Official Protocol Title:	Phase 1/2 Study of Intratumoral G100 With Or Without Pembrolizumab or Rituximab In Patients With Follicular Non-Hodgkin's Lymphoma
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CLINICAL PROTOCOL

Phase 1/2 Study Of Intratumoral G100 With Or Without Pembrolizumab or Rituximab In Patients With Follicular Non-Hodgkin's Lymphoma

Protocol Number:	IMDZ-G142
Investigational Agent(s):	G100 (glucopyranosyl lipid A stable emulsion, GLA-SE) and Pembrolizumab and Rituximab
Sponsor's Name:	Immune Design 1616 Eastlake Ave. E, Suite 310 Seattle, WA 98102
Version and Date:	Version 04B November 15, 2018
IND Number:	BB-IND 15708

INVESTIGATOR'S SIGNATURE PAGE

Investigator: _____

Study Number: IMDZ-G142

Product Name(s): G100 and Pembrolizumab or Rituximab

Study Title: Phase 1/2 Study Of Intratumoral G100 With Or Without Pembrolizumab or Rituximab In Patients With Follicular Non-Hodgkin's Lymphoma

Document Date: November 15, 2018

As Principal Investigator, I agree to:

1. Keep all documentation supplied to me or developed by me concerning this study, and that has not been previously published, in the strictest confidence. This documentation includes, but is not limited to, the Investigator's Brochure and Case Report Forms (CRFs)
2. That the study will not commence without prior written approval of a properly constituted Institutional Review Board. No changes will be made to the study Protocol without prior written approval of Immune Design and the Institutional Review Board, except where necessary to eliminate an immediate hazard to patients
3. Implement and conduct the study diligently and in strict compliance with the protocol, good clinical practices and all applicable laws and regulations
4. Accurately transfer all required data from each patient's source document to the CRFs. The original CRFs will be submitted to the Sponsor in a timely manner at the completion of the trial, or as otherwise specified by the Sponsor
5. Keep a complete and accurate accounting during and at the completion of the trial of all procedures performed with the drug provided by the Sponsor
6. Allow authorized representatives of Immune Design or regulatory authority representatives to conduct on-site visits to review, audit and copy trial documents. I will personally meet with these representatives at mutually convenient times to answer any trial-related questions
7. Provide the Sponsor with an investigator's summary within 90 days of completion of the final trial visit for the last patient enrolled, or as designated by Sponsor
8. Maintain all information supplied by the Sponsor in confidence and, when this information is submitted to an Institutional Review Board (IRB), Ethical Review Committee, or another group, it will be submitted with a designation that the material is confidential.

This protocol was designed and will be conducted, recorded, and reported in compliance with the principles of Good Clinical Practice (GCP) guidelines. These guidelines are stated in U.S. federal regulations as well as "Guidance for Good Clinical Practice," International Council on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use.

I have read this protocol in its entirety, including the preceding statements, and I agree to comply with all aspects of this trial.

_____

Investigator Printed Name

_____ _____

Investigator Signature Date

_____

Institution Name

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2.0 GENERAL INFORMATION

2.1 Sponsor Information

Trial Sponsor:

Immune Design
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Sponsor's Medical Monitor:

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2.2 Protocol Revision History

Version	Date	Comment
01	12 March 2015	Initial Release
02	05 November 2015	This amendment adds a treatment arm to Part 2 Patient Expansion to examine the sequential addition of the anti-PD1 antibody pembrolizumab to intratumoral G100. The new Patient Expansion treatment group will randomize 12 patients each to receive either G100 or G100 with sequentially administered pembrolizumab. The title has been modified to reflect this. Other changes include the addition of new objectives/endpoints for the analysis of G100 with sequentially administered pembrolizumab; background, safety information, dose and dose modifications for the use of pembrolizumab; added marginal zone B cell lymphomas as potentially eligible indications for Part 1 Dose Escalation and changed NHL description from "follicular" to "low-grade" NHL to clarify the expanded population in Part 1 objective/endpoints ; additional exclusion criteria for patients with the potential to be randomized and treated with pembrolizumab; addition of thyroid function tests as part of safety analyses for patients receiving pembrolizumab; added a baseline beta-2-microglobulin test; revision of the G100 study drug description section; addition of clinical response assessment by International Working group criteria for NHL; clarification that PD will be assessed by irRC criteria; clarification that FLIPI criteria will be collected and evaluated; added information about the International Working group criteria and FLIPI as new Appendices; clarification in the Synopsis that patients achieving CR, PR or SD will be followed as long as feasible to assess long term outcome; added that photographic documentation should be considered for visually accessible lesions; correction of a visit 10 blood draw for TCR analysis in Section 10.0; modification of the DLT criteria to exclude moderate grade 3 injection site reactions if they improve within 14 days; clarification of DLT criteria for patients receiving pembrolizumab and role of DMC safety reviews of pembrolizumab adverse events; changed the follow up of G100 patients who withdraw early to 30 days to match pembrolizumab treated patients; in the Schedule of Events for pembrolizumab therapy clarified that all AEs/SAEs and events of clinical interest experienced from time of enrollment through 30 days following cessation of treatment would be reported and that all SAEs would be collected up to 90 days following the last dose of pembrolizumab. Based on the consensus guidelines from the Cardiovascular and Interventional Radiology Society of Europe, clarified that for low risk injection/biopsies such as a superficial lymph node or subcutaneous mass, non-steroidal anti-inflammatory drugs (NSAIDs), aspirin, or clopidogrel may be used by the patient and do not have to be withheld.

Version	Date	Comment
02.1	23 March 2016	UK specific Amendment. In this version, an abbreviation list has been included, the investigators and sites have been updated. The contraception sections have been updated to reflect the recommended types of contraception and definitions. Updated contraception language has been added to Inclusion criteria #7 and #8, Section 8.1.6 and in the new Appendix F. The Schedule Events in Sections 3 and 10 have been updated to include at least monthly pregnancy testing for female patients while receiving study drug. The SAE reporting language has been clarified such that only serious events that are considered at least possibly related and are considered unexpected will be expedited as reports to regulatory agencies.
03	05 January 2017	Updated list of all current investigators and sites. Added Part 3 G100 20µg Dose Expansion arm and language inserted throughout the protocol to allow treatment of up to 25 subjects at the 20 µg dose using the same tumor size entrance criteria as the other non-Large Tumor arms. Added new Schedule of Events table 3.4 for Part 3. Corrected changes addressed by Administrative letter dated 17June2016: DLT definition by adding a "not" and corrected inconsistent criteria language in Section 10.3.12 and 10.3.13 where required tumor shrinkage was listed as 50% instead of 75%. The requirement for 75% or less shrinkage has now been removed and now states if the lesion has not "regressed completely". The requirement to receive a second course of G100 has been modified to allow patients with PD who do not require immediate therapy to be eligible for a second course. Clarified treatment windows. Added potential assessments of PFS and OS. Changed follow-up radiology assessments to every 3-4 months in the second year and to at least every 6 months during year 3 and subsequent years to match current practice for this indication. Updated contraceptive language to be more specific in the Inclusion Criteria and added detailed information about contraception in Appendix F. Removed egg lecithin as a possible allergen since it is not part of the G100 product used in this study. Added UK specific language regarding contraceptives and pregnancy testing. Updated information in Appendix B regarding IrRC tumor measurements. Added the ability to potentially request and collect additional blood and/or tumor samples for biomarkers studies. Additional administrative changes were made throughout the document to ensure clarity and consistency throughout the protocol.

Version	Date	Comment
04	31 July 2018	Added Part 4, a new dose escalation and expansion arm to examine G100 in combination with pembrolizumab in relapsed or refractory FL. This arm will investigate the effect of 20µg of G100 in combination with pembrolizumab without radiation therapy in single and multiple tumor lesions on safety, clinical effect and changes in immune biomarkers and permit an assessment of activity that will permit the design of future studies of G100 and pembrolizumab. Added Part 5, a new dose escalation and expansion to examine the safety and preliminary clinical efficacy of G100 in combination with rituximab in FL. This arm will first examine the safety of escalating doses of G100 administered into a single lesion in combination with rituximab administered at a standard induction regimen. After establishing the maximum safe dose in a single lesion and systemic exposure, a Patient Expansion will then be performed by injecting single or multiple tumor masses with G100 at 20µg/lesion to provide additional data on safety, clinical efficacy, and biomarker changes associated with the new combination regimen. This study will provide an assessment of activity that will permit the design of future studies of G100 and rituximab. An updated Investigator Brochure and Safety language was received from Merck for pembrolizumab and this new safety language has been incorporated throughout this protocol.
04A	31 August 2018	Revised the Inclusion criteria for Part 4 to only include patients with relapsed or refractory disease after ≥3 prior therapies, reduced the number of patients to be enrolled, and revised the statistical section and general treatment sections to reflect this. Part 5 was revised to limit the intratumoral G100 treatment to a single tumor mass during Patient Expansion with either the highest dose determined to be safe during Dose Escalation or the most biologically active and safe dose if determined to be different than the MTD. In addition, the number of patients was reduced, the statistical section and general treatment sections were revised to reflect this. Corrected formatting errors, spelling and added minor word and sentence changes throughout. These corrections included the numbering of Exclusion criteria to be continuous, correction of minor issues with figures, window of pregnancy testing in Section 12.7 and clarifications to the procedures to be followed for Parts 4 and 5.
04B	15 November 2018	An exploratory objective of evaluating Pharmacokinetics and Pharmacodynamic properties of G100 and appropriate sample collection were added. DLT criteria for Parts 4 and 5 were updated and are now consistent for G100, pembrolizumab and rituximab. For Part 4 and Part 5, retreatment criteria timing were clarified. For Part 5, patient eligibility criteria were updated to include patients who have relapsed or refractory CD20+ follicular NHL and who have received at least 1, but not more than 2 prior systemic therapy. Exclusion criteria have been updated to exclude prior G100 therapy. Addition of the use of the Lugano criteria for lymphoma (Cheson 2014) to evaluate clinical response as an additional analysis was clarified at the Sponsor level. A provision to collect radiographic images for central storage and independent radiology review was added.

2.3 List of Abbreviations and Glossary of Terms

Abbreviation	Description
ADCC	antibody dependent cellular cytotoxicity
AE	adverse event
AF	aqueous formulation
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
BUN	blood urea nitrogen
CD	cluster of differentiation
CFR	code of federal regulations
CRF	case report form
CR	complete response
CpG	C-G motifs
CTCAE	Common Toxicity Criteria for Adverse Events
DC	dendritic cell
DCF	Data Clarification Form
DKA	diabetic ketoacidosis
DLT	dose-limiting toxicity
DMC	data monitoring committee
ECG	electrocardiogram
ECI	event of clinical interest
ECOG	Eastern Cooperative Oncology Group
EOS	End of Study
EU	European Union
FLIPI	Follicular Lymphoma International Prognostic Index
G-CSF	granulocyte-colony stimulating factor
GCP	Good Clinical Practice
GM-CSF	granulocyte-macrophage colony stimulating factor
GVHD	graft versus host disease
FCBP	female of child bearing potential
FDA	Food and Drug Administration
Hgb	Hemoglobin
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Council on Harmonization
IEC	independent ethics committee
IgG	immunoglobin G
IHC	immunohistochemistry
IL	interleukin

Abbreviation	Description
INR	international normalised ratio
IRB	institutional review board
irCR	immune-related complete response
irPD	immune-related progressive disease
irPR	immune-related partial response
irRC	immune related response criteria
irSD	immune-related stable disease
IT	Intratumoral
IV	intravenous(ly)
mAb	monoclonal antibody
MHC	major histocompatibility complex
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCI	National Cancer Institute
NHL	non-Hodgkin's lymphoma
NSAID	non-steroidal anti-inflammatory drug
NSCLC	non-small-cell lung cancer
NYHA	New York Heart Association
ORR	overall response rate
OS	overall survival
PCR	polymerase chain reaction
PD	progressive disease
PD-1	programmed death receptor-1
PDL	programmed death ligand
PFS	progression-free survival
PI	principal investigator
PK	Pharmacokinetics
PR	partial response
PTT	partial thromboplastin time
q2W	every 2 weeks
q3W	every 3 weeks
qd	every day
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SC	subcutaneous
SD	stable disease
SE	stable emulsion
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SOP	standard operating procedure

Abbreviation	Description
SPD	sum of the products of the two largest perpendicular diameters
TILs	tumor infiltrating lymphocytes
TLR	toll-like receptor
TNF	tumor necrosis factor
TSH	thyroid-stimulating hormone
TTP	time-to-progression
UK	United Kingdom
ULN	upper limit of normal
WBC	leukocyte count
WHO	World Health Organization

3.0 TRIAL SYNOPSIS AND SCHEDULE OF EVENTS

3.1 Trial Synopsis

Title:	Phase 1/2 Study Of Intratumoral G100 With Or Without Pembrolizumab or Rituximab In Patients With Follicular Non-Hodgkin's Lymphoma
Sponsor:	Immune Design
Trial Site(s):	**US sites:** Augusta University, Augusta, GA. City of Hope, Duarte, CA. Emory University, Atlanta, GA, Greenville Health System, Greenville, SC. Moffitt, Tampa, FL. Northwest Medical Specialties, Tacoma, WA. Oregon Health Sciences University (OHSU), Portland, OR. UCSF, San Francisco, CA University of Utah/Huntsman Cancer Center, Salt Lake City, UT. Washington University, St. Louis, MO. Yale University, New Haven, CT. **European Sites:** Royal Marsden Hospital, London, UK The Christie NHS Trust – Christie Hospital, Manchester, UK. Hopital Ponchaillou – CHU de Rennes, Rennes, FR Clínica Universidad de Navarra, Pamplona, ESP Hospital Universitario Virgen Macarena, Seville, ESP Hospital De La Santa Creu I Sant Pau.Barcelona, ESP (Sites may be added or removed)
Principal Investigator(s):	Weiyun Ai, M.D. PhD., UCSF Nancy Bartlett, M.D., Washington University Locke Bryan M.D., Augusta University Jorge Chaves, M.D. Northwest Medical Specialties Elizabeth Cull, M.D., Greenville Health System Christopher Flowers, M.D., Emory University Ahmad Halwani, M.D., University of Utah Alex Herrera, M.D., City of Hope Iris Isufi, M.D., Yale University Bela Kis, M.D. PhD., Moffitt Craig Okada, M.D. Ph.D., OHSU Ian Chau, M.D., Royal Marsden Hospital Kim Linton, M.D., Christie Hospital, Manchester, UK Roch Houot, M.D. PhD., CHU Rennes, FR Javier Briones, M.D. PhD., Hospital De La Santa Creu I Sant Pau.Barcelona, ESP Luis de la Cruz, M.D. PhD, Hospital Universitario Virgen Macarena, ESP Carlos Panizo, M.D., Clínica Universidad de Navarra, Pamplona, ESP

Start Date:	June 2015
Trial Phase:	Phase 1/2
Investigational Drug Product(s):	G100 (glucopyranosyl lipid A stable emulsion, GLA-SE) and Pembrolizumab or Rituximab
Objectives:	**Primary:** • In Part 1: Evaluate the safety and tolerability of ascending doses of intratumoral G100 in patients with low-grade non-Hodgkin's lymphoma (NHL) receiving local radiation • In Part 2: Assess the safety and tolerability of intratumoral G100 or sequential intratumoral G100 and anti-programmed cell death protein 1 (PD-1) therapy in patients with follicular NHL receiving local radiation • In Part 3: Evaluate the safety and tolerability of 20 µg/dose of intratumoral G100 in patients with low-grade NHL receiving local radiation • In Part 4: Evaluate safety and preliminary clinical efficacy of intratumoral G100 at 20µg/lesion in single or multiple tumor lesions and pembrolizumab (anti-PD-1) therapy in patients with relapsed or refractory follicular NHL who have received at least 3 prior systemic treatments, one of which was or included an anti-CD20 antibody • In Part 5: Evaluate safety and preliminary clinical efficacy of standard induction therapy with rituximab (anti-CD20) in combination with escalating doses of intratumoral G100 in single tumor lesions in patients with follicular NHL who have received at least one or two prior treatment(s) **Secondary:** • Assess clinical responses by Immune-related Response Criteria (irRC) using bi-dimensional measurements and time to progression (TTP) as a preliminary indication of efficacy For comparison, clinical responses will also be assessed by the International Working Group response criteria and Lugano criteria for lymphomas (Cheson 2014). • Assess abscopal tumor responses in non-treated, distal tumor sites **Exploratory:** • Evaluate pre- and post-regimen tumor tissue and blood for exploratory biomarkers of immunologic and tumor response

	• Part 4 and Part 5, explore pharmacokinetic and pharmacodynamic properties of G100 • Assess clinical responses by Immune-related Response Criteria (irRC) and Lugano criteria for lymphomas using independent radiology review
Endpoints:	**Primary:** • Part 1: The nature, frequency and severity of adverse events (AEs) and laboratory abnormalities up through Study Day 28 in patients with low-grade NHL receiving intratumoral G100 and local radiation • Part 2: The nature, frequency and severity of AEs and laboratory abnormalities occurring in patients with follicular NHL receiving local radiation and either intratumoral G100 alone or sequential intratumoral G100 and anti-PD-1 therapy • Part 3: The nature, frequency, and severity of AEs and laboratory abnormalities occurring in patients with follicular NHL receiving local radiation and G100 at 20 µg/dose • Part 4: The nature, frequency and severity of AEs and laboratory abnormalities and the frequency of clinical responses occurring in patients with follicular NHL receiving intratumoral G100 at 20 µg/lesion in single or multiple tumor masses and pembrolizumab therapy • Part 5: The nature, frequency and severity of AEs and laboratory abnormalities and the frequency of clinical responses occurring in patients with follicular NHL receiving rituximab therapy in combination with escalating doses of intratumoral G100 in single tumor lesions **Secondary:** • The nature, frequency and severity of AEs and laboratory abnormalities until 21 days after G100 regimen is completed or discontinued • Clinical responses by irRC using bi-dimensional measurements and expressed as partial response (PR), complete response (CR), stable disease (SD), or progressive disease (PD), time-to-progression (TTP) and/or progression-free survival (PFS) as a preliminary indication of efficacy • As an exploratory comparison, assess clinical responses by the International Working Group response criteria for lymphomas (For determining PD, the irRC criteria will be used). Sponsor will assess for clinical responses by the Lugano criteria for lymphomas (Cheson 2014). • Abscopal tumor responses in non-treated, distal tumor sites

	Exploratory: • Assessment of blood and tumor samples for exploratory biomarkers of immunologic and tumor response • For Part 4 and 5, explore the pharmacokinetic and pharmacodynamic properties of IT G100
Patient Population:	Patients with follicular low-grade NHL with tumor masses accessible for intratumoral injection and, if enrolled on Parts 1, 2, or 3, local radiation therapy.
Sample Size:	In Part 1, Dose Escalation, up to 12 evaluable patients In Part 2, • Patient Expansion group: up to 24 additional patients randomly assigned to receive G100 or sequential administration of G100 and pembrolizumab • Large Tumor group: up to 4 evaluable patients (Optional) to receive G100 at 20 µg/dose In Part 3, • G100 Expansion 20 µg Dose group: up to 25 evaluable patients to receive G100 at 20 µg/dose In Part 4, • G100 at 20µg/dose Into Single Or Multiple Tumor Lesions Plus Pembrolizumab: 22 efficacy evaluable patients as defined in the Statistical Section will be enrolled In Part 5, • G100 Plus Rituximab: During Dose Escalation 12-24 patients and during Patient Expansion 20 efficacy evaluable patients as defined in the Statistical Section will be enrolled
Inclusion Criteria:	1) Follicular low-grade NHL (grades 1, 2, 3A): either treatment naïve or relapsed or refractory following at least one prior treatment. For France, patients with either relapsed or refractory only. In Part 1 Dose Escalation only, in addition to follicular NHL, marginal zone B cell lymphomas: either treatment naïve or relapsed or refractory following at least one prior treatment. • In Part 4, enrollment is limited to relapsed or refractory follicular NHL patients who have received at least 3 prior systemic treatments, one of which was or included an anti-CD20 antibody. • In Part 5, enrollment will include relapsed or refractory CD20+ follicular NHL following at least one but not more than 2 prior treatments.

	2) Tumor mass(es) accessible for intratumoral injection and are being considered for local radiation therapy and at least one additional site of disease outside the radiation field for assessment of distal (abscopal) response (imaging assisted injections are allowed following approval by Medical Monitor) • For Parts 4 and 5, radiation therapy is omitted. Measurable tumor mass(es) accessible for intratumoral injection must be present for treatment and assessment of response. 3) ≥18 years of age 4) Life expectancy of ≥6 months per the investigator 5) Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 6) Electrocardiogram (ECG) without evidence of clinically significant arrhythmia or ischemia 7) If female of childbearing potential (FCBP), willing to undergo pregnancy testing and agrees to use two methods of birth control or is considered highly unlikely to conceive during the dosing period and for three months after last study treatment, or if receiving pembrolizumab, four months after last treatment (See Section 8.1.9 and Appendix F for details) 8) If male and sexually active with a FCBP, must agree to use effective contraception such as latex condom or is sterile (e.g., following a surgical procedure) during the dosing period and for three months after last study treatment, or if receiving pembrolizumab, four months after last treatment (See Section 8.1.9 and Appendix F for details)
Exclusion Criteria:	1) Cancer therapies, including chemotherapy, radiation (non-study regimen related), biologics or kinase inhibitors, granulocyte-colony stimulating factor (G-CSF) or granulocyte-macrophage colony stimulating factor (GM-CSF) within 4 weeks prior to the first scheduled G100 dose 2) Investigational therapy within 4 weeks prior to G100 dosing 3) Prior administration of G100 or other intratumoral immunotherapeutics 4) Inadequate organ function including: a. Marrow: Peripheral blood leukocyte count (WBC) <3000/mm^3, absolute neutrophil count ≤1500/mm^3, platelets <75000/mm^3, or hemoglobin <10 gm/dL b. Hepatic: alanine aminotransferase (ALT), and aspartate aminotransferase (AST) >2.5 × the upper limit of normal (ULN), total serum bilirubin >1.5 × ULN (patients with Gilbert's Disease may be included if their total bilirubin is ≤3.0 mg/dL) c. Renal: Creatinine >1.5 × ULN

	d. Other: international normalised ratio (INR) or partial thromboplastin time (PTT) >1.5 × ULN 5) Significant immunosuppression from: a. Concurrent, recent (≤4 weeks ago) or anticipated treatment with systemic corticosteroids at any dose, or b. Other immunosuppressive medications such as methotrexate, cyclosporine, azathioprine or conditions such as common variable hypogammaglobulinemia 6) Pregnant or nursing 7) Myocardial infarction within 6 months of study initiation, active cardiac ischemia or New York Heart Association (NYHA) Grade III or IV heart failure 8) History of other cancer within 2 years (except non-melanoma cutaneous malignancies and cervical carcinoma in situ) 9) Recent (<1 week ago) clinically significant infection, active tuberculosis or evidence of active hepatitis B, hepatitis C or human immunodeficiency virus (HIV) infection 10) Central nervous system involvement with lymphoma, including parenchymal and leptomeningeal disease. In Parts 4 and 5, any involvement with lymphoma in a closed or confined space such as the retroorbital area will need to be pre-approved by the Medical Monitor. 11) Significant autoimmune disease, including active non-infectious pneumonitis, with the exception of alopecia, vitiligo, hypothyroidism or other conditions that have never been clinically active or were transient and have completely resolved and require no ongoing therapy. (Replacement therapy for hypothyroidism or diabetes is allowed.) 12) Psychiatric, other medical illness or other condition that in the opinion of the principle investigator (PI) prevents compliance with study procedures or ability to provide valid informed consent 13) History of significant adverse or allergic reaction to any component of G100, if enrolled in Part 2 or Part 4, pembrolizumab and/or any of its excipients, and if enrolled in Part 5, anti-CD20 antibodies including rituximab and/or any of its excipients 14) Use of anti-coagulant agents or history a significant bleeding diathesis. {If a superficial lymph node or subcutaneous (SC) mass is to be injected, patients on agents such as non-steroidal anti-inflammatory drugs (NSAIDs), aspirin, or clopidogrel are eligible and these agents do not have to be withheld. For procedures with moderate or significant risk of bleeding, long-acting agents such as aspirin or clopidogrel should be discussed with the Medical Monitor and may need to be discontinued before G100 therapy.}

	For patients enrolled in Part 2 or Part 4 with the potential to receive pembrolizumab: 15) Has a history of (non-infectious) pneumonitis that required steroids or has current pneumonitis or interstitial lung disease 16) Has received a live vaccine within 30 days prior to the first dose of study drug (Applies to patients who may receive either pembrolizumab or rituximab). Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster (chicken pox), yellow fever, rabies, Bacillus Calmette–Guérin (BCG), and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (e.g., FluMist®) are live attenuated vaccines and are not allowed. 17) Has undergone prior allogeneic hematopoietic stem cell transplantation within the last 5 years. (Subjects who have had a transplant greater than 5 years ago are eligible as long as there are no symptoms of graft versus host disease [GVHD].) 18) Has had an allogeneic tissue/solid organ transplant 19) Has received prior therapy with an anti-PD-1, anti-programmed death ligand (PD-L)1, or anti-PD-L2 agent or if the patient has previously participated in Merck MK-3475 clinical trials or was previously treated with an agent directed to another stimulatory or co-inhibitory T-cell receptor (e.g., CTLA-4, OX 40, CD137) and was discontinued from that treatment due to a Grade 3 or higher immune-related adverse event.

Trial Design:	This is a Phase 1/2, open label, trial of G100 in patients with low grade follicular NHL. G100 is composed of glucopyranosyl lipid A formulated in a stable emulsion (GLA-SE). GLA is a fully synthetic toll-like receptor (TLR)-4 agonist that is a potent stimulator of innate immune responses. In this study, G100 will be administered intratumorally into tumors of follicular NHL patients in order to generate anti-tumor immune responses. GLA in either the stable emulsion (SE) formulation or an aqueous formulation (GLA-AF) has been examined in >1000 patients as an adjuvant for various infectious agent and cancer vaccines as well as in 2 ongoing clinical studies involving patients with Merkel Cell carcinoma or sarcoma where it has been administered intratumorally, either alone or in combination with local radiation therapy. G100 has demonstrated the ability to stimulate immune responses with an acceptable safety profile. *In Part 1, Dose Escalation,* patients with accessible tumors that are being considered for radiation therapy will receive standard local radiation followed by intratumoral injections of G100 into the irradiated mass(es). Two dose levels will be examined and a 3+3 sequential dose escalation design will be used. All patients will receive a regimen consisting of standard low dose radiation (2 Gy every day [qd] x2, 4 Gy total) to the target tumor mass(es). G100 will be injected intratumorally beginning 1 day following completion of radiation therapy (Study Day 2), a second dose will be administered 3-5 days later (Study Day 5 to 7) and then dosing will continue weekly for up to 4 additional doses (6 total) as long as the tumor remains of sufficient size for injection. A single lesion within the radiation field will be targeted to receive each dose of G100. If the lesion regresses, another lesion within the radiation field will be chosen for treatment (as described in the protocol). If the tumor mass has not regressed completely from baseline, dosing may continue for 3 additional weekly intratumoral doses (9 total). Two dose levels of G100 are planned: ▪ Cohort 1: 5 μg ▪ Cohort 2: 10 μg Initially, three patients will be scheduled to receive G100 at the first dose level. Dose escalation will be contingent upon acceptable safety data obtained during the first 28 days of observation following initiation of the regimen. A dose level cohort will be expanded from three to six if one of the first three patients experiences a dose-limiting toxicity (DLT). Further patient accrual into that dose level cohort (or higher) will be suspended as soon as ≥2 patients in that cohort experience DLT, or when otherwise deemed clinically appropriate by the investigator or Sponsor medical monitor. After the 28-day DLT observation period for the final patient in a cohort is complete, if less than one third of the patients enrolled in that cohort developed a DLT, advancement to the next dose-level cohort can begin.

	Patients will be considered evaluable if they have received at least three G100 injections and have completed Day 28 safety monitoring OR have experienced DLT. Patients who experienced DLT during the safety period will not be replaced. All other patients who have not received at least three G100 injections and/or do not complete the Day 28 safety monitoring period for reasons other than treatment-related toxicity will be replaced. Following completion of the dose escalation stage of the trial, the maximum tolerated dose (MTD) or maximum safe dose (highest dose level examined in the study) will be defined as the highest dose reached in which less than one third of the patients in the cohort experienced a DLT. *In Part 2*, depending on the results of Part 1 and the MTD/maximum safe dose, two groups of patients may be examined, Patient Expansion With or Without Pembrolizumab and (optional) Large Tumor groups. *Part 2, Patient Expansion With or Without Pembrolizumab group:* Up to 24 patients will be randomly assigned and treated with single-agent intratumoral G100 or with the sequential administration of intratumoral G100 and pembrolizumab at the MTD or maximum safe dose of G100 determined in Part 1. This portion of the study is designed to be exploratory. Data indicate that inhibitory immune checkpoint pathways are up-regulated in the tumor microenvironment and that interfering with these regulatory pathways can lead to improved tumor responses in preclinical models. Treatment will follow the same dose regimen as in Part 1 and consist of G100 at the MTD or maximum safe dose and local radiation therapy. If the tumor mass has not regressed completely following 6 doses, treatment may continue for 3 additional weekly intratumoral doses (9 total). For patients randomized to anti-PD-1 therapy, on Day 14, pembrolizumab treatment will be initiated at a standard dose of 200 mg intravenously (IV) and then administered every 3 weeks (Q3W) IV for up to 2 years or until disease progression or unacceptable toxicity. For pembrolizumab, dose modification for AEs attributed to the drug will follow the guidelines as recommended for the product and as outlined in the protocol. The main goal of Part 2, Patient Expansion With Or Without Pembrolizumab, is to gain safety information, immunologic data and early clinical experience with these regimens to allow planning for future studies with these agents. *Part 2, Large Tumor group:* If the G100 dose consisting of 10 µg of the GLA component is determined to be the maximal safe dose and the Data Monitoring Committee (DMC) agrees, an optional treatment group for Large Tumor patients will be treated. Preclinical data indicates a dose response to G100 and this will be explored in these patients. In this group, up to 4 patients with injectable lymphoma mass(es) 4 cm or greater in total size (based on the sum of the measurements of the single greatest dimension of each the tumor(s) within the planned radiation field) will be enrolled and will receive G100 consisting of 20 µg of the GLA component per dose. This will allow greater distribution of the G100 within the large tumor mass(es) and

	the examination of safety and dose effect. Treatment would be administered on the same treatment schedule as in Part 1 except that the G100 dose would be 20 µg of the GLA component. The dose will be administered to a single large target lesion or distributed among 2 or more lesions within the radiation field. If the target lesion(s) regresses, a different lesion within the radiation field will be chosen for treatment, if available. If the tumor mass has not regressed completely following 6 doses, treatment may continue for 3 additional weekly intratumoral doses (9 total). *Part 3, G100 Expansion of 20 µg Dose group:* Following completion of enrollment of the Part 2 Patient Expansion With or Without Pembrolizumab group (as determined by Sponsor), and when at least 3 patients are enrolled in the Large Tumor Group with follow-up to at least Day 28, and contingent upon determining an acceptable safety profile following a review of G100 alone data, commencement of Part 3 will begin. Up to 25 patients with follicular NHL will be enrolled to receive local radiation therapy and intratumoral G100 at 20 µg/dose following the same treatment schedule as in Part 1 and Part 2 where G100 was administered alone. Large tumors are ***not*** required, and patients with any injectable tumor mass regardless of size may participate. Data from another study in sarcoma and early data from this trial have not demonstrated any safety concerns with the 20-µg dose level, and to date, all reported events considered at least possibly related to the study agent have only been grade 1 or 2. Compared to baseline, post-treatment tumor biopsies have demonstrated significant increases in immune infiltrates within the tumor of some patients suggesting that this dose level should be explored further. The dose will be administered to a single target lesion or distributed among 2 or more lesions within the radiation field. If the target lesion(s) regresses, a different lesion within the radiation field will be chosen for treatment, if available. If the tumor mass has not regressed completely following 6 doses, treatment may continue for 3 additional weekly intratumoral doses (9 total). Data will be monitored continuously for safety, clinical effect, and exploratory biomarkers. *Part 4, G100 at 20µg/lesion Into Single Or Multiple Tumor Masses Plus Pembrolizumab:* Data from Parts 1-3 of this study demonstrate that intratumoral G100 at the highest dose examined (20µg) has been well-tolerated with only grade 1 or 2 related AEs and no DLTs reported with its use. This higher dose has been associated with increased numbers of infiltrating CD8 T cells into the tumor (TILs), and greater numbers of CD8 TILs have been statistically associated with the development of objective clinical responses. In Part 2, the combination of G100 (10 µg) and pembrolizumab was well-tolerated without new or unexpected toxicities, and the addition of pembrolizumab resulted in more clinical responses, deeper abscopal tumor shrinkage, and a higher number of tumor infiltrating CD8 T cells. Therefore Part 4 will examine the 20µg dose of G100 in 1 or more tumor lesions (up to 4 lesions) plus pembrolizumab in order to establish safety and examine clinical and biomarker responses in patients receiving increasing total systemic doses of G100.

	Part 4 will consist of a Dose Escalation group to evaluate and establish the safety of injecting 20µg of G100 into multiple lesions (up to 4 lesions) in combination with pembrolizumab and a Patient Expansion group to assess clinical responses with this regimen. At least 22 relapsed or refractory follicular NHL patients who received ≥3 prior systemic therapies will be treated in Part 4. Twenty-two efficacy evaluable patients as defined in the Statistical Section will be enrolled. During Dose Escalation, safety will be assessed using a 3+3 design where sequential cohorts of patients will be treated with intratumoral G100 at 20µg/lesion in 1, 2, 3, or 4 tumor lesions corresponding to systemic G100 exposure of 20, 40, 60 or 80µg G100. Once the 20 µg systemic dose level cohort (20 µg injected in 1 lesion) has been established to be reasonably safe, patients who do not qualify to enroll on the next dose level cohort due to insufficient numbers of potentially injectable lesions may enter Patient Expansion at that single lesion dose level. As each higher systemic dose level (40 µg, 60 µg, 80 µg) in multiple lesions is established to be well-tolerated, additional patients who otherwise qualify for the study but are unable to be treated on Dose Escalation due to insufficient numbers of injectable lesions will be allowed to enroll into the Patient Expansion portion of the study at the established safe dose levels. If complete enrollment of 22 efficacy evaluable patients is reached before Dose Escalation is complete, the Sponsor may choose to continue enrollment into just the Dose Escalation cohorts with up to 12 patients to fill all or some of the remaining cohort(s). Treatment will follow a similar dose regimen as in "Part 2, Patient Expansion With or Without Pembrolizumab" group, except that radiation therapy has been omitted. G100 will be injected intratumorally beginning on Day 0, a second dose will be administered 5-7 days later (Study Day 5-7) and then dosing will continue weekly for up to 4 additional doses (6 total) as long as the tumor remains of sufficient size for injection. At least 1 lesion will be targeted to receive each dose of G100. If the lesion regresses, another lesion will be chosen for treatment (as described in the protocol). If the patient is entered in a cohort where more than one lesion is injected (cohorts 2 to 4), as many easily accessible tumors will be targeted and treated as specified for the cohort. Imaging assisted injections are allowed but the feasibility and safety of these treatments must be discussed first and approved by the Medical Monitor. If the tumor mass has not regressed completely from baseline, dosing may continue for 3 additional weekly intratumoral doses (9 total). On Day 14, pembrolizumab treatment will be initiated at a standard dose of 200 mg intravenously (IV) and then be administered every 3 weeks (q3W) IV for up to 2 years or until disease progression or unacceptable toxicity. *Part 4 Dose Escalation* In the Dose Escalation portion, safety will be assessed using a 3+3 design where 12 to 24 patients will be assigned to sequential cohorts of escalating

	number of G100 injected lesions in combination with standard dose pembrolizumab (Figure 6). Four cohorts are planned: ▪ Cohort 1: G100 20 µg/lesion in 1 tumor ▪ Cohort 2: G100 20 µg/lesion in 2 tumor lesions (40 µg total) ▪ Cohort 3: G100 20 µg/lesion in 3 tumor lesions (60 µg total) ▪ Cohort 4: G100 20 µg/lesion in 4 tumor lesions (80 µg total) Once a Cohort dose level is established to be safe, patients who do not meet the criteria of sufficient numbers of injectable tumors to enter the next dose Cohort will be enrolled in a Patient Expansion group at a systemic dose level that has already been established as safe. Initially, three patients will be scheduled to receive G100 at the first dose level. Dose escalation will be contingent upon acceptable safety data obtained during the first 28 days of observation following initiation of the regimen. A dose level cohort will be expanded from three to six if one of the first three patients experiences a dose-limiting toxicity (DLT). Further patient accrual into that dose level cohort (or higher) will be suspended as soon as ≥2 patients in that cohort experience DLT, or when otherwise deemed clinically appropriate by the investigator or Sponsor Medical Monitor. After the 28-day DLT observation period for the final patient in a cohort is complete, if less than one third of the patients enrolled in that cohort developed a DLT, advancement to the next dose-level cohort can begin. During Dose Escalation, patients will be considered evaluable for determination of *safety and dose-level cohort advancement* if they have received at least three complete G100 treatments and 1 dose of pembrolizumab and have completed Day 28 safety monitoring OR have experienced DLT. Patients who experienced DLT during the safety period will not be replaced. All other patients who have not received at least three G100 treatments and 1 dose of pembrolizumab and/or do not complete the Day 28 safety monitoring period for reasons other than treatment-related toxicity will be replaced. Following completion of the Dose Escalation portion of Part 4, the maximum tolerated dose or maximum safe dose (highest dose level examined in the study) will be defined as the highest dose reached in which less than one third of the patients in the cohort experienced a DLT. *Potential Dose Modification During Dose Escalation* G100 is a local therapy with systemic immune responses. Therefore, the safety profile may differ from that of systemically administered agents. In order to further investigate this, if 2 or more DLTs are observed in the initial cohort at 20 µg of G100, the Sponsor, in agreement with the independent DMC may choose to examine a new cohort of patients to better understand whether or not the DLTs associated with the injection of a single lesion

might be abrogated by decreasing the dose and administering the lower single lesion dose of 10 µg into multiple lesions. Intratumoral G100 10µg in a single lesion in combination with pembrolizumab was established to be well-tolerated in Part 2 of this study. Thus, this new cohort would examine the safety of G100 10µg administered into 2 injectable lesions and would use the same 3+3 design described above. Based on a review of the safety profile of this new cohort and in agreement with the independent DMC, further dose escalation cohorts may be investigated using this lower dose of 10 µg/lesion and a similar dose escalation schema as described above where up to 4 lesions may be potentially treated.

For pembrolizumab, dose modification for AEs attributed to the drug will follow the guidelines as recommended for the product and as outlined in the protocol.

Part 4 Patient Expansion

Once the G100 20 µg systemic dose level has been established to have an acceptable safety profile, patients who otherwise qualify for the study but do not have the requisite number of injectable tumor masses to enroll on the dose cohort currently under evaluation may be enrolled into a Patient Expansion group. The Patient Expansion group will begin to evaluate clinical response (ORR) and biomarker changes of G100 plus pembrolizumab combination. An exploratory analysis will also be performed in those who are considered $TLR4^{high}$.

The per lesion dose during Patient Expansion will be 20µg/lesion. The total administered dose of G100 will depend on the safety established with each dose cohort. Determination of the number of potential injectable lesions will be made by the investigator in consultation with Medical Monitor.

As the safety of each dose cohort is established, the number of allowed injectable lesions in Patient Expansion will be as follows:

Established Safe Systemic Dose	Treatment In Patient Expansion
20 µg dose level	20 µg in 1 lesion
40 µg dose level	20 µg in up to 2 lesions
60 µg dose level	20 µg in up to 3 lesions
80 µg dose level	20 µg in up to 4 lesions

Patient enrollment will be monitored. It is planned that 22 efficacy evaluable patients will be treated with intratumoral G100 and IV pembrolizumab in Part 4 in order to provide sufficient data for evaluation of efficacy (see Statistical Section). Patients who received G100 20µg/lesion during Dose Escalation in Part 4 may be included in the clinical response analysis.

Part 5, G100 Plus Rituximab: Studies have demonstrated the potential for additive or synergistic effects of the combination of G100 and rituximab. G100 has been shown to increase the number of inflammatory and activated

	immune cells within the tumor microenvironment, including T cells, NK cells, macrophage and dendritic cells. Rituximab can potentially increase the loading/pulsing of dendritic cells with tumor antigen, leading to more effective antigen presentation of rare tumor antigens. Rituximab and other similar antibodies that bind to tumor cells and debris have been previously shown to facilitate the uptake and processing of tumor antigens by dendritic cells through opsonization/phagocytosis. In addition, a known mechanism of action of rituximab is through antibody dependent cellular cytotoxicity (ADCC). In preclinical work, the combination of G100 with rituximab demonstrated enhanced ADCC. Therefore, G100 in combination with rituximab can increase the amount of tumor antigen processed by dendritic cells potentially leading to greater T cell stimulation/activity; in addition, the combination could enhance tumor cytotoxicity by activating and increasing the number of ADCC effector cells. In this study, a Dose Escalation will be performed first followed by Patient Expansion. During Dose Escalation 12-24 patients and during Patient Expansion 20 efficacy evaluable patients as defined in the Statistical Section will be enrolled. Patient enrollment will be monitored. Patients who received G100 during Dose Escalation in Part 5 may be included in clinical response analysis. Data from the G142 study indicate that the G100 intratumoral dose of 20µg is relatively safe with only grade 1 or 2 related AEs reported and no DLTs and that this higher dose appears to induce greater numbers of infiltrating CD8 T cells into the tumor. Recent preclinical data indicate that G100 doses greater than 20 µg can lead to improved survival of animals in tumor models, further supporting that additional dose exploration may be warranted. Therefore, this arm will examine escalating doses of G100 plus rituximab in a single tumor site utilizing a 3+3 design in order to establish safety and examine clinical and biomarker responses. Once the highest safe dose/systemic exposure is determined from the Dose Escalation portion of the study, all safety, efficacy and biomarker data will be reviewed by the Sponsor (in collaboration with the independent DMC) and either the highest dose determined to be safe or the most biologically active and safe dose (if different than the MTD) will be chosen for further investigation. A Patient Expansion group would then begin. Details of Dose Escalation and Patient Expansion are described below. *Part 5, Dose Escalation* In the Dose Escalation portion, safety and efficacy of G100 injected into a single tumor lesion without radiation will be assessed using a 3+3 design where patients will be assigned to sequential cohorts of escalating doses of intratumoral G100 in combination with standard dose induction therapy with rituximab (Figure 8 and Figure 9). Treatment will begin on Day 0 with rituximab 375mg/m^2 IV and continue weekly for a total of 4 doses. If there are no DLTs or significant safety events after the first dose of rituximab, G100 will be injected intratumorally beginning on Day 1, and then dosing

	will continue weekly for 3 additional doses (4 total) on a visit schedule that coincides with rituximab treatments as long as the tumor remains of sufficient size for injection. One lesion will be targeted to receive each dose of G100. If the lesion regresses, another lesion will be chosen for treatment. Imaging assisted injections are allowed but the feasibility and safety of these treatments must be discussed first and approved by the Medical Monitor. If the tumor lesion has not regressed completely after the first 4 doses of G100, dosing may continue for 2 additional weekly intratumoral doses (6 total). Following restaging, the patient may be eligible for a second course of G100. Four cohorts G100 plus rituximab are planned and will be enrolled sequentially: • Cohort 1: G100 20 µg in single tumor lesion • Cohort 2: G100 40 µg in a single tumor lesion • Cohort 3: G100 60 µg in a single tumor lesion • Cohort 4: G100 80 µg in a single tumor lesion Initially, 3 patients will be scheduled to receive G100 at the first dose level. Dose escalation will be contingent upon acceptable safety data obtained during the first 28 days of observation following initiation of the regimen. A dose level cohort will be expanded from 3 to 6 if one of the first 3 patients experiences a dose-limiting toxicity (DLT). Further patient accrual into that dose level cohort (or higher) will be suspended as soon as ≥2 patients in that cohort experience DLT, or when otherwise deemed clinically appropriate by the investigator or Sponsor Medical Monitor. After the 28-day DLT observation period for the final patient in a cohort is complete, if less than one third of the patients enrolled in that cohort developed a DLT, advancement to the next dose-level cohort can begin. During Dose Escalation, patients will be considered evaluable for determination of safety and dose-level cohort advancement if they have received at least 3 complete G100 treatments and 3 doses of rituximab and have completed Day 28 safety monitoring OR have experienced DLT. Patients who experienced DLT during the safety period will not be replaced. All other patients who have not received at least 3 G100 treatments and 3 doses of rituximab and/or do not complete the Day 28 safety monitoring period for reasons other than treatment-related toxicity will be replaced. Based on ongoing evaluation of study data, the Sponsor may decide to complete fewer than the planned 4 dose cohorts and proceed directly to the Patient Expansion portion of the study. Following completion of the dose escalation stage of the trial, the MTD will be defined as the highest dose reached in which less than one third of the patients in the cohort experienced a DLT. If no DLTs are experienced in the first 3 patients enrolled at highest dose of 80µg, the 80µg dose per lesion will be determined to be the "maximum safe dose" examined in this study and

	dose escalation will be considered complete. An additional 3 patients may then be enrolled for a total of 6 patients at that dose level and safety stopping rules will be followed. If after the Sponsor and DMC review all safety data it is determined that there are no safety issues requiring the separation of the first dose of rituximab and G100, the regimen may be modified to administer both on Day 0 during Patient Expansion. *Part 5, Patient Expansion* Once the MTD/maximum safe dose has been established, all safety, clinical and biomarker data will be reviewed and a recommended dose for further exploration will be made. The Patient Expansion would then begin and would enroll patients to receive G100 IT at the recommended dose into a single tumor mass in combination with rituximab. Patients enrolled on Part 5 Patient Expansion will be analyzed on the basis of the ORR. An exploratory analysis will also be performed in those who are considered $TLR4^{high}$. Patients will be enrolled with the intent of obtaining data from at least 20 efficacy evaluable patients as defined in the Statistical Section. Patients who received G100 at the recommended dose during Dose Escalation in Part 5 may be included in clinical response analysis. G100 is a local therapy with systemic immune responses. Therefore, the safety profile may differ from that of systemically administered agents. In order to further investigate this, after establishment of an MTD, the Sponsor in agreement with the independent DMC may choose to examine one additional cohort of patients to better understand whether or not the DLTs associated with the injection of a single lesion might be abrogated by splitting the dose and administering into two separate lesions. The data from this cohort may help determine if the tolerability of G100 was limited due to the injection of a single tumor mass or to the total systemic exposure. In this additional cohort, 3-6 patients would be treated at the total systemic dose level associated with DLTs but divided and distributed into two tumor masses instead of one. For example, if the MTD in a single tumor mass were determined to be 40µg due to DLTs occurring at 60µg/lesion, the dose of this cohort would be 30µg/lesion injected separately into 2 tumor masses. In the event that the 20µg dose level (Cohort 1) experiences DLTs, a cohort of 10µg/lesion administered into 2 lesions may be explored. The information from this additional cohort could help the design of future studies. The decision whether or not to open this cohort would be made when the Dose Escalation data is reviewed following the determination of the MTD. No additional treatment cohorts are planned beyond this one group. Following this evaluation, patients would be enrolled into the Patient Expansion group and would receive G100 injected into a single lesion at the recommended dose.

	For rituximab, dose modification for AEs attributed to the drug will follow the guidelines as recommended for the product and as outlined in the protocol. *For All Parts (1 to 5)* *Retreatment / Second Course:* Following the G100 course of treatment, if a patient is determined to have achieved SD or better or has PD that does not require immediate therapy, has an additional site of disease outside of the prior radiation field (Parts 1, 2, or 3) that is amenable to injection, and has not had significant treatment emergent AEs (including events that would be considered a DLT) as determined by the investigator and the Sponsor, the patient may be eligible to receive a second course of G100. For patients enrolled on Parts 4 or 5, the same previously injected tumor site(s) may be targeted or a replacement site(s) may be chosen. Six weeks or more after completion of the first course of G100 treatment, the second course would begin and consist of G100 alone (no radiation and no additional rituximab for patients enrolled on Part 5) at the same dose received during the first course of therapy. Treatment would be administered on a similar weekly schedule as the first course except without radiation therapy (or rituximab therapy). G100 will be injected intratumorally beginning on Day 0, a second dose will be administered 5 to 7 days later and then dosing will continue weekly for up to 4 additional doses (6 total) as long as the tumor remains of sufficient size for injection. For Parts 1 to 3, a single lesion will be targeted to receive each dose of G100. If the lesion regresses, another lesion will be chosen for treatment. If the tumor mass has not regressed completely, dosing may continue for 3 additional weekly intratumoral doses (9 total). If the patient had been receiving pembrolizumab as part of their therapy, the anti-PD-1 antibody would continue as scheduled during the second course. For Part 4, dosing may continue into multiple lesions as selected for their initial course; for Part 5, the number of G100 doses is limited to 6 treatments of a single lesion. Dose regimen interruption in a single patient may be made by the clinical investigator if it is deemed in the best interest of patient safety. The study Medical Monitor should be consulted prior to or immediately upon the decision to interrupt therapy. Safety will be reviewed on a regular basis by an independent DMC and the Sponsor. These reviews may lead to modification or stopping of the treatment program. Tumor imaging will be performed during the screening visit (baseline) and then approximately every 8 weeks thereafter for the first year, every 3 to 4 months for the second year, and then at least every 6 months for the third and subsequent years until disease progression as defined by the irRC. Pre- and post-treatment tumor biopsies (e.g., core biopsies) will be obtained for histologic review and exploratory immune analyses, including cell phenotype, tumor expression of TLR4, and genomic analyses of T cells. Post-treatment biopsies will be performed in patients with accessible tumors

	within 3 weeks after the last planned G100 injection. Peripheral blood will be drawn for immune assays and biomarker tests at time points listed in the Study Procedures.
Duration of Patient Participation:	Patients will continue with clinical assessments every 8 weeks and will have imaging assessments every 8 weeks for the first year, every 3 to 4 months for the second year, and then at least every 6 months for the third and subsequent years until disease progression as defined by the irRC. If the patient experiences PD, the expected duration of a patient's participation and follow-up in the trial is approximately 1 year (or longer if the patient agrees) to determine clinical status and time to next treatment.
Dosing Limiting Toxicity:	DLTs will be used to establish safety parameters for stopping dose escalation and will follow a standard 3+3 study design. AE severity assessments will be performed using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v4.03 or newer. Unacceptable toxicity is defined when two or more subjects in a dose level cohort develop DLTs considered at least possibly related to the study regimen. Further dosing at that level will be discontinued. Hospitalizations primarily intended to expedite diagnostic evaluations or for elective surgery will not be considered as serious adverse events (SAEs) for the purpose of ascertaining DLT. The occurrence of any of the following toxicities during the first 28 days will be considered a DLT, if assessed by the investigator to be possibly, probably, or definitely related to any component of study treatment (G100, pembrolizumab, or rituximab): 1. Grade 4 nonhematologic toxicity (not laboratory). 2. Grade 4 hematologic toxicity lasting ≥7 days, except thrombocytopenia: • Grade 4 thrombocytopenia of any duration • Grade 3 thrombocytopenia associated with clinically significant bleeding 3. Any nonhematologic AE ≥Grade 3 in severity should be considered a DLT, with the following exceptions: Grade 3 fatigue lasting ≤3 days; Grade 3 diarrhea, nausea, or vomiting without use of anti-emetics or anti-diarrheals per standard of care; Grade 3 rash without use of corticosteroids or anti-inflammatory agents per standard of care. 4. Any Grade 3 or Grade 4 non-hematologic laboratory value if: • Clinically significant medical intervention is required to treat the subject, or

	• The abnormality leads to hospitalization, or • The abnormality persists for >1 week. • The abnormality results in a Drug-induced Liver Injury (DILI) • Exceptions: Clinically nonsignificant, treatable, or reversible laboratory abnormalities including liver function tests, uric acid, etc. 5. Febrile neutropenia Grade 3 or Grade 4: • Grade 3 is defined as ANC <1000/mm^3 with a single temperature of >38.3 degrees C (101 degrees F) or a sustained temperature of ≥38 degrees C (100.4 degrees F) for more than 1 hour • Grade 4 is defined as ANC <1000/mm^3 with a single temperature of >38.3 degrees C (101 degrees F) or a sustained temperature of ≥38 degrees C (100.4 degrees F) for more than 1 hour, with life-threatening consequences and urgent intervention indicated. 6. Prolonged delay (>2 weeks) in initiating Cycle 2 due to treatment-related toxicity. 7. Any treatment-related toxicity that causes the participant to discontinue treatment during Cycle 1. 8. Grade 5 toxicity. 9. Missing >25% of study drug doses as a result of treatment-related AE(s) during the first cycle.
Maximum Tolerated Dose/ Maximum Safe Dose Examined:	The MTD will be defined as the highest G100 dose level studied in which less than one third of patients in a cohort experience DLT. If the MTD is declared at the final dose level, the highest dose will be considered the maximum safe dose examined in the trial.
Progressive Disease:	The irRC using bi-dimensional measurements will be used to determine disease progression. Immunomodulatory agents can induce tumor size changes due to immune inflammatory reactions and do not represent true tumor progression. To help mitigate false determinations of tumor growth, irRC requires a confirmation of PD at least 4 weeks later with imaging and/or by direct tumor measurement. In addition, the appearance of new lesions does not define disease progression but their size measurements are added to the tumor burden calculation.

Stopping Rules	During the initial 28-day treatment period, dosing will be suspended at any dose level (and higher) if DLTs are observed in 2 or more patients during Part 1 or during Dose Escalation of Part 4 or Part 5. During patient expansion of Parts 2, 3, 4 and 5, dosing will be suspended if DLT considered at least possibly related to the study medications are observed during the first 28 days in one third or more patients within a group receiving the same treatment (assuming a minimum of 6 patients receiving the same dose and treatment regimen and would represent the initial denominator: In Parts 2 and 3, G100 alone; in Parts 2 and 4, G100/pembrolizumab, in Part 5, G100/rituximab) All AEs and DLTs observed during dose escalation of any treatment arm and/or patient expansion meeting the criteria of a stopping rule will be reviewed by the DMC. If there is disagreement between the DMC and the investigator's assessment regarding the relationship of the event to study agent or to the clinical relevance (e.g., lab abnormality), the Sponsor in consultation with the DMC may determine to stop the treatment or continue. In the later case, the AE may become a medical event of interest and be tracked closely for additional events occurring in the future with intratumoral G100.
Safety Monitoring:	G100 safety will be monitored by evaluating both solicited and spontaneously reported AEs, including reactogenicity, symptoms, physical examination findings, vital signs, laboratory findings, ECGs and discontinuations for AEs. Monitoring will be continuous. An independent DMC will operate in accord with a signed charter, will consist of 2 oncologists, and will provide independent review/assessment of all safety data on a regular basis to minimize risks to study patients. The DMC and Sponsor will review all DLTs and SAEs considered at least possibly related to the study regimen as they are reported on an ongoing basis. In addition, the DMC and Sponsor will review all safety data for any trends at least once every 3 months. SAE reports considered at least possibly related to the study regimen and are unexpected will be expedited to regulatory authorities, investigators and DMC members. These reviews may lead to modification of the treatment program. In Part 2, two groups of patients are planned: Patient Expansion (G100 alone and sequential G100 and pembrolizumab) and Large Tumor groups (optional). The Patient Expansion With Or Without Pembrolizumab group will begin once the MTD / maximum safe dose is determined from Part 1. Based on the results of Part 1 and the safety profile of the highest dose level, the DMC will recommend whether or not to open the optional Large Tumor treatment group. The Large Tumor group will only be possible if the 10 µg/dose level is determined to be safe. *In Part 3, G100 Expansion of 20 µg Dose Group,* treatment may begin after enrollment into Part 2 Patient Expansion (G100 alone and sequential G100 and pembrolizumab) has been completed (as determined by Sponsor), at least

	3 patients have been enrolled in the Large Tumor group and observed to at least Day 28, and an acceptable safety profile has been determined. The Sponsor in consultation with the DMC will review the safety profile of G100 alone data from Part 1 and 2. Commencement of Part 3 will be contingent upon determination of an acceptable safety profile of G100 alone data at that evaluation timepoint. In Part 3, up to 25 patients will be enrolled to receive local radiation therapy and intratumoral G100 at 20 µg/dose following the same treatment schedule as in Part 1 and Part 2 where G100 was administered alone. *In Part 4, G100 at 20µg/lesion Into Single Or Multiple Tumor Masses Plus Pembrolizumab Group,* treatment may begin after enrollment into Part 3 has been completed (as determined by Sponsor), and an acceptable safety profile has been determined by the Sponsor in consultation with the DMC. In Part 4, at least 22 evaluable patients will be enrolled to receive sequential IT G100 at 20 µg/lesion and pembrolizumab at 200mg IV every 3 weeks following the same treatment schedule as in Part 2 where G100 was administered with pembrolizumab, except without radiation therapy. During dose escalation, sequential cohorts of patients will be treated with intratumoral G100 at 20µg/lesion in 1, 2, 3, or 4 tumor masses corresponding to local and systemic G100 exposure of 20, 40, 60 or 80µg of the GLA component. Patient Expansion will be allowed to begin at each dose level as safety is established for each cohort and agreed upon with the DMC. Twenty-two efficacy evaluable patients as defined in the Statistical Section will be enrolled. *In Part 5, G100 Plus Rituximab,* treatment may begin after enrollment into Part 3 has been completed (as determined by Sponsor), and an acceptable safety profile has been determined by the Sponsor in consultation with the DMC. In Part 5, patients will be enrolled to receive IT G100 and standard induction rituximab without radiation therapy. During Dose Escalation, sequential cohorts of 3-6 patients will be treated with intratumoral G100 at 20, 40, 60 or 80 µg/dose into a single tumor mass. Once the highest safe dose/systemic exposure is determined from the Dose Escalation portion of the study, all safety, efficacy and biomarker data will be reviewed by the Sponsor (in collaboration with the independent DMC) and either the highest dose determined to be safe or the most biologically active and safe dose (if different than the MTD) will be chosen for further investigation. The Patient Expansion would then begin and would treat patients with G100 at the recommended dose in a single lesion in combination with rituximab. Overall, 20 efficacy evaluable patients as defined in the Statistical Section will be enrolled In addition to the stopping rules (DLTs within the initial 28 days), these DMC safety reviews may lead to modification or stopping of the treatment program if related, treatment-emergent AEs indicate a safety profile that is inconsistent or significantly worse than reported with the use of G100 alone or pembrolizumab alone or rituximab alone.

	During Part 2 and based on the continuous review of safety events, if the dose of 10 μg G100 is used during Patient Expansion and subsequently determined to have an increased safety risk, the DMC may recommend and the Sponsor may choose to reduce the dose of G100 to 5 μg or they may recommend stopping the G100 treatment. If the 5 μg dose level is determined not to be safe by the independent DMC, treatment with G100 will be stopped. Following evaluation by the DMC and the Sponsor, a further modification to the dose/treatment schedule could be recommended. *During Part 4* and based on the continuous review of safety events, if the dose of 20 μg/lesion G100 plus pembrolizumab is subsequently determined to have an increased safety risk, the DMC may recommend and the Sponsor may choose to reduce the dose of G100 to 10μg or they may recommend stopping the G100 treatment. *Similarly during Part 5*, if G100 plus rituximab is subsequently determined to have an increased safety risk, the DMC may recommend and the Sponsor may choose to reduce the dose of G100 or they may recommend stopping the G100 treatment. As described in the Part 5 design, an optional cohort may be examined where the dose level associated with a DLT is split in two lesions in order to help determine if the lack of tolerability of the dose was due to the treatment of a single lesion or was limited due to the total systemic G100 exposure. Following evaluation by the DMC and the Sponsor, a further modification to the dose/treatment schedule could be recommended. All patients treated with one or more injections of G100 will be considered part of the safety data set. Patients will be followed every 8 weeks until disease progression as defined by the irRC. Patients with disease progression by irRC (or symptomatic deterioration) will be followed thereafter every 8-12 weeks by telephone or clinical visit for up to one year (or longer if the patient agrees) after first study injection as long as they are able to engage in follow-up. Follow-up will ascertain vital status (survival status) as well as cancer status (e.g., lymphoma transformation), post-treatment anti-cancer therapy (including time to next treatment, treatment details, and clinical response), and any SAE that might be possibly related to G100 treatment. Patients followed on this study have developed delayed objective tumor responses occurring >18 months from study start. If patients develop late responses after initial IrRC progression but have not received additional therapy, they may be asked to consent to additional follow-up of clinical response and biomarker analyses.

Data Analysis:	An interim analysis will be performed on the first 6 to 12 evaluable subjects in Part 1 who have completed the Day 77 assessment or completed an end of study evaluation. **Safety:** Tabulation, summarization and descriptive statistics will be performed for all safety information including AEs, SAEs, laboratory findings and discontinuations of patients at all data collection time points. No formal statistical hypothesis will be tested. **Immunogenicity:** Tabulation, summarization and descriptive statistics will be performed describing the baseline and post G100 administration peripheral blood lymphocyte subsets. Analyses will be performed to determine if there are any statistically significant changes from baseline values. An exploratory analysis will be performed to examine TLR4 expression in baseline tumor cells and will be investigated to understand if there is an association between baseline TLR4 expression levels and clinical outcome. Association between other pre-existing/post treatment immunogenicity biomarkers and clinical outcome will also be explored. **Tumor Response:** Anti-tumor activity as defined by irRC using bidimensional measurements will be reported. The primary analysis will be based on investigator's assessment. Independent radiology review will be supportive. As a comparison, tumor response using the International Working Group and Lugano (Cheson 2014) criteria for lymphoma will also be analyzed. IrRC will be used to determine PD. The main differences between the criteria are that the IrRC requires confirmatory restaging to determine if tumor size increase is due to true progression instead of immune inflammation and that new lesions add to tumor size calculations are not determinants of PD by themselves. Please see Appendix B for details. Progression-free survival and/or TTP will be plotted as a Kaplan-Meier curve. Disease control rate (CR, PR, and SD) and overall response rate (ORR or CR + PR) will be reported. Time to next treatment, overall survival (OS), and the Follicular Lymphoma International Prognostic Index (FLIPI) may also be examined as exploratory analyses. **Independent radiology review of tumor assessments:** The Sponsor may request at any time that radiographic images of tumor assessments for all or select patients be submitted to central storage facility for the purpose of an independent radiology assessment of tumor responses. All patients starting with protocol version 4B will be required to provide an

	informed consent for such central storage and independent radiology review prior to study treatment. Part 4 In Part 4, G100 plus pembrolizumab, at least 22 evaluable patients will be enrolled and treated as part of a Dose Escalation group or a Patient Expansion group with intratumoral G100 in combination with pembrolizumab. The purpose of this treatment regimen will be to explore the safety and preliminary clinical efficacy and biomarker changes of patients treated with G100 at a dose of 20 µg/lesion injected in single or multiple lesions. The administered dose of G100 will depend on the number of potentially injectable lesions and whether the MTD has been established during Dose Escalation. One or more lesions will be targeted for injection and each lesion would receive 20µg of G100 intratumorally (or 10 µg G100 if 20 µg/lesion in a single lesion is not tolerated) as long as the total number of treated tumor lesions and total systemic dose does not exceed the MTD (if established) or 80 µg total dose (20 µg injected in 4 lesions). This analysis is designed to be exploratory and will evaluate safety, clinical outcome and exploratory biomarkers to guide further clinical development. Clinical efficacy including ORR and DOR will be evaluated in relapsed or refractory follicular NHL patients who received ≥3 prior systemic therapies. For this analysis, 22 efficacy evaluable patients will be required. Efficacy evaluable patients are patients who received at least 3 doses of G100 at 20 µg/lesion and at least 1 dose of pembrolizumab, had at least one post baseline tumor assessment, and had no major protocol deviations that impact the efficacy of the study treatment or the assessment of response. Patients who received G100 20µg/lesion during Dose Escalation in Part 4 may be included in clinical response analysis. With a target ORR of 40%, if ≤5 responders are observed among 22 evaluable patients, we will conclude futility with 7.2% error rate. The Sponsor will use this analysis to decide whether to continue further clinical development of this regimen. Early acceptance of treatment at the end of the 22 evaluable patients is not permitted. If the true ORR for this group is 20% and 20% ORR is considered not clinically meaningful, the probability of observing ≤5/22 responders and stopping the study is 73.3%. Part 5 In Part 5, G100 Plus Rituximab, after Dose Escalation has been completed, patients will be treated with intratumoral G100 at the recommended dose level in combination with rituximab. The purpose of this Patient Expansion group will be to explore the safety and clinical outcome of patients treated at a biologically active and safe G100 dose level administered into single tumor lesion in combination with rituximab. This analysis is designed to be exploratory and will evaluate safety, clinical outcome and exploratory biomarkers.

	An exploratory analysis will be performed on 20 efficacy evaluable relapsed or refractory FL patients and will include analyses of the frequency and duration of CRs. Efficacy evaluable patients are patients who received at least 3 injections of G100 at the recommended dose and 3 doses of rituximab, had at least one post baseline tumor assessment, and had no major protocol deviations that impact the efficacy of the study treatment or the assessment of response. Five or more CRs in 20 patients treated with G100 plus rituximab will signal an improvement of CR rate over 10%. Patients who received G100 at the recommended dose during Dose Escalation in Part 5 may be included in clinical response analysis. With 20 efficacy evaluable patients, and a historical CR rate of 10%, assuming a true CR rate of 32% in the G100 plus rituximab, this subgroup analysis has 82% power to detect a signal of an improvement in CR rate from 10% at a 1-sided alpha of 0.05.

3.2 Schedule of Events: Part 1, Dose Escalation and Part 2, Patient Expansion (G100 alone) and Large Tumor Groups

Visit	1	2	3	4	5	6	7	8	9	10	10A	10B	11	12	Follow-up	LT Follow-up after PD
Timeline – weeks	-4 to 0	-1	0			1	2	3	4	5	6	7	8	11	Day 112 then every 8 weeks[h]	Every 8-12 weeks
Timeline – days	-30 to -1	-7 to -1	0	1	2	5 to 7	14	21	28	35	42	49	56	77		
Procedures																
Informed consent / HIPAA	X															
Inclusion / exclusion criteria	X															
Demographics / Medical	X	X														
History of cancer therapy	X	X														X[g]
Report all AEs and SAEs		X			X	X	X	X	X	X	X	X	X	X[e]		
Report possibly-related SAEs															X	X
Record any previous / concomitant medications	X	X			X	X	X	X	X	X	X	X	X	X	X	X[g]
Vital signs		X			X	X	X	X	X	X	X	X	X	X	X	
Physical exam[a]		X			X	X	X	X	X	X	X	X	X	X	X	
ECG (12-Lead)	X													X		
Tumor staging, including CT, MRI, and/or other modalities	X												X[b]	X[b]	X[h]	
ECOG		X			X	X	X	X	X	X	X	X	X	X	X	
HIV, HepB, and HepC (5 mL)		X														
Beta-2-microglobulin (5 mL)		X														
Blood for phenotyping/profiling		X								X			X			
Blood for safety labs (10 mL)		X			X	X	X	X	X	X	X	X	X	X	X	
Thyroid function tests[f] (5 mL)		X														
Blood for T cell gene profiling		X								X			X			
Urinalysis		X														
Pregnancy test[c]		X												X		
Local Radiation 2Gy qd x2			**X**	**X**												

Visit	1	2	3	4	5	6	7	8	9	10	10A	10B	11	12	Follow-up	LT Follow-up after PD
Timeline – weeks	-4 to 0	-1	0			1	2	3	4	5	6	7	8	11	Day 112 then every 8 weeks[h]	Every 8-12 weeks
Timeline – days	-30 to -1	-7 to -1	0	1	2	5 to 7	14	21	28	35	42	49	56	77		
Procedures																
G100 dosing					**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**			
Tumor biopsy	X												X[d]	X[d]		
Clinical Status, treatment history																X[g]
Blood volume per visit (mL)		38	0	0	10	10	10	10	10	23	10	10	23	10	10	
Total blood volume		38	38	38	48	58	68	78	88	111	121	131	154	164	174	

[a] Physical exam also includes tumor measurements of treated and any untreated lesions measurable by exam. If appropriate, photographs should be taken to document lesions.

[b] Day 56 restaging CT or MRI scans should be performed if the optional treatment #9 is not given. If a PET CT is used, a standard high resolution CT series should be obtained rather than low resolution scans for tumor measurements. However, PET scans should not be used to determine disease progression since it is expected that PET avidity will increase with the type of inflammation induced by this treatment and may lead to false positive results. Confirmation of disease progression by CT or MRI must be performed 4 or more weeks later per IrRC. If the 9th dose is given, then CT/MRI should be delayed to Day 63 to 77. Photographs: if the tumor can be measured and assessed visually, photographic documentation with measurements should be considered in order to keep a record and help assess any response to treatment (may be performed at any time during study)

[c] Pregnancy test should only be performed on FCBP. Urine pregnancy test is recommended and must be performed (and negative) within 7 days prior to starting study treatment and on day 77. Site may use serum pregnancy test if part of their procedures. For patients in the UK and France, urine pregnancy tests must also be performed every month or sooner while the patient is receiving G100.

[d] Post-treatment biopsy should be done on Day 56 +/- 7 days for patients not receiving optional treatment #9. If the 9th dose is given, biopsy should be delayed to Day 63 to 77.

[e] Patients should have all AEs reported for at least 30 days following the last dose of the G100 study agent. This includes those who withdraw early before completion of the study.

[f] Thyroid function tests (including TSH) should be performed at screening in those patients being evaluated to participate and be randomized in Part 2 G100 vs. G100 plus pembrolizumab.

[g] Patients will receive telephone follow-up or clinic visit every 8 to 12 weeks after disease progression until 1 year after first study injection. Follow-up will include vital status (survival), cancer status (e.g., lymphoma transformation), and post-treatment anti-cancer therapy including time to next treatment, treatment details, and clinical response. If the patient agrees, the site may periodically (e.g. every 2 to 4 months) contact the patient beyond 1 year to check on vital and cancer status.

[h] Imaging studies during Follow-up will occur on Day 112, every 8 weeks thereafter for the first year, every 3 to 4 months for the second year, and then at least every 6 months for the third and subsequent years.

3.3 Schedule of Events: Part 2, Sequential Administration of G100 and anti-PD-1

Visit	1	2	3	4	5	6	7	8	9	10	10A	10B	11	12	Follow-up	LT Follow-up after PD
Timeline – weeks	-4 to 0	-1	0			1	2	3	4	5	6	7	8	11	14+	**Every 8-12 weeks**
Timeline – days	-30 to -1	-7 to -1	0	1	2	5 to 7	14	21	28	35	42	49	56	77	D98… q21d	
Procedures																
Informed consent / HIPAA	X															
Inclusion / exclusion criteria	X															
Demographics / Medical	X	X														
History of cancer therapy	X	X														X[g]
Report all AEs and SAEs		X			X	X	X	X	X	X	X	X	X	X	X[e]	X[e]
Report possibly-related SAEs																X[g]
Record any previous / concomitant medications	X	X			X	X	X	X	X	X	X	X	X	X	X	X[g]
Vital signs		X			X	X	X	X	X	X	X	X	X	X	X	
Physical exam[a]		X			X	X	X	X	X	X	X	X	X	X	X	
ECG (12-Lead)	X													X		
Tumor staging, including CT, MRI, and/or other modality[f]	X												X[i]	X[i]	X[h]	
ECOG		X			X	X	X	X	X	X	X	X	X	X	X	
Thyroid function tests (5 mL)		X											X		X[b]	
HIV, HepB, and HepC (5 mL)		X														
Beta-2-microglobulin (5 mL)		X														
Blood for cell phenotyping / profiling		X								X			X			
Blood for safety labs (10 mL)		X			X	X	X	X	X	X	X	X	X	X	X	
Blood for T cell gene profiling and biomarkers		X								X			X			
Urinalysis		X														
Pregnancy test[c]		X					X							X		
Local Radiation 2Gy qd x2			**X**	**X**												
G100 dosing					**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**			

Visit	1	2	3	4	5	6	7	8	9	10	10A	10B	11	12	Follow-up	LT Follow-up after PD
Timeline – weeks	-4 to 0	-1	0			1	2	3	4	5	6	7	8	11	14+	**Every 8-12 weeks**
Timeline – days	-30 to -1	-7 to -1	0	1	2	5 to 7	14	21	28	35	42	49	56	77	D98… q21d	
Procedures																
Pembrolizumab dosing							**X**			**X**			**X**	**X**	**X**	
Tumor biopsy	X[d]												X[d]	X[d]		
Clinical Status																X[g]
Blood volume per visit (mL)		38	0	0	10	10	10	10	10	23	10	10	28	10		
Total blood volume		38	38	38	48	58	68	78	88	111	121	131	159	169		

[a] Physical exam also includes tumor measurements of treated and any untreated lesions measurable by exam. If appropriate, photographs should be taken to document lesions.

[b] Thyroid function tests (including TSH) should be performed at screening and then every 6 weeks (following initiation of pembrolizumab) or as indicated by patient symptoms during pembolizumab therapy to screen for immune mediated thyroid changes.

[c] Pregnancy test should only be performed on FCBP. Urine pregnancy test is recommended and must be performed (and negative) within 7 days prior to starting study treatment, Day 14 prior to the first dose of pembrolizumab, and day 77. Site may use serum pregnancy test if part of their procedures. For patients in the UK and France, urine pregnancy tests must also be performed every month or sooner while the patient is receiving G100.

[d] For the pre-treatment tumor biopsy, baseline excisional or core biopsy should be obtained from the treatment target lesion or non-target lesion (preferably near the target lesion). Post-treatment tumor biopsy should be performed on Day 56 +/- 7 days for patients not receiving optional treatment #9. If a 9th dose is given, then biopsy should be delayed to Day 63 to 77. The biopsies should be performed on the treated tumor if feasible. If the primary treated site is not available, a different site should be chosen. **The biopsy site location and whether or not it was treated with G100, radiation, or was an abscopal site must be recorded/documented.**

[e] For patients enrolled on the pembrolizumab arm, all adverse events experienced from the time of enrollment through 30 days following cessation of treatment will be reported by the investigator. Any event of clinical interest (ECI) experienced through 30 days following cessation of treatment should be reported within 24 hours to the Sponsor. Any SAE due to any cause other than progression of the cancer under study that occurs through 90 days following cessation of pembrolizumab treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, must be reported within 24 hours to the Sponsor. After the 90-day reporting period, any SAE that comes to the attention of the site staff that may be causally related to study drug (i.e., the event is considered possibly, probably or definitely caused by the drug) must be reported to Sponsor regardless of time elapsed.

[f] Assessment of disease should include CT or MRI of chest, abdomen, pelvis. Other assessments such as CT scan of head or bone marrow biopsy should be performed if indicated for the individual patient. **However, PET scans should not be used to determine disease progression since it is expected that PET avidity will increase with the type of inflammation induced by this treatment and may lead to false positive results.** For this reason, PET scans are not recommended. If a PET CT is used, a standard high resolution CT series should be obtained rather than low resolution scans and only the CT imaging should be used to determine tumor measurements. Confirmation of disease progression by CT or MRI must be performed 4 or more weeks later per IrRC. In addition to restaging scans, if the tumor can be measured and assessed visually, photographic documentation with measurements should be considered in order to keep a record and help assess any response to treatment (may be performed at any time during study).

[g] Patients will receive telephone follow-up or clinic visit every 8 to 12 weeks after disease progression until 1 year after first study injection. Follow-up will include vital status (survival), cancer status (e.g., lymphoma transformation), and post-treatment anti-cancer therapy including time to next treatment, treatment details, and clinical response. If the patient agrees, the site may periodically (e.g. every 2 to 4 months) contact the patient beyond 1 year to check on vital and cancer status.

[h] Imaging studies during Follow-up will occur, on Day 112 to 119, every 8 weeks thereafter for the first year, every 3 to 4 months for the second year, and then at least every 6 months for the third and subsequent years.

[i] Day 56 restaging CT or MRI scans should be performed if the optional treatment #9 is not given. If a PET CT is used, a standard high resolution CT series should be obtained rather than low resolution scans and only the CT imaging should be used to determine tumor measurements. PET scans should not be used to determine disease progression. Confirmation of disease progression by CT or MRI must be performed 4 or more weeks later per IrRC. If the 9th dose is given, then CT/MRI should be delayed to Day 63 to 77. Photographs: if the tumor can be measured and assessed visually, photographic documentation with measurements should be considered to keep a record and help assess any response to treatment (may be performed at any time during study.

3.4 Schedule of Events: Part 3, G100 Expansion of 20 µg Dose Group

Visit	1	2	3	4	5	6	7	8	9	10	10 A	10B	11	12	Follow-up	LT Follow-up after PD
Timeline – weeks	-4 to 0	-2	0			1	2	3	4	5	6	7	8	11	Day 112 then every 8 weeks[j]	Every 8-12 weeks
Timeline – days	-30 to -1	-14 to -1	0	1	2	5 to 7	14	21	28	35	42	49	56	77		
Procedures																
Informed consent / HIPAA	X															
Inclusion / exclusion criteria	X															
Demographics / Medical	X	X														
History of cancer therapy	X	X														X[g]
Report all AEs and SAEs		X			X	X	X	X	X	X	X	X	X	X[e]		
Report possibly-related SAEs															X	X[g]
Record any previous / concomitant medications	X	X			X	X	X	X	X	X	X	X	X	X	X	X[g]
Vital signs		X			X	X	X	X	X	X	X	X	X	X	X	
Physical exam[a]		X			X	X	X	X	X	X	X	X	X	X	X	
ECG (12-Lead)	X													X		
Tumor staging, including CT, MRI, and/or other modalities[h]	X												X[b]	X[b]	X[j]	
ECOG		X			X	X	X	X	X	X	X	X	X	X	X	
HIV, HepB, and HepC (5 mL)		X														
Beta-2-microglobulin (5 mL)		X														
Blood for safety labs (10 mL)		X			X	X	X	X	X	X	X	X	X	X	X	
Thyroid function tests[f] (5 mL)		X														
Blood for T cell gene profiling		X								X			X			
Urinalysis		X														
Pregnancy test[c]		X												X		
Local Radiation 2Gy qd x2			**X**	**X**												
G100 dosing					**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**			

Visit	1	2	3	4	5	6	7	8	9	10	10 A	10B	11	12	Follow-up	LT Follow-up after PD
Timeline – weeks	-4 to 0	-2	0			1	2	3	4	5	6	7	8	11	Day 112 then every 8 weeks[j]	Every 8-12 weeks
Timeline – days	-30 to -1	-14 to -1	0	1	2	5 to 7	14	21	28	35	42	49	56	77		
Procedures																
Tumor biopsy	X[i]												X[d]	X[d]		
Clinical Status, treatment history																X[g]
Blood volume per visit (mL)		33	0	0	10	10	10	10	10	18	10	10	18	10	10	
Total blood volume		33	33	33	43	53	63	73	83	101	111	121	139	149	159	

[a] Physical exam also includes tumor measurements of treated and any untreated lesions measurable by exam. If appropriate, photographs should be taken to document lesions.

[b] Day 56 restaging CT scans should be performed if the optional treatment #9 is not given. If the 9th dose is given, then CT should be delayed to Day 63 to 77. Photographs: if the tumor can be measured and assessed visually, photographic documentation with measurements should be considered in order to keep a record and help assess any response to treatment (may be performed at any time during study)

[c] Pregnancy test should only be performed on FCBP and must be performed (and negative) within 7 days prior to starting study treatment and on Day 77. Urine pregnancy test is recommended. Site may use serum pregnancy test if part of their procedures. For patients in the UK and France, urine pregnancy tests must also be performed every month or sooner while the patient is receiving G100.

[d] Post-treatment biopsy should be done on Day 56 +/- 7 days for patients not receiving optional treatment #9. If the 9th dose is given, biopsy should be delayed to Day 63 to 77. If the primary treated site is not available, a different site should be chosen. **The biopsy site location and whether or not it was treated with G100, radiation or was an abscopal site must be documented.**

[e] Patients should have all AEs reported for at least 30 days following the last dose of the G100 study agent. This includes those who withdraw early before completion of the study.

[f] Thyroid function tests should include TSH

[g] Patients will receive telephone follow-up or clinic visit every 8 to 12 weeks after disease progression until 1 year after first study injection. Follow-up will include vital status (survival), cancer status, and post-treatment anti-cancer therapy including time to next treatment, treatment details, and clinical response. If the patient agrees, the site may periodically (e.g. every 2 to 4 months) contact the patient beyond 1 year to check on vital and cancer status.

[h] Assessment of disease should include CT or MRI of chest, abdomen, pelvis. Other assessments such as CT scan of head or bone marrow biopsy should be performed if indicated for the individual patient.- **However, PET scans should not be used to determine disease progression since it is expected that PET avidity will increase with the type of inflammation induced by this treatment and may lead to false positive results.** For this reason, PET scans are not recommended. If If a PET CT is used, a standard high resolution CT series should be obtained rather than low resolution scans and only the CT imaging should be used to determine tumor measurements. Confirmation of disease progression by CT or MRI must be performed 4 or more weeks later per IrRC.

[i] For pre-treatment tumor biopsy, baseline excisional or core biopsy should be obtained from the treatment target lesion or non-target lesion (preferably near the target lesion).

[j] Imaging studies during Follow-up will occur on Day 112 and every 8 weeks thereafter for the first year, every 3 to 4 months for the second year, and then at least every 6 months for the third and subsequent years.

3.5 Schedule of Events: Part 4, G100 at 20µg/lesion Into Single Or Multiple Tumor Masses Plus Pembrolizumab

Visit	1	2	3	4	5	6	7	8	8A	8B	9	10	Follow-up	LT Follow-up after PD
Timeline – weeks	-4 to 0	-2	0	1	2	3	4	5	6	7	8	11	14+	**Every 8-12 weeks**
Timeline – days	-30 to -1	-14 to -1	0	5 to 7	14	21	28	35	42	49	56	77	D98 q21d	
Procedures														
Informed consent / HIPAA	X													
Inclusion / exclusion criteria	X													
Demographics / Medical	X	X												
History of cancer therapy	X	X												X[g]
Report all AEs and SAEs		X	X	X	X	X	X	X	X	X	X	X	X[e]	X[e]
Report possibly-related SAEs														X[g]
Record any previous / concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X[g]
Vital signs		X	X	X	X	X	X	X	X	X	X	X	X	
Physical exam[a]		X	X	X	X	X	X	X	X	X	X	X	X	
ECG (12-Lead)	X											X		
Tumor staging, including CT, MRI, and/or other modality[f]	X										X[i]	X[i]	X[h]	
ECOG		X	X	X	X	X	X	X	X	X	X	X	X	
Thyroid function tests (5 mL) TSH, T3 or Free T3, Free T4[b]		X									X		X	
HIV, HepB, and HepC (5 mL)		X												
Beta-2-microglobulin (5 mL)		X												
Blood for safety labs (10 mL)		X	X	X	X	X	X	X	X	X	X	X	X	
Blood for Pharmacokinetics/ Pharmacodynamics (10 mL)[j]			X[j]		X[j]									
Urinalysis		X												
Pregnancy test[c]		X			X							X	X[c]	
G100 dosing			**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**			
Pembrolizumab dosing					**X**			**X**			**X**	**X**	**X**	
Tumor biopsy	X[d]										X[d]	X[d]		
Clinical Status														X[g]
Blood volume per visit (mL)		25	30	10	30	10	10	10	10	10	15	10		
Total blood volume[j]		25	55	65	95	105	115	125	135	145	160	170		

[a] Physical exam also includes tumor measurements of treated and any untreated lesions measurable by exam. If appropriate, photographs should be taken to document lesions.

[b] Thyroid function tests (including TSH) should be performed at screening and then every 6 weeks (following initiation of pembrolizumab) or as indicated by patient symptoms during pembolizumab therapy to screen for immune mediated thyroid changes.

[c] Pregnancy test should only be performed on FCBP. Urine pregnancy test is recommended and must be performed (and negative) within 72 hours (3 days) prior to starting G100 and then before pembrolizumab on Day 14, and on day 77. Site may use serum pregnancy test if part of their procedures. In UK and France, urine pregnancy tests must also be performed every month or sooner while receiving G100 and/or pembrolizumab.

[d] For the pre-treatment tumor biopsy, baseline excisional or core biopsy should be obtained from the treatment target lesion or non-target lesion (preferably near the target lesion). Post-treatment tumor biopsy should be performed as close to 2 weeks following the last dose of G100 as possible: on Day 42 to 56 for patients receiving 6 doses if G100 or, if a 9th dose is given, then biopsy should be delayed to Day 63 to 77. The biopsies should be performed on the treated tumor if feasible. If the primary treated site is not available, a different site should be chosen. **The location of the biopsy site and whether or not it was treated with G100 or was an abscopal site must be recorded/documented. If the patient has both treated and untreated tumor sites amenable to biopsy, separate biopsies of each site should be performed.**

[e] For patients receiving pembrolizumab, all adverse events experienced from the time of enrollment through 30 days following cessation of treatment will be reported by the investigator. Any event of clinical interest (ECI) experienced through 30 days following cessation of treatment should be reported within 24 hours to the Sponsor. Any SAE due to any cause other than progression of the cancer under study that occurs through 90 days following cessation of pembrolizumab treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, must be reported within 24 hours to the Sponsor. After the 90-day reporting period, any SAE that comes to the attention of the site staff that may be causally related to study drug (i.e., the event is considered possibly, probably or definitely caused by the drug) must be reported to Sponsor regardless of time elapsed.

[f] Assessment of disease should include CT or MRI of chest, abdomen, pelvis. Other assessments such as CT scan of head or bone marrow biopsy should be performed if indicated for the individual patient. **However, PET scans should not be used to determine disease progression since it is expected that PET avidity will increase with the type of inflammation induced by this treatment and may lead to false positive results**. If a PET CT is used, a standard high resolution CT series should be obtained rather than low resolution scans and only the CT imaging should be used to determine tumor measurements. Confirmation of disease progression by CT or MRI must be performed 4 or more weeks later per IrRC. In addition to restaging scans, if the tumor can be measured and assessed visually, photographic documentation with measurements should be considered in order to keep a record and help assess any response to treatment (may be performed at any time during study).

[g] Patients will receive telephone follow-up or clinic visit every 8 to 12 weeks after disease progression until 1 year after first study injection. Follow-up will include vital status (survival), cancer status (e.g., lymphoma transformation), and post-treatment anti-cancer therapy including time to next treatment, treatment details, and clinical response. If the patient agrees, the site may periodically (e.g., every 2 to 4 months) contact the patient beyond 1 year to check on vital and cancer status.

[h] Imaging studies during Follow-up will occur on Day 112 to 119 for patients receiving 6 doses of G100 or on Day133 to 140 for patients receiving 9 doses of G100. Imaging studies should then occur every 8 weeks thereafter for the first year, every 3 to 4 months for the second year, and then at least every 6 months for the third and subsequent years.

[i] Day 56 restaging CT or MRI scans should be performed if the optional treatment #9 is not given. If a PET CT is used, a standard high resolution CT series should be obtained rather than low resolution scans and only the CT imaging should be used to determine tumor measurements. PET scans should not be used to determine disease progression since it is expected that PET avidity will increase with the type of inflammation induced by this treatment and may lead to false positive results. Confirmation of disease progression by CT or MRI must be performed 4 or more weeks later per IrRC. If the 9th dose is given, then CT/MRI should be delayed to Day 63 to 77. Photographs: if the tumor can be measured and assessed visually, photographic documentation with measurements should be considered to keep a record and help assess any response to treatment (may be performed at any time during study)

[j] A plasma sample for Pharmacokinetics/Pharmacodynamics analysis will be drawn within 2 hours prior to the first administration of G100 and 6 hours after the first administration of G100 or pembrolizumiab, if applicable.

3.6 Schedule of Events: Part 5, G100 Plus Rituximab

Visit	1	2	3	4	5	6	7	8	8A	8B	9	10	Follow-up	LT Follow-up after PD
Timeline – weeks	-4 to 0	-2	0		1	2	3	4	5	6	8	16	24+ every 8 weeks	**Every 8-12 weeks**
Timeline – days	-30 to -1	-14 to -1	0	1	7	14	21	28	35	42	56	112	D168	
Procedures														
Informed consent / HIPAA	X													
Inclusion / exclusion criteria	X													
Demographics / Medical	X	X												
History of cancer therapy	X	X												X[g]
Report all AEs and SAEs		X	X	X	X	X	X	X	X	X	X	X	X[e]	X[e]
Report possibly-related SAEs													X	X[g]
Record any previous / concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X[g]
Vital signs		X	X	(X[b])	X	X	X	X	X	X	X	X	X	
Physical exam[a]		X	X	(X[b])	X	X	X	X	X	X	X	X	X	
ECG (12-Lead)	X										X			
Tumor staging, including CT, MRI, and/or other modality[f]	X										X	X	X[h]	
ECOG		X	X		X	X	X	X	X	X	X	X	X	
HIV, HepB, and HepC (5 mL)		X												
Beta-2-microglobulin (5 mL)		X												
Blood for safety labs (10 mL)		X	X	X	X	X	X	X	X	X	X	X	X	
Blood for Pharmacokinetics/ Pharmacodynamics (10 mL)[j]			X[j]	X[j]										
Blood for T cell gene profiling and biomarkers		X[i]						X[k]		X[k]				
Urinalysis		X												
Pregnancy test[c]		X									X			
G100 dosing				**X**	**X**	**X**	**X**	**X**	**X**					
Rituximab dosing			**X**		**X**	**X**	**X**							
Tumor biopsy	X[d]							X[d]		X[d]				
Clinical Status														X[g]
Blood volume per visit (mL)[i]		36	20	30	10	10	10	18 or 26	10	18 or 26	10	10		
Total blood volume[i]		36	56	76	86	96	106	124 or 132	134 or 142	160	170	180		

[a] Physical exam also includes tumor measurements of treated and any untreated lesions measurable by exam. If appropriate, photographs should be taken to document lesions.

[b] Physical exam and vital signs should be done if the patient reports adverse events following their first rituximab dose.

[c] Pregnancy test should only be performed on FCBP. Urine pregnancy test is recommended and must be performed (and negative) within 72 hours (3 days) prior to starting study treatment and day 56. Site may use serum pregnancy test if part of their procedures. In UK and France, urine pregnancy tests must also be performed every month or sooner while receiving G100.

[d] For the pre-treatment tumor biopsy, baseline excisional or core biopsy should be obtained from the treatment target lesion or non-target lesion (preferably near the target lesion). Post-treatment tumor biopsy should be performed as close to 2 weeks following the last dose of G100 as possible: on Day 28 to 35 for patients receiving 4 doses and, if 6 doses are given, then the biopsy should be delayed to Day 42 to 56. The biopsies should be performed on the treated tumor if feasible. If the primary treated site is not available, a different site should be chosen. **The location of the biopsy site and whether or not it was treated with G100 or was an abscopal site must be recorded/documented. If the patient has both treated and untreated tumor sites amenable to biopsy post G100, separate biopsies of each site should be performed.**

[e] All adverse events experienced from the time of enrollment through 30 days following cessation of treatment (including those patients who withdraw early) will be reported by the investigator. Any adverse event designated as a Clinical/Medical Event of Interest experienced through 30 days following cessation of treatment should be reported within 24 hours to the Sponsor. Any SAE due to any cause other than progression of the cancer under study that occurs through 30 days following cessation of treatment must be reported within 24 hours to the Sponsor. After the reporting period, any SAE that comes to the attention of the site staff that may be causally related to study drug (i.e., the event is considered possibly, probably or definitely caused by the drug) must be reported to Sponsor regardless of time elapsed.

[f] Assessment of disease should include CT or MRI of chest, abdomen, pelvis. Other assessments such as CT scan of head or bone marrow biopsy should be performed if indicated for the individual patient. **However, PET scans should not be used to determine disease progression since it is expected that PET avidity will increase with the type of inflammation induced by this treatment and may lead to false positive results**. If a PET CT is used, a standard high resolution CT series should be obtained rather than low resolution scans and only the CT imaging should be used to determine tumor measurements. Confirmation of disease progression by CT or MRI must be performed 4 or more weeks later per IrRC. In addition to restaging scans, if the tumor can be measured and assessed visually, photographic documentation with measurements should be considered in order to keep a record and help assess any response to treatment (may be performed at any time during study).

[g] Patients will receive telephone follow-up or clinic visit every 8 to 12 weeks after disease progression until 1 year after first study injection. Follow-up will include vital status (survival), cancer status (e.g., lymphoma transformation), and post-treatment anti-cancer therapy including time to next treatment, treatment details, and clinical response. If the patient agrees, the site may periodically (e.g. every 2 to 4 months) contact the patient beyond 1 year to check on vital and cancer status.

[h] Imaging studies during Follow-up will occur, on Day 168, every 8 weeks thereafter for the first year, every 3 to 4 months for the second year, and then at least every 6 months for the third and subsequent years.

[i] Patients treated on Part 5 will have an additional 8ml drawn for T cell gene and biomarker analyses on Day 0

[j] Pharmacokenetics/Pharmacodynamics plasma samples will be drawn within 2 hours prior to first rituximab administration, within 2 hours prior to the first G100 administration, and 6 hours after the first G100 administration.

[k] Patients treated on Part 5 will have an additional 8ml drawn for T cell gene and biomarker analyses on either Day 28 or 42 depending whether or not the patient received 4 or 6 G100 injections (see Lab Manual for details). The additional blood is reflected as the larger blood volume collection beginning on either Day 28 or 42.

3.7 Schedule of Events: Optional Retreatment / Second Course

Visit	1	2	3	4	5	6	7	7A	7B	8	9	Follow-up	LT Follow-up after PD
Timeline – weeks	6+ wks after last restaging		1	2	3	4	5	6	7	8	11	Day 112 then every 8 weeks[9] *(3 weeks if receiving pembro)	Every 8-12 weeks
Timeline – days	-14 to -1	0	5 to 7	14	21	28	35	42	49	56	77		
Procedures													
Report all AEs and SAEs	X	X	X	X	X	X	X	X	X	X	X[6]	X[6]	X[6,7]
Report possibly-related SAEs												X[6]	X[6,7]
Record any previous / concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X[7]
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	
Physical exam[1]	X	X	X	X	X	X	X	X	X	X	X	X	
ECG (12-Lead)											X		
Tumor staging, including CT, MRI, and/or other modalities[8]	X[2]									X[3]	X[3]	X[9]	
ECOG	X	X	X	X	X	X	X	X	X	X	X	X	
Blood for cell phenotyping / profiling[10]	X						X			X			
Blood for safety labs (10 mL)	X	X	X	X	X	X	X	X	X	X	X	X	
Blood for T cell gene profiling and biomarkers	X						X			X			
Pregnancy test[4]	X										X		
G100 dosing*		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**			
Tumor biopsy	X[5]									X[5]	X[5]		
Clinical Status, treatment history													X[7]
Blood volume per visit (mL)	23	10	10	10	10	10	15	10	10	23	10	10	
Total blood volume	23	33	43	53	63	73	88	98	108	131	141	151	

[1] Physical exam also includes tumor measurements of treated and any untreated lesions measurable by exam. If appropriate, photographs should be taken to document lesions.

[2] CT scan should be repeated if last CT was done 8 or more weeks prior to planned starting date of second course of therapy. If the last scan indicated tumor regression that might now be an objective PR or CR, the scan should be repeated.

[3] Day 56 restaging CT scans should be performed if the optional treatment #9 is not given. If the 9th dose is given, then CT should be delayed to Day 63 to 77.

[4] Pregnancy test should only be performed on FCBP. Urine pregnancy test is recommended and must be performed (and negative) within 7 days prior to starting study treatment and repeated on Day 77. Site may use serum pregnancy test if part of their procedures. For patients in UK and France, urine pregnancy tests must also be performed every month or sooner while the patient is receiving G100.

[5] For Parts 1, 2 and 3, pre-treatment biopsy should be performed if one was not collected after the first course of G100 or if it has been ≥ 3 months from the last G100 treatment; otherwise it is optional. For Parts 4 and 5, new biopsies should be obtained pre- and post- G100 from the planned new treatment site. For pre-treatment biopsy, baseline excisional samples should be obtained from the treatment target lesion or non-target lesion (near the target lesion). Post-treatment tumor biopsy should be performed as close to 2 weeks following the last dose of G100 as possible: on Day 42 to 56 for patients receiving 6 doses if G100 or, if a 9th dose is given, then biopsy should be delayed to Day 63 to 77. The biopsies should be performed on the treated tumor if feasible. If the primary treated site is not available, a different site should be chosen. **The biopsy site location and whether or not it was treated with G100, radiation, or was an abscopal site must be recorded / documented. For Parts 4 and 5, patients who have both treated and untreated tumor sites amenable to biopsy post treatment should have collections done on both sites.**

[6] Patients receiving G100 alone who complete or withdraw early before completion of the study should have all AEs reported for at least 30 days following the last dose of the G100 study agent. For pembrolizumab patients, all AEs experienced from the time of enrollment through 30 days following cessation of treatment will be reported by the investigator. Any ECI experienced through 30 days following cessation of treatment should be reported within 24 hours to the Sponsor. Any SAE due to any cause other than progression of the cancer under study that occurs through 90 days following cessation of pembrolizumab treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, must be reported within 24 hours to the Sponsor. After the 90-day reporting period, Any SAE that comes to the attention of the site staff that may be causally related to study drug must be reported to Sponsor regardless of time elapsed. For patients receiving G100 alone or with rituximab (Parts 1, 2, 3, 5), after the End of Study Visit (Day77) or 30 days after the last dose of study agent whichever is longer, patients receiving G100 alone or G100 plus rituximab will be followed for possibly related SAEs only, and any SAE that comes to the attention of the site staff that may be causally related to study drug (i.e., the event is considered possibly, probably or definitely caused by the drug) must be reported to Sponsor regardless of time elapsed.

[7] Patients will receive telephone follow-up or clinic visit every 8 to 12 weeks after disease progression until 1 year after first study injection. Follow-up will include vital status (survival), cancer status (e.g., lymphoma transformation), and post-treatment anti-cancer therapy including time to next treatment, treatment details, and clinical response. If the patient agrees, the site may periodically (e.g. every 2 to 4 months) contact the patient beyond 1 year to check on vital and cancer status.

[8] Assessment of disease should include CT or MRI of chest, abdomen, pelvis. Other assessments such as CT scan of head or bone marrow biopsy should be performed if indicated for the individual patient. **However, PET scans should not be used to determine disease progression since it is expected that PET avidity will increase with the type of inflammation induced by this treatment and may lead to false positive results**. If a PET CT is used, a standard high resolution CT series should be obtained rather than low resolution scans and only the CT imaging should be used to determine tumor measurements. Confirmation of disease progression by CT or MRI must be performed 4 or more weeks later per IrRC. In addition to restaging scans, if the tumor can be measured and assessed visually, photographic documentation with measurements should be considered in order to keep a record and help assess any response to treatment (may be performed at any time during study).

[9] Imaging studies during Follow-up will occur on Day 112 to 119 for patients receiving 6 doses of G100 or on Day133 to 140 for patients receiving 9 doses of G100. Imaging studies should then occur every 8 weeks (± 14 days) thereafter for the first year, every 3 to 4 months for the second year, and then at least every 6 months for the third and subsequent years.

[10] Cell phenotyping will not be done in patients on Parts 3, 4, or 5.

[*] Patients on Parts 2 or 4 who receive pembrolizumab will continue on their every 3-week schedule while receiving this course of G100. Thyroid function tests should continue every 6 weeks and for Part4 include TSH, T3 or FT3, and FT4. If possible the treatment with pembrolizumab should be synched with this schedule; if not, then continue to follow Part 2: Section 10.3.15.1 or Part 4: Section 10.3.22.1 on pembrolizumab treatment days. Patients on Part 5 G100 plus rituximab may receive up to 6 doses of G100.

4.0 INTRODUCTION AND RATIONALE

Follicular low grade non-Hodgkin's lymphomas (NHL) are typically sensitive to many different anti-cancer modalities including chemotherapy, biologics, and radiation, but despite this, remain incurable (Friedberg 2011). Lymphomas are responsive to passive immunotherapy with agents such as monoclonal antibodies (mAbs) and adoptive cell therapy and to active immunotherapy approaches with agents that stimulate the host's own immune system to fight their own cancer. Active immunotherapy holds particular promise in that it has the potential to provide lifelong lasting protection against these malignancies and their recurrence through immunologic memory. In NHL, active immunotherapy approaches have led to significant tumor reduction and long-lasting disease-free intervals in some patients.

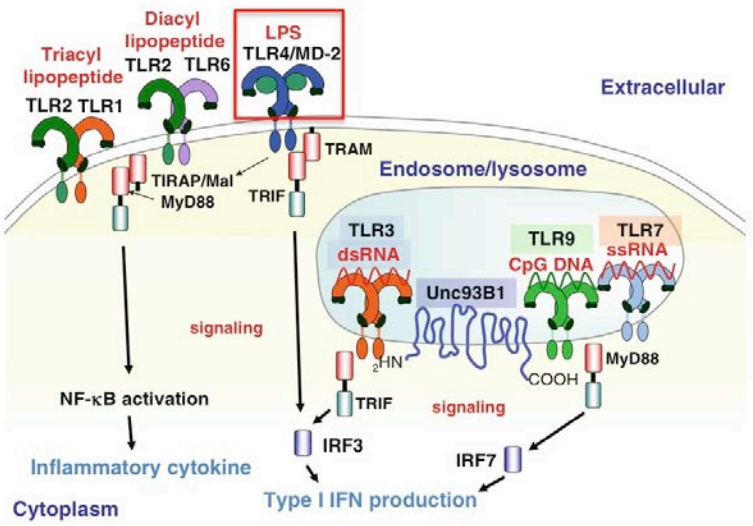
B cell NHL are unique in that they harbor a recognized tumor-specific antigen, the idiotype protein (B cell antigen receptor), which is genetically different from any other B cell in the host and is expressed at high levels. In small clinical studies where patient specific idiotype proteins were manufactured and provided in the form of a protein-adjuvant vaccine or protein pulsed dendritic cells (DCs), immune response were induced that in some patients that led to tumor responses lasting several years (Hsu 1996; Hsu 1997; Timmerman 2002). However, challenges of manufacturing of patient-specific idiotype proteins have not allowed wide use of these antigens.

Newer approaches have focused on using the tumor itself to provide a source of both recognized "specific" antigens like the idiotype protein and unidentified "endogenous" antigens present within the tumor. In preclinical studies, intratumoral injection of DCs in combination with systemic chemotherapy could completely eradicate established and metastatic lymphoma in animal models (Tong 2001; Song 2005). In these studies, the injected DCs were able to ingest and process antigens released from the dying or apoptotic tumor cells and induced a systemic immune response against the tumor that was mediated by cluster of differentiation (CD)8 T cells. Although promising, DC manufacturing was required. Alternatively, a more convenient method would to activate DC directly in situ and avoid the requirement of *ex vivo* cell production.

The activation of immune responses in cancer patients has been challenging because DCs at the tumor site are often dysfunctional and unable to prime T cells efficiently. Several biological agents, such as CD40L, 4-1BBL, tumor necrosis factor (TNF), oligodeoxynucleotides containing certain unmethylated C-G motifs (CpG) (Li 2007) and toll-like receptor (TLR)-4 agonists activate DCs and B cells by inducing their expression of costimulatory molecules and by triggering cytokine production. TLR4 agonists are particularly suited for this approach. (Figure 1). TLR4 is a cell surface receptor that is critical for the recognition of lipopolysaccharide (LPS), an integral component of gram-negative bacteria. TLR4 reside on the cell surface as opposed to TLR 9, a common target of CpGs, which is mainly expressed in the endosomal compartment. TLR4 agonists activate antigen-presenting cells (APCs) and induce acute inflammatory responses including production of chemokines and cytokines that mediate inflammatory reactions. Activation of TLR4 induces two distinct signaling pathways controlled

by (i) myeloid differentiation primary response gene 88 (MyD88)/myeloid differentiation primary response gene 88-adapter-like (MAL) which results in activation of nuclear factor (NF)-kB for induction of a number of NF-kB- dependent genes and inflammatory cytokines, and (ii) TIR-domain-containing adapter-inducing interferon-β (TRIF)/TIR-domain-containing adapter-inducing interferon-β-related adaptor molecule (TRAM) which induces production of type I interferons (IFN) (Coler 2011). TLR4 also plays a non-redundant role in eliciting DC maturation, which is of key importance for effective priming naive T cells and initiating potent immune responses. Recent studies have demonstrated that both MyD88 and TRIF synergize for maximal DC activation.

Figure 1: Toll-like Receptor (TLR) Ligands And Signaling

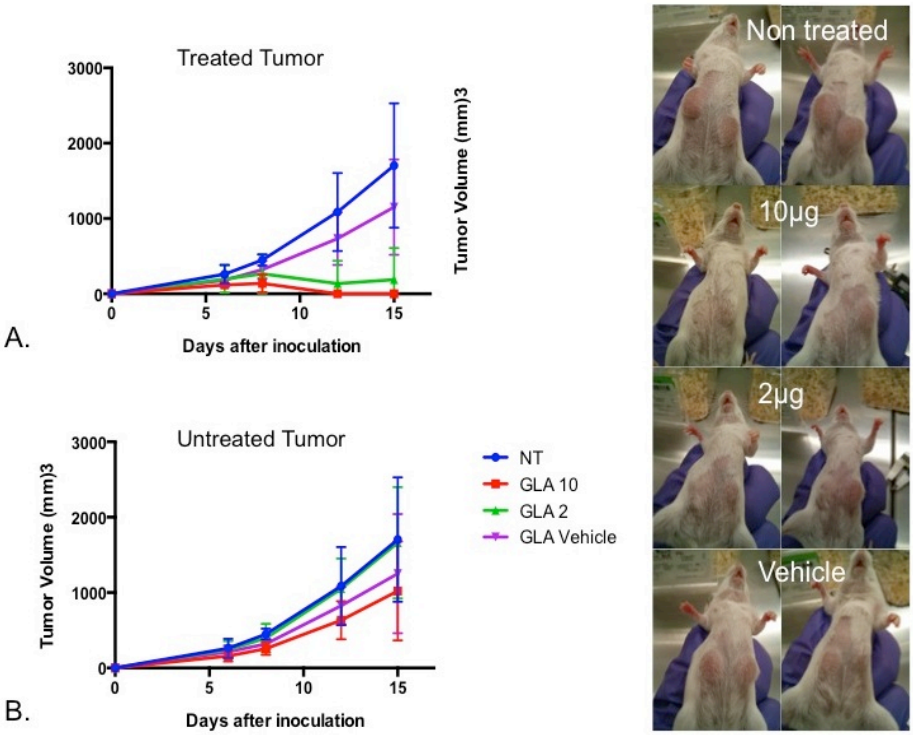


Toll-like receptors (TLRs) recognize bacterial and viral components. TLR ligands induce TLRs homodimer or heterodimer to trigger the activation of signaling molecules. TLR4 recognizes LPS to form a homodimer. TLR3, TLR7, and TLR9 localize in intracellular compartment and recognize pathogen-derived nucleotides like double-strand RNA, single- strand RNA, and CpG-containing DNA, respectively. TLR1/TLR2, TLR2/TLR6, and TLR4 activate MyD88 pathway through TIRAP, which is a membrane-association molecule, to induce inflammatory cytokines. In addition, TLR4 activates TRAM and TRIF to induce type I interferon through activating IRF3. (from Saitoh, Chapter 4, Innate Immune Regulation and Cancer Immunotherapy, Springer, Editor Wang, Saitoh 2012)

Immune Design's G100 agent is a potent TLR4 agonist. G100 is composed of glucopyranosyl lipid A (GLA) formulated in a stable emulsion (SE). GLA a fully synthetic TLR4 agonist that is a potent stimulator of innate immune responses. GLA improves the immunogenicity of a wide variety of antigens by increasing the magnitude of the T helper (Th)1 immune response marked by a high antigen-specific immunoglobin G (IgG)2a:IgG1 ratio and increased production of IFN-γ, TNFα, and interleukin (IL)-12 compared to IL-4, IL-5, and IL-13. In preclinical models

of lymphoma and other cancers, injections of G100 intratumorally alone has led to tumor regression and slowing of tumor progression (Figure 2).

Figure 2: Intratumoral G100 in non-Hodgkin's lymphoma (NHL) Model



A20 tumor cells ($5x10^6$) were injected subcutaneously at sites on both the right and left abdomen. G100 was injected into the right abdominal site only on days 6, 8, and 11 with the indicated dose of 2 µg or 10 µg of G100. Panel A, Treated Tumor, demonstrates the effect of G100 compared to SE vehicle alone or no treatment in the treated right abdominal lesion. Panel B, Untreated Tumor, demonstrates the distal (abscopal) effect of this treatment on the left side, untreated abdominal lesion. (Barfi and Levy, Stanford, unpublished data)

GLA has been extensively evaluated in human subjects formulated in stable oil-in-water emulsion or in an aqueous formulation and has been examined in over 1000 patients as an adjuvant for various infectious agent and cancer vaccines. G100 has been examined in 2 ongoing clinical studies involving patients with Merkel Cell carcinoma or sarcoma where it has been administered intratumorally either alone or in combination with local radiation therapy. It has demonstrated the ability to stimulate immune responses with an acceptable safety profile.

In this study, Immune Design's G100 agent will be administered intratumorally in patients with follicular NHL and evaluated for safety, tolerability and for its ability to stimulate local and distal tumor responses following standard local radiation.

4.1 Study Overview

The overall goal of this study is to evaluate the safety and immunogenicity of repeat-dose intratumoral G100 administration in patients with NHL following standard local radiation therapy. In Part 1: Dose Escalation, two dose levels of G100 will be examined, 5 µg and 10 µg, using a standard 3+3 dose escalation design.

In Part 2, two groups of patients will be examined. In the first group, Patient Expansion With Or Without Pembrolizumab, up to 24 patients will be treated with G100 at the maximum tolerated dose (MTD) or maximum safe dose determined in Part 1 (Figure 3). In this portion of the study, patients will be randomized to receive either intratumoral G100 alone (Figure 4), or intratumoral G100 and sequential anti-programmed death receptor-1 (PD-1) antibody therapy (Figure 5). This portion of the study is designed to be exploratory. The main goal of Part 2, Patient Expansion With Or Without Pembrolizumab, is to gain safety information regarding these approaches to allow planning for future studies with these agents. The G100 treatment regimen will be identical to that used in Part 1, Dose Escalation (Figure 4). For patients randomized to receive pembrolizumab, the anti-PD-1 antibody begins on day 14 and follows a standard every 3-week schedule (Figure 5).

In the second group, Part 2, Large Tumors, a higher dose of G100 may be examined. If the G100 dose consisting of 10 µg of the GLA component is determined to be the maximal safe dose and the Data Monitoring Committee (DMC) agrees, an optional treatment group for Large Tumor patients will be treated. In this group, up to 4 patients with injectable lymphoma mass(es) $\geq$4 cm in total size (based on the sum of the measurements of the single greatest dimension of each the tumor(s) within the planned radiation field) will be enrolled and will receive G100 consisting of 20 µg of the GLA component per dose (Figure 4). This will allow greater distribution of the G100 within the large tumor mass(es) and the examination of safety and dose effect.

In Part 3, G100 Expansion of 20 µg Dose Group, treatment may begin after enrollment into Part 2 Patient Expansion (G100 alone and sequential G100 and pembrolizumab) has been completed (as determined by Sponsor), at least 3 patients in the Large Tumor group have been enrolled and observed to at least Day 28, and an acceptable safety profile has been determined. The Sponsor in consultation with the DMC will review the safety profile of G100 alone data from Part 1 and 2. Commencement of Part 3 will be contingent upon determination of an acceptable safety profile of G100 alone data at that evaluation timepoint. In Part 3, up to 25 patients will be enrolled to receive local radiation therapy and intratumoral G100 at 20 µg/dose following the same treatment schedule as in Part 1 and Part 2 where G100 was administered alone.

In Part 4, G100 at 20µg/lesion Into Single Or Multiple Tumor Masses Plus Pembrolizumab Group, treatment may begin after enrollment into Part 3 has been completed (as determined by Sponsor), and an acceptable safety profile has been determined. The goal of Part 4 is to obtain safety information, immunologic data and clinical response data with this higher G100 dose

regimen in combination with pembrolizumab in relapsed or refractory FL patients who have received at least 3 prior systemic therapies. In Part 4, at least 22 evaluable patients will be enrolled to receive IT G100 at 20 µg/lesion and pembrolizumab at 200mg IV every 3 weeks following the same treatment schedule as in Part 2 where G100 was administered with pembrolizumab, except without radiation therapy. In this dose escalation arm, sequential cohorts of patients will be treated with intratumoral G100 at 20µg/lesion in 1, 2, 3, or 4 tumor masses corresponding to local and systemic G100 exposure of 20, 40, 60 or 80µg of the GLA component (Figure 6). If the tumor mass(es) has not regressed completely following the initial 6 weekly doses, treatment may continue for 3 additional weekly intratumoral doses (9 total) (Figure 7). On Day 14, pembrolizumab treatment will be initiated at a standard dose of 200 mg intravenously (IV) and then administered every 3 weeks (q3W) IV for up to 2 years or until disease progression or unacceptable toxicity. For pembrolizumab, dose modification for AEs attributed to the drug will follow the guidelines as recommended for the product and as outlined in the protocol.

Once the 20 µg systemic dose level cohort (20 µg injected in 1 lesion) has been established to be reasonably safe, patients who do not qualify to enroll on the next dose level cohort due to insufficient numbers of potentially injectable lesions may enter Patient Expansion at that single lesion dose level. As each higher systemic dose level (40 µg, 60 µg, 80 µg) in multiple lesions is established to be well-tolerated, additional patients who otherwise qualify for the study but are unable to be treated on Dose Escalation due to insufficient numbers of injectable lesions will be allowed to enroll into the Patient Expansion portion of the study at the established safe dose levels (Figure 6). Patient enrollment will be monitored. It is planned that 22 efficacy evaluable patients will be treated with intratumoral G100 and IV pembrolizumab in Part 4 in order to provide sufficient data for evaluation of efficacy (see Statistical Section). Patients who received G100 20µg/lesion during Dose Escalation in Part 4 may be included in the clinical response analysis.

If complete enrollment of 22 evaluable patients is reached before Dose Escalation is complete, the Sponsor may choose to continue enrollment into just the Dose Escalation cohorts with up to 12 patients to fill all or some of the remaining cohort(s). The main goal of Part 4, is to obtain safety information, immunologic data and clinical response data with this higher G100 dose regimen in combination with pembrolizumab and to determine if further studies are warranted.

In Part 5, G100 Plus Rituximab, treatment may begin after enrollment into Part 3 has been completed (as determined by Sponsor), and an acceptable safety profile has been determined by the Sponsor in consultation with the DMC. The goal of Part 5 is to obtain safety information, immunologic data and clinical response data with this higher G100 dose regimen in combination with rituximab in FL patients. In Part 5, patients will be enrolled to receive IT G100 and standard induction rituximab without radiation therapy. During dose escalation, sequential cohorts of 3-6 patients will be treated with intratumoral G100 at 20, 40, 60 or 80 µg/dose into a single tumor mass in combination with a standard induction regimen of rituximab 375mg/m^2 IV

weekly x4 (Figure 8). Treatment will begin with rituximab on Day 0, and after evaluation of rituximab related adverse events, G100 would begin on Day 1 (See Figure 9). If there are no significant toxicities, treatment with rituximab and G100 would continue and subsequent administrations would be given during the same visits. Once the highest safe dose/systemic exposure is determined from the Dose Escalation portion of the study, all safety, efficacy and biomarker data will be reviewed by the Sponsor (in collaboration with the independent DMC) and either the highest dose determined to be safe or the most biologically active and safe dose (if different than the MTD) will be chosen for further investigation. The Patient Expansion portion of the study would then begin and patients would receive G100 at this recommended dose level into a single tumor mass in combination with rituximab. Patient enrollment will be monitored with the goal of enrolling 20 efficacy evaluable patients as defined in the Statistical Section. Patients who received G100 during Dose Escalation in Part 5 may be included in clinical response analysis.

For All Parts (1 to 5)

Retreatment / Second Course: Following the G100 course of treatment, if a patient is determined to have achieved stable disease (SD) or better or has progressive disease (PD) that does not require immediate therapy, has an additional site of disease outside of the prior radiation field (Parts 1, 2, or 3) that is amenable to injection and the patient has not had significant treatment emergent adverse events (AE) (including events that would be considered a dose-limiting toxicity [DLT]) as determined by the investigator and the Sponsor, the patient may be eligible to receive a second course of G100 (Figure 10). For patients enrolled on Parts 4 or 5, the same previously injected tumor sites may be targeted or a replacement site(s) may be chosen. Six weeks or more after completion of the first course of G100 treatment, the second course would begin and consist of G100 alone (no radiation and no additional rituximab) at the same dose received during the first course of therapy. Treatment would be administered on a similar weekly schedule as the first course except without radiation therapy (or rituximab therapy) .

Figure 3: Part 2, Patient Expansion With Or Without Pembrolizumab

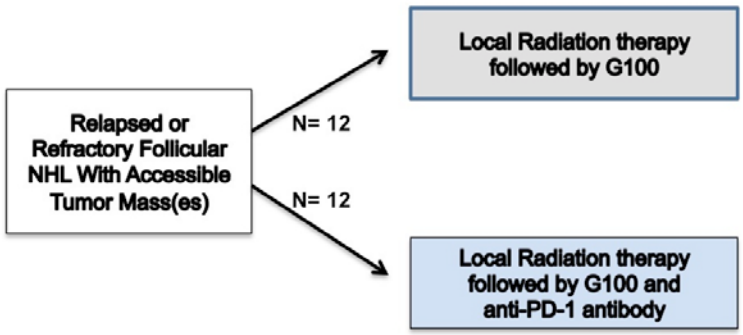


Figure 4: Treatment Schema for Part 1, Part 2 Patient Expansion G100 Alone, Part 2 Large Tumor Group, and Part 3, G100 Expansion of 20 µg Dose Group

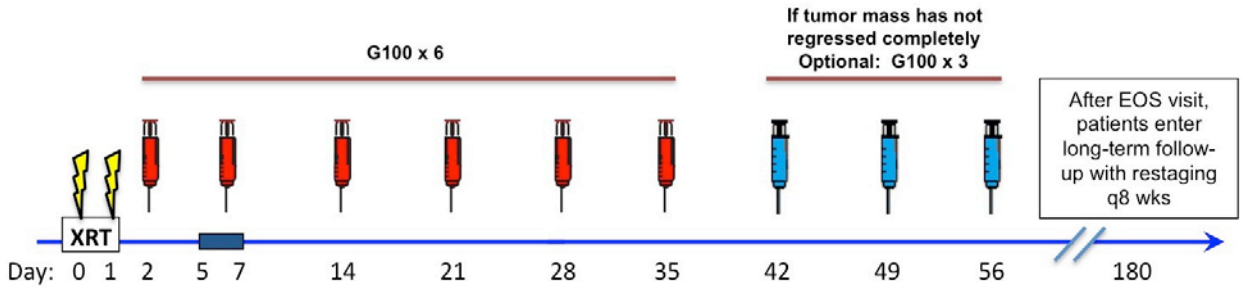


Figure 5: Treatment Schema for Part 2, Sequential G100 and Pembrolizumab

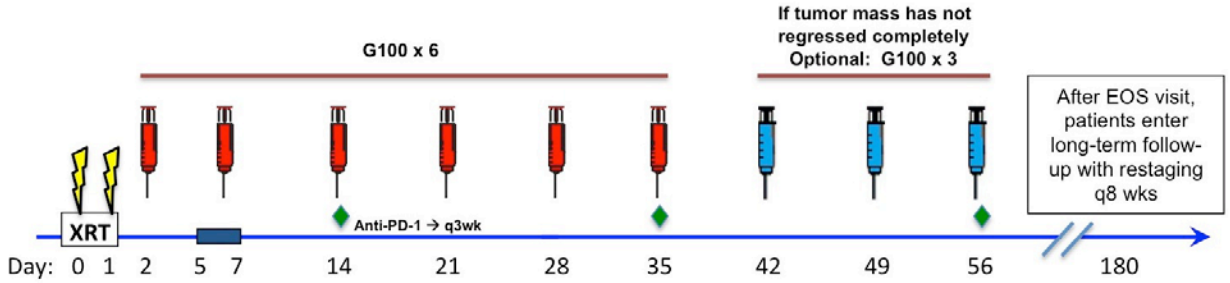


Figure 6: Dose Escalation And Expansion Of Part 4: G100 at 20µg/dose Into Single Or Multiple Tumor Lesions Plus Pembrolizumab Group

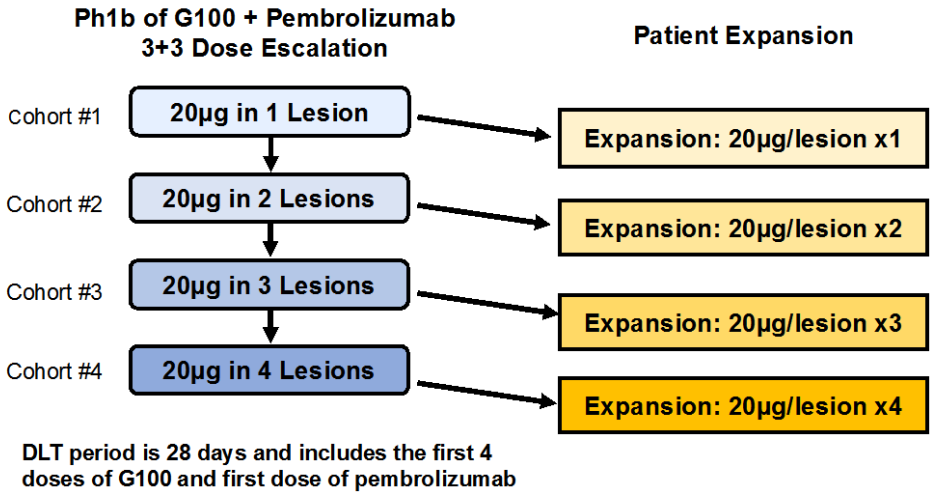


Figure 7: Part 4, G100 at 20µg/lesion Into Single Or Multiple Tumor Lesions Plus Pembrolizumab Group

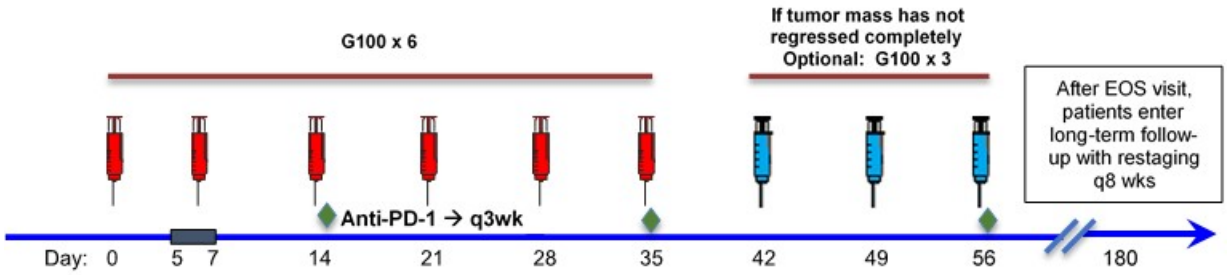


Figure 8: Part 5, G100 Plus Rituximab

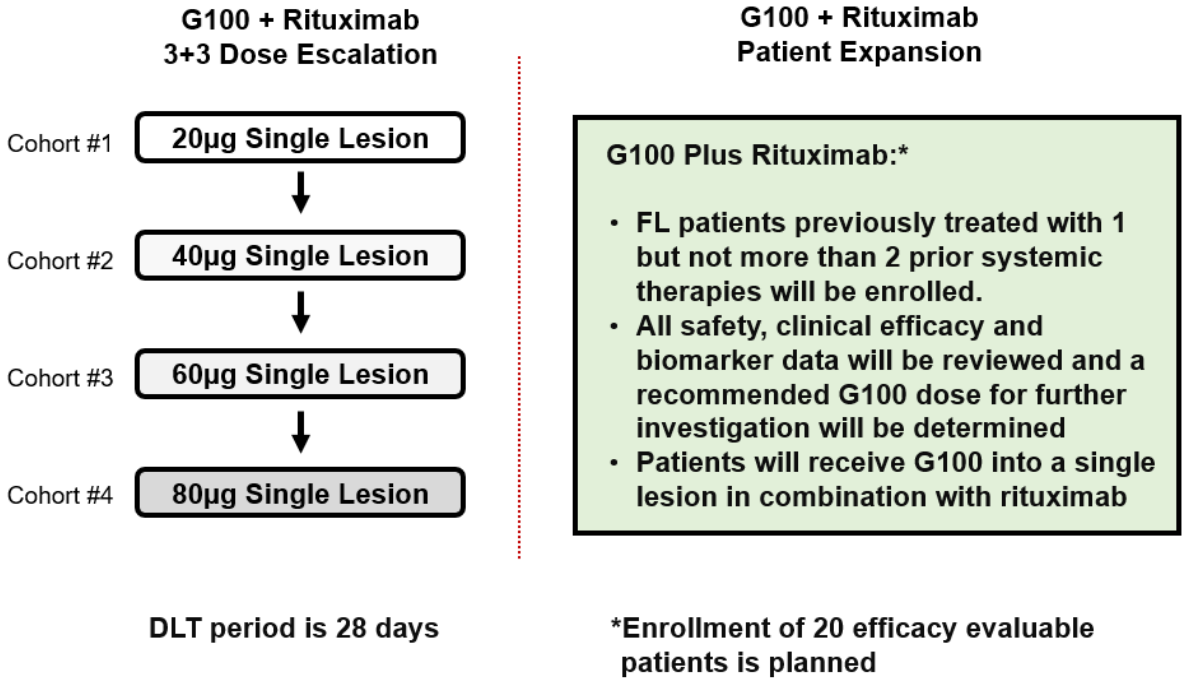


Figure 9: Part 5, G100 Plus Rituximab

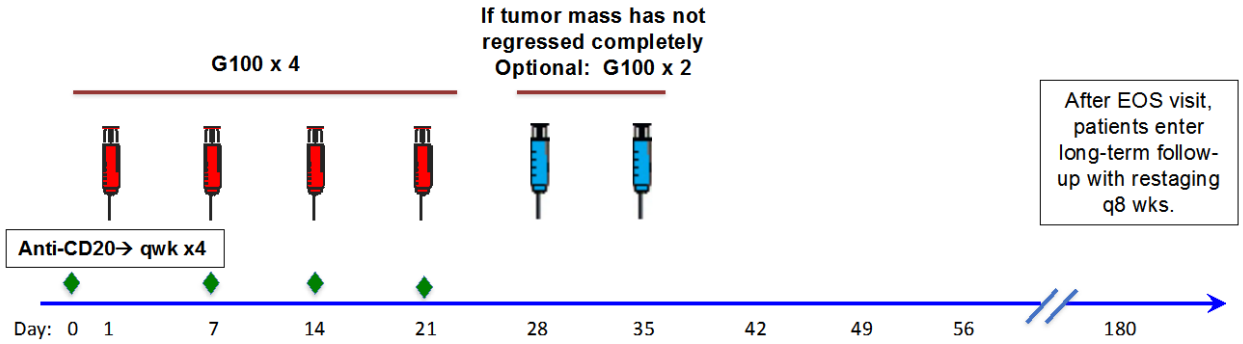
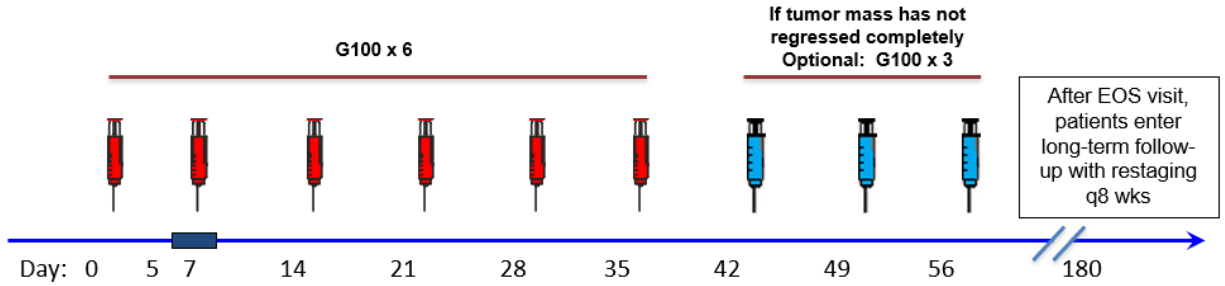


Figure 10: For Parts 1 to 5, Optional Retreatment / Second Course

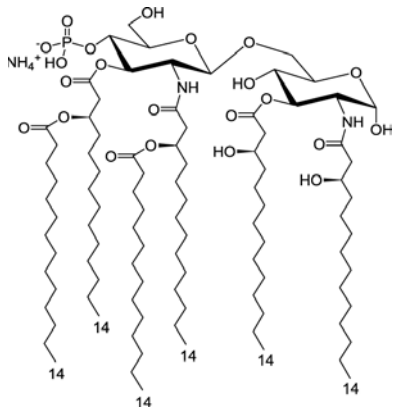


NOTE: Part 5 is limited up to 6 doses

4.2 G100: Glucopyranosyl Lipid A Stable Emulsion, GLA-SE

In this study, G100 will be administered intratumorally in order to generate an immune response against endogenous tumor antigens. G100 consists of a SE formulation of GLA, or glucopyranosyl lipid A, a fully synthetic glycolipid acyl component of endotoxin lipid A with the molecular formula of $C_{96}H_{184}N_3O_{22}P$ and a molecular weight of 1,762.31 (Figure 11). G100 is manufactured by high-pressure micro-fluidization followed by filter-sterilization. It contains squalene (oil), glycerol, tocopherol (vitamin E), synthetic dimyristoylphosphatidylcholine, surfactant (poloxamer) and ammonium phosphate buffer. The emulsion is filled aseptically into vials and appears as a milky-white liquid.

Figure 11: Structure of GLA



4.3 Summary of Known and Potential Risks to Human Patients

Over 1000 human subjects have been injected with GLA in either the SE formulation (GLA-SE) or a second aqueous formulation (AF), with or without antigen. Dosing has ranged from 0.5 to 10 µg with repeat dosing and has primarily been given subcutaneous (SC) or intramuscular (IM). Eleven patients have received up to 7 doses of 5 µg G100 intratumorally with or without local radiation. More than 270 human subjects treated with GLA in different regimens (with or without antigen and via different dosing methods) have had 1 year of systematic post-vaccination follow-up, and there have been no long latency AEs or autoimmune or inflammatory AEs (Table 1).

Table 1: Total Subjects Treated and Total Doses of GLA Administered to Human Subjects Through August 2014

Study Treatment	Exposure	N
Any GLA Product	Total doses administered	2299
	Total subjects treated	1065
	GLA 0.5 µg	6
	GLA 1.0 µg	274
	GLA 2.0 µg	332
	GLA 2.5 µg	63
	GLA 5.0 µg	349
	GLA 10.0 µg	41
GLA-AF	Total doses administered	576
	Total subjects treated	255
GLA-SE	Total doses administered	1723
	Total subjects treated	810

The majority of the human experience to date with GLA has been as an adjuvant with infectious agent or cancer associated protein antigens. The most commonly observed AEs have been injection site reactions of mild to moderate severity using the conservative "2007 FDA Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials." The only laboratory abnormalities of note have been transient increases in acute phase reactants (C-reactive protein [CRP] and fibrinogen) and peripheral blood neutrophils.

The safety findings across multiple studies including different formulations of GLA suggest that the dose response for GLA safety will vary with different co-administered antigens. The 5 μg dose of GLA-SE administered with a complex and highly immunogenic influenza (Fluzone®) split virus resulted in 3 of 4 subjects developing Grade 2 AEs (2007 Preventive Vaccine Grading Scale above) of arthralgia, myalgia, fatigue, and chills. However, an investigator-initiated study performed in Brazil has indicated that 50 μg of recombinant hookworm protein administered with a 10 μg dose of GLA-SE 3 times over 2 months was well tolerated. Fewer than 4% of AEs reported in association with GLA containing vaccines have been considered Grade 3 or higher in severity.

The AEs considered expected include injection site reactions, fever, fatigue, chills, myalgia, and arthralgia. There are insufficient data to date to establish that the safety profile is substantially different when GLA-SE is administered by either the IM or SC route of administration or as the SE or AF formulation.

Twenty-five serious adverse events (SAEs) have been reported from all GLA-SE clinical trials to date, most temporally dissociated from vaccination and no reports considered possibly, probably or definitely related to GLA treatment. The majority of these events were elective hospitalizations for surgical procedures. One SAE has been reported within 2 weeks of vaccine administration: A 37-year-old female was enrolled and vaccinated, with 3.8 μg investigational recombinant avian influenza protein + 1.0 μg GLA-SE and eight days later was observed overnight in a hospital setting, where cardiac enzymes and electrocardiogram (ECG) were normal. The patient was discharged with ibuprofen 800 mg, aspirin 325 mg, and omeprazole 40 mg with a discharge diagnosis of costochondritis.

In separate pilot studies, intratumoral injections of 5 μg G100 have been administered to patients with Merkel cell carcinoma and to patients with advanced sarcoma. As of 05 February 2015, 11 patients have been enrolled and treated in these ongoing studies. Six patients have received G100 treatment before, during and after radiation therapy. No grade 3 or higher AEs have been reported and the majority of events have consisted of grade 1 or 2 local reaction, pain and fatigue. In early results, 1 patient with biopsy proven, locoregional Merkel cell carcinoma was found to have a pathologic complete response (CR) following resection of the treated lesion. Tumor-specific cytotoxic T cells were found in a draining lymph node adjacent to the tumor mass, supporting the concept that clinically meaningful induction of anti-tumor immune activity can be achieved by this approach.

4.3.1 Safety Profile of G100 in Follicular Lymphoma

As of August 2018, 50 pts have been enrolled and treated on Parts 1, 2 and 3 of the G142 study. Some of this data was presented at ASCO 2017 and ASH 2017. Safety was evaluated using CTCAE version 4.03 and was reviewed by an independent Data Monitoring Committee following completion of each cohort and then at least quarterly. During G100 Dose Escalation, no related SAEs or dose limiting toxicity (DLT) were reported at dose levels of 5, 10 and 20µg/dose. Of all patients who received G100 as a single agent, all AEs considered at least possibly related to G100 were CTCAE Grade 1 or 2.

To date, the most common AEs considered related to G100 were injection site reactions (34%: includes terms of injection site: reactions, discomfort, pain, tenderness, erythema, bruising), nausea (10%), lymphocyte count decreased (10%), white blood cell count decreased (10%), fatigue (8%), chills (6%), fever (6%), myalgias (6%), abdominal discomfort/pain (6%), alkaline phosphatase increased (6%) and anemia (6 %).

Overall, the addition of pembrolizumab to G100 did not result in unexpected or worsening toxicity than has been reported with pembrolizumab alone. In the G100 and pembrolizumab group, two subjects experienced immune mediated toxicities considered related to pembrolizumab consisting of colitis/adrenal insufficiency or grade 2 hypothyroidism. The patient with adrenal insufficiency initially experienced grade 3 colitis and was treated with prolonged steroids. During steroid withdrawal, the patient experienced an SAE of grade 3 adrenal insufficiency with fatigue/weakness, hyponatremia, and hypocalcemia that required hospitalization. The event has completely resolved and was considered not related to G100 but probably related to pembrolizumab and to the prolonged steroid use and withdrawal.

4.4 Rationale for G100 Therapy

Intratumoral administration of TLR4 agonists can activate local DCs and other immune cells to react to local cancer cells despite the immunosuppressive nature of the tumor microenvironment. This approach has the potential to stimulate immune responses against known “specific” as well as previously unrecognized “endogenous” tumor antigens. This locally generated anti-tumor response would be expected to result in a systemic immunity and lead to regression of distal untreated lesions (abscopal response). In preclinical models and in ongoing clinical studies of Merkel cell carcinoma and sarcoma patients, intratumoral G100 has demonstrated early evidence of clinical activity with a reasonable safety profile. In this trial, intratumoral G100 therapy of patients with follicular NHL will be examined. These malignancies are known to contain tumor-specific antigens and have demonstrated responsiveness to active immunotherapy approaches with idiotype vaccines, with intratumoral DCs and with intratumoral CpGs. This may indicate that NHL are an ideal indication to investigate this approach.

This study will be performed in multiple parts. In Part 1, Dose Escalation, the safety and tolerability of 5 µg or 10 µg of G100 will be investigated following standard local radiation

therapy. Based on the safety profile, the MTD or maximal safe dose will be determined and used to treat additional patients. In Part 2, two groups of patients will be examined. In the first group, Patient Expansion with or without pembrolizumab, up to 24 patients will be treated with G100 at the MTD or maximum safe dose determined in Part 1. In this portion of the study, patients will be randomized to receive either intratumoral G100 alone or intratumoral G100 and sequential anti-PD-1 antibody therapy. This portion of the study is designed to be exploratory. In the second group, Part 2 Large Tumors, a higher dose of G100 may be examined. If the G100 dose consisting of 10 µg of the GLA component is determined to be the maximal safe dose and the DMC agrees, an optional treatment group for Large Tumor patients will be treated, where up to 4 patients with injectable lymphoma mass(es) 4 cm or greater in total size (based on the sum of the measurements of the single greatest dimension of each the tumor(s) within the planned radiation field) will be enrolled and will receive G100 consisting of 20 µg of the GLA component per dose. Following completion of enrollment into Part 2 Patient Expansion (G100 alone and sequential G100 and pembrolizumab) as determined by Sponsor, when at least 3 patients in the Large Tumor group have been enrolled and observed to at least Day 28 and an acceptable safety profile has been determined, Part 3 may begin. In Part 3, up to 25 patients will be enrolled to receive local radiation therapy and intratumoral G100 at 20 µg/dose following the same treatment schedule as in Part 1 and Part 2 where G100 was administered alone. Data from another study in sarcoma and early data from this trial have demonstrated no safety concerns with the 20 µg dose level, and to date, all reported events considered at least possibly related to the study agent have only been grade 1 or 2. Compared to baseline, post-treatment tumor biopsies have demonstrated significant increases in immune infiltrates within the tumor of some patients suggesting that this dose level should be explored further. In Parts 4 and 5, higher doses of G100 in combination with pembrolizumab or rituximab will be examined. Both arms will begin after Part 3 has completed and established safety with G100 at 20 µg/lesion and both will start with Dose Escalation to establish the safety of the total systemic dose of G100 administered.

4.4.1 Rationale for G100 Dose

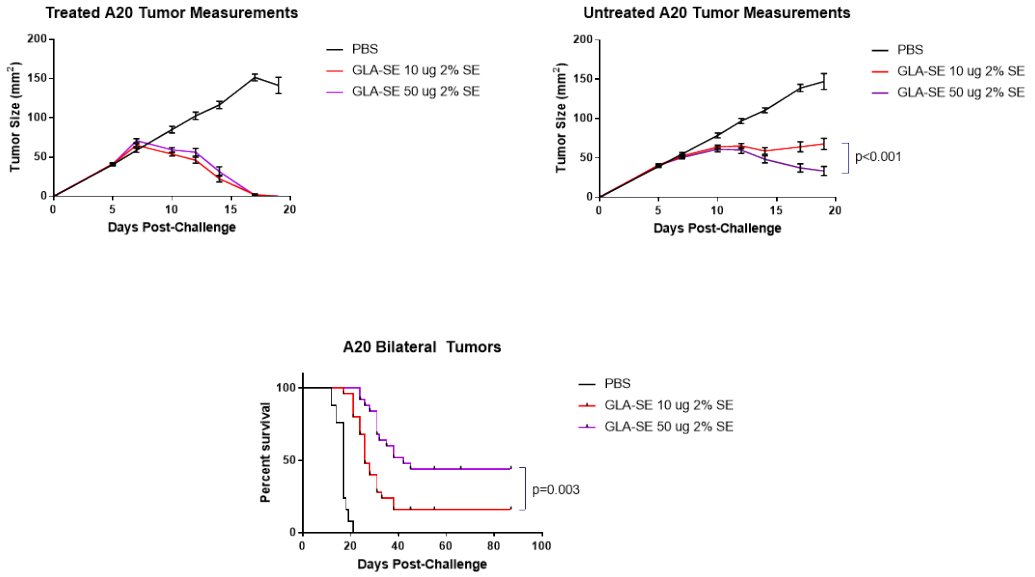
In preclinical models, there has been a suggestion of a dose response for intratumoral G100 when doses up to 10 µg were used. In Part 1, two dose levels of G100 will be examined. The starting dose of 5 µg G100 was selected because it has demonstrated acceptable safety in prior clinical studies of product candidates containing GLA involving over 300 patients when given IM or SC and can be administered in small volumes of the most extensively studied 2% oil/water SE formulation to facilitate intratumoral administration. Multiple injections of this dose level have been administered intratumorally in 11 patients with Merkel cell carcinoma or sarcoma both with and without accompanying radiation therapy and a reasonable safety profile has emerged. The higher dose of 10 µg GLA has also been used clinically in over 40 patients as an adjuvant for IM and SC vaccine treatments in both healthy volunteers and cancer patients. Reasonable safety profiles have been observed at this dose level in the past, and if this dose demonstrates reasonable safety in Part 1, it will be used to treat subjects in the Patient Expansion group. If the 10 µg dose of G100 is determined to be the maximal safe dose and if the DMC agrees, an

optional treatment group for Large Tumor patients will be treated. In this group, up to 4 patients with injectable lymphoma mass(es) 4 cm or greater in total size will be enrolled and will receive G100 consisting of 20 µg of the GLA component per dose. This will allow greater distribution of the G100 within the large tumor mass(es) and the examination of safety and dose effect.

A new treatment arm, G100 Expansion of 20 µg Dose Group, was added to expand the experience with G100 at 20 µg/dose. This higher dose has been examined in over 3 patients with sarcoma where each patient has received 12 doses of intratumoral G100. Principle investigator (PI) reported patient safety events were minimal and were only grade 1 or 2. There were no grade 3 or serious events considered at least possibly related to the study agent. The profile was similar to that of patients treated with G100 at 5 µg or 10 µg/dose in the same study. At the time of this amendment, 4 patients have been treated in the Large Tumor Group and 14 patients in Part 3 with 20 µg/dose. The emerging safety profile has been similar to that of 10 µg/dose treated patients. Therefore, there does not appear to be any new safety concerns.

In preclinical studies using the A20 lymphoma model, a side-by-side comparison of GLA-SE at 10ug/dose vs. 50ug/dose showed that higher dose (50 ug) has more potent anti-tumor effects and resulted in significantly better overall survival (Figure 12). Early exploratory data from sarcoma patients treated with the 20 µg dose indicate an increase in tumor immune infiltrates compared with lower treatment doses. Therefore, exploration of the higher dose level appears warranted.

Figure 12: Intratumoral Injection Of 50µg G100 Is More Potent Than 10 µg Of G100 In A20 Lymphoma.



Balb/c mice received A20 cell inoculation on Day 0 on both flanks. After the tumor became palpable (Day 5), treatment was initiated. G100 (10 ug or 50ug in 2%SE and diluted in 50uL of PBS) or control PBS of the same volume was injected into the tumor on the right side. Tumor growth on both treated and untreated tumors were monitored by caliper measurement. Results shown are combined data from three independent studies (N=25 mice per group).

The original concentration of G100 would have required a 2-mL volume to deliver a 20 µg dose. Highly concentrated formulations of G100 have been prepared and all patients on the G142 study have received G100 using these preparations. Doses of G100 >20 µg can be delivered in small volumes, and therefore, dose escalation beyond 20 µg as proposed for Parts 4 and 5 is feasible.

4.4.2 Rationale for Radiotherapy with Intratumoral G100

Recent studies with CpGs (a TLR9 agonist) administered intratumorally plus local radiation therapy have been associated with tumor responses at local and distant sites, both in mycosis fungoides (Kim 2012) and B cell lymphoma (Brody 2010). Local radiation therapy is thought to increase tumor immunogenicity by inducing tumor cell apoptosis and death and thereby releasing endogenous tumor antigens for cross-presentation by local DCs. In addition, radiation can increase tumor major histocompatibility complex (MHC) Class I expression and help facilitate DC migration to regional lymph nodes (Lugade 2005).

As discussed, G100 is a very potent TLR4 agonist that can promote the stimulation of DCs and immune effector cells. The combination of intratumoral G100 and radiation would be expected to augment the release of tumor antigens and enhance cross-presentation by DCs and the effective stimulation of anti-tumor immunity. TLR4 agonists may have an advantage over TLR9 agonists such as CpGs in this approach. TLR4 reside and are accessible on the cell surface as opposed to TLR 9, which is mainly expressed in the endosomal compartment. TLR4 agonists also stimulate both the MyD88 and TRIF pathways leading to broad immune stimulation through NF-kB and induction of type I INF (Figure 1).

For Part 4, the G100 regimen will examine the use of higher doses of G100 without radiation therapy to see if the increased dose can compensate for any benefit from radiation. This could potentially simplify the regimen by eliminating this portion of the treatment. Similarly, in Part 5, G100 plus Rituximab, radiation will not be used.

4.4.3 Rationale for Proposed G100 Schedule Selection

G100 will be administered by intratumoral injection into tumor mass(es) within the local radiation treatment field once on Day 2, with a second dose on Day 5 to 7 and then weekly for a total of 6 doses (Figure 4). At the end of the 6 doses, if the tumor has not regressed completely, 3 additional intratumoral weekly doses may be given. Non-clinical studies suggest that multiple injections 1 to 2 times per week generate the most durable and highest magnitude responses. NHL tends to be very responsive to local radiation therapy, and 6 doses of G100 may be the optimal number of doses that can be applied before significant tumor regression occurs. Three additional G100 doses are an option for those patients with potentially slower responding disease.

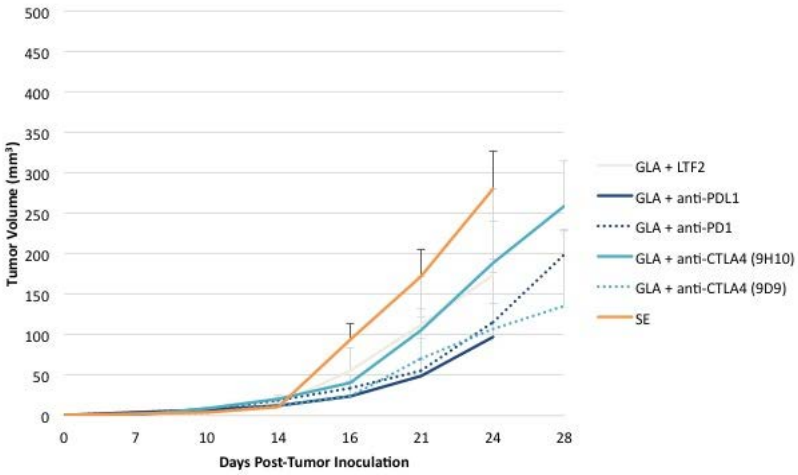
4.5 Rationale for anti-PD-1 Therapy and Proposed Schedule

High levels of the programmed death ligand (PD-L)-1 molecule are expressed on a wide variety of cancer cells or on histiocytes and other cells within the tumor microenvironment. The binding of the PD-1 on tumor-infiltrating T cells to its ligand PD-L1 leads to an inhibition of anti-tumor immune activity. The PD-1/L1 axis is an immune checkpoint inhibitor that when activated negatively affects the ability of T cells to proliferate, generate cytokines, and kill cancer cells (Mellman 2011; Pardoll 2012). Blocking the interaction of PD-1 with its ligands, PD-L1 and PD-L2, with a mAb against PD-1 can restore immune function, increase migration of T cells from the invasive margin into the tumor, and enhance anti-tumor immune responses. The proliferation of intratumoral CD8 T cells was recently shown to directly correlate with reduction in tumor size (Tumeh 2014). Several checkpoint inhibitor mAbs are undergoing clinical evaluation; pembrolizumab (Keytruda, Merck) was recently approved and is the first anti-PD-1 antibody available in the United States (US). In its approved indication, unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor, pembrolizumab has demonstrated an overall response rate of 24% (FDA 2014; Keytruda product label 2018).

Clinically, anti-PD-1/L1 blocking antibodies are active as a single agent but are limited in their ability to induce objective responses (CR and partial response [PR]). For this treatment to have a clinical effect, it is hypothesized that tumor-reactive T cells are present, but are being suppressed by this pathway. Blocking this axis would restore anti-tumor immunity. One theory that can explain why anti-PD1/L1 blocking antibodies do not result in higher response rates is that non-responding patients do not have pre-existing effective anti-tumor T cells present that are being suppressed (Tumeh 2014). As a corollary, if more patients had pre-existing anti-tumor immune responses, then these anti-PD-1/L1 agents could potentially be more effective.

In patients with cancer, the PD-1/L1 pathway would be expected to diminish any anti-tumor immune response, and it stands to reason that CD8 T cells generated by the immune response to G100 would eventually be affected by this pathway. Therefore, G100 activity might be enhanced by blocking the PD-1/L1 pathway, especially in the presence of tumor or cells within the tumor microenvironment expressing PD-L1. This effect can be demonstrated in tumor-bearing animals, where blocking PD-1 in combination with active immunization with G100 controlled tumor growth significantly better than animals treated with G100 alone (Figure 13).

Figure 13: Intratumoral G100 Plus Check Point Inhibitors In The B16 Melanoma Model



On Day 0, B6 mice were injected with 5 x 10^5 B16F10 cells, footpad. On Day 4 and every 3-4 days thereafter, G100 (5 µg GLA/2% SE) was administered intratumorally either with or without anti-PD-1, anti-PD-L1, anti-CTLA4 (2 antibody clones) or control (100 µg intraperitoneal injection). The anti-tumor effect of anti-PD-1, anti-PD-L1 and anti-CTLA4 antibodies were additive or synergistic when combined with G100.

There is reasonable rationale that an optimal dose schedule of an active immune approach with an anti-PD-1/L1 may require that a T-cell response be induced before introducing PD-1/L1 blockade. Therefore, the dose regimen for this study administers two doses of G100 before initiating an anti-PD-1 blocking antibody. In this regimen (Figure 5), G100 is first administered on Day 2 and a second dose is given on Day 5 to 7. Then beginning on Day 14, anti-PD-1 therapy is given around the time of the 3rd dose of G100 and is continued every 3 weeks (Q3W) for up to 2 years or until disease progression or unacceptable toxicity. The separation of each agent in time is expected to allow an assessment of the benefit of adding each agent toward the development of anti-tumor immune responses and help distinguish the contribution of each agent to any safety events that might be observed.

4.5.1 Pembrolizumab Background and Clinical Trials

Pembrolizumab is a potent humanized immunoglobulin G4 (IgG4) monoclonal antibody (mAb) with high specificity of binding to the programmed cell death 1 (PD-1) receptor, thus inhibiting its interaction with programmed cell death ligand 1 (PD-L1) and programmed cell death ligand 2 (PD-L2). Based on preclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1. Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an intravenous (IV) immunotherapy for advanced malignancies. Keytruda® (pembrolizumab) is indicated for the treatment of patients across a number of indications. For more details on specific indications refer to the Investigator's Brochure.

Refer to the Investigator's Brochure (IB)/approved labeling for detailed background information on MK-3475.

4.5.2 Pharmaceutical and Therapeutic Background

The importance of intact immune surveillance function in controlling outgrowth of neoplastic transformations has been known for decades (Disis 2010). Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T-cells/FoxP3+ regulatory T-cells (T-regs) correlates with improved prognosis and long-term survival in solid malignancies, such as ovarian, colorectal, and pancreatic cancer; hepatocellular carcinoma; malignant melanoma; and renal cell carcinoma. Tumor-infiltrating lymphocytes can be expanded ex vivo and reinfused, inducing durable objective tumor responses in cancers such as melanoma (Dudley 2005; Hunder 2008).

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene *Pdcd1*) is an immunoglobulin (Ig) superfamily member related to cluster of differentiation 28 (CD28) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) that has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2) (Greenwald 2005; Okazaki 2001).

The structure of murine PD-1 has been resolved (Zhang 2004). PD-1 and its family members are type I transmembrane glycoproteins containing an Ig-variable–type (IgV-type) domain responsible for ligand binding and a cytoplasmic tail responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif, and an immunoreceptor tyrosine-based switch motif. Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases, SHP-1 and SHP-2, to the immunoreceptor tyrosine-based switch motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3 zeta (CD3ζ), protein kinase C-theta (PKCθ), and zeta-chain-associated protein kinase (ZAP70), which are involved in the CD3 T-cell signaling cascade (Okazaki 2001; Chemnitz 2004; Sheppard 2004; Riley 2009). The mechanism by which PD-1 down-modulates T-cell responses is similar to, but distinct from, that of CTLA-4, because both molecules regulate an overlapping set of signaling proteins (Parry 2005; Francisco 2010). As a consequence, the PD-1/PD-L1 pathway is an attractive target for therapeutic intervention in non-Hodgkins lymphomas.

4.5.3 Pre-clinical and Clinical Trials

Therapeutic studies in mouse models have shown that administration of antibodies blocking PD-1/PD-L1 interaction enhances infiltration of tumor-specific CD8+ T cells and ultimately leads to tumor rejection, either as a monotherapy or in combination with other treatment modalities (Hirano 2005; Blank 2004;Weber 2010; Strome 2003; Spranger 2014; Curran 2010; Pilon-Thomas 2010). Anti-mouse PD-1 or anti-mouse PD-L1 antibodies have demonstrated antitumor responses in models of squamous cell carcinoma, pancreatic carcinoma, melanoma, acute myeloid leukemia and colorectal carcinoma (Strome 2003; Curran 2010; Pilon-Thomas 2010; Nomi 2007; Zhang 2004). In such studies, tumor infiltration by CD8+ T cells and increased IFN-γ, granzyme B and perforin expression were observed, indicating that the mechanism underlying the antitumor activity of PD-1 checkpoint inhibition involved local infiltration and activation of effector T cell function *in vivo* (Curran 2010). Experiments have confirmed the *in vivo* efficacy of anti-mouse PD-1 antibody as a monotherapy, as well as in combination with chemotherapy, in syngeneic mouse tumor models (see the Investigator's Brochure [IB]).

4.5.4 Justification for Dose

The planned dose of Pembrolizumab for this study is 200 mg every 3 weeks (Q3W). Based on the totality of data generated in the Keytruda development program, 200 mg Q3W is the appropriate dose of Pembrolizumab for adults across all indications and regardless of tumor type. As outlined below, this dose is justified by:

- Clinical data from 8 randomized studies demonstrating flat dose- and exposure-efficacy relationships from 2 mg/kg Q3W to 10 mg/kg every 2 weeks (Q2W),
- Clinical data showing meaningful improvement in benefit-risk including overall survival at 200 mg Q3W across multiple indications, and
- Pharmacology data showing full target saturation in both systemic circulation (inferred from pharmacokinetic [PK] data) and tumor (inferred from physiologically-based PK [PBPK] analysis) at 200 mg Q3W.

Among the 8 randomized dose-comparison studies, a total of 2262 participants were enrolled with melanoma and non-small cell lung cancer (NSCLC), covering different disease settings (treatment naïve, previously treated, PD-L1 enriched, and all-comers) and different treatment settings (monotherapy and in combination with chemotherapy). Five studies compared 2 mg/kg Q3W versus 10 mg/kg Q2W (KN001 Cohort B2, KN001 Cohort D, KN002, KN010, and KN021), and 3 studies compared 10 mg/kg Q3W versus 10 mg/kg Q2W (KN001 Cohort B3, KN001 Cohort F2 and KN006). All of these studies demonstrated flat dose- and exposure-response relationships across the doses studied representing an approximate 5- to 7.5-fold difference in exposure. The 2 mg/kg (or 200 mg fixed-dose) Q3W provided similar responses to the highest doses studied. Subsequently, flat dose-exposure-response relationships were also

observed in other tumor types including head and neck cancer, bladder cancer, gastric cancer and classical Hodgkin Lymphoma, confirming 200 mg Q3W as the appropriate dose independent of the tumor type. These findings are consistent with the mechanism of action of Pembrolizumab, which acts by interaction with immune cells, and not via direct binding to cancer cells.

Additionally, pharmacology data clearly show target saturation at 200 mg Q3W. First, PK data in KN001 evaluating target-mediated drug disposition (TMDD) conclusively demonstrated saturation of PD-1 in systemic circulation at doses much lower than 200 mg Q3W. Second, a PBPK analysis was conducted to predict tumor PD-1 saturation over a wide range of tumor penetration and PD-1 expression. This evaluation concluded that Pembrolizumab at 200 mg Q3W achieves full PD-1 saturation in both blood and tumor.

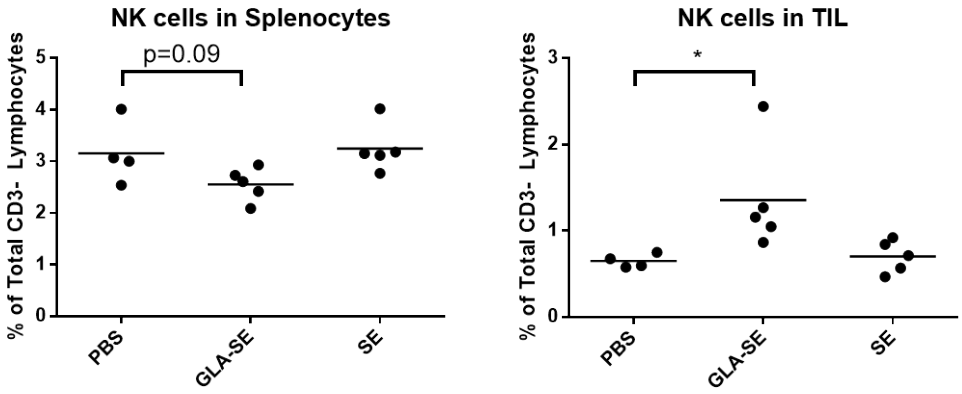
Finally, population PK analysis of Pembrolizumab, which characterized the influence of body weight and other participant covariates on exposure, has shown that the fixed-dosing provides similar control of PK variability as weight based dosing, with considerable overlap in the distribution of exposures from the 200 mg Q3W fixed dose and 2 mg/kg Q3W dose. Supported by these PK characteristics, and given that fixed-dose has advantages of reduced dosing complexity and reduced potential of dosing errors, the 200 mg Q3W fixed-dose was selected for evaluation across all Pembrolizumab protocols.

4.6 Rationale for Rituximab Therapy and Proposed Schedule

Rituximab either as a single agent or in combination with other agent(s) has become an essential treatment and a backbone of therapies used to treat follicular lymphomas and other B cell malignancies. The clinical anti-tumor activity of this anti-CD20 antibody appears to derive from its ability to facilitate antibody-dependent cellular cytotoxicity (ADCC), directly inducing apoptosis of lymphoma cells (studies with cross-linked antibody), and activating complement dependent cytotoxicity. (Rituximab label 2010; Hsu 2002)

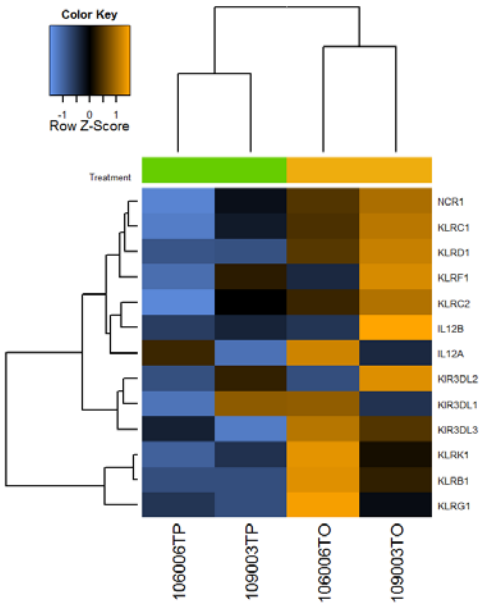
The mechanism of action of G100 complements that of rituximab. ADCC requires the presence of activated NK cells, macrophages and other phagocytic cells. G100 releases cytokines and can attract and increase the number of activated NK and other phagocytic cells in the tumor microenvironment (Figure 14). In clinical studies of intratumoral G100 in patients with sarcoma, G100 was associated with an increase of inflammatory macrophages of M1 phenotype, indicating an increased activity (Seo 2017). Preliminary nanostring gene expression analysis using tumor biopsy collected from FL patients before or after G100 treatment showed induction of genes associated with NK cell function, including FcgR2A, FcgR3A, 2B4, Granzyme A, etc. As shown in Figure 15, heatmap analysis of genes from two representative patients shows higher levels of genes expression of multiple NK cell receptors. This data would support the potential synergy between G100 and rituximab. Further testing using PBMC from healthy donors and rituximab-coated target Raji cells showed that pre-incubation of PBMC with GLA (0.2 or 1 µg/mL for 48hr) significantly enhanced the lysis of target cells at different concentrations of rituximab (Figure 16).

Figure 14: G100 Increases NK Cells In The Tumor Microenvironment



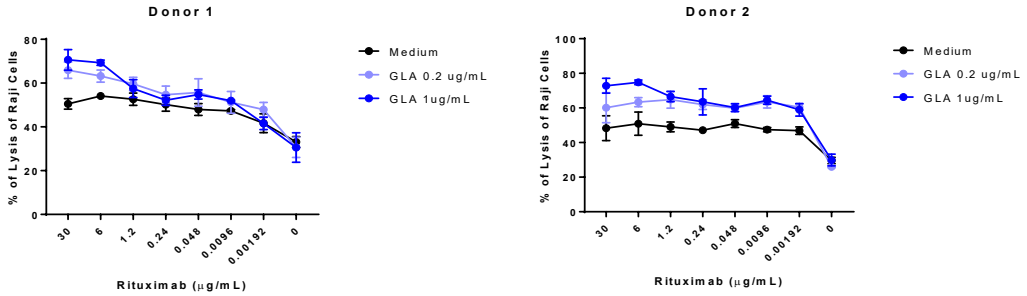
Balb/c mice with established A20 tumors received 2 intratumoral G100 injection. Tumors were collected at 2 hours after the last injection and tumor infiltrating lymphocytes (TIL) were isolated by Ficoll gradient centrifugation and stained with antibodies for CD4, CD8, CD3, CD19, and NKp46. Shown are the percentages of NK cells out of total $CD3^-$ lymphocytes (non-T cells). Each dot represents an individual mouse. *, $p<0.05$. The percentages of NK cells was also evaluated in splenocytes, and there was a trend of decreasing numbers in splenocytes, suggesting the possibility that increased NK cells in TIL may be due to increased trafficking of NK cells from periphery to tumor.

Figure 15: G100 Induces Genes Related To NK Cell Function In FL Patients



Pre-G100 and post-G100 biopsies from FL patients were collected. RNA from these tumors was isolated and then 200ng of total RNA was used for nanostring gene expression analyses using the panCancer Immune Profiling panel. The results were analyzed using nSolver software after normalization. The heatmap shows unsupervised clustering of 13 genes related to NK cell function in two pre-G100 samples (106006TP, 109003TP) and two post-G100 samples (106006TO, 109003TO). Blue color indicates low gene expression levels; Orange color indicates high gene expression levels. Specific genes are labeled and identified to the right of the heatmap.

Figure 16: GLA Enhances Rituximab-Mediated ADCC



Fresh PBMC were isolated from healthy donors. PBMC were incubated with medium alone or with GLA-AF (0.2 or 1 ug/mL) for 48hr. Raji cells were stained with CFSE and mixed with PBMC at an Effector to Target ratio of 50:1 in combination in media containing increasing concentrations of rituximab. After incubation at 37°C for 4hr, the percentage of dead target cells ($CFSE^+PI^+$) and live target cells ($CFSE^+PI^-$) were measured by flow cytometry and the percentage of cell lysis was calculated.

Another important aspect of rituximab is its ability to induce tumor apotosis and facilitate phagocytosis and tumor antigen presentation by dendritic cells. Tumor-specific antigens that can be recognized by the immune system represent a small proportion of all proteins in the surrounding environment available for processing by dendritic cells. Therefore, methods that facilitate targeting and increase the loading of dendritic cells with tumor-specific antigens would be expected to increase the stimulation, development, and activity of cytolytic T cells. In studies using autologous tumor, T cells and dendritic cells obtained from patients previously immunized with patient specific idiotype proteins, rituximab coated tumor cells were rapidly opsonized and processed by dendritic cells. These tumor-pulsed dendritic cells could then be used to stimulate and expand previously primed cytotoxic T cells that were capable of specifically killing tumor cells (Hsu 2002). Similar preclinical studies using mouse models have demonstrated a survival advantage to animals immunized with rituximab coated or anti-Id antibody coated autologous tumor (Manzur 2012, Franki 2008). These studies indicated that coating tumor cells with opsonizing antibodies could direct these relatively rare tumor antigens to be taken up/loaded and processed by dendritic cells, thereby increasing the potential anti-tumor activity of immunotherapy approaches such as G100 that use autologous tumor as a source of antigen.

Rituximab for the treatment of NHL is well established and the primary treatment (induction) regimen (375 mg/m2 IV weekly x4 doses) has not changed since its original approval in 1997. Although extended / maintenance therapy has been examined in multiple large studies, its use has remained controversial and can lead to increased side effects including infections and low white blood counts (Rituxan label 2010). In low tumor burden patients, maintenance therapy did not result in improvement in time to treatment failure compared to retreatment at time of

progression with rituximab (Kahl 2014). Therefore, for this study, the standard induction therapy of rituximab without maintenance will be used in combination with G100.

4.7 Safety Monitoring

G100 safety will be monitored by evaluating both solicited and spontaneously reported AEs, including reactogenicity, symptoms, physical examination findings, vital signs, laboratory findings, ECGs and discontinuations for AEs. Subjects will be encouraged to call and/or return to the site if they have any significant concerns regarding AEs.

The independent DMC will operate in accord with a signed charter and be advisory to the Sponsor. In Part 1, the DMC will review all DLTs and SAEs considered at least possibly related to study agent on an ongoing basis and will review all safety data for any trends at least once every 3 months. SAE reports considered at least possibly related to the study regimen and are unexpected will be expedited to regulatory authorities, investigators and DMC members. All patients treated with one or more doses of G100 will be considered part of the safety data set. The independent DMC will review all safety data and make recommendations regarding safety concerns, determination of DLTs, and the conduct of the study. Modifications to the treatment program may arise out of such reviews.

In Part 2, two groups of patients are planned, Patient Expansion With Or Without Pembrolizumab and (optional) Large Tumor patients. The Patient Expansion group will receive intratumoral G100 or sequential intratumoral G100 and pembrolizumab and will begin once the MTD / maximum safe dose is determined from Part 1. Based on the results of Part 1 and safety profile of the highest dose level, the DMC will recommend whether or not to open the optional Large Tumor treatment group. Enrollment in the Large Tumor group will only be possible if the 10 µg/dose level is determined to be safe.

During Part 2 and based on the continuous review of safety events, if the dose of 10 µg G100 is used during Patient Expansion and subsequently determined to have an increased safety risk, the DMC may recommend and the Sponsor may choose to reduce the dose of G100 to 5 µg or they may recommend stopping the G100 treatment. If the 5 µg dose level is determined not to be safe by the independent DMC, treatment with G100 will be stopped. Following evaluation by the DMC and the Sponsor, a further modification to the dose/treatment schedule could be recommended.

In Part 3, G100 Expansion of 20 µg Dose Group, treatment may begin after enrollment into Part 2 Patient Expansion (G100 alone and sequential G100 and pembrolizumab) has been completed (as determined by Sponsor), at least 3 patients in the Large Tumor group have been enrolled and observed to at least Day 28, and an acceptable safety profile has been determined. The Sponsor in consultation with the DMC will review the safety profile of G100 alone data from Part 1 and 2. Commencement of Part 3 will be contingent upon determination of an acceptable safety profile of G100 alone data at that evaluation timepoint. In Part 3, up to

25 patients will be enrolled to receive local radiation therapy and intratumoral G100 at 20 µg/dose following the same treatment schedule as in Part 1 and Part 2 where G100 was administered alone.

In Part 4, Sequential G100 at 20µg/lesion Into Single Or Multiple Tumor Masses Plus Pembrolizumab Group, treatment may begin after enrollment into Part 3 has been completed (as determined by Sponsor), and an acceptable safety profile has been determined by the Sponsor in consultation with the DMC. In Part 4, at least 22 evaluable patients will be enrolled to receive sequential IT G100 at 20 µg/lesion and pembrolizumab at 200mg IV every 3 weeks following the same treatment schedule as in Part 2 where G100 was administered with pembrolizumab, except without radiation therapy (Figure 7). In this dose escalation arm, sequential cohorts of patients will be treated with intratumoral G100 at 20 µg/lesion in 1, 2, 3, or 4 tumor masses corresponding to local and systemic G100 exposure of 20, 40, 60 or 80 µg of the GLA component. Patient Expansion will be allowed to begin at each dose level as safety is established for each cohort and agreed upon with the DMC (Figure 6). Twenty-two efficacy evaluable patients as defined in the Statistical Section will be enrolled.

In Part 5, G100 Plus Rituximab, treatment may begin after enrollment into Part 3 has been completed (as determined by Sponsor), and an acceptable safety profile has been determined by the Sponsor in consultation with the DMC. In Part 5, patients will be enrolled to receive IT G100 and standard induction rituximab without radiation therapy. During dose escalation, sequential cohorts of 3-6 patients will be treated with intratumoral G100 at 20, 40, 60 or 80 µg/dose into a single tumor mass. Once the MTD/maximum safe dose has been established, all safety, clinical and biomarker data will be reviewed and a recommended dose for further exploration will be made. The Patient Expansion would then begin and would treat patients with G100 at the recommended dose in a single lesion in combination with rituximab. Overall, 20 efficacy evaluable patients as defined in the Statistical Section will be enrolled.

Potential Dose Modification During Dose Escalation:

During Part 4 and based on the continuous review of safety events, if the dose of 20 µg/lesion G100 is subsequently determined to have an increased safety risk, the DMC may recommend and the Sponsor may choose to reduce the dose of G100 to 10µg and potentially to re-examine escalation with this lower dose/lesion regimen or they may recommend stopping the G100 treatment.

G100 is a local therapy with systemic immune responses. Therefore, the safety profile may differ from that of systemically administered agents. In order to further investigate this, if 2 or more DLTs are observed in the initial cohort at 20 µg of G100, the Sponsor, in agreement with the independent DMC may choose to examine a new cohort of patients to better understand whether or not the DLTs associated with the injection of a single lesion might be abrogated by decreasing the dose and administering the lower single lesion dose of 10 µg into multiple

lesions. Intratumoral G100 10 µg in a single lesion in combination with pembrolizumab was established to be well-tolerated in Part 2 of this study. Thus, this new cohort would examine the safety of G100 10 µg administered into 2 injectable lesions and would use the same 3+3 design described above. Based on a review of the safety profile of this new cohort and in agreement with the independent DMC, further dose escalation cohorts may be investigated using this lower dose of 10 µg/lesion and a similar dose escalation schema as described above where up to 4 lesions may be potentially treated.

Similarly during Part 5, if G100 plus rituximab is subsequently determined to have an increased safety risk, the DMC may recommend and the Sponsor may choose to reduce the dose of G100 or they may recommend stopping the G100 treatment. In order to further investigate this, after establishment of an MTD, the Sponsor in agreement with the independent DMC may choose to examine one additional cohort of patients to better understand whether or not the DLTs associated with the injection of a single lesion might be abrogated by splitting the dose and administering the lower single lesion dose into two lesions. The data from this cohort may help determine if the tolerability of G100 was limited due to the injection of a single tumor mass or to the total systemic exposure with this agent. In this additional cohort, 3-6 patients would be treated at the total systemic dose level associated with DLTs but divided and distributed into two tumor masses instead of one. For example, if the MTD in a single tumor mass were determined to be 40 µg due to DLTs occurring at 60 µg/lesion, the dose of this cohort would be 30 µg/lesion injected separately into 2 tumor masses. In the event that the 20 µg dose level (Cohort 1) experiences DLTs, a cohort of 10 µg/lesion administered into 2 lesions may be explored. The information from this additional cohort could help the design of future studies. The decision whether or not to open this cohort would be made when the Dose Escalation data is reviewed following the determination of the MTD. No additional treatment cohorts are planned beyond this one group. Following this evaluation, patients would be enrolled into the Patient Expansion group and would receive G100 injected into a single lesion at the recommended dose.

Following each safety evaluation by the DMC and the Sponsor, a further modification to the dose/treatment schedule could be recommended. For all treatment groups, the DMC and Sponsor will review all events meeting the criteria for DLTs and all SAEs considered at least possibly related to the study regimen as they are reported on an ongoing basis. In addition, the DMC and Sponsor will review all safety data for any trends at least once every 3 months. SAE reports considered at least possibly related to the study regimen and are unexpected will be expedited to regulatory authorities, investigators, and DMC members. In addition to the stopping rules (DLTs within the initial 28 days), these reviews may lead to modification or stopping of the treatment program if related, treatment-emergent AEs indicate a safety profile that is inconsistent or significantly worse than previously reported with the use of either G100 or pembrolizumab alone or rituximab alone.

All AEs and DLTs observed during dose escalation of any treatment arm and/or patient expansion meeting the criteria of a stopping rule will be reviewed by the DMC. If there is

disagreement between the DMC and the investigator's assessment regarding the relationship of the event to study agent or to the clinical relevance (e.g., lab abnormality), the Sponsor in consultation with the DMC may determine to stop the treatment or continue. In the later case, the AE may become a medical event of interest and be tracked closely for additional events occurring in future with IT G100

All patients treated with one or more injections of G100 will be considered part of the safety data set. Patients will be followed every 8 weeks until disease progression as defined by the irRC. Patients with disease progression by irRC (or symptomatic deterioration) will be followed thereafter every 8-12 weeks by telephone or clinical visit for up to one year (or longer if the patient agrees) after first study injection as long as they are able to engage in follow-up. Follow-up will ascertain vital status (survival status) as well as cancer status (e.g., lymphoma transformation), post-treatment anti-cancer therapy (including time to next treatment, treatment details, and clinical response), and any SAE that might be possibly related to G100 treatment.

Patients with disease progression by the immune-related Response Criteria (irRC) (Wolchok 2009) will be followed thereafter every three months by telephone or clinic visit for up to one year after first study treatment to ascertain clinical status.

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Primary Objective

- In Part 1: Evaluate the safety and tolerability of ascending doses of intratumoral G100 in patients with low-grade NHL receiving local radiation
- In Part 2: Assess the safety and tolerability of intratumoral G100 or sequential intratumoral G100 and anti-PD-1 therapy in patients with follicular NHL receiving local radiation
- In Part 3: Evaluate the safety and tolerability of 20 µg/dose of intratumoral G100 in patients with low-grade NHL receiving local radiation
- In Part 4: Evaluate safety and preliminary clinical efficacy of intratumoral G100 at 20µg/lesion in single or multiple tumor lesions and pembrolizumab (anti-PD-1) therapy in patients with relapsed or refractory follicular NHL who have received at least 3 prior systemic treatments, one of which was or included an anti-CD20 antibody
- In Part 5: Evaluate safety and preliminary clinical efficacy of standard induction therapy with rituximab (anti-CD20) in combination with escalating doses of intratumoral G100 in single tumor lesions in patients with follicular NHL who have received at least one or two prior treatment(s)

5.2 Secondary Objectives

- Assess clinical responses by irRC using bi-dimensional measurements and time-to-progression (TTP) as a preliminary indication of efficacy

  For comparison, clinical responses will also be assessed by the International Working Group response criteria and Lugano criteria for lymphomas (Cheson 2014).

- Assess abscopal tumor responses in non-treated, distal tumor sites

5.3 Exploratory Objective

- For Part 4 and 5, explore pharmacokinetic and pharmacodynamic properties of G100
- Evaluate pre- and post-regimen tumor tissue and blood for exploratory biomarkers of immunologic and tumor response
- To assess clinical responses by Immune-related Response Criteria (irRC) and Lugano criteria for lymphomas using independent radiology review

5.4 Primary Endpoint

- Part 1: The nature, frequency and severity of AEs and laboratory abnormalities up through Study Day 28 in patients with low-grade NHL receiving intratumoral G100 and local radiation
- Part 2: The nature, frequency and severity of AEs and laboratory abnormalities occurring in patients with follicular NHL receiving local radiation and either intratumoral G100 alone or sequential intratumoral G100 and anti-PD-1 therapy
- Part 3: The nature, frequency, and severity of AEs and laboratory abnormalities occurring in patients with follicular NHL receiving local radiation and G100 at 20 µg/dose
- Part 4: The nature, frequency and severity of AEs and laboratory abnormalities and the frequency of clinical responses occurring in patients with follicular NHL receiving intratumoral G100 at 20 µg/lesion in single or multiple tumor masses and pembrolizumab therapy
- Part 5: The nature, frequency and severity of AEs and laboratory abnormalities and the frequency of clinical responses occurring in patients with follicular NHL receiving rituximab therapy in combination with escalating doses of intratumoral G100 in single tumor lesions

5.5 Secondary Endpoints

- The nature, frequency and severity of AEs and laboratory abnormalities until 21 days after G100 regimen is completed or discontinued

- Clinical responses by irRC using bi-dimensional measurements and expressed as PR, CR, SD, or PD, and TTP and/or progression-free survival (PFS) as a preliminary indication of efficacy
- As an exploratory comparison, assess clinical responses by the International Working Group response criteria for lymphomas. (For determining PD, the irRC criteria will be used.) Sponsor will assess for clinical responses by the Lugano criteria for lymphomas (Cheson 2014).
- Abscopal tumor responses in non-treated, distal tumor sites

5.6 Exploratory Endpoints

- For Part 4 and 5, Explore pharmacokinetic and pharmacodynamic properties of G100
- Assess blood and tumor samples for exploratory biomarkers of immunologic and tumor response

6.0 INVESTIGATIONAL PLAN

6.1 Overall Trial Design and Plan

This is a Phase 1/2, open label, trial of G100 in patients with low grade follicular NHL. G100 is composed of GLA formulated in a SE. GLA is a fully synthetic TLR4 agonist that is a potent stimulator of innate immune responses. In this study, G100 will be injected into tumors of follicular NHL patients in order to generate anti-tumor immune responses. GLA in either the SE formulation or an AF has been examined in >1000 patients as an adjuvant for various infectious agent and cancer vaccines as well as in 2 ongoing clinical studies involving patients with Merkel Cell carcinoma or sarcoma where it has been administered intratumorally either alone or in combination with local radiation therapy. It has demonstrated the ability to stimulate immune responses with an acceptable safety profile.

In Part 1, Dose Escalation, patients with accessible tumors that are being considered for radiation therapy will receive standard local radiation followed by intratumoral injections of G100 into the irradiated mass(es). Two dose levels will be examined and a 3+3 sequential dose escalation design will be used. All patients will receive a regimen consisting of standard low dose radiation (2Gy every day [qd] x2, 4 Gy total) to the target tumor mass(es). G100 will be injected intratumorally beginning 1 day following completion of radiation therapy (Study Day 2), a second dose will be administered 3-5 days later (Study Day 5 to 7) and then dosing will continue weekly for up to 4 additional doses (6 total) as long as the tumor remains of sufficient size for injection. A single lesion within the radiation field will be targeted to receive each dose of G100. If the lesion regresses, another lesion within the radiation field will be chosen for treatment (as described in Section 8.1.3.2). If the tumor mass has not regressed completely dosing may continue for 3 additional weekly intratumoral doses (9 total).

Two dose levels of G100 are planned:

- Cohort 1: 5 µg
- Cohort 2: 10 µg

Initially, three patients will be scheduled to receive G100 at the first dose level. Dose escalation will be contingent upon acceptable safety data obtained during the first 28 days of observation following initiation of the regimen. A dose level cohort will be expanded from three to six if one of the first three patients experiences a DLT. Further patient accrual into that dose level cohort (or higher) will be suspended as soon as ≥2 patients in that cohort experience DLT, or when otherwise deemed clinically appropriate by the investigator or Sponsor medical monitor. After the 28-day DLT observation period for the final patient in a cohort is complete, if less than one third of the patients enrolled in that cohort developed a DLT, advancement to the next dose-level cohort can begin.

Patients will be considered evaluable if they have received at least three G100 injections and have completed Day 28 safety monitoring OR have experienced DLT. Patients who experienced DLT during the safety period will not be replaced. All other patients who have not received at least three G100 injections and/or do not complete the Day 28 safety monitoring period for reasons other than treatment-related toxicity will be replaced.

Following completion of the dose escalation stage of the trial, the maximum tolerated dose (MTD) or maximum safe dose (highest dose level examined in the study) will be defined as the highest dose reached in which less than one third of the patients in the cohort experienced a DLT.

In Part 2, depending on the results of Part 1 and the MTD/maximum safe dose, two groups of patients may be examined, Patient Expansion With Or Without Pembrolizumab and (optional) Large Tumor groups.

In the first group, Patient Expansion With or Without Pembrolizumab: Up to 24 patients will be randomly assigned and treated with single agent intratumoral G100 or with the sequential administration of intratumoral G100 and pembrolizumab at the MTD or maximum safe dose of G100 determined in Part 1. This portion of the study is designed to be exploratory. Data indicate that inhibitory immune checkpoint pathways are up-regulated in the tumor microenvironment and that interfering with these regulatory pathways can lead to improved tumor responses in preclinical models. Treatment will follow the same dose regimen as in Part 1 (Figure 4) and consist of G100 at the MTD or maximum safe dose and local radiation therapy. For patients randomized to anti-PD-1 therapy, on Day 14, pembrolizumab treatment will be initiated at a standard dose of 200 mg intravenously (IV) and then administered Q3W IV for up to 2 years or until disease progression or unacceptable toxicity (Figure 5). For pembrolizumab, dose modification for AEs attributed to the drug will follow the guidelines as recommended for the product and as outlined in the protocol. The main goal of Part 2, Patient Expansion With Or

Without Pembrolizumab, is to gain safety information, immunologic data and early clinical experience with these regimens to allow planning for future studies with these agents.

In the second group, Part 2, Large Tumors: a higher dose of G100 may be examined. If G100 at the 10 µg/dose is determined to be the maximal safe dose and the DMC agrees, an optional treatment group for Large Tumor patients will be treated. Preclinical data indicates a dose response to G100 and this will be explored in these patients. In this group, up to 4 patients with injectable lymphoma mass(es) 4 cm or greater in total size (based on the sum of the measurements of the single greatest dimension of each the tumor(s) within the planned radiation field) will be enrolled and will receive G100 at 20 µg/dose. This will allow greater distribution of the G100 within the large tumor mass(es) and the examination of safety and dose effect. Treatment would be administered on the same treatment schedule as in Part 1 except that the G100 dose be at 20 µg. The dose would be administered to a single large target lesion or distributed among 2 or more lesions within the radiation field. If the target lesion(s) regresses, a different lesion within the radiation field will be chosen for treatment, if available. If the tumor mass has not regressed completely following 6 doses, treatment may continue for 3 additional weekly intratumoral doses (9 total).

In Part 3, G100 Expansion of 20 µg Dose Group, up to 25 patients with follicular NHL will be enrolled to receive local radiation therapy and intratumoral G100 at 20 µg/dose. Part 3 would begin following: (a) completion of enrollment of the Part 2 Patient Expansion With or Without Pembrolizumab group (as determined by Sponsor), (b) enrollment of at least 3 patients on the Large Tumor Group with follow-up to at least Day 28, and (c) determination of an acceptable safety profile following a review of G100 alone data. Large tumors are ***not*** required, and patients with any injectable tumor may participate. Data from another study in sarcoma and early data from this trial have not demonstrated any safety concerns with the 20-µg dose level, and to date, all reported events considered at least possibly related to the study agent have only been grade 1 or 2. Compared to baseline, post-treatment tumor biopsies have demonstrated significant increases in immune infiltrates within the tumor of some patients suggesting that this dose level should be explored further. The dose will be administered to a single target lesion or distributed among 2 or more lesions within the radiation field. If the target lesion(s) regresses, a different lesion within the radiation field will be chosen for treatment, if available. If the tumor mass has not regressed completely following 6 doses, treatment may continue for 3 additional weekly intratumoral doses (9 total). Data will be monitored continuously for safety, clinical effect and exploratory biomarkers.

Part 4, G100 at 20µg/lesion Into Single Or Multiple Tumor Masses Plus Pembrolizumab: Data from Parts 1-3 of this study demonstrate that intratumoral G100 at the highest dose examined (20 µg) has been well-tolerated with only grade 1 or 2 related AEs and no DLTs reported with its use. This higher dose has been associated with increased numbers of infiltrating CD8 T cells into the tumor (TILs), and greater numbers of CD8 TILs have been statistically associated with the development of objective clinical responses. In Part 2, the combination of G100 (10 µg) and

pembrolizumab was well-tolerated without new or unexpected toxicities, and the addition of pembrolizumab resulted in more clinical responses, deeper abscopal tumor shrinkage, and a higher number of tumor infiltrating CD8 T cells. Therefore Part 4 will examine the 20 µg dose of G100 in 1 or more tumor lesions (up to 4 lesions) plus pembrolizumab in order to establish safety and examine clinical and biomarker responses in patients receiving increasing total systemic doses of G100.

Part 4 will consist of a Dose Escalation group to evaluate and establish safety of injecting 20µg of G100 into multiple lesions (up to 4 lesions) in combination with pembrolizumab and a Patient Expansion group to assess clinical responses with this regimen. At least 22 relapsed or refractory follicular NHL patients who received ≥3 prior systemic therapies will be treated in Part 4. Twenty-two efficacy evaluable patients as defined in the Statistical Section will be enrolled.

During Dose Escalation, safety will be assessed using a 3+3 design where sequential cohorts of patients will be treated with intratumoral G100 at 20µg/lesion in 1, 2, 3, or 4 tumor lesions corresponding to systemic G100 exposure of 20, 40, 60 or 80 µg G100. Once the 20 µg systemic dose level cohort (20 µg injected in 1 lesion) has been established to be reasonably safe, patients who do not qualify to enroll on the next dose level cohort due to insufficient numbers of potentially injectable lesions may enter Patient Expansion at that single lesion dose level.
As each higher systemic dose level (40 µg, 60 µg, 80 µg) in multiple lesions is established to be well-tolerated, additional patients who otherwise qualify for the study but are unable to be treated on Dose Escalation due to insufficient numbers of injectable lesions will be allowed to enroll into the Patient Expansion portion of the study at the established safe dose levels.
If complete enrollment of 22 efficacy evaluable patients is reached before Dose Escalation is complete, the Sponsor may choose to continue enrollment into just the Dose Escalation cohorts with up to 12 patients to fill all or some of the remaining cohort(s).

Treatment will follow a similar dose regimen as in "Part 2, Patient Expansion With or Without Pembrolizumab" group, except that radiation therapy has been omitted. G100 will be injected intratumorally beginning on Day 0, a second dose will be administered 5-7 days later (Study Day 5-7) and then dosing will continue weekly for up to 4 additional doses (6 total) as long as the tumor remains of sufficient size for injection. At least 1 lesion will be targeted to receive each dose of G100. If the lesion regresses, inject around the area where the lesion was until the course is complete. If the patient is entered in a cohort where more than one lesion is injected (cohorts 2 to 4), as many easily accessible tumors will be targeted and treated as specified for the cohort. Imaging assisted injections are allowed but the feasibility and safety of these treatments must be discussed first and approved by the Medical Monitor. If the tumor mass has not regressed completely from baseline, dosing may continue for 3 additional weekly intratumoral doses (9 total). On Day 14, pembrolizumab treatment will be initiated at a standard dose of 200 mg intravenously (IV) and then be administered every 3 weeks (Q3W) IV for up to 2 years or until disease progression or unacceptable toxicity.

Part 4 Dose Escalation

In the Dose Escalation portion, safety will be assessed using a 3+3 design where 12 to 24 patients will be assigned to sequential cohorts of escalating number of G100 injected lesions in combination with standard dose pembrolizumab (Figure 6). Four cohorts are planned:

- Cohort 1: G100 20 µg/lesion in 1 tumor
- Cohort 2: G100 20 µg/lesion in 2 tumor lesions (40µg total)
- Cohort 3: G100 20 µg/lesion in 3 tumor lesions (60µg total)
- Cohort 4: G100 20 µg/lesion in 4 tumor lesions (80µg total)

Once a Cohort dose level is established to be safe, patients who do not meet the criteria of sufficient numbers of injectable tumors to enter the next dose Cohort will be enrolled in a Patient Expansion group at a systemic dose level that has already been established as safe.

Initially, three patients will be scheduled to receive G100 at the first dose level. Dose escalation will be contingent upon acceptable safety data obtained during the first 28 days of observation following initiation of the regimen. A dose level cohort will be expanded from three to six if one of the first three patients experiences a dose-limiting toxicity (DLT). Further patient accrual into that dose level cohort (or higher) will be suspended as soon as ≥2 patients in that cohort experience DLT, or when otherwise deemed clinically appropriate by the investigator or Sponsor Medical Monitor. After the 28-day DLT observation period for the final patient in a cohort is complete, if less than one third of the patients enrolled in that cohort developed a DLT, advancement to the next dose-level cohort can begin.

During Dose Escalation, patients will be considered evaluable for determination of safety and dose-level cohort advancement if they have received at least three complete G100 treatments and 1 dose of pembrolizumab and have completed Day 28 safety monitoring OR have experienced DLT. Patients who experienced DLT during the safety period will not be replaced. All other patients who have not received at least three G100 treatments and 1 dose of pembrolizumab and/or do not complete the Day 28 safety monitoring period for reasons other than treatment-related toxicity will be replaced.

Following completion of the Dose Escalation portion of Part 4, the maximum tolerated dose (MTD) or maximum safe dose (highest dose level examined in the study) will be defined as the highest dose reached in which less than one third of the patients in the cohort experienced a DLT.

Potential Dose Modification During Dose Escalation:

G100 is a local therapy with systemic immune responses. Therefore, the safety profile may differ from that of systemically administered agents. In order to further investigate this, if 2 or

more DLTs are observed in the initial cohort at 20 µg of G100, the Sponsor, in agreement with the independent DMC may choose to examine a new cohort of patients to better understand whether or not the DLTs associated with the injection of a single lesion might be abrogated by decreasing the dose and administering the lower single lesion dose of 10 µg into multiple lesions. Intratumoral G100 10 µg in a single lesion in combination with pembrolizumab was established to be well-tolerated in Part 2 of this study. Thus, this new cohort would examine the safety of G100 10 µg administered into 2 injectable lesions and would use the same 3+3 design described above. Based on a review of the safety profile of this new cohort and in agreement with the independent DMC, further dose escalation cohorts may be investigated using this lower dose of 10 µg/lesion and a similar dose escalation schema as described above where up to 4 lesions may be potentially treated.

For pembrolizumab, dose modification for AEs attributed to the drug will follow the guidelines as recommended for the product and as outlined in the protocol.

Part 4 Patient Expansion:

Once the G100 20 µg systemic dose level has been established to have an acceptable safety profile, patients who otherwise qualify for the study but do not have the requisite number of injectable tumor masses to enroll on the dose cohort currently under evaluation may be enrolled into a Patient Expansion group. The Patient Expansion group will begin to evaluate clinical response (ORR) and biomarker changes of G100 plus pembrolizumab combination. An exploratory analysis will also be performed in those who are considered $TLR4^{high}$.

The per lesion dose during Patient Expansion will be 20 µg/lesion. The total administered dose of G100 will depend on the safety established with each dose cohort. Determination of the number of potential injectable lesions will be made by the investigator in consultation with Medical Monitor.

As the safety of each dose cohort is established, the number of allowed injectable lesions in Patient Expansion will be as follows:

Established Safe Systemic Dose	Treatment In Patient Expansion
20 µg dose level	20 µg in 1 lesion
40 µg dose level	20 µg in up to 2 lesions
60 µg dose level	20 µg in up to 3 lesions
80 µg dose level	20 µg in up to 4 lesions

Patient enrollment will be monitored. It is planned that 22 efficacy evaluable patients will be treated with intratumoral G100 and IV pembrolizumab in Part 4 in order to provide sufficient data for evaluation of efficacy (see Statistical Section). Patients who received G100 20 μg/lesion during Dose Escalation in Part 4 may be included in the clinical response analysis.

Part 5, G100 Plus Rituximab: Studies have demonstrated the potential for additive or synergistic effects of the combination of G100 and rituximab. G100 has been shown to increase the number of inflammatory and activated immune cells within the tumor microenvironment, including T cells, NK cells, macrophage and dendritic cells. Rituximab can potentially increase the loading/pulsing of dendritic cells with tumor antigen, leading to more effective antigen presentation of rare tumor antigens. Rituximab and other similar antibodies that bind to tumor cells and debris have been previously shown to facilitate the uptake and processing of tumor antigens by dendritic cells through opsonization/phagocytosis. In addition, a known mechanism of action of rituximab is through antibody dependent cellular toxicity (ADCC). In preclinical work, the combination of G100 with rituximab demonstrated enhanced ADCC. Therefore, G100 in combination with rituximab can increase the amount of tumor antigen processed by dendritic cells potentially leading to greater T cell stimulation/activity; in addition, the combination could enhance tumor cytotoxicity by activating and increasing the number of ADCC effector cells.

In this study, a Dose Escalation will be performed first followed by Patient Expansion. During Dose Escalation 12-24 patients and during Patient Expansion 20 efficacy evaluable patients as defined in the Statistical Section will be enrolled. Patient enrollment will be monitored. Patients who received G100 during Dose Escalation in Part 5 may be included in clinical response analysis.

Data from the G142 study indicate that the G100 intratumoral dose of 20 μg is relatively safe with only grade 1 or 2 related AEs reported and no DLTs and that this higher dose appears to induce greater numbers of infiltrating CD8 T cells into the tumor. Recent preclinical data indicate that G100 doses greater than 20 μg can lead to improved survival of animals in tumor models, further supporting that additional dose exploration may be warranted. Therefore this arm will examine escalating doses of G100 plus rituximab in a single tumor site utilizing a 3+3 design in order to establish safety and examine clinical and biomarker responses. Once the highest safe dose/systemic exposure is determined, from the Dose Escalation portion of the study, all safety, efficacy and biomarker data will be reviewed by the Sponsor (in collaboration with the independent DMC) and either the highest dose determined to be safe or the most biologically active and safe dose (if different than the MTD) will be chosen for further investigation. A Patient Expansion group would then begin. Details of Dose Escalation and Patient Expansion are described below.

Part 5, Dose Escalation :

In the Dose Escalation portion, safety and efficacy of G100 injected into a single tumor lesion without radiation will be assessed using a 3+3 design where patients will be assigned to

sequential cohorts of escalating doses of intratumoral G100 in combination with standard dose induction therapy with rituximab. (Figure 8) Treatment will begin on Day 0 with rituximab 375mg/m^2 IV and continue weekly for a total of 4 doses. If there are no DLTs or significant safety events after the first dose of rituximab, G100 will be injected intratumorally beginning on Day 1, and then dosing will continue weekly for 3 additional doses (4 total) on a visit schedule that coincides with rituximab treatments as long as the tumor remains of sufficient size for injection. One lesion will be targeted to receive each dose of G100. If the lesion regresses, another lesion will be chosen for treatment. Imaging assisted injections are allowed but the feasibility and safety of these treatments must be discussed first and approved by the Medical Monitor. If the tumor lesion has not regressed completely after the first 4 doses of G100, dosing may continue for 2 additional weekly intratumoral doses (6 total). Following restaging, the patient may be eligible for a second course of G100.

Four cohorts G100 plus rituximab are planned and will be enrolled sequentially:

- Cohort 1: G100 20 µg in single tumor lesion
- Cohort 2: G100 40 µg in a single tumor lesion
- Cohort 3: G100 60 µg in a single tumor lesion
- Cohort 4: G100 80 µg in a single tumor lesion

Initially, 3 patients will be scheduled to receive G100 at the first dose level. Dose escalation will be contingent upon acceptable safety data obtained during the first 28 days of observation following initiation of the regimen. A dose level cohort will be expanded from 3 to 6 if one of the first 3 patients experiences a dose-limiting toxicity (DLT). Further patient accrual into that dose level cohort (or higher) will be suspended as soon as ≥2 patients in that cohort experience DLT, or when otherwise deemed clinically appropriate by the investigator or Sponsor. After the 28-day DLT observation period for the final patient in a cohort is complete, if less than one third of the patients enrolled in that cohort developed a DLT, advancement to the next dose-level cohort can begin.

During Dose Escalation, patients will be considered evaluable for determination of safety and dose-level cohort advancement if they have received at least 3 complete G100 treatments and 3 doses of rituximab and have completed Day 28 safety monitoring OR have experienced DLT. Patients who experienced DLT during the safety period will not be replaced. All other patients who have not received at least 3 G100 treatments and 3 doses of rituximab and/or do not complete the Day 28 safety monitoring period for reasons other than treatment-related toxicity will be replaced. Based on ongoing evaluation of study data, the Sponsor may decide to complete fewer than the planned 4 dose cohorts and proceed directly to the Patient Expansion portion of the study.

Following completion of the dose escalation stage of the trial, the maximum tolerated dose (MTD) will be defined as the highest dose reached in which less than one third of the patients in

the cohort experienced a DLT. If no DLTs are experienced in the first 3 patients enrolled at highest dose of 80 µg, the 80 µg dose per lesion will be determined to be the "maximum safe dose" examined in this study and dose escalation will be considered complete. An additional 3 patients may then be enrolled for a total of 6 patients at that dose level and safety stopping rules will be followed. If after the Sponsor and DMC review all safety data it is determined that there are no safety issues requiring the separation of the first dose of rituximab and G100, the regimen may be modified to administer both on Day 0 during Patient Expansion.

Part 5, Patient Expansion:

Once the MTD/maximum safe dose has been established, all safety, clinical and biomarker data will be reviewed and a recommended dose for further exploration will be made. The Patient Expansion would then begin and would enroll patients to receive G100 IT at the recommended dose into a single tumor mass in combination with rituximab. Patients enrolled on Part 5 Patient Expansion will be analyzed on the basis of the ORR. An exploratory analysis will also be performed in those who are considered $TLR4^{high.}$

G100 is a local therapy with systemic immune responses. Therefore, the safety profile may differ from that of systemically administered agents. In order to further investigate this, after establishment of an MTD, the Sponsor in agreement with the independent DMC may choose to examine one additional cohort of patients to better understand whether or not the DLTs associated with the injection of a single lesion might be abrogated by splitting the dose and administering into two separate lesions. The data from this cohort may help determine if the tolerability of G100 was limited due to the injection of a single tumor mass or to the total systemic exposure. In this additional cohort, 3-6 patients would be treated at the total systemic dose level associated with DLTs but divided and distributed into two tumor masses instead of one. For example, if the MTD in a single tumor mass were determined to be 40 µg due to DLTs occurring at 60 µg/lesion, the dose of this cohort would be 30 µg/lesion injected separately into 2 tumor masses. In the event that the 20 µg dose level (Cohort 1) experiences DLTs, an optional cohort of 10 µg/lesion administered into 2 lesions may be explored. The information from this optional cohort could help the design of future studies. The decision whether or not to open this cohort would be made when the Dose Escalation data is reviewed following the determination of the MTD. No additional treatment cohorts are planned beyond this one group. Following this evaluation, patients would be enrolled into the Patient Expansion group and would receive G100 injected into a single lesion at the recommended dose.

For rituximab, dose modification for AEs attributed to the drug will follow the guidelines as recommended for the product and as outlined in the protocol.

For All Parts (1 to 5)

Retreatment / Second Course: Following the G100 course of treatment, if a patient is determined to have achieved SD or better or has PD that does not require immediate therapy, has an

additional site of disease outside of the prior radiation field (Parts 1, 2, or 3) that is amenable to injection, and has not had significant treatment emergent AEs (including events that would be considered a DLT) as determined by the investigator and the Sponsor, the patient may be eligible to receive a second course of G100. For patients enrolled on Parts 4 or 5, the same previously injected tumor site(s) may be targeted or a replacement site(s) may be chosen.

Six weeks or more after completion of the first course of G100 treatment, the second course would begin and consist of G100 alone (no radiation and no additional rituximab for patients enrolled on Part 5) at the same dose received during the first course of therapy. Treatment would be administered on a similar weekly schedule as the first course except without radiation therapy (or rituximab therapy). G100 will be injected intratumorally beginning on Day 0 (instead of Study Day 2), a second dose will be administered 5 to 7 days later and then dosing will continue weekly for up to 4 additional doses (6 total) as long as the tumor remains of sufficient size for injection. For Parts 1 to 3, a single lesion will be targeted to receive each dose of G100. If the lesion regresses, another lesion will be chosen for treatment. If the tumor mass has not regressed completely, dosing may continue for 3 additional weekly intratumoral doses (9 total). If the patient had been receiving pembrolizumab as part of their therapy, the anti-PD-1 antibody would continue as scheduled during the second course. For Part 4, dosing may continue into multiple lesions as selected for their initial course; for Part 5, the number of G100 doses is limited to 6 treatments of a single lesion.

Dose regimen interruption in a single patient may be made by the clinical investigator if it is deemed in the best interest of patient safety. The study Medical Monitor should be consulted prior to or immediately upon the decision to interrupt therapy. Safety will be reviewed on a regular basis by an independent DMC and the Sponsor. These reviews may lead to modification or stopping of the treatment program.

Tumor imaging will be performed during the screening visit (baseline) and then approximately every 8 weeks thereafter for the first year, every 3 to 4 months for the second year, and then at least every 6 months for the third and subsequent years until disease progression as defined by the irRC. Pre- and post-treatment tumor biopsies (e.g., core biopsies) will be obtained for histologic review and exploratory immune analyses, including cell phenotype, tumor expression of TLR4, and genomic analyses of T cells. Post-treatment biopsies will be performed in patients with accessible tumors within 3 weeks after the last planned G100 injection. Peripheral blood will be drawn for immune assays and biomarker tests at time points listed in the Study Procedures.

6.2 Dose-Limiting Toxicities

DLTs will be used to establish safety parameters for stopping dose escalation and will follow a standard 3+3 study design. AE severity assessments will be performed using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v4.03 or newer. Unacceptable toxicity is defined when two or more subjects in a dose level cohort develop DLTs

considered at least possibly related to the study regimen Further dosing at that level will be discontinued. Hospitalizations primarily intended to expedite diagnostic evaluations or for elective surgery will not be considered as SAEs for the purpose of ascertaining DLT.The occurrence of any of the following toxicities during the first 28 days will be considered a DLT, if assessed by the investigator to be possibly, probably, or definitely related to any component of study treatment (G100, pembolizumab, or rituximab).

1. Grade 4 nonhematologic toxicity (not laboratory)
2. Grade 4 hematologic toxicity lasting ≥7 days, except thrombocytopenia:
    - Grade 4 thrombocytopenia of any duration
    - Grade 3 thrombocytopenia associated with clinically significant bleeding
3. Any nonhematologic AE ≥Grade 3 in severity should be considered a DLT, with the following exceptions: Grade 3 fatigue lasting ≤3 days; Grade 3 diarrhea, nausea, or vomiting without use of anti-emetics or anti-diarrheals per standard of care; Grade 3 rash without use of corticosteroids or anti-inflammatory agents per standard of care.
4. Any Grade 3 or Grade 4 nonhematologic laboratory value if:
    - Clinically significant medical intervention is required to treat the subject, or
    - The abnormality leads to hospitalization, or
    - The abnormality persists for >1 week.
    - The abnormality results in a Drug induced Liver Injury (DILI)
    - Exceptions: Clinically nonsignificant, treatable, or reversible laboratory abnormalities including liver function tests, uric acid, etc.
5. Febrile neutropenia Grade 3 or Grade 4:
    - Grade 3 is defined as ANC <1000/mm3 with a single temperature of >38.3 degrees C (101 degrees F) or a sustained temperature of ≥38 degrees C (100.4 degrees F) for more than 1 hour
    - Grade 4 is defined as ANC <1000/mm3 with a single temperature of >38.3 degrees C (101 degrees F) or a sustained temperature of ≥38 degrees C (100.4 degrees F) for more than 1 hour, with life-threatening consequences and urgent intervention indicated.
6. Prolonged delay (>2 weeks) in initiating Cycle 2 due to treatment-related toxicity.
7. Any treatment-related toxicity that causes the participant to discontinue treatment during Cycle 1.
8. Grade 5 toxicity.
9. Missing >25% of study drug doses as a result of treatment-related AE(s) during the first cycle.

6.3 Stopping Rules

During the initial 28-day treatment period, dosing will be suspended at any dose level (and higher) if DLTs are observed in 2 or more patients during Part 1 or during Dose Escalation of Part 4 or Part 5. During patient expansion of Parts 2, 3, 4 and 5, dosing will be suspended if DLTs considered at least possibly related to any study medication are observed during the first 28 days in one third or more patients within a group receiving the same treatment (assuming a minimum of 6 patients receiving the same dose and treatment regimen and would represent the initial denominator: In Parts 2 and 3, G100 alone; in Parts 2 and 4, G100/pembrolizumab, in Part 5, G100/rituximab)

All AEs and DLTs observed during dose escalation of any treatment arm and/or patient expansion meeting the criteria of a stopping rule will be reviewed by the DMC. If there is disagreement between the DMC and the investigator's assessment regarding the relationship of the event to study agent or to the clinical relevance (e.g., lab abnormality), the Sponsor in consultation with the DMC may determine to stop the treatment or continue. In the later case, the AE may become a medical event of interest and be tracked closely for additional events occurring in the future with intratumoral G100.

6.4 Maximum Tolerated Dose/Maximum Safe Dose

The MTD will be defined as the highest G100 dose level studied in which less than one third of patients in a cohort experience DLT. If the MTD is declared at the final dose level, the highest dose will be considered the maximum safe dose examined in the study.

6.5 Dosing Delays / Dose Modifications

There are no adjustments for dose delay for a given patient, and treatment delays of >14 days from the treatment plan will not be allowed. If a patient experiences a DLT, treatment of that patient will be suspended. A subject may be considered for receiving further injections of the G100 investigational drug product on a case-by-case basis after the PI and medical monitor, in consultation with the independent DMC, have evaluated the risk/benefit ratio for a subject. As an example, for subjects who have experienced a tumor response and had a non-life- and non-organ-threatening DLT, continuation of treatment as per protocol may be considered.

7.0 SELECTION OF PATIENTS

This study plans to enroll patients with follicular NHL and other indolent lymphomas. In Part 1, Dose Escalation, up to 12 evaluable patients may be enrolled. In Part 2, for the Patient Expansion With or Without Pembrolizumab group, up to 24 additional patients and for the optional Large Tumor Group up to 4 evaluable patients will be enrolled. In Part 3, G100 Expansion of 20 µg Dose Group, up to 25 patients may be enrolled. In Part 4, Sequential G100 at 20 µg/lesion Into Single Or Multiple Tumor Masses Plus Pembrolizumab Group, 22 efficacy

evaluable patients will be enrolled. In Part 5, G100 Plus Rituximab, 12-24 patients will be enrolled during Dose Escalation and 20 efficacy evaluable patients, during Patient Expansion.

7.1 Inclusion Criteria

In order to be enrolled in the study, patients must meet ***all*** of the following inclusion criteria:

1) Follicular low-grade NHL (grades 1, 2, 3A): either treatment naïve or relapsed or refractory following at least one prior treatment. For France, patients with either relapsed or refractory only. In Part 1 Dose Escalation only, in addition to follicular NHL, marginal zone B cell lymphomas: either treatment naïve or relapsed or refractory following at least one prior treatment.
    - In Part 4, enrollment is limited to relapsed or refractory follicular NHL patients who have received at least 3 prior systemic treatments, one of which was or included an anti-CD20 antibody.
    - In Part 5, enrollment will include relapsed or refractory CD20+ follicular NHL following at least one but not more than 2 prior treatments.
2) Tumor mass(es) accessible for intratumoral injection and are being considered for local radiation therapy and at least one additional site of disease outside the radiation field for assessment of distal (abscopal) response. (Imaging assisted injections are allowed following approval by Medical Monitor)
    - For Parts 4 and 5, radiation therapy is omitted. Measurable tumor mass(es) accessible for intratumoral injection must be present for treatment and assessment of response.
3) ≥18 years of age
4) Life expectancy of ≥6 months per the investigator
5) Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
6) ECG without evidence of clinically significant arrhythmia or ischemia
7) If female of childbearing potential (FCBP), willing to undergo pregnancy testing and agrees to use two methods of birth control or is considered highly unlikely to conceive during the dosing period and for three months after last study treatment, or if receiving pembrolizumab, four months after last treatment (See Section 8.1.9 and Appendix F: References for details)
8) If male and sexually active with a FCBP, must agree to use effective contraception such as latex condom or is sterile (e.g., following a surgical procedure) during the dosing period and for three months after last study treatment, or if receiving pembrolizumab, four months after last treatment (See Section 8.1.9 and Appendix F: References for details)

7.2 Exclusion Criteria

If any of the following are met, the patient will not be eligible for the study:

1) Cancer therapies, including chemotherapy, radiation (non-study regimen related), biologics or kinase inhibitors, granulocyte-colony stimulating factor (G-CSF) or granulocyte-macrophage colony stimulating factor (GM-CSF) within 4 weeks prior to the first scheduled G100 dose
2) Investigational therapy within 4 weeks prior to G100 dosing
3) Prior administration of G100 or other intratumoral immunotherapeutics
4) Inadequate organ function including:
    a. Marrow: Peripheral blood leukocyte count (WBC) <3000/mm^3, absolute neutrophil count ≤1500/mm3, platelets <75000/mm^3, or hemoglobin <10 gm/dL
    b. Hepatic: alanine aminotransferase (ALT), and aspartate aminotransferase (AST) >2.5 × the upper limit of normal (ULN), total serum bilirubin >1.5 × ULN (patients with Gilbert's Disease may be included if their total bilirubin is ≤3.0 mg/dL)
    c. Renal: Creatinine >1.5 × ULN
    d. Other: international normalized ratio (INR) or partial thromboplastin time (PTT) >1.5 × ULN
5) Significant immunosuppression from:
    a. Concurrent, recent (≤4 weeks ago) or anticipated treatment with systemic corticosteroids at any dose, or
    b. Other immunosuppressive medications such as methotrexate, cyclosporine, azathioprine or conditions such as common variable hypogammaglobulinemia
6) Pregnant or nursing
7) Myocardial infarction within 6 months of study initiation, active cardiac ischemia or New York Heart Association (NYHA) Grade III or IV heart failure
8) History of other cancer within 2 years (except non-melanoma cutaneous malignancies and cervical carcinoma in situ)
9) Recent (<1 week ago) clinically significant infection, active tuberculosis or evidence of active hepatitis B, hepatitis C or human immunodeficiency virus (HIV) infection
10) Central nervous system involvement with lymphoma, including parenchymal and leptomeningeal disease. In Parts 4 and 5, any involvement with lymphoma in a closed or confined space such as the retroorbital area will need to be pre-approved by the Medical Monitor.

11) Significant autoimmune disease, including active non-infectious pneumonitis, with the exception of alopecia, vitiligo, hypothyroidism or other conditions that have never been clinically active or were transient and have completely resolved and require no ongoing therapy. (Replacement therapy for hypothyroidism or diabetes is allowed.)

12) Psychiatric, other medical illness or other condition that in the opinion of the PI prevents compliance with study procedures or ability to provide valid informed consent

13) History of significant adverse or allergic reaction to any component of G100, and if enrolled in Part 2 or Part 4, pembrolizumab and/or any of its excipients, and if enrolled in Part 5, anti-CD20 antibodies including rituximab and/or any of its excipients

14) Use of anti-coagulant agents or history a significant bleeding diathesis. {If a superficial lymph node or subcutaneous mass is to be injected, patients on agents such as non-steroidal anti-inflammatory drugs (NSAIDs), aspirin, or clopidogrel are eligible and these agents do not have to be withheld. For procedures with moderate or significant risk of bleeding, long-acting agents such as aspirin or clopidogrel should be discussed with the Medical Monitor and may need to be discontinued before G100 therapy.}

For patients enrolled in Part 2 or Part 4 with the potential to receive pembrolizumab:

15) Has a history of (non-infectious) pneumonitis that required steroids or has current pneumonitis or interstitial lung disease

16) Has received a live vaccine within 30 days prior to the first dose of study drug (Applies to patients who may receive either pembrolizumab or rituximab). Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster (chicken pox), yellow fever, rabies, Bacillus Calmette–Guérin (BCG), and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (e.g., FluMist®) are live attenuated vaccines and are not allowed.

17) Has undergone prior allogeneic hematopoietic stem cell transplantation within the last 5 years. (Subjects who have had a transplant greater than 5 years ago are eligible as long as there are no symptoms of graft versus host disease [GVHD].)

18) Has had an allogeneic tissue/solid organ transplant

19) Has received prior therapy with an anti-PD-1, anti-programmed death ligand (PD-L)1, or anti-PD-L2 agent or if the patient has previously participated in Merck MK-3475 clinical trials or was previously treated with an agent directed to another stimulatory or co-inhibitory T-cell receptor (e.g., CTLA-4, OX 40, CD137) and was discontinued from that treatment due to a Grade 3 or higher immune-related adverse event.

8.0 TRIAL REGIMENS

8.1 G100 Investigational Drug

GLA, glucopyranosyl lipid A, is a TLR4 agonist that activates specific cells of the immune system. TLR4 agonists activate DCs and induce acute inflammatory responses including production of chemokines and cytokines that mediate leukocyte infiltration, stimulation of DC maturation and induction of adaptive immune responses. Several completed clinical studies with vaccines containing GLA administered to healthy subjects have shown that GLA is generally well tolerated and is associated with heightened immune responses.

G100 (GLA-SE) is a stable oil-in-water emulsion and will be used in this study in NHL. G100 is formulated in a high-pressure microfluidizer and appears as a milky white liquid. It is composed of GLA with the SE vehicle which includes excipients squalene (oil), glycerol, tocopherol, synthetic dimyristoylphosphatidylcholine, surfactant (poloxamer) and buffer (ammonium phosphate). G100 is filter-sterilized and the emulsion is filled aseptically into each vial.

8.1.1 G100 Packaging and Labeling

G100 (GLA-SE) will be supplied in 3 mL single use vials and will be packaged according to current GMP guidelines and applicable national laws and regulations. Detailed information and instructions for the preparation of G100 product for the specific Study Part/Cohort will be included in the Study Pharmacy Manual.

8.1.2 Storage and Disposition of the G100 Investigational Drug Product

G100 (GLA-SE) should be stored at 2 - 8°C. Specific instructions for the admixture and administration of G100 are provided in the Study Pharmacy Manual. G100 Dose Preparation for Administration to the Patient

8.1.3 G100 Preparation

The GLA-SE vial is single use. Specific instructions for the appropriate dose concentration, preparation and administration will be provided in the Pharmacy Manual.

For intratumoral administration into the lymphoma lesions, the dose of GLA will be fixed based on the dose cohort and will consist of 5, 10 or 20 µg/dose/lesion in Parts 1 to 4 and up to 80 µg/lesion in Part 5. The maximum total dose of drug that can be injected in one patient on a given day will be determined by the dose cohort the patient is assigned to and the outcome of the MTD/maximal safe dose determination. Details on the preparation of the study agent and dose concentration and volume will be provided in the Pharmacy Manual.

8.1.4 G100 Administration

For Parts 1, 2, or 3, patients with follicular NHL with at least one tumor mass that is being considered for radiation therapy that is also accessible and assessed to be safe for intratumoral injection are eligible for enrollment. In Part 4 and Part 5, similar patients are eligible for enrollment except that radiation therapy has been omitted. All patients must also have a second site where tumor response can be assessed. For example, the second untreated, abscopal site could be a measurable tumor lesion or involvement of skin. For Parts 4 and 5, the G100 treated site(s) and a non-injected site (unless not available and prior approval is provided by Medical Monitor) must be measurable (Index) lesions and be followed by imaging studies and recorded. Skin lesions and other lesions measured by exam are acceptable if lesions can be measured by reproducible methods and preferably if photographically documented.

Parts 1, 2 or 3: For Parts 1, 2 or 3, target tumor lesions will be treated with local radiation therapy at a standard dose (2Gy x2). The day after radiation therapy is complete, for Part 1 Dose Escalation and Part 2 Patient Expansion, the target tumor lesion will be injected with either 5, 10 or 20 μg of GLA depending on the assigned dose level. Although more than one tumor mass may receive radiation, injections of each dose should be administered completely to one superficial radiated tumor when feasible. The ability to inject tumors with G100 is dependent on the elasticity or fibrotic nature of the tumor mass and can be quite variable. In general, lesions >1 cm in diameter will be able to accommodate 0.5 mL and lesions closer to 2 cm can accommodate 1.0 or more mL injections of G100. If not, adjacent masses within the radiation field may be targeted and as much of the full dose should be given. Based on the clinical trial experience with other intratumoral approaches in NHL, it should be expected that there will be peritumoral administration of G100 from either direct or extravasation following injection; this has not changed the clinical safety, immunologic or clinical results of those agents (personal communication, Stanford University). Based on the >1000 subjects receiving GLA by either IM, SC or intradermal (ID) routes of administration, there is no expectation of any safety issues for peritumoral administration of G100. If during therapy, the G100 treated target lesion regresses significantly and cannot be injected, any other remaining lesions within the radiation field may be chosen for therapy, or if not possible due to technical issues, the dose may be distributed among 2 or more lesions. The total dose of G100 administered should be recorded for each treatment. Skin overlying the lesion should be prepped and sterilized using standard methods; the use of local anesthesia will be at the discretion of the treating physician. It is expected that the injected tumor mass will regress during G100 treatment due to the radiation therapy. At the discretion of the investigator, should the lesion(s) within the radiation treatment field become too small or inaccessible for injection, G100 therapy will stop and the patient will continue to be followed for tumor response at distal sites and for long-term clinical status.

In the optional treatment group for Large Tumor patients, up to 4 patients with injectable lymphoma mass(es) 4 cm or greater in total size will be enrolled and receive G100 consisting of 20 μg of the GLA component per dose. In Part 3, G100 Expansion of 20 μg Dose Group, up to

25 patients will be enrolled and treated with 20 µg/dose. Treatment with G100 would be administered on the same treatment schedule as in Part 1 except that the dose would be higher (See Figure 4). Depending on the treatment volume, the dose should be administered to a single large target lesion or distributed among 2 or more lesions within the radiation field. If the target lesion(s) regresses, a different lesion(s) within the radiation field will be chosen for treatment, if available.

Parts 4 and 5: In Part 4, patients will be treated with G100 at 20 µg/lesion in combination with pembrolizumab, and the treatment schedule will follow that in Figure 7. Overall, 22 efficacy evaluable patients as defined in the Statistical Section will be enrolled. In Part 5, 12-24 patients will be treated during Dose Escalation and 20 efficacy evaluable patients as defined in the Statistical Section will be enrolled following the treatment schedule in Figure 9. For Parts 4 and 5, radiation therapy has been omitted. Once identified, easily accessible lesion(s) will be targeted to receive each dose of G100. If the initially injected lesion(s) regresses before completion of therapy, another site may be chosen for treatment. If the patient is entered in a cohort where more than one lesion is injected (Part 4, cohorts 2 to 4 or expansion group), as many easily accessible tumors will be targeted and treated as specified for the cohort treatment group. Imaging assisted injections are allowed but the feasibility and safety of these treatments must be discussed first and approved by the Medical Monitor.

As much of the full dose as possible should be given and the total dose of G100 administered should be recorded for each administration. As noted above, it should be expected that there will be peritumoral administration of G100 from either direct or extravasation following injection. In Parts 1 to 4, if the tumor mass has not regressed completely following 6 doses, treatment may continue for 3 additional weekly intratumoral doses (9 total). At the discretion of the investigator, should the G100 treated lesion(s) become too small or inaccessible for injection, G100 therapy will stop and the patient will continue to be followed for tumor response at distal sites and for long-term clinical status. In Part 5, up to 6 doses will be administered.

For All Parts (1 to 5)

Retreatment / Second Course: Patients may be eligible to receive a second course of G100 if they achieved SD or better or have PD that does not require immediate therapy, have accessible and injectable lesions outside the prior radiation field, and have not had significant treatment emergent AEs (including events that would be considered a DLT) as determined by the investigator and the Sponsor. For patients enrolled on Parts 4 or 5, the same previously injected tumor sites may be targeted or a replacement site(s) may be chosen.

Six weeks or more after completion of the first course of G100 treatment, the second course would begin and consist of G100 alone (no radiation and no additional rituximab) at the same dose received during the first course of therapy. Treatment would be administered on a similar weekly schedule as the first course except without radiation therapy (or rituximab therapy). G100 will be injected intratumorally beginning on Day 0 (instead of Study Day 2), a second dose

will be administered 5 to 7 days later and then dosing will continue weekly for up to 4 additional doses (6 total) as long as the tumor remains of sufficient size for injection. For Parts 1 to 3, a single lesion will be targeted to receive each dose of G100. If the lesion regresses, another lesion will be chosen for treatment. If the tumor mass has not regressed completely, dosing may continue for 3 additional weekly intratumoral doses (9 total). If the patient had been receiving pembrolizumab as part of their therapy, the anti-PD-1 antibody would continue as scheduled during the second course. For Part 4, dosing may continue into multiple lesions as selected for their initial course; for Part 5, the number of G100 doses is limited to 6 treatments of a single lesion.

If the patient has any grade 3 toxicity, either attributable to the treatment or affecting the area of the injections, G100 injections will be held until toxicity resolves to grade 2 or lower. For grade 2 local toxicities, treatments should continue. However if the investigator has concerns, treatment may be held and a delay should be discussed with the Sponsor. Delays of greater than 2 weeks will not be allowed.

8.1.5 Pembrolizumab Background

In Part 2, Patient Expansion With Or Without Pembrolizumab and Part 4, Sequential G100 plus Pembrolizumab, patients will receive this anti-PD-1 antibody sequentially following G100 as an investigational agent for the treatment of follicular lymphoma. The study agent will be provided by Merck, the manufacturer of pembrolizumab.

Pembrolizumab is a potent humanized immunoglobulin G4 (IgG4) monoclonal antibody (mAb) with high specificity of binding to the programmed cell death 1 (PD-1) receptor, thus inhibiting its interaction with programmed cell death ligand 1 (PD-L1) and programmed cell death ligand 2 (PD-L2). Based on preclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1. Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an intravenous (IV) immunotherapy for advanced malignancies. Keytruda® (pembrolizumab) is indicated for the treatment of patients across a number of indications. For more details on specific indications refer to the Investigator's Brochure.

Refer to the Investigator's Brochure (IB)/approved labeling for detailed background information on MK-3475.

8.1.5.1 Pembrolizumab Dose Selection (Preparation)

The rationale for selection of dose of pembrolizumab to be used in this trial is provided in Section 4.5.4, Rationale for Pembrolizumab Dose Selection. Details on preparation and administration of pembrolizumab are provided in the Pharmacy Manual.

8.1.5.2 Pembrolizumab Investigational Product

Clinical Supplies will be provided by the Sponsor as summarized in Table 2.

Table 2: Product Descriptions

Product Name & Potency	Dosage Form
MK-3475 50 mg	Lyophilized Powder for Solution for Infusion
MK-3475 100 mg/ 4mL	Solution for Infusion

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of trial treatments in accordance with the protocol and any applicable laws and regulations.

8.1.5.3 Timing of Dose Administration

Following the End of Study (EOS) Visit on Day 77, trial treatment of pembrolizumab may be administered up to 5 days before or after the scheduled dosing day of each cycle due to administrative reasons.

Note: Dosing interruptions are permitted in the case of medical / surgical events or logistical reasons (i.e., elective surgery, unrelated medical events, patient vacation, holidays) not related to study therapy. Patients should be placed back on study therapy within 3 weeks of the scheduled interruption. The reason for interruption should be documented in the subject's study record.

8.1.5.4 Pembrolizumab Administration

For patients randomized or assigned to receive pembrolizumab, treatment will be administered beginning on Study Day 14 after all procedures and assessments have been completed.

Pembrolizumab will be administered as a dose of 200 mg using a 30-minute IV infusion. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window between -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes -5 min/+10 min).

The Pharmacy Manual contains specific instructions for the preparation of the pembrolizumab infusion and administration of infusion solution.

8.1.5.5 Dose Modification for Pembrolizumab

AEs associated with Pembrolizumab exposure may represent an immunologic etiology. These immune-related AEs (irAEs) may occur shortly after the first dose or several months after the last dose of Pembrolizumab treatment and may affect more than on body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, most irAEs were reversible and could be managed with

interruptions of Pembrolizumab, administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation. Based on the severity of irAEs, withhold or permanently discontinue Pembrolizumab and administer corticosteroids. Dose modification and toxicity management guidelines for irAEs associated with Pembrolizumab are provided in Table 3.

Table 3: Dose Modification and Toxicity Management Guidelines for Immune-related AEs Associated with Pembrolizumab

General instructions:

1. Corticosteroid taper should be initiated upon AE improving to Grade 1 or less and continue to taper over at least 4 weeks.
2. For situations where Pembrolizumab has been withheld, Pembrolizumab can be resumed after AE has been reduced to Grade 1 or 0 and corticosteroid has been tapered. Pembrolizumab should be permanently discontinued if AE does not resolve within 12 weeks of last dose or corticosteroids cannot be reduced to ≤10 mg prednisone or equivalent per day within 12 weeks.
3. For severe and life-threatening irAEs, IV corticosteroid should be initiated first followed by oral steroid. Other immunosuppressive treatment should be initiated if irAEs cannot be controlled by corticosteroids.

Immune-related AEs	Toxicity grade or conditions (CTCAEv4.0)	Action taken to Pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
Pneumonitis	Grade 2	Withhold	Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	Monitor participants for signs and symptoms of pneumonitis Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment Add prophylactic antibiotics for opportunistic infections
	Grade 3 or 4, or recurrent Grade 2	Permanently discontinue		
Diarrhea / Colitis	Grade 2 or 3	Withhold	Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	Monitor participants for signs and symptoms of enterocolitis (i.e., diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (i.e., peritoneal signs and ileus). Participants with ≥ Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis. Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
	Grade 4	Permanently discontinue		
AST / ALT elevation or Increased bilirubin	Grade 2	Withhold	Administer corticosteroids (initial dose of 0.5-1 mg/kg prednisone or equivalent) followed by taper	Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable
	Grade 3 or 4	Permanently discontinue	Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	

Type 1 diabetes mellitus (T1DM) or Hyperglycemia	Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold	Initiate insulin replacement therapy for participants with T1DM Administer anti-hyperglycemic in participants with hyperglycemia	Monitor participants for hyperglycemia or other signs and symptoms of diabetes.
Hypophysitis	Grade 2	Withhold	Administer corticosteroids and initiate hormonal replacements as clinically indicated.	Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue[1]		
Hyperthyroidism	Grade 2	Continue	Treat with non-selective beta-blockers (e.g., propranolol) or thionamides as appropriate	Monitor for signs and symptoms of thyroid disorders.
	Grade 3 or 4	Withhold or permanently discontinue[1]		
Hypothyroidism	Grade 2-4	Continue	Initiate thyroid replacement hormones (e.g., levothyroxine or liothyronine) per standard of care	Monitor for signs and symptoms of thyroid disorders.
Nephritis and Renal dysfunction	Grade 2	Withhold	Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper.	Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1 or 2	Withhold	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
All other immune-related AEs	Intolerable/ persistent Grade 2	Withhold	Based on type and severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3	Withhold or discontinue based on the type of event. Events that require discontinuation include and not limited to: Guillain-Barre Syndrome, encephalitis		
	Grade 4 or recurrent Grade 3	Permanently discontinue		

[1] Withhold or permanently discontinue Pembrolizumab is at the discretion of the investigator or treating physician.

NOTE: For participants with Grade 3 or 4 immune-related endocrinopathy where withhold of Pembrolizumab is required, Pembrolizumab may be resumed when AE resolves to ≤Grade 2 and is controlled with hormonal replacement therapy or achieved metabolic control (in case of T1DM).

8.1.5.6 Other allowed dose interruptions for Pembrolizumab

Dosing interruptions are permitted in the case of medical / surgical events or logistical reasons not related to study therapy (e.g., elective surgery, unrelated medical events, patient vacation, and/or holidays). Subjects should be placed back on study therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with the Sponsor. The reason for interruption should be documented in the patient's study record.

8.1.6 Rescue Medications & Supportive Care for Pembrolizumab

Participants should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of AEs with potential immunologic etiology are outlined along with the dose modification guidelines in Section 8.1.5.5, Table 3. Where appropriate, these guidelines include the use of oral or IV treatment with corticosteroids, as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to Pembrolizumab.

Note: If after the evaluation of the event, it is determined not to be related to Pembrolizumab, the investigator does not need to follow the treatment guidance. Refer to Table 3 in Section 8.1.5.5 for guidelines regarding dose modification and supportive care.

It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event.

Note: In addition to Table 3, supportive and treatment information may be found in the investigator brochure in the "Warnings and Precautions" section of the company core data sheet provided in the Appendix of that document and also provided in the product label.

8.1.7 Dose modification and toxicity management of infusion-reactions related to Pembrolizumab

Pembrolizumab may cause severe or life threatening infusion-reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines on Pembrolizumab associated infusion reaction are provided in Table 4.

Table 4: Pembrolizumab Infusion Reaction Dose Modification and Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	• Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs.	• **Stop Infusion.** • Additional appropriate medical therapy may include but is not limited to: • IV fluids • Antihistamines • NSAIDs • Acetaminophen • Narcotics • Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. • If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr. to 50 mL/hr.). Otherwise dosing will be held until symptoms resolve and the participant should be premedicated for the next scheduled dose. **Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug treatment**	Participant may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of analgesic).
Grades 3 or 4 **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 ventilator support indicated	• **Stop Infusion.** • Additional appropriate medical therapy may include but is not limited to: • Epinephrine** • IV fluids • Antihistamines • NSAIDs • Acetaminophen • Narcotics • Oxygen • Pressors • Corticosteroids • Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. • Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. Participant is permanently discontinued from further study drug treatment.	No subsequent dosing
Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the Common Terminology Criteria for Adverse Events v4.0 (CTCAE) at http://ctep.cancer.gov		

8.1.8 Rituximab Background

In Part 5, patients will receive this anti-CD20 antibody in combination with G100 as an investigational agent for the treatment of follicular lymphoma. Rituximab is an approved standard treatment for follicular lymphoma patients: approved regulatory labeling and institutional guidelines for dose, administration including premedication, contraindications, warnings and precautions should be followed. Rationale for addition of rituximab and details of Part 5 design are described in Section 4.1 and 6.1. Treatment regimen is presented in Figure 9. Brief summary of administration, warnings and precautions is summarized below.

8.1.8.1 Rituximab Dose

Rituximab dose is 375 mg/m2 as an IV infusion administered on Day 0 and then continued once weekly for 4 doses on a schedule as described in Section 4.1 and 6.1 and Figure 9. No maintenance therapy will be used in this study.

8.1.8.2 Rituximab Investigational Product

Commerically available rituximab will be used as the standard of care therapy for follicular lymphoma unless institutional or regional regulations request otherwise.

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of trial treatments in accordance with the protocol and any applicable laws and regulations.

8.1.8.3 Rituximab Administration

For patients in Part 5, treatment will be administered beginning on Study Day 0 after all procedures and assessments have been completed.

Rituximab will be administered as a dose of 375 mg/m2 IV infusion. Premedicate before each infusion with acetaminophen and an antihistamine or other appropriate premedication regimen as specified by local institutional guidelines. First Infusion: Initiate infusion at a rate of 50 mg/hr. In the absence of infusion toxicity, increase infusion rate by 50 mg/hr increments every 30 minutes, to a maximum of 400 mg/hr. Subsequent Infusions: Initiate infusion at a rate of 100 mg/hr. In the absence of infusion toxicity, increase rate by 100 mg/hr increments at 30-minute intervals, to a maximum of 400 mg/hr. Interrupt the infusion or slow the infusion rate for infusion reactions. Continue the infusion at one-half the previous rate upon improvement of symptoms.

8.1.8.4 Dose Modification, Warning and Precuations for Rituximab

Approved regulatory rituximab labeling and institutional guidelines for contraindications, warnings and precautions should be followed. Some of them are briefly summarized below.

Infusion Reaction

Rituxan can cause severe, including fatal, infusion reactions. Severe reactions typically occurred during the first infusion with time to onset of 30−120 minutes. Rituxan-induced infusion reactions and sequelae include urticaria, hypotension, angioedema, hypoxia, bronchospasm, pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, cardiogenic shock, anaphylactoid events, or death.

Premedicate patients with an antihistamine and acetaminophen prior to dosing. Institute medical management (e.g., glucocorticoids, epinephrine, bronchodilators, or oxygen) for infusion reactions as needed. Depending on the severity of the infusion reaction and the required interventions, temporarily or permanently discontinue rituximab. Resume infusion at a minimum 50% reduction in rate after symptoms have resolved. Closely monitor the following patients: those with pre-existing cardiac or pulmonary conditions, those who experienced prior cardiopulmonary adverse reactions, and those with high numbers of circulating malignant cells (≥25,000/mm3).

Tumor Lysis Syndrome

Acute renal failure, hyperkalemia, hypocalcemia, hyperuricemia, or hyperphosphatemia from tumor lysis, some fatal, can occur within 12−24 hours after he first infusion of rituximab in patients with NHL. A high number of circulating malignant cells (≥25,000/mm3) or high tumor burden, confers a greater risk of TLS. Administer aggressive intravenous hydration and anti-hyperuricemic therapy in patients at high risk for TLS. Correct electrolyte abnormalities, monitor renal function and fluid balance, and administer supportive care, including dialysis as indicated.

Severe Mucocutaneous Reactions

Mucocutaneous reactions, some with fatal outcome, can occur in patients treated with rituximab. These reactions include paraneoplastic pemphigus, Stevens-Johnson syndrome, lichenoid dermatitis, vesiculobullous dermatitis, and toxic epidermal necrolysis. The onset of these reactions has varied from 1−13 weeks following rituximab exposure. Discontinue rituximab in patients who experience a severe mucocutaneous reaction. The safety of readministration of rituximab to patients with severe mucocutaneous reactions has not been determined.

Progressive Multifocal Leukoencephalopathy (PML)

JC virus infection resulting in PML and death can occur in rituximab-treated patients with hematologic malignancies or with autoimmune diseases. The majority of patients with hematologic malignancies diagnosed with PML received rituximab in combination with chemotherapy or as part of a hematopoietic stem cell transplant. The patients with autoimmune diseases had prior or concurrent immunosuppressive therapy. Most cases of PML were diagnosed within 12 months of their last infusion of rituximab.

Consider the diagnosis of PML in any patient presenting with new-onset neurologic manifestations. Evaluation of PML includes, but is not limited to, consultation with a neurologist, brain MRI, and lumbar puncture. Discontinue rituximab in patients who develop PML.

Hepatitis B Virus (HBV) Reactivation

Hepatitis B virus (HBV) reactivation with fulminant hepatitis, hepatic failure, and death can occur in patients with hematologic malignancies treated with rituximab. The median time to the diagnosis of hepatitis was approximately 4 months after the initiation of rituximab and approximately one month after the last dose.

Screen patients at high risk of HBV infection before initiation of rituximab. Closely monitor carriers of hepatitis B for clinical and laboratory signs of active HBV infection for several months following rituximab therapy. Discontinue rituximab and any concomitant chemotherapy in patients who develop viral hepatitis, and institute appropriate treatment including antiviral therapy.

Infections

Serious, including fatal, bacterial, fungal, and new or reactivated viral infections can occur during and up to one year following the completion of rituximab-based therapy. New or reactivated viral infections included cytomegalovirus, herpes simplex virus, parvovirus B19, varicella zoster virus, West Nile virus, and hepatitis B and C. Discontinue rituximab for serious infections and institute appropriate anti-infective therapy.

Cardiovascular

Discontinue rituximab infusions for serious or life-threatening cardiac arrhythmias. Perform cardiac monitoring during and after all infusions of rituximab for patients who develop clinically significant arrhythmias, or who have a history of arrhythmia or angina.

Renal

Severe, including fatal, renal toxicity can occur after rituximab administration in patients with NHL. Renal toxicity has occurred in patients who experience tumor lysis syndrome and in patients with NHL administered concomitant cisplatin therapy during clinical trials. Monitor closely for signs of renal failure and discontinue rituximab in patients with a rising serum creatinine or oliguria.

Immunization

The safety of immunization with live viral vaccines following Rituxan therapy has not been studied and vaccination with live virus vaccines is not recommended.

Laboratory Monitoring

In patients with lymphoid malignancies, during treatment with rituximab, obtain complete blood counts (CBC) and platelet counts prior to each rituximab course.

Further details regarding the safety, dose, and dose adjustments of rituximab are reviewed in the product label (Rituximab PI 2018)

8.1.9 Contraception

G100, rituximab and/or pembrolizumab may have adverse effects on a fetus in utero. Furthermore, it is not known if G100 and/or pembrolizumab have transient adverse effects on the composition of sperm.

Subjects should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. Therefore, non-pregnant, non-breast-feeding FCBP may only be enrolled if they are willing to use 2 methods of birth control or are considered highly unlikely to conceive. Highly unlikely to conceive is defined as 1) surgically sterilized, or 2) postmenopausal (a woman who is ≥45 years of age and has not had menses for greater than 1 year will be considered postmenopausal), or 3) not heterosexually active for the duration of the study. Abstinence is only acceptable as "true abstinence" when it is in line with the preferred and usual lifestyle of the patient and not a periodic occurrence (see Appendix F). The two birth control methods can be either two barrier methods or a barrier method plus a hormonal method to prevent pregnancy. Subjects should start using birth control from study Visit 1 throughout the study period up to 120 days after the last dose of study therapy if receiving pembrolizumab or at least 90 days if only receiving G100.

The following are considered adequate barrier methods of contraception: diaphragm, condom (by the partner), copper intrauterine device, sponge, or spermicide as per local regulations or guidelines. Appropriate hormonal contraceptives will include any registered and marketed contraceptive agent that contains an estrogen and/or a progestational agent (including oral, SC,

intrauterine, or IM agents). See Appendix F for additional details and definitions of highly effective agents.

For male patients, acceptable contraception includes documented sterility such as what is achieved following surgical sterilization (vasectomy or orchiectomy) or use of male condom. If the partner is a woman of childbearing potential, supplemental contraception with hormonal or barrier methods should be considered.

In order to participate in the study, subjects must adhere to the contraception requirement (described above) for the duration of the study and during the follow-up period defined in Section 12.7. If there is any question that a subject will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

8.1.10 Use in Pregnancy

If a subject inadvertently becomes pregnant while on treatment with G100, rituximab and/or pembrolizumab, the subject will immediately be removed from the study. The site will contact the subject at least monthly and document the subject's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the Sponsor without delay and within 24 hours if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Sponsor. If a male subject impregnates his female partner the study personnel at the site must be informed immediately and the pregnancy reported to the Sponsor and followed as described above and in Section 12.7.

8.1.11 Use in Nursing Women

It is unknown whether G100, rituximab and/or pembrolizumab is excreted in human milk. Since many drugs are excreted in human milk, and because of the potential for serious adverse reactions in the nursing infant, subjects who are breast-feeding are not eligible for enrollment.

8.2 Subject Withdrawal/Discontinuation Criteria

8.2.1 Discontinuation of Study Therapy after Complete Response (CR)

Discontinuation of treatment may be considered for subjects who have attained a confirmed CR that have been treated for at least 24 weeks with pembrolizumab and had at least 2 treatments with pembrolizumab beyond the date when the initial CR was declared.

For patients receiving pembrolizumab who experience grade 2 pneumonitis, the patient should be discontinued from study treatment but continued to be monitored.

8.2.2 Investigational Drug Accountability

Under no circumstances is it permitted to use study supplies for any purposes other than those specified in this Protocol.

The investigator or medically qualified, authorized delegate will be provided with forms to enable accurate recording of all study doses at the study facility at all times. The investigator, or designee, must sign a statement that he/she has received the investigational product intended for the study. At all times, the accountability of supplied, used and remaining doses of study drug must match. At the end of the study, it must be possible to reconcile delivery records with those of used and unused stocks. Account must be given of any discrepancies.

8.3 Radiation

Patients will receive local palliative radiation to their tumor masses as part of normal cancer care. For this study, a standard short 2-day course of therapy of 2Gy qd × 2 is recommended as the optimal dose to allow G100 treatment to begin shortly after starting radiation and to minimize any immune suppressive effects from the treatment. Other details and planning are at the discretion of the radiation therapist. Modifications to the dose should be discussed with Immune Design. Although steroids are sometimes used for radiation treatment related effects, use of concomitant or prophylactic steroids are not allowed on this study due to their potential immunosuppressive effects.

As part of this study, the injected lesion is followed for local effect, and untreated, abscopal lesions are followed for systemic treatment effect. Therefore the G100 treated / irradiated lesion should be one of the Index (target) lesions followed for response. In addition, the radiation treatment field should be reviewed by the radiation therapist to confirm the identity of all irradiated lesions and untreated “abscopal” lesions to be used to follow treatment response.

Patients in Parts 4 and 5 will not receive radiation.

8.4 Prior and Concomitant Therapy

8.4.1 Prior Therapy

Any investigational agent or therapy is prohibited during the 28 days prior to enrollment. Cancer therapies, including chemotherapy, radiation, biologic, or kinase inhibitors or immunotherapy, G-CSF or GM-CSF are not allowed within 4 weeks prior to the first scheduled G100 dosing. Systemic corticosteroid use and live vaccines are not permitted within four weeks prior to dosing. Patients who have previously received intratumoral therapies are not permitted.

8.4.2 Prohibited Concomitant Therapy

The following treatments will be prohibited during study until the EOS visit or tumor progression:

- Any investigational drug other than G100, rituximab or pembrolizumab if enrolled on that study arm, is prohibited during the study
- Any systemic corticosteroid (including prednisone of any dose) within four weeks of first study treatment and during the study period (Intermittent use of inhaled or topical steroids is acceptable but chronic use or high doses where systemic absorption is expected should be discussed and approved by the Sponsor). For patients receiving pembrolizumab, systemic glucocorticoids may be used to modulate symptoms from an event of suspected immunologic etiology. However, the event should be discussed with the Medical Monitor before continuing therapy.
- Other concurrent immunosuppressive medications such as methotrexate, cyclosporine, azathioprine
- Concomitant chemotherapy, immunotherapy not specified in this protocol, or biologic therapy
- Except as given per protocol regimen, radiotherapy
- Anti-coagulation therapy – due to the increased risk of bleeding at the site of injection. Based on the consensus guidelines from the Cardiovascular and Interventional Radiology Society of Europe, if a patient is to have a superficial lymph node or subcutaneous mass injected, NSAIDs, aspirin, or clopidogrel may be used and do not have to be withheld (Patel 2012; Patel 2013). For procedures with moderate or significant risk of bleeding, long-acting agents such as aspirin or clopidogrel should be discussed with the Medical Monitor and may need to be discontinued before beginning G100 therapy.
- Live vaccines within 30 days prior to the first dose of study treatment and while participating in the study. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (e.g., FluMist®) are live attenuated vaccines and are not allowed.

Due to the potential increase risk of bleeding following intratumoral injection, it is recommended that drugs that might increase bleeding be avoided (example: aspirin, clopidogrel, etc.). For similar reasons, injections involving deeper structures such as organs and those requiring imaging guided injection assistance must be reviewed and pre-approved by the Medical Monitor.

8.4.3 Permitted Concomitant Therapy

The following medications will be permitted:

- Antihistamines
- Anti-emetics
- Anti-diarrheals
- If a patient is to have a superficial lymph node or subcutaneous mass injected, NSAIDs, aspirin, or clopidogrel are acceptable and do not have to be withheld. For procedures with moderate or significant risk of bleeding, long-acting agents such as aspirin or clopidogrel should be discussed with the Medical Monitor and may need to be discontinued before G100 therapy.

9.0 ASSESSMENTS OF SAFETY AND EFFICACY

9.1 Safety Assessments

The investigator is responsible for the appropriate medical care and safety of patients who have entered this study. The investigator must notify the Sponsor within 24 hours if either of the following events occurs:

- Any event meeting the criteria for an SAE

All patients will be evaluated at baseline and at regular intervals as presented in the Schedule of Events in Section 3.2 through Section 3.7, and Section 10.0. Safety assessments will include solicited and unsolicited symptoms, physical examination findings, vital signs, documentation of AEs, ECGs as applicable, clinical laboratory evaluations, and deviations or discontinuations attributed to AEs.

9.2 Clinical Efficacy Assessments

Clinical responses will be examined using the irRC criteria and the International Working Group response criteria for lymphomas. Immunotherapeutic agents may cause tumor size increases due to inflammation and not due to true tumor growth. Therefore, confirmation of PD is important to help rule out inflammatory processes. The irRC criteria using bidimensional measurements attempts to do this by requiring confirmation of PD findings at least 4 weeks after the initial PD finding(s). In addition, new lesions contribute to the overall tumor burden measurements and do not automatically signal PD. The irRC is based on World Health Organization (WHO) bi-dimensional response criteria. However, the more commonly used method to measure NHL responses is the International Working Group response criteria for malignant lymphoma (Cheson 2007). Therefore, for this study, tumor response will be examined both by the irRC and the International Working group criteria for lymphomas. The irRC will be used in the determination of PD (see Appendix B for details).

9.3 Tumor Response Based Upon irRC Criteria

Patients will be evaluated for tumor response per the modified irRC measurement criteria (Wolchok 2009) and expressed as PR, CR or SD every 8 weeks (Appendix B). As noted above, the irRC requires that PD be confirmed by repeat imaging studies or tumor measurements at least 4 weeks following the initial question of tumor size increase and any new lesion is not automatically counted as disease progression.

9.4 International Working Group Response Criteria for Malignant Lymphoma or the Lugano Criteria and Disease Response Assessment

Lymphoma response assessment by computerized tomography (CT) is based on the International Working Group response criteria for malignant lymphoma (positron emission tomography [PET] is not required for follicular NHL) (Cheson 2007) or the Lugano criteria (Cheson 2014). Local reading (investigator assessment with site radiology reading) will be used to determine subject eligibility and for subject management. The Sponsor may request radiologic images for a retrospective analysis of subject eligibility and treatment response to be performed by a central vendor. Assessment of lymphoma B symptoms should occur with each lymphoma disease response assessment.

For this IT G100 treatment, PET or PET-CT scans must not be used for determination of disease progression. G100 will induce inflammation within the tumor and will cause false positive PET scan results. This has been observed in patients. Therefore CT or MRI imaging or direct exam measurements must be used for the determination of suspected disease progression. (Note: accurate tumor measurements obtained from CT scans using standard high resolution and standard image spacing obtained as part of a PET-CT study are acceptable)

9.5 Immune Response Assessments

The following immune monitoring will be conducted:

- Evaluation of immune cell profiling in tumor samples pre- and post-therapy
- Evaluation of immune cell phenotyping of blood (Parts 1 and 2 only)
- T cell receptor profiling of tumor and blood from baseline and over the course of the trial

Details for sample handling will be provided in the Study Manual.

9.6 Exploratory Biomarkers

Pre- and post- treatment blood and/or tumor samples will be collected for exploratory analyses of potential biomarkers of G100 immunogenicity and clinical tumor response. A number of exploratory analyses are being investigated but the predictive value of such tests is not known. It is hoped that data collected from these exploratory tests will help to define a set of biomarkers

that might be used in future studies to help define the ability of G100 to stimulate anti-tumor immune responses, to help stratify patients who might respond to this treatment and/or to determine a minimum therapeutic dose. Exploratory blood tests may include profiling of immune cells during the course of treatment by phenotyping, evaluation of TLR4 expression on tumor cells, and by evaluation of T cell receptor repertoires by gene sequence analyses. Tumor samples will be examined for evidence of anti-tumor cellular immunity (e.g., CD8 T cell or NK cell infiltration, tumor necrosis, etc.) by immunohistochemistry (IHC) and for evidence of immune suppression within the tumor microenvironment. Any blood or tumor samples will only be used to examine the patient's immune response, their cancer, or to help evaluate any potential toxicity arising in the study. The samples will not be examined for unrelated research or to examine unrelated genes or diseases.

10.0 STUDY PROCEDURES

The schedule of events/study procedures is presented in Section 3.2 through Section 3.7.

10.1 Visit Windows

The treatment windows below apply unless otherwise specified in the study procedures that there is a different event window. For Visit 1, in Parts 1, 2, 3, 4, and 5 all screening procedures will have the windows of Days -30 to -1. For Visit 2, in Parts 1 and 2, screening procedures will have windows of Days -7 to -1; for Visit 2, in Part 3, 4, and 5 a window of Days -14 to -1 will apply, except as otherwise specified in the procedures. All dosing-treatment visits will have a window of ± 2 days from the day specified. After completion of G100 treatment, follow-up visits will have a window of ±1 week (7 days). Following the Day 77 EOS Visit, patients receiving pembrolizumab will have a window of ±5 days for pembrolizumab dose administration and will have a window of ±14 days for restaging radiographic studies. If a dose interruption beyond the windows listed above is required, this should be discussed and approved by the medical monitor; treatment delays of >14 days from the treatment plan will not be allowed.

10.2 Registration

Once patients have been properly consented, and all inclusion/exclusion criteria have been documented as being met, patients will be registered into the trial. Patients should be registered within 30 days prior to their anticipated dosing start date (Day 0). This is an open-label trial. Patients enrolled into the Part 2, Patient Expansion With Or Without Pembrolizumab group will be randomly assigned to receive either intratumoral G100 alone or intratumoral G100 and sequential pembrolizumab. Patients enrolled into Part 4, Sequential G100 at 20µg/lesion Into Single Or Multiple Tumor Masses Plus Pembrolizumab will be assigned at the time of enrollment to a Dose Escalation cohort or Expansion group (See Figure 6). Patients enrolled into Part 5, G100 Plus Rituximab will be assigned at the time of enrollment to a Dose Escalation cohort or to an Expansion group (See Figure 8).

No trial-specific staging or biopsy procedures will be undertaken prior to completion of the consenting process. However, if a patient has had tests performed prior to providing informed consent as part of "standard of care" (considered standard for the patient and routine medical practice, based upon their presentation at the time), and these tests are required for study entry and **all** of the following conditions are met, then these data may be allowed as part of the study data:

- The tests fulfill all requirements of the study; i.e., are complete and follow the procedures outlined in the study;
- The tests have been completed within the specified number of days to perform pre-treatment assessments; and
- It is medically unwise to repeat a test/procedure or it poses undue additional risk to the patient.

10.3 Study Procedures

Patients receiving pembrolizumab will follow Visit 1 to 6 (Sections 10.3.1 to 10.3.5). For Part 2, patients will then follow Sections 10.3.11 to 10.3.15 for the remainder of their treatment. For Part 4, patients will follow Visit 1 and 2 (Sections 10.3.1 to 10.3.2) and then Sections 10.3.16 to 10.3.22.2. For Part 5, patients will follow Visit 1 and 2 (Sections 10.3.1 to 10.3.2) and then Sections 10.3.23 to 10.3.29.2.

10.3.1 Visit 1: Screening and Enrollment (Day -30 to Day -1) – Baseline Visit 1

Patients will undergo the following screening and enrollment procedures within 1 to 30 days prior to Study Day 0:

1) Informed consent/Health Insurance Portability and Accountability Act (HIPAA) authorization.
    - Before inclusion into the study, each patient will receive complete information, both verbally and in writing, about the nature of the study, the anticipated risks and discomfort associated with the study, and also about the right to interrupt participation in the study at any time. Prior to participation in the study, each patient (or representative) will have signed the written, institutional review board (IRB)- or ethics committee (EC)-approved informed consent form (ICF) and HIPAA form if applicable.

2) Determination of patient eligibility.
    - Compliance with Inclusion/Exclusion criteria as presented in Section 7.0 above will be confirmed.
3) Demographics.
4) Medical History. (Any changes to Medical History from initial collection of data to Day -1 should be updated to the records).
    - To include a review of systems, general medical and surgical history, concomitant illnesses, and previous/concomitant medications
    - Tumor-specific therapy history - Oncologic baseline disease characteristics/history/ prior treatment/recent tumor growth will be recorded (diagnosis and stage of disease)
5) 12-Lead ECG
6) Assessment of diagnosis and stage of disease, including CT or magnetic resonance imaging (MRI) of chest, abdomen, pelvis. Other assessments such as CT scan of head, a body PET CT, or bone marrow biopsy should be performed if indicated for the individual patient. If a PET CT is used, a standard high resolution CT series should be obtained rather than low resolution scans. However, PET scans should not be used to determine disease progression since it is expected that PET avidity will increase with the type of inflammation induced by this treatment and may lead to false positive results.
7) Photographs: if the tumor can be measured and assessed visually, photographic documentation with measurements should be considered in order to keep a record and help assess any response to treatment (may be performed at any time during study)
8) Pre-treatment tumor biopsy. Baseline excisional or core biopsy should be obtained from the treatment target lesion or a non-target lesion (preferably near the target lesion).

10.3.2 Visit 2: Baseline Assessment 2 (Day -7 to -1 for Parts 1 and 2, and Day -14 to -1 for Part 3)

Patients will undergo the following evaluations within 1 to 7 days prior to Day 0. **For patients enrolled in Parts 3, 4, and 5, the window for assessments is Day -14 to -1, except where otherwise indicated.**

1) Demographics: confirm and update as needed.
2) Medical History: confirm and update as needed.
3) Review of AEs and SAEs. Note: During the Screening Period, new SAEs experienced by patients should be reported to Immune Design only if the events are considered related to study procedures. From Day 0 to the End-of-Treatment Visit, any new SAE should be reported to Immune Design.
4) Recording of any previous / concomitant medications.

5) Vital signs. To include temperature, pulse, and resting systolic and diastolic blood pressure measurements
6) Physical examination.
    a. To include height and weight
    b. Tumor measurements with specific measurements and location description of the lesions to be treated with G100 and disease sites to be followed for untreated distal tumor responses
7) ECOG performance status
8) Hepatitis B (e.g., hepatitis B surface antigen [HBsAg]) and C testing (e.g., hepatitis C virus [HCV] RNA qualitative).
    a. HIV testing.
9) For patients in Part 1 and Part 2 (not collected in Parts 3, 4, or 5), blood sample draw for baseline cell phenotyping / profiling. Instructions will be outlined in the Study Manual.
10) For patients in Parts 1, 2, 3, and 5 (not Part 4), blood sample draw for baseline T cell receptor gene profiling. Instructions will be outlined in the Study Manual.
11) Safety Labs - Hematology
    a. WBC with differential count
    b. Absolute neutrophil count (ANC)
    c. Red blood cell (RBC) count
    d. Hemoglobin (Hgb)
    e. Hematocrit
    f. Platelet count
    g. If not already performed for screening of inclusion/exclusion criteria, prothrombin time (PT)/PTT and INR (for baseline only)
12) Safety labs - Clinical chemistry
    a. Sodium
    b. Chloride
    c. Potassium
    d. Random glucose
    e. Blood urea nitrogen (BUN)
    f. Creatinine
    g. Calcium

h. AST/serum glutamic oxaloacetic transaminase (SGOT)

i. ALT/serum glutamic pyruvic transaminase (SGPT)

j. Total bilirubin

k. Alkaline phosphatase

l. Lactic acid dehydrogenase

m. Total protein

n. Albumin

13) Serum Beta-2-microglobulin (Baseline only)

14) Urinalysis (Baseline Only). Urine samples will be analyzed by dipstick for:

a. Protein

b. Glucose

c. Blood

d. Leukocytes

e. Nitrites

f. Urobilinogen

g. Bilirubin

h. pH

i. Specific gravity

j. Ketones

15) Urine pregnancy test for FCBP. (Serum pregnancy test may be performed for any urine pregnancy assay if site standard operating procedure [SOP] allows this test. (For treatment groups, Parts 1, 2, 3 and Large Tumor, all pregnancy testing must be performed {and be negative} within Days -7 to -1 and for Parts 4 and 5, within 72 hours of prior to starting study treatment). Note: For patients in the United Kingdom (UK) and France, urine pregnancy tests must also be performed every month or sooner while the patient is receiving G100 and/or pembrolizumab.

16) If enrolled or potentially could be randomized and enrolled onto the pembrolizumab arm: Baseline thyroid function tests, which at a minimum should include thyroid-stimulating hormone (TSH). For patients on Part 4, tests should include TSH, Triiodothyronine (T3) or Free Triiodothyronine (FT3), Free thyroxine (FT4): Patients randomized to receive pembrolizumab should be monitored for changes in thyroid function every 6 weeks after starting pembrolizumab treatment and as indicated based on clinical signs and symptoms of thyroid disorders.

10.3.3 Visit 3 and Visit 4: Radiation Therapy (Day 0 and Day 1)

Patients receive local radiation therapy to tumor mass identified for intratumoral treatment. Standard 2Gy each day × 2 is recommended. Treatment plan will be determined by the treating radiation therapist. Changes in doses should be discussed with Immune Design.

As part of this study, the injected lesion(s) is followed for local effect, and untreated, abscopal lesions are followed for systemic treatment effect. Therefore the G100 treated / irradiated lesion should be one of the Index (target) lesions followed for response. In addition, the radiation treatment field should be reviewed by the radiation therapist to confirm the identity of all irradiated lesions and untreated "abscopal" lesions to be used to follow treatment response. (For the purpose of this study, abscopal tumor site refers to a lesion that is not irradiated or injected / treated that can be followed for shrinkage that would indicate a systemic immune effect)

10.3.4 Visit 5: G100 Treatment #1 (Day 2)

Patients will return for initiation of G100 the day after radiation therapy. Note that on each immunization day, all procedures and blood draws must be done before. The following will be completed:

1) Review of AEs and SAEs
2) Recording of any previous / concomitant medications
3) Vital signs
4) Symptom-directed physical exam
5) Assessment and measurements of tumor to be treated with G100 and measureable untreated distal tumor lesions by exam
6) ECOG status
7) Safety labs as in Section 10.3.2– Hematology, Clinical chemistry
8) G100 administration

10.3.5 Visit 6: G100 Dose #2 (Day 5-7)

Patients will return for the second dose of G100 on either Day 5, 6, or 7. Note that on each immunization day, all procedures and blood draws must be done before dosing. The following will be completed:

1) Review of AEs and SAEs
2) Recording of any previous / concomitant medications
3) Vital signs
4) Symptom-directed physical exam

5) Assessment and measurements of tumor treated with G100 and measureable untreated distal tumor lesions by exam
6) ECOG status
7) Safety labs as in Section 10.3.2 – Hematology, Clinical chemistry
8) G100 administration

10.3.6 Visits 7, 8, 9, 10: G100 Doses #3, 4, 5, 6 (Days 14, 21, 28, 35)

Patients will return for their G100 doses #3, 4, 5, and 6. Note that on each immunization day, all procedures and blood draws must be done before dosing. The following will be completed:

1) Review of AEs and SAEs
2) Recording of any previous / concomitant medications
3) Vital signs
4) Symptom-directed physical exam
5) Assessment and measurements of tumor treated with G100 and measureable untreated distal tumor lesions by exam
6) ECOG status
7) Safety labs as in Section 10.3.2 – Hematology, Clinical chemistry
8) On Day 35, Visit 10 only, blood for cell phenotyping / profiling (collected from patients in Parts 1 and 2; not collected in Part 3) and for T cell gene profiling (collected for Parts 1, 2, and 3)
9) G100 administration (Note: If the tumor regressed and is no longer of sufficient size for injection per evaluation by the investigator and there are no alternate lesions within the irradiated area, the remaining G100 treatments and treatment visits may be cancelled. The patient should then continue with Clinical Assessment visits beginning on Day 56)

10.3.7 Optional Visit 10A, 10B: G100 Doses # 7, 8 (Days 42, 49)

For patients in Parts 2 and 3 whose treated tumor has not regressed completely, dosing may continue for 3 additional weekly intratumoral treatments (9 total) with doses #7 and 8 given on these visits. Note that on each immunization day, all procedures and blood draws must be done before dosing. The following will be completed:

1) Review of AEs and SAEs
2) Recording of any previous / concomitant medications
3) Vital signs
4) Symptom-directed physical exam

5) Assessment and measurements of tumor treated with G100 and measureable untreated distal tumor lesions by exam
6) ECOG status
7) Safety labs as in Section 10.3.2 – Hematology, Clinical chemistry
8) Optional G100 administration of Doses #7, 8 in qualified patients. (Note: If the tumor regressed and is no longer of sufficient size for injection per evaluation by the investigator and there are no alternate lesions within the irradiated area, the remaining G100 treatments and treatment visits may be cancelled. The patient should then continue with Clinical Assessment visits beginning on Day 56)

10.3.8 Visit 11: Clinical Assessment and Optional G100 Dose # 9 (Day 56)

This is a mandatory Clinical Assessment visit. For patients whose treated tumor has not regressed completely, 3 optional treatments may continue and the final dose #9 may be given on this visit. Note that on each immunization day, all procedures and blood draws must be done before dosing. The following will be completed:

1) Review of AEs and SAEs
2) Recording of any previous / concomitant medications
3) Vital signs
4) Symptom-directed physical exam
5) Assessment and measurements of tumor treated with G100 and measureable untreated distal tumor lesions by exam
6) ECOG status
7) Safety labs as in Section 10.3.2– Hematology, Clinical chemistry
8) For patients in Part 1 and Part 2, blood for cell phenotyping / profiling (not collected in Part 3)
9) Blood for T cell gene profiling
10) For patients in the UK, urine pregnancy test
11) Assessment of disease including CT or MRI of chest, abdomen, pelvis. Other assessments such as CT of the head, body PET CT, or bone marrow biopsy should be performed if indicated. Day 56 (+/- 7 days) restaging CT or MRI scans should be performed if the optional treatment #9 is not given. If the 9th dose is given, then imaging studies should be delayed to Day 63 to 77. If a PET CT is used, a standard high resolution CT series should be obtained rather than low resolution scans for tumor measurements. However, PET scans should not be used to determine disease progression since it is expected that PET avidity will increase with the type of inflammation induced by this treatment and may lead to false positive results.

12) Photographs: if the tumor can be measured and assessed visually, photographic documentation with measurements should be considered in order to keep a record and help assess any response to treatment (may be performed at any time during study)

13) Post Treatment tumor biopsy. Post-treatment tumor biopsy of available tumor (treated or untreated tumor to investigate systemic response) should be performed on Day 56 +/- 1 week for patients not receiving optional treatment #9. If the 9th dose is given, then the biopsy should be delayed to Day 63 to 77. The biopsies should be performed on the treated tumor if feasible; if not available, a different site should be chosen. The location from where the sample was obtained (treated, non-treated, irradiated or non-irradiated, untreated distal site) must be recorded.

14) Optional G100 administration of Dose #9 in qualified patients

10.3.9 Visit 12: Post-Immunization / End of Study Visit (Day 77)

The following will be completed:

1) Review of AEs and SAEs (Note: Patients should have all AEs reported for at least 30 days following the last dose of the G100 study agent. This includes those who withdraw early before completion of the study.)
2) Recording of any previous / concomitant medications
3) Vital signs
4) Symptom-directed physical exam
5) Assessment and measurements of tumor treated with G100 and measureable untreated distal tumor lesions by exam
6) ECOG status
7) Safety labs as in Section 10.3.2 – Hematology, Clinical chemistry
8) 12-lead ECG
9) Urine pregnancy test for FCBP. (Serum pregnancy test may be performed for any urine pregnancy assay if site SOP allows this test.)
10) If the optional 9th dose was given, then imaging studies should be delayed to Day 63 to 77. Assessment of disease including CT or MRI of chest, abdomen, and pelvis should be performed. Other assessments such as CT of the head, body PET CT, or bone marrow biopsy should be completed if indicated. If a PET CT is used, a standard high resolution CT series should be obtained rather than low resolution scans for tumor measurements. However, PET scans should not be used to determine disease progression since it is expected that PET avidity will increase with the type of inflammation induced by this treatment and may lead to false positive results.

11) Photographs: if the tumor can be measured and assessed visually, photographic documentation with measurements should be considered in order to keep a record and help assess any response to treatment (may be performed at any time during study)

12) If the optional 9th dose was given, then the post-treatment tumor biopsy of available tumor (treated or untreated tumor to investigate systemic response) should be performed Day 63 to 77. The biopsies should be performed on the treated tumor if feasible; if not available, a different site should be chosen. The location from where the sample was obtained (treated, non-treated, irradiated or non-irradiated, untreated distal site) must be recorded.

10.3.10 Long-Term Follow-up Visits

10.3.10.1 Visits Before Disease Progression (Day 112, then every 8 weeks)

1) Any SAE that comes to the attention of the site staff that may be causally related to study drug must be reported to Immune Design regardless of time elapsed.
2) Recording of any previous / concomitant medications.
3) Vital signs
4) Symptom-directed physical examination
5) Assessment and measurements of tumor treated with G100 and measureable untreated distal tumor lesions by exam
6) ECOG performance status
7) Assessment of disease including CT or MRI (chest, abdomen, pelvis) (to be repeated 4 weeks later to confirm disease progression as defined by irRC). Other assessments such as a CT of head, body PET CT, or bone marrow biopsy should be performed if indicated. If a PET CT is used, a standard high resolution CT series should be obtained rather than low resolution scans for tumor measurements. However, PET scans should not be used to determine disease progression since it is expected that PET avidity will increase with the type of inflammation induced by this treatment and may lead to false positive results. Imaging studies will occur on Day 112, every 8 weeks thereafter for the first year, every 3 to 4 months for the second year, and then at least every 6 months for the third and subsequent years.
8) Photographs: if the tumor can be measured and assessed visually, photographic documentation with measurements should be considered in order to keep a record and help assess any response to treatment (may be performed at any time during study)
9) Safety labs as in Section 10.3.2– Hematology, Clinical chemistry

10.3.10.2 After Disease Progression (Every 8 to 12 Weeks)

Patients will receive telephone follow-up or clinic visit every 8 to 12 weeks after disease progression until 1 year after first study injection. Follow-up will include vital status (survival status), cancer status, and post-treatment anti-cancer therapy including time to next treatment, treatment details, and clinical response. If the patient agrees, the site may periodically

(e.g., every 2 to 4 months) contact the patient beyond 1 year to check on vital and cancer status (e.g., lymphoma transformation). In addition, any SAE and that comes to the attention of the site staff that may be causally related to study drug must be reported to Immune Design, regardless of time elapsed.

Note: Sections 10.3.11 to 10.3.15 apply only to patients randomized to receive pembrolizumab on Part 2, Patient Expansion With Or Without Pembrolizumab

10.3.11 Visits 7, 8, 9, 10: G100 Doses #3, 4, 5, 6 (Days 14, 21, 28, 35)

Patients will return for their G100 doses #3, 4, 5, and 6. Note that on each immunization day, all procedures and blood draws must be done before dosing. The following will be completed:

1) Review of AEs and SAEs
2) Recording of any previous / concomitant medications
3) Vital signs
4) Symptom-directed physical exam
5) Assessment and measurements of tumor treated with G100 and measureable untreated distal tumor lesions by exam
6) ECOG status
7) Safety labs as in Section 10.3.2– Hematology, Clinical chemistry
8) On Day 35, Visit 10 only, blood for cell phenotyping / profiling and for T cell gene profiling
9) G100 administration (Note: If the tumor regressed and is no longer of sufficient size for injection per evaluation by the investigator and there are no alternate lesions within the irradiated area, the remaining G100 treatments and G100 only treatment visits may be cancelled. The patient should then continue with pembrolizumab and Clinical Assessment visits)
10) Urine pregnancy test on Day 14 prior to pembrolizumab. Note: For patients in the UK and France, urine pregnancy tests must also be performed every month or sooner while the patient is receiving G100 and/or pembrolizumab.
11) On Day 14 and 35, administer pembrolizumab

10.3.12 Optional Visit 10A, 10B: G100 Doses # 7, 8 (Days 42, 49)

For patients whose treated tumor has not regressed completely dosing may continue for 3 additional weekly intratumoral treatments (9 total) with doses #7 and 8 given on these visits. Note that on each immunization day, all procedures and blood draws must be done before dosing. The following will be completed:

1) Review of AEs and SAEs

2) Recording of any previous / concomitant medications
3) Vital signs
4) Symptom-directed physical exam
5) Assessment and measurements of tumor treated with G100 and measureable untreated distal tumor lesions by exam
6) ECOG status
7) Safety labs as in Section 10.3.2 – Hematology, Clinical chemistry
8) Optional G100 administration of Doses #7, 8 in qualified patients. (Note: If the tumor regressed and is no longer of sufficient size for injection per evaluation by the investigator and there are no alternate lesions within the irradiated area, the remaining G100 treatments and G100 only treatment visits may be cancelled. The patient should then continue with pembrolizumab and Clinical Assessment visits)

10.3.13 Visit 11: Clinical Assessment and Optional G100 Dose # 9 (Day 56)

This is a mandatory visit for Clinical Assessment. For patients whose treated tumor has not regressed completely, 3 optional treatments may continue and the final dose #9 may be given on this visit. Note that on each immunization day, all procedures and blood draws must be done before dosing. The following will be completed:

1) Review of AEs and SAEs
2) Recording of any previous / concomitant medications
3) Vital signs
4) Symptom-directed physical exam
5) Assessment and measurements of tumor treated with G100 and measureable untreated distal tumor lesions by exam
6) ECOG status
7) Safety labs as in Section 10.3.2 – Hematology, Clinical chemistry
8) Thyroid function tests (including TSH)
9) Blood for cell phenotyping /profiling
10) Blood for T cell gene profiling
11) For patients in the UK, urine pregnancy test

12) Assessment of disease including CT or MRI of chest, abdomen, pelvis (Day 56 +/- 7 days). Other assessments such as CT of the head, body PET CT, or bone marrow biopsy should be performed if indicated. If a PET CT is used, a standard high resolution CT series should be obtained rather than low resolution scans for tumor measurements. However, PET scans should not be used to determine disease progression since it is expected that PET avidity will increase with the type of inflammation induced by this treatment and may lead to false positive results.

13) Photographs: if the tumor can be measured and assessed visually, photographic documentation with measurements should be considered in order to keep a record and help assess any response to treatment (may be performed at any time during study)

14) Post Treatment tumor biopsy. Post-treatment tumor biopsy of available tumor (treated or untreated tumor) should be performed (Day 56 +/- 1 week) on patients not receiving optional treatment #9 to investigate systemic response. If the 9th dose is given, then the biopsy should be delayed to Day 63 to 77. The biopsies should be performed on the treated tumor if feasible; if not available, a different site should be chosen. The location from where the sample was obtained (treated, non-treated, irradiated or non-irradiated, untreated distal site) must be recorded.

15) Optional G100 administration of Dose #9 in qualified patients

16) Administer pembrolizumab

10.3.14 Visit 12: Post-Immunization / End of Safety Visit (Day 77)

The following will be completed:

1) Review of AEs and SAEs
2) Recording of any previous / concomitant medications
3) Vital signs
4) Symptom-directed physical exam
5) Assessment and measurements of tumor treated with G100 and measureable untreated distal tumor lesions by exam
6) ECOG status
7) Safety labs as in Section 10.3.2 – Hematology, Clinical chemistry
8) 12-lead ECG
9) Urine pregnancy test for FCBP. (Serum pregnancy test may be performed for any urine pregnancy assay if site SOP allows this test.) Note: For patients in the UK and France, urine pregnancy tests must also be performed every month or sooner while the patient is receiving G100 and/or pembrolizumab.
10) Administer pembrolizumab

10.3.15 Long-Term Follow-up Visits

10.3.15.1 Visits For Anti-PD-1 Therapy and Before Disease Progression (Day 98, then every 3 weeks)

1) Any SAE that comes to the attention of the site staff that may be causally related to G100 must be reported to Immune Design regardless of time elapsed.
2) All AEs experienced from the time of enrollment through 30 days following cessation of pembrolizumab treatment will be reported by the investigator. Any event of clinical interest (ECI) experienced through 30 days following cessation of treatment should be reported within 24 hours to the Sponsor. Any SAE due to any cause other than progression of the cancer under study that occurs through 90 days following cessation of pembrolizumab treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, must be reported within 24 hours to the Sponsor. After the 90-day reporting period, any SAE that comes to the attention of the site staff that may be causally related to pembrolizumab must be reported to Sponsor regardless of time elapsed.
3) Recording of any previous / concomitant medications.
4) Vital signs
5) Symptom-directed physical examination
6) Assessment and measurements of tumor treated with G100 and measureable untreated distal tumor lesions by exam
7) ECOG performance status
8) Beginning on Day 112 to 119 and then repeat every 8 weeks: Assessment of disease including CT or MRI (chest, abdomen, pelvis) (to be repeated 4 or more weeks later to confirm disease progression as defined by irRC). Other assessments such as a CT of head, body PET CT, or bone marrow biopsy should be performed if indicated. If a PET CT is used, a standard high resolution CT series should be obtained rather than low resolution scans for tumor measurements. However, PET scans should not be used to determine disease progression since it is expected that PET avidity will increase with the type of inflammation induced by this treatment and may lead to false positive results. Imaging studies will occur every 8 weeks for the first year, every 3 to 4 months for the second year and then at least every 6 months for the third and subsequent years.
9) Photographs: if the tumor can be measured and assessed visually, photographic documentation with measurements should be considered in order to keep a record and help assess any response to treatment (may be performed at any time during study)
10) Safety labs as in Section 10.3.2 – Hematology, Clinical chemistry. For patients in France and the UK, urine pregnancy tests must also be performed every month or sooner while the patient is receiving G100 and/or pembrolizumab.

11) For patients in the UK, urine pregnancy tests must also be performed every month or sooner while the patient is receiving G100 and/or pembrolizumab.

12) Beginning Day 98, thyroid function tests (including TSH). Tests should then be repeated every 6 weeks to monitor for changes in thyroid function during treatment and as indicated based on clinical signs and symptoms of thyroid disease.

13) Administer pembrolizumab. Continue Q3W until disease progression or unacceptable toxicity for up to a total of 2 years. Discontinuation of treatment may be considered for subjects who have attained a confirmed CR that have been treated for at least 24 weeks with pembrolizumab and had at least 2 treatments with pembrolizumab beyond the date when the initial CR was declared.

10.3.15.2 Visits After Disease Progression (Every 8 to 12 Weeks)

Patients will receive telephone follow-up or clinic visit every 8 to 12 weeks after disease progression until 1 year after first study injection. Follow-up will include vital status (survival status), cancer status (e.g., lymphoma transformation), and post-treatment anti-cancer therapy including time to next treatment, treatment details, and clinical response. If the patient agrees, the site may periodically (e.g., every 2 to 4 months) contact the patient beyond 1 year to check on vital and cancer status. In addition, any SAE that comes to the attention of the site staff that may be causally related to G100 must be reported to Immune Design, regardless of time elapsed. All AEs experienced from the time of enrollment through 30 days following cessation of pembrolizumab (and/or G100, whichever is longer) treatment will be reported by the investigator. Any ECI experienced through 30 days following cessation of treatment should be reported within 24 hours to the Sponsor. Any SAE due to any cause other than progression of the cancer under study that occurs through 90 days following cessation of pembrolizumab treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, must be reported within 24 hours to the Sponsor. After the 90-day reporting period, any SAE that comes to the attention of the site staff that may be causally related to pembrolizumab must be reported to Sponsor regardless of time elapsed.

Note: Sections 10.3.16 to 10.3.22.2 apply only to patients enrolled to receive G100 and pembrolizumab on Part 4, Sequential G100 at 20µg/lesion Into Single Or Multiple Tumor Masses Plus Pembrolizumab

10.3.16 Visit 3: G100 Treatment #1 (Day 0)

For Part 4, patients will be assigned to a treatment cohort or cohort expansion and the number of lesions to be injected and location will be agreed upon before initiation of therapy. Note for Part 4, radiation therapy has been omitted, and that on each immunization day, all procedures and blood draws must be done before dosing except for the pharmacokinetics/ pharmacodynamics 6 hours pose the first G100 treatment or pembrolizumab, if applicable. The following will be completed:

1) Review of AEs and SAEs
2) Recording of any previous / concomitant medications
3) Vital signs
4) Symptom-directed physical exam
5) Assessment and measurements of tumor to be treated with G100 and measureable untreated distal tumor lesions by exam
6) ECOG status
7) Safety labs and pharmacokinetics/ pharmacodynamic labs as in Section 10.3.2– Hematology, Clinical chemistry
8) G100 administration

10.3.17 Visit 4: G100 Dose #2 (Day 5-7)

Patients will return for the second dose of G100 on either Day 5, 6, or 7. Note that on each immunization day, all procedures and blood draws must be done before dosing. The following will be completed:

1) Review of AEs and SAEs
2) Recording of any previous / concomitant medications
3) Vital signs
4) Symptom-directed physical exam
5) Assessment and measurements of tumor treated with G100 and measureable untreated distal tumor lesions by exam
6) ECOG status
7) Safety labs as in Section 10.3.2 – Hematology, Clinical chemistry
8) G100 administration

10.3.18 Visits 5, 6, 7, 8: G100 Doses #3, 4, 5, 6 (Days 14, 21, 28, 35)

Patients will return for their G100 doses #3, 4, 5, and 6. Note that on each immunization day, all procedures and blood draws must be done before dosing. The following will be completed:

1) Review of AEs and SAEs
2) Recording of any previous / concomitant medications
3) Vital signs
4) Symptom-directed physical exam
5) Assessment and measurements of tumor treated with G100 and measureable untreated distal tumor lesions by exam
6) ECOG status
7) Safety labs as in Section 10.3.2– Hematology, Clinical chemistry
8) Pharmacokinetics and Pharmacodynamic labs (Visit 5 Day 15 only)
9) G100 (20 µg/lesion) administration (Note: If the injected tumor(s) regressed and is no longer of sufficient size for injection (either intra- or peritumoral) per evaluation by the investigator and there are no easily accessable alternate lesions – i.e., There are no longer any injectable lesions, the remaining G100 treatments and G100 only treatment visits may be cancelled. The patient should then continue with pembrolizumab and Clinical Assessment visits)
10) Urine pregnancy test on Day 14 prior to pembrolizumab. Note: For patients in UK and France, urine pregnancy tests must also be performed every month or sooner while the patient is receiving G100 and/or pembrolizumab.
11) On Day 14 and 35, administer pembrolizumab

10.3.19 Optional Visit 8A, 8B: G100 Doses # 7, 8 (Days 42, 49)

For patients whose treated tumor(s) has not regressed completely dosing may continue for 3 additional weekly intratumoral treatments (9 total) with doses #7 and 8 given on these visits. Note that on each immunization day, all procedures and blood draws must be done before dosing. The following will be completed:

1) Review of AEs and SAEs
2) Recording of any previous / concomitant medications
3) Vital signs
4) Symptom-directed physical exam
5) Assessment and measurements of tumor treated with G100 and measureable untreated distal tumor lesions by exam
6) ECOG status

7) Safety labs as in Section 10.3.2 – Hematology, Clinical chemistry
8) Optional G100 (20µg/lesion) administration of Doses #7, 8 in qualified patients. (Note: If the injected tumor(s) regressed and is no longer of sufficient size for injection (either intra- or peritumoral) per evaluation by the investigator and there are no easily accessable alternate lesions – i.e., There are no longer any injectable lesions, the remaining G100 treatments and G100 only treatment visits may be cancelled. The patient should then continue with pembrolizumab and Clinical Assessment visits.

10.3.20 Visit 9: Clinical Assessment and Optional G100 Dose # 9 (Day 56)

This is a mandatory visit for Clinical Assessment. For patients whose treated tumor has not regressed completely, the three optional treatments may continue and the final dose #9 may be given on this visit. Note that on each immunization day, all procedures and blood draws must be done before dosing. The following will be completed:

1) Review of AEs and SAEs
2) Recording of any previous / concomitant medications
3) Vital signs
4) Symptom-directed physical exam
5) Assessment and measurements of tumor treated with G100 and measureable untreated distal tumor lesions by exam
6) ECOG status
7) Safety labs as in Section 10.3.2 – Hematology, Clinical chemistry
8) Thyroid function tests including TSH, T3 or FT3, and FT4
9) For patients in UK and France, urine pregnancy tests must also be performed every month or sooner while the patient is receiving G100 and/or pembrolizumab.
10) Assessment of disease including CT or MRI of chest, abdomen, pelvis. Other assessments such as CT of the head, body PET CT, orbone marrow biopsy should be performed if indicated. Day 56 (+/- 7 days) restaging CT or MRI scans should be performed if the optional treatment #9 is not given. If the 9th dose is given, then imaging studies should be delayed to Day 63 to 77. If a PET CT is used, a standard high resolution CT series must be obtained rather than low resolution scans and only the CT imaging should be used for tumor measurements. PET scans should not be used to determine disease progression since it is expected that PET avidity will increase with the type of inflammation induced by this treatment and may lead to false positive results.
11) Photographs: if the tumor can be measured and assessed visually, photographic documentation with measurements should be considered in order to keep a record and help assess any response to treatment (may be performed at any time during study)

12) Post Treatment tumor biopsy. Post-treatment tumor biopsy of available tumor (treated or untreated tumor) should be performed as close to 2 weeks after last G100 dose as possible: Day 42 to 56 for patients receiving 6 doses of G100 or, if the 9th dose is given, then the biopsy should be delayed to Day 63 to 77. The biopsies should be performed on the treated tumor if feasible and if available; in addition, a second abscopal site should also be biopsied if feasible. The location from where the sample was obtained (treated, non-treated, irradiated or non-irradiated, untreated distal site) must be recorded.

13) Optional G100 administration of Dose #9 in qualified patients

14) Administer pembrolizumab

10.3.21 Visit 10: Post-Immunization / End of Safety Visit (Day 77)

The following will be completed:

1) Review of AEs and SAEs
2) Recording of any previous / concomitant medications
3) Vital signs
4) Symptom-directed physical exam
5) Assessment and measurements of tumor treated with G100 and measureable untreated distal tumor lesions by exam
6) ECOG status
7) Safety labs as in Section 10.3.2 – Hematology, Clinical chemistry
8) 12-lead ECG
9) Urine pregnancy test for FCBP. (Serum pregnancy test may be performed for any urine pregnancy assay if site SOP allows this test.) Note: For patients in UK and France, urine pregnancy tests must also be performed every month or sooner while the patient is receiving G100 and/or pembrolizumab.
10) If the 9th dose is given, then imaging studies should be performed Day 63 to 77 instead of Day 56. Assessment of disease including CT or MRI of chest, abdomen, pelvis should be performed. Other assessments such as CT of the head, body PET CT, or bone marrow biopsy should be performed if indicated. If a PET CT is used, a standard high resolution CT series must be obtained rather than low resolution scans and only the CT imaging should be used for tumor measurements. PET scans should not be used to determine disease progression since it is expected that PET avidity will increase with the type of inflammation induced by this treatment and may lead to false positive results.

11) Post Treatment tumor biopsy. If the 9th dose is given, then the biopsy should be peformed as close to 2 weeks after the last G100 dose as possible (Day 63 to 77). Post-treatment tumor biopsy of available tumor (treated or untreated tumor) should be performed to investigate systemic response. The biopsies should be performed on the treated tumor if feasible and if available; in addition, a second abscopal site should also be biopsied if feasible. The location from where the sample was obtained (treated, non-treated, irradiated or non-irradiated, untreated distal site) must be recorded.

12) Administer pembrolizumab

10.3.22 Long-Term Follow-up Visits

10.3.22.1 Visits For Anti-PD-1 Therapy and Before Disease Progression (Day 98, then every 3 weeks)

1) Any SAE that comes to the attention of the site staff that may be causally related to G100 must be reported to Immune Design regardless of time elapsed.

2) All AEs experienced from the time of enrollment through 30 days following cessation of pembrolizumab treatment will be reported by the investigator. Any event of clinical interest (ECI) experienced through 30 days following cessation of treatment should be reported within 24 hours to the Sponsor. Any SAE due to any cause other than progression of the cancer under study that occurs through 90 days following cessation of pembrolizumab treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, must be reported within 24 hours to the Sponsor. After the 90-day reporting period, any SAE that comes to the attention of the site staff that may be causally related to pembrolizumab must be reported to Sponsor regardless of time elapsed.

3) Recording of any previous / concomitant medications.

4) Vital signs

5) Symptom-directed physical examination

6) Assessment and measurements of tumor treated with G100 and measureable untreated distal tumor lesions by exam

7) ECOG performance status

8) Beginning on Day 112 to 119 for patients receiving 6 doses of G100 or on Day133 to 140 for patients receiving 9 doses of G100 and then repeat every 8 weeks (±14 days): Assessment of disease including CT or MRI (chest, abdomen, pelvis) (to be repeated 4 or more weeks later to confirm disease progression as defined by irRC). Other assessments such as a CT of head, body PET CT, or bone marrow biopsy should be performed if indicated. **However, PET scans should not be used to determine disease progression** since it is expected that PET avidity will increase with the type of inflammation induced by this treatment and can lead to false positive results. For this reason, PET scans are not recommended. If a PET CT is used, a standard high resolution CT series must be obtained rather than low resolution scans and

only the CT imaging should be used for tumor measurements. Imaging studies will occur every 8 weeks for the first year, every 3 to 4 months for the second year and then at least every 6 months for the third and subsequent years.

9) Photographs: if the tumor can be measured and assessed visually, photographic documentation with measurements should be considered in order to keep a record and help assess any response to treatment (may be performed at any time during study)

10) Safety labs as in Section 10.3.2 – Hematology, Clinical chemistry.

11) For patients in UK and France, urine pregnancy tests must also be performed every month or sooner while the patient is receiving G100 and/or pembrolizumab.

12) Beginning Day 98, thyroid function tests including TSH, T3 or FT3, and FT4. Tests should then be repeated every 6 weeks to monitor for changes in thyroid function during treatment and as indicated based on clinical signs and symptoms of thyroid disease.

13) Administer pembrolizumab. Continue Q3W until disease progression or unacceptable toxicity for up to a total of 2 years. Discontinuation of treatment may be considered for subjects who have attained a confirmed CR that have been treated for at least 24 weeks with pembrolizumab and had at least 2 treatments with pembrolizumab beyond the date when the initial CR was declared.

10.3.22.2 Visits After Disease Progression (Every 8 to 12 Weeks)

Patients will receive telephone follow-up or clinic visit every 8 to 12 weeks after **confirmed** disease progression (or symptomatic deterioration with therapy) for at least 1 year after first study injection. Follow-up will include vital status (survival status), cancer status, and post-treatment anti-cancer therapy including time to next treatment, treatment details, and clinical response. If the patient agrees, the site may periodically (e.g., every 2 to 4 months) contact the patient beyond 1 year to check on vital and cancer status. Delayed objective responses have been observed on this study at >18 months from Day 0. Therefore, if the patient should experience a clinical regression and has not received any additional therapy, the patient may be asked for consent to collect clinical information such as imaging studies and biomarkers.

Any SAE that comes to the attention of the site staff that may be causally related to G100 must be reported to Immune Design, regardless of time elapsed. All AEs experienced from the time of enrollment through 30 days following cessation of pembrolizumab (and/or G100, whichever is longer) treatment will be reported by the investigator. Any ECI experienced through 30 days following cessation of treatment should be reported within 24 hours to the Sponsor. Any SAE due to any cause other than progression of the cancer under study that occurs through 90 days following cessation of pembrolizumab treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, must be reported within 24 hours to the Sponsor. After the 90-day reporting period, any SAE that comes to the attention

of the site staff that may be causally related to pembrolizumab must be reported to Sponsor regardless of time elapsed.

Note: Sections 10.3.23 to 10.3.29.2 apply only to patients enrolled on Part 5, G100 Plus Rituximab

10.3.23 Visit 3: Rituximab Treatment #1 (Day 0)

For Part 5, patients will be assigned to a Dose Escalation treatment cohort or to a Patient Expansion arm at the time of study enrollment. The treatment dose and the single lesion to be injected and its location will be agreed upon with the Medical Monitor before initiation of therapy. Note for Part 5, radiation therapy has been omitted, and that on each immunization day, all procedures and blood draws must be done before dosing except for the pharmacokinetics/ pharmacodynamic blood draw 6 hours post the G100 first treatment. The following will be completed:

1) Review of AEs and SAEs
2) Recording of any previous / concomitant medications
3) Vital signs
4) Symptom-directed physical exam
5) Assessment and measurements of tumor to be treated with G100 and measureable untreated distal tumor lesions by exam
6) ECOG status
7) Safety labs and Pharmacokinetics/Pharmacodynamics labs as in Section 10.3.2– Hematology, Clinical chemistry
8) Rituximab administration

10.3.24 Visit 4: G100 Dose #1 (Day 1)

Patients will return the next day for their first dose of G100. Note that on each immunization day, all procedures and blood draws must be done before dosing. The following will be completed:

1) Review of AEs and SAEs, including those associated with the first dose of rituximab
2) Recording of any previous / concomitant medications
3) Vital signs
4) Symptom-directed physical exam if indicated by adverse events
5) Safety labs and Pharmacokinetics/ Pharmacodynamics labs as in Section 10.3.2 – Hematology, Clinical chemistry

6) G100 administration

Note: Following completion of the Dose Escalation portion of the study, if after a review of all safety, and with agreement of the independent DMC, it is determined that there are no safety concerns (e.g., significant rituximab first dose infusion reactions or potential of overlap of toxicities) that would prevent the administration of both G100 and rituximab on Day 0, the Sponsor may choose to administer G100 following rituximab on Day 0 and eliminate Visit 4.

10.3.25 Visits 5, 6, 7: G100 Doses #2, 3, 4 (Days 7, 14, 21) and Rituximab Doses #2, 3, 4 (Days 7, 14, 21)

Patients will return for their G100 doses #2, 3, 4 and rituximab doses #2, 3, 4. Note that on each immunization day, all procedures and blood draws must be done before dosing. The following will be completed:

1) Review of AEs and SAEs
2) Recording of any previous / concomitant medications
3) Vital signs
4) Symptom-directed physical exam
5) Assessment and measurements of tumor treated with G100 and measureable untreated, non-injected distal tumor lesions by exam
6) ECOG status
7) Safety labs as in Section 10.3.2– Hematology, Clinical chemistry
8) G100 administration (Note: If the injected tumor(s) regressed and is no longer of sufficient size for injection (either intra- or peritumoral) per evaluation by the investigator and there are no easily accessable alternate lesions – i.e., There are no longer any injectable lesions, the remaining G100 treatments and G100 only treatment visits may be cancelled. The patient should then continue with rituximab and Clinical Assessment visits)
9) On Days 7, 14 and 21, administer rituximab

10.3.26 Visits 8, 8A and 8B (Days 28, 35, 42): Visit and Optional G100 Doses # 5, 6 (Days 28, 35)

At the discretion of the PI, patients whose injected or observed tumor(s) have not regressed completely may continue G100 dosing for 2 additional weekly intratumoral treatments (6 total) with doses #5 and 6 given on Visits 8 and 8A (Days 28 and 35). These patients should follow the Schedule of Events for Visits 8, 8A, and 8B.

Patients who will only receive 4 doses of G100 must follow the Schedule of Events for Visit 8 and should not return for Visits 8A or 8B.

Note that on each immunization day, all procedures and blood draws must be done before dosing. The following will be completed:

1) Review of AEs and SAEs
2) Recording of any previous / concomitant medications
3) Vital signs
4) Symptom-directed physical exam
5) Assessment and measurements of tumor treated with G100 and measureable untreated, non-injected distal tumor lesions by exam
6) ECOG status
7) Safety labs as in Section 10.3.2 – Hematology, Clinical chemistry
8) For patients who will receive 6 doses of G100, optional G100 administration of Doses #5, 6 in qualified patients are given on Visits 8 and 8A (Days 28 and 35). (Note: If the injected tumor(s) regressed and is no longer of sufficient size for injection (either intra- or peritumoral) per evaluation by the investigator and there are no easily accessable alternate lesions – i.e., There are no longer any injectable lesions, the remaining G100 treatments and G100 only treatment visits may be cancelled. The patient should then continue with Clinical Assessment visits.
9) On Visit 8 (Day 28), patients who only receive 4 or fewer doses of G100, blood for T cell gene profiling and biomarkers (see Lab Manual for collection guidelines) and tumor biopsy should be obtained as close to 2 weeks following the last dose of G100 as possible (Biopsy window: Day 28 to 35)

   On Visit 8B (Day 42), patients who received 5 or 6 doses of G100, blood for T cell gene profiling and biomarkers and tumor biopsy should be obtained as close to 2 weeks following the last dose of G100 as possible (Biopsy window, Day 42 to 56)

   Note: Patients treated on Part 5 will have an additional 8ml drawn for T cell gene and biomarker analyses on either Day 28 or 42 depending whether or not the patient received 4 or 6 G100 injections (see Lab Manual for details). The additional blood is reflected as the larger blood volume collection beginning on either Day 28 or 42.

   Post Treatment Tumor Biopsies should be performed on the treated tumor if feasible and if available; in addition, a second non-injected site should also be biopsied if feasible. **The location where the sample was obtained (injected or non-injected distal site) must be recorded.**
10) For patients in UK and France, urine pregnancy tests must also be performed every month (Day 28) or sooner while the patient is receiving G100. (Otherwise, urine pregnancy test on Day 77)

10.3.27 Visit 9: Clinical Assessment (Day 56)

This is a mandatory visit for Clinical Assessment. The following will be completed:

1) Review of AEs and SAEs
2) Recording of any previous / concomitant medications
3) Vital signs
4) Symptom-directed physical exam
5) Assessment and measurements of tumor treated with G100 and measureable untreated, non-injected distal tumor lesions by exam
6) ECOG status
7) Safety labs as in Section 10.3.2 – Hematology, Clinical chemistry
8) Urine pregnancy test for FCBP (Serum pregnancy test may be performed for any urine pregnancy assay if site SOP allows this test.) Note: For patients in the UK, urine pregnancy tests must also be performed every month or sooner while the patient is receiving G100
9) 12-lead ECG
10) Assessment of disease including CT or MRI of chest, abdomen, pelvis (Day 56 ±7 days). Other assessments such as CT of the head or bone marrow biopsy should be performed if indicated. **However, PET scans should not be used to determine disease progression since it is expected that PET avidity will increase with the type of inflammation induced by this treatment and can lead to false positive results.** For this reason, PET scans are not recommended. If a PET CT is used, a standard high resolution CT series must be obtained rather than low resolution scans and only the CT imaging should be used for tumor measurements.
11) Photographs: if the tumor can be measured and assessed visually, photographic documentation with measurements should be considered in order to keep a record and help assess any response to treatment (may be performed at any time during study)

10.3.28 Visit 10: Post-Immunization / End of Safety Visit (Day 112)

The following will be completed:

1) Review of AEs and SAEs: All AEs experienced from the time of enrollment through 30 days following cessation of G100 treatment will be reported by the investigator. Any event of clinical/medical interest experienced through 30 days following cessation of treatment should be reported within 24 hours to the Sponsor. Any SAE that comes to the attention of the site staff that may be causally related to G100 must be reported to Sponsor regardless of time elapsed
2) Recording of any previous / concomitant medications

3) Vital signs
4) Symptom-directed physical exam
5) Assessment and measurements of tumor treated with G100 and measureable untreated distal tumor lesions by exam
6) Assessment of disease including CT or MRI of chest, abdomen, pelvis (Day 112 ±7 days). Other assessments such as CT of the head or bone marrow biopsy should be performed if indicated. **However, PET scans should not be used to determine disease progression since it is expected that PET avidity will increase with the type of inflammation induced by this treatment and can lead to false positive results.** For this reason, PET scans are not recommended. If a PET CT is used, a standard high resolution CT series must be obtained rather than low resolution scans and only the CT imaging should be used for tumor measurements.
7) ECOG status
8) Safety labs as in Section 10.3.2 – Hematology, Clinical chemistry

10.3.29 Long-Term Follow-up Visits

10.3.29.1 Visits Before Disease Progression (Day 168, then every 8 weeks)

1) Any SAE that comes to the attention of the site staff that may be causally related to G100 must be reported to Immune Design regardless of time elapsed.
2) Recording of any previous / concomitant medications.
3) Vital signs
4) Symptom-directed physical examination
5) Assessment and measurements of tumor treated with G100 and measureable untreated distal tumor lesions by exam
6) ECOG performance status
7) Beginning on Day 168 ± 7 days and then repeat every 8 weeks ±14 days: Assessment of disease including CT or MRI (chest, abdomen, pelvis) (to be repeated 4 or more weeks later to confirm disease progression as defined by irRC). Other assessments such as a CT of head or bone marrow biopsy should be performed if indicated. **However, PET scans should not be used to determine disease progression** since it is expected that PET avidity will increase with the type of inflammation induced by this treatment and can lead to false positive results. For this reason, PET scans are not recommended. If a PET CT is used, a standard high resolution CT series must be obtained rather than low resolution scans and only the CT imaging should be used for tumor measurements. Imaging studies will occur every 8 weeks for the first year, every 3 to 4 months for the second year and then at least every 6 months for the third and subsequent years.

8) Photographs: if the tumor can be measured and assessed visually, photographic documentation with measurements should be considered in order to keep a record and help assess any response to treatment (may be performed at any time during study)
9) Safety labs as in Section 10.3.2 – Hematology, Clinical chemistry.

10.3.29.2 Visits After Disease Progression (Every 8 to 12 Weeks)

Patients will receive telephone follow-up or clinic visit every 8 to 12 weeks after **confirmed** disease progression (or symptomatic deterioration with therapy) for at least 1 year after first study injection. Follow-up will include vital status (survival status), cancer status (e.g., lymphoma transformation), and post-treatment anti-cancer therapy including time to next treatment, treatment details, and clinical response. If the patient agrees, the site may periodically (e.g., every 2 to 4 months) contact the patient beyond 1 year to check on vital and cancer status. Delayed objective responses have been observed on this study at >18 months from Day 0. Therefore, if the patient should experience a clinical regression and has not received any additional therapy, the patient may be asked for consent to collect clinical information such as imaging studies and biomarkers.

Any SAE that comes to the attention of the site staff that may be causally related to G100 must be reported to Immune Design, regardless of time elapsed. All AEs experienced from the time of enrollment through 30 days following cessation of G100 will be reported by the investigator. Any clinical/medical event of interest experienced through 30 days following cessation of treatment should be reported within 24 hours to the Sponsor.

10.4 Optional Retreatment / Second Course with G100 (Parts 1, 2, 3, 4 and 5)

Following the initial G100 course of treatment, if a patient is determined to have achieved SD or better or has PD that does not require immediate therapy (requires Medical Monitor pre-approval), has an additional site of disease outside of the prior radiation field that is amenable to injection (Parts 1, 2, or 3) and the patient has not had significant treatment emergent AEs (including events that would be considered a DLT) as determined by the investigator and the Sponsor, the patient may be eligible to receive a second course of G100. For patients enrolled on Parts 4 or 5, the same previously injected tumor site(s) may be targeted or a replacement site(s) may be chosen.

Six weeks or more after completion of the first course of G100 treatment the second course would begin and consist of G100 alone (no radiation or additional rituximab) at the same dose received during the first course of therapy. Treatment would be administered on a similar weekly schedule as the first course except without radiation therapy (or rituximab). Most of the visit procedures are identical to the initial G100 treatment schedule (except Visit numbers) and sections are referred to below.

For patients receiving pembrolizumab, treatment with the anti-PD-1 antibody would continue on its schedule during the second course of G100. In addition, all recurring safety bloods specific to pembrolizumab including thyroid function should continue. For reference, the treatment schedule for the initial set of visits are listed/linked below. *If possible the treatment with pembrolizumab should be synched with this schedule in order to collect and examine safety bloods on the same schedule as G100. If not, then continue to follow the Q3W schedule as outlined in Section 10.3.15.1 for Part 2 and 10.3.22.1 for Part 4 patients, "Visits For Anti-PD-1 Therapy and Before Disease Progression".*

10.4.1 Visit 1: Baseline Evaluation Days -14 to -1

1) Review of AEs and SAEs
2) Recording of any previous / concomitant medications
3) Vital signs
4) Symptom-directed physical exam
5) Assessment and measurements of tumor treated with G100 and measureable untreated, non-injected distal tumor lesions by exam
6) ECOG status
7) Safety labs as in Section 10.3.2 – Hematology, Clinical chemistry
8) For patients in Part 1 and Part 2, blood for cell phenotyping / profiling (not collected in Part 3, 4, or 5)
9) Blood for T cell gene profiling and biomarkers (Not collected in Part 4)
10) Assessment of disease including CT or MRI of chest, abdomen, pelvis. Other assessments such as CT of the head or bone marrow biopsy should be performed if indicated. (CT scan or MRI should be repeated if the last study was done 8 or more weeks prior to planned starting date of second course of therapy. If the last scan indicated tumor regression that might now be an objective PR/CR, the imaging studies should be repeated.) **PET scans should not be used to determine disease progression since it is expected that PET avidity will increase with the type of inflammation induced by this treatment and can lead to false positive results.** For this reason, PET scans are not recommended. If a PET CT is used, a standard high resolution CT series must be obtained rather than low resolution scans and only the CT imaging should be used for tumor measurements. Imaging studies will occur every 8 weeks for the first year, every 3 to 4 months for the second year and then at least every 6 months for the third and subsequent years.
11) Tumor biopsy: For Parts 1, 2 and 3, pre-second course treatment biopsy should be performed if one was not collected after the first course of G100 or if the last G100 treatment was >3 months prior to the start of the second course. For pre-treatment biopsy, baseline excisional samples should be obtained from the treatment target lesion or non-target lesion (near the target lesion). For Parts 4 and 5, ***new*** biopsies are mandatory unless collected

within 2 weeks of planned start of second course and should be obtained from the planned new treatment site. Both the treated and untreated sites post G100 should be biopsied if feasible.

12) Urine pregnancy test for FCBP must be performed (and negative) within 7 days prior to study treatment. (Serum pregnancy test may be performed for any urine pregnancy assay if site allows this test). Note: For patients in the UK and France, urine pregnancy tests must also be performed every month or sooner while the patient is receiving G100 and/or pembrolizumab.

10.4.2 Visit 2: G100 Treatment #1 (Day 0)

Patients will return for initiation of G100. Note that on each immunization day, all procedures and blood draws must be done before dosing. The following will be completed:

1) Review of AEs and SAEs
2) Recording of any previous / concomitant medications
3) Vital signs
4) Symptom-directed physical exam
5) Assessment and measurements of tumor to be treated with G100 and measureable untreated distal tumor lesions by exam
6) ECOG status
7) Safety labs as in Section 10.3.2 – Hematology, Clinical chemistry
8) G100 administration. For Part 4, if multiple lesions were injected initially, the choice of lesions to inject for the second course must be discussed and agreed upon with the Medical Monitor and could include previously treated lesions based on availability of lesions or technical issues.

10.4.3 Visit 3: G100 Dose #2 (Day 5-7)

Follow procedures outlined in Section 10.3.5, G100 Dose #2 (Day 5-7).

10.4.4 Visits 4, 5, 6, 7: G100 Doses #3, 4, 5, 6 (Days 14, 21, 28, 35)

Follow procedures outlined in Section 10.3.6, G100 Doses #3, 4, 5, 6 (Days 14, 21, 28, 35) or if receiving pembrolizumab, Section 10.3.11 for patients on Part 2, or Section 10.3.18 for patients on Part 4 (see Section 10.3.22.1 for description of timing of pembrolizumab dosing). Patients on Part 5 are limited to 6 doses of G100.

10.4.5 Optional Visit 7A, 7B: G100 Doses # 7, 8 (Days 42, 49)

Follow procedures outlined in Section 10.3.7, Optional G100 Doses #7, 8 (Days 42, 49) or if receiving pembrolizumab, Section 10.3.12 for patients on Part 2 or Section 10.3.19 for patients on Part 4.

10.4.6 Visit 8: Clinical Assessment and Optional G100 Dose # 9 (Day 56)

Follow procedures outlined in Section 10.3.8, Clinical Assessment and Optional G100 Dose # 9 (Day 56) or if receiving pembrolizumab, Section 10.3.13 for patients on Part 2 or Section 10.3.20 for patients on Part 4. Day 56 (± 7 days) restaging CT or MRI scans should be performed if the optional treatment #9 is not given. **PET scans should not be used to determine disease progression since it is expected that PET avidity will increase with the type of inflammation induced by this treatment and can lead to false positive results.** For this reason, PET scans are not recommended. If a PET CT is used, a standard high resolution CT series must be obtained rather than low resolution scans and only the CT imaging should be used for tumor measurements. If the 9th dose is given, then scans should be delayed to Day 63 to 77.

Post-treatment tumor biopsy should be performed as close to 2 weeks following the last dose of G100 as possible: on Day 42 to 56 for patients receiving 6 doses of G100 or, if the 9th dose is given, then biopsy should be delayed to Day 63 to 77. The biopsies should be performed on the treated tumor if feasible; if not available, a different site should be chosen. The location from where the sample was obtained (treated, non-treated, irradiated or non-irradiated, untreated distal site) must be recorded. For Parts 4 and 5, patients should have injected and non-injected lesions biopsied if feasible.

10.4.7 Visit 9: Post-Immunization / End of Study Visit (Day 77)

Follow procedures outlined in Section 10.3.9, Post-Immunization / EOS Visit (Day 77) or if receiving pembrolizumab, Section 10.3.14 for patients on Part 2 or Section 10.3.21 for patients on Part 4. If the 9th dose is given, then restaging CT or MRI scans and biopsy should be delayed to Day 63 to 77.

10.4.8 Long-Term Follow-up Visits

Follow procedures outlined in Section 10.3.10.1 for Visits Before Disease Progression (Day 112, then every 8 weeks) or Section 10.3.29.1 for patients on Part 5 or if receiving pembrolizumab, Section 10.3.15.1 for patients on Part 2 or Section 10.3.22.1 for patients on Part 4. (Day 98, then Q3W).

Note for Part 4, imaging studies during Follow-up will occur on Day 112 to 119 for patients receiving 6 doses of G100 or on Day133 to 140 for patients receiving 9 doses of G100. Imaging studies should then occur every 8 weeks (±14 days) thereafter for the first year, every 3 to 4 months for the second year, and then at least every 6 months for the third and subsequent years.

Follow procedures outlined in Section 10.3.10.2 for Visits After Disease Progression (every 8 weeks) or Section 10.3.29.2 for patients on Part 5 or if receiving pembrolizumab, Section 10.3.15.2 for patients on Part 2 or Section 10.3.22.2 for patients on Part 4.

10.4.9 Additional Biomarker Testing

For patients in any treatment group (and at any time), if a patient develops progression, a tissue biopsy should be obtained. The biopsies should be performed on the treated tumor if feasible; if not available, a different site should be chosen. The location from where the sample was obtained (treated, non-treated, irradiated or non-irradiated, untreated distal site) must be recorded.

In addition, for patients who are having a change in clinical outcome or immune response or on the basis of emerging data, additional tests for exploratory biomarkers may be extremely important to help investigate their response. Of note, on this study, very delayed objective tumor responses have occurred >18 months after study initiation. These additional tests may require additional blood or tumor (and may be requested at any time). For example, a patient may be demonstrating a significant tumor response and additional blood may be required to fully investigate the patient's anti-tumor immune response or a fine needle aspirate (FNA) might be requested to examine a gene signature at a specific timepoint after study therapy. Patients be may be asked to provide baseline blood (or tumor) and/or post-treatment samples to be used for these type of analysis. In these cases, the patient may be asked permission for additional blood or tumor samples to be collected for these exploratory assays.

11.0 PATIENT WITHDRAWAL

While patients will be encouraged to continue on study for safety follow-up, patients **MUST** be discontinued from receiving further study agent for the following reasons:

1) Withdrawal of informed consent (patient's decision to withdraw for any reason).
2) Pregnancy [NOTE: All FCBP should be instructed to contact the investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period) at any time during study participation].
3) Termination of the study for safety or other reasons.
4) Imprisonment or the compulsory detention for treatment of either a psychiatric or physical (e.g., infectious disease) illness.
5) Any clinical AE, laboratory abnormality or intercurrent illness that, in the opinion of the investigator, indicates that continued dosing on the study is not in the best interest of the patient.
6) Patients who cannot tolerate G100 or outpatient study procedures.

Unless consent is withdrawn and the patient is unwilling to continue with safety follow-up, the patient is lost to follow-up, or the study is terminated, all efforts should be made to continue safety monitoring of all patients who received G100 as outlined in Sections 10.3.10, 10.3.15, 10.3.22, 10.3.29, or 10.4.8. In addition, the procedures described in Sections 10.3.9, 10.3.14, 10.3.21, 10.3.28, or 10.4.7 should be done at the last site visit if feasible.

Patients who withdraw from the study prior to the EOS Visit should be followed for new AEs for at least 30 days after their last dose of G100. If the subject withdraws prematurely and is unwilling to continue safety follow-up, any subsequent SAE that may be causally related to G100 that comes to the attention of the site staff should be reported to Immune Design.

For patients receiving pembrolizumab, all AEs experienced from the time of enrollment through 30 days following cessation of pembrolizumab and/or G100 treatment, whichever is later, will be reported by the investigator. Any ECI experienced through 30 days following cessation of treatment should be reported within 24 hours to the Sponsor. Any SAE due to any cause other than progression of the cancer under study that occurs through 90 days following cessation of pembrolizumab treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, must be reported within 24 hours to the Sponsor. After the 90-day reporting period, any SAE that comes to the attention of the site staff that may be causally related to pembrolizumab or to G100 must be reported to Sponsor regardless of time elapsed.

12.0 ADVERSE EVENTS

All patients who receive at least one study injection or another study-related procedure will be considered evaluable for safety parameters. This includes any untoward signs (including abnormal laboratory findings) or symptoms experienced by the patient from the time of enrollment until the EOS / Post Vaccination Safety Visit (i.e., last study visit before long-term follow-up). For patients enrolled on the pembrolizumab arm, all AEs experienced from the time of enrollment through 30 days following cessation of treatment will be reported by the investigator. Safety will be evaluated for all treated patients using the *NCI CTCAE v.4.03* or newer. Safety assessments will be based on medical review of both solicited and spontaneously reported AEs, including symptoms, physical examination findings, vital signs, laboratory findings, ECGs, and discontinuations for AEs. The nature, severity, and frequency of AEs will be monitored on an ongoing basis for risk assessment and to determine if risk management interventions are warranted (i.e., expedited notification of safety findings to investigators, IRBs or regulators; update of IB and ICF risks and re-consenting study patients; revision of safety monitoring procedures; revision of eligibility criteria or other study procedures; etc.).

Progression of the cancer under study is not considered an AE unless it is considered to be drug-related by the investigator.

All SAEs that are unexpected and considered possibly, probably or definitely related to study regimen will be reported to the FDA and IRB in accordance with the requirements in 21 code of federal regulations (CFR) §312.32.

12.1 Definitions

Adverse Event (AE) - Any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product, medical treatment or procedure and which does not necessarily have to have a causal relationship with this regimen. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, medical treatment or procedure whether or not considered possibly, probably or definitely related to the medicinal product.

Unexpected Adverse Event – An AE is "unexpected" when its nature (specificity), severity, or frequency are not consistent with the known or foreseeable risk of AE associated with the research procedures described in the protocol, informed consent form, or the investigator brochure.

Serious Adverse Event (SAE) – Any AE occurring that results in any of the following outcomes:

1) Death.
2) A life-threatening AE.
3) Inpatient hospitalization or prolongation of existing hospitalization.
   Note: Hospitalizations not to be reported as SAEs include admissions for planned medical/surgical procedure (such as scheduled tumor excision or debulking surgery) or routine health assessment requiring admission for baseline/trending of health status documentation (e.g., routine colonoscopy) or admission for social purposes such as lack of housing, economic inadequacy, care-giver respite, or family circumstances.
4) A persistent or significant disability/incapacity.
5) Results in a congenital anomaly/birth defect.
6) Is a medically important condition which is judged by a health care professional as serious.

The term "life-threatening" refers to an event in which the subject was at risk of death at the time of the event, and it does not refer to an event that hypothetically might have caused death if it were more severe.

Disability refers to a substantial disruption of a person's ability to conduct normal life function.

Medical and scientific judgment will be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately

life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the outcomes listed in the definition above. These may also be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; or blood dyscrasias or convulsions that do not result in hospitalization.

When there is doubt regarding an AE meeting the criteria for an SAE, the investigator should default to reporting the AE as an SAE.

There are special circumstances in which an SAE reporting form is used to communicate important clinical trial safety observations that may not constitute an SAE.

1) Pregnancy: Although pregnancy is not considered an SAE and is instead a normal human experience, all pregnancies reported in the month before or month after last G100 investigational injection must be reported to Sponsor. If enrolled onto the pembrolizumab arm, pregnancies and lactations that occur through 120 days following cessation of pembrolizumab or 30 days if the subject initiates new anticancer therapy, whichever is earlier, must be reported by the investigator. (See Section 12.7)
2) Overdose: As defined for this study, an overdose is defined as the accidental or intentional administration of any dose of the G100 product that is considered both excessive and medically important. For reporting purposes, an overdose will be considered, regardless of adverse outcome, as an important medical event. All cases of overdose must be reported immediately to the Sponsor.
3) Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor for Pembrolizumab. For this trial, an overdose will be defined as ≥1000 mg (5 times the dose) of pembrolizumab. No specific information is available on the treatment of overdose of pembrolizumab. In the event of overdose, the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

12.2 Adverse Event Severity

All AEs will be evaluated according to the NCI CTCAE v4.03 or newer (2010) http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf. For AEs not listed in this reference scale, severity will be assessed by the investigator according to the criteria in Table 5.

Table 5: Adverse Event Severity Assessment

Grade 1 (Mild)	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2 (Moderate)	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.
Grade 3 (Severe)	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living (ADL)**.
Grade 4 (Life threatening)	Life-threatening consequences; urgent intervention indicated.
Grade 5 (Death)	Death related to AE.

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Changes in the severity of an AE should be documented to enable an assessment of the duration of the event at each level of intensity. Adverse events characterized as intermittent require documentation of onset and duration of each episode.

12.3 Relationship to Investigational Drug

The investigator will report his or her interpretation of the relationship between an AE and the study treatment on the basis of their clinical judgment and the definitions in Table 6.

Table 6: Assessment of Relationship

Definitely related	AEs clearly attributable to study regimen administration
Probably related	AEs for which there is a reasonable possibility of causal association to study regimen
Possibly related	AEs for which there is confounding by comorbidities, medications or other considerations but for which it is not unreasonable that the AE may have been caused by study regimen. Note that it is not appropriate to invoke “you can’t rule it out.”
Not related	AEs that are considered clearly not causally related to study regimen, or for which there is a clear alternative explanation

AE = adverse event

If there is any question whether or not an AE is possibly, probably or definitely related, the investigator should default to conservatism in categorization. Similarly, the investigator should default to conservatism by calling an AE an SAE if there is doubt regarding the serious nature of an AE, if it meets one of the definitions described above.

12.4 Adverse Event Collection Period

All enrolled patients in Parts 1, 2, 3, 4, and 5 will have periodic assessment of clinical and laboratory AEs. All AEs will be collected at the EOS / Post-Vaccination Safety Visit and for 30 days after the last dose of study agent whichever is longer (if receiving pembrolizumab, see below). Thereafter, any SAE that comes to the attention of the site staff that may be causally related to study drug (i.e., the event is considered possibly, probably or definitely caused by the drug) must be reported to Sponsor regardless of time elapsed.

Patients who withdraw from the study prior to the EOS Visit should be followed for new AEs for at least 30 days after their last dose of G100. If the subject withdraws prematurely and is unwilling to continue safety follow-up, any subsequent SAE that may be causally related to G100 that comes to the attention of the site staff should be reported to Immune Design.

For patients receiving pembrolizumab, any serious AE, or follow up to a serious AE, including death due to any cause other than progression of the cancer under study that occurs through 90 days following cessation of treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, must be reported within 24 hours to the Sponsor either by electronic media or paper. In addition, any event of clinical interest (ECI) experienced through 30 days following cessation of treatment should be reported within 24 hours to the Sponsor.

For Pembrolizumab:

- All AEs or ECIs (Events of Clinical Interest) from the time of treatment/ allocation through 30 days following cessation of study treatment must be reported by the investigator.
- All AEs meeting serious criteria, from the time of treatment/ allocation through 90 days following cessation of study treatment, or 30 days following cessation of study treatment if the participant initiates new anticancer therapy, whichever is earlier must be reported by the investigator
- All pregnancies and exposure during breastfeeding, from the time of treatment/ allocation through 120 days following cessation of study treatment, or 30 days following cessation of study treatment if the participant initiates new anticancer therapy must be reported by the investigator.

- Additionally, any SAE brought to the attention of an investigator at any time outside of the time period specified above must be reported immediately to the Sponsor if the event is considered to be drug-related.

12.5 Adverse Event Reporting

At each study visit (including unscheduled visits), the investigator, or designee, will determine whether any AEs have occurred. AEs will be reported in the patient's medical record and on the AE case report form (CRF) page and each will be classified according to the criteria in Section 12.1 and Section 12.2. If known, the diagnosis should be recorded, in preference to the listing of individual signs and symptoms. Any pre-existing conditions that are detected as part of the initial screening procedures will need to be reported in the medical history and not as an AE. However, pre-existing conditions that worsen enrollment should be reported as an AE.

Adverse events will be reported to FDA in accordance with the requirements outlined in 21 CFR §312.32. Deaths due to cancer progression will not be reported as expedited events. The Investigator will continue to monitor the patient until any new, changed, or worsened AE resolves, returns to baseline, or until the Investigator and Immune Design agree that follow-up is no longer necessary. AEs must be followed until resolution whenever possible.

12.6 Serious Adverse Event Reporting

If an SAE occurs, Immune Design must be notified within 24 hours of awareness of the event by the investigator. If the SAE is fatal or life-threatening, Immune Design must be notified immediately, irrespective of the extent of available AE information. In the rare event that the investigator or designee does not become aware of the occurrence of a SAE immediately, the investigator or designee must report the event within 24 hours of their awareness and document the time of when his/her first awareness occurred. For all SAEs, the investigator or designee is obligated to pursue and provide information to Immune Design in accordance with the timeframes for reporting specified above. In addition, an investigator may be requested to obtain specific additional follow-up information in an expedited fashion. This information may be more detailed than that captured on the AE CRF. In general, this will include a description of the AE in sufficient detail to allow for a complete medical assessment of the case and independent determination of causality.

New SAEs experienced by patients during the Screening Period (pre-study treatment) will be reported to Immune Design if the events are considered related to study procedures. New SAEs determined to be related to study tests or procedures (not including cancer-related events) and any hospitalizations that are experienced by patients from the time of signing the informed consent until Day 0 (start of G100 treatment) will be noted on the SAE form and CRF. From Day 0 until the EOS / Post Vaccination Safety Visit, any new SAE will be noted on the SAE form and CRF. After the EOS / Post Vaccination Safety Visit, any SAE that comes to the

attention of the site staff that may be causally related to study drug (i.e., there is a reasonable possibility that the event may have been caused by the drug) will be reported to Immune Design.

For patients receiving pembrolizumab, any SAE, or follow up to an SAE, including death due to any cause other than progression of the cancer under study that occurs through 90 days following cessation of treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, must be reported within 24 hours to the Sponsor either by electronic media or paper.

SAEs will be monitored until they have resolved, returned to baseline, or they are not clinically significant, stable, or do not require additional follow-up, as judged by the Investigator and Immune Design.

The SAE contact and reporting information are provided in Appendix E.

12.7 Pregnancy

Sexually active men and FCBP must use an effective method of birth control during the course of the study, in a manner such that risk of failure is minimized. Before enrolling FCBP in this clinical trial, all FCBP must be advised of the importance of avoiding pregnancy during trial participation and the potential risk factors for an unintentional pregnancy. All patients (men and women) must sign an informed consent form documenting this discussion. (See conception warnings for pembrolizumab, Sections 8.1.9 – 8.1.11)

All FCBP must have a negative pregnancy test within 7 days for Parts 1, 2, or 3 and within 72 hour for Parts 4 and 5 prior to the study regimen initiation. If the pregnancy test is positive, the subject must not be enrolled in the study.

In addition, all FCBP should be instructed to contact the investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period) at any time during study participation.

If following initiation of study dosing, it is subsequently discovered that a trial subject is pregnant or may have been pregnant within one month before or after study regimens will be permanently discontinued and the patient will be followed as possible by the investigator or designated health care professional to determine pregnancy outcomes for both mother and baby. If a male patient enrolled in study has a female sexual partner who becomes pregnant after initiation of study, then the study subject should be asked permission for the investigator (or designated health care professional) to approach his partner for permission to follow-up with the pregnant partner to determine outcomes for both mother and baby.

For patients receiving pembrolizumab, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a subject (spontaneously reported to them) that occurs during the trial or within 120 days of completing the trial or 30 days following cessation of

treatment if the subject initiates new anticancer therapy, whichever is earlier. All subjects who become pregnant must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported. Such events must be reported within 24 hours to the Sponsor either by electronic media or paper.

12.8 Events of Clinical Interest /Medical Events of Interest

Selected non-serious and serious AEs that may be associated with G100 or pembrolizumab are also known as ECI / MEOI and must be reported to the Sponsor.

For the time period beginning when the consent form is signed until treatment allocation/randomization, any ECI, or follow up to an ECI, that occurs to any subject must be reported within 24 hours to the Sponsor if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation/randomization through 30 days following cessation of treatment, any ECI, or follow up to an ECI, whether or not related to the Sponsor's product, must be reported within 24 hours to the Sponsor, either by electronic media or paper. Electronic reporting procedures can be found in the electronic data capture (EDC) data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

For G100, ECI / MEOIs may be added to the Investigator Brochure as clinical experience with G100 increases and will be used to capture additional information on these events of interest.

For Pembrolizumab, Events of clinical interest for this trial include:

1) an overdose of Sponsor's product, as defined in Section 12.1 - Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor, that is not associated with clinical symptoms or abnormal laboratory results.
2) an elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

   *Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The trial site guidance for assessment and

follow up of these criteria can be made available. It may also be appropriate to conduct additional evaluation for an underlying etiology in the setting of abnormalities of liver blood tests including AST, ALT, bilirubin, and alkaline phosphatase that do not meet the criteria noted above. In these cases, the decision to proceed with additional evaluation will be made through consultation between the study investigators and the Sponsor Clinical Director. However, abnormalities of liver blood tests that do not meet the criteria noted above are not ECIs for this trial.

12.9 Data Monitoring Committee

A DMC will be established to provide independent review of safety data and to assure that the risk to patients is minimized. The DMC will be composed of 2 oncologists. The DMC will review all related and unexpected (i.e., expedited) SAEs and DLTs as individual cases arise and will perform periodic reviews of all AEs, laboratory results, and patient discontinuations.

Safety data will be collected and monitored on an ongoing basis throughout the study. Immune Design will summarize all available safety and laboratory data on all patients at regular intervals (at least every 3 months) during the study, as specified in the DMC charter. Immune Design and the DMC will conduct separate reviews of these data for any safety trends that might impact the treatment of patients. Safety issues that arise out of such ongoing reviews could lead to modifications of the treatment program.

The DMC may convene on an ad-hoc basis to evaluate any urgent safety issues. Upon request, the DMC will be granted access to any available data pertinent to the issues under evaluation. Immune Design will provide cumulative data, as specified in the DMC charter, to the DMC for review, including clinical laboratory values, AEs, SAEs, medical events of interest, and patient discontinuations.

13.0 PROTOCOL DEVIATIONS

A protocol deviation is any change, divergence or departure from the study design or procedures defined in the protocol.

Important protocol deviations are a subset of protocol deviations that might significantly affect the completeness, accuracy, and/or reliability of the study data or that might significantly affect a subject's rights, safety or wellbeing such as enrolling subjects in violation of key eligibility criteria or failing to collect data necessary to interpret primary endpoints, the PI prescribing or administering the wrong dose, or the study subject being scheduled to return for follow-up intervention outside the protocol-dictated window as a convenience to the patient or study staff.

There will be unforeseen circumstances that are beyond the investigator's control (e.g., a patient not attending a scheduled follow-up visit). Prior approval will not be granted in these situations, but the investigator should report these events upon determining that a deviation has occurred.

The investigator is responsible for complying with and adhering to IRB procedures for reporting protocol deviations and violations. All protocol deviations should be documented and forwarded to Immune Design or its authorized representative.

Protocol deviations will be collected during the study, and reported by Immune Design or its authorized representative to the FDA and IRBs yearly in the annual report. Participating investigators will receive regular updates regarding their site's deviations.

14.0 STATISTICAL CONSIDERATIONS

14.1 Study Endpoints

The study endpoints include both clinical safety and immunogenicity. Where possible, parameters will be quantified for direct comparisons among the five study groups; however, due to the small sample size and the primary objective to evaluate vaccine safety and immunogenicity, all analyses will be exploratory in nature.

14.2 Sample Size

In Part 1, Part 2, and Part 3, up to 65 evaluable patients will be enrolled. In Part 1, Dose Escalation, a total of two pre-defined dose levels will be studied (see Section 4.1). For cohort 1, each patient will receive a total of 6 planned injections and up to 3 additional injections depending on the treated tumor response. A conventional "3+3" design will be used during Part 1 for dose assessment and escalation. The first cohort of 3 patients will be enrolled at the lowest dose level. If 0/3 patients experience DLT, the next cohort will be enrolled into the next higher dose. If 1/3 patients experience DLT, the current dose level will be expanded to a total of 6 patients. If 1/6 patients experience DLT, dose escalation may occur. If 2 or more patients in dose cohort experience DLT at any time, the MTD has been exceeded. The MTD or maximum safe dose (if at the highest dose level) is defined as the highest dose in which less than one third of patients in the cohort experienced a DLT.

Once the MTD or maximum safe dose examined in the study has been determined, Part 2 will begin. In the optional Large Tumor group, up to 4 patients will be treated and safety will be examined.

In Part 2, Patient Expansion, up to 24 patients (12 per treatment group) will be randomly assigned to receive treatment with either G100 alone or the sequential administration of G100 and pembrolizumab. The dose of G100 will be the MTD / maximum safe dose determined in Part 1. This portion of the study will provide additional safety, immunogenicity and early efficacy data of G100 at the MTD / maximum safe dose and provide initial data on the sequential administration of G100 and pembrolizumab. This analysis is designed to be exploratory but will provide important data to guide further development. While the sample size is not based on formal power calculations, it is expected to provide adequate preliminary data to inform subsequent trials and to reject an indication should no clinical benefit occur. For example, if the

true ORR is 20%, we will conclude futility with a 6.9% error rate if 0 response is observed in 12 patients. In that case, the Sponsor would terminate that study arm for development.

In Part 3, G100 Expansion of 20 μg Dose Group, up to 25 patients will be enrolled and treated with intratumoral G100 at 20 μg/dose following radiation therapy. The purpose of this group would be to explore the safety and potential clinical responses at the higher dose level. The number of patients was chosen to provide a similar cohort treated with G100 alone in Parts 1 and 2 for descriptive comparison. In those portions of the study, 18 patients (3 at 5 μg/dose; 15 at 10 μg/dose) may receive intratumoral G100 alone following radiation therapy.

In Part 4, G100 Plus Pembrolizumab, at least 22 evaluable patients will be enrolled and treated as part of a Dose Escalation group or a Patient Expansion group with intratumoral G100 in combination with pembrolizumab. The purpose of this treatment regimen will be to explore the safety and preliminary clinical efficacy and biomarker changes of patients treated with G100 at a dose of 20 μg/lesion injected in single or multiple lesions. The administered dose of G100 will depend on the number of potentially injectable lesions and whether the MTD has been established during Dose Escalation. One or more lesions will be targeted for injection and each lesion would receive 20μg of G100 intratumorally (or 10 μg G100 if 20 μg/lesion in a single lesion is not tolerated) as long as the total number of treated tumor lesions and total systemic dose does not exceed the MTD (if established) or 80 μg total dose (20 μg injected in 4 lesions). This analysis is designed to be exploratory and will evaluate safety, clinical outcome and exploratory biomarkers to guide further clinical development. Clinical efficacy including ORR and DOR will be evaluated in relapsed or refractory FL patients who received ≥3 prior systemic therapies.

For this analysis, 22 efficacy evaluable patients will be required. Efficacy evaluable patients are patients who received at least 3 doses of G100 at 20 μg/lesion and at least 1 dose of pembrolizumab, had at least one post baseline tumor assessment, and had no major protocol deviations that impact the efficacy of the study treatment or the assessment of response. Patients who received G100 20μg/lesion during Dose Escalation in Part 4 may be included in clinical response analysis. With a target ORR of 40%, if ≤5 responders are observed among 22 evaluable patients, we will conclude futility with 7.2% error rate. The Sponsor will use this analysis to decide whether to continue further development of this regimen. Early acceptance of treatment at the end of the 22 evaluable patients is not permitted. If the true ORR for this group is 20% and 20% ORR is considered not clinically meaningful, the probability of observing ≤5/22 responders and stopping the study is 73.3%.

In Part 5, G100 Plus rituximab, after Dose Escalation has been completed, patients will be treated with intratumoral G100 at the recommended dose level in combination with rituximab. The purpose of this Patient Expansion group will be to explore the safety and clinical outcome of patients treated at a biologically active and safe G100 dose level administered into single tumor lesion in combination with rituximab. This analysis is designed to be exploratory and will evaluate safety, clinical outcome and exploratory biomarkers.

An exploratory analysis will be performed on 20 efficacy evaluable relapsed or refractory FL patients and will include analyses of the frequency and duration of CRs. Efficacy evaluable patients are patients who received at least 3 injections of G100 at the recommended dose and 3 doses of rituximab, had at least one post baseline tumor assessment, and had no major protocol deviations that impact the efficacy of the study treatment or the assessment of response. Five or more CRs in 20 patients treated with G100 plus rituximab will signal an improvement of CR rate over 10%. For reference, the probability of observing ≤4 CRs in 20 patients is 5.1% if the true CR rate is 40% (the targeted CR rate). Patients who received G100 at the recommended dose during Dose Escalation in Part 5 may be included in clinical response analysis. With 20 efficacy evaluable patients, and a historical CR rate of 10%, assuming a true CR rate of 32% in the G100 plus rituximab, this subgroup analysis has 82% power to detect a signal of an improvement in CR from 10% at a 1-sided alpha of 0.05.

14.3 Definition and Analysis of Primary and Secondary Endpoints

14.3.1 Safety

All enrolled patients who receive at least one injection of study drug or undergo a study-related procedure will be included in the safety analysis. The highest toxicity grades per patient will be tabulated for AEs and laboratory measurements, and the number and percent of patients reporting AEs will be quantified. Listings will be required for all on-study deaths, SAEs, DLT, and AEs that lead to withdrawal from study. Narratives for all SAEs and deaths on-study will be required.

14.3.2 Immunogenicity

All enrolled patients who receive at least one injection of study drug and have an immunogenicity sample will be included in the exploratory immunogenicity analysis. Tabulation, summarization and descriptive statistics will be performed describing the baseline and post G100 peripheral blood and tumor lymphocyte subsets. Analyses will be performed to determine if there are any statistically significant changes from baseline values. Association between pre-existing and post treatment immunogenicity biomarkers (e.g., baseline TLR4 expression) and clinical outcome will be explored.

14.3.3 Tumor Response

Anti-tumor activity as defined by irRC using bi-dimensional tumor measurement will be reported. The primary analysis will be based on investigator's assessment. Independent radiology review will be supportive. As a comparison, clinical responses will also be examined by the International Working Group and by Lugano criteria for lymphomas (Cheson 2014)). Progression-free survival and/or TTP will be evaluated and will be plotted as a Kaplan-Meier curve. Disease control rate (CR, PR, and SD) and ORR (or CR + PR) will be reported. As exploratory analyses, time to next treatment, overall survival (OS), and Follicular Lymphoma

International Prognostic Index (FLIPI) scores may be examined (Frederico 2009; Solar-Celigny 2004).

Independent radiology review of tumor assessments

The Sponsor may request at any time that radiographic images of tumor assessments for all or select patients be submitted to central storage facility for the purpose of an independent radiology assessment of tumor responses. All patients starting with protocol version 4B will be required to provide an informed consent for such central storage and independent radiology review prior to study treatment.

14.3.4 Pharmacokinetic and Pharmacodynamic

All enrolled patients who receive at least one injection of study drug and have a pharmacokinetics/ pharmacodynamics sample will be included in the exploratory pharmacokinetics/ pharmacodynamics analysis. Tabulation and summarization will be performed to describe the baseline and post G100 results by timepoint. Data permitting, statistical analysis will be performed to characterize the pharmacokinetics/ pharmacodynamics profile of G100.

14.4 Interim Analysis

An analysis will be performed once the MTD or maximum safe dose examined in the study is established in Part 1 Dose Escalation. All data from the relevant subjects through Day 77 EOS evaluation will be monitored, cleaned, and reconciled to create an interim analysis SAS dataset. Part 2 Patient Expansion is designed to be exploratory. Data will be assessed for each patient as it becomes available. Based on the statistical considerations described above, an interim analysis of responses observed in the first 12 patients in Part 2 will be performed to determine whether or not the study should continue or be terminated early.

15.0 DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

Information on the CRF will be verifiable to source documents. Other records that will be considered source documents include, but are not limited to, hospital records, clinic charts, radiographic data, laboratory reports and pathology reports. Copies of source documents that should be sent to Immune Design or its authorized representative, if requested, include hospital or clinic records, radiographic data, laboratory reports, pathology reports, operative summaries and discharge reports. Other source documents may include hospital discharge summaries, if available, or information in lieu of a discharge summary, such as discharge orders or progress notes; any relevant notes pertaining to AEs, additional surgical procedures, or deaths and autopsy reports. Any documentation sent from the site should be redacted to exclude patient identifying information.

16.0 DATA QUALITY ASSURANCE

Immune Design performs quality assurance checks on all clinical studies that it sponsors. Before the enrollment of any patient in this study, Immune Design or its authorized representative and the investigator will review the Protocol, the Investigator Brochure, the CRFs and instructions for completing them, the procedure for obtaining informed consent and the procedure for reporting AEs/SAEs. Site monitoring visits will be performed by Immune Design or its authorized representative on a regular basis pursuant to its Monitoring Plan. During these visits, information recorded on the CRFs will be verified against source documents. After the CRFs are received by Immune Design or its authorized representative, they will be reviewed for safety information, legibility, completeness, accuracy and logical consistency. The data will be entered into a database. Additional computer programs that identify selected Protocol deviations, out-of-range data, and other data errors may be used to help monitor the study. As necessary, requests for clarification or correction will be sent to the investigator.

Independent auditors from Immune Design or its authorized representative will be allowed by the investigator to audit data and records for GCP compliance In addition, inspections may be conducted by appropriate regulatory authorities.

Data entered in the CRF will be source verified for accuracy and completeness. In addition, protocol compliance and compliance with FDA regulations and International Conference on Harmonization (ICH) Good Laboratory Practices (GCP) guidelines will be verified.

17.0 ETHICS

17.1 Independent Ethics Committee (IEC) or Institutional Review Board (IRB)

The Protocol and the ICFs must have the approval of a properly constituted IRB responsible for approving clinical studies. The signed IRB approval letter must specify the date of Protocol and ICF approval and identify the documents approved including the investigator's name, the Protocol version, date and title. Any patient materials or advertisements used to recruit volunteers should also be reviewed and approved by the IRB. Clinical supplies will not be shipped until a signed approval letter from the IRB has been received and a contractual agreement has been signed by Immune Design or its authorized representative and the clinical site.

17.2 Ethical Conduct of the Study

All investigators on the protocol must have received formal training in the ethical conduct of human research. The study will be conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki. All CRFs, compliance with the protocol, compliance with GCP, and compliance with the FDA's Code of Federal Regulations (21 CFR, as applicable) and ICH GCP will be monitored by an independent monitor routinely at each institution

participating in this trial. This process, as well as the process for the documentation of the monitoring, will be documented in detail in the Clinical Monitoring Plan.

17.3 Patient Information and Consent

Written informed consent must be obtained from the patient prior to performing any study-related procedures, including Screening assessments. The investigator or investigator's designee will provide background information on the study, including the benefits and risks of the investigative regimen. The investigator or investigator's designee will also encourage the prospective patient to ask questions about the study and will provide the prospective patient with sufficient opportunity to consider whether or not to participate.

Original signed ICFs must be filed in the patient records at the site. A copy of the signed consent must also be provided to the patient.

The patient ICF template that has been provided for this study may be revised by an investigator or an IRB based on the institution's requirements. However, all changes requested by an investigator or an IRB, even those that are not substantial and/or do not affect the rights, safety or welfare of a patient, must be approved by Immune Design. If Immune Design determines that the revisions are substantial and/or affect the rights, safety or welfare of a patient, the ICF must be reviewed and approved by both Immune Design and local IRB before the ICF can be utilized.

17.4 Patient Confidentiality

Patient names shall not be revealed to Immune Design or its authorized representative. Only the patient identifier will be recorded in the CRF, and if the patient's name appears on any other document, it must be redacted and replaced with the patient identifier before a copy of the document is supplied to Immune Design or its authorized representatives. Study findings stored on a computer will be stored in accordance with local data protection laws. In the event of accidental communication of such information, immediate steps to redact the information from all study files will be implemented, with appropriate documentation in the patient study file.

18.0 DATA HANDLING AND RECORD KEEPING

18.1 Source Documents

Information on the CRF should be verifiable to source documents. Other records that will be considered source documents include, but are not limited to, hospital records, clinic charts, radiographic data, laboratory reports and pathology reports. Copies of source documents that should be sent to Immune Design or its authorized representative, if requested, include operative summaries and discharge reports. Other source documents may include hospital discharge summaries, if available, or information in lieu of a discharge summary, such as discharge orders or progress notes; any relevant notes pertaining to AEs, additional surgical procedures, or deaths and autopsy reports.

18.2 Case Report Forms

The investigator is responsible for maintaining adequate and accurate medical records from which information will be transferred into the study database. The CRFs should be completed by the investigator or delegated personnel. In the context of this protocol, CRF will refer to either paper form or electronic data or both.

CRFs will be provided to the Sponsor for each patient. No data will be recorded directly on the CRF without source documentation. Data/corrections entered will be signed or initialed by the study personnel undertaking that procedure.

For corrections that become necessary after in-house data verification procedures, Data Clarification Forms (DCFs) will be used.

Only complete CRFs, reviewed and signed by the investigator indicating his/her assurance of the accuracy of all recorded data, will be accepted. It is expected that the Investigator and his/her staff will cooperate with the monitoring team and provide any missing data or data clarifications in a timely manner.

18.3 Record Retention

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with Immune Design. It is the responsibility of Immune Design to inform the Investigator/ institution as to when these documents no longer need to be retained.

Essential documents are those documents, which individually and collectively, permit evaluation of the conduct of a trial and the quality of the data produced. These documents serve to demonstrate the compliance of the Investigator, Sponsor, and monitor with the standards of GCP and with all applicable regulatory requirements. Any or all of the documents should be available for audit by the Sponsor's auditor and inspection by the regulatory authorities.

Immune Design or its authorized representative will maintain all records related to this investigational study, according to 21 CFR §312.32 and any other local regulatory requirements. In addition, paragraph 4.9.5 of the ICH E6 (GCP) guideline applies.

19.0 FINANCING AND COMPENSATION

The financial aspects of the trial are documented in an agreement between the Sponsor and the investigator/institution. Details regarding Sponsor-provided insurance/indemnity, subject compensation and costs to patients are documented in an agreement between the Sponsor and the

investigator/the institution. A summary of this information for the subject is also provided in the informed consent.

20.0 PROTOCOL AMENDMENTS

Any amendment to the study protocol must be approved by Immune Design. A protocol amendment may not be implemented until after it has been submitted to the FDA and approved by the IRB, unless immediate implementation of the change is necessary for patient safety. In this case, the protocol change must be documented in an amendment and reported to the IRB within five working days. Once a protocol amendment has received approval from Immune Design, the investigator will submit it to the IRB for written approval. The approval letter, signed by the IRB Chair, must refer specifically to the investigator, the protocol title, the protocol amendment number, and the date of the protocol amendment. Immune Design is responsible for submitting all protocol amendments to the FDA.

21.0 PUBLICATION POLICY

It is expected that the results of this study will be published in a peer-reviewed journal. A publication plan for the primary results will be discussed with the investigators and established before the start of the trial. Any manuscripts reporting the results of this clinical trial must be provided to the Sponsor by the Principal Investigator for review and comment prior to submission for publication. Immune Design will have 30 days from the date of receipt for review, and shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that the Sponsor's confidential and proprietary data, in addition to the Sponsor's intellectual property rights, are protected. Abstracts, press releases, and other media presentations must also be forwarded to the Sponsor prior to release. No publication, manuscript, or other form of public disclosure shall contain any of the Sponsor's confidential/ proprietary information. Co-authorship of subsequent publications with Immune Design personnel will be discussed and mutually agreed upon before submission of a manuscript to a publisher.

APPENDIX A: ECOG Performance Status

ECOG PERFORMANCE STATUS*	
Grade	**Definition**
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

*As published in Oken et al. (Oken 1982)

APPENDIX B: IMMUNE-RELATED RESPONSE CRITERIA (irRC)

Immune based therapies pose a challenge for response measurements because the inflammatory response of an immune reaction can mimic disease progression. For this reason, the irRC was created to help evaluate and prevent the incorrect assignment of progressive disease to these situations, primarily by requiring confirmation of PD and by not immediately concluding that new lesions represent PD. The irRC was originally based on WHO bi-dimensional measurements and will be used for this study. A RECIST based irRC has been evaluated and commonly used for solid cancers. At this time, a similar NHL-specific irRC does not exist. For this reason, the irRC based on bi-dimensional measurements as well as the more commonly used International Working Group Criteria for Lymphomas will both be examined to determine response in this study.

The irRC was originally developed to systematically characterize additional patterns of response in patients with advanced melanoma. Underlying WHO criteria were evolved into irRC (Wolchok 2009). The definitions of the irRC and guidelines on how they can be used in clinical practice are detailed below.

Anti-tumor response based on total measurable tumor burden: For the irRC, only index and measurable new lesions are taken into account (in contrast to conventional WHO criteria, which do not require the measurement of new lesions, nor do they include new lesion measurements in the characterization of evolving tumor burden). At the baseline tumor assessment, the sum of the products of the two largest perpendicular diameters (SPD) of all index lesions is calculated. At each subsequent tumor assessment, the SPD of the index lesions and of new, measurable lesions are added together to provide the total tumor burden:

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

The WHO criteria were developed for solid cancer indications and have not been adapted yet for lymphomas. In WHO solid cancer criteria, abnormal new lesions are counted if $\geq 5 \times 5$ mm and up to 5 new lesions per organ: 5 new cutaneous lesions and 10 visceral lesions would be evaluated.

For the purpose of this trial, the criteria for minimal lymph node / lymphoma tumor dimensions for determining an abnormal lesion will be >1.5cm in the longest axis, or if 1.1 to 1.5 cm in longest axis, the short axis must be 1 cm or more. This follows that of standard international working group criteria for lymphomas. A minimum of a 0.5cm increase will be required for a previously normal small node (i.e., <1cm in short axis) to be re-classified as a new lesion. In addition, to allow a comparison to the Cheson International Working Group Criteria, up to 6 dominant nodes / masses will be evaluated and followed for determination of response instead of the 5 lesions maximum for irRC (5 lesions per organ, 10 visceral lesions and 5 cutaneous).

A comparison of the use of SPD in WHO criteria versus the use of tumor burden in irRC is presented below. **Comparison between WHO Criteria and the irRC**

	WHO	irRC
New, measurable lesion (i.e., ≥5 x 5 mm)	Always represent PD	Incorporated into tumor burden
New, nonmeasurable lesions (i.e., <5 x 5 mm)	Always represent PD	Do not define progression (but preclude irCR)
Non-index lesions	Changes contribute to defining best objective response of CR, PR, SD, and PD	Contribute to defining irCR (complete disappearance required)
CR	Disappearance of all lesions in two consecutive observations not less than 4 wk apart	Disappearance of all lesions in two consecutive observations not less than 4 wk apart
PR	≥50 percent decrease in SPD of all index lesions compared with baseline in two observations at least 4 wk apart, in absence of new lesions or unequivocal progression of non-index lesions	≥50 percent decrease in tumor burden compared with baseline in two observations at least 4 wk apart
SD	50 percent decrease in SPD compared with baseline cannot be established nor 25 percent increase compared with nadir, in absence of new lesions or unequivocal progression of non-index lesions	50 percent decrease in tumor burden compared with baseline cannot be established nor 25 percent increase compared with nadir
PD	At least 25 percent increase in SPD compared with nadir and/or unequivocal progression of non-index lesions and/or appearance of new lesions (at any single time point)	At least 25 percent increase in tumor burden compared with nadir (at any single time point) in two consecutive observations at least 4 wk apart

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

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

- Immune-related complete response (irCR), complete disappearance of all lesions (whether measurable or not, and no new lesions)
  - confirmation by a repeat, consecutive assessment no less than 4 wk from the date first documented
- Immune-related partial response (irPR), decrease in tumor burden ≥50% relative to baseline confirmed by a consecutive assessment at least 4 wk after first documentation
- Immune-related stable disease (irSD), not meeting criteria for irCR or irPR, in absence of irPD
- Immune-related progressive disease (irPD), increase in tumor burden ≥25% relative to nadir (minimum recorded tumor burden)
  - confirmation by a repeat, consecutive assessment no less than 4 wk from the date first documented

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

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

APPENDIX C: REVISED INTERNATIONAL WORKING GROUP RESPONSE CRITERIA FOR MALIGNANT LYMPHOMAS.

At this time, an NHL-specific irRC does not exist. For this reason, the irRC based on bi-dimensional measurements as well as the more commonly used International Working Group Criteria for Lymphomas (Cheson 2007) will both be examined to determine response in this study.

Details on the International Working Group Criteria for Lymphomas can be found in Cheson, et al., Journal of Clinical Oncology, 2007.

Table 2. Response Definitions for Clinical Trials

Response	Definition	Nodal Masses	Spleen, Liver	Bone Marrow
CR	Disappearance of all evidence of disease	(a) FDG-avid or PET positive prior to therapy; mass of any size permitted if PET negative (b) Variably FDG-avid or PET negative; regression to normal size on CT	Not palpable, nodules disappeared	Infiltrate cleared on repeat biopsy; if indeterminate by morphology, immunohistochemistry should be negative
PR	Regression of measuable disease and no new sites	≥ 50% decrease in SPD of up to 6 largest dominant masses; no increase in size of other nodes (a) FDG-avid or PET positive prior to therapy; one or more PET positive at previously involved site (b) Variably FDG-avid or PET negative; regression on CT	≥ 50% decrease in SPD of nodules (for single nodule in greatest transverse diameter); no increase in size of liver or spleen	Irrelevant if positive prior to therapy; cell type should be specified
SD	Failure to attain CR/PR or PD	(a) FDG-avid or PET positive prior to therapy; PET positive at prior sites of disease and no new sites on CT or PET (b) Variably FDG-avid or PET negative; no change in size of previous lesions on CT		
Relapsed disease or PD	Any new lesion or increase by ≥ 50% of previously involved sites from nadir	Appearance of a new lesion(s) > 1.5 cm in any axis, ≥ 50% increase in SPD of more than one node, or ≥ 50% increase in longest diameter of a previously identifed node > 1 cm in short axis Lesions PET positive if FDG-avid lymphoma or PET positive prior to therapy	> 50% increase from nadir in the SPD of any previous lesions	New or recurrent involvement

Abbreviations: CR, complete remission; FDG, [^{18}F]fluorodeoxyglucose; PET, positron emission tomography; CT, computed tomography; PR, partial remission; SPD, sum of the product of the diameters; SD, stable disease; PD, progressive disease.

APPENDIX D: FOLLICULAR LYMPHOMA INTERNATIONAL PROGNOSTIC INDEX (FLIPI)

FLIPI was developed to help evaluate and choose treatments for patients with follicular lymphomas. FLIPI was originally described in 2004 (Solal-Celigny 2004). Characteristics at diagnosis were collected from 4167 patients with follicular lymphoma diagnosed between 1985 and 1992. A proposed index was then tested on a patient set and five adverse prognostic factors were selected: age (>60 vs. ≤60 years old), Ann Arbor stage (III/IV vs. I/II), hemoglobin (<120g/L vs. ≥120g/L), number of nodal sites (>4 vs. ≤4) and serum lactate dehydrogenase (LDH; > normal vs. ≤normal). A score is assigned based on the number of risk factors and place patients into low, intermediate or high risk groups that correlate with overall survival differences. Because FLIPI was based on patients treated prior to chemoimmunotherapy, a prospective study FLIPI2 study was conducted with n=1093 subjects (Frederico 2009). Three prognostic factors were removed (stage, number of nodal sites, and LDH) and three were added (Beta-2-microglobulin, largest involved node >6cm, and bone marrow involvement. Differences in risk factor scores correlate with progression free survival differences. FLIPI2 has not yet been widely used in studies.

For this trial, data will be collected to examine both FLIPI1 (original) and FLIPI2 as exploratory analyses of enrolled patients.

Adverse Factor	FLIPI 1	FLIPI 2
Age	>=60 years	>60 years
Ann Arbor Stage	Stage III/IV	NA
Hemoglobin level	<120 g/L	<120 g/L
Serum LDH level	>ULN	NA
Number of nodal sites	>4	NA
Bone marrow involvement	NA	+
Beta-2-microglobulin	NA	>ULN
LoDLIN	NA	>6cm

Outcome Based on FLIPI 1 (original Solal-Celigny 2004)				
Risk Group	**# Risk factors**	**Percentage of patients**	**5-year OS rate**	**10-year OS rate**
Low	0-1	36%	91%	71%
Intermediate	2	37%	78%	51%
High	>=3	27%	53%	36%

Outcome Based on FLIPI 2 (Federico 2009)				
Risk Group	**# Risk factors**	**Percentage of patients**	**3-year PFS rate**	**5-year PFS rate**
Low	0	20%	91%	80%
Intermediate	1-2	53%	69%	51%
High	3-5	27%	51%	19%

APPENDIX E: SERIOUS ADVERSE EVENT CONTACT INFORMATION

STUDY CONTACT FOR REPORTING SERIOUS ADVERSE EVENTS	
Everest Clinical Research Inc.	
Telephone:	+1-905-752-5219 (office) or +1-416-997-0778 (mobile)
Fax:	+1-877-327-7733
Email:	SAE forms to datafax@ecrscorp.com Supplemental information to everestsafety@ecrscorp.com

APPENDIX F: CONTRACEPTION

Acceptable contraception used in this study is described in Section 8.1.9. For reference the definitions and recommended contraception agents are further described here.

(Reference: Clinical Trial Facilitation Group, CTFG, "Recommendations related to contraception and pregnancy testing in clinical trials", 15Sept2014, www.hma.eu).

For Women:

As noted in Section 8.1.9, non-pregnant, non-breast-feeding women may only be enrolled if they are willing to use 2 methods of birth control or are considered highly unlikely to conceive. Acceptable combinations of birth control are described in Section 8.1.9. Highly unlikely to conceive is defined as 1) surgically sterilized, or 2) postmenopausal (a woman who is ≥45 years of age and has not had menses for greater than 1 year will be considered postmenopausal), or 3) not heterosexually active for the duration of the study. Abstinence (#3) is only acceptable as "true abstinence" when it is in line with the preferred and usual lifestyle of the patient and not a periodic occurrence.

Birth Control Methods Which May Be Considered As "Highly Effective"

For the purpose of this guidance, methods that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered as highly effective birth control methods. Such methods include:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation[1]:
  - Oral
  - Intravaginal
  - Transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation[1]:
  - Oral
  - Injectable
  - Implantable [2]
  - Intrauterine device (IUD) [2]
  - Intrauterine hormone-releasing system (IUS) [2]
  - Bilateral tubal occlusion [2]
  - Vasectomized partner [2,3]
  - Sexual abstinence [4]

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[1] Hormonal contraception may be susceptible to interaction with the Investigational Medicinal Product (IMP), which may reduce the efficacy of the contraception method (see Section 4.3).

[2] Contraception methods that in the context of this guidance are considered to have low user dependency.

[3] Vasectomized partner is a highly effective birth control method provided that partner is the sole sexual partner of the FCBP trial participant and that the vasectomized partner has received medical assessment of the surgical success.

[4] In the context of this guidance sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

Acceptable Birth Control Methods Which May Not Be Considered As Highly Effective

Acceptable birth control methods that result in a failure rate of more than 1% per year include:

- Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action
- Male or female condom with or without spermicide
- Cap, diaphragm or sponge with spermicide

The combination of male condom with either cap, diaphragm or sponge with spermicide (double barrier methods) are also considered acceptable forms of contraception, but they are not individually considered highly effective birth control methods.

For Men:

As noted in Section 8.1.9, acceptable contraception for male patients with partners who are FCBP includes documented sterility such would occur following surgical sterilization (vasectomy or orchiectomy) or use of male condom. In addition, supplemental contraception with hormonal or barrier methods should be considered.

Acceptable contraception includes:

- Male condom
- Documented Sterility (example from surgical vasectomy or orchiectomy)

If a female partner is pregnant, use of a male condom is recommended.

Birth Control Methods Which Are Considered Unacceptable In Clinical Trials

Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception. Female condom and male condom should not be used together.

APPENDIX G: REFERENCES

1. Blank C, Brown I, Peterson AC, Spiotto M, Iwai Y, et al. (2004) PD-L1/B7H-1 inhibits the effector phase of tumor rejection by T cell receptor (TCR) transgenic CD8+ T cells. Cancer Res. 64(3): p. 1140-5.
2. Brody JD, Ai WZ, Czerwinski DK, Torchia JA, Levy M, et al. (2010) In situ vaccination with a TLR9 agonist induces systemic lymphoma regression: a phase I/II study. Journal of clinical oncology: official journal of the American Society of Clinical Oncology. 28:4324-32.
3. Chemnitz JM, Parry RV, Nichols KE, June CH, Riley JL. (2004) SHP-1 and SHP-2 Associate with Immunoreceptor Tyrosine-Based Switch Motif of Programmed Death 1 upon Primary Human T Cell Stimulation, but Only Receptor Ligation Prevents T Cell Activation. The Journal of Immunology. 173: 945–954.
4. Cheson BD, Pfistner B, Juweid ME, Gascoyne RD, Specht L, et al. (2007) Revised response criteria for malignant lymphoma. Journal of clinical oncology: official journal of the American Society of Clinical Oncology. 25:579-86.
5. Cheson BD, Fisher RI, Barrinbgton SF, Cavalli F, Schwartz LH, et al. (2014) Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification. Journal of Clinical Oncology. 32 (27): 3059-3067.
6. Coler RN, Bertholet S, Moutaftsi M, Guderian JA, Windish HP, et al. (2011) Development and characterization of synthetic glucopyranosyl lipid adjuvant system as a vaccine adjuvant. PloS one. 6:e16333.
7. Curran MA, Montalvo W, Yagita H, Allison JP. (2010) PD-1 and CTLA-4 combination blockade expands infiltrating T cells and reduces regulatory T and myeloid cells within B16 melanoma tumors. Proc Natl Acad Sci U S A. 107(9): p. 4275-80.
8. Disis ML. (2010) Immune Regulation of Cancer. Journal of Clinical Oncology. 28 (29):4531-4538.
9. Dudley ME, Wunderlich JE, Yang JC, Sherry RM, Topalian SL, et al.(2005) Adoptive Cell Transfer Therapy Following Non-Myeloablative but Lymphodepleting Chemotherapy for the Treatment of Patients With Refractory Metastatic Melanoma. Journal of Clinical Oncology.0732-183.
10. FDA. (2014) FDA approves Keytruda for advanced melanoma First PD-1 blocking drug to receive agency approval. US Food and Drug Administration. September 4, 2014.

11. Federico M, Bellei M, Marcheselli L, Luminari S, Lopez-Guillermo A, et al. (2009) Follicular lymphoma international prognostic index 2: a new prognostic index for follicular lymphoma developed by the international follicular lymphoma prognostic factor project. Journal of clinical oncology: official journal of the American Society of Clinical Oncology. 27:4555-62.

12. Francisco LM, Sage PT, and Sharpe AH. (2010) The PD-1 pathway in tolerance and autoimmunity. Immunological Reviews. 0105-2896.

13. Franki SN, Steward KK, Betting DJ, Kafi K, Tamada RE, Timmerman JM. (2008) Dendritic cells loaded with apoptotic antibody-coated tumor cells provide protective immunity against B-cell lymphoma in vivo. Blood.111(3):1504-11.

14. Friedberg J, Mauch P, Rimsza L, Fisher R. (2011) Non-Hodgkin's Lymphomas. In: VT D, Lawrence T, Rosenberg S, eds. Cancer, Principles and Practice of Oncology. Philadelphia: Lippincott Williams & Wilkins.

15. Greenwald RJ, Freeman GJ, and Sharpe AH. (2005) The B7 Family Revisited. Annual Reviews. 23:515–48.

16. Hirano F, Kaneko K, Tamura H, Dong H, Wang S, et al. (2005) Blockade of B7-H1 and PD-1 by monoclonal antibodies potentiates cancer therapeutic immunity. Cancer Res. 65(3): p. 1089-96.

17. Hsu FJ and Komarovskaya M. (2002) CTLA-4 blockage maximizes antitumor T-cell activation by dendritic cells presenting idiotype protein or opsonized anti-CD20 antibody-coated lymphoma cells. J Immunotherapy. 25 (6):455-68.

18. Hsu FJ, Benike C, Fagnoni F, Liles TM, Czerwinski D, et al. (1996) Vaccination of patients with B-cell lymphoma using autologous antigen-pulsed dendritic cells. Nature medicine. Jan;2(1):52-8.

19. Hsu FJ, Caspar CB, Czerwinski D, Kwak LW, Liles TM, et al. (1997) Tumor-specific idiotype vaccines in the treatment of patients with B-cell lymphoma--long-term results of a clinical trial. Blood. 89:3129-35.

20. Hunder NN, Wallen H, Cao J, Hendricks DW, Reilly JZ, et al. (2008) Treatment of metastatic melanoma with autologous CD4+ T cells against NY-ESO-1. N Engl J Med. 358(25):2698-703.

21. Kahl BS, Hong F, Williams ME, Gascoyne RD, Wagner LI, et al. (2014) Rituximab extended schedule or re-treatment trial for low-tumor burden follicular lymphoma: Eastern Cooperative Oncology Group Protocol E4402. J Clin Oncol. 32:3096-3102.

22. Kim YH, Gratzinger D, Harrison C, Brody JD, Czerwinski DK, et al. (2012) In situ vaccination against mycosis fungoides by intratumoral injection of a TLR9 agonist combined with radiation: a phase 1/2 study. Blood. 119:355-63.

23. Li J, Song W, Czerwinski DK, Varghese B, Uematsu S, et al. (2007) Lymphoma immunotherapy with CpG oligodeoxynucleotides requires TLR9 either in the host or in the tumor itself. Journal of immunology.179:2493-500.

24. Lugade AA, Moran JP, Gerber SA, Rose RC, Frelinger JG, Lord EM. (2005) Local radiation therapy of B16 melanoma tumors increases the generation of tumor antigen-specific effector cells that traffic to the tumor. Journal of immunology. 174:7516-23.

25. Manzur S, Cohen S, Haimovich J, and Hollander N. (2012) Enhanced therapeutic effect of B cell-depleting anti-CD20 antibodies upon combination with in-situ dendritic cell vaccination in advanced lymphoma. Clin. Exp. Immunol. 170 (3): 291-9.

26. Mellman I, Coukos G, and Dranoff G. (2011) Cancer immunotherapy comes of age. Nature. 480:480-9.

27. Merck. Keytruda Product Label. (2018).

28. Nomi T, Sho M, Akahori T, Hamada K, Kubo A, et al. (2007) Clinical significance and therapeutic potential of the programmed death-1 ligand/programmed death-1 pathway in human pancreatic cancer. Clin Cancer Res. 13(7): p. 2151-7.

29. Okazaki T, Maeda A, Nishimura H, Kurosaki T, Honjo T. (2001) PD-1 immunoreceptor inhibits B cell receptor-mediated signaling by recruiting src homology 2-domain-containing tyrosine phosphatase 2 to phosphotyrosine. Proc Natl Acad Sci USA. 98(24):13866-71.

30. Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, et al. (1982) Toxicity and response criteria of the Eastern Cooperative Oncology Group. American journal of clinical oncology. 5:649-55.

31. Pardoll DM. (2012) The blockade of immune checkpoints in cancer immunotherapy. Nature reviews Cancer. 12:252-64.

32. Parry RV, Chemnitz JM, Frauwirth KA, Lanfranco AR, Braunstein I, et al. (2005) CTLA-4 and PD-1 Receptors Inhibit T-Cell Activation by Distinct Mechanisms. Mol Cell Biol. 0270-7306.

33. Patel IJ, Davidson JC, Nikolic B, Salazar GM, Schwartzberg MS, et al. (2012) Consensus guidelines for periprocedural management of coagulation status and hemostasis risk in percutaneous image-guided interventions. Journal of vascular and interventional radiology: JVIR. 23:727-36.

34. Patel IJ, Davidson JC, Nikolic B, Salazar GM, Schwartzberg MS, et al. (2013) Addendum of newer anticoagulants to the SIR consensus guideline. Journal of vascular and interventional radiology: JVIR. 24:641-5.

35. Pilon-Thomas S, Mackay A, Vohra N, Mule JJ. (2010) Blockade of programmed death ligand 1 enhances the therapeutic efficacy of combination immunotherapy against melanoma. J Immunol. 184(7): p. 3442-9.

36. Riley JL. (2009) PD-1 signaling in primary T cells. Immunological Reviews. 0105-2896.

37. Rituximab [package insert]. South San Francisco: Genentech, Inc. (2010). https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/103705s5311lbl.pdf

38. Saitoh S. (2012) Toll-like Receptors and Their Regulatory Mechanisms. In: Wang, ed. Innate Immune Regulation and Cancer Imunotherapy. New York: Springer. 39-50.

39. Seo YD, Kim EY, Conrad EU, O'Malley RB, Cooper S, et al. (2017) Intratumoral injection of the toll-like receptor 4 (TLR4) agonist G100 induces a T-cell response in the soft tissue sarcoma microenvironment. Cancer Research. 77 (13) Supplement 2947.

40. Sheppard KA, Fitz LJ, Lee JM, Benander CG, Judith A, et al.(2004) PD-1 inhibits T-cell receptor induced phosphorylation of the ZAP70/CD3 signalosome and downstream signaling to PKC. FEBS Letters. 0014-5793.

41. Solal-Celigny P, Roy P, Colombat P, White J, Armitage JO, et al. (2004) Follicular lymphoma international prognostic index. Blood. 104:1258-65.

42. Song W, and Levy R. (2005) Therapeutic vaccination against murine lymphoma by intratumoral injection of naive dendritic cells. Cancer research. 65:5958-64.

43. Spranger S, Koblish HK, Horton B, Scherle PA, Newton R, Gajewski TF. (2014) Mechanism of tumor rejection with doublets of CTLA-4, PD-1/PD-L1, or IDO blockade involves restored IL-2 production and proliferation of CD8(+) T cells directly within the tumor microenvironment. J Immunother Cancer. 2: p. 3.

44. Strome SE, Dong H, Tamura H, Voss SG, Flies DB, et al., (2003) B7-H1 blockade augments adoptive T-cell immunotherapy for squamous cell carcinoma. Cancer Res. 63(19): p. 6501-5.

45. Timmerman JM, Czerwinski DK, Davis TA, Hsu FJ, Benike C, et al. (2002) Idiotype-pulsed dendritic cell vaccination for B-cell lymphoma: clinical and immune responses in 35 patients. Blood. 99:1517-26.

46. Tong Y, Song W, and Crystal RG. (2001) Combined intratumoral injection of bone marrow-derived dendritic cells and systemic chemotherapy to treat pre-existing murine tumors. Cancer research. 61:7530-5.

47. Tumeh PC, Harview CL, Yearley JH, Shintaku IP, Taylor EJ, et al. (2014) PD-1 blockade induces responses by inhibiting adaptive immune resistance. Nature. 515:568-71.

48. Weber J. (2010) Immune checkpoint proteins: a new therapeutic paradigm for cancer--preclinical background: CTLA-4 and PD-1 blockade. Semin Oncol. 37(5): p. 430-9.

49. Wolchok JD, Hoos A, O'Day S, Weber JS, Hamid O, et al. (2009) Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. Clinical cancer research : an official journal of the American Association for Cancer Research. 15:7412-20.

50. Zhang PD, Schwartz JC, Guo X, Bhatia S, Cao E, et al. (2004) Structural and functional analysis of the costimulatory receptor programmed death-1. Immunity. 20 (3):337-47.