A PHASE 1B/3 MULTICENTER, RANDOMIZED, OPEN-LABEL TRIAL OF TALIMOGENE LAHERPAREPVEC IN COMBINATION WITH PEMBROLIZUMAB FOR THE TREATMENT OF SUBJECTS WITH RECURRENT OR METASTATIC SQUAMOUS CELL CARCINOMA OF THE HEAD AND NECK

"Etude T-VEC ORL"
Sponsor: Amgen

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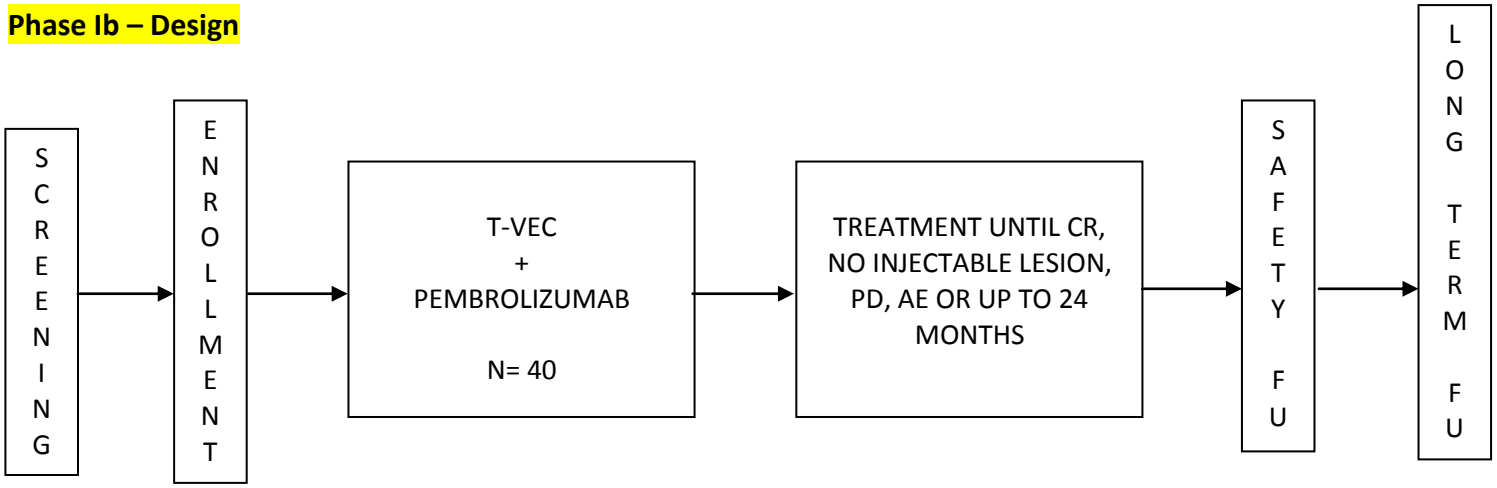
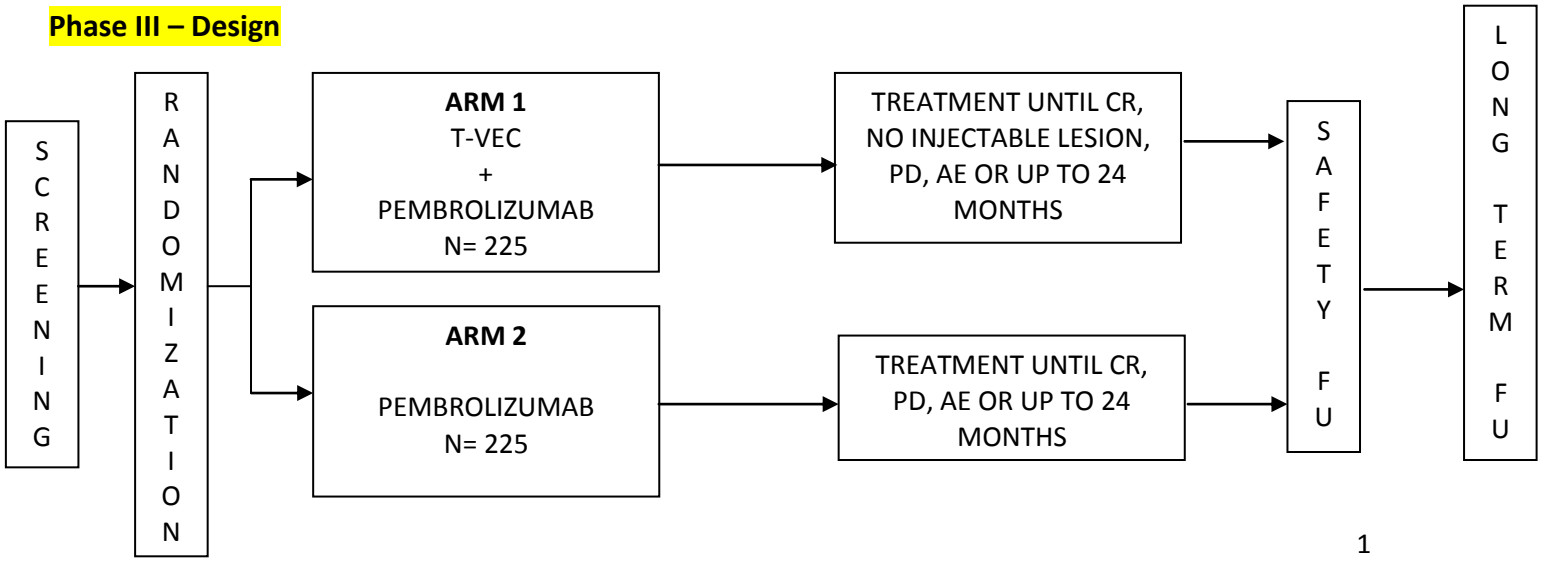
DESIGN DE L'ETUDE

Environ 40 patients seront inclus dans la phase Ib de l'étude, puis 450 seront ensuite randomisés (1:1) dans la phase III, selon les 2 schémas suivants :

Phase Ib – Design



Phase III – Design



OBJECTIF DE L'ÉTUDE

L'objectif de cette étude est d'examiner la tolérance et l'efficacité du produit médical d'Amgen appelé talimogène laherparepvec chez des personnes atteintes de cancer de la tête et du cou à cellules squameuses, récurrent ou métastatique, en association avec un le pembrolizumab.

CRITERES D'INCLUSION/EXCLUSION

#	INCLUSION CRITERIA	
1	Subject has provided informed consent prior to initiation of any study-specific activities/procedures	
2	Male or female age ≥ 18 years at the time of informed consent	
3	Histologically confirmed diagnosis of metastatic or recurrent SCCHN. Disease must be unsuitable for curative surgical resection and must not be amenable to curative radiotherapy	
4	Disease must have progressed after treatment with a platinum-containing regimen and should be defined as either one of the following: - recurrence/progression within 6 months of prior multimodal therapy using platinum (eg, locally advanced setting) - disease progression or recurrence after prior platinum therapy in the recurrent or metastatic setting	
5	Subject must be candidate for intralesional therapy administration defined as one or more of the following: - at least 1 injectable cutaneous, subcutaneous, or nodal SCCHN tumor ≥ 10 mm in longest diameter - multiple injectable SCCHN tumors that in aggregate have a longest diameter of ≥ 10 mm	
6	Subject must have radiographically measurable disease per RECIST 1.1 (Eisenhauer et al, 2009). Target lesions must not be chosen from a previously irradiated field unless there has been radiographically and/or pathologically documented tumor progression in that lesion prior to enrollment	
7	ECOG performance status of 0 or 1	
9	Adequate organ function determined within 14 days prior to enrollment, defined as follows:	ANC ≥ 1.5 x 109/L
		platelet count ≥ 100 x 109/L
		hemoglobin ≥ 9 g/dL (without need for hematopoietic growth factor or transfusion support)
		serum creatinine ≤ 1.5 x upper limit of normal (ULN), OR creatinine clearance ≥ 60 mL/min for subject with creatinine levels > 1.5 x ULN. (Note: Creatinine clearance need not be determined if the baseline serum creatinine is within normal limits. Creatinine clearance should be determined per institutional standard)
		serum bilirubin ≤ 1.5 x ULN OR direct bilirubin ≤ ULN for a subject with total bilirubin level > 1.5 x ULN
		AST ≤ 2.5 x ULN OR ≤ 5 x ULN for subject with liver metastases
		ALT ≤ 2.5 x ULN OR ≤ 5 x ULN for subject with liver metastases
		international normalization ratio (INR) or prothrombin time (PT) ≤ 1.5 x ULN, unless the subject is receiving anticoagulant therapy, in which case PT and partial thromboplastin time (PTT)/activated PTT (aPTT) must be within therapeutic range of intended use of anticoagulants
		PTT or aPTT ≤ 1.5 x ULN unless the subject is receiving anticoagulant therapy as long as PT and PTT/aPTT is within therapeutic range of intended use of anticoagulants
10	Female subject of childbearing potential should have a negative urine or serum pregnancy test within 72 hours prior to enrollment. If urine pregnancy test is positive or cannot be confirmed as negative, a serum pregnancy test will be required	

11	**Phase 3:** Subject has a formalin fixed paraffin embedded tumor sample (archival sample obtained within 3 months prior to day 1 and no systemic therapy given since the biopsy or newly obtained biopsy) from the primary or metastatic lesion that is adequate for PD-L1 assessment prior to randomization (sites will be blinded to PD-L1 analysis). Subject must submit the tumor sample during screening for PD-L1 expression testing at a central laboratory. Subjects with an inadequate or indeterminate archival sample may obtain a new biopsy and subjects with an inadequate or indeterminate newly obtained biopsy may undergo re-biopsy at the discretion of the investigator. If applicable, biopsies should be obtained outside of the field of maximum radiation dose delivered, whenever possible
12	**Phase 3:** Have results from local testing of HPV of tumor specimen for oropharyngeal cancer defined as p16 IHC testing using the CINtec® assay and a 70% cutoff point. If the assay is unavailable locally, sites should be willing to submit archived or recently biopsied formalin-fixed paraffin-embedded tumor tissue (block or unstained tumor slides) from either the primary or metastatic lesion for central laboratory testing. Note: HPV stratification in this trial will be performed using local or central testing of HPV status in subjects with oropharynx cancer. Oral cavity, hypopharynx, and larynx cancer are not required to undergo HPV testing by p16 IHC as by convention, they are assumed to be HPV negative
13	**Phase 1b:** Subject has a formalin fixed paraffin embedded tumor sample (archival tumor sample obtained within 3 months prior to day 1 and no systemic therapy given since biopsy) OR be willing to undergo newly obtained biopsy prior to the first dose of investigational product (day 1). Subjects who are unable to provide acceptable tissue may not be enrolled unless there has been prior agreement with the sponsor

#	**EXCLUSION CRITERIA**
1	Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least four weeks prior to the first dose of trial treatment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids for at least 7 days prior to trial treatment. This exception does not include carcinomatous meningitis which is excluded regardless of clinical stability
2	Primary nasopharyngeal carcinoma
3	Subject at risk of airway compromise in the event of postinjection tumor swelling/inflammation based on investigator judgment
4	Previous treatment with 3 or more systemic regimens given for recurrent and/or metastatic disease (Phase 3 study)
5	History of other malignancy within the past 3 years with the following exceptions: - malignancy treated with curative intent and with no known active disease present and has not received chemotherapy for ≤ 3 years before enrollment and felt to be at low risk for recurrence by the treating physician - adequately treated non-melanoma skin cancer without evidence of disease at the time of enrollment - adequately treated cervical carcinoma in situ without evidence of disease at the time of enrollment - adequately treated breast ductal carcinoma in situ without evidence of disease at the time of enrollment - prostatic intraepithelial neoplasia without evidence of prostate cancer at the time of enrollment - adequately treated superficial or in situ carcinoma of the bladder without evidence of disease at the time of enrollment
6	Evidence of active, non-infectious pneumonitis
7	History of interstitial lung disease (ILD)
8	Prior therapy with talimogene laherparepvec, pembrolizumab, other anti-PD-1, any other antibody or drug specifically targeting T-cell co-stimulation or immune check point pathway

9	Prior enrollment and initiation of treatment on any pembrolizumab (MK-3475) trial (even if receiving comparator arm therapy)
10	History or evidence of active autoimmune disease that has required systemic treatment in past 2 years (ie, with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc) is not considered a form of systemic treatment
11	Evidence of clinically significant immunosuppression such as the following: - as organ transplant, other signs or symptoms of clinical immune system suppression - any severe congenital or acquired cellular and/or humoral immune deficiency - diagnosis of immunodeficiency - concurrent opportunistic infection - receiving systemic immunosuppressive therapy (> 2 weeks) or within 7 days prior to the first dose of study treatment, including oral steroid doses > 10 mg/day of prednisone or equivalent except for management of adverse events and CNS metastases during the course of the study. Subjects that require intermittent use of bronchodilators or local steroid injection will not be excluded from the study
12	Active herpetic skin lesions or prior complications of herpetic infection (eg, herpetic keratitis or encephalitis)
13	Requires intermittent or chronic treatment with an antiherpetic drug (eg, acyclovir), other than intermittent topical use
14	Prior chemotherapy, radiotherapy, biological cancer therapy or major surgery within 28 days prior to enrollment or has not recovered to CTCAE grade 1 or better from adverse event due to cancer therapy administered more than 28 days prior to enrollment Note: Subjects with ≤ grade 2 neuropathy and alopecia are an exception to this criterion and may qualify for the study
15	Currently participating or have participated in a study (treatment period only) of an investigational agent or used an investigational device within 28 days of enrollment
16	Expected to require other cancer therapy while on study with the exception of local palliative radiation treatment to the site of bone and other metastasis
17	Other investigational procedures while participating in this study are excluded
18	Known human immunodeficiency virus (HIV) disease
19	Has acute or chronic active hepatitis B virus or hepatitis C virus infection or received treatment with nucleotide analogs such as those used in the treatment of hepatitis B virus (eg, lamivudine, adefovir, tenofovir, telbivudine, entecavir), ribavirin, or interferon alpha within 12 weeks of initiation of study treatment
20	Received live vaccine within 28 days prior to enrollment
21	Female subject is pregnant or breast-feeding, or planning to become pregnant during study treatment and through 3 months after the last dose of talimogene laherparepvec or 4 months after the last dose of pembrolizumab, whichever is later
22	Female subject of childbearing potential who is unwilling to use acceptable method(s) of effective contraception during study treatment and through 3 months after the last dose of talimogene laherparepvec or 4 months after the last dose of pembrolizumab, whichever is later. (Note: Women not of childbearing potential are defined as: Any female who is postmenopausal [age > 55 years with cessation of menses for 12 or more months or less than 55 years but not spontaneous menses for at least 2 years or less than 55 years and spontaneous menses within the past 1 year, but currently amenorrheic (eg, spontaneous or secondary to hysterectomy), AND with postmenopausal gonadotropin levels (luteinizing hormone and follicle-stimulating hormone levels 40 IU/L) or postmenopausal estradiol levels (< 5 ng/dL) or according to the definition of "postmenopausal range" for the laboratory involved] or who have had a hysterectomy, bilateral salpingectomy, or bilateral oophorectomy). Note: Acceptable methods of effective contraception are defined in the informed consent form. Where required by local laws and regulations, additional country-specific contraception requirements may be outlined in a country-specific protocol supplement at the end of the Appendix Section of protocol OR Male subject who is unwilling to use acceptable method of effective contraception during pembrolizumab treatment and through 4 months after the last dose of pembrolizumab. Note: Acceptable methods of effective contraception are defined in the informed consent form. Additional country-

	specific contraception requirements may be defined in a country-specific protocol supplement at the end of the Appendix Section of protocol as required by local laws and regulations
23	Sexually active subjects and their partners unwilling to use male or female latex condom to avoid potential viral transmission during sexual contact while on treatment and within 30 days after treatment with talimogene lapherparepvec
24	Subject has known sensitivity to any of the products or components to be administered during dosing
25	Subject likely to not be available to complete all protocol-required study visits or procedures, and/or to comply with all required study procedures to the best of the subject and investigator's knowledge
26	History or evidence of psychiatric, substance abuse, or any other clinically significant disorder, condition or disease (with the exception of those outlined above) that, in the opinion of the investigator or sponsor physician, if consulted, would pose a risk to subject safety or interfere with the study evaluation, procedures or completion
27	Is or has an immediate family member (eg, spouse, parent/legal guardian, sibling, or child) who is investigational site or sponsor staff directly involved in the this trial, unless prospective institutional review board (IRB)/independent ethics committee (IEC) approval (by chair or designee) is given allowing exception to this criterion for a specific subject
28	Subject who is unwilling to minimize exposure with his/her blood or other body fluids to individuals who are at higher risks for HSV-1 induced complications (immunosuppressed individuals, HIV-positive individuals, pregnant women, or children under the age of 1 year) during talimogene laherparepvec treatment and through 30 days after the last dose of talimogene laherparepvec