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Pilot randomized pre-surgical evaluation of agonist anti-CD27 monoclonal antibody varlilumab on immunologic activities of IMA950 vaccine plus poly-ICLC in patients with WHO grade II low-grade glioma

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		post-vaccine follow-up procedures and cautionary use of steroid based inhalers.		
6	5/30/2019	Edited to add volume and tube requirements for PK draws, change storage temperature of immune monitoring blood samples from 4°C to room temperature, update CTCAE version from 4 to 5.0, and clarify that the vaccine will be held for any ≥ Grade 2 non-regimen limiting toxicity (except lymphopenia or flu-like symptoms) until it returns to Grade 1 if it is felt to be related to therapy.	No	
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9	4/12/2020	Edited to reflect that surgical resection of at least 0.3 grams of tumor tissue is expected and that a patient must have at least 200 mg tissue available for tumor-infiltrating leukocytes (TILs) in order to be eligible for the study	No	

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PROTOCOL SYNOPSIS

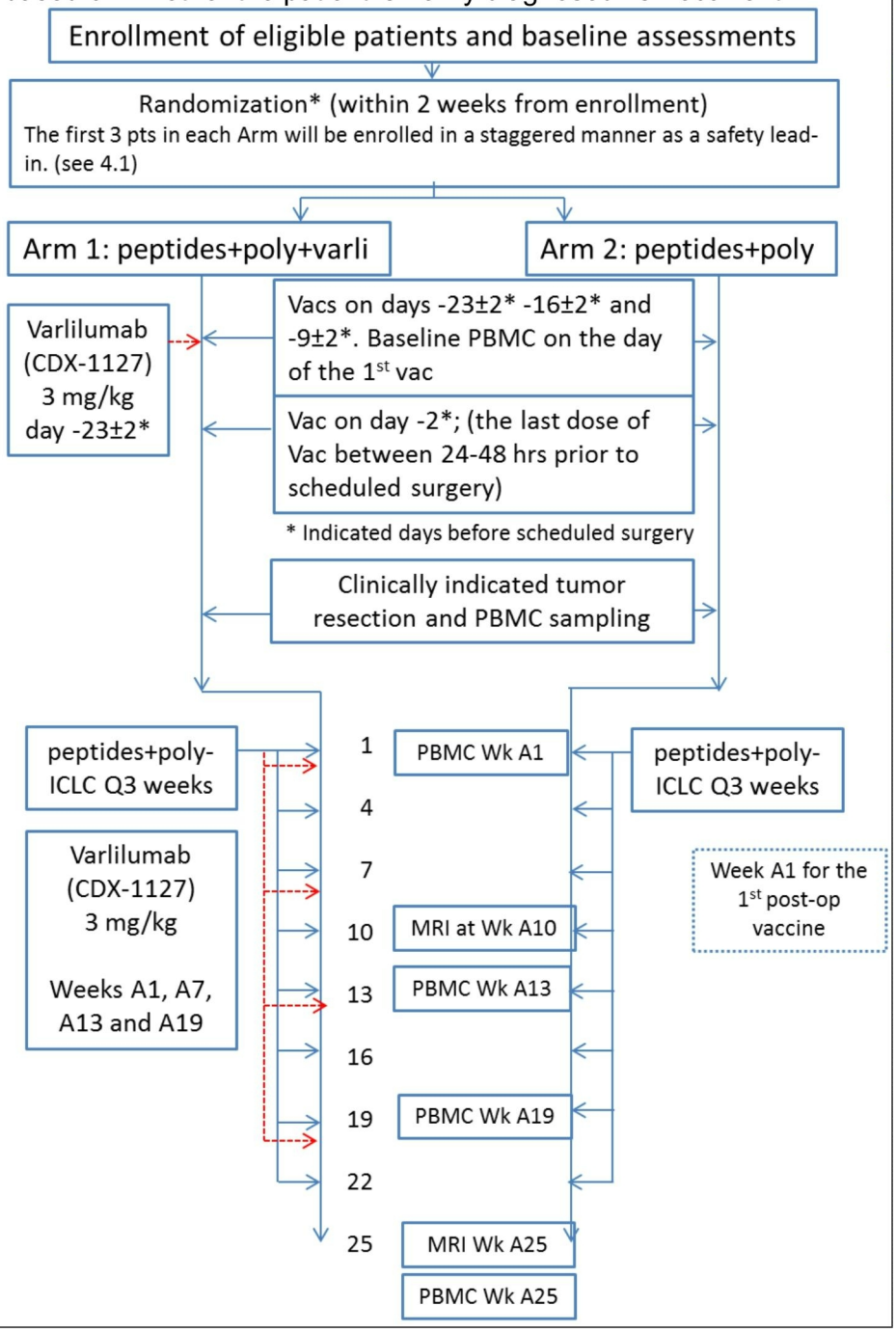
Protocol Title:	**Pilot randomized pre-surgical evaluation of agonist anti-CD27 monoclonal antibody varlilumab on immunologic activities of IMA950 vaccine plus poly-ICLC in patients with WHO grade II low-grade glioma**
Site Numbers & Names:	University of California San Francisco (UCSF)
Research Hypothesis:	Addition of agonist anti-CD27 monoclonal antibody varlilumab will enhance induction of effector T-cell response against antigens in IMA950 vaccine in patients with WHO grade II low-grade glioma

Key Inclusion and Exclusion Criteria	Inclusion Criteria: • Patients must be ≥ 18 years old. • Pathological criteria – Participants must have WHO grade II astrocytoma, oligoastrocytoma or oligodendriglioma that has been histologically confirmed by prior biopsy or surgical resection. If patients have already undergone biopsy and have pathological diagnosis in a non-UCSF institute, pathology must be reviewed and confirmed at UCSF. • Patients must be positive for HLA-A2 based on flow-cytometry or genotyping • Before enrollment, patients must show non-enhancing T2-FLAIR lesions that need to be surgically resected and are likely WHO grade II glioma. • Surgical resection of at least 0.5 grams of tumor • Both newly diagnosed (with available pathological diagnosis) and recurrent patients can be eligible. Prior radiation therapy (RT) after the initial diagnosis will be allowed but there must be at least 6 months from the completion of RT (or radiosurgery) to signed informed consent. • Prior chemotherapy and any systemic molecularly targeted anti-tumor therapy will be allowed. • Patients must have a Karnofsky performance status (KPS) of ≥ 70%. • Off or low dose (≤ 4 mg/day by Decadron) corticosteroid at least two weeks before the first pre-surgical vaccine • Adequate organ function within 14 days of study registration including: 1) Adequate bone marrow reserve: absolute neutrophil (segmented and bands) count (ANC) ≥1.0 x 10^9/L, absolute lymphocytes ≥400/μL, platelets ≥100 x 10^9/L; hemoglobin ≥ 8 g/dL; 2) Hepatic: - Total bilirubin ≤ 1.5 x upper limit of normal (ULN) and SGPT (ALT) ≤ 2.5 x upper limit of normal (ULN), and 3) Renal: Normal serum creatinine or creatinine clearance ≥60 ml/min/1.73 m^2 • Must be free of systemic infection. Subjects with active infections (whether or not they require antibiotic therapy) may be eligible after complete resolution of the infection. Subjects on antibiotic therapy must be off antibiotics for at least 7 days before beginning treatment. • Sexually active females of child bearing potential must agree to use adequate contraception (diaphragm, birth control pills, injections, intrauterine device [IUD], surgical sterilization, subcutaneous implants, or abstinence, etc.) for the duration of the vaccination period. Sexually active males must agree to use barrier contraceptive for the duration of the vaccination period. • Patient must sign an informed consent document indicating that they are aware of the investigational nature of this study, which includes an authorization for the release of their protected health information Key Exclusion Criteria: • Presence of gliomatosis cerebri, cranial or spinal leptomeningeal metastatic disease • Presence of T1 Gadolinium (Gd) –enhancing lesions (on MRI) suggestive of high-grade glioma • Pathological diagnosis for the resected tumor demonstrates transformation to higher grade (i.e. WHO grade III or IV) or gliomas. If a patient who received pre-surgical vaccines is diagnosed as high-grade glioma (HGG), the patient will be withdrawn from the study and considered for therapeutic options for HGG (trials for HGG or standard of care). The tumor tissue of such a case would be brought to the lab before the pathological diagnosis is made; and thus would be processed before the lab is informed of the final HGG diagnosis. Because HGG tissue may still reflect the vaccine effects, we will evaluate the tumor tissue to help us develop future approaches for HGG. • Pregnant women are excluded from this study. Pregnancy testing will be performed on all menstruating females within 14 days prior to study enrollment • Uncontrolled intercurrent illness including, but not limited to ongoing or active infection (e.g. active or chronic hepatitis B and C), symptomatic congestive heart failure, unstable angina pectoris, or psychiatric illness/social situations that would limit compliance with study requirements

	• History or current status of immune system abnormalities such as hyperimmunity (e.g., autoimmune diseases) that needed to be treated by systemic therapy, such as immuno-suppressants and hypoimmunity (e.g., myelodysplatic disorders, marrow failures, AIDS, transplant immunosuppression). • Receiving ongoing treatment with immunosuppressive drugs, or dexamethasone > 4mg

Study Schema: Drugs / Doses / Length of Treatment)

We plan to enroll 30 patients (15 patients/arm with randomization) on this study as summarized in the schema below. The randomization will take place in a 1:1 ratio between the two arms with the stratification based on whether the patient is newly diagnosed vs. recurrent.



	1) Arm 1: Patients will receive IMA950+poly-ICLC and CDX-1127 2) Arm 2: Patients will receive IMA950+poly-ICLC. Drugs included in the current regimen are: 1) IMA950 peptides; 2) poly-ICLC and 3) CDX-1127. IMA950 and poly-ICLC will be administered as one formulation containing 4.96 mg total IMA950 peptides and 1.4 mg poly-ICLC subcutaneously (s.c.) at sub-inguinal sites. CDX-1127 will be administered intravenously (i.v.) at 3 mg/kg Pre-surgical phase: On days -23±2, -16±2, -9±2 and -2 relative to the scheduled surgery: All patients receive s.c. injections of IMA950/poly-ICLC vaccine. The 4th dose of pre-surgery IMA950/poly-ICLC vaccine must be administered between 24-48 hrs prior to scheduled surgery. PBMC sample (60-80 mL/draw) is obtained on the day of the 1st vaccine (on day -23±2); also at the D-23±2 visit, PK samples (1 x 10 cc red top tube/draw) will be collected prior to varlilumab administration and 30 minutes (±5 minutes) after the infusion has ended. For Arm 1 patients, Varlilumab (CDX-1127) will be administered i.v. on the day of the first vaccine immediately following the s.c. vaccination. Surgery: The resected tumor tissue will be sent to the BTRC tumor bank. Post-surgery phase: For All patients, at least two weeks after the post-op steroid is tapered, but within 10 weeks post-surgery, the IMA950/poly-ICLC vaccines will be resumed and repeated every 3 weeks for 8 doses (Weeks A1, A4, A7, A10, A13, A16, A19 and A22; defining Week A1 as the week of the first post-surgery vaccine dose). The vaccines will be injected s.c. in the upper fronto-medial side of right thigh with 48±6 hours post-vaccination phone assessment. Patients will be evaluated for any possible adverse events (AEs), regimen limiting toxicity (RLT), and clinical response during clinic visits. For Arm 1 patients, Varlilumab (CDX-1127) will be administered i.v. on the day of A1, A7, A13 and A19 vaccines following the s.c. vaccination and PK samples (1 x10 cc red top tube/draw) will be collected prior to varlilumab administration and 30 minutes (± 5 minutes) after the infusion has ended . Weeks A1, A13, A19 and A25: PBMC samples (80 mL/draw) will be obtained to monitor induction of anti-IMA950 T-cell responses as well as T-cell and myeloid cell subsets by flow-cytometry. Post-Op (within 4 weeks before Week A1) Weeks A10 and A25: MRI scans

Study Objectives:	**Primary (two co-primary endpoints):** **Safety:** We will evaluate the incidence and severity of adverse events associated with the treatment regime, with an early stopping rule based on the frequency of Regimen Limiting Toxicity (RLT). **Immunological activity.** We will determine the magnitude of CD4+ and CD8+ T-cell responses against the IMA950 peptides in pre- and post-vaccine PBMC using a novel, flow-cytometry-based 2D *ex vivo* assay system. We will determine whether Arm 1 patients demonstrate significantly higher magnitude of response compared with Arm 2 patients. **Exploratory** 1. To evaluate IMA950-reactive T-cell infiltration and CXCL9/10 expression in tumors resected from Arm 1 and Arm 2 patients (We will compare these readouts between the two groups in a preliminary manner and the historical control patients who were enrolled in IRB# 15-17078 vaccine study). 2. To evaluate IMA950-reactive T-cell receptor (TCR) clonotypes in tumors resected from Arm 1 and Arm 2 patients (We will compare this between the two groups in a preliminary manner (and the historical control patients who were enrolled in IRB# 15-17078 vaccine study). 3. To estimate overall survival (OS) and progression-free survival (PFS). PFS evaluation will use the Response Assessment in Neuro-Oncology (RANO) response criteria for diffuse low-grade glioma (LGG). 4. We will evaluate PBMC responses against IMA950 are associated with PFS and frequency of IMA950 reactive T-cells in the tumor. 5. To tabulate tumor objective response rate (ORR) according to LGG RANO, if there is measurable tumor. 6. To evaluate phenotype of leukocytes in PBMC samples. We will evaluate the phenotype (activation and exhaustion markers) on IMA950-reactive T-cells and the numbers of regulatory leukocyte subsets such as immature myeloid cells (IMCs), CD4+ T cells, CD4+/Foxp3+ regulatory T cells in both tumors and PBMCs in an exploratory manner. 7. To evaluate the pharmaco-kinetics (PK) for varlilumab
Study Design:	Randomized two arm clinical trial (pilot study)

Accrual Goal: (Total number of patients)	30 evaluable patients **Evaluable patients** are study-eligible patients (i.e., those meeting all of the protocol inclusion/exclusion criteria) who receive at least four post-surgery vaccines. Patients who receive at least 4 post-surgery vaccines will not be replaced because their PBMC on week 13 would allow for the primary endpoint evaluation. Subjects who are considered non-evaluable will be replaced. Patients who are found to have WHO grade III or IV high-grade glioma at the time of resection will not be eligible for the post-surgery vaccine phase and will be replaced.
Accrual Rate: (Number of patients expected per month)	We plan 18-24 months of accrual (1-2 patients/month)

1 Objectives

1.1 Primary Objectives

We will evaluate our hypothesis **that addition of agonist anti-CD27 monoclonal antibody varlilumab will enhance induction of effector T-cell response against antigens in IMA950 vaccine in patients with WHO grade II low-grade glioma**. There are 2 co-primary endpoints:

1.1.1 **Safety**: We will evaluate the incidence and severity of adverse events associated with the treatment regime, with an early stopping rule based on the frequency of Regimen Limiting Toxicity (RLT).

1.1.2 **Immunological Activity**: We will determine the response rate and magnitude of $CD4^+$ and $CD8^+$ T-cell responses against the IMA950 peptides in pre- and post-vaccine PBMC using a novel, flow-cytometry-based 2D *ex vivo* assay system. We will determine whether Arm 1 patients demonstrate higher response rate and/or magnitude of response compared with Arm 2 patients.

1.2 Exploratory Objectives

1.2.1 To evaluate whether resected tumors from Arm 1 patients demonstrate significantly higher levels of IMA950-reactive T-cell infiltration and CXCL9/10 expression compared with those resected from Arm 2 (and/or the historical control patients who were enrolled in IRB# 15-17078 vaccine study).

1.2.2 To evaluate whether resected tumors from Arm 1 patients demonstrate significantly higher frequencies of IMA950-reactive T-cell receptor (TCR) clonotypes compared with those resected from Arm 2 (and/or the historical control patients who were enrolled in IRB# 15-17078 vaccine study).

1.2.3 To estimate overall survival (OS) and progression-free survival (PFS). PFS evaluation will use the Response Assessment in Neuro-Oncology (RANO) response criteria for diffuse low-grade glioma (LGG)2.

1.2.4 To evaluate whether PBMC responses against IMA950 are associated with PFS and frequency of IMA950-reactive T-cells in the tumor.

1.2.5 To tabulate tumor objective response rate (ORR) according to LGG RANO2, if there is measurable tumor.

1.2.6 To evaluate phenotype of leukocytes in PBMC samples. We will evaluate the phenotype (activation and exhaustion markers) on IMA950-reactive T-cells and the numbers of regulatory leukocyte subsets such as immature myeloid cells (IMCs), CD4+ T cells, CD4+/Foxp3+ regulatory T cells in both tumors and PBMCs in an exploratory manner.

1.2.7 To evaluate the pharmacokinetics (PK) for varlilumab.

2 Background

2.1 Low Grade Gliomas

Low-grade gliomas (LGG), the most common of which are pilocytic astrocytomas, diffuse astrocytomas, and oligodendrogliomas are a diverse family of central nervous system (CNS) neoplasms that occur in children and adults. Based on data from the American Cancer Society and Central Brain Tumor Registry of the United States (CBRTUS), approximately 1,800 LGG were diagnosed in 2006, thus representing approximately 10% of newly diagnosed primary brain tumors in the United States.[3,4] Pilocytic astrocytomas (WHO grade I) are the most common brain tumor in children 5 to 19 years of age[4.] Diffuse astrocytomas and oligodendrogliomas are all considered WHO grade II low grade gliomas (LGG) and are more common in adults. Pilocytic astrocytomas are generally well circumscribed histologically and radiographically and amenable to cure with gross total resection. In contrast, the diffuse astrocytomas and oligodendrogliomas are more infiltrative and less amenable to complete resection.[5,6] From a molecular genetics standpoint, the most common alterations in LGG are *IDH1* mutations[7] and mutations in the tumor suppressor gene *TP53*, located on chromosome 17, the gene product of which is a multifunctional protein involved in the regulation of cell growth, cell death (apoptosis), and transcription.[8,9] Additionally, several molecular factors are of favorable prognostic

significance, particularly the presence of 1p/19q co-deletion and *isocitrate dehydrogenase (IDH)* mutations (reviewed in)[2].

WHO grade II LGGs are at risk to undergo malignant transformation into more aggressive and lethal WHO grade III or IV high-grade glioma (HGG)[5,6,10,11]. Even with a combination of available therapeutic modalities (i.e., surgery, radiation therapy [RT], chemotherapy), the invasive growth and resistance to therapy exhibited by these tumors results in recurrence and death in most patients[10-18]. Although postoperative RT in LGG significantly improves 5-year progression-free survival (PFS), it does not prolong overall survival (OS) compared with delayed RT given at the time of progression[13,14]. Early results from a randomized trial of radiation therapy plus procarbazine, lomustine, and vincristine (PCV) chemotherapy for supratentorial adult LGG (RTOG 9802) demonstrated improved PFS in patients receiving PCV plus RT compared RT alone[19]. Nonetheless, PCV is considerably toxic and currently not widely used for management of glioma patients. Although chemotherapy with temozolomide (TMZ) is currently being investigated in LGG patients, it is unknown whether it confers improved OS in these patients[5]. Further, our recent study has indicated that 6 of 10 LGG cases treated with TMZ progressed to HGG with markedly increased exome mutations and, more worrisome, driver mutations in the RB and AKT-mTOR pathways, with predominant C>T/G>A transitions at CpC and CpT dinucleotides, strongly suggesting a signature of TMZ-induced mutagenesis[20]; this study also showed that in 43% of cases, at least half of the mutations in the initial tumor were undetected at recurrence, while IDH mutations were the only type of mutations that persisted in the initial and recurrent tumors[20]. These data suggests the possibility that treatment of LGG patients with TMZ may enhance oncogenic mutations and genetic elusiveness of LGG, therefore calling for development of safer and effective therapeutic modalities such as vaccines.

Taken together, LGG are considered a premalignant condition for HGG, such that novel interventions to prevent malignant transformation need to be evaluated in patients with LGG. Immunotherapeutic modalities, such as vaccines, may offer a safe and effective option for these patients due to the slower growth rate of LGG (in contrast with HGG), which should allow sufficient time for multiple immunizations and hence high levels of anti-glioma immunity. Because patients with LGGs are generally not as immuno-compromised as patients with HGG, they may also exhibit greater immunological response to and benefit from the vaccines. Further, the generally mild toxicity of vaccines may improve quality of life compared with chemotherapy or RT.

2.2 Cancer Vaccines: Challenges and Suitable Target Populations

Cancer vaccines are designed to induce systemic immunity against antigens expressed by tumor cells (tumor antigens [TA]). In recent years, molecular characterization of T cell-epitopes within TAs has contributed to the evolution of tumor immunology into a sophisticated science, one based on solid molecular findings.[21,22] Although some early success has been reported in cancer vaccine clinical trials that use TA-derived T-cell epitope-peptides[23], objective responses were rarely seen in patients with advanced

cancers who are often severely immuno-compromised. Furthermore, rapid progression in these patients often restricts the ability to perform multiple immunizations, which appear to be essential for a positive rate and magnitude of TA-specific immunity.[24-26] Indeed, recent results suggest that cancer vaccines are more effective in the presence of minimal residual or early phase disease, owing to a favorable effector/target ratio and to more intact host immunity as compared to individuals with metastatic/advanced disease.[27,28]

In addition, our knowledge and understanding of factors that can improve the efficacy of cancer vaccines are constantly evolving. These factors include development of novel adjuvants, such as Toll-like receptor (TLR) ligands.[29-32] These considerations indicate that the potential of cancer vaccines has not been fully realized and that the preclinical and clinical results achieved so far should be regarded as stimuli to further explore tumor responsiveness to cancer vaccines. The challenging and fascinating task of tumor immunology continues to be the identification of suitable targets and strategies to achieve successful immune responses.

2.3 Central Nervous System (CNS) Immunology and Glioma Vaccines

The cellular mechanisms underlying the “immunologically privileged” status of the brain and brain tumors have been well characterized during recent decades.[33,34] Through this characterization, it has become clear that this “privileged” status is not absolute. This is demonstrated in cases of paraneoplastic cerebellar degeneration[35,36] and experimental allergic encephalomyelitis (EAE), which resembles the pathology of multiple sclerosis in human[37], exposure of CNS-derived T-cell antigens to the systemic immune system can lead to induction of specific T-cell responses that recognize and attack immune targets located in the CNS. These findings led us to explore the possibility that effective active immunization strategies against CNS tumors can be developed. We are dedicated to developing novel immunization approaches for patients with gliomas.[38-44] Early phase clinical trials by us[38] and others[45-51] of over 75 malignant glioma patients have demonstrated the safety and preliminary therapeutic benefits of peripheral vaccinations using autologous glioma tissue-derived bulk antigens.

2.4 Importance of type-1 chemokine CXCL10 for migration of vaccine-induced effector T cells to the brain tumor.

Based on the cytokine-producing profiles and functions, T-cell immune responses are classified into at least four distinct subsets: type-1, type-2, type-17 and regulatory T-cells [52-54]. We demonstrated that tumor-specific type-1 T-cells, which predominantly secrete IFN-γ[55] can efficiently traffic into CNS tumor sites and mediate effective therapeutic efficacy[56] via the type-1 chemokine CXCL10, which is primarily induced by IFN-γ[56-59]. Despite the importance of the type-1 T-cell response, cancers, including glioma, secrete numerous cytokines that diminish type-1 responses[60-62] and promote tumor proliferation[63,64] and immune escape[65].

We have reported that co-administration of poly-ICLC in vaccine regimens significantly enhances CNS tumor-trafficking of vaccine-induced effector T-cells as well as therapeutic

effects in rodent CNS tumor models in CXCL10-dependent manners, including the GL261 glioma.[32] **Figure. 1** demonstrates the expression of CXCL10 mRNA using *in situ* hybridization in mouse brain sections containing GL261 glioma.[66] Treatment of mice with subcutaneous GAA-vaccines and poly-ICLC resulted in a remarkably high level expression of CXCL10 mRNA in i.c. GL261 glioma compared with mice treated with mock-vaccine, GAA-vaccine alone, and poly-ICLC alone. Furthermore, blockade of CXCL10 abolished efficient accumulation of effector T-cells in the glioma site, suggesting a critical role of CXCL10[56,58,66]. HGG patients receiving DC vaccine plus poly-ICLC showed a robust CXCL10 induction[67]. These data provide us with a solid basis to develop glioma-vaccine studies using poly-ICLC as an adjuvant.

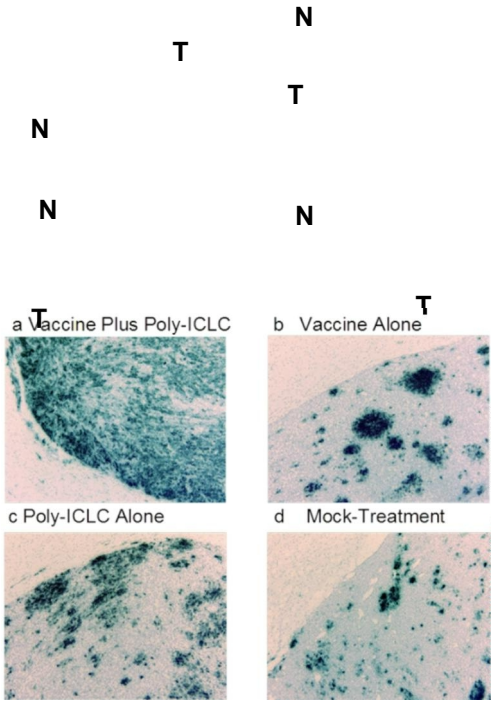


Figure 1. *In situ* hybridization demonstrates upregulated expression of CXCL10 mRNA in GL261 glioma treated with GAA-specific vaccines and i.m. poly:ICLC. Mice bearing GL261 glioma in the brain received either: a) the combination of poly:ICLC and GAA-vaccine; b) GAA-vaccine alone; c) i.m. poly:ICLC alone or d) mock-treatment alone on days 2, 12 and 22 post-tumor inoculation. On day 23 following tumor inoculation (one day following the third s.c and i.m. treatments), brain tissues were collected. Paraformaldehyde-fixed tissue sections were hybridized with a radioactive antisense mouse CXCL10 specific riboprobe and exposed to autoradiography. Hematoxylin background for cell densities. Please note selective CXCL10 induction in the tumor (T) vs. normal brain (N). The original

2.5 IMA950 as a novel, multi-peptide glioma vaccine

The IMA950 vaccine was developed by Immatics and European academic investigators[1], and includes 12 peptides, 9 human leukocyte antigen (HLA)-A*02 class I epitopes, an elongated class I epitope, one class II epitope, and the synthetic Hepatitis B virus marker peptide IMA-HBV-001. Peptides presented at the cell surface reflect the protein content of the cell; those on HLA class I molecules comprise the critical peptidome elements interacting with $CD8^+$ T-cells. From *ex vivo* (i.e. surgically resected but not cultured) HLA-$A*02^+$ GBM tissue, they eluted >3,000 HLA-A*02-restricted peptides, then selected 10 GBM-associated antigens based on the following criteria: 1) high expression in tumors; 2) very low or absent expression in healthy tissues; 3) implication in gliomagenesis, and 4) immunogenicity. Patients' $CD8^+$ T-cells that were stimulated with IMA950 peptides *in vitro* specifically killed tumor cells. Further, $CD8^+$ T cells infiltrating GBM tissue (without vaccine) recognized IMA950 antigens.[1]

IMA950 was investigated in a first-in-man study sponsored by Cancer Research UK (CR-UK) in patients with newly diagnosed GBM (sponsor protocol number: CR0902-11, EUDRACT-2009-015971-28, NCT01222221). Enrollment of 45 patients started in October 2010 and has been completed in February 2013. This study compared vaccine-specific T-cell responses as a randomized two arm study. In cohort 1 at least the first 3 vaccinations were given before initial chemoradiotherapy (CRT), while in cohort 2, vaccinations started after completion of the standard-of care CRT but before the first cycle of maintenance TMZ. Patients received up to 11 vaccinations of IMA950 [plus granulocyte macrophage-colony stimulating factor (GM-CSF) in some vaccines] over 24 weeks (on day 1, 2, 3, 8, 22 and thereafter every 4 weeks). Of 23 analyzed patients, the vast majority showed $CD8^+$ vaccine-induced immune responses (91% immune responders, 57% multi-peptide responders). A mean number of 2.3 immune responses per patient have been observed so far in this trial.

Two further clinical trials with IMA950 are completed or ongoing: A Phase I study at the US National Cancer Institute (NCI) (study code: IMA950-102, NCI protocol: 11-C-0192) was conducted in six patients with stable disease after completion of first line CRT with TMZ and at least four maintenance cycles of TMZ treatment. In this trial, a single low-dose pre-treatment with cyclophosphamide was followed by IMA950 vaccinations plus GM-CSF (with first 8 vaccinations) and imiquimod (with all IMA950 vaccinations). The first patient received their first vaccination with IMA950 in April 2012 and the trial was closed in April 2014.

CER-12-213 (immatics code IMA950-104) is an investigator Initiated Trial, sponsored by University of Geneva in Switzerland, with PhD MD Pierre-Yves Dietrich as Principal Investigator. In this monocentric trial, patients with newly diagnosed GBM are vaccinated with IMA950 plus i.m. poly-ICLC as an immunomodulator concurrently to maintenance temozolomide after chemoradiotherapy. The first patient entered the trial in September 2013.

Expression of IMA950 antigens in WHO grade II glioma and recurrent glioma. We have performed RNA-seq analyses of 9 GAAs included in IMA950[1] in 11 paired cases in which primary tumors were WHO Grade II LGGs and recurred as WHO grade II, III or IV gliomas. We also compared the expression levels of IMA950 antigens and GAAs we included in the previous UPCI 07-057 and 08-135 studies (i.e. IL-13Rα2, EphA2, WT1 and survivin). Expression levels of IMA950 antigens were found to be significantly higher than IL-13Rα2, EphA2, WT1 and Survivin (data not shown). The expression pattern of IMA950 antigens seems to be categorized into the following two groups: 1) ones expressed in both primary and recurrent cases; and 2) ones that are expressed at higher levels in recurrent, especially recurrent GBM. For example, as shown in **Figure 2**, FABP7 appears to be expressed at high levels (i.e., higher than 50 FPKM (fragments per kilobase of exon per million fragments mapped) in both primary WHO Grade II LGGs and recurrent gliomas. Interestingly, it appears as though FABP7 is expressed at higher levels in primary LGGs that recurred as Grade IV compared with other primary LGG cases that recurred as Grade II or III, although not statistically significant perhaps due to the small sample size ($p=0.24$ by the Wilcoxon rank sum test). If this is confirmed in a larger number of cases, it may support development of novel vaccine strategies targeting FABP7 for prevention of transformation to Grade IV GBM. While expression levels of IGFBP3 seems lower than that of FABP7, IGFBP3 seems to be expressed almost exclusively in recurrent Grade IV

GBM (p=0.01 by the Wilcoxon rank sum test). ***Overall, these data suggest that IMA950 is a better vaccine formulation than one we used previously, and can be both therapeutic and prophylactic by both targeting existing LGG cells and preventing the recurrence of glioma***. Furthermore, and perhaps most importantly, we found that at least 6 of 9 IMA950 antigens are overexpressed (relative to normal brain) in both primary WHO grade II LGGs and recurrent gliomas, including HGGs (not shown) providing us with a strong rationale to use IMA950 antigens in our proposed study.

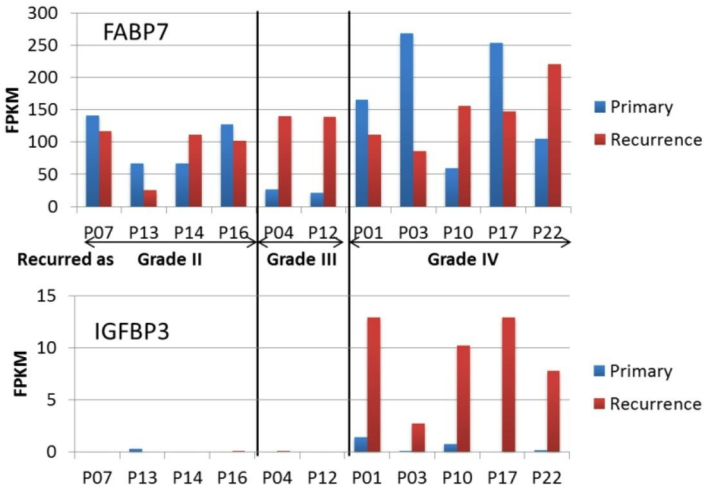


Figure 2. Expression of vaccine-targetable GAAs in paired primary and recurrent gliomas. Patients (n=11) with initial pathological diagnosis of WHO Grade II glioma with *TP53* mutation and intact 1p19q (Primary; blue bars) recurred with Grade II (P07, P13, P14 and P16), Grade III (P04 and P12) or Grade IV (P01, P03, P10, P17 and P22) gliomas (Recurrence; red bars). Expression of FABP7 (upper panel) and IGFBP3 (lower panel), each of which contains an HLA-A2-binding CTL epitope, was evaluated by RNA-seq. FPKM, fragments per kilobase of exon per million fragments mapped. Please note that: 1) It appears that FABP7 is expressed at higher levels in primary tumors that recurred as Grade IV compared with other cases that recurred as Grade II or III (p=0.24 by the Wilcoxon rank sum test);

2.6 Varlilumab (CDX-1127) – Monoclonal Antibody Targeting CD27

Varlilumab (CDX-1127) is a fully human monoclonal antibody (mAb) against CD27, which belongs to the tumor necrosis factor α receptor superfamily (TNFRSF) and has overlapping activity with other TNFRSF members including CD40, 4–1BB (CD137), and OX-40.[68] Like CD40, CD27 can be effectively manipulated with activating antibodies to induce potent anti-tumor responses, and may result in less toxicities due to its restricted expression and regulation. CDX-1127 is an agonist anti-CD27 mAb that has been shown to activate human T cells in the context of T cell receptor stimulation. In pre-clinical models, CDX-1127 has been shown to mediate anti-tumor effects[68-70] and may be particularly effective in combination with other immunotherapies. For instance, poly-ICLC synergizes with CDX-1127 in enhancing peptide vaccine-induced T-cell immune response in mice (**Figure 3**).

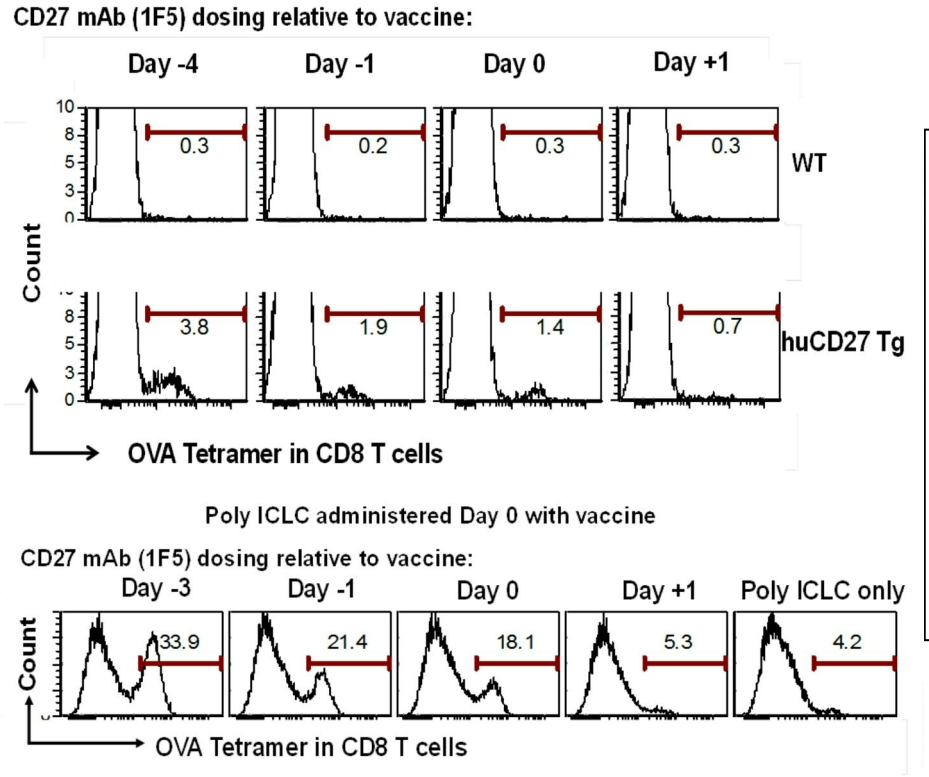


Figure 3. Administration of anti-CD27 mAb Prior to Peptide-Vaccine in the Absence or Presence of TLR Agonist poly-ICLC. huCD27-Tg mice were intraperitoneally injected with anti-CD27 mAb (50mg) on various days related to subcutaneous injection of vaccine (anti-OVA, 5 mg) plus or minus TLR agonist Poly ICLC (20 mg) on day 0. Spleens were collected on day 7 and assessed by tetramer staining. These results show that the enhanced antigen-specific CD8 T cell activation is dependent on the timing of anti-CD27 antibody

Using purified T cells from healthy subjects, concomitant signaling through the T-cell receptor (TCR) for antigen is required for CDX-1127 drug activity.[68] Since the vast majority of lymphocytes will not be receiving TCR signaling, widespread activation of T cells should not be seen. Importantly, when T cells are activated through TCR stimulation and CDX-1127, they undergo multiple cell divisions, secrete cytokines with a dominant proinflammatory signature (IFN-γ, IL-2 and TNFα), and express activation markers consistent with an activated phenotype. Gene expression microarray analysis revealed modulation of intracellular signaling, protein kinases, growth and cytokine-chemokine pathways. These data provide us with a strong basis to combine CDX-1127 with HLA-binding peptide-based vaccines that are aimed at stimulation of antigen-specific T-cells through TCR stimulation.

Ongoing Clinical Trial in Solid Tumors and Hematologic Malignancies.

CDX-1127 is currently in Phase 1 development for the treatment of both solid tumors and hematologic malignancies. The study is evaluating the safety, pharmacokinetics, immune response and anti-tumor activity of i.v. weekly administration with escalating doses (range 0.1 mg/kg – 10 mg/kg,) of CDX-1127 in patients with solid tumors that are more likely to be responsive to the immune system and B-cell hematologic malignancies known to express CD27.

In both the solid tumor and hematologic dose-escalations, (n=25 and 24, respectively), the pre-specified maximum dose level (10 mg/kg) was reached without identification of an MTD. In consideration of immunological activity observed in the dose escalation groups, the 3 mg/kg dose level was selected for further evaluation in the initial expansion cohorts. Thirty-one patients have been treated in solid tumor-specific expansion cohorts (16 melanoma and 15 RCC) at the 3 mg/kg dose level. Varlilumab has been well tolerated. Treatment-related events that were reported in ≥5% patients have been fatigue (27%), nausea (13%), decreased appetite (10%), headache (9%), rash maculo-papular (9%), diarrhea (7%), vomiting (7%), oedema peripheral, pyrexia and pruritus (all at 5%). Three Grade 3 treatment-related events have occurred: hyponatremia, decreased appetite and decreased lymphocyte count, all in the solid tumor dose-escalation cohort. A patient treated with Varlilumab at 1 mg/kg experienced the DLT of Grade 3 hyponatremia, which resolved after three weeks without treatment. There was one grade 4 treatment-related event of asthma in the solid tumor RCC expansion cohort. A 62 year old male renal cell carcinoma patient treated with Varlilumab at 3 mg/kg presented with the potentially treatment-related SAEs of “Bronchospasm” and “asthma”. The patient had lung metastases and asthma, with a history of hospitalization for asthma and seasonal exacerbations of asthma, including worsening of symptoms in the late summer. The event responded to treatment with bronchodilators and corticosteroids in the ER and did not require hospitalization. The patient subsequently discontinued study treatment due to progression of disease. Two months after the last dose of varlilumab, the patient was hospitalized for grade 4 asthma requiring intubation, but recovered with medical treatment. Another treatment-related SAE occurred in a RCC patient who developed a grade 2 infusion reaction 1hr after the 1st varlilumab infusion (3 mg/kg). The event responded to medical management in the ER and the patient went on to get additional varlilumab infusions with pre-medication without further infusion reactions.

Overall, varlilumab at 3 mg/kg was very well tolerated and demonstrated clear biologic activity in advanced, treatment-refractory patient populations, which continue to support the rationale for combination studies with other immune activating therapies.

2.7 Previous use of Poly-ICLC (Hiltonol) in glioma patients

Multicenter glioma clinical trials using poly-ICLC as monotherapy

In a recent multi-center study of glioblastoma patients[71], 21 of the 24 subjects (88%) receiving 20 µg/kg poly-ICLC alone intramuscularly (i.m.) three times weekly reported at least one adverse event. The incidence of adverse events was reported by the worst grade for an event for an individual subject. The majority of adverse events were classified as either grade 1 (71 of 104 or 68%) or grade 2 (28 of 104 or 27%) toxicity. There were only 3 of 104 (3%) and 2 of 104 (2%) events reported as a grade 3 or grade 4 event, respectively. The most frequently reported events (toxicities) were fatigue (15 subjects), local ‘pain-

other' (10 subjects), and myalgia (9 subjects). Only 57 out of 380 events were definitely or probably ascribed to poly-ICLC. [71]

In a separate trial of patients with multiply-recurrent anaplastic glioma receiving the same dose i.m. [72], all 24 subjects treated (100%) reported at least one adverse event. The majority of adverse events reported were classified as either grade 1 (41 of 63 or 65%) or grade 2 (14 of 63 or 22%). Of the 63 events, were 7 (11%) were grade 3 and only 1 (2%) was grade 4. The most frequently reported adverse events were fatigue (9 subjects), transient increases in SGOT, SGPT and alkaline phosphatase (4 subjects each) and pain, type not specified (4 subjects). Only 19 out of 406 events were definitely or probably ascribed to poly-ICLC.[72]

Subcutaneous poly-ICLC in normal volunteers

In a trial of a single dose of 1.6 mg subcutaneous (s.c.) poly-ICLC in normal volunteers, no treatment-related, grade 4, or serious adverse events were reported. Nonetheless, volunteers receiving poly-ICLC developed erythema and induration at the site of injection. Systemic reactions included transient flu-like symptoms, such as malaise, headache, fever, and chills, which were generally mild to moderate in severity. In addition, there were no clinically significant changes in complete blood cell counts and serum chemistries, including liver function tests, 3 and 7 days after poly-ICLC administration.[73]

UPCI 07-057 and 08-135 Pilot vaccine studies[74]

We recently completed a bi-institutional pilot study of s.c. vaccinations with synthetic peptides for GAA epitopes and the tetanus toxoid peptide emulsified in Montanide-ISA-51 every 3 weeks for 8 courses, and i.m. administration of poly-ICLC in human leukocyte antigen (HLA)-$A2^+$ patients with: newly diagnosed high-risk LGG without prior RT (UPCI 07-057: Cohort 1); newly diagnosed high-risk LGG with prior RT (UPCI 07-057: Cohort 2); and recurrent LGG (UPCI 08-135). Primary endpoints were safety and $CD8^+$ T-cell responses against vaccine-targeted GAAs, assessed by Enzyme-Linked Immuno-SPOT (ELISPOT) assays. Treatment response was evaluated clinically and by MR imaging. Targeted GAAs were EphA2, IL-13Rα2, survivin, and WT1.

In the UPCI 07-057 study, high-risk subsets of these LGG patients are defined as astrocytoma or oligoastrocytoma histology plus any one of the following conditions: 1) age ≥40 with any extent resection; 2) age 18-39 with incomplete resection; or 3) age 18-39 with neurosurgeon-defined gross total resection with tumor size ≥ 4 cm in diameter. We enrolled 13, 1 and 10 patients in UPCI 07-057 Cohorts 1, 2 and UPCI 08-135, respectively. No dose-limiting non-CNS toxicities have been encountered except for one case with Grade 3 fever (UPCI 07-057: Cohort 1). ELISPOT assays demonstrated robust IFN-γ responses against at least 3 of the 4 GAA epitopes in 10 and 4 cases of Cohorts 1 and 3, respectively. Cohort 1 patients demonstrated significantly higher IFN-γ responses than Cohort 3 patients.

Median progression-free survival (PFS) periods since the 1st vaccine was 17 months in Cohort 1 (range 10-47+) and 12 months in Cohort 3 (range 3-41+). Only one patient with a large astrocytoma in Cohort 2 has been progression-free for over 67 months. Although further follow-up is required to mature PFS data, our results demonstrate that the regimen in these patients is well tolerated, and induces robust type-1 anti-GAA T-cell responses. These data also suggest that patients with LGG are suitable for vaccine therapy.

2.8 Rationale

This is a pilot pre-surgical vaccine study in HLA-A2$^+$ adults with WHO grade II glioma, for which surgical resection of the tumor is clinically indicated. Co-primary objectives are to determine: 1) the safety of the novel combination of s.c. administered IMA950 and poly-ICLC and i.v. varlilumab in the neoajduvant approach; and 2) whether addition of i.v. varlilumab increases the response rate and magnitude of CD4$^+$ and CD8$^+$ T-cell responses against the IMA950 peptides in post-vaccine PBMC samples obtained from participating patients.

Although cancer immunotherapy has shown some promise, objective response rates in patients receiving cancer vaccines are still low, and the ultimate success of cancer vaccines appears to rely upon novel combinational strategies, such as ones with potent agonists for co-stimulatory pathways or antagonists against immune-checkpoint pathways. As discussed in Section 2, the novel agonistic anti-CD27 mAb varlilumab strongly synergizes with poly-ICLC to enhance antigen-specific T-cell responses against vaccines in mouse models. As tolerability and immunological activity of varlilumab at 3 mg/kg have been demonstrated in phase I single agent clinical studies, now it is time to evaluate whether the addition of varlilumab enhances the vaccine activity in human patients. To address this question, adult patients with WHO grade II glioma are most suitable for two main reasons: 1) these patients are highly responsive to peptide-vaccines based on our recent clinical study (Section 2); and 2) these patients are with slow-growing but lethal tumors without effective treatment; and thus there is a strong need to develop effective and safe treatment modalities. Hence, we will evaluate our hypothesis that addition of varlilumab will enhance induction of effector T-cell response against antigens in IMA950 vaccine in these patients.

To date, evaluation of vaccine effects in the human glioma tumor-microenvironment (TME) has been conducted in patients who receive the vaccine and subsequently develop recurrent tumors that need to be surgically resected. This is not ideal for evaluation of vaccine effects because of: 1) the inconsistency in the timing of sampling among the patients; and 2) the fact that such a patient's tumor has already acquired resistance against the immunological intervention, making it not possible to evaluate the positive impacts of the intervention (e.g. infiltration of vaccine-induced T-cells). In fact, the TME of most successful patients with sustained positive clinical response (partial or complete response) or stable disease will never be evaluated unless we implement prospective studies to evaluate the tumors following the study interventions. Therefore, we plan a novel pre-surgical evaluation of the vaccine regimen using IMA950 and poly-ICLC with or without varlilumab.

The current study employs IMA950 because we found that at least 6 of 9 IMA950 antigens are overexpressed (relative to normal brain) in both primary WHO grade II LGGs and recurrent gliomas, including HGGs (**Figure 2**). These data suggest that IMA950 vaccines may provide both therapeutic and prophylactic immunities by targeting both existing LGG cells and recurrent HGG cells, respectively. Furthermore, previous vaccine studies using IMA950 have shown preliminary but promising immune responses in GBM patients as discussed earlier in Section 2. With regard to the dose level, 5 mg total peptides/dose was well tolerated and immunologically active (Section 2), and thus has been selected for the current study. [75,76]

Poly-ICLC has a potent CXCL10-inducing effects in both mouse[66] and human gliomas[67] (Section 2.4), LGG patients demonstrate strong response and safety profile in vaccines including poly-ICLC (UPCI 07-057 and 08-135). Furthermore, GBM patients receiving vaccines made of IMA950 and poly-ICLC as a mixture have demonstrated promising immune responses (Section 2; CER-12-213; immatics code IMA950-104). Hence, we have chosen to use poly-ICLC in the current study. The proposed dose (1.4 mg/dose) is based on tolerability and immunological activities observed in UCPI 07-057 and 08-135 studies.[74] These provide us with a strong basis to select the combination of IMA950 and poly-ICLC in the current study.

Varlilumab enhances induction of antigen specific T-cell responses especially in combination with poly-ICLC. The effect of varlilumab requires T-cells to be engaged with major histocompatibility complex (MHC)-peptide complex, indicating that varlilumab would selectively activate vaccine-stimulated T-cells but not other T-cells.

With regard to the period and the number of vaccines for pre-surgical arm, our design is based on our preclinical studies showing CXCL10 induction and TIL enhancement following 3 cycles of vaccine and poly-ICLC administration spanning 20 days (Figure 1 in Section 2.4). The number of total vaccines and cycle intervals, as well as poly-ICLC dose are based on safety and immune-response data from the LGG vaccine studies UPCI 07-057/08-135 (peptide plus poly-ICLC). The proposed dose of varlilumab is based on phase I studies as summarized in Section 2.6.

3 Patient Selection

3.1 Inclusion Criteria

3.1.1 Patients must be ≥ 18 years old

3.1.2 Pathological criteria - Patients must have a newly diagnosed or recurrent WHO grade II astrocytoma, oligoastrocytoma or oligodendriglioma that has been histologically confirmed by prior biopsy or surgical resection. If the pathological diagnosis was made outside of UCSF, the pathology must be reviewed and confirmed at UCSF.

3.1.3 Patients must be positive for HLA-A2 based on flow-cytometry or genotyping.

3.1.4 Before enrollment, patients must show non-enhancing T2-FLAIR lesions that are amenable to surgical resection. Surgical resection of at least 0.3 grams of tumor is expected to ensure adequate evaluation of the study endpoints.

3.1.5 Prior radiation therapy (RT) after initial diagnosis will be allowed but there must be at least 6 months from the completion of RT (or radiosurgery). Prior chemotherapy and any systemic molecularly targeted anti-tumor therapy will be allowed, and there must be at least 28 days from the last temodar chemotherapy, 42 days for nitrosourea; at least 14 days from the last dose for chemotherapy regimens given continuously or on a weekly basis with limited potential for delayed toxicity.

3.1.6 Karnofsky performance status (KPS) ≥ 70% (Appendix I)

3.1.7 Off or low dose (≤ 4 mg/day by Decadron) corticosteroid for at least for 2 weeks before the first pre-surgical vaccine

3.1.8 Adequate organ function within 28 days of study registration including:
Adequate bone marrow reserve: absolute neutrophil (segmented and bands) count (ANC) ≥1.0 x 10^9/L, absolute lymphocyte count (ANC) ≥4.0 x 10^8/L, platelets ≥100 x 10^9/L; hemoglobin ≥ 8 g/dL

Hepatic: Total bilirubin ≤ 1.5 x upper limit of normal (ULN) for age and SGPT (ALT) ≤ 2.5 x upper limit of normal (ULN) for age

Renal: Normal serum creatinine or creatinine clearance ≥60 ml/min/1.73 m^2

3.1.9 Must be free of systemic infection. Subjects with active infections (whether or not they require antibiotic therapy) may be eligible after complete resolution of the infection. Subjects on antibiotic therapy must be off antibiotics for at least 7 days before beginning treatment.

3.1.10 Women of child-bearing potential and men must agree to use adequate contraception (ex. Hormonal or barrier method of birth control or abstinence) prior to study entry and for the duration of study participation (until one month after the last vaccine) since the effects of the current regimen on the developing human fetus are unknown. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately.

3.1.11 Patient must sign an informed consent document indicating that they are aware of the investigational nature of this study, which includes an authorization for the release of their protected health information

3.2 Exclusion Criteria

3.2.1 Presence of gliomatosis cerebri, cranial or spinal leptomeningeal metastatic disease

3.2.2 Presence of T1 Gadolinium (Gd) –enhancing lesions (on MRI) suggestive of high-grade glioma

3.2.3 Pathological diagnosis for the resected tumor demonstrates transformation to higher grade (i.e. WHO grade III or IV) gliomas. If a patient is diagnosed as HGG upon resection after receiving the pre-surgical treatment, the patient will be withdrawn from the study and considered for therapeutic options for HGG (trials for HGG or standard of care). The tumor tissue of such a case would be brought to the lab before the pathological diagnosis is made; and thus would be processed before the lab is informed of the final HGG diagnosis. Because HGG tissue may still reflect the

vaccine effects, we will evaluate the tumor tissue to help us develop future approaches for HGG.[75,76]

3.2.4 Pregnant women are excluded from this study because IMA950 and poly-ICLC are drugs with the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with IMA950 plus poly-ICLC (IMA950-poly-ICLC hereafter) vaccine, breastfeeding should be discontinued if the mother is treated with IMA950-poly-ICLC vaccine.

3.2.5 Uncontrolled intercurrent illness including, but not limited to ongoing or active infection (including active/chronic hepatitis B and C), symptomatic congestive heart failure, unstable angina pectoris, or psychiatric illness/social situations that would limit compliance with study requirements

3.2.6 History or current status of immune system abnormalities such as hyperimmunity (e.g., autoimmune diseases) that needed to be treated by systemic therapy, such as immuno-suppressants and hypoimmunity (e.g., myelodysplatic disorders, marrow failures, AIDS, transplant immunosuppression).

3.2.7 Any isolated laboratory abnormality suggestive of a serious autoimmune disease (e.g. hypothyroidism): Antinuclear antibody, thyroid-stimulating hormone (TSH), free thyroxine (FT4), rheumatoid factor

3.2.8 Any condition that could potentially alter immune function (AIDS, multiple sclerosis, diabetes, renal failure)

3.2.9 Ongoing treatment with immunosuppressive drugs or dexamethasone > 4mg

3.2.10 Use of any of the following concurrent treatment or medications:

- radiation therapy
- chemotherapy
- interferon (e.g. Intron-A®)
- allergy desensitization injections
- growth factors (e.g. Procrit®, Aranesp®, Neulasta®)
- Interleukins (e.g. Proleukin®)
- any investigational therapeutic medication

3.2.11 Prior cancer diagnosis except the following:

- squamous cell cancer of the skin without known metastasis
- basal cell cancer of the skin without known metastasis
- carcinoma in situ of the breast (DCIS or LCIS)
- carcinoma in situ of the cervix

3.2.12 Any other acute or chronic medical or psychiatric condition or laboratory abnormality that could increase the risk associated with trial participation or trial drug administration or could interfere with the interpretation of trial results and, in the judgment of the investigator, would make the patient inappropriate for entry into the trial.

3.2.13 Participants with known addiction to any drugs

3.3 Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this trial.

4 Enrollment Plan/ Patient Registration and Randomization

4.1 Registration and Randomization

Eligible patients will be entered on study at UCSF by the Study Coordinators. All patients who sign the informed consent document will be registered in OnCore and the Brain Tumor Research Center Tissue Bank database.

Arm 1: Patients will receive IMA950- poly-ICLC vaccine plus varlilumab. **Arm 2**: Patients will receive IMA950- poly-ICLC vaccine alone.

The study is designed with a staggered safety lead-in with the first 3 patients assigned to Arm 2. The first 3 patients of the study will be enrolled in Arm 2 in a staggered manner as follows. After the first patient of the study is enrolled in Arm 2, Patient number 2 and 3 will not be enrolled until the previous patient receives 4 pre-surgery vaccines and recover from clinically indicated surgery for at least 6 weeks after surgery without a regimen-limiting toxicity (RLT) to confirm the safety of IMA950-poly-ICLC vaccine.

If any of the first 3 patients on Arm 2 shows a RLT (see definition in section 5.3), an additional 3 patients (patients 4, 5 and 6) will be enrolled in the same, staggered manner in Arm 2 while Arm 1 enrollment is held. If 2 or more of the patients on Arm 2 show a RLT, the arm will be considered intolerable and the study will be closed. If only one total of the 6 patients shows an RLT in Arm 2, the randomized design will be cancelled and the study will proceed with Arm 2 only to primarily evaluate the safety of the Arm 2 regimen. When the study is completed with the total evaluable 15 patients in Arm 2, we will review the safety data, and discuss with the FDA and IRB regarding the extension of the study to Arm 1.

If none of the first 3 patients treated on Arm 2 demonstrates a RLT, then 3 further patients will be enrolled in Arm 1 (with varlilumab) in the same staggered manner (subsequent patients will not be enrolled until the respective previous patient receives 4 pre-surgery vaccines and recover from clinically indicated surgery for at least 6 weeks after surgery without an RLT to confirm the safety of IMA950-poly-ICLC-varli treatment. If one of first 3 patients on Arm 1 shows a **Regimen Limiting Toxicity** an additional 3 patients will be enrolled in the same, staggered manner in Arm 1. If 2 or more of the patients on Arm 1 show a RLT, the arm will be considered intolerable.

If Arm 2 is tolerable but Arm 1 is not, then, the study will be carried out with Arm 2 only.

If both arms are found tolerable, then subsequent patients will then be randomized into one of the two arms for the pre-surgical part of the study. **Arm 1**: Patients will receive IMA950-poly-ICLC vaccine plus varlilumab. **Arm 2**: Patients will receive IMA950-poly-ICLC vaccine alone. The randomization will take place in a 1:1 ratio between the two arms with the stratification based on whether the patient is newly diagnosed vs. recurrent.

Patients will be assigned to treatment by means of the UCSF Biostatistics Facility randomization system in an open label fashion. Information on the two arms will be loaded into the database and the treatment arm assigned to the subjects when the subject's initials and ID# are entered into the program. Results of randomization will not be blinded, and no placebo will be used.

4.2 Patients Who Are Registered and Do Not Receive Study Treatment

If a patient is registered to the study and is later found not able to begin study treatment, for whatever reason, the patient will be removed from study and treated at the physician's discretion. Such a patient will be replaced to complete the enrollment. If a patient receives any study therapy and then is discontinued for whatever reason, study staff will update the database for the patient's non-treatment status. Study data will be collected until the time the patient is taken off study. The reason for removal from study will be clearly indicated in the data base. The removed patient must be followed according to Section 5.2.8.

4.3 Replacement

Patients who receive at least 4 post-surgery vaccines will not be replaced because their PBMC on week 13 would allow for the primary endpoint evaluation. Subjects who are considered non-evaluable for the immunological endpoint will be replaced but still evaluated for the primary endpoint of safety and the secondary endpoint of efficacy. Evaluable patients for the immunological primary endpoint are study-eligible patients who receive at least four post-surgery vaccines. If the pathological diagnosis upon the resected tissue indicates WHO III or IV grade tumors, those patients will be ineligible for post-surgery courses and replaced.

5 Treatment Plan

5.1 Drug Information

5.1.1 IMA950

The drug product IMA950 comprises a mixture of 12 individual drug substances (peptides). IMA950 also contains Mannitol and Poloxamer 188 (Lutrol F68) as excipients in the formulation. Eleven of these peptides are TUMAPs derived from target proteins relevant in GBM. They include 9 HLA-A*02 class I binding peptides with the capacity to activate CTLs, one elongated class I-binding peptide, and one HLA class II-binding peptide with the capacity to activate helper T cells. In addition, IMA950 contains one HLA class I-binding

marker peptide from Hepatitis B virus core antigen with known immunogenicity. The lyophilisate, including peptides and excipients, is a white powder.

Storage conditions

IMA950 lyophilized powder for solution for injection should be stored at -20°C.

Shipment conditions

IMA950 lyophilized powder for solution for injection should be shipped at a temperature below -15°C. Upon receipt at clinical sites, IMA950 should be stored at -20°C.

Temperature excursions during transport, shipment and storage

Based on the good stability data at -20°C, +5°C, +25°C and +40°C it is justified to accept short term temperature excursions during transport, shipment and storage of IMA950 at clinical sites up to +25°C for a maximum of up 72 hours. It is not expected that a temperature excursion as defined above will have any influence on the quality of IMA950.

5.1.2 Poly-ICLC (Hiltonol)

Poly-ICLC is classified as an investigational new drug. It is a synthetic complex of polyinosinic and polycytidylic acid, stabilized with polylysine and carboxymethyl cellulose. The thermal denaturation point is 89.5ºC, about 40ºC above that of plain polyI.polyC; the resistance to hydrolysis is several times that of the parent compound, and it induces peak levels of about 1000-2000 IU of interferon-α per mL of serum in monkeys given 1 mg/kg intravenously.

Availability of Poly-ICLC

Poly-ICLC is available from Oncovir, Inc.

Contact: [redacted]

Storage & Stability of Poly-ICLC

Poly-ICLC is supplied in vials each containing 1cc of translucent solution with a concentration of 2 mg per cc. It is stable at room temperature for several days, but is better stored refrigerated at about 40ºF (not frozen).

5.1.3 Varlilumab

Description, Packaging and Labeling

Detailed technical information regarding varlilumab can be found in the Investigator's Brochure. Varlilumab is a recombinant, fully human mAb of the IgG1κ isotype that specifically binds human CD27.

Varlilumab Drug Product is formulated as a clear, colorless, sterile solution intended for single-use parenteral administration. Varlilumab is provided in vials containing a nominal volume of 10.0 ml of a buffered solution composed of 5.0 mg/mL varlilumab protein, Sodium Phosphate, Potassium Phosphate, Potassium Chloride, Sodium Chloride, and Polysorbate 80 with a pH of 7.0.

Varlilumab will be labeled according to the requirements of local law and legislation. A copy of label text will be made available to study sites upon request.

Storage and Handling for Varlilumab

Varlilumab drug product is shipped in insulated shippers and must be stored at 2 - 8°C (36 - 46°F) until use. A temperature log must be kept to document the refrigerator temperature. If the temperature is not maintained, Celldex should be contacted.

Varlilumab should be protected from light. However, sufficient light protection is provided by the secondary container (carton); no specific light protection is needed during preparation of the dosing solution and infusion.

Varlilumab is not formulated with a preservative. Therefore, once the sterile vials are entered (i.e., once varlilumab is drawn into a syringe), the drug should be used as soon as possible (typically within 3 hours if kept at room temperature or within 6 hours if refrigerated; or in accordance with any applicable institutional guidance).

Additional guidance regarding storage and handling of varlilumab will be provided within a pharmacy manual provided by Celldex.

5.2 Drug Preparation

Vaccine Preparation

Only qualified personnel who are familiar with procedures that minimize undue exposure to them and to the environment should undertake the preparation, handling, and safe disposal of biotherapeutic agents. Designated members of the pharmacy staff (pharmacist and technicians) with appropriate training and experience will be designated as the study pharmacists and will prepare the vaccine. The pharmacists will be responsible for preparing the study medication for each patient. The pharmacist who is on duty on the day of the vaccine administration will be required to complete a Dosage Preparation Record to document the preparation process for each vaccine dose.

On the day of the scheduled vaccine, following the confirmation of clinical and lab data, one IMA950 vial [containing 578 µg of each individual peptide (6.94 mg in total)] will be withdrawn from the freezer, dissolved in a total volume of 700 µL of 4.2% sodium hydrogen carbonate solution containing EDTA (0.0025% w/v). One poly-ICLC vial (containing 2 mg drug in 1 ml) will be removed from the refrigerator and placed on the refrigerated cold pack. Both will be kept on ice prior to the mixing procedure described below. Before use, each vial should be gently swirled to ensure uniform mixing of the contents. Avoid excessive or vigorous agitation; do not shake.

Aseptic technique should be employed in the preparation of all study to prepare the mixture of IMA950 and poly-ICLC. Using a 3 ml syringe with a 21G needle, the pharmacist will first withdraw 0.7 ml (1.4 mg) poly-ICLC solution from the vial. Then, using the same syringe and needle, the pharmacist will withdraw 0.5 ml reconstituted IMA950 solution (out of total 0.7 ml in the vial). The pharmacist will then aspirate an additional 0.1 ml of air (approximate) from the empty part of the IMA950 vial. The pharmacist will then gently mix the solution in the syringe by gentle swirling and slow, repeated inversion of the syringe. Do not shake. The pharmacist will then pull back on the plunger to clear any vaccine mixture from the needle, remove the needle, expel any air from the syringe and affix with a plastic luer cap to the syringe. At this point, there should be 1.2 ml solution of mixed IMA950 and poly-ICLC in the 3 ml syringe. The prepared syringe should be labeled and then placed on a refrigerated cool-pack for transport and storage until administration. The vaccine should be administered within 2 hours following the completion of the mixing procedure.

Varlilumab Preparation

Varlilumab (CDX-1127) is formulated as a clear, colorless sterile solution intended for single-use parenteral administration. Each vial contains a nominal 5.0 mg/mL Varlilumab (CDX-1127) protein in a 10.0 mL volume of buffered solution composed of Sodium Phosphate, Potassium Phosphate, Potassium Chloride, Sodium Chloride, and Polysorbate 80 with a pH of 7.0. The varlilumab dose to be administered will be diluted to a final volume of 90 ml for infusion, according to the instructions provided by Celldex in the pharmacy manual. No dilution is necessary in cases where the drug volume is greater than 90 ml.

5.3 Drug Administration

Drugs included in the current regimen are: 1) IMA950, 2) Hiltonol (poly-ICLC), and 3) varlilumab (CDX-1127). Dose vials for each of these drugs will be made under GMP conditions for administration. Refer to the IND's CMC for additional production information (The IND # TBN Hideho Okada, MD, PhD). IMA950 and poly-ICLC will be administered as one formulation containing 4.96 mg total IMA950 peptides and 1.4 mg poly-ICLC subcutaneously (s.c.) at sub-inguinal sites (IMA950-poly-ICLC vaccine). CDX-1127 will be administered intravenously (i.v.) at 3 mg/kg. Each dose must be administered at the

clinical trial site by appropriately trained staff. The rationale for doses, schedule and the selected combination are discussed in the background and rationale section (Section 2).

Each dose of vaccine must be administered at the clinical trial site by appropriately trained staff. It will be administered as one formulation containing IMA950 [413 µg of each peptide per injected dose (4.96 mg in total)] and 1.4 mg poly-ICLC subcutaneously (S.C.) at sub inguinal sites.

It is recommended that the injections be given approximately 10 cm below the inguinal ligament, within an appropriately sterilized area of 3-5 cm in diameter located over the femoral artery, on the right thigh for all injections unless an induration from the previous vaccine prevents the injection on the same site. In this case, the injection site will be altered to the corresponding area on the left thigh. The date and time of the reaction will be documented on the Vaccination Toxicity Assessment Form and patients will be called 48 ± 6 hours after injection to assess for local reaction.

Vaccine injections should not be given to areas of skin with dermatologic conditions (such as persistent injection site reactions, infection, edema, or scarring) that will not allow easy access for study drug administration or evaluation of localized adverse events. If such conditions or other circumstances contraindicate injections as outlined above for an individual patient, alternate sites can be used, but this should be discussed with the primary investigator.

Following each administration of vaccine, patients must remain in clinic for observation one hour to evaluate and treat any potential immediate hypersensitivity reactions.

Varlilumab (CDX-1127) should be administered as an IV. infusion (3 mg/kg) immediately following the SC. vaccine administration. Varlilumab should be administered as a 90-minute infusion using a volumetric pump with a 0.2 micron pore size, low-protein binding polyethersulfone (PES) membrane in-line filter. The infusion should be followed by a saline flush to clear the line. Varlilumab should not be administered as a bolus injection.

Following each administration, patients must remain in clinic for observation one hour to evaluate and treat any potential immediate hypersensitivity reactions.

Patients will be called 48 ± 6 hours after injection to assess for local reaction (see **Section 5.5.7** and **Appendix II**).

5.4 Screening

The screening procedures and assessments must be completed within 28 days or less of registration unless otherwise noted

- Informed consent
- Demographics
- Physical/neurological examination

- Vital signs
- Complete medical history
- KPS
- Review of concurrent medications
- MRI with and without contrast
- ECG
- UCSF pathology review for confirmation of WHO grade 2 glioma
- Complete blood count (CBC) with differential and platelet count
- Blood chemistry assessment, including:
    - Alkaline phosphatase, aspartate aminotransferase/alanine aminotransferase (ALT/AST), total bilirubin, calcium, blood urea nitrogen (BUN), creatinine, total protein, albumin, random glucose, potassium, sodium, chloride, bicarbonate
- Laboratory autoimmune assessment
    - Antinuclear antibody, thyroid-stimulating hormone (TSH), free thyroxine (FT4), rheumatoid factor
- Serum or urine pregnancy within 7 days prior to registration
- HBsAg, HBsAb and HBcAb for screening of active or chronic hepatitis B and C
- Urine analysis
- HLA typing prior to registration (must be positive for HLA-A2 based on flow-cytometry or genotyping) **HLA typing can be done at any time prior to registration; 28 days or less of registration does not apply.*

5.5 Treatment Period

5.5.1 Study Procedures: Days -23 ± 2; Days -16 ± 2; Days -9 ± 2; Days -2 ± 2

- Physical/neurological examination
- Vital signs – pre-treatment and one hour post-treatment
- Interval medical history
- KPS
- Review of concurrent medications
- Adverse event assessment
- Complete blood count (CBC) with differential and platelet count
- Blood chemistry assessment, including:
    - Alkaline phosphatase, aspartate aminotransferase/alanine aminotransferase (ALT/AST), total bilirubin, calcium, blood urea nitrogen (BUN), creatinine, total protein, albumin, random glucose, potassium, sodium, chloride, bicarbonate
- Vaccination with IMA-950 plus poly-ICLC (one formulation)
- **Varlilumab (Arm 1 patients only) on Day -23 ± 2**

- **Collection of 8 x 10cc green top tubes and 1 x 5cc red top tubes for research blood samples on Day -23 ± 2**
- **(Arm 1 patients only) on the day of Varlilumab infusion (Day-23 ± 2), PK samples (1 x 10 cc red top tube/draw) should be drawn from the arm contralateral to the infusion site prior to administration and at 30 minutes (±5 minutes) after the end of the varlilumab infusion. An additional sample should be drawn as soon as possible for any patients who experience an infusion reaction.**
- Assessment of vaccine injection site 48±6 hours post-injection which can be done either by phone or in person. Following Day -2 administration, the follow-up assessment will be on the day of surgery. The PI or a clinical co-investigator should visit the patient in the ward and make the assessments.

5.5.2 Study Procedures, Day 0 (Surgical date)

- Pre-operative MRI per institutional standard of care (with a window of -2 days)
- Intraoperative collection of ≥ 0.5 grams of tumor tissue, snap frozen
- Intraoperative collection of 8 x 10cc green top tubes and 1 x 5cc red top tubes for research blood samples

5.5.3 Study Procedure, Post-Op, within 14 ± 2 days of surgery

- Post-operative MRI
- Final pathology confirmation of WHO grade 2 glioma
- Review of expected date off of dexamethasone
- Vital signs
- Interval medical history
- KPS
- Review of concurrent medications
- Adverse event assessment
- Complete blood count (CBC) with differential and platelet count
- Blood chemistry assessment, including:
- Alkaline phosphatase, aspartate aminotransferase/alanine aminotransferase (ALT/AST), total bilirubin, calcium, blood urea nitrogen (BUN), creatinine, total protein, albumin, random glucose, potassium, sodium, chloride, bicarbonate

5.5.4 Study Procedures Week A1 (≥ 2 weeks after post-op steroids are tapered off and ≤ 10 weeks post-operatively)

These procedures must be completed **≤** 7 days to A1, unless otherwise noted.

- Patient should meet all prior eligibility criteria
- Physical/neurological examination
- Vital signs (pre-treatment and one hour post-treatment)
- Interval medical history

- KPS
- Review of concurrent medications
- Adverse event assessment
- Vaccination with IMA-950 plus poly-ICLC (one formulation)
- Varlilumab infusion **(Arm 1 patients only)**
- Complete blood count (CBC) with differential and platelet count
- Blood chemistry assessment, including: Alkaline phosphatase, aspartate aminotransferase/alanine aminotransferase (ALT/AST), total bilirubin, calcium, blood urea nitrogen (BUN), creatinine, total protein, albumin, random glucose, potassium, sodium, chloride, bicarbonate
- Collection of 8 x 10cc green top tubes and 1 x 5cc red top tubes for research blood samples
- **(Arm 1 patients only), PK samples (1 x 10 cc red top tube/draw) should be drawn from the arm contralateral to the infusion site prior to administration and at 30 minutes (±5 minutes) after the end of the varlilumab infusion. An additional sample should be drawn as soon as possible for any patients who experience an infusion reaction.**
- Assessment of vaccine injection site 48±6 hours post-injection which can be done either by phone or in person

5.5.5Study Procedures Week A4 - A22

These procedures must be completed every 3 weeks (± 7 days)

- Physical/neurological examination
- Vital signs (pre-treatment and one hour post-treatment)
- Interval medical history
- KPS
- Review of concurrent medications
- Adverse event assessment
- Vaccination with IMA-950 plus poly-ICLC (one formulation)
- Complete blood count (CBC) with differential and platelet count
- Blood chemistry assessment, including:
- Alkaline phosphatase, aspartate aminotransferase/alanine aminotransferase (ALT/AST), total bilirubin, calcium, blood urea nitrogen (BUN), creatinine, total protein, albumin, random glucose, potassium, sodium, chloride, bicarbonate
- **Varlilumab infusion (Arm 1 patients only) on Weeks A7, A13 and A19**
- **Collection of 8 x 10cc green top tubes and 1 x 5cc red top tubes for research blood samples on Weeks A13 and A19**
- **(Arm 1 patients only) on the day of Varlilumab infusion (Weeks A7, A13 and A19), PK samples (1 x 10 cc red top tube/draw) should be drawn from the arm contralateral to the infusion site prior to administration and at 30**

minutes (±5 minutes) after the end of the varlilumab infusion. An additional sample should be drawn as soon as possible for any patients who experience an infusion reaction.

- **MRI scan on Weeks A10**
- Assessment of vaccine injection site 48±6 hours post-injection which can be done either by phone or in person

5.5.6Study Procedures Week A25

These procedures must be completed ± 7 days

- Physical/neurological examination
- Vital signs
- Interval medical history
- KPS
- Review of concurrent medications
- Adverse event assessment
- Complete blood count (CBC) with differential and platelet count
- Blood chemistry assessment, including:
- Alkaline phosphatase, aspartate aminotransferase/alanine aminotransferase (ALT/AST), total bilirubin, calcium, blood urea nitrogen (BUN), creatinine, total protein, albumin, random glucose, potassium, sodium, chloride, bicarbonate
- Collection of 8 x 10cc green top tubes and 1 x 5cc red top tubes for research blood samples
- MRI scan
- ECG (if clinically indicated)

5.5.7 48 Hour Post-Vaccine Follow-up

Skin reactions secondary to the vaccine administration may lead to unique skin toxicity. Furthermore, the regime may cause systemic adverse events. Hence, observations for severe local and systemic reactions will be important. Patients will have follow-up at 48 ± 6 hours after each vaccine for adverse events. This may be by telephone assessment or in person.

If 48 ± 6 hours post-vaccine assessment is by telephone, the patient/parent/guardian will use the Vaccination Toxicity Assessment Form (Appendix III) to permit an accurate and consistent assessment of vaccine site reactions. Any telephone reported reactions consistent with ≥ Grade 3 should be followed by a clinic visit and appropriate management. Such a visit would ideally be with the primary research team and accomplished within 24-72 hours; however, if the patient is unable to travel to UCSF, then appropriate local referral will be facilitated (e.g., Dermatology, etc.).

Any telephone reported reactions ≤ Grade 2 should be followed by another phone call approximately 48 hours later (96 ± 6 hours post-vaccine). If telephone reported reaction at 96 ± 6 hours post-vaccine is still ≤ Grade 2 or improving, no further follow-up is necessary. However, if telephone reported reaction at 96 ± 6 hours is ≥ Grade 3 or worsening, the patient should be evaluated in person by a member of the research team. If the patient is unable to travel to UCSF, then appropriate local referral will be facilitated (e.g., Dermatology, etc.).

5.5.8 Study Procedures Post-Vaccine Follow-up

All patients, including those who discontinue protocol therapy early, will be followed for response and toxicity assessments until disease progression, start of a new therapy, or for a maximum of 24 months from study registration (whichever occurs earlier). Follow-up visits should be scheduled per standard-of-care for patients with stable WHO grade II glioma without active treatment (every 3 months). As overall survival is an endpoint of the study, subjects who discontinue protocol therapy must continue to be followed (every 3 months) for survival until death or the conclusion of the study.

For any patient with regimen limiting toxicity (RLT), follow-up will continue as medically appropriate for the specific toxicity until resolution to grade 1 or better or 3 months of no change (stabilization).

If treatment is discontinued for progression, the final study visit will be the final off-study visit, providing there is no ongoing grade 2 or greater treatment related toxicity.

- Physical/neurological examination
- Vital signs
- Interval medical history
- KPS
- Review of concurrent medications
- Adverse event assessment
- MRI scan
- Complete blood count (CBC) with differential and platelet count
- Blood chemistry assessment, including:
    - Alkaline phosphatase, aspartate aminotransferase/alanine aminotransferase (ALT/AST), total bilirubin, calcium, blood urea nitrogen (BUN), creatinine, total protein, albumin, random glucose, potassium, sodium, chloride, bicarbonate.

Serum chemistry and CBC tests are required at the first follow-up visit or when previous tests demonstrated any abnormality. If a patient does not show any abnormality during the course or at the first follow-up visit, that patient will not require CBC and chemistry on the follow-up visits per protocol.

5.6 Definition of Regimen Limiting Toxicities (RLT) and Suspension of Enrollment

5.6.1 Definition of RLT

Toxicity will be determined using the revised NCI Common Toxicity Criteria version 5.0 for Toxicity and Adverse Event Reporting (CTCAE) (http://ctep.info.nin.gov).

Management and dose modifications associated with the above adverse events are outlined in Section 5.7.

Participants will be observed for regimen limiting toxicity (RLT) throughout the study. The following are considered to be RLTs if they are judged possibly, probably or definitely associated with treatment. **Should they occur, individual participants will be taken off study and no further injections will be given.**

- Grade 2 or more any infusion reaction except for Grade 2 pain
- Grade 2 or more cytokine release syndrome
- Grade 2 or more bronchospasm or generalized uticaria (hypersensitivity)
- Grade 2 or more allergic reaction, such as exfoliative erythroderma, anaphylaxis, or vascular collapse
- Grade 2 or more autoimmune disease (e.g. hypothyroidism, autoimmune encephalitis)
- Any Grade 3 or more toxicity possibly, probably, or definitely related to the vaccine or Varlilumab with particular attention to the following events.

The following are also considered RLTs:

- Dosing delays > 6 weeks for IMA950+poly-ICLC vaccines or varlilumab (Arm 1 patients only) administration.
- Delay of the scheduled surgical resection for longer than 2 weeks possibly, probably or definitely related to toxicity of the study treatment.

The following are NOT considered RLTs:

- Grade 3 nausea, vomiting, or diarrhea that resolves to ≤ grade 1 with or without treatment within 48 hours
- Grade 3 flu-like symptoms that resolve within 24 hours with the use of acetaminophen 650-1000 mg or with any NSAID

5.6.2 Events Which Will Temporarily Halt Enrollment at Any Time:

Certain events will be considered unacceptable and a single occurrence will lead to temporary closure of enrollment while under review for attribution to study therapy (not related to surgical procedures):

- The occurrence of grade 3 or 4 toxicity, excluding local skin reaction and flu-like symptoms in 3 patients
- Toxicity requiring the use of pressors, including grade 4 vascular leak syndrome or grade 3 and 4 hypotension
- Toxicity requiring ventilation support, including grade 4 respiratory toxicity

- Severe brain or brainstem edema leading to grade 4 neurotoxicity and/or requiring significant CNS resuscitation such as Mannitol or artificial ventilation
- Patient death

5.7 Drug Administration Delay, Dose Reduction, and/or Discontinuation (Individual Patients)

5.7.1 Delay in treatment administration

Treatment will be delayed by 1 week if on the day of the planned vaccination

- Patient has a fever of > 101°F (38.3 °C)
- Treatment related side effects have not resolved to grade 1 or better (except for grade 2 lymphopenia and injection site reactions from prior IMA950+poly-ICLC vaccine).

If the continued inflammatory reactions at the injection site remain too severe in both legs to allow subsequent vaccines, the treatment will be suspended for up to 6 weeks from the originally scheduled date for the next vaccine. When the therapy is resumed after a delayed dose, subsequent schedules will be slid back to keep the original intervals. If the situation does not resolve in 6 weeks, this is considered RLT and the patient will be withdrawn from the protocol.

Vaccination will be held for any ≥ Grade 2 non-RLT AE (except grade 2 lymphopenia or flu-like symptoms), felt to be related to therapy, until they return to ≤ Grade 1.

Possible adverse events by IMA950-poly-ICLC vaccines and varlilumab are summarized in Section 5.8. In circumstances where assessment of an adverse event is limited, such as by intercurrent illness, or when laboratory studies are required to assess for other causes of toxicity, the treatment schedule may be interrupted for up to 6 weeks. Delay of one vaccine (and varlilumab if scheduled) administration by up to 6 weeks will not be considered a protocol violation if due to an adverse event, regardless of attribution. If one or more treatment cycle is delayed by longer than 6 weeks due to an adverse event, regardless of attribution, treatment must be discontinued.

In the case of hepatic enzyme elevation >4x baseline (which is Grade 2; 3-5 x ULN), or any other unforeseen intolerable side effects of grade 2 (except for flu-like symptoms) or greater but not meeting the RLT criteria in Section 5.3.1, IMA950-poly-ICLC vaccine will be discontinued until that toxicity has reduced to Grade 1 or less. If the vaccine cannot be re-initiated in 6 weeks, the participant will be withdrawn for the RLT.

In the pre-surgical phase:

- If the scheduled craniotomy is delayed longer than 2 weeks secondary to RLT, the patient will be withdrawn from the protocol

- If the scheduled craniotomy is delayed for reasons not related to toxicities, i.e. related to surgical scheduling issues or patient preference, patients will still be eligible if surgery is performed ≤ 35 days from randomization AND ≤ 4 days from last vaccine.

5.7.2 Dose reduction (applicable to poly-ICLC only)

If Grade 2 non-RLT AE recurs, poly-ICLC dose will be cut down to 50% of the original dose (0.7 mg). Pretreatment with acetaminophen 650-1000 mg or with any NSAID may be given. If further dosing is well tolerated, the original dose may be subsequently re-instituted at the discretion of the investigator. All dosage changes will be recorded in the treatment log.

Participants may remain on the 50% reduced dose of poly-ICLC for grade 1 or 2 hematologic toxicity, or grade 1 non-hematologic toxicity (except for grade 1 flu-like signs). If at the 50% dose level, there is not additional or new toxicity for a minimum of 2 weeks, the dose may be escalated back to the starting dose at the discretion of the investigator. Subsequent Grade 2 non-hematologic toxicities, should they occur, will require a dose reduction to 50%, and no further escalations will be allowed. If toxicity reoccurs at the reduced dose, the patient will be taken off treatment.

Because the IMA950 peptide vaccine is sequestered locally, and the immune response occurs primarily locally and in the draining lymph nodes, the dose of IMA950 does not need to be scaled up proportionately to the size (by weight or body surface area) of the recipient, as might be done for a drug whose effect is related to its distribution in body fluid. For the same reasons, dose de-escalation or dose reduction is not as meaningful as it would be with a drug with a narrow therapeutic index.

Modifications to the administered dose of varlilumab are not allowed because the proposed dose is considered the minimum biologically active dose, and there is not a dose-escalation plan in the current study.

5.7.3 Discontinuation of the regimen

Vaccine administration will be discontinued in the following situations:

- An RLT is observed
- If there is a delay of scheduled craniotomy greater than 2 weeks
- If there is a delay of vaccine dosing greater than 6 weeks due to treatment related toxicity or regimen-limiting toxicity (RLT)

5.8 Expected Risks and Toxicities of IMA950 Vaccination and Poly-ICLC

5.8.1 IMA950

Potential side effects of IMA950

As of the cut-off date for information from the CR0902-11 trial with IMA950 (13-Jun-13), a total of 45 patients had been treated with IMA950 plus GM-CSF. A total of 105 AEs considered at least possibly related to either IMA950 or GM-CSF (by the Investigator) have been observed in 28 patients. Twenty-four patients (53%) experienced a related injection site reaction, all of which where CTCAE Grade 1 or 2. Eleven related AEs, including pruritus and macula-papular rash, were seen in the skin and subcutaneous tissue across eight patients. All were CTCAE Grade 1 or 2. Nine patients have experienced 10 Suspected Unexpected Serious Adverse Reactions (SUSARs) considered at least possibly related to either IMP (IMA950 or GM-CSF) by the Investigator or the Sponsor which included neutropenia (two cases of CTCAE Grade 4), maculo-papular rash (CTCAE Grade 2), erythema multiforme (CTCAE Grade 2), anaphylaxis (CTCAE Grade 3), allergic reaction (CTCAE Grade 2), joint pain (CTCAE Grade 2), basal cell carcinoma of skin in situ (CTCAE Grade 1), fever (CTCAE Grade 1) and fatigue (CTCAE Grade 3).

Six patients have been treated in the IMA950-102 trial at the NCI as of the cut-off date (13-Jun-13). 49 AEs have been reported in the trial that have been considered by the Investigator at least possibly related to IMA950, GM-CSF, imiquimod or cyclophosphamide (CY). Injection site reactions were the most common immunization-related AEs, two SARs have been experienced by two patients (Herpes zoster reactivation, CTCAE Grade 3 and Allergic reaction, CTCAE Grade 2).

Allergic reactions or associated events (e.g. rash, pruritus) have been reported in association with IMA950 and the similar vaccines IMA901 and IMA910. From a total of 51 patients treated with IMA950 in both ongoing trials 2 allergic reactions, one anaphylaxis and several cases of rashes and /or pruritus have been reported with suspected relationship to IMA950 and GM-CSF (except for the case in IMA950-102 as GM-CSF was not given with the vaccination preceding the event).

The case of Herpes zoster reactivation occurred one week after the 6^{th} vaccination. The most likely cause was immunosuppression induced by the chemotherapy with TMZ. But due to the distribution of the zoster lesions near the vaccination site and the temporal relationship a causal contribution of IMA950, GM-CSF and imiquimod could not be ruled out. Reactivation of viral infections and herpes zoster infections has been identified as a potential risk to be monitored closely in studies with IMA950, especially in patients otherwise immunocompromised or at risk of opportunistic infections.

Special precautions on IMA950

The local and systemic reactions reported in clinical studies with immunotherapy (see above) occurred in a regimen which combined administration with other agents. To date, signs of severe autoimmune disease have not been reported in any of the published studies. Nonetheless, to minimize any potential risk for patients, special emphasis should be put on establishing any monitoring measures to detect potential development of

autoimmune disease, particularly autoimmune encephalitis. Any unclear inflammation of the bowel, the thyroid, or the pancreas should be documented meticulously and be followed up closely until it is resolved.

The possibility of occurrence of acute hypersensitivity reactions should also be considered. Therefore, patients should be carefully observed following vaccination for one hour. In case of clinically relevant events, standard medical treatment, e.g. anti-allergic and immunosuppressive treatment, should be applied.

Local inflammation at the vaccination site is to be anticipated as this is part of the intended mechanism of action of peptide vaccinations.

There may be the risk that opportunistic infections (e.g. Herpes zoster reactivation) might be triggered by IMA950 vaccinations in immunocompromised patients. Thus the monitoring of immune status parameters (e.g. CD4 counts) should be considered.

5.8.2 Poly-ICLC

Adverse Events for DC plus poly-ICLC vaccine (UPCI 05-115)[67]

In a previous Phase 1/2 study of αDC1 vaccine plus intramuscular (i.m.) injection of poly-ICLC (20 mcg/kg)[67] in 22 patients, there were no grade 3 or 4 toxicities, no deaths on study, and no DLT at any dose through the 1st booster phase (5 additional vaccines following the scheduled 4 initial vaccines). No incidences of autoimmunity were encountered through the 1st booster phase (total 9 vaccines). Toxicity profiles were comparable across dose levels (data not shown). Grade 1 or 2 injection site reactions were the most common (82%). Grade 1 flu-like symptoms, including fatigue (73%), myalgia (32%), fever (23%), chills/rigors (18%) and headache (32%), were common and usually limited to 24 hours after each vaccine. Grade 2 lymphopenia was recorded in one patient (5%).

Adverse Events for peptides plus poly-ICLC vaccine in WHO grade II LGG patients (UPCI 07-057/08-135)[77]

In our pilot study of peptide-based vaccines in combination with i.m. poly-ICLC (20 mcg/kg) in 23 WHO grade II glioma patients with high-risks for recurrence, principal toxicities included grade I and II injection site reactions (100%) and flu-like symptoms (fatigue, myalgia, fever, headache), which were usually limited to 48 hours after each vaccine and were controlled with acetaminophen or ibuprofen. Grade 1 leukopenia developed in 3 patients who previously received chemotherapy with temozolomide. No instances of autoimmunity were encountered. No RLT has been encountered except for one case who presented with Grade 3 fever and fatigue following the 7th vaccine. The symptoms subsided by the use of over-the-counter non-steroidal anti-inflammatory drug by the next day.

Adverse Event List(s) for poly-ICLC (Overall from all human experience)

The severity of adverse effects of poly-ICLC depends on several factors including dose, route of injection, and health status of the patient. Early Phase I studies were done to determine the maximum tolerated dose (MTD) under the assumption that this was also the most effective dose. In these studies with advanced cancer patients, it was found that the MTD was about 12 mg/m^2 i.v. in patients who were not terminally ill. Patients typically showed fevers of 40ºC, myalgia, arthralgia, malaise, and some nausea and vomiting. Fever was the primary dose-limiting factor. At this dose, the mean serum type I IFN level was 2000 IU/mL. While exogenous administration rarely attains this level, serum levels of 100 IU/mL after exogenous IFN administration are associated with the same types and degree of adverse effects as high dose poly-ICLC. In most of the early cancer trials, however, about 6 mg/m^2 poly-ICLC i.v. was generally used. It was subsequently shown that a low dose of poly-ICLC (<1mg/ m^2) was better than a high dose for enhancing immune effects, and that the higher dose actually inhibited a number of cell-associated immune functions. It was also found that i.m. injection brought about much milder side effects than i.v. administration. [78] [79] More specific side effects of poly-ICLC are listed below. Please note that these are generally at higher doses than the 1.4 mg proposed for this trial.

Discomfort at IM or SC injection site: The most common adverse effect is mild, transient discomfort at the site of i.m. injection. With subcutaneous (s.c.) injections, there is a transient mild to moderate grade 1 or 2 erythematous skin reaction. [73]. However, when combined with peptide vaccine plus Montanide s.c., it can produce a transient skin reaction with induration or sterile abscess. Biopsy of such lesions has demonstrated infiltration by T-cells sensitized to the peptide. It is not clear whether such responses are due to the peptide vaccine, poly-ICLC, Montanide, or the combination, but they have not been reported with just peptide and poly-ICLC.

Flu-like symptoms: Approximately 8 to 12 hours after doses of 10 to 50 mcg/kg i.m., patients may develop a mild flu-like syndrome with fever of less than 38ºC, which may last for about 12 hours, but responds readily to acetaminophen or aspirin. Mild myalgia, arthralgia, sometimes nausea, and malaise can be present during this period of time. This flu-like syndrome typically diminishes markedly after the first few poly-ICLC treatments. On very rare occasions in the course of treatment, patients who have been tolerating treatment uneventfully may develop a more pronounced fever with chills and malaise (typical of higher dose i.v. poly-ICLC) in response to an i.m. injection. This will typically resolve over 12 to 24 hours, responds to acetaminophen, and does not recur on subsequent dosing.

Hematologic abnormalities: Several cases of transient leukopenia have been reported. Poly-ICLC was restarted after a drug holiday in most cases, but leukopenia recurred in only one patient, with rapid resolution within two days after discontinuation of drug for the second time. High dose Poly-ICLC has been associated with a coagulopathy in dogs, but not in other species including primates. There has been no change in the expected

incidence of deep venous thrombosis, pulmonary embolus, or coagulopathy in multiple sclerosis, AIDS or malignant glioma patients on low dose i.m. poly-ICLC. One paralyzed multiple sclerosis patient treated with 100 mcg/kg i.v. suffered a fatal pulmonary embolus, which was not judged to be due to the drug.

Hepatic enzyme elevation: Mild (grade 1), transient (<7 days) hepatic enzyme elevations were described in a trial of 100 mcg/kg poly-ICLC given i.v. in multiple sclerosis patients. In three patients, this was prolonged for >7 days, but in all patients the enzymes returned to normal after temporary discontinuation of the poly-ICLC. Enzyme elevation was not typically seen with doses of 10 to 50 mcg/kg three times weekly. However, one patient receiving 20 mcg/kg three times per week had to be dropped from study because of a transient enzyme elevation that persisted slightly longer than the 4-week protocol cutoff. In addition, preclinical studies have shown increased hepatic NK cells, as well as suppression of the P450 hepatic enzyme system by poly-ICLC, as well as by IFN, but the clinical implications of this finding are not clear.[80], [81]

Seizures: Three glioma patients with epilepsy had seizures during a high febrile episode, but recovered uneventfully.

Transient peritumoral edema: In a pilot brain tumor trial, a few patients showed an increase in their gadolinium enhancing lesions after 3-6 months of i.m. poly-ICLC, followed by an apparent tumor response at 6-12 months and prolonged survival on continued treatment. (Salazar, Levy et al, 1996) Decadron was used as needed in first few months of treatment on that study. In a more recent follow-up open study in patients with advanced recurrent gliomas, several patients have shown increased peritumoral edema after several weeks of poly-ICLC therapy. This has resolved in all cases on continued poly-ICLC, with or without concomitant steroids. (Merchant, Young et al, 2000). Biopsy data in at least two patients treated with poly-ICLC also showed a peritumoral inflammatory response. These findings raise the possibility that poly-ICLC may at times be facilitating a relatively early immunologic response to the tumor, perhaps manifested by transient increased edema or gadolinium enhancement.

Multicenter glioma Clinical trial: In a recent multi-center study of glioblastoma patients, 21 of the 24 subjects (88%) receiving 20 mcg/kg poly-ICLC alone three times weekly reported at least one adverse event. The incidence of adverse events was reported by the worst grade for an event for an individual subject. The majority of adverse events were classified as either grade 1 (71 of 104 or 68%) or grade 2 (28 of 104 or 27%) toxicity. There were only 3 of 104 (3%) and 2 of 104 (2%) events reported as a grade 3 or grade 4 event, respectively. The most frequently reported events (toxicities) were fatigue (15 subjects), local ‘pain-other’ (10 subjects), and myalgia (9 subjects). Only 57 out of 380 events were definitely or probably ascribed to Poly-ICLC. [71]

In a separate trial in patients with multiply-recurrent anaplastic glioma receiving the same dose i.m., all 24 subjects treated (100%) reported at least one adverse event. The majority

of adverse events reported were classified as either grade 1 (41 of 63 or 65%) or grade 2 (14 of 63 or 22%). There were 7 of 63 (11%) grade 3 events and only 1 of 63 (2%) grade 4 event. The most frequently reported adverse events were fatigue (9 subjects), transient increases in SGOT, SGPT and alkaline phosphatase (4 subjects each) and pain, type not specified (4 subjects). Only 19 out of 406 events were definitely or probably ascribed to the poly-ICLC [72]

S.c. Poly-ICLC in Normal volunteers: In a trial of a single dose of 1.6 mg s.c. poly-ICLC in normal volunteers, no treatment-related, grade 3, or serious adverse events were reported. Nonetheless, volunteers receiving poly-ICLC developed erythema and induration at the site of injection. Systemic reactogenicity included transient flu-like symptoms, such as malaise, headache, fever, and chills, which were generally mild to moderate in severity). In addition, there were no clinically significant changes in complete blood cell counts and serum chemistries, including liver function tests, 3 and 7 d after poly-ICLC administration. [73]

Expected Adverse Events for the IMA950+poly-ICLC vaccine

In the vast majority of previous clinical studies, IMA950 and poly-ICLC have been evaluated in combination regimens with immunomodulatory agents. This is the case in the current study combining IMA950 and poly-ICLC. Hence, it may not be possible or informative to list expected AEs for each of IMA950 and poly-ICLC. Hence, the following tables summarize expected AEs for the vaccine composed of the mixture of IMA950 and poly-ICLC based on the past trials as reported to FDA and through communication [redacted] as well as Phase 1/2 evaluation of αDC1 vaccine in combination with poly-ICLC in patients with recurrent WHO grade III or IV gliomas (UPCI 05-115)[67]; and Pilot study of peptide-based vaccines in combination with poly-ICLC in WHO grade II gliomas with high risk factors (UPCI 07-057 and 08-135)[77].

Expected AEs that are listed below as Grade 2 do not require expedited reporting. These Grade 2 AEs are required to be reported in routine study data submissions. Grade 3 with hospitalization or 4 AEs on the list should still require expedited reporting. **Table 1** below includes only CTCAE grade 2 or higher toxicities reported. Any grade 2 or higher AE not on this list or in the accompanying text will be considered an unexpected AE.

Table 1

Grade 2:

CTCAE Category	Description
Constitutional Symptoms	Fever (in the absence of neutropenia)
Constitutional Symptoms	Rigors/Chills
Dermatology/Skin	Injection site reaction
Dermatology/Skin	Rash

Metabolic/laboratory	Hepatic enzyme elevation
Pain	Pain - Muscle pain
Pain	Pain - Joint pain
Pain	Pain - Headache
Hematologic	Transient leucopenia (<1 week)

Grade 3:

CTCAE Category	Description
Hematologic	Leukopenia; Anemia
Constitutional Symptoms	Fatigue (lethargy, malaise, asthenia)
Neurology	Peritumoral Edema
Skin	Urticaria

5.8.3 Varlilumab (CDX-1127)

As of a cut-off date of June 30, 2014, preliminary adverse event data are available in the clinical database for 82 out of the 83 patients treated with Varlilumab from 0.1 to 10 mg/kg. This includes 25 patients treated in the solid tumor dose-escalation (10 colorectal cancer, 7 melanoma, 3 ovarian cancer, 2 prostate cancer, 2 RCC and 1 NSCLA), 24 were treated in the B-cell malignancy dose escalation (10 diffuse large B-cell lymphoma, 5 follicular lymphoma, 7 Hodgkin lymphoma, and 2 non-Hodgkin B cell lymphoma NOS), and 2 patients with T-cell lymphoma. The 2 patients in the T-cell lymphoma cohort are being treated with 0.3 mg/kg, all other patients were treated with 0.1 to 10 mg/kg of varlilumab.

Dose-Limiting Toxicity

One Dose-Limiting Toxicity (DLT) has been reported. One patient with Stage III ovarian cancer experienced a DLT of asymptomatic Grade 3 hyponatremia (129 mmol/L), with onset 13 days after receipt of a single dose of Varlilumab at 1 mg/kg. The event resolved after three weeks without treatment.

Treatment Discontinuation due to Treatment-Related Toxicity

In addition to the DLT described above, five additional patients have discontinued treatment due to treatment-related adverse events. All subjects were in the dose-escalation hematologic malignancies cohort.

All-Causality Adverse Events

All reported adverse events, regardless of causality, are displayed in Appendix 1 in the Investigator Brochure. Grade 3-4 events reported in ≥4% of patients were hyponatremia (5 %), anemia (4%), and hypercalcaemia (4%). The most frequently reported adverse events, regardless of causality are displayed in **Table** 2.

Table 2. Most Frequently Reported Adverse Events Regardless of Causality (≥ 10%)

Preferred term	All Patients (n=82)
Fatigue	40 (49%)
Nausea	22 (27%)
Decreased appetite	18 (22%)
Dyspnoea	13 (16%)
Anaemia	12 (15%)
Oedema peripheral	12 (15%)
Diarrhoea	11 (13%)
Vomiting	11 (13%)
Headache	11 (13%)
Pain	10 (12%)
Constipation	9 (11%)
Chills	9 (11%)
Back pain	9 (11%)
Cough	9 (11%)
Abdominal pain	8 (10%)
Asthenia	8 (10%)
Pyrexia	8 (10%)
Arthralgia	8 (10%)
Insomnia	8 (10%)
Pruritus	8 (10%)
Rash maculo-papular	8 (10%)

Treatment-Related Adverse Events

Adverse events considered related to Varlilumab are displayed in Appendix 1 in the Investigator Brochure. Treatment-related events that were reported in ≥5% patients have been fatigue (27%), nausea (13%), decreased appetite (10%), headache (9%), rash maculo-papular (9%), diarrhea (7%), vomiting (7%), oedema peripheral, pyrexia and pruritus (all at 5%). Three Grade 3 treatment-related events have occurred: hyponatremia (the DLT described above), decreased appetite and decreased lymphocyte count, all in the solid tumor dose-escalation cohort. There was one grade 4 treatment-related event of asthma, as described below, in the solid tumor RCC expansion cohort.

Serious Adverse Events (SAEs)

The potentially treatment-related SAEs of “Bronchospasm” and “asthma” have occurred in a 62 year old male renal cell carcinoma patient treated with Varlilumab at 3 mg/kg. The patient had lung metastases and asthma, with a history of hospitalization for asthma and seasonal exacerbations of asthma, including worsening of symptoms in the late summer. Of note, during the infusion of an anti-PD-1 monoclonal antibody approximately 2 months prior, the patient had developed severe symptoms that included flushing, bronchospasms, hypoxia and tachycardia. Four days after the fourth infusion of Varlilumab he developed grade 2 worsening asthma/bronchospasm symptoms that did not respond to inhalation treatment at home. The event responded to treatment with bronchodilators and corticosteroids in the ER and did not require hospitalization. The patient subsequently discontinued study treatment due to progression of disease. Two months after the last dose of varlilumab, the patient was hospitalized for grade 4 asthma requiring intubation, but recovered with medical treatment.

A second treatment-related SAE occurred in a RCC patient who developed a grade 2 infusion reaction 1hr after the 1st varlilumab infusion (3 mg/kg). The event responded to medical management in the ER and the patient went on to get additional varlilumab infusions with pre-medication without further infusion reactions.

A cumulative summary tabulation of all reported SAEs, regardless of causality, is shown in **Table 3.** As noted above, three events in two subjects (bronchospasm, asthma and infusion reaction) were considered related to treatment with Varlilumab.

Table 3. Study CDX1127-01: Cumulative Summary of Serious Adverse Events by System Organ Class and Preferred Term

Body System / Preferred Term	Hematologic Malignancies (N=26)	Solid Tumors (N=56)	Total (N=82)
Blood And Lymphatic System Disorders			
Anaemia		2 (4%)	2 (2%)
Iron Deficiency Anaemia		1 (2%)	1 (1%)
Splenic Infarction		1 (2%)	1 (1%)
Cardiac Disorders			
Atrial Fibrillation		1 (2%)	1 (1%)
Gastrointestinal Disorders			
Constipation		1 (2%)	1 (1%)
Gastrointestinal Haemorrhage		1 (2%)	1 (1%)
Rectal Obstruction		1 (2%)	1 (1%)
Retroperitoneal Haemorrhage		1 (2%)	1 (1%)
Upper Gastrointestinal Haemorrhage		1 (2%)	1 (1%)
General Disorders and Administration Site Conditions			
Disease Progression		1 (2%)	1 (1%)
Fatigue	1 (4%)		1 (1%)
Malaise	1 (4%)		1 (1%)
Non-cardiac Chest Pain		1 (2%)	1(1%)
Pain		3 (5%)	3 (4%)
Infections And Infestations			
Pneumonia	1 (6%)	2 (4%)	3 (4%)
Sepsis	1 (4%)		1 (1%)
Viral Infection		1 (2%)	1 (1%)
Injury, Poisoning And Procedural Complications			
Fall	1 (4%)		1 (1%)
Femur Fracture		1 (2%)	1 (1%)
Hip Fracture		1 (2%)	1 (1%)
Humerus Fracture		1 (2%)	1 (1%)
Infusion Related Reaction		1 (2%)	1 (1%)
Vascular Pseudoaneurysm		1 (2%)	1 (1%)
Metabolism And Nutrition Disorders			
Dehydration		1 (2%)	1 (1%)
Failure To Thrive		1 (2%)	1 (1%)
Hypercalcaemia		2 (4%)	2 (2%)
Hypokalaemia		1 (2%)	1 (1%)
Musculoskeletal And Connective Tissue Disorders			
Arthralgia		1 (2%)	1(1%)
Bone Pain		1 (2%)	1(1%)
Musculoskeletal Chest Pain		1 (2%)	1(1%)
Musculoskeletal Pain		1 (2%)	1(1%)
Nervous System Disorders			

Body System / Preferred Term	Hematologic Malignancies (N=26)	Solid Tumors (N=56)	Total (N=82)
Spinal Cord Compression		1 (2%)	1 (1%)
Psychiatric Disorders			
Confusional State		1 (2%)	1 (1%)
Mental Status Changes	1 (4%)		1 (1%)
Renal and Urinary Disorders			
Renal Failure Acute		1 (2%)	1 (1%)
Reproductive System And Breast Disorders			
Pelvic Pain		1 (2%)	1(1%)
Respiratory, Thoracic And Mediastinal Disorders			
Acute Respiratory Distress Syndrome	1 (4%)		1 (1%)
Asthma		1 (2%)	1 (1%)
Bronchospasm		1 (2%)	1 (1%)
Dyspnoea	1 (4%)	2 (4%)	3 (4%)
Dyspnoea Exertional		1 (2%)	1 (1%)
Hypoxia		1 (2%)	1 (1%)
Pleural Effusion		1 (2%)	1 (1%)
Vascular Disorders			
Arterial Haemorrhage		1 (2%)	1 (1%)

5.8.4 Management of Infusion Reactions to Varlilumab

Varlilumab contains only human immunoglobulin protein sequences and is unlikely to be immunogenic. Infusion or hypersensitivity reactions are expected to be infrequent events. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgias, hypo- or hypertension, bronchospasm, or other symptoms. All grade 3 or 4 infusion reactions should be reported within 24 hours to the Celldex Medical Monitor and reported as an SAE. Infusion reactions should be graded according to NCI CTCAE (version 5.0) guidelines. Treatment guidelines are provided below.

For grade 1 symptoms: (Mild reaction; infusion interruption not indicated; intervention not indicated)
Remain at bedside and monitor subject until recovery from symptoms. The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen) at least 30 minutes before additional varlilumab administrations.

For grade 2 symptoms: (Moderate reaction requires therapy or infusion interruption but responds promptly to symptomatic treatment [e.g., antihistamines, non-steroidal anti-inflammatory drugs, narcotics, corticosteroids, bronchodilators, IV fluids]; prophylactic medications indicated for 24 hours).
Stop the varlilumab infusion, begin an IV infusion of normal saline, and treat the subject with diphenhydramine 50 mg IV (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen); remain at bedside and monitor subject until resolution of symptoms. Corticosteroid or bronchodilator therapy may also be administered as appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be

increased to 100% of the original infusion rate. Monitor subject closely. If symptoms recur then no further varlilumab will be administered at that visit. Administer diphenhydramine 50 mg IV, and remain at bedside and monitor the subject until resolution of symptoms. The amount of study drug infused must be recorded on the electronic case report form (eCRF). The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen) should be administered at least 30 minutes before additional varlilumab administrations. If necessary, corticosteroids (recommended dose: up to 25 mg of IV hydrocortisone or equivalent) may be used.

For grade 3 or grade 4 symptoms: (Severe reaction, grade 3: prolonged [i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion]; recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae [e.g., renal impairment, pulmonary infiltrates]. Grade 4: life threatening; pressor or ventilatory support indicated.)

Immediately discontinue infusion of varlilumab. Begin an IV infusion of normal saline, and treat the subject as follows. Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1,000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Subject should be monitored until the investigator is comfortable that the symptoms will not recur. Varlilumab will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor subject until recovery from symptoms. In the case of late-occurring hypersensitivity symptoms (e.g., appearance of a localized or generalized pruritus within 1 week after treatment), symptomatic treatment may be given (e.g., oral antihistamine, or corticosteroids).

5.8.5 Immune-related Adverse Events

While each of the immunotherapeutics (i.e. IMA-950, poly-ICLC and Varlilumab) has been very well-tolerated, we will carefully evaluate the safety of the proposed combination regimen. It is possible that the combination may elicit AEs that may not have been observed when these immunotherapeutics were evaluated separately. In this section, we discuss potential toxicities associated with the proposed combination as immune-related adverse events (irAEs), and provide guidelines for diagnosis and management of potential irAEs.

An irAE is defined as a clinically significant adverse event of any organ that is associated with study drug exposure and is consistent with an immune-mediated mechanism. Serologic, immunologic, and histologic (biopsy) data should be used to support an irAE diagnosis. Appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the adverse event. Most commonly irAEs in immunotherapy in general involve skin, gastrointestinal (GI) tract, endocrine organs and liver, but can involve any organ system. irAEs typically clinically manifest several weeks to a few months following initiation of immune enhancing anti-tumor therapy. Possible clinical manifestations include:

- Constitutional: fever, fatigue
- GI: diarrhea, colitis, constipation, hematochezia, melena, abdominal pain

• Skin: rash, pruritus, alopecia, desquamation
• Liver: elevated liver enzymes, hepatitis
• Endocrine: hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis, hypogonadism
• Ocular: conjunctivitis, iritis, uveitis
• Others: neuropathy, including Guillain-Barre syndrome, hemolytic anemia, thrombocytopenia

Management of Immune-related irAEs *General guidelines for treatment of irAEs*: When symptomatic therapy is inadequate or inappropriate, an irAE should be treated with systemic corticosteroids followed by a gradual taper over several weeks (customarily 2-4 weeks). If corticosteroids or other immunosuppressive agents are required for more than 4 weeks in duration to treat an irAE then it is recommended that patients also receive prophylaxis to protect against the emergence of opportunistic infections. Such prophylaxis should include protection against *Pneumocystis jiroveci* (formerly P carinii) and prevalent fungal strains, as well as considerations for any additional pathogens that may be indicated by the medical history (e.g., herpes simplex virus, cytomegalovirus) or the environment (e.g., occupation, recent travel) of the patient. Consultation with infectious disease specialists may be considered.

Gastrointestinal Tract: The differential diagnosis for patients presenting with abdominal pain should include colitis, perforation, or pancreatitis. Diarrhea (defined as either first watery stool, or increase in frequency 50% above baseline with urgency or nocturnal bowel movement, or bloody stool) should be further evaluated and infectious or alternate etiologies ruled out. Patients should be advised to inform the investigator if any diarrhea occurs, even if it is mild. Corticosteroid therapy is strongly recommended for the study treatment-related Grade 3 diarrhea/colitis and should be slowly tapered according to symptomatic response over at least 1 month. Patients with the study treatment-related Grade 2 diarrhea/colitis may be initially treated conservatively, but should be followed closely and immediately switched to corticosteroids if symptoms persist or worsen. For severe symptoms, prednisone 60 mg or equivalent may be required to control initial symptoms, and the dose should be gradually tapered over at least 1 month. Lower doses of prednisone may be considered for less severe cases of colitis. It is suggested that prednisone (for oral administration) or solumedrol (for i.v. administration) be the corticosteroids of choice in the treatment of colitis. Caution should be taken in the use of narcotics in patients with abdominal pain or colitis/diarrhea as narcotic use may mask the signs of colonic perforation.

If the event is prolonged or severe or is associated with signs of systemic inflammation or acute phase reactants (eg, increased C-reactive protein [CRP] or reactive thrombocytosis; or Neutrophil shift to immature bands), it is recommended that sigmoidoscopy (or colonoscopy, if appropriate) with colonic biopsy of 3 to 5 specimens block be performed. Patients with confirmed colitis should also have an ophthalmologic examination, including

a slit-lamp exam, to rule out uveitis. Test for stool white blood cells (WBC) and calprotectin (if locally available) should also be performed.

In severe corticosteroid refractory or relapsing cases, infliximab should be considered, unless contraindicated (i.e., sepsis and other serious infections). All such cases should be discussed with the sponsor study medical monitor.

Liver: In addition to protocol-scheduled liver function tests (LFTs), patients presenting with right upper quadrant abdominal pain, unexplained nausea, or vomiting should have LFTs performed immediately and reviewed before administering the next dose of study drug. Any increase in LFT should be evaluated to rule out non-inflammatory causes of hepatotoxicity including infections, disease progression or medications and followed with frequent LFT monitoring at approximately 3-day intervals until resolution. Any LFTs $\geq$ Grade 2 (for patients with normal baseline LFT) or LFT $\geq$ 2 times baseline values (for patients with baseline LFT of Grade 1 or 2) should prompt treating physicians to: (1) contact the medical monitor; (2) increase frequency of monitoring LFTs to at least every 3 days until LFT have stabilized or improved; (3) investigate to rule out non-irAE etiologies; and (4) initiate an autoimmunity evaluation. Disease progression, other malignancies, concurrent medications, viral hepatitis, and toxic etiologies should be considered and addressed, as appropriate. Imaging of the liver, gall bladder, and bile ducts should be considered to rule out neoplastic or other non-irAE-related causes for the increased LFTs. An antinuclear antibody (ANA), perinuclear anti-neutrophil cytoplasmic antibody (pANCA), and anti-smooth muscle antibody test should be performed if an autoimmune etiology is considered.

Patients with LFT elevations > 8x the upper limit of normal (ULN) that are judged to be due to the study regimen, should initiate high-dose corticosteroid therapy (e.g., methylprednisolone 2 mg/kg once or twice daily or equivalent) and permanently stop administration of all regimen treatment. In patients with > 8x ULN, LFTs should be performed daily until stable or declining for 5 consecutive days. LFTs should be monitored for at least 2 consecutive weeks to ensure sustained treatment response. If symptoms or LFT elevations are controlled, the corticosteroid dose should be gradually tapered over a period of at least 1 month. Flare in LFTs during this taper may be treated with an increase in the dose of steroid and a slower taper.

In patients without response to corticosteroid therapy within 3 to 5 days or who have an LFT flare during steroid tapering that is not responsive to an increase in steroids, addition of immunosuppression with mycophenolate mofetil should be considered after a gastroenterology/hepatology consult. Patients receiving immunosuppression for more than 4 weeks should be evaluated for prophylaxis of opportunistic infections.

Skin: A dermatologist should evaluate persistent or severe rash or pruritus. A biopsy should be performed if appropriate and if possible, photos of the rash should also be obtained. Low grade study therapy-mediated rash and pruritus may be treated with

symptomatic therapy e.g., antihistamines). Topical or parenteral corticosteroids may be required for more severe symptoms.

Endocrine: In the ipilimumab clinical development program, hypopituitarism presented with nonspecific complaints such as fatigue, confusion or impotence. Some patients had headache as the predominant presentation. The majority of patients with hypopituitarism demonstrated enlarged pituitary glands based on brain MRI. Low adrenocorticotropic hormone (ACTH) and cortisol were the most common biochemical abnormality; low thyroid stimulating hormone (TSH), testosterone or prolactin were also reported in some patients. Patients with unexplained symptoms such as fatigue, myalgias, impotence, mental status changes, or constipation should be investigated for the presence of thyroid, pituitary or adrenal endocrinopathies. An endocrinologist should be consulted if an endocrinopathy is suspected. Thyroid stimulating hormone and free T4 levels should be obtained to determine if thyroid abnormalities are present. TSH, prolactin and a morning cortisol level will help to differentiate primary adrenal insufficiency from primary pituitary insufficiency. Appropriate hormone replacement therapy should be instituted if an endocrinopathy is documented. A short course of high dose corticosteroids should be considered in an attempt to treat the presumed pituitary inflammation. It is possible that patients with immunotherapy-induced endocrinopathies may require life-long hormone replacement.

Other: An ophthalmologist should evaluate visual complaints with examination of the conjunctiva, anterior and posterior chambers, and retina. Visual field testing and an electroretinogram should also be performed. Uveitis or episcleritis may be treated with topical corticosteroid eye drops.

5.9 General Concomitant Medication and Supportive Care Guidelines

Medications taken in the month prior to registration should be recorded on the baseline case report form. These include prescription medications, over-the-counter medications, injected medications, biological products, blood products, imported drugs, or illicit drugs. Participants should be maintained on drugs that they were taking prior to entry unless a change in regimen is medically indicated.

- **Acceptable**

For fever, acetaminophen will be utilized (325 mg tabs, 1 or 2 p.o. every 4 hours). Pre-treatment of participants with acetaminophen may be instituted. Fevers lasting more than 8 hours after treatment will be evaluated in terms of potential infection.

For mild local pain, non-steroidal anti-inflammatory drugs (NSAIDS) or opiates (e.g., oxycodone, 5 –10 mg p.o. every 3-4 hours) at the treating physician’s discretion should be planned. Pain that is more than mild-moderate grade will be investigated for sources other than the therapy, and managed accordingly.

Dexamethasone should be 4 mg/day or less for at least one week prior to the initiation of the pre-surgical IMA950 vaccine+poly-ICLC therapy. Dexamethasone may be increased

up to 4 mg/day in the setting of pseudo-tumor progression, and tapered/discontinued as soon as possible.

Anti-seizure medications should be used as indicated.

Antiemetics, if necessary, can be administered at the discretion of the treating physician.

Other acceptable medications:

Topical corticosteroids
Nonsteroidal anti-inflammatory agents
Anti-histamines (e.g. Claritin®, Allegra®)
Chronic medications except those listed below
Influenza vaccines are permitted, but should be administered at least 2 weeks prior to or at least 2 weeks after a study vaccine.

- **Cautionary**

Steroid based inhalers (e.g., Advair®, Flovent®, Azmacort®) should be used with caution and the total daily use reviewed with the treating physician.

- **Unacceptable**

Interferon therapy (e.g. Intron-A®)
Chemotherapy
Allergy desensitization injections
Growth factors (e.g. Procrit®, Aranesp®, Neulasta®)
Interleukins (e.g. Proleukin®)
Other investigational medications
Illicit drugs

5.10 Duration of Therapy

In the absence of treatment delays due to AEs, treatment may continue Week 25 or until one of the following criteria applies:

- Rate limiting toxicity – as defined above
- Disease progression
- Intercurrent illness that prevents further administration of treatment
- Patient decides to withdraw from the study
- Participant is noncompliant with the non-treatment requirements of the study
- Pregnancy. Pregnant participants will continue to be followed for the duration of the pregnancy.
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator

Patients removed from study for unacceptable AEs will be followed until resolution or stabilization of the adverse event. Patients who discontinue study treatment will be followed for survival according to the long term follow-up. Documentation of AEs and concomitant medications will continue during follow-up.

5.11 Pseudo-Tumor Progression and Management Plans

A small percentage of participants on this study may experience ***pseudoprogression.*** In malignant glioma vaccine studies by us[67] and others[82], some vaccine-recipients have shown enlargement or appearance of new contrast-enhancement on MRI that resolved with or without concomitant steroids. These findings may be attributed to immunologic anti-tumor response rather than tumor progression (i.e., tumor pseudo progression). If pseudoprogression is suspected, the patient should be observed if asymptomatic or may be placed on dexamethasone (4 mg/d or lower) if symptomatic for up to one month, at which time an MRI scan should be repeated. If their steroid dose is ≤ 4 mg/d and if their repeat imaging indicates that they do not meet the criteria for disease progression, then participating patients will continue on study and receive study treatment as prescribed by the protocol; otherwise, they will be considered progression and taken off study.

Patients who meet the criteria to resume therapy will be categorized as having had pseudoprogression and will be classified as SD or PR/CR, depending on their imaging response after re-initiation of therapy, in comparison to the pretreatment baseline. In contrast, for patients in whom repeat imaging on increased steroids is unchanged or worse, and/or the patient's clinical status has not improved over a period of one month, a biopsy (or resection, if clinically indicated) will be considered to differentiate between pseudo- and true tumor progression. When a biopsy or resection is performed, the histopathological specimen will be examined for evidence of inflammatory/lymphocytic infiltration, indicative of pseudoprogression. If inflammatory infiltration and/or necrosis comprise the majority of the specimen, patients may remain on study and restart treatment once they are clinically stable and on ≤ 4 mg/day Decadron for at least one week. If the majority of the resected specimen consists of tumor, or if the patient does not have further surgery and does not meet criteria to resume therapy, the patient will be considered to have true progression and will be taken off treatment. Patients who have progressively enlarging tumor size or worsening symptoms despite increasing corticosteroids or enlargement that does not regress within one month, who are judged not to be candidates for biopsy/resection, will be considered to have progressive disease and taken off treatment.

Any cases of suspected tumor progression or pseudo-tumor progression will be carefully reviewed by the study investigators [redacted] to determine whether the subject should remain in the trial. In addition, pseudoprogression that necessitates intubation or pressors for >72 hours will be considered a regimen-limiting toxicity.

6 Study Parameters

Baseline evaluations will be conducted within 28 days prior to study enrollment. MRIs will be done ≤ 28 days prior to the randomization. In the event that the patient's condition is deteriorating, laboratory evaluations will be repeated within 48 hours prior to initiation of the next vaccination.

If a vaccine is missed or a subject's treatment and/or testing days need to be rescheduled due to the subject's inability to comply with the study calendar (i.e., hospitalizations, business and vacation travel plans, illness, transportation issues, holidays, family emergencies, etc.), a window of ± one week is available for rescheduling of treatment and procedures per the discretion of the treating physician investigator, and as discussed with the principal investigator.

	Scre ening	Pre-surgical				Sur ger y D0	Po st Op *	Post-Surgery Vaccines								Wk A25	Post vac. Follo w-up[4]
		D-23 ±2 #1	D-16 ±2 #2	D-9 ±2 #3	D-±2 #4			A 1 #1	A4 #2	A7 #3	A 10 #4	A 13 #5	A 16 #6	A 19 #7	A 22 #8		
Informed Consent	X																
Demographics	X																
Tumor Tissue						X											
HLA-A2	X																
Randomization	X^																
Pathology Review	X[1]						X										
IMA950+poly		X	X	X	X			X	X	X	X	X	X	X	X		
Varlilumab (Arm 1 only)		X						X		X		X		X			
Complete Medical History	X																
Interval Medical History		X	X	X	X		X	X	X	X	X	X	X	X	X	X	X
Review of Concurrent Meds	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X
Physical Exam	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X
Vital Signs#	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X
Weight	X							X								X	X
Performance Status	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X
Adverse Event Assessment		X	X	X	X		X	X	X	X	X	X	X	X	X	X	X
CBC w/diff plts	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X[4]
Serum chemistry[2]	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X[4]
Autoimmune assessment	X																
HBsAg HBsAb HBcAb	X															X	
B-HCG	X																
Urynalysis[3]	X																
ECG[8]	X															X	
MRI Scans	X					X[5]	X[6]				X					X	
Research Blood 8 x 10 cc green 1 x 5 cc red top		X				X		X				X		X		X	
PK for varli (2 x 10 cc red top)[7]		X						X		X		X		X			
48 ± 6 hours post-		X	X	X	X			X	X	X	X	X	X	X	X		

vac. Ph. follow-up																

^ Within 2 weeks from enrollment

* The post-surgery evaluations should be completed within 2 wks after the surgery. The first post-op vaccine at Wk A1 should be scheduled at least two weeks after the post-op steroid is tapered, but within 10 weeks post-surgery. If the pathological diagnosis upon the resected tissue indicates WHO III or IV grade tumors, those patients will be ineligible for post-surgery courses and replaced.

Vital Signs pre-treatment and one hour post-treatment

1. Indicated only if the patient has had previous biopsy or resection outside of UCSF for UCSF confirmation
2. Comprehensive metabolic panel (albumin, alkaline phosphatase, ALT, AST, bilirubin (total), calcium, chloride, CO2, creatinine, random glucose, potassium, protein [total], sodium, urea nitrogen)
3. Urinalysis will be performed at screening as standard of care to check kidney functions prior to study treatment
4. Follow-up. All patients, including those who discontinue protocol therapy early, will be followed for response and toxicity assessments until disease progression, start of a new therapy, or for a maximum of 24 months from study registration (whichever occurs earlier). Follow-up visits should be scheduled per standard-of-care for patients with stable WHO grade II glioma without active treatment (e.g. every 3 months). For any patient with ongoing grade 3 or greater treatment related toxicity at the discontinuation of study therapy, follow-up will continue as medically appropriate for the specific toxicity until resolution to grade 1 or better or 3 months of no change (stabilization). If progression is the reason for treatment discontinuation, the final study visit will be the final visit for the study, providing no ongoing grade 3 or greater treatment related toxicity. Serum chemistry and CBC tests are required at the first follow-up visit or when previous tests demonstrated any abnormality. If a patient does not show any abnormality during the course or at the first follow-up visit, that patient will not require CBC and chem on the follow-up visits per protocol.
5. Pre-op MRI is taken before surgery as standard of care.
6. Post-op MRI. If this was taken within 14 days of surgery and within 28 days prior to Wk A1 vaccine (the first vaccine post-surgery), this can be used as the baseline MRI scan for the post-op portion of the study treatment. Otherwise, we have to take another MRI scan to fit the 28 day window between the MRI scan and the Wk A1 vaccine.
7. On Varlilumab administration days, samples should be drawn from the arm contralateral to the infusion site prior to administration and at 30 minutes (±5 minutes) after the end of the varlilumab infusion. An additional sample should be drawn as soon as possible for any patients who experience an infusion reaction.
8. ECG is mandated as a part of the screening, but will be repeated on Week 25 only if clinically indicated.

Note: There is a window of ± 7 days available for rescheduling treatment and/or procedures at the discretion of the Sub-investigator, and as discussed with the Investigator if a course is missed or a subject's treatment and/or testing day(s) need to be rescheduled due to the subject's inability to comply with the study calendar (i.e., hospitalizations, business, vacation plans, travel from long distances for study treatment, in advance of the scheduled date to allow ready access to the result(s), reduce financial burden on the subject [i.e. non-US insurance coverage] or reduce travel inconvenience, illness, transportation issues, holidays, family emergencies, etc.).

7 Pathology/Tissue Bank

7.1 Pathology

Pathology must be reviewed in the UCSF pathology department

7.1.1 Review of Outside Pathology

If a patient presents with a biopsy from an outside institution of WHO grade 2 glioma, all H&E slides [and ideally unstained slides or a block] and a copy of the pathology report, will be reviewed by the UCSF pathology department to confirm pathology.

If WHO grade 2 glioma pathology is confirmed, the patient is eligible for the study

7.1.2 Laboratory Specimen Collection Procedures

Pathological criteria: 1) At the time of the clinically indicated surgical resection (post-pre-surgical therapy), the resected tumor will be subjected to pathological diagnosis by one of the 2 study neuro-pathologists at UCSF, [redacted] and diagnosed as WHO grade II glioma. If the tumor is found to be at higher grade (WHO grade III or IV), the patient will be ineligible for the post-surgery phase of the study, and replaced.

7.1.3 Tumor Tissue Collection

In the operation room, at the time of surgical resection, after adequate tissue is provided to UCSF Medical Center Pathology for diagnosis, the request is made that approximately 0.3 grams of remaining viable tumor tissue is acquired and divided as follows by the Brain Tumor Research Center Tissue Bank.

1. 300 mg tumor tissue is snap frozen and collected for banking

2. 200 mg tumor tissue will be kept fresh and used for flow cytometric analysis of tumor-infiltrating leukocytes (TILs)

Note: A patient must have at least 200 mg tumor tissue available for TIL to remain eligible for the study.

7.2 Peripheral Blood Samples for Immunologic Monitoring

At the time of clinically indicated surgical resection, peripheral blood samples (8 x 10 cc green top tubes and 1 x 5 cc red top tube) will be collected in the operating room. Samples will be labeled by study identification number and stored at room temperature until transferred to the Cancer Immunotherapy Lab for processing. Immunological assays will be performed by the Okada Lab.

At additional time points (see calendar of events) peripheral blood samples (8 x 10 cc green top tubes and 1 x 5 cc red top tube) will be collected by research staff. Samples will be labeled by study identification number and stored at stored at room temperature until transferred to the Cancer Immunotherapy Lab for processing. Immunological assays will be performed by the Okada Lab.

All assay samples will be de-identified.

7.3 Peripheral Blood Samples for Pharmacokinetics

In Arm 1 (with varlilumab) patients, at each of a total of 5 visits with varlilumab infusion (D-23 ± 2, A1, A7, A13, and A19), two peripheral blood samples (1 x 10 cc red top tube/draw) will be drawn from the arm contralateral to the infusion site prior to administration and at 30 minutes (± 5 minutes) after the end of the varlilumab infusion. An additional sample should be drawn as soon as possible for any patients who experience as infusion reaction. Samples will be stored at room temperature and sent to the Cancer Immunotherapy Lab for processing. Analysis will be performed by the Okada Lab.

7.4 Tissue Bank

All available participants' tumors (including ones obtained by the scheduled surgery in the protocol and ones that may be obtained after the study treatment due to progression) will be banked in the UCSF brain tumor research center (BTRC) tumor bank.

8 Correlative/Special Studies

8.1 Immunological Monitoring of PBMCs

Analyses of immune responses in PBMC will allow non-invasive evaluation of vaccine-induced immune response. As one of two co-primary endpoints of the current study, we will determine the response rate and magnitude of CD4+ and CD8+ T-cell responses against the IMA950 peptides in pre- and post-vaccine PBMC using a novel, flow-cytometry-based 2D *ex vivo* assay system. We will determine whether Arm 1 patients demonstrate higher response rate and/or magnitude of response compared with Arm 2 patients.

As the primary method of PBMC analysis, we will use a novel 2D multimer staining-based assays.[83] The use of fluorescently labeled MHC multimers has become an essential technique for analyzing disease- and therapy-induced T-cell immunity. However, limitations on available PBMCs from patients preclude a comprehensive analysis of T-cell immunity. To address this issue, Hadrup et al. developed a combinatorial encoding strategy that allows the parallel detection of a multitude of different T-cell populations in a single sample (2D multimer staining-based assays).[83] Detection of T-cells from PBMC by combinatorial encoding is as efficient as detection with conventionally labeled multimers but results in a substantially increased sensitivity and, most notably, allows comprehensive screens to be performed. We have confirmed that we can detect increases of IMA950-specific T-cells using PBMC samples obtained from GBM patients receiving IMA950 vaccines.

As the primary method to evaluate the relative immune response levels between two Arms, the relative magnitude of responses against each of IMA950 antigens will be compared between two Arms by comparing the sum of post-vaccine tetramer+ percentages of all time points from all patients in each of two Arms.

As an exploratory evaluation, a subject will be considered to be an immunological responder, if at any of two consecutive post-vaccine time points (i.e., Weeks A13, 19 and A25):

1. Presence of a CD4+ or CD8+ T cell population which shows positive tetramer staining against any of IMA950 antigens.

2. Four-fold increase of the frequency of the tetramer positive cells within the CD4+ or CD8+ T cell population at the considered post-vaccination time points versus the pre-vaccination time point.

Responders are to be classified based on the number of IMA-950 antigens to which the patient responded (e.g., responders to one antigen, two antigens, and ≥3 antigens). Numbers of these responders will be compared between Arm 1 and Arm 2.

8.2 Enzyme Linked Immuno-SPOT (ELISPOT) Assays

Frequencies of T-lymphocytes reactive to the IMA950+poly-ICLC vaccine in PBMC prior to and after the treatment can be measured by ELISPOT assay. The ELISPOT assays will be done at the same time point at least for one individual participant to avoid inter-assay variability. We will use IFN-γ ELISPOT as the readout to assess Type-1 T-cell response.

The detailed Standard Operation Procedures are available in Okada Lab. A subject will be considered to have responded, if at any of two consecutive post-vaccine time points, the number of spots is double that at baseline, and there are at least 10 spots/20,000 cells, and if the number of the post-vaccine spots is at least three times the standard-deviation of the pre-treatment value. This definition provides some protection against false positive response.

8.3 Flow Cytometric Analyses of Lymphocyte Subsets

Number of $CD33^{+}CD11b^{+}HLA\text{-}DR^{-or\ dim}$ IMCs, other myeloid cells (including $CD33^{+}CD11b^{+}HLA\text{-}DR^{+}$ cells), $CD4^{+}$, $CD8^{+}$ T cells and $CD4^{+}/Foxp3^{+}$ T regulatory cells at serial time points pre- and post-vaccines will be evaluated. These data will be evaluated in an exploratory manner.

8.4 Evaluation of Tumor Infiltrating Leukocytes (TILs)

We will evaluate TILs in tumor tissues obtained from patients who received pre-surgical treatment with the IMA950+poly-ICLC vaccine with or without varlilumab.

We will isolate TILs and evaluate whether surgically resected tumors from Arm 1 (IMA950+poly-ICLC vaccine **with** varlilumab) patients demonstrate significantly higher levels of vaccine-reactive T-cells and CXCL10 expression compared with:1) those resected from Arm 2 (IMA950+poly-ICLC vaccine **without** varlilumab) patients ; and 2) HLA-A2+ patients who underwent resection under IRB# 15-17078 vaccine study.

We will also compare T-cell clonotypes of TILs with those in post-vaccine PBMC. Specifically, we will determine whether T-cell clonotypes that are reactive to IMA950 peptides in PBMC are found in TILs. To this end, IMA950-specific multimer-positive T-cells in post vaccine PBMC will be sorted, and T-cell receptor β-chain usage in those populations will be determined. Then, we will evaluate whether those T-cell populations are increased in TILs obtained from Arm 1 patients compared with those obtained from Arm 2 (and IRB# 15-17078 vaccine study) patients. This method is expected to be more sensitive than traditional multimer-based analysis.

We will also perform multi-color flow cytometry to characterize infiltrating T-cells in terms of their number, phenotype, and reactivity to IMA950 peptides by 6-hr *in vitro* re-stimulation with IMA950 peptides followed by staining of cytoplasmic IFN-γ. These studies will allow us to evaluate whether vaccine-induced T-cells efficiently traffic to the brain tumor site and maintain their function and viability. We will also evaluate the number and phenotype of $CD33^{+}CD11b^{+}HLA\text{-}DR^{-or\ dim}$ immature myeloid cells (IMCs) and other myeloid cells (including $CD33^{+}CD11b^{+}HLA\text{-}DR^{+}$ cells) in TILs. RT-PCR will be applied to evaluate the

expression of chemokines, such as CXCL10, and immuno-regulatory substances, such as arginase-1.

9 Measurement of Effect

9.1 Primary Objectives

9.1.1 Safety

We will determine whether it is safe to administer pre-surgical IMA950+poly-ICLC in combination with varlilumab in patients with WHO grade 2 gliomas in whom surgical resection of tumor is clinically indicated.

Endpoints will therefore include incidence and severity of adverse events, using standard criteria as well as close clinical follow-up as would be performed normally in this group of participants following vaccinations. All reported or observed toxicities and adverse events at all clinic visits will be graded, documented and reported according to a standard toxicity table, the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40). We will consider the regimen is unacceptably toxic if the >33% of patients develop RLT (see Section 5.6). A participant who receives the scheduled pre-surgical vaccines, surgical resection and whose tumor is found to be WHO grade II glioma will not be replaced. If the scheduled surgery is delayed longer than 2 weeks for a toxicity or any vaccine dose is delayed for 5 weeks or longer for any reason, those patients are considered to have gone off-study due to RLT even if the toxicities/AEs do not meet the criteria of RLT defined in Section 5.3.1.

9.1.2 Immunogenicity

To evaluate the response rate and magnitude of $CD4^+$ and $CD8^+$ T-cell responses against IMA950 peptides in pre- and post-vaccine PBMC using the novel 2D multimer flow-cytometric analysis. We will also perform ELISPOT assays to evaluate the functional status of the antigen-specific T cells as cytokine-expression, and we are particularly interested in Type-1 (i.e. IFN-γ expressing) T cell response. While we use 2D multimer assay as the primary assay for its superior sensitivity, we will also use IFN-γ ELISPOT as the secondary assay for the immunological endpoint. We will determine whether Arm 1 patients demonstrate higher response rate and/or magnitude of response compared with Arm 2 patients.

9.2 Exploratory Objectives

As this study is not sufficiently powered to evaluate the following endpoints, data will be tabulated.

9.2.1 Evaluation of IMA950-reactive T-cell infiltration and CXCL9/10 expression in tumors resected from Arm 1 and Arm 2 patients

In surgically resected tumor tissues from Arm 1 (IMA950+poly-ICLC and varlilumab) and Arm 2 (IMA950+poly-ICLC alone) patients, we will evaluate numbers of tumor-infiltrating $CD4^+$ T-cells $CD8^+$ T-cells (by flow-cytometry) and CXCL10 expression (by RT-PCR). Among T-cells, we will evaluate IMA950-reactive populations by flow-cytometry. We will perform preliminary comparisons of these readouts between Arm 1 and Arm 2 patients. In our separate vaccine study using GBM6-PD lysate (IRB# 15-17078 vaccine study), there will be samples from the control group who received no therapy prior to surgery. Hence these samples will be also used to assess whether IMA950+poly-ICLC vaccine in the current study (and varlilumab in Arm 1) increases the number of T-cells in the tumor site.

9.2.2 To evaluate IMA950-reactive T-cell receptor (TCR) clonotypes in tumors resected from Arm 1 and Arm 2 patients

While studies in 9.2.1 will provide us with actual numbers of vaccine-reactive T-cells, we may not obtain sufficient (i.e. at least 1 x 10^6 tumor-infiltrating lymphocytes) numbers of T-cells to obtain reliable data. As a more sensitive approach, we will utilize a novel method developed by Adaptive Biotechnologies (ImmunoSEQ™) that simultaneously amplifies and sequences tens of thousands of rearranged T-cell receptor (TCR) complementarity-determining region 3 (CDR3)[63] in each of PBMCs as well as tumor tissue. Because the technology utilizes genomic DNA, the frequency of sequenced CDR3 chains is representative of the relative frequency of each CDR3 sequence in the starting population of T-cells. Clones identified in the activated T-cells will be tracked in both PBMC and tumor. To evaluate IMA-950 reactive T-cell populations with this method, first, from post-vaccine PBMC, we will isolate IMA-950-multimer positive populations using and flow-cytometry sorting, and will evaluate usage of CDR3 chain clones in these populations. Then, we will evaluate the presence of the same CDR3 sequences in tumor tissue, which would indicate the presence of IMA-950-reactive T-cells in the resected tumor. Like 9.2.1, we will perform preliminary comparisons of this readout between Arm 1 and Arm 2 patients as well as the historical control group who received no therapy prior to surgery.

9.2.3 Overall Survival (OS) and Progression-Free Survival (PFS)

PFS is defined as the duration of time from start of treatment to time of progression or death. Patients who have not yet progressed or died will be censored at the time of their last follow-up.

All patients will be followed for a minimum of 2 years, so that their actual 2-year OS and PFS can be determined. OS is defined as the time from start of treatment to time of death. Patients who have not yet died will be censored at the time of their last follow-up.

Tumor recurrence will be assessed minimally at week A25, and patients will be followed with MRI scans and clinical visits as standard of care. Even though we cannot schedule precise time points for follow-up MRIs (because that portion is not a part of the study), we will obtain 2-year PFS as exploratory data. Since LGGs are infiltrative tumors which typically do not enhance with contrast administration, for evaluation of response and PFS,

the tumor (i.e., target lesion) will be measured from the T2 or FLAIR MRI images. In case there is an enhancing lesion at the baseline, careful discussion will be made as to whether the pathology information as WHO grade II tumor truly represents the status of the tumor. If the enhancing tumor is still considered to be grade II, the size of the enhancing lesion will be used for evaluation.

9.2.4 Evaluation of PBMC responses against IMA950 in association with OS, PFS and frequency of IMA950 reactive T-cells in the tumor

We will attempt to determine whether vaccine-reactive T-cells in PBMC: 1) correlate with clinical benefits, such as PFS and OS; 2) correlate with observations in the glioma TME; and 3) is higher in Arm 1 over Arm 2 patients.

9.2.5 To tabulate tumor objective response rate (ORR) (According to LGG RANO if there is measurable tumor after surgery).

9.2.6 RANO response criteria for low-grade glioma[2]

Complete response: Complete response requires all the following criteria compared with the baseline scan: (1) Complete disappearance of the lesion on T2 or FLAIR imaging (if enhancement had been present, it must have resolved completely); (2) no new lesions, no new T2 or FLAIR abnormalities apart from those consistent with radiation effects, and no new or increased enhancement; (3) patients must be off corticosteroids or only on physiological replacement doses; and (4) patients should be stable or improved clinically

Partial response: Partial response requires all of the following criteria compared with the baseline scan: (1) greater than or equal to 50% decrease in the product of perpendicular diameters of the lesion on T2 or FLAIR imaging sustained for at least 4 weeks compared with baseline; (2) no new lesions, no new T2 or FLAIR abnormalities apart from those consistent with radiation effects, and no new or increased enhancement; and (3) patients should be on a corticosteroid dose that should not be greater than the dose at time of baseline scan, and should be stable or improved clinically

Minor response: Minor response requires the following criteria compared with baseline: (1) a decrease of the area of non-enhancing lesion on T2 or FLAIR MR imaging between 25% and 50% compared with baseline; (2) no new lesions, no new T2 or FLAIR abnormalities apart from those consistent with radiation effect, and no new or increased enhancement; and (3) patients should be on a corticosteroid dose that should not be greater than the dose at time of baseline scan, and should be stable or improved clinically

Stable disease: Stable disease is present if the changes do not qualify for complete, partial, or minor response, or progression and requires: (1) stable area of non-enhancing abnormalities on T2 or FLAIR imaging; (2) no new lesions, no new T2 or FLAIR

abnormalities apart from those consistent with radiation effect, and no new or increased enhancement; and (3) patients should be on a corticosteroid dose that should not be greater than the dose at time of baseline scan, and should be stable or improved clinically

Progression: Progression is defined by any of the following: (1) development of new lesions or increase of enhancement (radiological evidence of malignant transformation); (2) a 25% increase of the T2 or FLAIR non-enhancing lesion on stable or increasing doses of corticosteroids compared with baseline scan or best response after initiation of therapy, not attributable to radiation effect or to comorbid events; (3) definite clinical deterioration not attributable to other causes apart from the tumor, or decrease in corticosteroid dose; or (4) failure to return for evaluation because of death or deteriorating condition, unless caused by documented non-related disorders

Although the above RANO criteria do not allow increase of steroid for CR, PR and SD, if a possibility of pseudo-tumor progression is suspected, patients may be placed on dexamethasone, up to 4 mg/day, and reimaged 4-8 weeks later. If they require > 4mg/day dexamethasone, or if their repeat imaging study continues to meet the criteria for disease progression, the patient will be taken off study and further study treatment will be discontinued. However, if the steroid dose is 4mg/day or less and if the repeat imaging does not meet the criteria for disease progression, then the patient will continue on study and receive study treatment as prescribed by the protocol. Any cases of suspected tumor progression or pseudo-tumor progression should be reviewed by the PI to determine whether the subjects should remain in the trial.

9.2.7 Evaluation of leukocyte phenotypes in PBMC samples

Using flow-cytometry, we will also evaluate the numbers of lymphocyte subsets such as immature myeloid cells, $CD4^+$ T cells, $CD4^+/Foxp3^+$ regulatory T cells in TIL and PBMC in an exploratory manner. These plans (in this paragraph) are immunological evaluations; however, do not compose the primary endpoints due to their exploratory nature. We will evaluate expression of perforin/IFN-γ (function) and Annexin-V (an apoptotic cell marker) in $CD4^+$ and $CD8^+$ T-cells, $CD33^+CD11b^+HLA\text{-}DR^-$ or dim immature myeloid cells and other myeloid cells (including $CD33^+CD11b^+HLA\text{-}DR^+$ cells) per milligram of tumor tissue. We will use RT-PCR to evaluate expression of arginase-1, ROS, and NOS in flow-sorted myeloid cells.

9.2.8 Evaluation of pharmacokinetics for varlilumab

We will evaluate pharmacokinetics in patients receiving Varlilumab in the current regimen. On varlilumab administration days, samples should be drawn from the arm contralateral to the infusion site prior to administration and at 30 minutes (±5 minutes) after the end of the varlilumab infusion. An additional sample should be drawn as soon as possible for any patients who experience an infusion reaction.

10 Adverse Event Documentation and Reporting

Toxicity and adverse events will be classified according to NCI's Common Terminology Criteria for Adverse Events V 5.0 (CTCAE) and reported as detailed below. A copy of the CTCAE can be downloaded from http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40.

All grade 3 and above adverse events, the severity and the investigator's determination of attribution and causality will be entered into OnCore, whether or not the event is believed to be associated with the investigational vaccine. We will report any grade 3, 4 or 5 toxicity that occurs during the vaccination period or during post-treatment follow-up (until disease progression or for a maximum of 24 months from study enrollment, whichever occurs earlier). Appropriate medical treatments will be initiated immediately in response to grade 3 or 4 toxicities per institutional guidelines.

10.1 Definitions

The following definitions are based on the Code of Federal Regulations (21 CFR 312.32(a)).

Adverse Event: Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An adverse event (also referred to as an adverse experience) can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, and does not imply any judgment about causality. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

Suspected Adverse Reaction: Any adverse event for which there is a reasonable possibility that the study drug caused the adverse event. For purposes of IND safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event.

Life-Threatening Adverse Event Or Life-Threatening Suspected Adverse Reaction: An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

Serious Adverse Event or Serious Suspected Adverse Reaction: An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death
- A life-threatening adverse event
- 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 serious 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.

If either the IND sponsor or the investigator believes the event is life-threatening or serious, the event must be evaluated by the sponsor for expedited reporting (21CFR 312.32).

Unexpected adverse event or unexpected suspected adverse reaction: An adverse event or suspected adverse reaction is considered “unexpected” if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended. Thus, adverse events that occur as part of the disease process or underlying medical conditions are considered unexpected; however, they will not be reportable.

Expedited (Rapid) Reporting: Certain events may require rapid notification to entities providing patient safety oversight (e.g. IRB, FDA) as detailed in the current section 10.

10.2 Recording Requirements

All observed or volunteered adverse events (serious or non-serious) and abnormal test findings, regardless of study group or suspected causal relationship to the study drug(s) will be recorded in the subjects’ case histories. For all adverse events, sufficient information will be pursued and/or obtained so as to permit 1) an adequate determination of the outcome of the event (i.e., whether the event should be classified as a *serious adverse event*) and; 2) an assessment of the casual relationship between the adverse event and the study drug(s).

AEs or abnormal test findings felt to be associated with the investigational drug or study treatment(s) will be followed until the event (or its sequelae) or the abnormal test finding resolves or stabilizes at a level acceptable to the Sponsor-Investigator.

10.3 Abnormal Test Findings

An abnormal test finding will be classified as an *adverse event* if one or more of the following criteria are met:

- The test finding is accompanied by clinical symptoms.
- The test finding necessitates additional diagnostic evaluation(s) or medical/surgical intervention; including significant additional concomitant drug treatment or other therapy.

Note: simply repeating a test finding, in the absence of any of the other listed criteria, does not constitute an AE.

- The test finding leads to a change in study dosing or discontinuation of subject participation in the clinical study.
- The test finding is considered an AE by the Sponsor-Investigator of the IND application.

10.4 Review of Safety Information: Sponsor Responsibilities[1]

The IND sponsor must promptly review all information relevant to the safety of the drug obtained or otherwise received from foreign or domestic sources, including information derived from any clinical or epidemiological investigations, animal or in vitro studies, reports in the scientific literature, and unpublished scientific papers, as well as reports from foreign regulatory authorities and reports of foreign commercial marketing experience for drugs that are not marketed in the United States.

Note: The requirements of the Sponsor for the reporting of suspected adverse drug reactions to the FDA differ from the requirements of the Investigator (refer to Section 10.5) for the reporting of adverse events to the Sponsor.

10.5 Review of Safety Information: Investigator Responsibilities[2]

(a) Progress reports. The investigator shall furnish all reports to the sponsor of the drug who is responsible for collecting and evaluating the results obtained. The sponsor is required under 312.33 to submit annual reports to FDA on the progress of the clinical investigations.

(b) Safety reports. An investigator must immediately report to the sponsor any serious adverse event, whether or not considered drug related, including those listed in the protocol or investigator brochure and must include an assessment of whether there is a reasonable possibility that the drug caused the event. Study endpoints that are serious adverse events (e.g., all-cause mortality) must be reported in accordance with the protocol unless there is evidence suggesting a causal relationship between the drug and the event (e.g., death from anaphylaxis). In that case, the investigator must immediately report the

[1] 21 CFR Sec. 312.50
[2] 21 CFR Sec. 312.64

event to the sponsor. The investigator must record non-serious adverse events and report them to the sponsor according to the timetable for reporting specified in the protocol.

(c) Final report. An investigator shall provide the sponsor with an adequate report shortly after completion of the investigator's participation in the investigation.

10.6 IND safety reports (12CFR 312.32)

The Sponsor must notify FDA and all participating investigators (i.e., all investigators to whom the sponsor is providing drug under its INDs or under any investigator's IND) in an IND safety report of potential serious risks, from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after the sponsor determines that the information qualifies for reporting under Sections 10.7 10.8, 10.9, 10.10 below. In each IND safety report, the sponsor must identify all IND safety reports previously submitted to FDA concerning a similar suspected adverse reaction, and must analyze the significance of the suspected adverse reaction in light of previous, similar reports or any other relevant information.

IND Sponsor Reporting to FDA

<table>
<tr><th>Agency</th><th>Criteria for reporting</th><th>Timeframe</th><th>Form to Use</th><th>Submission address/ fax numbers</th></tr>
<tr><td rowspan="5">FDA</td><td>Unexpected and fatal or life threatening suspected adverse reaction</td><td>As soon as possible but no later than 7 Calendar-Day</td><td rowspan="3">FDA prefers MedWatch 3500a Form however use of the UCSF SAE form is acceptable</td><td rowspan="4">Telephone or fax SAE to IND/IDE review division project manager – follow-up with written report submitted as an amendment to the IND within 15 days of knowledge of event</td></tr>
<tr><td>1) serious and unexpected suspected adverse reaction or

2) increased occurrence of serious suspected adverse reactions over that listed in the protocol or investigator

brochure or

3) findings from other sources</td><td>As soon as possible but no later than 15 Calendar-Day</td></tr>
<tr><td>Any grade 2 to 5 autoimmune</td><td rowspan="2">As soon as possible but no later than 7 Calendar-Day</td></tr>
<tr><td>Any halting of the study enrollment due to dose limiting toxicity or other early study stop</td><td>Summary letter</td></tr>
<tr><td>Deaths and all other events per CFR 312.33</td><td>At time of FDA annual report</td><td>Summary format</td><td>Submit as an amendment to the IND</td></tr>
</table>

10.7 Serious and unexpected suspected adverse reaction

The Sponsor must report any suspected adverse reaction that is both serious and unexpected. The sponsor must report an adverse event as a suspected adverse reaction

only if there is evidence to suggest a causal relationship between the drug and the adverse event, such as:

- A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome);
- One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (e.g., tendon rupture);
- An aggregate analysis of specific events observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group.

10.8 Findings from other studies

The Sponsor must report any findings from epidemiological studies, pooled analysis of multiple studies, or clinical studies (other than those reported under section 7.6.1), whether or not conducted under an IND, and whether or not conducted by the sponsor, that suggest a significant risk in humans exposed to the drug. Ordinarily, such a finding would result in a safety-related change in the protocol, informed consent, investigator brochure (excluding routine updates of these documents), or other aspects of the overall conduct of the clinical investigation.

10.9 Findings from animal or in vitro testing

The sponsor must report any findings from animal or in vitro testing, whether or not conducted by the sponsor, that suggest a significant risk in humans exposed to the drug, such as reports of mutagenicity, teratogenicity, or carcinogenicity, or reports of significant organ toxicity at or near the expected human exposure. Ordinarily, any such findings would result in a safety-related change in the protocol, informed consent, investigator brochure (excluding routine updates of these documents), or other aspects of the overall conduct of the clinical investigation.

10.10 Increased rate of occurrence of serious suspected adverse reactions

The sponsor must report any clinically important increase in the rate of a serious suspected adverse reaction over that listed in the protocol or investigator brochure.

10.11 Submission of IND safety reports

The sponsor must submit each IND safety report in a narrative format or on FDA Form 3500A or in an electronic format that FDA can process, review, and archive. FDA will periodically issue guidance on how to provide the electronic submission (e.g., method of transmission, media, file formats, preparation and organization of files). The sponsor may submit foreign suspected adverse reactions on a Council for International Organizations of Medical Sciences (CIOMS) I Form instead of a FDA Form 3500A. Reports of overall

findings or pooled analyses from published and unpublished in vitro, animal, epidemiological, or clinical studies must be submitted in a narrative format. Each notification to FDA must bear prominent identification of its contents, i.e., "IND Safety Report," and must be transmitted to the review division in the Center for Drug Evaluation and Research or in the Center for Biologics Evaluation and Research that has responsibility for review of the IND. Upon request from FDA, the sponsor must submit to FDA any additional data or information that the agency deems necessary, as soon as possible, but in no case later than 15 calendar days after receiving the request.

10.12 Unexpected fatal or life-threatening suspected adverse reaction reports

The sponsor must also notify FDA of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible but in no case later than 7 calendar days after the sponsor's initial receipt of the information.

10.13 Reporting format or frequency

FDA may require a sponsor to submit IND safety reports in a format or at a frequency different than that required under this paragraph. The sponsor may also propose and adopt a different reporting format or frequency if the change is agreed to in advance by the director of the FDA review division that has responsibility for review of the IND.

10.14 Reporting study endpoints

Study endpoints (e.g., mortality or major morbidity) must be reported to FDA by the sponsor as described in the protocol and ordinarily would not be reported under section 10.6 above. However, if a serious and unexpected adverse event occurs for which there is evidence suggesting a causal relationship between the drug and the event (e.g., death from anaphylaxis), the event must be reported under *Serious and unexpected suspected adverse reaction* as a serious and unexpected suspected adverse reaction even if it is a component of the study endpoint (e.g., all-cause mortality).

10.15 Follow-up

- The sponsor must promptly investigate all safety information it receives.
- Relevant follow-up information to an IND safety report must be submitted as soon as the information is available and must be identified as such, i.e., "Follow-up IND Safety Report."
- If the results of a sponsor's investigation show that an adverse event not initially determined to be reportable under section IND safety reports of this section is so reportable, the sponsor must report such suspected adverse reaction in an IND safety report as soon as possible, but in no case later than 15 calendar days after the determination is made.

10.16 Disclaimer

A safety report or other information submitted by a sponsor under this part (and any release by FDA of that report or information) does not necessarily reflect a conclusion by

the sponsor or FDA that the report or information constitutes an admission that the drug caused or contributed to an adverse event. A sponsor need not admit, and may deny, that the report or information submitted by the sponsor constitutes an admission that the drug caused or contributed to an adverse event.

10.17 Reporting adverse events to the responsible IRB

In accordance with applicable policies of the UCSF Institutional Review Board (IRB), the Sponsor-Investigator will report, to the IRB, any observed or volunteered adverse event that is determined to be 1) *associated with the investigational drug or study treatment(s)*; 2) *serious*; and 3) *unexpected*. Adverse event reports will be submitted to the IRB in accordance with the respective IRB reporting guidelines.

Applicable adverse events will be reported to the IRB as soon as possible and, in no event, later than 10 calendar days following the sponsor-investigator's receipt of the respective information. Adverse events which are 1) *associated with the investigational drug or study treatment(s)*; 2) *fatal or life-threatening*; and 3) *unexpected* will be reported to the IRB within 24 hours of the Sponsor-Investigator's receipt of the respective information.

Follow-up information to a reported adverse event will be submitted to the IRB as soon as the relevant information is available. If the results of the Sponsor-Investigator's follow-up investigation show that an adverse event that was initially determined to not require reporting to the IRB does, in fact, meet the requirements for reporting; the Sponsor-Investigator will report the adverse event to the IRB as soon as possible, but in no event later than 10 calendar days, after the determination was made.

11 Data Collection and Monitoring

Both patient accrual and toxicity are recorded in OnCore and monitored weekly by the principal investigator. Once all patients are off active study treatment (i.e., are on follow-up only), the accrual/toxicity reviews will occur every 6 months rather than monthly. Annual IRB renewals will be filed outlining accrual/toxicity information from the prior year.

11.1 Data Safety Monitoring Plan

A DSMP for this study consists of monitoring safety issues in the form of AEs and data to evaluate the efficacy and effectiveness of the study. All such events that meet UCSF IRB reporting guidelines are submitted on an ongoing basis throughout the renewal interval. Events that do not meet the reporting guidelines are reviewed and placed in the regulatory file for this trial. All events, whether reportable or not, are stored with the study files (electronically and/or as a hard-copy) and reviewed monthly by the study team. Study progress is also assessed by the study team on a monthly basis during the conduct of this trial. This assessment includes discussion of recruitment, screening and accrual issues as well as study conduct (dosing, study tests and procedures, response data, patient follow-

up, deviations, confidentiality, etc.). In addition, new scientific publications or data that suggest changes to the current trial may be warranted will be discussed should they arise.

This cumulative DSMP ensures that the risk-to-benefit ratio will be closely monitored for any changes. At the time of IRB renewal, the data and safety monitoring activities outlined above will be summarized and included on the IRB renewal report.

The UCSF Helen Diller Family Comprehensive Cancer Center (HDFCCC) Data and Safety Monitoring Committee (DSMC) is responsible for monitoring data quality and subject safety for all HDFCCC institutional clinical studies. A summary of DSMC activities for this study include:

- **Review of subject data in each arm**
- **Review of suspected adverse reactions considered "serious"**
- **Monitor monthly as subjects are enrolled, depending upon accrual**
- **Minimum of a yearly regulatory audit**

Adverse Event Review and Monitoring

All clinically significant adverse events, whether or not unexpected, and whether or not considered to be associated with the use of the study drug, will be entered into OnCore®, UCSF's Clinical Trial Management System.

All adverse events entered into OnCore® will be reviewed on a weekly basis at the Site Committee meetings. The Site Committee will review and discuss the selected toxicity, the toxicity grade, and the attribution of relationship of the adverse event to the administration of the study drug.

In addition, all suspected adverse reactions considered "serious" are entered into OnCore® and will be reviewed and monitored by the Data and Safety Monitoring Committee on an ongoing basis and discussed at DSMC meetings, which takes place every 6 weeks.

If a death occurs during the treatment phase of the study or within 30 days after the last administration of the study drug and is determined to be related either to the study vaccine or to a study procedure, the investigator or his/her designee must notify the DSMC Chair within 1 business day of knowledge of the event. The contact may be by phone or email.

Increase in Adverse Event Rates

If an increase in the frequency of Grade 3 or 4 adverse events (above the rate reported in the protocol) is noted in the study, a report will be submitted to the DSMC at the time the increased rate is identified. The report will indicate if the incident of adverse events observed in the study is above the range stated in the Investigator Brochure.

If at any time the investigator stops enrollment or stops the study due to safety issues, the DSMC Chair and DSMC manager must be notified within 1 business day via email. The DSMC must receive a formal letter within 10 business days and the IRB must be notified.

Data and Safety Monitoring Committee contacts:

DSMC Chair: [redacted]

DSMC Manager: [redacted]

11.2 Record Retention

In accordance with FDA regulations, the investigator shall retain records for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA is notified.

12 Statistical Considerations

12.1 Statistical Analysis Plan

12.1.1 Primary Safety Objective: *Evaluate the incidence and severity of adverse events associated with the treatment regime.* The proportion of patients experiencing Regimen Limiting Toxicity (RLT, Section 5.3.1) in each arm will be tabulated with 95% exact (Clopper-Pearson) confidence intervals. The proportions of patients experiencing RLT will be compared between arms by the Fisher's exact test. The power of this test is described in Section 12.3. The early stopping rule for RLT is described in Section 12.2.

12.1.2 Primary Immunogenicity Objective: *Detection of vaccine-induced immune response in pre- and post-vaccine PBMC.* The standardized difference between pre- and post-vaccine PBMC will be compared between arms via a two-sample Student's *t* test. We assume the magnitude of difference will be greater in Arm 1 than Arm 2. If the *t* test assumptions are not met and the data cannot be transformed in such a way that the assumptions are met, a Wilcoxon Rank Sum test will be used. Based on a one-sided two-sample equal variance t-test, the statistical power will be 80% with 15 patients per arm if the difference between arms is at least 0.8 with a standard deviation for both arms of 1.0 with a significance level of 0.10.

12.1.3 Exploratory Efficacy Objective: Evaluation of IMA950-reactive T-cell infiltration and CXCL9/10 expression in tumors resected from Arm 1 and Arm 2 patients. In surgically resected tumor tissues from Arm 1 (IMA950+poly-ICLC and varlilumab) and Arm 2 (IMA950+poly-ICLC alone) patients, we will evaluate numbers of tumor-

infiltrating $CD4^+$ T-cells $CD8^+$ T-cells (by flow-cytometry) and CXCL10 expression (by RT-PCR).This comparison will be made via two-sample t-tests unless the assumptions are not met then a Wilcoxon alternative will be employed.

12.1.4 Exploratory Efficacy Objective: *To evaluate IMA950-reactive TCR clonotypes in tumors resected from Arm 1 and Arm 2 patients.* Our expectation is to see a higher number of copies of vaccine-specific TCRs (frequency/total tumor DNA) in Arm 1 samples than in Arm 2 samples. This comparison will be made via two-sample t-tests unless the assumptions are not met then a Wilcoxon alternative will be employed.

12.1.5 Exploratory Efficacy Objective: *To estimate overall survival (OS) and progression-free survival (PFS) in the two arms.* Product limit (Kaplan-Meier) estimates of the OS and PFS functions will be calculated with 95% Greenwood confidence regions. The trial is not adequately powered for the log-rank test that compares survival functions between arms.

12.1.6 Exploratory Efficacy Objective: Evaluation of PBMC responses against IMA950 in association with OS, PFS and frequency of IMA950 reactive T-cells in the tumor. The association of the immunological parameter with PFS and OS will be evaluated using proportional hazards (Cox) regression. Frequencies will be tabulated.

12.1.7 Exploratory Efficacy Objective: *Tabulate tumor objective response rate (ORR).* The (multinomial) distributions of responses in patients with measurable tumors (Section 9.2.3) will be calculated with simultaneous (Sison & Glaz) confidence regions. The trial is not adequately powered for a comparison between arms using Fisher's exact test.

12.1.8 Exploratory Efficacy Objective: *Evaluation of leukocyte phenotypes in PBMC samples.* Frequencies will be tabulated to compare the distributions of the phenotypes between arms.

12.1.9 Exploratory Efficacy Objective: *Evaluation of pharmacokinetics for varlilumab.* The purpose of this exploratory efficacy objective is to capture minimum and maximum values for the different pharmacokinetics measures. The purpose is not testing hypothesis; therefore descriptive statistics will be reported.

12.2 Stopping Rule for Toxicity

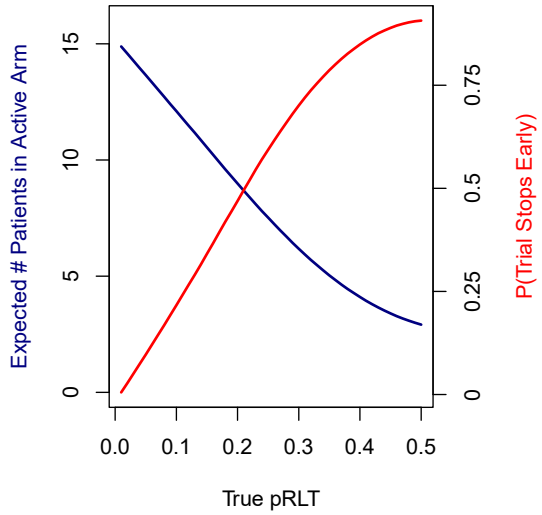
The trial will be stopped for toxicity if the number of patients experiencing RLT in either arm is excessive. A probability of RLT (pRLT) exceeding 0.33 would be considered prohibitively high. Based on the previous experience in UPCI 07-057 and UPCI 08-135, we believe the expected pRLT is 1/20, and that the probability pRLT is equal to or greater than 0.33 is 0.05. We will use a continuous Bayesian beta-binomial monitoring rule: stop the trial if the estimated P(RLT>0.33)>0.33. We will use a beta prior distribution with

parameters α=0.09 and β=1.71, representing our beliefs above. The stopping rule is specified in the table.

# Patients	# RLT	# Patients	# RLT
3	2	12	4
4	2	13	5
5	2	14	5
6	3	15	5
7	3		
8	3		
9	3		
10	4		
11	4		

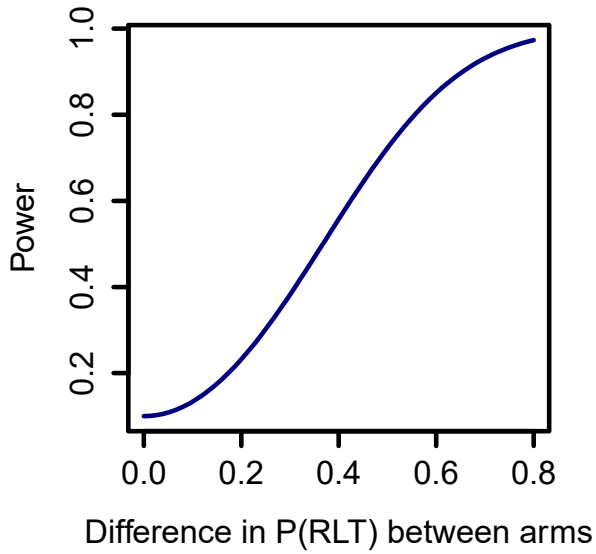
Stopping rule for toxicity: for the given number of patients in the either arm, the trial is halted if the number of RLTs equals the given number

The operating characteristics of this rule were determined by Monte Carlo simulation and are displayed in the graph. It is seen that if the true pRLT>0.33, the expected number of patients enrolled is five and the probability the trial stops early is 0.75, but if the true pRLT=0.1, the probability the trial stops early equals 0.2.



Operating characteristics of the stopping rule. The blue line is the expected number of patients in the trial (left axis) and the red line is the probability the trial stops early (right axis) as a function of the true (unobserved) pRLT.

12.3 Justification of Design



The statistical power of the trial for the safety primary objectives is displayed in the plot.

For the primary safety endpoint, the power of the comparison of P(RLT) between the two arms is presented in terms of the arithmetical difference in the true P(RLT).

13 Budgetary Considerations

Neither subjects, nor their insurance provider, will be charged for the costs of any of the procedures performed for the purpose of this research study. Subjects will be charged, in the standard manner, for any procedures performed for their routine medical care (clinic visits, physical examinations, and laboratory tests to measure blood counts and chemistries). All MRI scans obtained will be considered standard of care for the management of a patient with WHO grade II glioma and will be billed to the patient's insurance provider. Subjects will be responsible for any costs for routine care not covered by their insurance provider, including any applicable co-payments, co-insurances and deductibles.

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APPENDIX I - Data and Safety Monitoring Plan for a Phase 1 Dose Escalation Institutional Study or Vaccine Trial

The UCSF Helen Diller Family Comprehensive Cancer Center (HDFCCC) Data and Safety Monitoring Committee (DSMC) is responsible for monitoring data quality and subject safety for all HDFCCC institutional clinical studies. A summary of DSMC activities for this study include:

- Review of subject data in each cohort
- Review of suspected adverse reactions considered "serious"
- Approval of dose escalation by DSMC Chair (or qualified alternate)
- Monthly monitoring (depending on study accrual)
- Minimum of a yearly regulatory audit

Monitoring and Reporting Guidelines

Investigators will conduct continuous review of data and subject safety and discuss each subject's treatment at weekly Site Committee meetings. These discussions are documented in the Site Committee meeting minutes. For each dose level, the discussion will include the number of patients, significant toxicities in accordance with the protocol, doses adjustments, and observed responses.

All institutional Phase 1 therapeutic studies are designated with a high risk assessment; therefore, the data is monitored once per month as subjects are enrolled through the DLT period.

Adverse Event Review and Monitoring

All clinically significant adverse events, whether or not unexpected, and whether or not considered to be associated with the use of the study drug, will be entered into OnCore®, UCSF's Clinical Trial Management System.

All clinically significant adverse events entered into OnCore® will be reviewed on a weekly basis at the Site Committee meetings. The Site Committee will review and discuss the selected toxicity, the toxicity grade, and the attribution of relationship of the adverse event to the administration of the study drug(s).

In addition, all suspected adverse reactions considered "serious," entered into OnCore® will be reviewed and monitored by the Data and Safety Monitoring Committee on an ongoing basis and discussed at DSMC meetings, which take place every six (6) weeks.

If a death occurs during the treatment phase of the study or within 30 days after the last administration of the study drug(s) and it is determined to be related either to the study drug(s) or to a study procedure, the Investigator or his/her designee must notify the DSMC Chair within **1 business day** of knowledge of the event. The contact may be by phone or e-mail.

Dose Escalations

At the time of dose escalation, a written report will be submitted to the DSMC Chair (or qualified alternate) describing the cohorts, dose levels, adverse events, safety reports, and any Dose Limiting

Toxicities observed, in accordance with the protocol. The report will be reviewed by the DSMC Chair (or qualified alternate) and written authorization to proceed or a request for more information will be issues within **2 business days** of the request. Approval for the dose escalation by the DSMC Chair (or qualified alternate) must be obtained prior to implementation.

Increase in Adverse Event Rates

If an increase in the frequency of Grade 3 or 4 adverse events (above the rate reported in the Investigator Brochure or package insert) is noted in the study, a report should be submitted to the DSMC at the time the increased rate is identified. The report will indicate if the incidence of AEs observed in the study is within the range stated in the Investigator Brochure or package insert.

If at any time the Investigator stops enrollment or stops the study due to safety issues the DSMC Chair and administrator must be notified within **1 business day** via e-mail. The DSMC must receive a formal letter within **10 business days** and the IRB must be notified.

Data and Safety Monitoring Committee Contacts:

DSMC Chair: [redacted]
Phone:
Email:
Address:
UCSF
San Francisco, CA 94158

DSMC Monitors
[redacted]
UCSF Helen Diller Family Comprehensive Cancer Center
San Francisco, CA 94143

APPENDIX II - Performance Status Criteria

Karnofsky Performance Scale	
Percent	Description
100	Normal, no complaints, no evidence of disease.
90	Able to carry on normal activity; minor signs or symptoms of disease.
80	Normal activity with effort; some signs or symptoms of disease.
70	Cares for self, unable to carry on normal activity or to do active work.
60	Requires occasional assistance, but is able to care for most of his/her needs.
50	Requires considerable assistance and frequent medical care.
40	Disabled, requires special care and assistance.
30	Severely disabled, hospitalization indicated. Death not imminent.
20	Very sick, hospitalization indicated. Death not imminent.
10	Moribund, fatal processes progressing rapidly.
0	Dead.

APPENDIX III - Vaccination Toxicity Assessment Form

Measurement of local reaction will be performed by the patient. At the time of injection, study staff should mark the outline of the 3-5 cm injection site on the skin. Patients will then be instructed by the site to measure the area of local reaction at its perceived maximum, 48 ± 6 hours after administration of vaccine. Patients should lay the provided template, printed on transparency (shown below) so that the bull's eye is centered over the injection area, and trace the area of local reaction onto the transparency using a permanent marker. When the transparency is returned at the next study visit, site staff will record the bidimensional diameters of the reaction in the CRF.

Study ID (entered by site)

Date/time of administration (entered by site) | | | | | | | | | | : | | |

DD MM YY Hou Min

48 hr assessment: Date/time of measurement (entered by patient) | | | | | | | | | | : | | |

DD MM YY Hou Min

96 hr assessment: Date/time of measurement : | | | | | | | | | | |