A Phase I Safety and Tolerability Study of VAXINIA (CF33-hNIS), a Novel Chimeric Oncolytic Poxvirus, Administered Intratumorally or Intravenously in Adults with Metastatic or Advanced Solid Tumors.

IMUGENE
Developing Cancer Immunotherapies

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Background

- CF33 is a novel chimeric oncolytic poxvirus, encoding the human Sodium-Iodide Symporter (hNIS) transgene. The transgene is inserted in place of the viral thymidine kinase gene at the J2R locus, resulting in attenuation of viral replication in normal cells. The engineered virus selectively replicates in tumor cells and leads to tumor cell lysis, releasing tumor- and virus-associated antigens and stimulating antitumor immunity.
- This is an open-label, dose-escalation, multi-center phase I study evaluating the safety of CF33-hNIS administered intratumorally (IT) or intravenously (IV), either as a monotherapy or in combination with pembrolizumab in patients with metastatic or advanced solid tumors.

Objectives

Primary
- To evaluate safety of IV and IT CF33-hNIS in monotherapy and in combination with pembrolizumab.
- To determine Recommended Phase 2 Dose (RP2D) of CF33-hNIS in monotherapy and in combination with pembrolizumab.

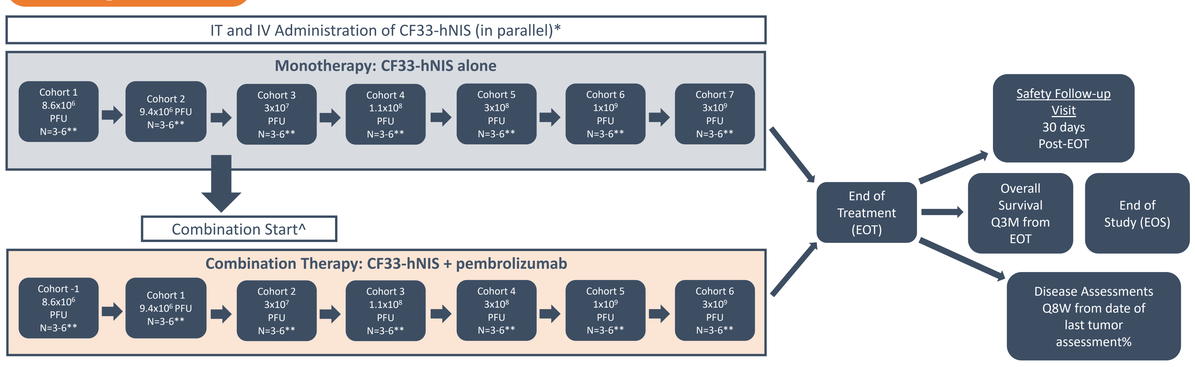
Secondary
- To evaluate the anti-tumor activity of CF33-hNIS administered as a monotherapy and in combination with pembrolizumab based on objective response rate (ORR) using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 and immune Response Evaluation Criteria in Solid Tumors (iRECIST) v1.1
- To evaluate the efficacy of IT and IV CF33-hNIS administered as a monotherapy and in combination with pembrolizumab:
  - Progression-free survival (PFS)
  - Overall survival (OS)
  - Duration of Response (DOR)
  - Disease Control Rate (DCR)
- To evaluate viral titers of CF33-hNIS
- To evaluate infection of tumors with CF33-hNIS

Exploratory
- To evaluation antiviral immune activation

Methods

Study Design
- The study will follow a traditional 3+3 dose escalation scheme independently for each route of CF33-hNIS administration (IT and IV) and for each therapy regimen, monotherapy and combination therapy (Figure 1).
- Enrollment in the monotherapy regimen will begin first. In the first monotherapy cohort only, the IT route of administration will complete the DLT-period before the IV route of administration will begin. The DLT period for the monotherapy arm is 21 days and 42 days for the combination therapy arm.
- Enrollment in IT Cohort 1 ($9.4x10^6$ PFU) for the combination regimen (CF33-hNIS + pembrolizumab) will begin when the IT monotherapy Cohort 2 ($9.4x10^6$ PFU) has completed the DLT-period. Enrollment in IV Cohort 1 ($9.4x10^6$ PFU) for the combination regimen (CF33-hNIS + pembrolizumab) will begin when the IV monotherapy Cohort 2 ($9.4x10^6$ PFU) has completed the DLT period.
- Enrollment in any subsequent combination regimen cohort will begin when the monotherapy DLT assessment has been completed in the same cohort (dose and route).
- Regardless of treatment regimen or route of administration, treatment with CF33-hNIS will be administered on C1D1 and C1D8. Subsequent treatment with CF33-hNIS will occur on Day 1 of every 3-week cycle (Q3W).
- For patients receiving combination treatment, pembrolizumab (200 mg Q3W) will be administered after CF33-hNIS beginning on C2D1 and Q3W thereafter.
- Patients may receive CF33-hNIS and pembrolizumab (if receiving combination therapy) until a treatment discontinuation criterion is met but no longer than 2 years from the first dose. CF33-hNIS can be continued beyond 2 years if there is continued clinical benefit.

Figure 1



*The IV route of administration may only begin once the IT route of administration completes the DLT-period in monotherapy Cohort 1 only. For all other cohorts, initiation of enrollment for each route of administration in the monotherapy cohorts will be assessed independently.
**A cleared monotherapy or combination cohort may be expanded to a total of 20 patients with cohort review committee (CRC) endorsement to collect additional safety and efficacy data.
%For those discontinuing with at least stable disease
^The IV route of administration may only begin once the IT route of administration completes the DLT-period in combination Cohort 1 only. For all other cohorts, initiation of enrollment for each route of administration in the combination cohorts will be assessed independently. Enrollment in a particular route of administration in a combination cohort will begin after the same route of administration has completed the DLT-period in the monotherapy cohort.
#Combination Cohort-1 will not open unless 1) the monotherapy cohort at the same dose is determined to be the Maximum Tolerated Dose (MTD) or 2) the MTD is exceeded in the combination Cohort 1 and de-escalation to the $8.6x10^5$ PFU cohort is necessary.

Dose Escalation Schema
- Up to 6 evaluable patients will be treated for each route of administration (IT and IV) and for each regimen (monotherapy and combination). Dosing of CF33-hNIS will be by cohort: $8.6x10^5$, $9.4x10^6$, $3x10^7$, $1.1x10^8$, $3x10^8$, $1x10^9$, and $3x10^9$ PFU.
- Up to 7 cohorts will be investigated in the monotherapy setting (per route of administration) and up to 6 cohorts in the combination cohort (per route of administration). The doses are as follows:

Dose Level (PFU)	Monotherapy CF33-hNIS (IT and IV)	Combination CF33-hNIS (IT and IV) + pembrolizumab (IV)
8.6×10^5	Cohort 1	Cohort -1*
9.4×10^6	Cohort 2	Cohort 1^
3×10^7	Cohort 3	Cohort 2
1.1×10^8	Cohort 4	Cohort 3
$3 \times 10^{8+}$	Cohort 5	Cohort 4
$1 \times 10^{9+}$	Cohort 6	Cohort 5
$3 \times 10^{9+}$	Cohort 7	Cohort 6

The DLT-periods for the monotherapy and combination regimens are as follows:
- **Monotherapy** - One full cycle (2 doses of CF33-hNIS) and the C2D1 safety assessments
- **Combination** - Two full cycles (3 doses of CF33-hNIS and 1 dose of pembrolizumab) and the C3D1 safety assessments

*This cohort would be included only if 1) the monotherapy cohort at the same dose is determined to be the Maximum Tolerated Dose (MTD) or 2) the MTD is exceeded in the combination Cohort 1 and de-escalation to the 8.6×10^5 cohort is necessary. ^Will begin after the DLT period has been cleared in monotherapy Cohort 2. +Nominal dose shown; actual dose will be updated based on release testing.

Methods (Continued)

Key Eligibility Criteria

Patient Inclusion Criteria

1. Written informed consent from patient or legally authorized representative.
2. Age ≥ 18 years old on the date of consent.
3. Life expectancy of at least 3 months.
4. Any histologically or cytologically confirmed metastatic or advanced solid tumor with documented radiological progression per RECIST v1.1 following at least two prior lines of systemic SOC treatment in the metastatic/advanced setting (which may have included prior ICI treatment).
5. Eastern Cooperative Oncology Group (ECOG) performance status 0 – 2.
6. At least one measurable lesion as defined by RECIST v1.1 criteria.
7. For patients receiving IT administration, lesion(s) must be superficial or subcutaneous and easily accessible, and target lesions must be a minimum of 1 cm (longest dimension).
8. Willing to provide archival or fresh tumor tissue during the Screening Period and fresh tissue on C2D1 and EOT.
9. Adequate renal, hepatic, and hematologic function.

Patient Exclusion Criteria

1. Prior treatment with an oncolytic virus.
2. Continuous systemic treatment with corticosteroids.
3. Active autoimmune disease.
4. Inadequate pulmonary function.
5. Prior allogeneic tissue/organ transplant or other medical conditions requiring ongoing treatment with immunosuppressive drugs or any condition resulting in a systemic immunosuppressed state.
6. Uncontrolled brain or other central nervous system (CNS) metastases.
7. History of documented congestive heart failure.
8. Pregnant or lactating females.
9. Major surgery within 4 weeks prior to study treatment and/or minor surgery (excluding biopsy) within 1 week prior to study treatment.
10. Receipt of a vaccination within 4 weeks of study treatment.

Planed analysis

Efficacy
- Tumour response will be assessed by the investigator following RECIST v1.1 and iRECIST v1.0 criteria with Contrast-enhanced CT or MRI scans performed every 6 weeks.

Safety
- Safety evaluations will be based on adverse events defined with NCI CTCAE Version 5.0 criteria as well as changes in the patient's physical examination findings, vital signs, clinical laboratory results, and electrocardiogram (ECG) findings.

Correlatives
- Viral replication will be assessed with Single-Photon Emission Computerized Tomography (SPECT) imaging using Technetium-99. SPECT imaging will be performed 3 to 7 days after C1D1 and 3 to 7 days after C2D1.
- Pre- and on-treatment tumour biopsies will be examined for changes in viral replication, hNIS transgene expression, PD-L1 expression and immune cell infiltrates.
- Peripheral blood draws will be used to examine changes in cytokine, PBMCs populations, and T cell repertoire.
- Viral shedding will also be examined by both PCR and plaque assays.

Status / Enrollment

Dose level (PFU)	CF33-hNIS Monotherapy		CF33-hNIS + Pembrolizumab	
	IT	IV	IT	IV
8.6×10^5	●	●	N/A	N/A
9.4×10^6	●	●	●	●
3×10^7	●	●	●	●
1.1×10^8	●	●	●	●
3×10^8	●	●	●	●
1×10^9	●	●	●	●
3×10^9	●	●	●	●

● Complete ● Enrolling ● Pending Enrollment

Study Information

Status: Recruiting

ClinicalTrials.gov ID: NCT05346484

Number of sites
- Approximately 10 participating sites in the United States and Australia.

Number of patients
- During the dose-escalation phase, up to 6 evaluable patients will be treated in each cohort per route of administration (IV and IT) and treatment regimen (monotherapy and combination).
- Once a monotherapy or combination cohort has been cleared to obtain additional safety and efficacy information, the number of patients in that cohort may be expanded to a total of 20 patients with CRC agreement.
- In total, up to 150 patients will be enrolled.

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