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Phase II Trial of Utomilumab and ISA101b Vaccination in Patients with HPV-16-Positive Incurable Oropharynx Cancer

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1.0. Introduction

Infection with Human Papillomavirus (HPV) causes substantial cancer burden including nearly all cervical, majority of oropharyngeal, and a significant percentage of anal, penile, vulvar, and vaginal cancers. The HPV vaccines currently available are only preventive, must be given before sexual debut/HPV exposure, and have little market penetration. Additionally, the latent period between exposure and diagnosis of cancer is decades-long; therefore, even if vaccine use is increased in the near term, high risk HPV-related cancers will continue to increase and persist for decades to come.

Recent work has identified signaling pathways between tumor and immune cells which act to suppress immune rejection. Inhibition of signaling with antibodies to key proteins, cytotoxic T lymphocyte antigen-4 (CTLA-4) and programmed death receptor-1 (PD-1), has resulted in very promising tumor shrinkage and prolonged survival in patients with a variety of cancers, including lung cancer, a tumor long-considered non-immunogenic. Specifically in platin-refractory squamous cancer of the head and neck (SCCHN), including HPV+ oropharyngeal squamous carcinomas (OPSCC), inhibition of PD-1 with nivolumab is associated with superior progression-free and overall survival (PFS, OS) rates compared to standard non- platin cytotoxins and cetuximab (1). However, only 16% (95% CI:11-22) of patients with HPV+ OPSCC respond, with a median OS of 9 months. Very similar response and survival rates have been reported with pembrolizumab in similar patients (2). These data emphasize the importance of addressing mechanisms of resistance to immune response. Preliminary results from our rial of nivolumab and an HPV-16 synthetic long peptide vaccine (ISA101) (NCT02426892) support that concept, based on a response rate that is more than doubled relative to nivolumab alone in patients with HPV+ oropharynx cancer (3). This observation underlines the potential to target non-self, HPV- specific antigens with vaccination and potentially synergize with immune checkpoint therapies

In the trial described herein, a T cell co-stimulatory agonist monoclonal antibody targeting CD137 (4-1BB), utomilumab will be combined with ISA101b, further exploring the hypothesis that immune therapy for HPV-related cancers should directly engage the immune response to viral antigens to maximize efficacy.

1.1 Rationale

1.1.1 Utomilumab (PF-05082566): Utomilumab is an investigational intravenous (IV) fully human IgG2 monoclonal antibody that binds to the extracellular domain of human 4-1BB with high affinity and specificity and is capable of 4-1BB agonism. 4-1BB (CD137), first identified as an inducible costimulatory receptor expressed on activated T cells, is a membrane spanning glycoprotein of the Tumor Necrosis Factor (TNF) receptor superfamily. Current understanding of 4-1BB indicates that expression is generally activation dependent and encompasses a broad subset of immune cells. 4-1BB is undetectable on the surface of naive T cells but expression increases upon activation. Upon 4-1BB activation, pro-survival members of the TNFR-associated factor (TRAF 1 and 2) are recruited to the 4-1BB cytoplasmic tail resulting in downstream activation of NFkB and the Mitogen Activated Protein (MAP) Kinase cascade including Erk, Jnk, and p38 MAP kinases. NFkB activation leads to upregulation of Bfl-1 and Bcl-XL, pro-survival members of the Bcl-2 family. The pro-apoptotic protein Bim is downregulated in a TRAF1 and Erk dependent manner (4).

Numerous studies of murine and human T cells indicate that 4-1BB promotes enhanced cellular proliferation, survival, and cytokine production (5). Reports have shown that 4-1BB agonist mAbs increase costimulatory molecule expression and markedly enhance cytolytic T

lymphocyte responses, resulting in anti-tumor efficacy in various models. 4-1BB agonist mAbs have demonstrated efficacy in prophylactic and therapeutic settings and both monotherapy and combination therapy tumor models and have established durable anti-tumor protective T cell memory responses (6). 4-1BB agonists also inhibit autoimmune reactions in a variety of autoimmunity models (7). This dual activity of 4-1BB offers the potential to provide anti-tumor activity while dampening autoimmune side effects that can be associated with immunotherapy approaches that break immune tolerance (8-9).

1.1.2 ISA101: ISA101 is a therapeutic HPV-16 vaccine consisting of 9 overlapping long E6 peptides (25-mer to 32-mer E6 peptides) and 4 overlapping long E7 peptides (35-mer E7 peptides) (SLP-HPV-16 vaccine). These peptides overlap by 10 to 18 residues and cover the complete sequence of HPV16 E6 and E7 oncoproteins. These long peptides have the capacity to effectively deliver antigens to dendritic cells (DC). Proper DC activation by adjuvant then induces $CD4^+$ and $CD8^+$ T-cell responses by MHC class I and MHC class II presentation of the HPV16 E6/E7 processed epitope peptides and provision of secondary co-stimulatory signals. Properly activated CD4 T cells increase surface CD40-ligand (CD40L) expression, causing DC activation through CD40L-CD40 triggering. This in turn leads to CD8 T cell activation associated with expansion of CD8+ cytotoxic T cells capable to reach and kill tumor cells that express E6 and E7 epitopes.

In patients with high-grade premalignant vulvar lesions (VIN) the prototype HPV-16- SLP vaccine produced regression of lesions in 15/19 patients at 12 months of follow up and 9/19 had complete disappearance of disease that was durable in all 9 at 24 months (10). Importantly, complete clinical responses were correlated with stronger interferon- gamma-associated T cell responses and all complete responders developed HPV-16 specific immunity. Subsequently a pilot study in 12 patients with advanced cervical cancer indicated that T-cell responses are enhanced when combining appropriately timed chemotherapy (carboplatin/paclitaxel) and the HPV-16 vaccine (10, 11). The mechanisms of enhanced immune response upon delivery of a single vaccine dose 2 weeks after the last dose in the second cycle of carboplatin/taxol chemotherapy appeared to be depletion of myeloid derived suppressor cells without depletion of T cell function or numbers. An additional Phase 2 trial in patients with advanced cervical cancer, CervISA, is being conducted to evaluate the optimal dose of ISA101, with or without interferon alpha, that produces a robust immune response.

In the trial proposed herein, a second formulation of the vaccine (ISA101b) will be used. ISA101b is missing one E7 peptide, leaving a gap in coverage of only 7 amino acids. The new vaccine is under evaluation for both safety and immunogenicity in the CervISA trial, with qualitative comparison to ISA101 planned (ISA101-ISA101b Investigator's Brochure v10a). However, the small gap in coverage is not predicted to affect immunogenicity substantively.

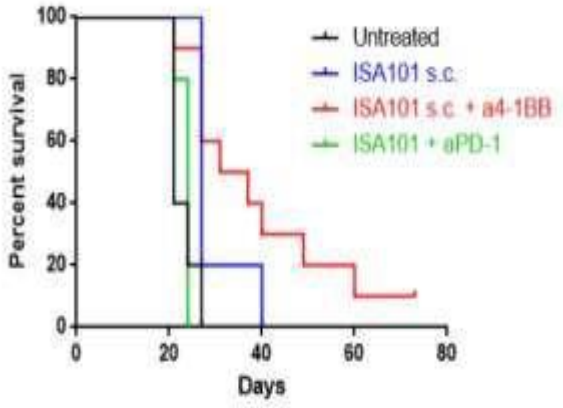
1.1.3 Combination of Utomilumab and ISA 101: The immunologically foreign nature of the HPV E6 and E7 proteins, coupled with their critical role in maintaining the oncogenic state, makes them ideal target antigens for therapeutic cancer vaccination. While peptide-, protein-, viral- and DNA-based vaccines targeting E6 and E7 have been studied both pre-clinically and in clinical trials, most fail to induce regression of established HPV+ tumors (12). While a number of these vaccines extend survival, few can induce regression of established cancer, suggesting that the T cells they elicit lack the capacity to overcome the suppressive tumor microenvironment and eradicate bulky disease (13). Of the HPV E6/E7 vaccines in clinical trials, ISA101 has demonstrated noteworthy efficacy inducing regression of high-grade VIN lesions and meriting evaluation in combination studies with cytokine therapy, chemotherapy, and immune checkpoint blockade for the treatment of metastatic HPV^+ cancers.

Within the tumor microenvironment, tumor and stromal cells engage co-inhibitory receptors on T cells to attenuate potentially tumoricidal immunity (14). We have previously shown that combination blockade of two of these T cell checkpoint receptors, CTLA-4 and PD-1, promotes synergistic tumor rejection of murine melanoma (15). Activation of T cell co-stimulatory receptors using agonist antibodies, alone or in combination with checkpoint blockade, can also extend T cell survival and effector function with the microenvironment and promote tumor rejection (16). Among co-stimulatory receptors, we have found that the tumor necrosis factor receptor superfamily member 4-1BB, the target of utomilumab, has a unique capacity to activate both T cells and antigen presenting cells (APC), which fosters generation of an exquisitely cytotoxic T cell phenotype termed ThEO/TcEO (17).

Recently, we demonstrated a unique potential of 4-1BB agonist antibodies to potentiate the therapeutic effects of an HPV E6/E7 vaccine against both sub-cutaneous and vaginally implanted HPV^+ tumors in a murine syngeneic pre-clinical model (18). Neither provision of OX-40 or CD40 agonist antibodies, nor blockade of the checkpoint receptors CTLA-4 or PD-1 could replicate the therapeutic efficacy of 4-1BB agonist antibodies in this setting. As the HPV vaccine used in these studies is not available clinically, we have also confirmed that 4-1BB agonist antibodies enhance the therapeutic efficacy of the ISA101 vaccine when used in the same syngeneic HPV^+ tumor model (Figure 1). The goal of the proposed study is to augment the E6/E7-specific T cells generated by therapeutic HPV vaccination with ISA101 so that they can expand in magnitude, infiltrate sites of HPV^+ tumor, and maintain effector function in the suppressive microenvironment.

With the above mentioned background, we propose this study in patients with incurable HPV-16+ cancers. Initially we will confine eligibility to patients with HPV + OPSCC who are platin refractory (progression on or within 6 months of platin treatment) during definitive or palliative treatment and naïve to PD-1 inhibitors. This homogeneity will minimize variables that could confound interpretation of efficacy or immune monitoring in blood and tumor. Should the primary endpoint (ORR ≥ 6/25) be achieved in patients with platin-refractory OPSCC, additional cohorts of patients with HPV-16+ anogenital primary cancers will be considered.

Figure 1: TC-1 Tumor Survival with ISA101 + Immunotherapy



1.1.4 Dose and Schedule of Utomilumab

An ongoing phase 1 trial of utomilumab, alone in patients with mixed solid tumors, or in combination with rituximab for patients with CD20+ non-Hodgkin's lymphoma, has accrued 86 solid tumor patients and 47 patients with lymphoma as of June 2016. (NCT01307267). Dose levels from 0.006 mg/kg to 10 mg/kg i.v. every 4 weeks have been studied and generally well tolerated. For toxicity summary see 1.4.4. Efficacy signals in both the solid tumor and lymphoma cohorts of the above trial have been limited to the lower dose levels (0.3 - 2.4 mg/kg). Specifically with utomilumab mono-therapy, two patients with Merkel cell carcinoma attained CR and PR at 0.24 and 0.6 mg/kg, respectively and one patient with melanoma attained PR. Notably, only one patient with head and neck cancer has been treated. Pharmacokinetic data from 68 patients receiving doses from 0.006 to 5 mg/kg showed that only 7% of inter-patient variability was related to body weight. In addition, simulations indicated that exposure was similar between body weight- based and fixed dosing regimens. Thus, fixed dosing of utomilumab will be used in this trial. We will investigate a dose of 100

mg given i.v. every 4 weeks, corresponding roughly to 1.5 mg/kg. At cycle 3 the dose will be reduced to 50 mg to hopefully avoid up-regulation of PD-1 expression and increase in soluble 4-1BB that may be induced at prolonged dosing at 100 mg . Both 50 and 100 mg doses of utomilumab are being studied in combination with avelumab and an OX-40 agonist mab (NCT02554812). Utomilumab dosing starts on Cycle 1 Day 1.

1.1.5 Dose and Schedule of ISA 101

In completed and ongoing clinical studies with HPV-16-SLP, the precursor vaccine to ISA101, over 180 patients with HPV-induced pre-malignancy of the cervix and vulva have been administered the vaccine at least once at doses ranging from 20 to 300 µg per peptide [ISA101-101b Investigators Brochure, June 2016 (20) (21). Previous clinical trials utilizing HPV-16-SLP formulated with Montanide as monotherapy have demonstrated an acceptable safety profile for patients with malignancy, induction of robust T cell immune responses compared to pre-vaccination values, and clinical efficacy in patients with high grade VIN (10) (22). In patients with cervical dysplasia and advanced cervical cancer, it has been possible to show induction of specific T cell responses utilizing the HPV-16-SLP monotherapy approach (11, 23), but these remained below the level associated with clinical responses in the VIN trial, and therefore, as expected without convincing clinical impact. This indicates the need for improvement by co-treatment in patients with late stage HPV16-positive cancer.

A phase I/II clinical trial, exploring the aforementioned chemo-immunotherapy co-treatment, called CervISA (NCT02128126), sponsored by ISA, is currently ongoing in Europe. This trial is investigating the safety and tolerability of different dose levels of ISA101 with or without pegylated interferon-alpha (IFNα) in combination with carboplatin and paclitaxel in patients with recurrent/metastatic incurable cervical cancer. Dose determination for the current trial has been chosen on the basis of CervISA and other trials that have shown 100 mcg per peptide given s.c. every 3 weeks x 3 doses to be safe and to elicit appropriate anti- HPV-16 immune response (10, 22). The vaccine is delivered in two 0.5 ml injections, containing the E6 and E7 peptides, respectively. ISA 101b dosing starts on Cycle 1 Day 1. As indicated above, evaluation of the immunogenicity of the newly formulated vaccine ISA101b will be included in the CervISA trial.

1.2 Research Hypothesis

In patients with incurable HPV-16 + OPSCC, the combination of ISA101b and the 4-1BB (CD137) agonistic antibody, utomilumab, will produce HPV-specific immune response and increased clinical efficacy, in comparison to historical data with standard anti-PD-1 therapy (nivolumab), with an acceptable safety profile.

1.3 Objectives

1.3.1 Primary Objective

- To determine the antitumor activity, as reflected in overall response rate (ORR), of utomilumab combined with ISA 101 in patients with incurable HPV^{+} OPSCC.

1.3.2 Secondary Objectives

- To evaluate safety and tolerability of utomilumab combined with ISA101 in patients with incurable HPV$^+$ oropharyngeal squamous cell carcinoma (OPSCC).

- To evaluate immune-related ORR, duration of response, progression-free and overall survival (PFS, OS), and immune-related PFS

- To assess the value of peripheral and intra-tumoral ThEO/TcEO phenotype T cell formation as a pharmacologic and/or response predictive biomarker for utomilumab and ISA101b.

- To assess the value of peripheral and intra-tumoral HPV E7 specific CD8 T cell frequencies as a pharmacologic and/or response predictive biomarker for utomilumab and ISA101b.

1.3.3 Exploratory Objectives:

- To explore other potential predictive biomarkers of response in tumor specimens and peripheral blood

1.4 Mechanism of Action

1.4.1 Mechanism of action of SLP- HPV- 16 Vaccine

The proposed mode of action in relation to therapy of HPV-associated malignancies, is based on the fact that SLP of 25-35 amino acids in length require an obligatory processing step by DC in order for the resulting short peptides to bind to MHC class I and II molecules and become transported to the cell surface. DC can very efficiently process and present long peptides following direct cytoplasmic uptake and only DC can do this efficiently. Short exact MHC class I-binding peptides, in contrast, bind exogenously to MHC class I molecules of all nucleated cells that express surface MHC class I. Since most of these cells are not professional antigen-presenting cells such as DC, this leads to suboptimal antigen processing and presentation in the absence of co-stimulatory molecules. In addition the use of exact MHC class I-binding peptides does not stimulate CD4+ T cell immunity, which is a prerequisite for optimal expansion of CD8+ killer cells and for CD8+ T cell memory.

Pharmacokinetic parameters for ISA101 were not determined in the pre-clinical studies. Studies with other SLP vaccines, however, indicate that the distribution of the peptides is mainly restricted to the draining lymph nodes (20) (24). Furthermore, the investigational product is not metabolized in the conventional sense: the peptides are taken up by antigen presenting cells, which process the peptides into smaller entities, called T-cell epitopes, which are presented on the surface of the antigen presenting cell (APC). In the meantime, the APC traffics to a draining lymph node, where naive T cells recognize the T-cell epitopes and are activated by these epitopes. The peptides are degraded within APCs through normal degradation pathways.

1.4.2 Mechanism of action of utomilumab

In pre-clinical studies, utomilumab has exhibited the ability to increase lymphocyte proliferation. In small animal models developed to test the *in vivo* function, utomilumab was able to enhance expansion of human leukocytes in a dose dependent manner as evidenced by an increase in the proportion of human CD45+ cells in the peripheral blood of engrafted

mice. Similarly, a dose dependent increase in the proportion of human leukocytes expressing the proliferation marker Ki-67 was noted. In addition, utomilumab treatment of cynomolgus monkeys in single or multiple dose studies increased proliferation among cytotoxic central memory T-cells (CD8 TCM) in peripheral blood mononuclear cell (PBMC) samples. Taken together, these data demonstrate evidence of utomilumab's ability to enhance lymphocyte response *in vivo*.

Single-agent utomilumab has demonstrated the ability to promote anti-tumor immune activity in pre-clinical studies. Human tumor cell lines representing melanoma, colon, and prostate tumor types were tested in a xenogenic transplant model. Utomilumab does not bind to murine 4-1BB; therefore, primary human peripheral blood mononuclear cells (PBMC) from a healthy volunteer donor were mixed with tumor cells to set up the animal model. Once tumors were established, animals were treated with Utomilumab with efficacy against all 3 tumor types.

1.4.3 HPV Positive Malignancies

The causal role of HPV infections in the development of preneoplastic lesions and subsequent carcinoma has been unambiguously established (25) (26). Genital infections with high-risk HPV are mainly acquired through sexual activity (27-29) and are highly prevalent in young sexually active individuals. In the majority of infected subjects the infection is cleared within one year (30, 31). However, infection with the high-risk HPV type 16 (HPV16) is associated with a greater risk for progression and is most common in patients with HPV-related cancer (25, 32). HPV-16 encodes the two tumor-specific oncoproteins E6 and E7 that can elicit a favorable immune response in which specific T-cells play a critical role in the control and elimination of the HPV infection. The virus- specific interferon-γ (IFNγ)-producing CD4+ cells (Th1 cells) and CD8+ cytotoxic T- lymphocytes (CTL) are able to recognize peptides processed from the oncoproteins E6 and E7 and contribute to the virus elimination (33, 34).

However, in case of an uncontrolled persistent infection with a high-risk HPV type, the expression of the viral oncoproteins E6 and E7 contributes to the development of (pre)malignancies. Apparently, the spontaneous HPV-specific T-cell response fails in these patients and there is no or a negligible activation and expansion of the proper HPV16-specific CD4+ and CD8+ T cells (33, 34)

Persistent HPV infection causes a variety of solid cancers including oropharyngeal, cervical, vulvar, vaginal, anal and penile cancers. HPV-related cancers are cured in the majority of cases when discovered at early stages with multimodality therapy including surgery, radiation therapy and chemotherapy. However, distant metastases may arise after longer intervals and in unusual sites (35, 36). Locoregional and distant recurrence are both problematic in advanced stage patients. Some patients with locoregional recurrence can be salvaged with multi-modal therapy.

Standard treatment of incurable advanced disease, specifically in the case of HPV+ OPSCC consists of platinum- based doublet systemic chemotherapy +/- cetuximab, and yields median OS rates of ~ 1 year for both incurable locoregional and metastatic recurrence (37). Very recent data with the PD-1 inhibitors, nivolumab and pembrolizumab, in platin-refractory squamous cancer of head and neck (SCCHN), including HPV + OPSCC, demonstrates ORR of 16% and median OS of 8-9 months (1, 2). An FDA indication has been granted for pembrolizumab and nivolumab in HNSCC patients previously treated with platin-containing chemotherapy. These data do represent a substantive advance, but also underline the fact that a significant percentage of patients do not substantially benefit from PD-1 inhibition.

Clearly novel immunotherapy approaches merit evaluation in HPV+ OPSCC and other HPV-related cancers.

1.4.4 HPV-16 SLP and ISA101 Clinical Results

1.4.4.1 Clinical pharmacology summary

Early studies were performed with a similar prototype vaccine manufactured at the Leiden University Medical Center (LUMC), identified as HPV-16-SLP. ISA101 is manufactured by a contract manufacturing organization for current trials sponsored or supported by ISA Therapeutics. Data developed with HPV-16-SLP may provide important information to help guide the development of ISA101 with respect to mechanism of action, the safety profile and biologic activity. Data from studies performed with the prototype vaccine, HPV-16-SLP, as distinct from ISA101, are specifically identified within this document.

Clinical experience with HPV-16-SLP, the prototype of ISA101, has been obtained from several investigator-sponsored studies and available data have been provided to ISA. Initial clinical trials of HPV-16-SLP were mainly designed to assess the safety, tolerability and immunogenicity. ISA's access to the safety data in these trials data is limited, and the data may not be complete as these studies have not been conducted, monitored or audited by ISA. ISA engaged an independent reviewer, Dr. M. van Poelgeest, in late 2011 to assess clinical safety data from studies conducted through November 18, 2011. This safety analysis focused on the two most common and important allergic reactions to ISA101: local injection site and systemic allergic reactions. This analysis provides the primary basis for understanding of the safety profile of HPV-16-SLP and hence, ISA101. More recent data on HPV-16-SLP have also been incorporated, as well as all available non-clinical and clinical data on ISA 101 through May 31, 2014.

Preclinical efficacy studies showed significant activity of the papilloma virus long peptide approach. In a preclinical model of HPV16-induced cervical cancer, vaccination with a single synthetic long peptide of HPV-16 E7 induced a strong HPV-16 specific immune response in inbred B6 mice, increased survival and mediated eradication of existing tumours. A second preclinical disease model in outbred rabbits used a set of long overlapping peptides of the entire sequence of cottontail rabbit papilloma virus E6 and E7, mimicking persistent HPV infections and related papilloma induced lesions. In this model, the long peptide vaccination approach resulted in similar effects: a strong induction of a papilloma-specific immune response, clearing of viral DNA and control of papilloma induced wart growth.

Pharmacokinetic parameters of ISA101 were not assessed in the preclinical studies. Studies with other synthetic long peptides, however, indicate that the distribution of the peptides is mainly restricted to DC in the draining lymph nodes (24).

1.4.4.2 Safety summary

Toxicology studies in rats (HPV-16-SLP) and rabbits (ISA101) showed that the vaccine induced high antibody levels against the immunogen and was well tolerated systemically after subcutaneous (s.c.) administration at high doses. In these studies, the vaccine was given together with an adjuvant, Montanide ISA 51 VG, hereafter referred to simply as Montanide, to mimic clinical studies. Doses in the rat were up to 120 µg per peptide per injection, while in the rabbit study the animal dose (300 µg per peptide per injection) was the same absolute dose as used in clinical trials, i.e. not adjusted for body weight or surface area.

Local inflammation at the injection site was volume dependent which suggests that the formulation was at least partially responsible for this effect. The irritation persisted throughout the studies; recovery started when treatment stopped but was not completely resolved within

the 14-day recovery period. Systemic effects included transient, minor decreases in albumin content and albumin to globulin (A/G) ratios in the blood, increased spleen weight, and microscopic minor inflammatory changes in lungs, spleen and lymph nodes. These effects are considered indicative of an immune and/or inflammatory response. The immune responses are primarily local in nature and occur in microenvironments of the draining lymph nodes.

Clinical experience with ISA101, per se, is limited as clinical studies were initiated in June 2013. Two trials with ISA101 are enrolling patients as of the date of writing this protocol,

CervISA: An open label phase I/II study in patients with advanced or metastatic (stage IVb) or recurrent HPV-16 positive cervical cancer for whom no curative treatment options exist.

VACCAIN1: A study of ISA101 administered by intradermal injection without Montanide in patients with Anal Intraepithelial Neoplasia (AIN).

In supporting clinical studies with HPV-16-SLP-Montanide approximately 180 patients with HPV-induced pre-malignant lesions and malignancies of the cervix and vulva have been administered the vaccine at least once at doses ranging from 50 to 300 µg per peptide. Of these patients, approximately 18 (~10%) have terminated vaccination due to local and/or systemic adverse events.

The most important adverse events associated with HPV-16-SLP systemic effects include fever, chills, nausea, malaise and fatigue. Local reactions at the vaccination site include pain, redness swelling and itching. Adverse effects of HPV-16-SLP appear to be reported at a greater frequency and severity in patients with premalignant disease compared to patients with advanced cervix carcinoma. Generally the adverse events after HPV-16-SLP vaccination do not exceed grade 2 according to the CTC criteria. However, a number of more serious adverse events (CTC criteria grade 3), have been reported, including systemic allergic reactions and more serious local reactions such as ulcerations or fistulas at the vaccination sites that have led to withdrawal from study treatment in approximately 7% and 5.5% of subjects, respectively. Visible, grade 2 ulceration, abscess formation and fistulas with granulomatous inflammation have been observed for approximately 24 months after vaccination, particularly in patients with pre-malignant disease. In addition, a significant number (~10-20%) of patients with pre-malignant disease have reported fatigue, fever and chills of up to CTC grade 3. For details see the ISA101-101b Investigator Brochure (21).

Local swelling and discoloration of different size and intensity has persisted for a prolonged period (one year or more) in the majority of patients who have received HPV-16-SLP in Montanide. In some cases these complaints require specific treatment of the vaccination site by a dermatologist. In some patients, local excision led to alleviation of the symptoms. Long term follow up for up 12 months of the first VIN study (P88/89) revealed visible or palpable lesions in about 75% of the patients; about half of the biopsies showed a granulomatous inflammatory reaction, sometimes resulting in the formation of scar tissue.

In addition to local reactions, systemic allergic reactions leading to study withdrawal have been reported in approximately 7% of patients who have received HPV-16-SLP. One patient also reported difficulty in breathing. Patients have responded to an anti- histamine, in those instances when it was given. Vaccinations should therefore only be administered in a clinic

where immediate treatment of severe allergic reactions is possible.

An odorous breath lasting up to approximately > 24 hours, most likely due to the DMSO component in the vaccine formulation, was also a frequently reported side effect.

Table 1. HPV-16-SLP safety overview in malignant diseases; local injection site reactions

Malignant diseases (N=69)				
Range (x-y%) - severity grade		**Grade 1 (%)**	**Grade 2 (%)**	**Grade 3**
Grade1: 29-31%	Erythema	25-27	29-31	0
Grade 2: 69-70% Grade 3: 0%	Pain	96-98	2-4	0
	Induration or	48-50	35-37	0
	Nodules	NA		
	Ulceration	NA		
	Itching	25-27	7-8	0
	Pigmentation	NA		

Table 2. HPV-16-SLP safety overview in malignant diseases; systemic reactions, withdrawals and SAEs

Malignant diseases (N=69)					
Systemic reactions (%)* Max				**Withdrawals (number, reasons)**	**SAE** (number, type)**
	Grade 1 (%)	**Grade 2 (%)**	**Grade 3(%)**		
Fever	10-12	10-12	0	N=3 1 death duo to local recurrence 1 inconvience 1 systemic side effect	N=0
Chills	17-19	0	0		
Malaise	9-11	2-3	0		
Nausea	7-9	0	0		
Vomitin	2-3	0	0		
Dizziness	1-2	0	0		
s Rash	9-10	1-2	0		
Headach	0	2-3	0		
e Fatigue	10-12	3-4	0		
Flu like symptoms	9-11	3-4	0		
Tingling	2-3	0	0		
extremities	6-8	0	0		
Swelling	1-2	0	0		
extremities	0	2-3	0		

* 34 patients died in the Phase I End-stage CxCA study in the follow-up phase between 2-17 months, due to PD.
** In study CHDR0919, the pilot chemo-immunotherapy study (N=18 of which 6 patient did not receive vaccination), 7 SAEs in 7 patients were reported: 2 deaths due to metastatic disease (one received HPV-16-SLP vaccination); 4 complications as result of advanced oncological disease (3 received HPV-16-SLP vaccination); 1 complication with standard treatment of oncological disease (no HPV-16-SLP vaccination). Other adverse event data from this study are not yet available.

For a more detailed description of the local and systemic side effects in the various studies with HPV-16-SLP, see ISA101-ISA101b Investigator's Brochure (21).

The vegetable sourced adjuvant Montanide is based on mineral oil and is a more pure form of mineral oil than Freund's incomplete adjuvant (IFA). It is an adjuvant that non- specifically

induces an immune response and functions as a depot for the peptides, to assure a slow and consistent release. In preclinical mouse experiments the adjuvants IFA or Montanide were shown to be safe and to support robust anti-T cell immunity induced by long peptides.

In this study Montanide will be used for emulsification of the peptides before injection, resulting in a formulation of DMSO/WFI/Montanide of 20/30/50%. The dose level of ISA101b peptides is 100 micorgams/peptide and is based on available data from the CervISA trial. In clinical trials conducted previously, HPV-16-SLP was also formulated in DMSO/WFI (or PBS)/Montanide 20/30/50%, and administered at the same highest dose and same volume of Montanide.

The subcutaneous route of administration has been used in the preclinical experiments in rats and rabbits conducted by ISA Pharmaceuticals B.V. (ISA). These repeated dose toxicology studies involved dosing the vaccine reconstituted and emulsified in DMSO and Montanide in the same manner as proposed for the clinic. In both species the vaccine was well tolerated systemically after repeated s.c. administration although local inflammation at the site of injection could be attributed to the adjuvant Montanide [Investigator's Brochure, Montanide ISA 51 VG, August 2013].

Although the use of the adjuvant Montanide has been associated with a number of side effects, most notably of a local nature, the evidence that this adjuvant is needed for robust T cell response induction by ISA101 is strong and the side effects are considered acceptable for a therapeutic vaccine modality that is capable of the induction of vigorous T cell immune responses against HPV-16 E6/E7 in patients with HPV induced malignancies.

1.4.4.3 Antitumor activity summary

Clinical experience with ISA101, per se, is limited as clinical studies were initiated in June 2013.

C ervISA: An open label phase I/II study in patients with advanced or metastatic (stage IVb) or recurrent HPV-16 positive cervical cancer for whom no curative treatment options exist. This is a sequential group study of patients who have advanced (stage IIIb-IVa with involvement of lymph nodes beyond the renal vein) or metastatic (stage IVb) or recurrent HPV-16 positive cervical cancer for whom no curative treatment options exist. All subjects will receive ISA101 in Montanide by subcutaneous injection at the dose levels described in Table 1. The study was designed to enroll cohorts of six patients each to evaluate the safety and HPV-specific immune responses following different vaccination regimens. Patients will receive chemotherapy considered standard of care for this disease: starting with carboplatin at an AUC of 6 plus paclitaxel at a dose of 175 mg/m^2 dose reductions in chemotherapy are allowed, consistent with the standard of care, with continuation of vaccination (with or without pegylated IFNα, depending on the assigned cohort). The maximum total treatment duration for a patient is six cycles (1 cycle is 21 days) of carboplatin and paclitaxel for a total of 18 weeks, if there are no dose interruptions or delays. On Day 15 (±3 days) of cycles 2, 3 and 4, the vaccination scheme of ISA101 with or without pegylated IFNα (depending on cohort assignment in Table 1) will start. The patients will be vaccinated with a fixed dose of ISA101 every three weeks for a total of three ISA101 vaccinations. Four dose levels of ISA101 may be assessed.

The primary endpoints of the study are safety and HPV-specific immune responses. The secondary endpoints are antitumor efficacy according to RECIST 1.1 (overall response rate, disease control rate, progression free survival). Exploratory endpoints include general responsiveness of the immune system. As of May, 2014, only the first cohort was evaluated, and patient recruitment is ongoing. The AEs and SAEs observed to date appear to be expected complications of advanced cervical cancer and/or standard chemotherapy. Virtually

all of the AEs and SAEs that are reported as “related" to the protocol-specified therapy (e.g. thrombocytopenia, neutropenia, anemia), are expected complications of chemotherapy. No new or unexpected safety concerns potentially related to ISA101 have been identified in this ongoing study to date.

VACCAIN1: A study of ISA101 administered by intradermal injection without Montanide in patients with Anal Intraepithelial Neoplasia (AIN). Study ISA101- AIN is an investigator initiated study, which is designed to assess therapeutic vaccination against HPV-16 with ISA101 for the treatment of anal intraepithelial neoplasia in HIV- positive (HIV^+) men. It should be noted that this study is being conducted using ISA101 *without Montanide* administered by intradermal (i.d.) injection. The Academic Medical Center in Amsterdam has started a sequential group dose-response study with ISA101 in HIV-positive MSM, with 3 different dosage schedules, based on intra-patient dose escalation: schedule I: 1,5,10 µg, schedule II: 5,10,20 µg and schedule III: 10,20,40 µg of ISA101 administered i.d. with a three-week interval. Each dosage schedule will be evaluated with or without the co-administration of pegylated interferon-α (Pegintron 1 µg/kg s.c.) on the day of vaccine administration. Each vaccination schedule is to be tested in 5 patients. The vaccination regimen that induces the best HPV-16-specific response with an acceptable safety profile will be considered the optimal schedule in this clinical setting. The size of this dose group will be increased to a total of 20 patients by vaccinating an additional 15 patients.

Data developed with HPV-16-SLP may inform the development of ISA101 with respect to mechanism of action, the safety profile and biologic activity. However, due to changes in manufacturing and analytical methods, HPV-16-SLP and ISA101 are considered different products from a regulatory point of view. The clinical trials described below are all investigator-sponsored studies of the prototype vaccine HPV-16-SLP. As summarized in the following tables, multiple studies evaluating HPV-16-SLP vaccination have been conducted in the past. These studies using HPV-16-SLP have included patients with different types of high-risk pre-malignant and malignant HPV-induced diseases (Table 3).

Table 3. HPV-16-SLP vaccination clinical trials.

Study ID	Indication	Study design	Key (immunological) results
Pre-malignant diseases			
P88/89 Phase II	High-grade VIN	22 patients: 4 vaccinations at 3 week interval	Clinical responses in women with HPV-16 positive, grade VIN3, correlated with induction of HPV-16 specific immunity (1).
P06.227 Phase II	High-grade CIN	9 patients (planned 50): Two arms, placebo controlled, at 3 week interval	Vaccination of HSIL patients results in increased HPV-16- specific T-cell immunity. (43). Study was terminated after 9 of planned 50 patients were recruited, due to lack of recruitment.
P06.226	Low-grade CIN or persistent PAPII	50 patients: 4 vaccinations at 3 week interval, three arms, placebo controlled	Robust HPV-16-specific T-cell responses detected after vaccination (44).

Study ID	Indication	Study design	Key (immunological) results

P08.062 Phase II	High-grade VIN or VaIN	39 patients: Two arms, 4 vaccinations at 3 week interval	Patients with high-grade VIN (or VaIN) Analysis is pending.
Malignant diseases			
P88/89 Phase I	End-stage cervical cancer	43 patients: 4 vaccinations at 3 week interval	The vaccinations resulted in a strong and broad T-cell response (2).
P88/89 Phase II	FIGO stage 1B1 cervical cancer	6 patients: 4 vaccinations at 3 week interval	The HPV-16 E6 and E7 SLP increases the number and activity of HPV-16-specific CD4(+) and CD8(+) T-cells to a broad array of epitopes in all patients (45).
P05.086 Phase II	End-stage gynecological cancer	20 patients: 4 vaccinations at 3 week interval	The HPV-16-SLP vaccine induced a broad IFNγ-associated T-cell response in patients with advanced or recurrent HPV-16-induced gynecological carcinoma but neither induced tumor regression nor prevented progressive disease (15).
CHDR0912 Pilot chemo-immuno therapy	Advanced or recurrent cervical cancer where carboplatin/paclitaxel is appropriate	18 patients: 6 patients carboplatin/paclitaxel only 12 patients vaccinated on D15 of cycle 2 of carboplatin/paclitaxel	Interim analysis a single vaccine dose of HPV-16-SLP +Montanide could induce strong T cell responses if the timing in relation to chemotherapy delivery was optimized (46) and *unpublished observations*).

1.4.5 Utomilumab: Clinical Results

An ongoing phase 1 trial of utomilumab, alone in patients with mixed solid tumors, or in combination with rituximab for patients with CD20+ non-Hodgkin's lymphoma, has accrued 86 patients with mixed solid tumors as of June 2016 (NCT01307267). Dose levels from 0.006 mg/kg to 10 mg/kg i.v. every 4 weeks have been studied. The most frequently observed treatment-emergent adverse event (TEAE) (≥ 10% of patients; all grades) was fatigue (11.6%). TEAEs were mostly grade 1-2 with 3 grade 3 AEs (ALT elevation, fatigue, and hyponatremia). Causality of the grade 3 ALT elevation was ultimately assessed by the investigator as not related to utomilumab. Three treatment-related SAEs were reported in 2 patients: enterocolitis, decreased appetite, and pneumonitis. One patient permanently discontinued treatment for grade 2 treatment-related enterocolitis. Uncommon grade 1-2 TEAEs included cough, headache, and decreased lymphocyte count in anemia, dizziness, fatigue, muscle spasm, nausea/ vomiting, pyrexia and rash. Significantly, and in contrast to another anti-CD-137 antibody, urelumab (BMS663513), no hepatotoxicity related to utomilumab has been observed. (8) (9) (19). In the 47 pts in the lymphoma cohort, most frequent TEAEs were fatigue (23%) and infusion reactions (21%). TEAES related to utomilumab were either grade 1 or 2 in severity and none led to treatment discontinuation.

Efficacy signals in the solid tumor cohort of the above trial have been limited to the lower dose levels (0.3 - 2.4 mg/kg). Specifically with utomilumab mono-therapy, two patients with Merkel cell carcinoma attained CR and PR at 0.24 and 0.6 mg/kg, respectively and one patient with melanoma attained PR. Notably, only one patient with head and neck cancer has been treated. In the lymphoma cohort, 8 patients with follicular lymphoma achieved CR (4) or PR (4) and one patient each with Hodgkin's lymphoma and Mantle Cell lymphoma achieved PR.

Pharmacokinetic data from 68 patients receiving doses from 0.006 to 5 mg/kg showed that only 7% of inter-patient variability was related to body weight. In addition, simulations indicated that exposure was similar between body weight-based and fixed dosing regimens.

A phase I trial of utomilumab and pembrolizumab accrued 23 patients. The most frequent treatment-related AEs were fatigue (35%), rash (26%) pruritus (22%), pyrexia (17%), nausea, decreased appetite, dry skin and mouth (13% each). Treatment-related AEs were mostly grade1 or 2. Grade 3 events in 2 pts were adrenal insufficiency and hypokalemia. No patients discontinued treatment due to toxicity. There were no treatment-related grade 4 or 5 AEs or deaths. There were no DLTs, clinically significant EKG or vital signs changes reported. Efficacy signals included 6 patients with CR or PR (small cell lung cancer, head and neck cancer, renal cell cancer (2 pts), anaplastic thyroid cancer, and non-small cell lung cancer.

Evolving data from an ongoing trial with utomilumab in combination with other immune checkpoint modulators suggests that response in PD-1/L1 treated patients is infrequent. Thus, our trial will include only patients who are naïve to PD-1/L1 inhibitors, and platin-resistant, the population for whom PD-1 inhibitors are currently indicated by the FDA.

1.5 Overall Risk/Benefit Assessment

Subjects with recurrent/metastatic incurable HPV-positive oropharyngeal and anogenital tract cancers represent a population for whom immunotherapy holds potential that has yet to be realized. HPV-16-SLP, the precursor vaccine to ISA 101, induced HPV-16 proliferative T cell responses in approximately 50% of patients with end-stage gynecological cancers, but did not cause any objective tumor regression. These data provide rationale to pursue combination strategies to amplify immune response.

Similarly, the 16% ORR to both nivolumab and pembrolizumab (1,2) with anti- PD-1 therapy in platin-refractory HPV-positive OPSCC demonstrates the promise of this approach, and at the same time, the need to pursue relevant combinations. In a recently completed trial we have studied the combination of ISA-101 with nivolumab with objective response in 8/22 (36%) patients with recurrent HPV-16 + OPSCC, doubling the rate of response expected from nivolumab alone (3). The OS from this trial is also quite promising with a median OS of 17.5 mos, and a randomized trial is planned to confirm these findings. The trial of utomilumab and ISA101b is the second trial in our HPV-related Moon Shot project to study rational immunotherapy combinations for HPV-related cancers. While this combination builds on our own preclinical data and its clinical translation is clearly a high priority, we envision its greatest value will be as a foundational regimen on which to add other checkpoint modulators for these virally driven cancers. For example, the correct sequencing of utomilumab and αPD-1/L1 therapy is being studied both in syngeneic models and clinically, possibly prelude to the next trial in our series..

ISA 101 has been very well-tolerated with injection site reactions the most common AE. Systemic reactions, typically readily manageable with anti-histamines or steroids, have also been observed, but typically at 300 mcg/peptide. The combination of ISA101 and nivolumab has been very well tolerated in 24 patients of our ongoing trial with mainly grade 1 toxicity and only two grade 3 enzymye elevations (one hepatic, one pancreatic) that quickly resolved when treatment was held. Given the excellent tolerance for both ISA101 and utomilumab as monotherapy, we predict good tolerance for the combination. To assure safety, we will continuously assess toxicity in cohorts of 4 subjects (section 6.3.4) throughout the conduct of the trial.

Accrual rate: The ISA101/nivolumab trial accrued 24 pts/12 months and we predict a similar rate of 2 pts/month and completion of accrual in ~ 1 year.

Depending upon the results of treatment in OPSCC patients and additional clinical experience with utomilumab amendments may be issued to study other doses of utomilumab and/or accrue expansion cohorts of patients with HPV-16 + anogenital cancers.

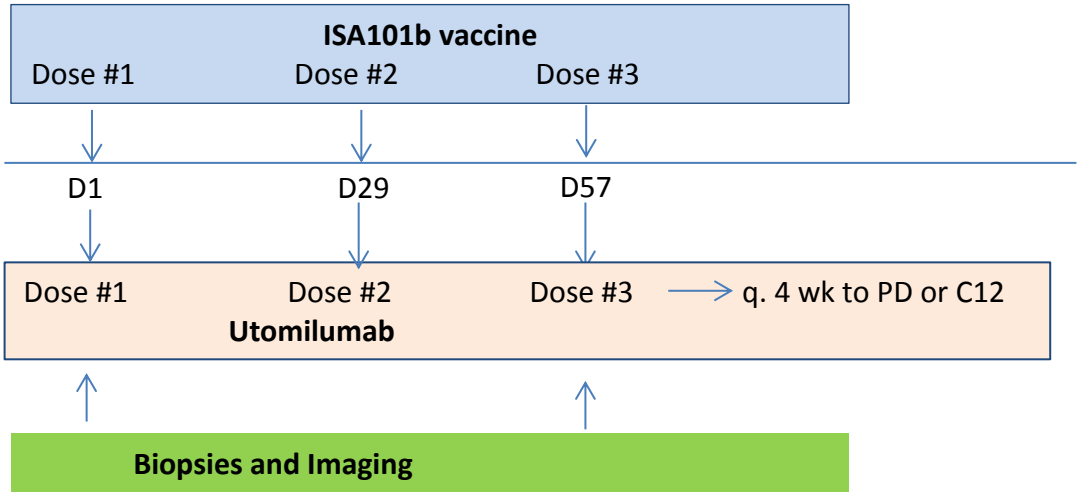
2.0 Investigational Plan

2.1 Study Design and Duration:

This is a single arm Phase 2 study in adult (≥ 18 years old) male and female subjects with platin-refractory (recurrence on or within 6 mos of platin treatment in definitive or palliative setting), PD-1/L1 inhibitor naïve, recurrent/ metastatic HPV+ OPSCC. Patients could have received up to two prior regimens for recurrent cancer.

We will evaluate ISA101b and utomilumab at doses which have previously proven safe in completed and ongoing trials (i.e., 100 ug/peptide ISA101, 50- 100 mg utomilumab).(Figure 2 and 3). Toxicity monitoring (CTCAE v4.03) (Section 6.2) will be in groups of 4 patients. The DLT window will be 2 cycles (8 wks) of utomilumab. For details see section 6.3.4.

Figure 2: Utomilumab + ISA101b Trial Design



- ISA101b sc at 100 mcg/peptide in Montanide adjuvant for 3 doses, q 4 wks
- Utomilumab administered i.v. q 4 wks C1-2 100 mg, C3-12 50 mg until PD, toxicity, or 1 yr
- Imaging: baseline and q 8 wks
- Biopsies: baseline, restaging at 8 wks, on progression
- Blood: baseline, pre-vaccine doses 2 and 3, prior to utomilumab C 4, C 8, C12 or at PD.

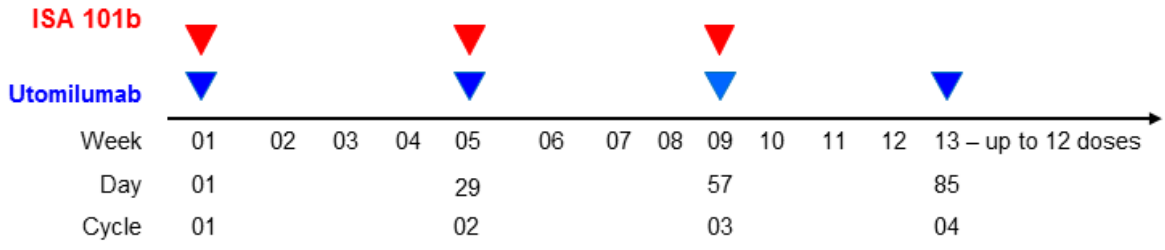


Figure 3: Utomilumab+ ISA101b Treatment Schedule

Subjects will undergo screening evaluation to determine eligibility within 28 days prior to trial inclusion. A cycle is 4 weeks in duration. The primary endpoint is objective response rate with a target ORR ≥ 30%. Response and progression will be evaluated in this study using the new international criteria proposed by revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline version 1.1 (Appendix 1).

This study will consist of 3 phases: screening (Table 5), treatment (Table 6), and follow- up (Table 7).

This study will end when analysis of survival is complete. Including follow-up, duration of the trial will be ~3 years.

2.2 Study Population

For entry into the study the following criteria must be met:

2.2.1 Inclusion Criteria

1) Signed Written Informed Consent

a) Subjects must have signed and dated an IRB/IEC approved written informed consent form in accordance with regulatory and institutional guidelines. This must be obtained before the performance of any protocol related procedures that are not part of normal subject care.

b) Subjects must be willing and able to comply with scheduled visits, treatment schedule, laboratory tests and other requirements of the study.

2) Target Population

a. Men and women ≥ 18 years of age

b. Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 1

c. Subjects with histologically- or cytologically-documented incurable Human Papillomavirus (HPV)-positive OPSCC. HPV-16 serotype will be assessed by Cervista assay (Section 4.1.1)

d. Subjects can be treatment naïve or may have had two prior regimens for recurrent cancer. They must be naïve to treatment with PD-1/L1 or CTLA-4 inhibitors.

e. Subjects must have progression within 6 mos of platin exposure during definitive or palliative therapy

f. Subjects must have measurable disease by CT or MRI per RECIST 1.1 criteria; Radiographic Tumor Assessment performed within 28 days of study inclusion.

g.Target lesions may be located in a previously irradiated field if there is documented (radiographic) disease progression in that site.

h. Subject entering the study will need to consent for mandatory biopsy at study entrance and as an optional procedure prior to C3 for biomarker evaluation
4. Biopsy should be excisional, incisional or core needle. Fine needle aspiration is insufficient.
i. Prior chemotherapy, , monoclonal antibody therapy, must have been completed at least 4 weeks prior to start. Radiotherapy or radiosurgery must have been completed at least 2 weeks prior to start.
j. All baseline laboratory requirements will be assessed and should be obtained within -14 days of study registration. Screening laboratory values must meet the following criteria
i) WBCs ≥ 2000/microL
ii) Neutrophils ≥ 1500/microL iii) Platelets ≥ 100 x 10^3/microL iv) Hemoglobin ≥ 9.0 g/dL Patients must not be transfused for at least 14 days prior to study entry
v) Serum creatinine of ≤ 1.5 X ULN or creatinine clearance > 50 mL/minute (using Cockcroft/Gault formula)
Female CrCl= (140- age in years) x weight in kg x 0.85
72 x serum creatinine in mg/ dL
Male CrCl= (140- age in years) x weight in kg x 1.00
72 x serum creatinine in mg/ dL
vi) AST ≤ 2.5X ULN
vii) ALT ≤ 2.5X ULN
viii) Total bilirubin ≤ 1.5 x ULN (except subjects with Gilbert Syndrome who must have total bilirubin <3.0 mg/dl)

3) Age and Reproductive Status

a) Women of childbearing potential (WOCBP) must use method(s) of contraception for 30 days + 5 half-lives (60 days) of the study drugs. For a teratogenic study drug and/or when there is insufficient information to assess teratogenicity (preclinical studies have not been done), a highly effective method(s) of contraception (failure rate of less than 1% per year) is required. Highly effective birth control in this study is defined as a double barrier method.

Examples include a condom (with spermicide) in combination with a diaphragm, cervical cap, or intrauterine device (IUD). The individual methods of contraception should be determined in consultation with the investigator.
b) WOCBP must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to the start of investigational product.
c) Women must not be breastfeeding
d) Men who are sexually active with WOCBP must use any contraceptive method with a failure rate of less than 1% per year. The investigator shall review contraception methods and the time period that contraception must be followed.

Men that are sexually active with WOCBP must follow instructions for birth control for a period of 90 days plus the time required for the investigational drug to undergo 5 half- lives (60 days).

2.2.2 Exclusion Criteria

1) Target Disease Exceptions

a. Subjects with active CNS metastases are excluded. Subjects are eligible if CNS metastases are adequately treated and subjects are neurologically returned to baseline (except for residual signs or symptoms related to the CNS treatment) for at least 4 weeks prior to enrollment. In addition, subjects must be either off corticosteroids, or on a stable or decreasing dose of ≤ 10 mg daily prednisone (or equivalent) for 2 weeks.
b. Subjects with carcinomatous meningitis.

2) Medical History and Concurrent Diseases

a. Subjects with active, known or suspected systemic autoimmune disease. Subjects with vitiligo, type I diabetes mellitus, residual hypothyroidism due to autoimmune thyroiditis only requiring hormone replacement, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.

b. Subjects with a condition requiring systemic treatment with either corticosteroids (>10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of start. Inhaled or topical steroids, and adrenal replacement steroid doses > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.

c. Prior therapy with anti-CD137or ISA101.

d. Subjects with a history of interstitial lung disease.

e. Other active malignancy requiring concurrent intervention.

f. Subjects with previous malignancies (except non-melanoma skin cancers, and the following in situ cancers: bladder, gastric, colon, endometrial, cervical/dysplasia, melanoma, or breast) are excluded unless a complete remission was achieved at least 2 years prior to study entry AND no additional therapy is required during the study period

g. Subjects with toxicities attributed to prior anti-cancer therapy other than alopecia and fatigue that have not resolved to grade 1 (NCI CTCAE version 4.03) or baseline before administration of study drug.

h. Subjects who have not recovered from the effects of major surgery or significant traumatic injury at least 14 days before the first dose of study treatment.

i. Treatment with any investigational agent within 28 days of first administration of study Treatment.

3) Physical and Laboratory Test Findings

a) Known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS).

b) Positive test for hepatitis B virus surface antigen (HBV sAg) or hepatitis C virus ribonucleic acid (HCV RNA) indicating acute or chronic infection.

4) Allergies and Adverse Drug Reaction

History of allergy or intolerance (unacceptable adverse event) to study drugs components.

5) Sex and Reproductive Status

a) WOCBP who are pregnant or breastfeeding

b) Women with a positive pregnancy test at enrollment or prior to administration of study medication

6) Other Exclusion Criteria

a) Any other serious or uncontrolled medical disorder, active infection, physical exam finding, laboratory finding, altered mental status, or psychiatric condition that, in the opinion of the investigator, would limit a subject's ability to comply with the study requirements, substantially increase risk to the subject, or impact the interpretability of study results.

b) Prisoners or subjects who are involuntarily incarcerated.

c) Subjects who are compulsorily detained for treatment of either a psychiatric or physical (eg, infectious disease) illness

2.2.3 Women of Childbearing Potential

A Woman of Childbearing Potential (WOCBP) is defined as any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) or is not postmenopausal. Menopause is defined clinically as 12 months of amenorrhea in a woman over age 45 in the absence of other biological or physiological causes.

2.3 Concomitant Treatments

2.3.1 Prohibited and/or Restricted Treatments

The following medications are prohibited during the study (unless utilized to treat a drug-related adverse event):

- Immunosuppressive agents
- Immunosuppressive doses of systemic corticosteroids (except as stated in Section 2.3.3).
- Any concurrent antineoplastic therapy (ie, chemotherapy, hormonal therapy, immunotherapy, extensive, radiation therapy, or standard or investigational agents)

Palliative and supportive care for disease related symptoms (including local radiotherapy, bisphosphonates and RANK-L inhibitors) may be offered to all subjects prior to first dose of study therapy (prior radiotherapy must have been completed at least 2 weeks prior to start).

2.3.2 Other Restrictions and Precautions

Subjects with active, known or suspected systemic autoimmune disease. Subjects with vitiligo, type I diabetes mellitus, residual hypothyroidism due to autoimmune thyroiditis only requiring hormone replacement, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.

Subjects are excluded if they have a condition requiring systemic treatment with either corticosteroids (>10mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of start. Inhaled or topical steroids, and adrenal replacement steroid doses > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.

2.3.3 Permitted Therapy

Subjects are permitted the use of topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption). Physiologic replacement doses of systemic corticosteroids (eg, prednisone ≤ 10 mg/day) are permitted. A brief (less than 3 weeks) course of corticosteroids for prophylaxis (eg, contrast dye allergy) or for treatment of non-autoimmune conditions (e.g., delayed-type hypersensitivity reaction caused by a contact allergen) is permitted.

The potential for overlapping toxicities with radiotherapy and utomilumab or ISA 101 currently is not known. Therefore, palliative radiotherapy is not permitted while receiving the study drugs.

2.4 Discontinuation of Subjects from Treatment

Subjects MUST discontinue investigational products at the discretion of the investigator for any of the following reasons:

- Withdrawal of informed consent (subject's decision to withdraw for any reason)
- Any clinical adverse event (AE), laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the subject
- Pregnancy
- Termination of the study
- Loss of ability to freely provide consent through imprisonment or involuntary incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness

Additional protocol-specific reasons for discontinuation (See Section 3.3.5**)**

All subjects who discontinue should comply with protocol specified follow-up and survival procedures as outlined in section 4.2.2. The ONLY exception to this requirement is when **a subject withdraws consent** for all study procedures or loses the ability to consent freely (ie, is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

3.0 Treatments

3.1 Study Treatments

The Investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution, and usage of investigational products ISA101b and utomilumab in accordance with the protocol and any applicable laws and regulations.

Investigational product documentation must be maintained that includes all processes required to ensure study drug is accurately administered. This includes documentation of study drug storage, administration and, as applicable, storage temperatures, re- constitution, and use of required processes (e.g. required diluents, administration sets).

Recommended safety measures for preparation and handling of utomilumab and ISA101b include laboratory coats and gloves.

3.2 Handling and Dispensing

Utomilumab (PF095082566) will be supplied for the study by Pfizer Global Clinical Supply, Worldwide Research and Development. Drug supplies will be shipped with Drug Shipment and Proof of Receipt form. This form will be completed, filed, and shipment confirmed as directed on the form.

Utomilumab is a sterile, colorless solution intended for IV administration. It is presented at a concentration of 10 mg/mL with a nominal volume of 10 mL in glass vials closed with a rubber stopper and sealed with an aluminum overseal. The vial is intended for single use only. PF-05082566 will be shipped in transport cool containers (2°C to 8°C) that are monitored with temperature control monitoring devices.

See the dosage and administration instructions section of the Utomilumab Investigational Product Manual for instructions on preparation for administration.

Utomilumab will be given by i.v. infusion over one hour once every 4 weeks on Day 1 of each cycle.

Utomilumab must not be used for any purpose other than the trial.

Any unused portion of the solution should be discarded in biohazard waste disposal with final disposal by accepted local and national standards of incineration.

ISA101b and montanide will be shipped by ISA with Drug Shipment and Proof of Receipt form.

ISA101b is a lyophilized powder of the two peptides/drug products which must be stored in glass vials in the dark at -20°C as specified in the pharmacy manual. ISA101b vaccine will be packaged in an open-label fashion.

The ISA101b vaccine contains nine HPV-16 E6 and three HPV-16 E7 SLP. For technical details reference is made to the IB (21). The peptides are dissolved in dimethylsulfoxide and subsequently diluted in WFI and emulsified with Montanide as detailed in the pharmacy manual. The final ratio of dimethylsulfoxide / WFI / Montanide is 20/30/50.

The vaccine will be injected in two s.c. injections, containing the two HPV-16 SLP products, in two anatomically distinct locations (e.g., one in an upper, and one in a lower extremity).
The final formulation for s.c. administration consists of 20/30/50 v/v/v-% DMSO/WFI/Montanide.

The maximum recommended hold time between ISA101b vaccine preparation and administration is 2 hours. Care must be taken to assure sterility of the prepared solution as the product does not contain any anti-microbial preservative or bacteriostatic agent.

3.3 Selection and Timing of Dose/Dose Reduction
Utomilumab will be given intravenously for approximately 60 minute IV infusion, on Day 1 of a treatment cycle every 4 weeks. . Utomilumab may be held for persistent toxicity as detailed in the next section. There are no premedications recommended for utomilumab on the first cycle. If an acute infusion reaction is noted, subjects should be managed according to Section 3.3.6.

ISA101b will be administered at 3 specific time points, on day 1 of the first 3 treatment cycles (Day1, 29 and 57). On each occasion it will be administered as two s.c. injections (one injection for each set of peptides) in two anatomically distinct locations (e.g. one injection in an upper extremity and the other in a lower extremity or one in each upper extremity with different sites used for each at each specified ISA101b vaccination timepoint). Dose of ISA 101b will be 100 mcg per peptide.

Utomilumab infusion will precede ISA101b vaccination. Patients should be observed for approximately one hour following completion of utomilumab infusion prior to ISA101b vaccine. Post vaccination patients are observed for 3 hrs.

3.3.1 Dose Delay Criteria
Tumor assessments for all subjects should continue as per protocol even if dosing is interrupted.

3.3.1.1 Investigational Drugs Dose Delay Criteria
Utomilumab and/or ISA101b administration should be delayed for the following:

- Any Grade ≥ 2 non-skin, drug-related adverse event, with the following exceptions:
  - Grade 2 drug-related fatigue that does not require a treatment delay
- Any Grade ≥ 3 skin, drug-related adverse event

- Any Grade ≥ 3 drug-related laboratory abnormality, with the following exceptions for lymphopenia, leukopenia, AST, ALT, or total bilirubin:
  - Grade ≥ 3 lymphopenia or leukopenia does not require dose delay
  - Asymptomatic Grade 3/4 increase in amylase/lipase does not require dose delay
  - If a subject has a baseline AST, ALT or total bilirubin that is within normal limits, delay dosing for drug-related Grade ≥ 2 toxicity
  - If a subject has baseline AST, ALT, or total bilirubin within the Grade 1 toxicity range, delay dosing for drug-related Grade ≥ 3 toxicity
- Any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of study medication.

3.3.2 Dose Reductions
There are no dose reductions for toxicity from Utomilumab or ISA101b

3.3.3 Criteria to Resume Dosing
3.3.3.1 Criteria to Resume Treatment with utomilumab
Subjects may resume treatment with utomilumab when the drug-related AE(s) resolve(s) to Grade ≤ 1 or baseline, with the following exceptions:

- Subjects may resume treatment in the presence of Grade 2 fatigue

Subjects who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity

- Subjects with baseline AST/ALT or total bilirubin in the Grade 1 toxicity range who require dose delays for reasons other than a 2-grade shift in AST/ALT or total bilirubin may resume treatment in the presence of Grade 2 AST/ALT OR total bilirubin
- Subjects with combined Grade 2 AST/ALT AND total bilirubin values meeting discontinuation parameters (Section 3.3.5) should have treatment permanently discontinued
- Drug-related pulmonary toxicity, diarrhea, or colitis must have resolved to baseline before treatment is resumed. Drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment
- If treatment is delayed > 6 weeks, the subject must be permanently discontinued from study therapy, except as specified in Section 3.3.5.

3.3.3.2 Criteria to Resume Treatment with ISA101b
Subjects may resume treatment with ISA101b when the drug-related AE(s) resolve(s) to Grade ≤ 1.

3.3.4 Treatment After Initial Evidence of Radiological Disease Progression
Immunotherapeutic agents such as utomilumab may produce antitumor effects by potentiating endogenous cancer-specific immune responses. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with cytotoxic agents, and can manifest as a clinical response after an initial increase in tumor burden or even the appearance of new lesions.

If radiologic imaging shows disease progression, tumor assessment should be repeated ≥4 weeks later in order to confirm the observation. Assigned study treatments may be continued at the Investigator's discretion while awaiting radiologic confirmation of disease progression.

Patients may receive study treatments while waiting for confirmation of PD if they are clinically stable as defined by the following criteria：

- Absence of clinical signs and symptoms (including worsening of laboratory values) of disease progression.
- No decline in ECOG performance status.
- Absence of rapid progression of disease by radiographic imaging.
- Absence of progressive tumor at critical anatomical sites (eg, cord compression) requiring urgent alternative medical intervention.

If patients are treated beyond progression as above, documentation of discussion with the subject regarding this action should be documented in the medical record.

If repeat imaging no longer shows PD but rather CR, PR or stable disease (SD) compared to the initial scan, treatment may be continued/resumed. In determining whether or not the tumor burden has increased or decreased, Investigators should consider all target as well as non-target lesions. If the repeat imaging confirms PD, patients should be discontinued from the trial.

3.3.5 Treatment Discontinuation Criteria

Utomilumab should be discontinued for grade ≥ 3 hematologic/non-hematologic toxicity with the following EXCEPTIONS:

- Transient (≤6 hours) flu-like
- symptoms or fever, which is controlled with medical management.
- Transient (≤24 hours) fatigue, local reactions, headache that resolves to Grade ≤1.
- Nausea and vomiting controlled by medical therapy
- Diarrhea, skin toxicity, or liver function test (ALT, AST, or GGT) that resolves to ≤ Grade 1 in less than 7 days after medical management (eg,immunosuppressant treatment) has been initiated.
- Amylase or lipase abnormality that is not associated with symptoms or clinical manifestations of pancreatitis.
- Tumor flare phenomenon defined as local pain, irritation, or rash localized at sites of known or suspected tumor.
- Non hematologic laboratory abnormality that does not require medical intervention or hospitalization
- Single non hematologic laboratory values that do not have any clinical correlate, and resolve to ≤ Grade 1 within 7 days with adequate medical management

Permanent discontinuation is indicated for grade 4 toxicity with the following EXCEPTIONS:

- Non hematologic laboratory abnormality that does not require medical intervention or hospitalization.
- Single non hematologic laboratory values that do not have any clinical correlate, and resolve within 7 days with adequate medical management.

3.3.6 Management of Infusion-Related Reactions

Since utomilumab is a monoclonal antibody and is administered IV, infusion-related reactions may occur (with symptoms such as fever, chills, rigors, diaphoresis, and headache). Treatment of the infusion-related reaction and modifications of the infusion(s) are mainly dependent upon severity, as indicated in Table 4:

Table 4. Treatment Modification for Symptoms of Infusion-Related Reactions

NCI CTCAE Grade	Treatment Modifications
Grade 1 – mild Mild transient reaction; infusion interruption not indicated; intervention not indicated.	Decrease the investigational product infusion rate by 50% and monitor closely for any worsening. The total infusion time should not exceed 120 minutes.
Grade 2 – moderate Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for □24 hours.	Stop investigational product infusion. Resume infusion at 50% of previous rate as soon as infusion-related reaction has resolved or decreased to at least Grade 1 in severity, and monitor closely for any recurrence or worsening.
Grade 3 or Grade 4 – severe or life-threatening Grade 3: Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae. Grade 4: Life-threatening consequences; urgent intervention indicated.	Stop the investigational product infusion immediately and disconnect bag infusion tubing from the patient. Investigational product treatment must be permanently discontinued.

IV=intravenous, NCI-CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Event,
NSAIDs=nonsteroidal anti-inflammatory drugs.

Once utomilumab infusion rate has been decreased by 50% due to an infusion-related reaction, it must remain so for all subsequent infusions. The total infusion time for utomilumab should not exceed 120 minutes.

Additional Modifications for Patients with Grade 2 Infusion-Related Reactions: In the event of a Grade 2 infusion-related reaction that does not improve or worsens after implementation of the modifications indicated in Table 4 (including reducing the infusion rate by 50%), the Investigator may consider treatment with corticosteroids, and the infusion should not be resumed for that cycle. At the next cycle, the Investigator may consider the addition of H2-blocker antihistamines (e.g., famotidine or ranitidine), meperidine, or ibuprofen to the mandatory premedication. Prophylactic steroids are NOT permitted.

3.3.7 Treatment of ISA101b Related Systemic Reactions

Systemic allergic reactions up to Grade 2 have been reported in approximately 7% of patients and have been controlled with antihistamines and/or epinephrine. Patients receiving ISA101b in Montanide should be closely monitored for the first 3 hours after vaccination. Immediate treatment of severe allergic reactions should be available, including staff well-trained in resuscitation, intravenous access for administration of fluids, antihistamines and corticosteroids, and epinephrine for intramuscular injection.

3.5 Destruction and Return of Study Drug

3.5.1 Destruction of Study Drug

For this study, study drugs (those supplied by Pfizer or ISA) such as partially used study drug containers, vials and syringes may be destroyed on site.

Any unused study drugs can only be destroyed after being inspected and reconciled by the responsible pharmaceutical company unless study drug containers must be immediately destroyed as required for safety, or to meet local regulations
On-site destruction is allowed provided the following minimal standards are met:

- On-site disposal practices must not expose humans to risks from the drug.
- On-site disposal practices and procedures are in agreement with applicable laws and regulations, including any special requirements for controlled or hazardous substances.
- Written procedures for on-site disposal are available and followed. The procedures must be filed with the site's SOPs and a copy provided to Pfizer or ISA (as appropriate) upon request or termination of the study, all unused and/or partially used study drug that was supplied by Pfizer or ISA must be returned to Pfizer or ISA, respectively.

It is the investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

4 ASSESSMENT FOR SAFETY AND EFFICACY

4.1 Safety Assessments

Safety assessments will be monitored at Screening (Baseline visit), during treatment according to the frequency for each treatment starting on Cycle 1 Day 1 and will continue at the specified frequency until discontinuation from the study. (See Tables 5, 6, 7)

Table 5. Flow Chart/Time and Events Schedule

Procedure	Screening Visit	Notes
Eligibility assessment		
Informed Consent	**X**	
Inclusion/Exclusion Criteria	**X**	
Medical and Tumor History	**X**	
Safety Assessment		
Vital Signs and Oxygen Saturation	**X**	Temperature, BP, HR, RR, O2 saturation by pulse oximetry (also monitor amount of supplemental oxygen if applicable) Obtain vital signs at screening visit and within 72 hours of first dose
Physical Exam[a]	**X**	Review of systems including measurements of Height and Weight, and ECOG Performance status
Laboratory Tests	**X**	Labs performed locally within 14 days prior to start of treatment: CBC with differential including neutrophil and lymphocyte count,

		Serum chemistry (BUN or serum urea level, serum creatinine, sodium, potassium, calcium, magnesium, phosphate, chloride, and bicarbonate, glucose), AST, ALT, total bilirubin, alkaline phosphatase, albumin, LDH, TSH, free T3, free T4, HBV sAg, HCV RNA, HIV1/2 immunoassay
Cervista assay	**X**	Historical result or assessment during screening acceptable.
Pregnancy Test	**X**	Performed within **24** hours of registration (serum or urine for WOCBP only)
Procedure		
Assessment (of signs and symptoms)	**X**	After obtaining Informed Consent, assess all signs and symptoms within 14 days of study registration, prior to study treatment initiation.
Concomitant Medication collection	**X**	Within 14 days of registration
Efficacy assessments		
Radiographic Tumor Assessment (CT or MRI of neck, chest, abdomen, pelvis) of all known or suspected disease sites.	**X**	Should be performed within 28 days of start of treatment. CT/MRI of brain (with contrast) should only be performed in subjects with a known history of treated brain metastases. Known or suspected disease (including CNS) should be imaged at the screening visit and at subsequent on- study assessments.
Biomarker Assessment		
Mandatory tumor biopsy	**X**	

a. Signs and symptoms present within 14 days prior to start of treatment (regardless of relationship to disease) will be recorded.

4.1.1 Cervista HPV Assay

Tumors are required to be HPV-16 positive in order to be eligible.

Testing for HPV genotype will be performed with the Cervista assay and conducted according to previously published data (38). This assay is not PCR-based but uses proprietary Invader chemistry, a signal- amplification method for the detection of specific nucleic acid sequences (Hologic, Inc.). The Cervista assay uses oligonucleotide mixtures containing probes specific for the L1, E6, and E7 genomic regions of high risk HPV genotypes. Oligonucleotides targeting the human histone 2 gene (H2be, HIST2H2BE) serve as an internal control for detection of cellular DNA. A signal-to-noise value, referred to as fold over zero (FOZ), is determined for each specimen. The FOZ cutoff value for a positive result is 2.13.

Table 6. On –study assessment

Procedure (visit time window ± 3 days)	**C1D1**		**C2D1**		**≥C3D1 Q 28 days**	**Notes**
Tumor Biopsy at first response evaluation						Prior to C3 (or earlier if restaging performed early to
Safety Assessment						
Vital Signs and Oxygen saturation	**X**		**X**		**X**	Temperature, BP, HR, RR, O2 saturation by pulse oximetry (also monitor amount of supplemental oxygen if applicable) prior to dosing and at any time a subject has any new or worsening respiratory symptoms
Adverse Events (AE) Serious Adverse Events (SAE) Assessment	**X**		**X**		**X**	
Physical Exam	**X**		**X**		**X**	Review of systems including measurements of weight, and ECOG Performance status
Complete blood count (CBC)	**X**		**X**		**X**	Includes WBC count with differential, ANC, lymphocyte count, hemoglobin, hematocrit, and platelet count
Serum Chemistry Tests	**X**		**X**		**X**	Serum chemistry (BUN or serum urea level, serum creatinine, sodium, potassium, calcium, magnesium, phosphate, chloride, and bicarbonate, glucose), LDH
Liver Function Testing (Results obtained within **72** hours prior to dosing on utomilumab infusion days)	**X**		**X**		**X**	

Thyroid Function Testing	**X**		**X**		**X**	
Whole blood for research and immunology studies[a]	**X**				**X**	C8D1and at PD, or C12D1
Review of Concomitant Medications	**X**		**X**		**X**	Concomitant medications taken throughout the study duration should be recorded within the medical record.
Pregnancy Test	**C1D1 and every 28 days**					
Efficacy Assessments						
Radiographic Tumor Assessment[b]					**X**	**Every 8 weeks (± 7 days)**
Clinical Drug Supplies						
Utomilumab	**X**		**X**		**X**	
ISA101b vaccine	**X**		**X**		**X**	**3 doses: C1D1, C2D1, C3D1**

a. Whole blood will be collected pre-treatment C1D1, pre-vaccination C2D1 and C3D1, pre-utomilumab C4D1 and C8D1, and at disease progression or study completion C12D1.

[b]Subjects will be evaluated for response according to RECIST 1.1 and immune-related response criteria.

Table 7. Follow-up and Survival Procedures

Procedure	**Initial Follow-up phase: Follow-up #1 to occur 30 days (±7 days) after last dose. follow-up #2 to occur approximately 70 days (±7 days)**	**Further Follow-up Phase (beyond follow- up #2)**	**Notes**
Radiographic Tumor Assessment[a]	**X**	**X**	For subjects who discontinue study treatment for reasons other than PD, follow up scans should be performed every 8 weeks (± 7 days) until PD, withdrawal of consent, death, lost to follow-up, or start of a subsequent anticancer therapy

Tumor Biopsy for response evaluation			At progression (optional)
Safety Assessment			
Vital Signs	**X**	**X**	
Physical Exam	**X**	**X**	Review of systems including measurements of Weight, and ECOG Performance status
Adverse Events (AE) and Serious Adverse Event (SAE) Assessment[b]	**X**	**X**	
Complete blood count (CBC)	**X**	**X**	Includes WBC count with differential, ANC, lymphocyte count, hemoglobin, hematocrit, and platelet count
Serum Chemistry Tests	**X**	**X**	Serum chemistry (BUN or serum urea level, serum creatinine, sodium, potassium, calcium, magnesium, phosphate, chloride, and bicarbonate, glucose), LDH
Review of Concomitant Medications	**X**		
Collection of Survival Information[c]	**X**	**X**	Direct contact (office visit) or phone call

a. *Radiographic assessments for subjects who have not experienced PD **must** be obtained every 8 weeks (±7 days), and **not** delayed until follow-up #1 or #2. Patients with PD by RECIST 1.1 criteria at any point may be allowed to remain on study drugs unless they are demonstrating evidence of clinical progression. If the investigator feels the patient is benefiting and should continue on study, this should be documented in the medical record.*
b. *Subjects will have two follow-up visits for safety within the first 100 days from the last dose of study therapy. Beyond 100 days from the last dose of study therapy, subjects will be followed for ongoing drug-related adverse events until resolved, return to baseline or deemed irreversible, or until lost to follow-up, withdrawal of study consent, or start of a subsequent anti-cancer therapy.*
c. *All subjects will be followed for overall survival every 3 months until death, being lost to follow-up, or withdrawal of study consent, for up to 1.5 years (18 months).*

4.2 Efficacy Assessments

4.2.1 Screening (Baseline visit) and On-Study Efficacy Assessments

Study evaluations will take place in accordance with Table 5, and according to RECIST 1.1 (Appendix 1). High resolution CT with PO/IV contrast or contrast-enhanced MRI are the preferred imaging modalities for assessing radiographic tumor response. If a subject has a

known allergy to contrast material, use local prophylaxis standards to obtain the assessment with contrast if at all possible, or use the alternate modality. In cases where contrast is strictly contraindicated, a non-contrast scan will suffice. All known or suspected sites of disease should be assessed at screening and at subsequent assessments using the same imaging method and technique. If more than one method is used at screening, then the most accurate method according to RECIST 1.1 should be used when recording data, and should again be used for all subsequent assessments. Bone scan, PET scan, or ultrasound are not adequate for assessment of RECIST response. In selected circumstances where such modalities are the sole modality used to assess certain non-target organs, those non- target organs may be evaluated less frequently. For example, bone scans may need to be repeated only when complete response is identified in target disease or when progression in bone is suspected. Subjects with a history of brain metastasis should have surveillance MRI approximately every 12 weeks or as per local standard of care, or sooner if clinically indicated. Radiographic tumor assessments will be conducted at Week 8 (± 7 days) and every 8 weeks thereafter until disease progression (or until discontinuation of study therapy), lost to follow-up, withdrawal of study consent, or start of a subsequent anti-cancer therapy. Tumor assessments for all subjects should continue as per protocol even if dosing is interrupted. Tumor measurements should be made by the same investigator or radiologist for each assessment whenever possible. Changes in tumor measurements and tumor responses to guide ongoing study treatment decisions will be assessed by the investigator using RECIST 1.1 (see Appendix 1).

4.2.2 Follow-up and Survival Procedures

Subjects who discontinue study treatment prior to progression, and subjects being treated beyond disease progression, will be followed with radiographic tumor assessments every 8 weeks (±7 days) until documented or further disease progression, withdrawal of study consent, lost to follow-up, or beginning of a subsequent anti-cancer treatment.

Radiographic assessments should be performed according to Section 4.1.
Survival will be followed for up to 1.5 years after progression, either by direct contact (office visits) or via telephone contact, according to Table 7 until death, withdrawal of study consent, or lost to follow-up.

4.2.3 Primary Efficacy Assessment

This study has primary endpoint of ORR See section 6.5 for definitions of ORR. All subjects will be monitored by radiographic assessment on an every-8-week schedule [beginning from the first on-study assessment 8 weeks from start of treatment (±7 days)] to determine changes in tumor size according to Section 4.2.1. RECIST 1.1 criteria will be used for the assessment (see Appendix 1).

4.2.4 Secondary Efficacy Assessments

For secondary efficacy analyses (response rate by irRC, RECIST PFS, Immune-related PFS, subjects will be monitored by radiographic assessment on an every-8-week schedule beginning from the first on-study assessment 8 weeks from start of treatment (±7days)], as for the primary efficacy assessment and according to Section 4.2.1. RECIST 1.1 and ir-Response criteria will be used for the assessment (see Appendix 1-2). Survival information will be collected as for the primary efficacy assessment.

4.3 Other Assessments

4.3.1 Biomarker Assessments

Immune monitoring in tumor tissue and blood and tumor biopsies for the specimens from this trial may be supported by multiple sources, including, Industry sponsors (Pfizer, ISA), , HPV-Related Cancers Moonshot Flagship Project 3, and the MDACC Office of Clinical Research

Administration –sponsored Molecular Evaluation and /or Biopsy Related Support (MEBRS) program.

4.3.1.1 Peripheral Blood Markers

Up to 150 mL (within 24 hours) of peripheral blood will be collected for testing of biomarkers at the following time points:

- pre-vaccination C1D1, C2D1, and C3D1
- pre-utomilumab C4D1, C8D1
- At disease progression or study completion (C12D1).

The treating physician or designee will have the option to cancel the laboratory protocol collection for patient safety without protocol deviation.

4.3.1.2 Tumor Markers

Tumor tissue will be obtained at baseline, and as optional, and encouraged, procedures, prior to C3 (response evaluation), and at progression.

Where possible PBMC and tumor biopsy samples pre- and post- treatment will be analyzed for expression of costimulatory and co- inhibitory ligands on tumor cells as well as the corresponding costimulatory / coinhibitory receptors, phenotypic differentiation and activation markers on effector cells and immune cell subset analysis using the panel of antibodies previously established by Dr. Wistuba in Translational Molecular Pathology and in the Curran Laboratory.

PBMC and biopsy samples (if sufficient material is available) will be analyzed for at least 18 paramaters including TCRb, CD8, CD4, FoxP3, CD127, CD11c, CD14, CD16, CD33, CD56, CD68, Ki67, HLA-DR, Eomesodermin, KLRG1, Granzyme B, PD-1, and HLA-A2 HPV E7 Tetramer. Additional effort will be made to assess antigen specific responses from non-HLA-A2 patients, as well as to measure additional markers including Runx2, Granzyme K, CD45 RO, CD62L, CD44, CD15, and fixable Live Dead. The goal is to assess the emergence of the ThEO phenotype (Eomesodermin+KLRG1+Granzyme B+) in CD4 and CD8 T cells as well as NK cells. Also, any influence of utomilumab on the balance of suppressive versus antigen-presenting myeloid cells will also be assessed. Biopsy samples will be studied by flow cytometry if sufficient material is available, otherwise they will be used for IHC (CD8, KI67, Granzyme B, CD4, FoxP3) or for gene expression analysis or HiSeq RNA sequencing.

5.0 SAFETY MONITORING AND REPORTING

5.1 ADVERSE EVENTS: Definitions and Reporting

An ***Adverse Event (AE)*** is defined as any new untoward medical occurrence or worsening of a pre-existing medical condition in a subject or clinical investigation subject administered an investigational (medicinal) product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of investigational product, whether or not considered related to the investigational product.

The causal relationship to either or both study drugs is determined by a physician and should be used to assess all adverse events (AE). The casual relationship can be one of the following:

Related: There is a reasonable causal relationship between study drug administration (either ISA101b, utomilumab or both) and the AE.

Not related: There is not a reasonable causal relationship between administration of either of the two study drugs (or both) and the AE.

The term "reasonable causal relationship" means there is evidence to suggest a causal relationship to either or both investigational agents.

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. (In order to prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more AEs.)

AEs will be reported using the NCI Adverse Events Reporting Guidelines below.

Recommended Adverse Event Recording Guidelines

Attribution	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Unrelated	Phase I	Phase I	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III
Unlikely	Phase I	Phase I	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III
Possible	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III
Probable	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III
Definitive	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III

5.1.1 Serious Adverse Events Reporting

An adverse event or suspected adverse reaction is considered “serious” if, in the view of either the investigator or the sponsor, it results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience – any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred. It does not include an adverse experience that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly/birth defect.
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or

convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32).

- Important medical events as defined above, may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed
- Appropriate by the Principal Investigator or the IND Sponsor, IND Office.
- All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in "The University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy for Investigators on Reporting Serious Unanticipated Adverse Events for Drugs and Devices". Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to the IND Office, regardless of attribution (within 5 working days of knowledge of the event).
- **All life-threatening or fatal events,** that are unexpected, and related to the study drug, must have a written report submitted within **24 hours** (next working day) of knowledge of the event to the Safety Project Manager in the IND Office.
- Unless otherwise noted, the electronic SAE application (eSAE) will be utilized for safety reporting to the IND Office and MDACC IRB.
- Serious adverse events will be captured from the time of the first protocol-specific intervention, until 30 days after the last dose of drug, unless the participant withdraws consent. Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.
- Additionally, any serious adverse events that occur after the 30 day time period that are related to the study treatment must be reported to the IND Office. This may include the development of a secondary malignancy.

Potential drug induced liver injury (DILI) is also considered an important medical event. (See Section 5.5 for the definition of potential DILI.)
Suspected transmission of an infectious agent (eg, any organism, virus or infectious particle, pathogenic or non-pathogenic) via the study drug is an SAE.
Although pregnancy, overdose, cancer, and potential drug induced liver injury (DILI) are not always serious by regulatory definition, these events must be handled as SAEs. (See Section 5.3 for reporting pregnancies).

The following reasons for hospitalization or prolongation of existing hospitalization are not considered SAEs:

- Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition (specify what this includes)
- Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the 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

Note that treatment on an emergency outpatient basis that does not result in hospital admission and involves an event not fulfilling any of the definitions of a SAE given above is not a serious adverse event.

Reporting to FDA:
Serious adverse events will be forwarded to FDA by the IND Sponsor (Safety Project Manager IND Office) according to 21 CFR 312.32.

It is the responsibility of the PI and the research team to ensure serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the sponsor's guidelines, and Institutional Review Board policy.

5.1.2 Communication between Investigator and Pfizer and ISA

If applicable, SAEs must be collected that relate to any protocol-specified procedure (e.g., a biopsy). An SAE report should be completed for any event where doubt exists regarding its status of seriousness.

If the investigator believes that an SAE is not related to either study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy, or a complication of a study procedure), the relationship should be specified in the narrative section of the SAE Report Form.

SAEs, whether related or not related to study drug, and pregnancies must be reported to Pfizer and ISA within 24 hours. SAEs must be recorded on the SAE Report Form and for Pfizer, the Pfizer IIR SAE form and Reportable Event Fax Cover Sheer; pregnancies on a MD Anderson SAE Form and for Pfizer, the Exposure During Pregnancy supplemental form (electronic or paper forms). If the SAE is fatal or life-threatening transmission should occur immediately upon awareness.

If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports should include the same investigator term(s) initially reported.)

If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 72 hours to Pfizer and ISA using the same procedure used for transmitting the initial SAE report.

All SAEs should simultaneously be faxed to:
Pfizer Inc
Attention to Manali Talathi
Fax: 1-866-997-8322Email: Manali.Talathi@pfizer.com
ISA at: ISA Pharmaceuticals
Attention to Sonja Visscher Fax
Number: +31 71 33 22 311
Email: Visscher@isa-pharma.com.

5.2 Laboratory Test Abnormalities

The following laboratory abnormalities should be captured:

• Any laboratory test result that is clinically significant or meets the definition of an SAE
• Any laboratory abnormality that required the subject to have study drug discontinued or interrupted
• Any laboratory abnormality that required the subject to receive specific corrective therapy.

It is expected that wherever possible, the clinical, rather than the laboratory term would be used by the reporting investigator (eg, anemia versus low hemoglobin value).

5.3 Pregnancy

If, following initiation of the investigational product, it is subsequently discovered that a study subject is pregnant or may have been pregnant at the time of investigational product exposure, including during at least 5 half-lives after product administration, the investigational product will be permanently discontinued in an appropriate manner (e.g., dose tapering if necessary for subject safety). Protocol-required procedures for study discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy (e.g., x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated.

The investigator must immediately notify Pfizer and ISA of this event and complete and forward a MD Anderson SAE form to Pfizer and ISA within 72 hours and in accordance with SAE reporting procedures described in Section 5.1.2.

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported on the MD Anderson SAE form.

Any pregnancy that occurs in a female partner of a male study participant should be reported to Pfizer and ISA. Information on this pregnancy will be collected on the MD Anderson SAE Form.

5.4 Overdose

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as an SAE (see Section 5.1.1 for reporting details).

5.5 Potential Drug Induced Liver Injury (DILI)

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs (see Section 5.1.1. for reporting details).

Potential drug induced liver injury is defined as
1) AT (ALT or AST) elevation > 3 times upper limit of normal (ULN)

AND

2) Total bilirubin > 2 times ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase),
AND
3) No other immediately apparent possible causes of AT elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

5.6 Other Safety Considerations

Any significant worsening noted during interim or final physical examinations, laboratory evaluations, electrocardiograms, x-rays, and any other potential safety assessments, whether or not these procedures are required by the protocol, should also be recorded as an AE or SAE, as appropriate, and reported accordingly.

For recommendations regarding suspected pulmonary toxicity, diarrhea and colitis, suspected hepatotoxicity (including asymptomatic LFT elevations), or suspected endocrinopathy, please see Appendix 4: Management of Immune-Related Adverse Events.

ISA101b, which includes the adjuvant Montanide, may be associated with ulceration of abscess formation up to 2 years after the last vaccination. In addition, up to Grade 2 systematic allergic reactions may be expected in approximately 7% of subjects receiving ISA101b. Please refer to the Investigator Brochure for ISA101-101b regarding additional information on safety and risk management.

For the purpose of this study at MD Anderson Cancer Center, all patients will be registered in the Clinical Oncology Research System (CORE). All study related data will be captured in the Data Management Initiative (DMI). All adverse events, regardless of grade or attribution, will be documented in CORE.

6.0 STATISTICAL CONSIDERATIONS

6.1 Sample Size Determination

A two-stage design will be used testing the null hypothesis that the true response rate is 0.10 against a one-sided alternative of 30%. In the first stage, 15 evaluable patients will be accrued and response evaluated at week 8. If there are < 2 responses in these 15 patients, accrual will be stopped and the trial closed for futility. Otherwise, 10 additional patients will be accrued for a total of 25 evaluable patients. The null hypothesis will be rejected if 6 or more responses are observed in 25 patients. This design yields a type I error rate of 0.0328 and power of .8017 when the true response rate is 30%. A response summary will be submitted to the IND Medical Monitor after the 15th subject and at the end of the trial.

The Investigator is responsible for completing an Efficacy/Safety Summary Report, and submitting it to the IND Office Medical Affairs and Safety Group, for review and approval. This should be submitted after the first 5 evaluable patients, complete 8 weeks of study treatment, and every 5 evaluable patients thereafter.

This design requires a maximum accrual of 27 patients, to provide 25 evaluable patients treated with utomilumab and ISA101b.

6.2 Dose Limiting Toxicity (DLT)

Toxicities will be graded according to CTCAE version 4.03. Toxicity must have possible, probable, or definite attribution to the study drugs.

Table 1. Dose-Limiting Toxicity Definition	
Hematologic DLTs	Grade 4 neutropenia (ANC <0.5 x 109/L) lasting >7 days
	Febrile neutropenia (defined as ANC <1.0 x 109/L and fever >38.5°C) or documented grade >3 infection with ANC <1.0 x 109/L
	Platelet count <25,000/mm3 lasting > 7 days
	Grade 3-4 anemia
Non-Hematologic DLTs	
	Any grade 3-4 adverse event or grade 2 or greater ocular adverse event within 8 weeks of treatment. Grade 3 infusion reactions are exempt from the DLT definition. All grade 3 immune- related adverse events that resolve to grade 1 or less within 28 days are exempt from the DLT definition excluding: pancreatitis, colitis, and ocular, hepatic and endocrine toxicities.
Death	Death occurring within 30 days of receiving the investigational agents considered at least possibly attributed to the agent(s)

6.3 Stopping Rules for Toxicity

DLT will be monitored continuously in cohorts of 5 patients for all 27 patients to ensure safety using the method by Thall et al (40). The trial will be stopped early for toxicity if Prob(DLT> 30%) > 0.90 using a prior of beta (0.6, 1.4). Stopping boundaries corresponding to this probability criterion are to terminate the trial if (# of patients with DLT) / (# patients evaluated) >= 4/5, 6/10, 8/15, 9/20, and 11/25. The operating characteristics of this rule follow:

P(true)	P(stop)	p10	p25	p50	p75	p90	Avg # pts	Avg # toxicities
0.1	0.0006	27	27	27	27	27	26.99	2.70
0.2	0.0192	27	27	27	27	27	26.72	5.35
0.3	0.1628	20	27	27	27	27	25.14	7.54
0.4	0.5082	10	15	25	27	27	20.96	8.40
0.5	0.8329	5	10	15	20	27	15.68	7.83

Accrual rate is estimated at 2 patients per month.

Analysis plan: Summary statistics will be provided to summarize response, toxicity, and other categorical variables. Overall response rate by the RECIST 1.1 criteria will be estimated with 95% confidence interval. Progression free survival and overall survival will be summarized using the method of Kaplan and Meier and Cox proportional hazards model.

Logistic regression and Cox proportional hazards models will be conducted to assess the value of peripheral and intra-tumoral ThEO/TcEo phenotype T cell formation on various clinical responses. Specifically, logistic regression models will be used to assess ORR

and Cox models will be used for survival outcomes. In both models, T cell formation will be our independent variable.

6.4 Populations for Analyses

- All enrolled subjects: All subjects who signed an informed consent form and were registered.
- All treated subjects: All subjects who received at least one dose of ISA101b and/or one dose of utomilumab. This is the primary dataset for dosing and safety.
- Evaluable subjects: All subjects who receive at least one dose of ISA 101 and one dose of utomilumab and have had repeat imaging.
- Biomarker subjects: All treated subjects with pre-treatment tumor biopsy and blood biomarkers available

6.5 Endpoint Definitions

6.5.1 Primary Endpoint

The primary objective in the study will be measured by ORR defined as the sum of subjects with a CR and PR divided by the number of evaluable subjects 8 wks from start of treatment. Response can be identified on any date between start of treatment and date of progression. For the purposes of determining response in the first 15 evaluable pts (per the mini-max design), only patients who have completed at least one restaging assessment will be included. If there are no responses at that time, accrual of new patients will be held while active patients are further followed and declared to be responding or progressing.

-CR is defined as disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
-PR: is defined as at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
-PD is defined as at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also

demonstrate an absolute increase of at least 5 mm. Note: the appearance of one or more new lesions is also considered progression.
-SD is defined as neither sufficient shrinkage from the baseline study to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Best overall response (BOR) is defined as the best response designation, recorded between the date of start of treatment and the date of objectively documented progression per RECIST 1.1 (Appendix 1) or the date of subsequent anticancer therapy, whichever occurs first. For subjects without documented progression or subsequent anti-cancer therapy, all available response designations will contribute to the BOR determination. For subjects who continue utomilumab beyond progression, the BOR should be determined based on response designations recorded up to the time of the initial RECIST 1.1-defined progression.

6.5.2 Secondary Endpoints

- The first secondary endpoint is safety and tolerability which will be measured by the incidence of adverse events, serious adverse events, deaths, and laboratory abnormalities. Adverse event assessments and laboratory tests are performed at baseline, and continuously throughout the study at the beginning of each subsequent cycle.
- The second secondary endpoints are clinical efficacy parameters other than RECIST-defined ORR and include:
    - immune-related ORR (ir-ORR) (ir CR + irPR) at 8 weeks from the start of treatment by the irRC (Appendix 2). ORR using the irRC is derived from time-point response assessments (based on tumor burden) as follows:

- irCR, complete disappearance of all lesions (whether measurable or not, and no new lesions) with confirmation by a repeat, consecutive assessment no less than 4 wk from the date first documented
- irPR, decrease in tumor burden ≥50% relative to baseline confirmed by a consecutive assessment at least 4 weeks after first documentation
- irSD, not meeting criteria for irCR or irPR, in absence of irPD
-irPD, increase in tumor burden ≥25% relative to nadir (minimum recorded tumor burden) with confirmation by a repeat, consecutive assessment no less than 4 wk from the date first documented.
-Patients are considered to have irPR or irSD even if new lesions are present, as long as they meet the respective thresholds of response as described above. Furthermore, patients are not considered to have irPD if new lesions were present and the tumor burden of all lesions did not increase by ≥25%. In contrast to irCR, irPR, and irPD, a response of irSD does not require confirmation. Refer to Appendix 1 for more details about irRC.

    - PFS defined as the time from first day of treatment to the date of the first documented tumor progression (per RECIST 1.1), or death due to any cause. Subjects who die without a reported prior progression will be considered to have progressed on the date of their death. Subjects who did not progress or die will be censored on the date of their last evaluable tumor assessment. Subjects who did not have any on study tumor assessments and did not die will be censored on the date they were randomized. Subjects who started any subsequent anti- cancer therapy without a prior reported progression will be censored at the last evaluable tumor assessment prior to initiation of the subsequent anti-cancer therapy.
- irPFS is defined as the time from treatment to the date of the first documented tumor progression (per irRC), or death due to any cause.
- OS is defined as the time from treatment to the date of death.
- The third secondary endpoint is HPV-specific immune response (Section 4.3.1).

6.5.3 Exploratory Endpoints

Exploratory endpoints are other correlative markers of immune response (Section 4.3.1).

6.5.4 Safety Analyses

The safety analysis will be performed in all treated subjects. Descriptive statistics of safety will be presented using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. All treatment emergent AEs, drug- related AEs, SAEs and drug-related SAEs will be tabulated using worst grade per NCI CTCAE v 4.03 criteria by system organ class and preferred term.

On-study lab parameters including hematology, chemistry, liver function, thyroid function and renal function will be summarized using worst grade per NCI CTCAE v 4.03 criteria. Toxicity will be monitored continuously in cohorts of 5patients.

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APPENDIX 1

RECIST 1.1 CRITERIA

This Appendix has been excerpted from the full RECIST 1.1 criteria. For information pertaining to RECIST 1.1 criteria not contained in the study protocol or in this Appendix, please refer to the full publication (1)

1 ASSESSMENT OF OVERALL TUMOR BURDEN AND MEASURABLE DISEASE

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements. Measurable disease is defined by the presence of at least one measurable lesion.

1.1 Measurability of tumor

At baseline, tumor lesions/lymph nodes will be categorized measurable or non-measurable as follows. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

Measurable lesions must be accurately measured in at least one dimension (longest diameter in the plane of the measurement to be recorded) with a minimum size of:

- 10 mm by CT scan - (CT scan slice thickness no greater than 5 mm)
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable)
- 20 mm by chest x-ray
- Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

All measurements should be recorded in metric notation, using calipers if clinically assessed.

Special considerations regarding lesion measurability

Bone lesions:

- Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

Cystic lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above.

However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with prior local treatment:

• Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion.

Non-measurable lesions are all other lesions, including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis), as well as non-measurable lesions. Lesions considered non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

1.2 Method of assessment

The **same method of assessment and the same technique should be used** to characterize each identified and reported lesion at baseline and during follow-up. Imaging based evaluation should always be performed rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical examination. CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. Measurability of lesions on CT scan is based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness.

Chest x-ray: Chest CT is preferred over chest x-ray, particularly when progression is an important endpoint, since CT is more sensitive than x-ray, particularly in identifying new lesions. However, lesions on chest x-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and ≥10 mm diameter as assessed using calipers. For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may be reviewed at the end of the study.

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised.

Endoscopy, laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised.

Tumor markers: Tumor markers alone cannot be used to assess objective tumor response.

2 BASELINE DOCUMENTATION OF 'TARGET' AND 'NONTARGET' LESIONS

Target lesions: When more than one measurable lesion is present at baseline all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline.

Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, and should lend themselves to reproducible repeated measurements.
Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. All other pathological nodes (those with short axis ≥10 mm but < 15 mm) should not be considered non-target lesions. Nodes that have a short axis <10 mm are considered non-pathological and should not be recorded or followed.
A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.
Non-target lesions: All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as 'present', 'absent', or 'unequivocal progression'. In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (e.g., 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

3 TUMOR RESPONSE EVALUATION AND RESPONSE CRITERIA

3.1 Evaluation of target lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm. Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. Note: the appearance of one or more new lesions is also considered progression.
Stable Disease (SD): Neither sufficient shrinkage from the baseline study to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Special notes on the assessment of target lesions

• **Lymph nodes:** Lymph nodes identified as target lesions should always have the actual short axis measurement recorded and should be measured in the same anatomical plane as the baseline examination, even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of <10 mm.

• **Target lesions that become 'too small to measure':** All lesions (nodal and nonnodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g., 2 mm). If the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm.

However, when such a lesion becomes difficult to assign an exact measure to then: (i) if it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm.
(ii) if the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned (note: in case of a lymph node believed to be present and faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness).
Lesions that split or coalesce on treatment: When non-nodal lesions 'fragment', the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.

3.2 Evaluation of non-target lesions

While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.
Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis).
Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.
Progressive Disease (PD): Unequivocal progression of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression).
• The concept of progression of non-target disease requires additional explanation as follows:
• *When the patient also has measurable disease*: To achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status.
• *When the patient has only non-measurable disease*: To achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening such that the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more non- target lesions is usually not sufficient to qualify for unequivocal progression status. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are non-measurable) a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: i.e., an increase in tumor burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase diameter in a measurable lesion).
Examples include an increase in a pleural effusion from 'trace' to 'large', an increase in lymphangitic disease from localized to widespread, or may be described in protocols as

'sufficient to require a change in therapy'. If 'unequivocal progression' is seen, the patient should be considered to have had overall PD at that point.

3.3 New lesions

The appearance of new malignant lesions denotes disease progression. The finding of a new lesion should be unequivocal: i.e., not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor (for example, some 'new' bone lesions may be simply healing or flare of pre- existing lesions). This is particularly important when the patient's baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a 'new' cystic lesion, which it is not.

A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the patient who has visceral disease at baseline and while on study has a CT or MRI brain ordered which reveals metastases. The patient's brain metastases are considered to constitute PD even if he/she did not have brain imaging at baseline.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents new disease. If repeat scans confirm that there is a new lesion, then progression should be declared using the date of the initial scan.

3.4 Tumor markers

Tumor markers alone cannot be used to assess objective tumor responses. If markers are initially above the upper normal limit, however, they must normalize in order for a patient to be considered as having attained a complete response.

4 EVALUATION OF BEST OVERALL RESPONSE

4.1 Time point response

A response assessment should occur at each time point specified in the protocol.

For patients who have measurable disease at baseline Table 1 provides a summary of the overall response status calculation at each time point

Appendix Table 1. **Summary of the Overall Response Status Calculation [Time point response: patients with target (+/-) non-target disease]**

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

4.2 Missing assessments and inevaluable designation

When no imaging/measurement is done at all at a particular time point, the patient is not evaluable (NE) at that time point. If only a subset of lesion measurements are made at an assessment, usually the case is also considered NE at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would be most likely to happen in the case of PD.

4.3 Special notes on response assessment

When nodal disease is included in the sum of target lesions and the nodes decrease to 'normal' size (<10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of 'zero' on the case report form (CRF).

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as

'symptomatic deterioration'. Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target disease as shown in Appendix Table 1.

For equivocal findings of progression (e.g. very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

5 ADDITIONAL CONSIDERATIONS

5.1 Duration of response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded on study).

The duration of overall complete response is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment (in randomized trials, from date of start of treatment) until the criteria for progression are met, taking as reference the smallest sum on study (if the baseline sum is the smallest, this is the reference for calculation of PD).

5.2 Lesions that disappear and reappear

If a lesion disappears and reappears at a subsequent time point it should continue to be measured. However, the patient's response at the point in time when the lesion reappears will depend upon the status of his/her other lesions. For example, if the

patient's tumour had reached a CR status and the lesion reappeared, then the patient would be considered PD at the time of reappearance. In contrast, if the tumour status was a PR or SD and one lesion which had disappeared then reappears, its maximal diameter should be added to the sum of the remaining lesions for a calculated response: in other words, the reappearance of an apparently 'disappeared' single lesion amongst many which remain is not in itself enough to qualify for PD: that requires the sum of all lesions to meet the PD criteria. The rationale for such a categorization is based upon the realization that most lesions do not actually 'disappear' but are not visualized because they are beyond the resolving power of the imaging modality employed.

5.3 Use of FDG-PET

While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion. Confirmatory CT is recommended.

b. No FDG-PET at baseline and a positive FDG-PET at follow-up:

• If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD.

• If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan).

If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

Reference:

1 Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer. (2009); 45:228-247.

APPENDIX 2

Immune-related Response Criteria (irRC)

Antitumor response based on total measurable tumor burden

For the irRC, only index and measurable new lesions are taken into account (in contrast to conventional WHO criteria, which do not require the measurement of new lesions, nor do they include new lesion measurements in the characterization of evolving tumor burden). At the baseline tumor assessment, the sum of the products of the two largest perpendicular diameters (SPD) of all index lesions (five lesions per organ, up to 10 visceral lesions and five cutaneous index lesions) is calculated. At each subsequent tumor assessment, the SPD of the index lesions and of new, measurable lesions (≥5 × 5 mm; up to 5 new lesions per organ: 5 new cutaneous lesions and 10 visceral lesions) are added together to provide the total tumor burden:

$$\text{Tumor Burden} = \text{SPD}_{\text{index lesions}} + \text{SPD}_{\text{new, measurable lesions}}$$

Appendix Table 2. Comparison between WHO criteria and the irRC

	WHO	**irRC**
New, measurable lesions (i.e., ≥5 × 5 mm)	Always represent PD	Incorporated into tumor burden
New, nonmeasurable lesions (i.e., <5 × 5 mm)	Always represent PD	Do not define progression (but preclude irCR)
Non-index lesions	Changes contribute to defining BOR of CR, PR, SD, and PD	Contribute to defining irCR (complete disappearance required)
CR	Disappearance of all lesions in two consecutive observations not less than	Disappearance of all lesions in two consecutive observations not less than 4 wk apart
PR	≥50% decrease in SPD of all index lesions compared with baseline in two observations at least 4 wk apart, in absence of new lesions or unequivocal progression of non-index lesions	≥50% decrease in tumor burden compared with baseline in two observations at least 4 wk apart
SD	50% decrease in SPD compared with	50% decrease in tumor burden

	WHO	irRC
	baseline cannot be established nor 25% increase compared with nadir, in absence of new lesions or unequivocal progression of non-index lesions	compared with baseline cannot be established nor 25% increase compared with nadir
PD	At least 25% increase in SPD compared with nadir and/or unequivocal progression of non-index lesions and/or appearance of new lesions (at any single time point)	At least 25% increase in tumor burden compared with nadir (at any single time point) in two consecutive observations at least 4 wk apart

Time-point response assessment using irRC

Percentage changes in tumor burden per assessment time point describe the size and growth kinetics of both conventional and new, measurable lesions as they appear. At each tumor assessment, the response in index and new, measurable lesions is defined based on the change in tumor burden (after ruling out irPD). Decreases in tumor burden must be assessed relative to baseline measurements (i.e., the SPD of all index lesions at screening). The irRC were derived from WHO criteria and, therefore, the thresholds of response remain the same (Appendix Table 3). However, the irRC response categories have been modified from those of WHO criteria as detailed in Tables 2 and 3.

Table 3. Derivation of irRC overall responses

Measurable response	Nonmeasurable response		Overall respons
Index and new, measurable lesions (tumor burden),* %	Non-index lesions	New, nonmeasurable lesions	Using irRC
↓100	Absent	Absent	irCR†
↓100	Stable	Any	irPR†
↓100	Unequivocal progression	Any	irPR†
↓≥50	Absent/Stable	Any	irPR†
↓≥50	Unequivocal progression	Any	irPR†
↓<50 to <25↑	Absent/Stable	Any	irSD
↓<50 to <25↑	Unequivocal progression	Any	irSD
≥25?	Any	Any	irPD†

*Decreases assessed relative to baseline, including measurable lesions only (>5 × 5 mm).

†Assuming response (irCR) and progression (irPD) are confirmed by a second, consecutive assessment at least 4 weeks apart.

Overall response using the irRC

The overall response according to the irRC is derived from time-point response assessments (based on tumor burden) as follows:

irCR, complete disappearance of all lesions (whether measurable or not, and no new lesions)

- confirmation by a repeat, consecutive assessment no less than 4 wk from the date first documented

irPR, decrease in tumor burden ≥50% relative to baseline

- confirmed by a consecutive assessment at least 4 wk after first documentation

irSD, not meeting criteria for irCR or irPR, in absence of irPD

irPD, increase in tumor burden ≥25% relative to nadir (minimum recorded tumor burden)

- confirmation by a repeat, consecutive assessment no less than 4 wk from the date first documented

Patients were considered to have irPR or irSD even if new lesions were present, as long as they met the respective thresholds of response as described above. Furthermore, patients were not considered to have irPD if new lesions were present and the tumor burden of all lesions did not increase by ≥25%. In contrast to irCR, irPR, and irPD, a response of irSD does not require confirmation. It is important to note that irCR, irPR, and irSD include all patients with CR, PR, or SD by WHO criteria as well as those patients that shift to these irRC categories from WHO PD. Patients with irSD, particularly those with slow-declining tumor burden ≥25% from baseline at the last tumor assessment, are considered clinically meaningful because they show an objectively measurable reduction in tumor burden without reaching the 50% threshold that defines irPR (it represented an objectively measured reduction not commonly observed in the natural history of advanced melanoma patients).

If a patient is classified as having irPD at a post-baseline tumor assessment, then confirmation of irPD by a second scan in the absence of rapid clinical deterioration is required. The definition of confirmation of progression represents an increase in tumor burden ≥25% compared with the nadir at two consecutive time points at least 4 weeks apart. It is recommended that this be done at the discretion of the investigator because follow- up with observation alone may not be appropriate for patients with a rapid decline in performance status. Confirmation of irPD allows for the capture of all observed responses using the irRC (Table 2), as most of these late-responding patients have a trend toward response within 4 weeks after initial irPD. Whereas WHO criteria consider any new measurable lesion to indicate PD, determination of immune-related best overall response (irBOR) is based on changes in total tumor burden from the baseline (nadir, for irPD) tumor assessment, regardless of any initial increase in baseline lesions or the appearance of new lesions.

Appendix 3 Immune- Related Adverse Event Management Algorithms

These general guidelines constitute guidance to the Investigator and may be supplemented by discussions with the Medical Monitor representing the Sponsor. The guidance applies to all immuno-oncology agents and regimens.

A general principle is that differential diagnoses should be diligently evaluated according to standard medical practice. Non-inflammatory etiologies should be considered and appropriately treated.

Corticosteroids are a primary therapy for immuno-oncology drug-related adverse events. The oral equivalent of the recommended IV doses may be considered for ambulatory patients with low-grade toxicity. The lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Consultation with a medical or surgical specialist, especially prior to an invasive diagnostic or therapeutic procedure, is recommended.

The frequency and severity of the related adverse events covered by these algorithms will depend on the immuno-oncology agent or regimen being used.

Appendix Table 4. Management of Immune-Related Adverse Events

Gastrointestinal irAEs

Diarrhea / Colitis (NCI CTCAE v4.03)	Management	Follow-up
Grade 1 Diarrhea: <4 stools/day over baseline; Colitis: asymptomatic	Continue investigational product therapy Symptomatic treatment (eg, loperamide)	Close monitoring for worsening symptoms Educate patient to report worsening immediately If worsens: Treat as Grade 2 or 3/4
Grade 2 Diarrhea: 4 to 6 stools per day over baseline; IV fluids indicated <24 hours; not interfering with ADL Colitis: abdominal pain; blood in stool	Delay investigational product therapy Symptomatic treatment	If improves to Grade 1: Resume investigational product therapy If persists >5-7 days or recur: 0.5 to 1.0 mg/kg/day methylprednisolone or equivalent When symptoms improve to Grade 1, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume investigational product therapy per protocol. If worsens or persists >3 to 5 days with oral steroids: Treat as Grade 3 to 4

Grade 3 to 4 Diarrhea (Grade 3): ≥7 stools per day over baseline; incontinence; IV fluids ≥24 hrs; interfering with ADL Colitis (Grade 3): severe abdominal pain, medical intervention indicated, peritoneal signs Grade 4:Life-threatening perf.	Discontinue investigational product therapy per protocol 1.0 to 2.0 mg/kg/day methlyprednisolone IV or equivalent Add prophylactic antibiotics for opportunistic infections Consider lower endoscopy	If improves: Continue steroids until Grade 1, then taper over at least 1 month If persists >3 to 5 days, or recur after improvement: Add infliximab 5 mg/kg (if no contraindication), Note: Infliximab should not be used in cases of perforation or sepsis

Dermatological irAEs

Rash (NCI-CTCAE v4.03)	Management	Follow-up
Grade 1 to 2 Covering ≤ 30% body surface area	Symptomatic therapy (eg, antihistamines, topical steroids) Continue investigational product therapy	If persists >1 to 2 weeks or recurs: Consider skin biopsy Delay investigational product therapy Consider 0.5 to 1.0 mg/kg/day methylprednisolone IV or oral equivalent. Once improving, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume investigational product therapy If worsens: Treat as Grade 3 to 4
Grade 3 to 4 Covering >30% body surface area; life threatening consequences	Delay or discontinue investigational product therapy Consider skin biopsy Dermatology consult 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent	If improves to Grade 1: Taper steroids over at least 1 month and add prophylactic antibiotics for opportunistic infections Resume investigational product therapy
Pulmonary irAEs		
Grade of Pneumonitis (NCI-CTCAE v4.03)	Management	Follow-up
Grade 1 Radiographic changes only	Consider delay of investigational product therapy Monitor for symptoms every 2 to 3 days Consider Pulmonary and Infectious Disease consults	Re-image at least every 3 weeks If worsens: Treat as Grade 2 or Grade 3 to 4

Grade 2 Mild to moderate new symptoms	Delay investigational product therapy Pulmonary and Infectious Disease consults Monitor symptoms daily, consider hospitalization 1.0 mg/kg/day methyl-prednisolone IV or oral equivalent Consider bronchoscopy, lung biopsy	Re-image every 1 to 3 days If improves: When symptoms return to near baseline, taper steroids over at least 1 month and then resume investigational product therapy and consider prophylactic antibiotics If not improving after 2 weeks or worsening: Treat as Grade 3 to 4
Grade 3 to 4 Severe new symptoms; New / worsening hypoxia; life-threatening	Discontinue investigational product therapy Hospitalize Pulmonary and Infectious Disease consults 2 to 4 mg/kg/day methylprednisolone IV or IV equivalent Add prophylactic antibiotics for opportunistic infections Consider bronchoscopy, lung biopsy	If improves to baseline: Taper steroids over at least 6 weeks If not improving after 48 hours or worsening: Add additional immunosuppression (eg, infliximab, cyclophosphamide, intravenous immunoglobulin, or mycophenolate mofetil)

Hepatic irAEs

Liver Function Tests (LFT) Increase (NCI-CTCAE v4.03)	Management	Follow-up
Grade 1 Grade 1 AST or ALT > ULN to 3.0 x ULN and/or Total bilirubin > ULN to 1.5 x ULN	Continue investigational product therapy	Continue liver function monitoring If worsens: Treat as Grade 2 or 3 to 4
Grade 2 AST or ALT >3.0 to ≤5 x ULN and/or total bilirubin >1.5 to ≤3 x ULN	Delay investigational product therapy Increase frequency of monitoring to every 3 days	If returns to baseline: Resume routine monitoring, resume investigational product therapy If elevations persist >5 to 7 days or worsen : 0.5 to 1 mg/kg/day methylprednisolone or oral equivalent and when LFT returns to Grade 1 or baseline, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume investigational product therapy
Grade 3 to 4 AST or ALT >5 x ULN and /or total bilirubin >3 x ULN	**Management** Discontinue investigational product therapy Increase frequency of monitoring to every 1 to 2 days 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent. Add prophylactic antibiotics for opportunistic infections. Consult gastroenterologist Consider obtaining MRI/CT scan of liver and liver biopsy if clinically warranted	**Follow-up** If returns to grade 2 Taper steroids over min. 1 mo If no improvement >3-5 days, worsens or rebounds: Add mycophenolate mofetil 1 gm twice daily If no response within an additional3-5 days consider other immunosuppressants per local guidelines

Endocrine irAEs

Endocrine Disorder	Management	Follow-up
Asymptomatic TSH abnormality	Continue investigational product therapy If TSH <0.5 x LLN, or TSH > 2 x ULN, or consistently out of range in 2 subsequent measurements: include free T4 at subsequent cycles as clinically indicated; consider endocrinology consult	
Symptomatic endocrinopathy	Evaluate endocrine function Consider pituitary scan Symptomatic with abnormal lab / pituitary scan: Delay investigational product therapy 1 to 2 mg/kg/day methylprednisolone IV or by mouth equivalent Initiate appropriate hormone therapy No abnormal lab / pituitary MRI scan but symptoms persist: Repeat labs in 1 to 3 weeks / MRI in 1 month	If improves (with or without hormone replacement): Taper steroids over at least 1 month and consider prophylactic antibiotics for opportunistic infections Resume investigational product therapy Patients with adrenal insufficiency may need to continue steroids with mineralocorticoid component
Suspicion of adrenal crisis (eg, severe dehydration, hypotension, shock out of proportion to current illness)	Delay or discontinue investigational product therapy Rule out sepsis Stress dose of IV steroids with mineralocorticoid activity IV fluids Consult endocrinologist If adrenal crisis ruled out, then treat as above for symptomatic endocrinopathy	

ADL=activities of daily living, ALT=alanine aminotransferase, AST=aspartate aminotransferase,

irAE=immune-related AE=immune-related adverse event, IV=intravenous, LLN=lower limit of normal, MRI=magnetic resonance imaging, NCI-CTCAE=National Cancer Institute-Common Terminology Criteria for Adverse Events, NSAIDs=nonsteroidal anti-inflammatory drugs, T4=thyroxine, TSH=thyroid-stimulating hormone, ULN=upper limit of normal