the policies

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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, the Sponsor supports the publication of primary study results from multicenter studies in their entirety prior to any secondary analyses. Publication of individual center data unless ancillary study/data is discouraged. A publication in which the contribution of the Sponsor's personnel exceeded that of conventional monitoring will be considered for co-authorship provided all other criteria of International Committee of Medical Journal Editors are met.

13.F ARCHIVING

13.F.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 the Sponsor. The Sponsor must be notified if the Investigator assigns the study documentation to another party or moves it to another location.

13.F.2 Trial Master File

The Sponsor, or representative will archive the trial master file in accordance with GCP and applicable regulatory requirements, and will inform the Investigator when the archiving of the study documentation is no longer required.

13.G REVIEW COMMITTEE

13.G.1 Data and Safety Monitoring Board

The safety board will conduct periodic safety and efficacy reviews prior to dose escalation and expansion. This committee will be comprised of the Sponsor Medical Monitor and study Investigators. Its main mission will be to evaluate the benefit versus risk, to ensure the integrity of the data is respected at all times throughout the study and to give recommendations on its further conduct.

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APPENDIX A:
GUIDANCE TO THE INVESTIGATOR ON MANAGEMENT OF IMMUNE-MEDIATED ADVERSE REACTIONS

The recommendations in Appendix A should be seen as guidelines, and the treating physician should exercise clinical judgment based on the symptoms and condition of the individual patient.

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RECOMMENDED ADVERSE EVENTS MANAGEMENT FOR COLITIS/DIARRHEA

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Immune-Mediated Colitis/Diarrhea CTCAE v5 Grade	Study Treatment Management	Action and Supportive Care Guidelines	Diagnostic Considerations
Grade 1 • Colitis: Asymptomatic; clinical or diagnostic observations only; intervention not indicated • Diarrhea: Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	No change	Treat symptomatically (loperamide, oral hydration, electrolyte substitution and ADA colitis diet). Consider consultation with gastroenterologist for prolonged symptoms If symptoms are persistent, consider endoscopic evaluation If persists for >2 weeks, treat as Grade 2	All attempts should be made to rule out other causes such as metastatic disease, bacterial or parasitic infection, or viral gastroenteritis.

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Immune-Mediated Colitis/Diarrhea CTCAE v5 Grade	Study Treatment Management	Action and Supportive Care Guidelines	Diagnostic Considerations
Grade 2 • Colitis: Abdominal pain; mucus or blood in stool • Diarrhea: Increase of 4–6 stools per day over baseline; moderate increase in ostomy output compared to baseline; limiting instrumental ADL	Withhold study treatment until colitis or diarrhea improves and remains at Grade 0–1 after corticosteroid taper to ≤10 mg/day prednisone or equivalent	Treat symptomatically (loperamide, oral hydration, electrolyte substitution and ADA colitis diet). Consultation with gastroenterologist Consider colonoscopy ± esophagogastroduodenoscopy (EGD), or endoscopy Consider stool evaluation to rule out infectious etiology Consider stool inflammatory marker evaluation (i.e., lactoferrin and calprotectin) to differentiate functional vs. inflammatory diarrhea Consider abdominal and pelvic CT with contrast Treatment with systemic corticosteroids (1–2 mg/kg/day prednisone or equivalent) until resolution to ≤Grade 1 and taper over at least a month If no improvement within 2–3 days, treat as Grade 3	

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Immune-Mediated Colitis/Diarrhea CTCAE v5 Grade	Study Treatment Management	Action and Supportive Care Guidelines	Diagnostic Considerations
Grade 3 • Colitis: Severe abdominal pain; peritoneal signs • Diarrhea: Increase of ≥7 stools per day over baseline; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting selfcare ADL	Withhold study treatment until colitis or diarrhea improves and remains at Grade 0–1 after corticosteroid taper to ≤10 mg/day prednisone or equivalent Permanently discontinue study treatment if patient develops a 2nd episode of Grade 3 colitis or diarrhea upon re-challenge	Treat symptomatically (loperamide, oral hydration, electrolyte substitution and ADA colitis diet). Consultation with gastroenterologist Consider colonoscopy ± esophagogastroduodenoscopy (EGD), or endoscopy Consider stool evaluation to rule out infectious etiology Consider stool inflammatory marker evaluation (i.e., lactoferrin and calprotectin) to differentiate functional vs. inflammatory diarrhea Consider abdominal and pelvic CT with contrast Inpatient care for close monitoring and supportive care Treatment with systemic corticosteroids (1–2 mg/kg/day prednisone or equivalent) until resolution to ≤Grade 1 and taper over at least 1 month If no improvement with corticosteroid within 2–3 days, consider additional immunosuppressive therapy i.e., mycophenolate 0.5–1 g BID, infliximab 5 mg/kg IV	
Grade 4 • Colitis: Life-threatening consequences: urgent intervention indicated • Diarrhea: Life-threatening consequences; urgent intervention indicated	Permanently discontinue study treatment	Same as above Consider lower GI endoscopy if symptoms are refractory despite treatment or there is concern of new infections	

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RECOMMENDED ADVERSE EVENTS MANAGEMENT FOR DERMATOLOGIC TOXICITIES

Immune-related skin toxicities include maculopapular rash, dermatitis, rash generalized, dermatitis bullous, drug eruption, erythema, rash erythematous, rash macular, rash pruritic, and skin reaction. Guidance here is provided for maculopapular rash.

Immune-Mediated Skin Adverse Reactions CTCAE v5 Grade	Study Treatment Management	Action and Supportive Care Guidelines	Diagnostic Considerations
Grade 1 **Grade 2** lasting 1 week or less	No change	Treatment with mild to moderate potency topical steroids Treatment with oral antihistamine	All attempts should be made to rule out other causes such as metastatic disease, infection, contact dermatitis, effect of another drug, or a skin condition linked to another systemic disease.
Grade 2 lasting longer than 1 week Grade 3 Or suspected Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)	Withhold study treatment until skin reaction improves and remains at Grade 0–1 after corticosteroid taper to≤10 mg/day prednisone or equivalent	Consider consultation with dermatologist and skin biopsy for diagnosis of bullous dermatitis Treatment with systemic corticosteroids (1–2 mg/kg/day prednisone or equivalent) until resolution to ≤Grade 1 and taper over at least one month Consider treatment with medium to high potency topical steroids Treatment with oral antihistamine	
Grade 4 Or confirmed SJS or TEN	Permanently discontinue study treatment	Consultation with dermatologist and skin biopsy Treatment with high potency topical steroids AND with systemic corticosteroids (1–2 mg/kg/day prednisone or equivalent) until resolution to ≤Grade 1 and taper over at least one month	

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RECOMMENDED ADVERSE EVENTS MANAGEMENT FOR ENDOCRINE EVENTS

Immune-Mediated Hypothyroidism CTCAE v5 Grade	Study Treatment Management	Action and Supportive Care Guidelines	Diagnostic Considerations
Grade 1	No change	Monitor thyroid function more frequently (every 3–6 weeks) until resolution to baseline There should be low index of suspicion for immune-related endocrinopathy including checking TSH, T4, cortisol and adrenocorticotropic hormone levels if clinically appropriate.	Immune related endocrinopathies can have subtle and wide-ranging presentations. Refer to expert panel consensus guidance documents for further guidance. All attempts should be made to rule out other causes such as brain metastases, sepsis, and/or infection.
Grade 2	Withhold study treatment if clinically necessary	Consult with endocrinologist and provide supportive care per institutional guidelines. Replacement of thyroid hormone as indicated	
Grade 3-4	Withhold study treatment until hypothyroidism improves and remains at Grade 0–1 or is otherwise clinically stable	Consult with endocrinologist and provide supportive care per institutional guidelines. Replacement of thyroid hormone as indicated	

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Immune-Mediated Hypophysitis or Adrenal Insufficiency CTCAE v5 Grade	Study Treatment Management	Action and Supportive Care Guidelines	Diagnostic Considerations
Grade 1	No change	Hypo/hyperthyroid: Monitor thyroid function or other hormonal level more frequently (every 3–6 weeks) until resolution to baseline There should be low index of suspicion for immune-related endocrinopathy including checking TSH, T4, cortisol and adrenocorticotropic hormone levels if clinically appropriate.	Immune related endocrinopathies can have subtle and wide-ranging presentations. Refer to expert panel consensus guidance documents for further guidance. All attempts should be made to rule out other causes such as brain metastases, sepsis, and/or infection.
Grade 2–4	Withhold study treatment until hypophysitis or adrenal insufficiency improves and remains at Grade 0-1 after corticosteroid taper to ≤ 10 mg/day prednisone or equivalent or is otherwise clinically stable	Consult with endocrinologist and provide supportive care per institutional guidelines. Initial dose of 1-2 mg/kg/day prednisone or equivalent followed by a taper Replacement of relevant hormone(s) as indicated	

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Immune-Mediated Type I Diabetes Mellitus CTCAE v5 Grade	Study Treatment Management	Action and Supportive Care Guidelines	Diagnostic Considerations
Grade 1	No change	Monitor glucose level more frequently until resolution to baseline There should be low index of suspicion for immune-related endocrinopathy including checking TSH, T4, cortisol and adrenocorticotropic hormone levels if clinically appropriate.	Immune related endocrinopathies can have subtle and wide-ranging presentations. Refer to expert panel consensus guidance documents for further guidance. All attempts should be made to rule out other causes such as brain metastases, sepsis, and/or infection.
Grade 3–4 (hyperglycemia)	Withhold study treatment until diabetes mellitus returns to Grade 0–1 or is otherwise clinically stable	Consult with endocrinologist and provide supportive care per institutional guidelines. Initiate treatment with anti-hyperglycemics as clinically indicated.	

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RECOMMENDED ADVERSE EVENTS MANAGEMENT FOR HEPATITIS

Immune-Mediated Hepatitis Severity CTCAE v5 Grade	Study Treatment Management	Action and Supportive Care Guidelines	Diagnostic Considerations
Grade 1	No change	Monitor liver function tests (LFT) more frequently until resolution to baseline values	All attempts should be made to rule out other causes such as metastatic disease, progressive liver disease, viral hepatitis, alternative drug toxicity, infectious causes and/or myositis.
Grade 2 with: • Elevated ALT and AST >3 and ≤5 × ULN • Or total bilirubin >1.5 and ≤3 × ULN	Withhold study treatment until heptatis improves and remains at Grade 0-1 after corticosteroid taper to ≤ 10 mg/day prednisone or equivalent or returns to baseline AST or ALT after completion of corticosteroid taper	Monitor liver function tests (LFT) more frequently until resolution to baseline values Consider appropriate consultation with hepatologist and liver biopsy to establish etiology of hepatic injury, if necessary Consider inpatient monitoring for patients with ALT/AST >8 × ULN and or elevated total bilirubin >3 × ULN Treatment with systemic corticosteroids (1–2 mg/kg/day prednisone or equivalent) until resolution to ≤Grade 1 and taper over at least 1 month If no improvement within 3 days after initiation of systemic steroids, consider additional immunosuppressive therapy i.e., mycophenolate mofetil 0.5–1 g BID Several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased	
Grade 3 or 4 with: • Elevated ALT and AST >5 × ULN • Or total bilirubin >3 × ULN	Permanently discontinue study treatment	Same as above	

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RECOMMENDED ADVERSE EVENTS MANAGEMENT FOR NEUROLOGICAL ADVERSE EVENT

Immune-Mediated Neurotoxicity CTCAE v5 Grade	Study Treatment Management	Action and Supportive Care Guidelines	Diagnostic Considerations
Grade 1	No change	Closely monitor the patient If worsening, treat as Grade 2 or Grade 3–4, as clinically appropriate	If immune-mediated encephalitis is suspected, consider radiologic assessment and, if possible, CSF assessment for auto-immune antibodies.
Grade 2	Withhold study treatment until improves to baseline	Treat symptoms per local guidelines, e.g. 0.5–1 mg/kg/day methylprednisolone IV or PO equivalent If worsening, treat as Grades 3–4 Consider neurology consult	
Grades 3–4	Discontinue study treatment	Neurology consult required Treat symptoms per local guidelines AND give 1–2 mg/kg/day methylprednisolone IV If improves to Grade 2 – taper with corticosteroids over at least 4 weeks Consider adding prophylactic antibiotics for opportunistic infections If worsening or atypical presentation, consider IVIG or other immunosuppressive therapies per local guidelines	

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RECOMMENDED ADVERSE EVENTS MANAGEMENT FOR PNEUMONITIS

Immune-Mediated Pneumonitis CTCAE v5 Grade	Study Treatment Management	Action and Supportive Care Guidelines	Diagnostic Considerations
Grade 1 Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Consider withholding study treatment	Monitor symptoms every 2–3 days Consider consultation with pulmonologist Consider chest imaging (chest CT or chest x-ray) followed by serial imaging at least every 3 weeks to monitor resolution or progression May resume study treatment upon improvement or resolution. If no improvement, treat as Grade 2	All attempts should be made to rule out other causes such as metastatic disease, bacterial or viral infection.
Grade 2 Symptomatic; medical intervention indicated; limiting instrumental ADL	Withhold study treatment until pneumonitis improves and remains at Grade 0–1 after corticosteroid taper to ≤10 mg/day prednisone or equivalent Permanently discontinue study treatment if patient develops a 2nd episode of ≥Grade 2 pneumonitis upon re-challenge	Monitor symptoms daily; consider hospitalization Consider consultation with pulmonologist Consider chest imaging (chest CT or chest x-ray) followed by serial imaging at least every 3 weeks to monitor resolution or progression Consider bronchoscopy with bronchoalveolar lavage (BAL) to rule out infection and malignant lung infiltration Consider pulmonary function tests and laboratory work up for infections Treatment with systemic corticosteroids (1–2 mg/kg/day prednisone or equivalent) until resolution to ≤Grade 1 and taper over at least a month If symptoms do not improve within 48–72 hours of corticosteroid treatment, treat as Grade 3 Consider empiric antibiotics if infection has not yet been fully excluded	

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Immune-Mediated Pneumonitis CTCAE v5 Grade	Study Treatment Management	Action and Supportive Care Guidelines	Diagnostic Considerations
Grade 3–4 • Grade 3: Severe symptoms; limiting selfcare ADL; oxygen indicated • Grade 4: Life-threatening respiratory compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Permanently discontinue study treatment	Inpatient care Consultation with pulmonologist and infectious disease specialties Treatment with systemic corticosteroids (2–4 mg/kg/day prednisone or equivalent) until resolution to ≤Grade 1 and taper over at least 6 weeks If symptoms do not improve within 48–72 hours of corticosteroid treatment, consider additional immunosuppressive treatment i.e., mycophenolate mofetil 1–1.5 g BID, infliximab 5 mg/kg IV If symptoms worsen during steroid reduction, initiate a re-tapering of steroids starting at a higher dose of 80 or 100 mg followed by a more prolonged taper Consider bronchoscopy with bronchoalveolar lavage (BAL) to rule out infection and malignant lung infiltration Empiric antibiotics if infection has not yet been fully excluded Consider adding prophylactic antibiotics for opportunistic infections	

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RECOMMENDED ADVERSE EVENTS MANAGEMENT FOR RENAL EVENTS

Immune-Mediated Nephritis CTCAE v5 Grade	Study Treatment Management	Action and Supportive Care Guidelines	Diagnostic Considerations
Grade 1	No change	Provide symptomatic treatment. Monitor creatinine weekly; when it returns to baseline, resume routine creatinine monitoring per protocol	All attempts should be made to rule out other causes such as obstructive uropathy, progression of disease, or injury to other chemotherapy agents.
Grade 2	Withhold study treatment until nephritis improves and remains at Grade 0–1 after corticosteroid taper to ≤10 mg/day prednisone or equivalent	Consultation with nephrologist Treatment with systemic corticosteroids (1–2 mg/kg/day prednisone or equivalent) until resolution to ≤Grade 1 and taper over at least a month Consider prophylactic antibiotics for opportunistic infections Consider renal biopsy If elevations persist >7 days or worsen, treat as severe AE	
Grade 3 or 4	Permanently discontinue study treatment	Consultation with nephrologist in consideration of ultrasound and/or biopsy as appropriate Consider inpatient care and monitor creatinine daily Treatment with systemic corticosteroids (1–2 mg/kg/day prednisone or equivalent) until resolution to ≤Grade 1 and taper over at least a month If no improvement within 7 days after initiation of systemic steroids, consider additional immunosuppressive therapy i.e., mycophenolate mofetil 0.5–1 g BID	

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RECOMMENDED ADVERSE EVENTS MANAGEMENT FOR UVEITIS

Immune-Mediated Uveitis CTCAE v5.0 Grade	Study Treatment Management	Action and Supportive Care Guidelines	Diagnostic Considerations
Grade 1	No change	Consultation with ophthalmologist within 1 week Treatment with artificial tears	All attempts should be made to rule out other causes such as metastatic disease, infection, or other ocular disease (e.g., glaucoma or cataracts).
Grade 2	Withhold study treatment	Urgent consultation with ophthalmologist Treatment with topical/periocular/intravitreal corticosteroids and/or systemic corticosteroids guided by ophthalmologist May resume study treatment if resolved to ≤Grade 1 and systemic steroid is reduced to ≤10 mg. Topical/ocular steroids are permitted during study treatment.	
Grades 3–4	Permanently discontinue study treatment	Same as above If severe or refractory to steroid treatment, consider infliximab.	

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RECOMMENDED ADVERSE EVENTS MANAGEMENT FOR MYOCARDITIS

Immune-Mediated Uveitis CTCAE v4.0 Grade	Cemiplimab Dosing Management	Action and Supportive Care Guidelines	Diagnostic Considerations
Grade 1	Consider hold of therapy. Cemiplimab may be continued with close monitoring.	Investigation findings should be followed on serial repeat testing, such as serial troponin and CK-MB levels to monitor myocardial damage, and serial BNP levels to monitor cardiac failure. Repeat echocardiogram every 2 weeks until ejection fraction returns to normal, or has remained stable for > 6 weeks. Monitor for symptoms every 2-3 days. Seek cardiology consultation and perform diagnostic procedures as recommended by the cardiologist.	All attempts should be made to rule out other causes. A cardiology consultation is recommended.
Grade 2	Permanently discontinue Cemiplimab	Seek cardiology consultation; consider hospitalization; monitor symptoms daily. Investigate with appropriate cardiac investigations as described in Grade 1 event. Treat with systemic corticosteroids at a dose of 1-2 mg/kg per day.	
Grades 3–4	Permanently discontinue Cemiplimab	Achieve hemodynamic stabilization, if applicable. Seek cardiology consultation Treat with IV corticosteroids (e.g. methylprednisone 125 mg). When symptoms improve to Grade 1 or less, high-dose oral steroid (1-2 mg/kg once per day) taper should be started and continued for no less than 4 weeks. If high dose corticosteroids does not reduce symptoms within 48-72 hours, treat with infliximab at 5 mg/kg once every 2 weeks. Discontinue infliximab upon symptom relief and initiate a prolonged steroid taper over 45-60 days.	

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APPENDIX B:
KARNOFSKY PERFORMANCE STATUS SCALE DEFINITIONS RATING (%) CRITERIA

Able to carry on normal activity and to work; no special care needed.	100	Normal no complaints; no evidence of disease.
	90	Able to carry on normal activity; minor signs or symptoms of disease.
	80	Normal activity with effort; some signs or symptoms of disease.
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed.	70	Cares for self; unable to carry on normal activity or to do active work.
	60	Requires occasional assistance, but is able to care for most of his personal needs.
	50	Requires considerable assistance and frequent medical care.
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.	40	Disabled; requires special care and assistance.
	30	Severely disabled; hospital admission is indicated although death not imminent.
	20	Very sick; hospital admission necessary; active supportive treatment necessary.
	10	Moribund; fatal processes progressing rapidly.
	0	Dead

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