REQUEST FOR PROJECT TEAM MEMBER APPLICATION FOR CONDUCTING CLINICAL TRIALS USING TALIMOGENE LAHERPAREPVEC

The Cancer Therapy Evaluation Program (CTEP) is accepting Project Team Member Applications (PTMAs) for a project using talimogene laherparepvec (T-VEC, formerly OncoVEX^{GM-CSF}), which is being developed by CTEP in collaboration with Amgen. T-VEC is a herpes simplex virus type 1 (HSV-1) genetically engineered to selectively replicate in tumor cells and produce human granulocyte-macrophage colony-stimulating factor (GM-CSF) (Liu *et al.*, 2003). T-VEC is the first oncolytic immunotherapy to demonstrate clinical benefit in patients with melanoma in a phase 3 clinical study (Lichty *et al.*, 2014; Andtbacka *et al.*, 2015a).

Solicitation of the Project Team Member Application:

At the present time, the initial CTEP development plan will include two to three clinical trials, focusing on the objectives of understanding the mechanisms of action and expanding the therapeutic potential of T-VEC. The clinical settings being considered include locally advanced/metastatic breast cancer, bladder cancer, colorectal cancer, sarcomas, non-melanoma skin cancers, or other indications where intralesional injections are feasible. Investigational regimens may be based on monotherapy or combination with immune modulators such as PD-1 or CTLA-4 antagonists, other immunotherapies, or tumor-targeted therapies including standard of care.

CTEP invites the investigators to apply in the following categories:

1. **Clinician-scientists** with expertise in clinical studies of oncolytic virus, cancer immunotherapy, or the select clinical setting. (fill out **Part A** of the attached Application);
2. **Translational scientists** with expertise in biomarker studies, especially assessment of immunogenic cell death and cancer immune monitoring. (fill out **Part B** of the attached Application);
3. **Basic scientists** with expertise in oncolytic immunotherapy or cancer immunology. (fill out **Part C** of the attached Application).

(Please refer to page 4 for more details on the CTEP development plan for T-VEC)

Prospective team members may apply for multiple roles using a single application form by completing all the appropriate Parts. The Project Team will be recruited nationally and will prioritize the research questions regarding T-VEC in single-agent or combination trials, including prioritization of biomarker studies. It is anticipated that the clinicians on the T-VEC Project Team will be tasked with writing the Letters of Intent describing the study design, based upon the team's recommendations, for CTEP approval, and that these clinicians will ultimately lead the clinical studies. It is also anticipated that other extramural members of the drug project team will stay involved in the subsequent design and execution of the proposed trials.

It is anticipated that the T-VEC Project Team will begin meeting in mid/late September and continue through December in order to complete its work in about 2 months; all participants selected for the T-VEC Project Team are required to attend all teleconferences.

Background/Rationale

T-VEC is an oncolytic virus derived from a natural HSV-1 isolate with the genetic modifications including: 1) Deletion of the viral neurovirulence gene ICP34.5 to attenuate viral pathogenicity and enhance tumor-selective replication, 2) Deletion of viral gene ICP47 to reduce virally-mediated suppression of antigen presentation , and 3) Insertion of human GM-CSF to recruit and activate antigen presenting cells (Liu *et al.*, 2003). The potential mechanism of action of T-VEC involves both local tumor oncolysis and systemic anti-tumor immune activation. Intratumoral injection of T-VEC has demonstrated therapeutic benefit in patients with melanoma in a phase 3 trial, especially in the subgroup without visceral disease at baseline (Stage IIIB to IV-M1a) (Andtbacka *et al.*, 2015a).

Nonclinical Studies of T-VEC

Preclinical studies in immune-competent mice demonstrated that T-VEC conferred its antitumor activity through both local oncolysis and immune-mediated systemic effects (Liu *et al.*, 2003). T-VEC has been tested for efficacy in a variety of *in vitro* (cell line) and *in vivo* murine models and has been shown to eradicate tumors or substantially inhibit their growth at doses comparable to those used in clinical studies. The variant mT-VEC (expresses murine GM-CSF) was tested in Balb/c mice bearing syngeneic A20 lymphoma on bilateral flanks. Intratumoral injection of mT-VEC not only resulted in dose-related activity in the injected tumor, but also induced regression in the contralateral, non-injected tumors. Furthermore, mice previously treated with mT-VEC and cleared of the tumor, were protected from re-challenge with the same tumor line. Of note, viral replications outside the injected lesions have not been observed, suggesting induction of systemic, tumor-specific host immunity as a potential mechanism of action.

T-VEC has also shown augmented efficacy when combined with an anti-PD-1 antibody in a C57Bl/6 mouse MC38 colon carcinoma model (Piasecki *et al.*, 2015). Complete regression (CR) rates in the injected lesions were 8/10 with the combination vs. 2/10 with single agent. Tumor shrinkage in distant (noninjected) lesions was also greater, with CR observed in 2/10 *vs.* 0/10 mice. Flow cytometry studies of the peripheral blood showed that mT-VEC increased the amount of PD-L1$^+$ CD4 and CD8 T cells, and that the combination increased the percent of activated CD8$^+$ T cells.

Clinical Studies of T-VEC

As of June 19, 2015, there are 12 single-agent and combination T-VEC studies with Amgen or BioVex Limited as sponsor or collaborator (ClinicalTrials.gov). These trials are summarized in the two tables in this section.

T-VEC Single-Agent Trials sponsored by Amgen or BioVex (exclusive of Investigator Sponsored Studies)

Study NCT	Title	Phase	Disease/Indication	Planned accrual	References
N/A	A phase I/II clinical trial with OncoVEXGM-CSF in patients with solid tumours	1/2	Solid Tumors	30 Completed	Hu *et al.*, 2006
N/A	An exploratory study of the safety and biological activity of OncoVex (GM-CSF) in combination with radiotherapy and cisplatin in the treatment of locally advanced epithelial cancer of the head and neck	1/2	Head and Neck Cancer	17 Completed	Harrington *et al.*,2010
NCT00402025	OncoVEX GM-CSF in Patients With Unresectable Pancreatic Cancer	1	Unresectable pancreatic cancer	17 Completed	Chang *et al.*, 2012
NCT02014441	Single-arm Trial to Evaluate the Biodistribution and Shedding of Talimogene Laherparepvec	2	Melanoma	60 Ongoing	
NCT02366195	Single-arm Trial to Evaluate the Role of the Immune Response to Talimogene Laherparepvec in Unresected Melanoma	2	Unresected Stage IIIb to IVM1c melanoma	110 Ongoing	
NCT00289016	A Study of OncoVEXGM-CSF in Stage IIIc and Stage IV Malignant Melanoma	2	Melanoma	50 Completed	Senzer *et al.*, 2008; Kaufman *et al.*, 2010
NCT00769704[a]	Efficacy and Safety Study of OncoVEX GM-CSF Compared to GM-CSF in Melanoma	3	Melanoma	436 Completed	Andtbacka *et al.*, 2014; Ross *et al.*, 2014; Andtbacka *et al.*, 2015a; Kaufman *et al.*, 2015
NCT02297529	Expanded Access Study of Talimogene Laherparepvec for Treatment of Subjects With Unresected Stage IIIB-IVM1c Melanoma	3b	Unresected Stage IIIB to IVM1c melanoma (Europe)	N/A Ongoing	
NCT02173171[b]	Registry Study for Talimogene Laherparepvec	N/A	Melanoma	450 Ongoing	
NCT02211131	Efficacy and Safety of Talimogene Laherparepvec Neoadjuvant Treatment Plus Surgery Versus Surgery Alone for Melanoma	2	Resectable Stage IIIB, IIIC, or IVM1a melanoma	150 Ongoing	Andtbacka *et al.*, 2015b

N/A = not applicable; [a] The OPTiM study (GM-CSF as a comparator arm); [b] Observational registry enrolling by invitation

T-VEC Combination Trials

Study NCT	Title	Phase	Disease/Indication	Planned accrual	References
NCT01740297	Ipilimumab With or Without Talimogene Laherparepvec in Unresected Melanoma	1b/2	Melanoma	219 ongoing	Puzanov *et al.*, 2015
NCT02263508	Pembrolizumab (MK-3475) With or Without Talimogene Laherparepvec in Unresected Melanoma	1b/2	Melanoma	110 ongoing	Ribas *et al.*, 2015

Clinical experience with T-VEC: Clinical data are derived primarily from two monotherapy melanoma studies: the phase 3 OPTiM trial (NCT00769704) (Kaufman *et al.*, 2015; Andtbacka *et al.*, 2015a), and a phase 2 single arm melanoma study (NCT00289016) (Senzer er al, 2008) and one combination melanoma study and the phase 1b of the combination trial with ipilimumab (NCT01740297) (Puzanov *et al.*, 2015).

Efficacy:
The OPTiM study (the OncoVEX^{GM-CSF} Pivotal Trial in Melanoma) was a phase 3 study for patients with unresectable Stage IIIB to IV melanoma, with 2:1 randomization to intralesional T-VEC and subcutaneous (SQ) GM-CSF (Andtbacka *et al.*, 2015a). Between May 2009 and July 2011, 436 patients enrolled. The trial was positive for the primary endpoint of durable response rate (DRR) (defined as PR or CR lasting continuously for at least 6 months and beginning during the first 12 months of therapy). DRR with T-VEC was 16.3% (95% CI, 12.1- 20.5%) compared to 2.1% (95% CI, 0-4.5%) with GM-CSF (P<.001). The overall response rate (ORR) was also higher, and CR rate was 10.8% vs. <1%. Responses were observed in both injected and uninjected lesions, with 15% of evaluable, uninjected visceral lesions achieving ≥ 50% decrease in size (Andtbacka *et al.*, 2014; Kaufman *et al.*, 2014). Overall survival (OS) was also improved from 5.7% with GM-CSF to 26.4% with talimogene laherparepvec (P<0.0001, descriptive). Median OS was 23.3 months (95% CI, 19.5-29.6 months) in the T-VEC arm and 18.9 months (95% CI, 16.0-23.7 months) in the GM-CSF arm (HR, 0.79; 95% CI, 0.62-1.00; P=.051). Subgroup analysis revealed that the efficacy of T-VEC is most pronounced in patients with Stage IIIB, IIIC, or IVM1a melanoma and in patients with treatment-naive disease, while effect in patients with visceral metastasis appeared modest (Andtbacka *et al.*, 2015a), with no difference in OS improvement in IVM1b and IVM1c subgroups.

Efficacy data from the phase 1b portion of the ongoing phase 1b/2study of the combination of intralesional T-VEC with intravenous ipilimumab was reported at the American Society of Clinical Oncology 2015 Annual Meeting (Puzanov *et al.*, 2015). Full dose of T-VEC and ipilimumab 3 mg/kg every 3 weeks starting week 6 were tolerable. Per immune-related response criteria (data cutoff of December 22, 2014), the ORR in 18 evaluable patients was 56% (33% CRs), and the DRR was 44%. Median progression-free survival (PFS) was 10.6 months (2.6 to 19.3+ months). Median OS was not reached; 12-month and 18-months survival rates were 72.2% and 67%, respectively. On a lesion level, 8 and 5 of 16 uninjected index lesions regressed ≥ 50% and 100%, respectively.

Safety
In the OPTiM study, the most common adverse events (AEs) among 292 patients receiving T-VEC were fatigue (50%), chills (49%), and pyrexia (43%) (Andtbacka *et al.*, 2015a). Cellulitis at injection sites occurred in 5.6% patients (2.1% grade 3/4). AE related treatment discontinuation was reported in 4% and 2% patients on the T-VEC and GM-CSF arms, respectively. No fatal treatment-related AEs occurred.

As of December 22, 2014, 18 patients treated with T-VEC + ipilimumab in the phase 1b/2 study were evaluable for safety (Puzanov *et al.*, 2015). Grade 3/4 treatment-emergent AEs occurred in 32% of patients, and grade 3/4 immune-related AEs occurred in two patients (grade 3 hypophysitis and adrenal insufficiency; and grade 4 amylase + lipase elevations) (Puzanov *et al.*, 2015). There were no treatment-related deaths.

Immunological Biomarkers

Limited biomarker studies have been reported that examined the immune modulation effect of T-VEC in patients. In a phase 2 study of intralesional T-VEC in patients with Stage IIIC-IV melanoma, T-cell phenotypic characterization was performed tumor infiltrating lymphocytes (TILs) as well as PBLs from in patients treated with T-VEC and compared to control patients not treated with T-VEC (Kaufman *et al.*, 2010). In a patient achieving CR on T-VEC, TILs from post-treatment samples showed a high level of MART-specific T effector cells on ELISpot analysis and the CD8+ cells also demonstrated high levels of memory cell markers (CD45RO, HLA-DR, CD25, CD95 and PD-1). The TIL cells in T-VEC treated patients also showed lower frequencies of $CD4^+$ Tregs ($CD4^+FoxP3^+$), Ts cells ($CD8^+FoxP3^+$) and MDSC ($CD14^+CD11b^+HLA\text{-}DR^{lo/-}$), as compared to TILs from untreated control patients. These biomarker studies were limited by the lack pre-treatment biopsies for intra-patient comparison, but suggest that further examination of the immune modulation effects is warranted. In the T-VEC+ipilimumab study, T-VEC by itself increased activated CD8 ($HLA\text{-}DR^+CD3^+CD4^-$) T cells from baseline levels, and levels of activated CD8 T cells increased even further with the addition of ipilimumab (Puzanov *et al*., 2014).

Pharmaceutical Information

T-VEC is intended for direct injection into suitable non-neurological solid tumors. Dose schedules may vary for different tumors and indications. The initial dose should usually be at a lower concentration than subsequent doses to allow for seroconversion of HSV-1 seronegative status. In the OPTiM trial, the first dose of T-VEC was injected in volumes up to 4 mL at $1x10^6$ pfu/mL; subsequent doses were $1x10^8$ pfu/mL 3 weeks after the first dose and then once every 2 weeks for up to 24 doses.

CTEP's Plans for T-VEC Development

CTEP is soliciting applications for the T-VEC Project Team, to assist CTEP in developing the clinical and translational studies for the agent.

The scientific goals of CTEP's clinical development plan include: 1) Examine the mechanisms underlying the response or resistance to T-VEC, 2) Explore the potential clinical utility of T-VEC in locoregional tumor control, and 3) Explore strategies to enhance the therapeutic potential of T-VEC for both local and systemic tumor control, through combinations and biomarker studies.

CTEP's initial development may include 2-3 clinical trials. Listed below are the clinical settings being considered:

- Sarcoma, for single agent or combination regimens
- Breast cancer inoperable locoregional recurrence, for single agent or combination with immunotherapy
- Rectal cancer, for combination with chemoradiation
- Bladder cancer, for single agent or combination with immunotherapy
- Head and neck cancer, for combination
- Other clinical settings suitable for intratumoral injections may also be considered, if appropriate for the overall scientific objectives.

*Selection of the tumor types and clinical settings will be determined based on specific expertise of the applicants and the likelihood of achieving the clinical and scientific goals.

*The study regimen may be based on monotherapy or combination with other immunotherapy or other tumor targeted agents/regimens. CTEP has existing CRADAs for a number of novel agents, including checkpoint inhibitors and other immune-modulators as well as molecularly targeted agents.

*Biomarker studies in both injected and distant tumors will be incorporated in the clinical trials. Markers of interesting may include but are not limited to:

- Effects on tumor cells – Viral replication, Immunogenic cell death
- Effects on T cell repertoire, and functional/phenotypic markers
- Effects on inflammatory markers and cellular components in tumor

*Also of interest are translational studies in preclinical models. Murine version of T-VEC may be available for preclinical studies.

T-VEC Project Team Selection, Composition, and Tasks

The project team will be composed of intramural and extramural members. The extramural members will include:

1. **Clinician-scientists** with expertise in clinical studies of oncolytic virus, cancer immunotherapy, or the select clinical setting. (fill out **Part A** of the attached Application);
2. **Translational scientists** with expertise in biomarker studies, especially assessment of immunogenic cell death and cancer immune monitoring. (fill out **Part B** of the attached Application);
3. **Basic scientists** with expertise in oncolytic immunotherapy or cancer immunology. (fill out **Part C** of the attached Application).

Since the clinician scientists selected for the project team will be expected to lead the clinical trials that come out of this process, the evaluation criteria for the clinician scientists will include not only clinical trial expertise but also their documented record of accrual to the specific trials of interest.

The T-VEC Project Team will meet regularly by WebEx to review and discuss available evidence and determine promising strategies, identify specific biomarkers to evaluate these strategies, and evaluate clinical trial designs to test these strategies.

Questions regarding this request for applications may be addressed to Helen Chen, M.D., Senior Clinical Investigator, Investigational Drug Branch, CTEP, DCTD, NCI (phone: 240-276-6565; FAX: 240-276-7894; e-mail: helen.chen@nih.gov).

PTMAs should contain a clear indication of the applicant's desired role on the T-VEC Project Team (clinician scientist, translational scientist, or basic scientist). The PTMA should also be accompanied by an NIH Biosketch containing a personal statement indicating how the investigators would contribute to the project. The PTMAs should be sent to the Protocol and Information Office (PIO) at the address below by **5:00 PM Eastern Time (ET), September 29, 2015**. The most recent version of the PTMA form, available on the CTEP Website (http://ctep.cancer.gov), must be used. PTMAs should be submitted electronically to:

PIO, CTEP/DCTD/NCI
E-mail: pio@ctep.nci.nih.gov

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