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

7/17/2019

Statistical Analysis Plan Approvals

Protocol: IMDZ-G142

_____ DATE: _____

Michael M. Chen, M.Sc.
Sr. Director, Biostatistics and Data Management
Immune Design Corp.

_____ DATE: _____

Shanshan Zhao
Lead Statistical Programmer
Q2 Business Intelligence

_____ DATE: _____

Sergey Yurasov, M.D. Ph.D.
Senior Vice President & Chief Medical Officer
Immune Design Corp.

Statistical Analysis Plan Version Log

SAP Version	Protocol Version	Cohorts	Prepared by	Signed Off
SAP Draft Version 1.0, dated September 15, 2016	Protocol version 02 dated November 5, 2015	Cohort 1 & 2	Aurelie Le Maitre, M.Sc. Manager, Statistical Operations Everest Clinical Research	No
SAP Final Version	Protocol version 04B dated 15 November 2018	Cohort 1, 2, 3, 4, 5	Michael Chen, M.Sc. Sr. Director, Biostatistics and Data Management Immune Design	Yes

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List of Abbreviations

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
CTCAE	Common Toxicity Criteria for Adverse Events
DC	dendritic cell
DCF	Data Clarification Form
DLT	dose-limiting toxicity
DMC	data monitoring committee
ECG	electrocardiogram
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
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
irSD	immune-related stable disease
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
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SAP	Statistical Analysis Plan
SC	subcutaneous
SD	stable disease
SE	stable emulsion
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SOP	standard operating procedure
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
ULN	upper limit of normal
WHO	World Health Organization

1 Introduction

This Statistical Analysis Plan (SAP) documents the planned statistical methods for the analysis and display of data collected within the scope of Immune Design Corp. Protocol IMDZ-G142, version 04B dated 15 November 2018. The analysis of the data should allow changes in the plan to the extent that deviations from the original plan would provide a more reliable and valid analysis of the data. As such, deviations from this SAP must be substantiated by a sound statistical rationale and documented in the clinical study report (CSR).

This SAP details the analysis of the data collected in the study and the presentation of the results of the analyses. All TLFs will be generated based on ADaM datasets. ADaM dataset specifications will be developed to detail the programming specifications and mapping rules necessary to create the analysis datasets and the TLFs.

All statistical analyses will be performed using SAS® version 9.4.

2 Study Objectives

2.1 Primary Objective

- 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)

2.2 Secondary Objectives

- To 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) for Part 4 & Part 5 patients.
- To assess abscopal tumor responses in non-treated, distal tumor sites

2.3 Exploratory Objectives

- 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

3 Study Design

3.1 Study Design

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 stable emulsion (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 aqueous formulation (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) (Figure 2). 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 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. If the tumor mass has not regressed at least 75%, dosing may continue for 3 additional weekly intratumoral doses (9 total).

Two dose levels of G100 are planned:

- Cohort 1: 5 µg of GLA component
- Cohort 2: 10 µg of GLA component

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 (Figure 1).

Part 2, Patient Expansion With or Without Pembrolizumab group: Up to 24 patients will be randomly assigned and treated with single agent intratumoral G100 (Figure 2) or with the sequential administration of intratumoral G100 and pembrolizumab (Figure 3) 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 (Figure 2). For patients randomized to anti-PD-1 therapy (Figure 3), on Day 14, pembrolizumab treatment will be initiated at a standard dose of 200mg IV and then administered every 3 weeks IV for up to 2 years or until disease progression or unacceptable toxicity. For pembrolizumab, dose modification for adverse events 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: 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. 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 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 at least 75% 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 (Figure 4, Figure 5). 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 TLR4high.

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 determine if it's unlikely to reach the target ORR of 40%. 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 (Figure 6, Figure 7). During Dose Escalation 12-24 patients and during Patient Expansion 20 efficacy evaluable patients as defined in the Statistical Section of the protocol 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 375 mg/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 of 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. ORR in patients enrolled on Part 5 Patient

Expansion will be analyzed. 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. 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 (Figure 8). 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.

Figure 1: Part 2, Patient Expansion With Or Without Pembrolizumab

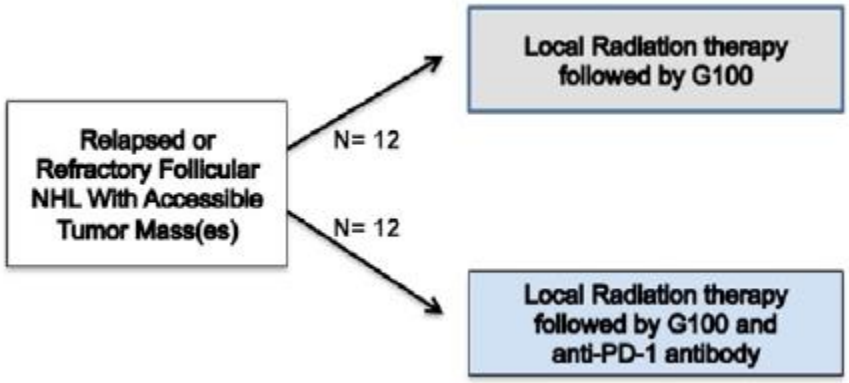


Figure 2: Treatment Schema for Part 1, Part 2 Patient Expansion G100 Alone, Part 2 Large Tumor Group, and Part 3, G100 Expansion of 20 µg Dose Group

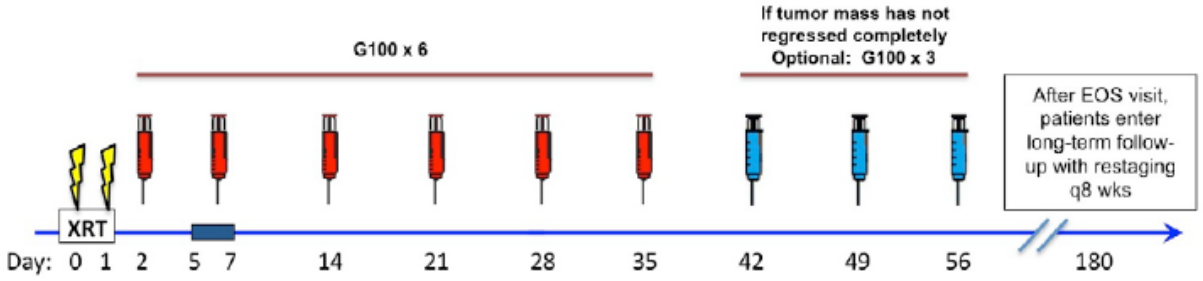


Figure 3: Treatment Schema for Part 2, Sequential G100 and Pembrolizumab

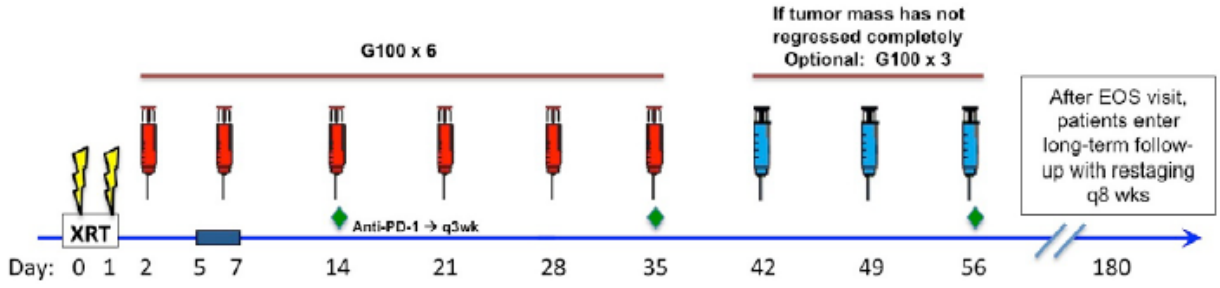


Figure 4: Dose Escalation And Expansion Of Part 4: G100 at 20µg/dose Into Single Or Multiple Tumor Lesions Plus Pembrolizumab Group

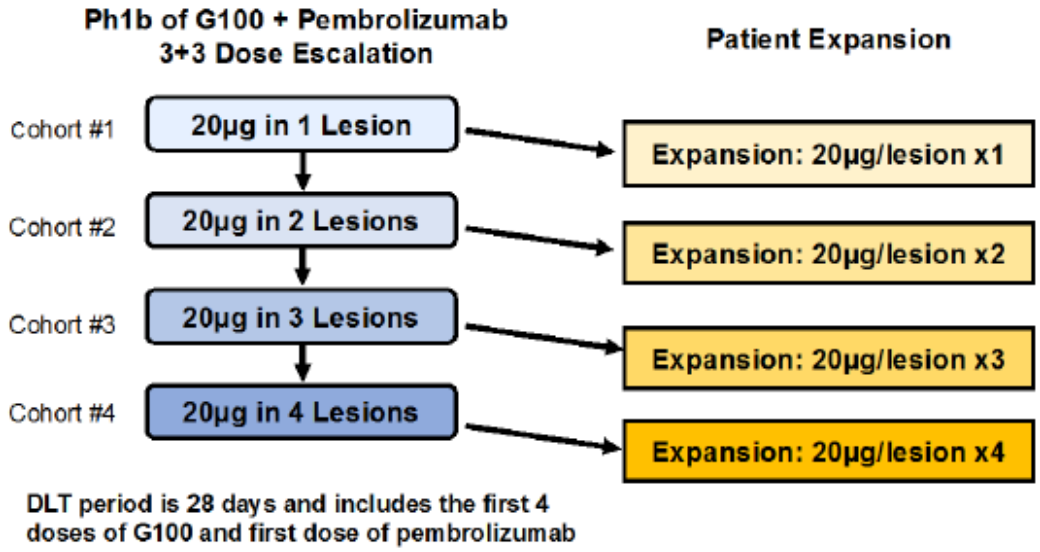


Figure 5: Part 4, G100 at 20µg/lesion Into Single Or Multiple Tumor Lesions Plus Pembrolizumab Group

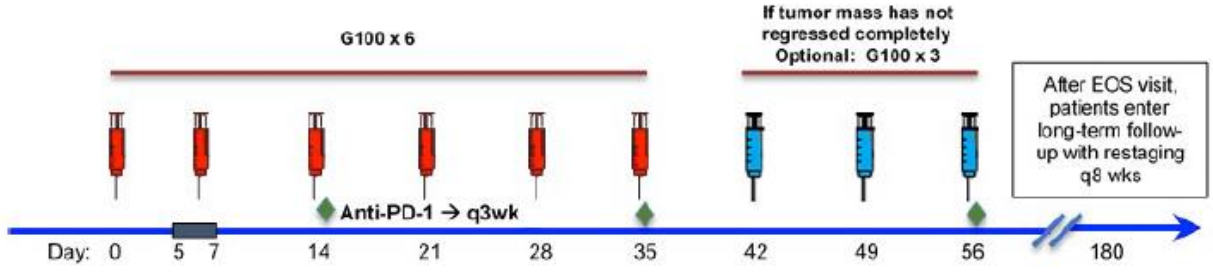


Figure 6: Part 5, G100 Plus Rituximab

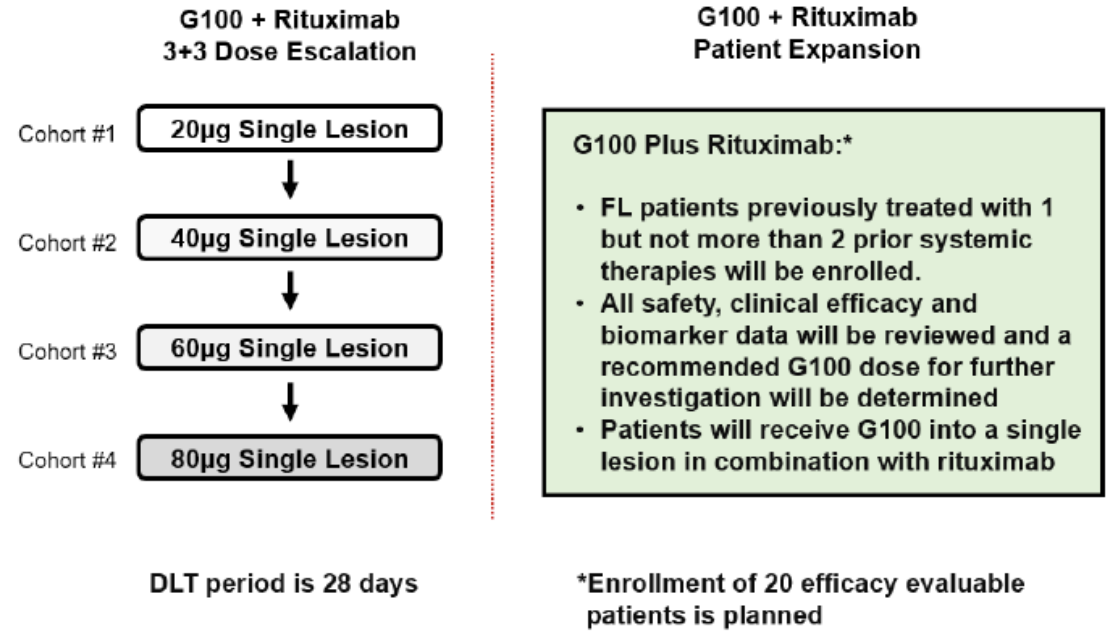


Figure 7: Part 5, G100 Plus Rituximab

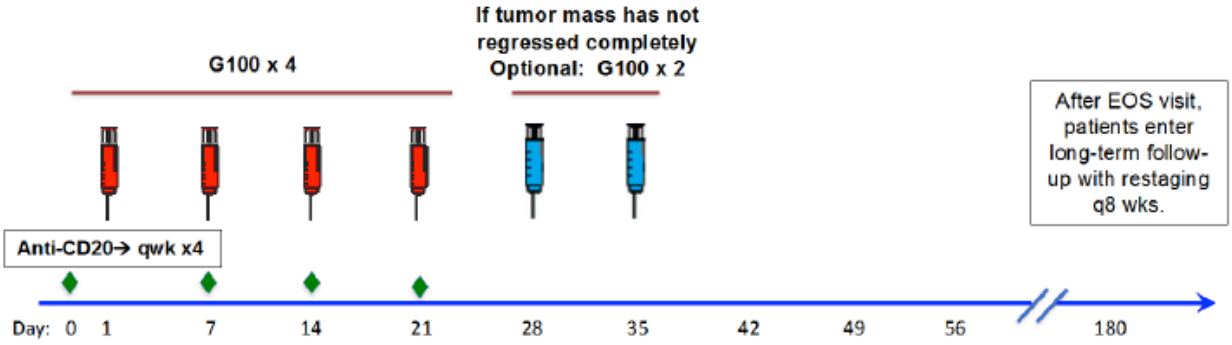
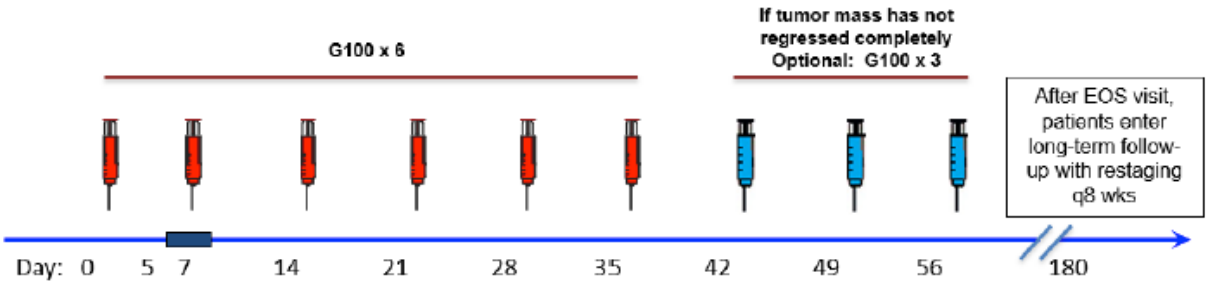


Figure 8: For Parts 1 to 5, Optional Retreatment / Second Course



NOTE: Part 5 is limited up to 6 doses

3.2 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.

3.3 Schedule of Procedures

The detailed schedule of procedures are specified in Table 1, Table 2, Table 3, Table 4, Table 5, and Table 6 below.

Table 1 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[b]	
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												
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.

Table 2 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			
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.

Table 3 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			
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.

Table 4 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.

Table 5 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)[l]		36	20	30	10	10	10	18 or 26	10	18 or 26	10	10		
Total blood volume[l]		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.

Table 6 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.

3.4 Sample Size Consideration

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. 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 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.

4 Analysis Populations

4.1 Enrolled Population

The enrolled population includes all patients who have passed screening and are enrolled into the study.

4.2 Safety Population

The Safety Population includes all enrolled patients who received at least one injection of G100 after standard local radiation. Safety data analyses will be conducted on all patients in the Safety Population according to the treatment received.

4.3 Efficacy Evaluable Population

The Efficacy Evaluable population includes all enrolled patients without major protocol deviations, who have received at least one injection of G100, and have had baseline and at least one post-baseline disease assessment.

The Efficacy Evaluable population will be used for the tumor response analysis based on irRC, including overall tumor response and time to disease progression (TTP).

5 Statistical Analysis

5.1 Data Summaries and Conventions

All data collected on case report forms will be provided in listings, except data collected only for confirmation of study entry criteria and for study administrative purposes. If any enrolled patient is found to not have valid documented informed consent, that patient's data will be excluded from the report, except as necessary to document the error.

Except where specified all continuous variables will be summarized with descriptive statistics (the number of non-missing values, mean, standard deviation, median, minimum and maximum) and all categorical variables will be summarized with frequency counts and percentages, by part, treatment, and overall.

5.2 Missing Data

For adverse events and concomitant medication, the imputation rule for start date and end date are defined in relevant sections (i.e, AE and subsequent therapies sections). For other analysis when necessary (e.g., OS analysis), dates without a specific day of the month (i.e., JAN2010) will be assigned the 15th day of the month and dates without a specific day or month (i.e., 2010) will be assigned the 15th day of June.

5.3 Patient Disposition

Patient disposition and the incidence of treatment discontinuation and study discontinuation (and the reasons for discontinuation) will be tabulated for all enrolled patients by part, treatment, and overall. The number and percentages of patients in each category will be reported. Patient disposition listing will be provided.

5.4 Protocol Deviations

The clinical study team will define CSR reportable protocol deviations and major protocol deviations that will exclude a patient from Efficacy Evaluable population. The clinical study team will review all potential protocol deviations at regular time interval during study conduct and prior to database lock. Protocol deviations will be categorized by deviation type. CSR reportable protocol deviation and major protocol deviations that will exclude a patient from Efficacy Evaluable population will be flagged. The patient incidence of CSR reportable protocol deviations will be summarized by deviation type based on Safety population.

5.5 Demographics and Baseline Information

5.5.1 Demographics and Baseline Characteristics

Patient demographic and baseline characteristics include Age, Sex, Childbearing Potential for Female, Race, Ethnicity, Height, Weight, and ECOG Performance Status will be summarized by part, treatment, and overall, for Safety and Efficacy Evaluable population. A separate summary by treatment will be provided.

5.5.2 Cancer History

Cancer history will be summarized by part, treatment, and overall, for Safety and Efficacy Evaluable population. The summary will include the following:

- Type of Lymphoma
- Histologic Type by WHO Classification at Diagnosis
- Did the WHO Classification Change?
- Histologic Type at Study Entry by WHO Classification
- Ann Arbor Stage at Diagnosis
- Did the Stage Change?
- Ann Arbor Stage at Study Entry

- Number of Nodal Sites
- Number of Index Lesions at Baseline
- Disease Status
- Tumor Growth / Progressive Disease at Study Entry

5.5.3 Medical and Surgical History

Medical and surgical history will be listed based on Safety population.

5.5.4 Prior Anti-Cancer Therapy

Prior anti-cancer therapy will be summarized by part, treatment, and overall, for Safety and Efficacy Evaluable population. A separate summary by treatment will be provided. The summary will include the following:

- Any Prior Therapy (Radiotherapy, Immunotherapy, Systemic Therapy, Other Therapy)
    - Type of Therapy
    - Intent of Treatment
    - Number of Any Prior Therapy
    - Number of Patients with Stem Cell/Bone Marrow Transplant
- Prior Systemic Therapy Regimen/Agents
    - Number of Prior Systemic Therapy
    - Best Response
    - Reason for Discontinuation from Prior Systemic Therapy Regimen

In addition, demographic and baseline characteristics, cancer history and anti-cancer therapy data will be presented in listings.

5.6 Efficacy Evaluation

Unless otherwise specified, efficacy analyses will be performed by part, treatment, and overall. A separate summary by treatment will be provided. Efficacy evaluation will be provided for the Efficacy Evaluable population. Efficacy evaluation based on the Safety population will be provided as a supportive analysis.

5.6.1 Tumor Growth Rate

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, new measurable lesions if any, are added to provide the total tumor burden:
Tumor Burden = SPD index lesions + SPD new measurable lesions

Post treatment initiation, spider plot (% change and change from baseline in SPD of index and new measurable lesions) for all visits will be presented for all lesion sites and abscopal sites. Waterfall plot (best % change and best change from baseline) will be presented for all lesion sites and abscopal sites.

Best percentage change in sum of tumor bi-dimensional products for abscopal lesions will be summarized by part, treatment, and overall.

5.6.2 Overall Response Rate (ORR) and Clinical Benefit Rate (CBR)

Overall response rate (ORR) using irRC will be defined as the number and percent of patients with best overall response of irCR or irPR. ORR with two-sided 95% Clopper-Pearson exact CI will be provided. Both unconfirmed and confirmed response using irRC criteria will be reported. The overall response using irRC is derived from time-point response assessments as follows:

- Immune-related complete response (irCR), complete disappearance of all lesions (whether measurable or not, and no new lesions), confirmed by a repeat, consecutive assessment no less than 4 weeks from first documentation
- Immune-related partial response (irPR), decrease in tumor burden >= 50% relative to baseline, confirmed by a consecutive assessment at least 4 weeks from 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, confirmed by a repeat, consecutive assessment no less than 4 weeks from first documentation

In confirmed ORR summary, patients with best response of unconfirmed irPR will be summarized as irSD.

Overall response rate (ORR) using IWG will be defined as the number and percent of patients with best overall response of CR or PR.

Clinical benefit rate (CBR) will be defined as the number and percent of patients with best overall response of complete response, partial response or stable disease. CBR using both irRC and IWG will be reported.

In addition, abscopal tumor reduction will be summarized.

Lesion assessment (lesion type, organ site, evaluation method, diameter, and lesion status), as well as patient overall response based on both irRC and IWG criteria for lymphomas at each visit and the best overall response, will be presented in a data listing.

Overall tumor response using irRC criteria for all tumor lesions, irradiated sites, non-irradiated sites and abscopal sites, and overall tumor response using IWG criteria for all tumor lesions will be summarized. Overall tumor response for the following subgroups will also be provided:

- Relapsed/Refractory Patients
- Treatment Native Patients
- Patients with MR (minor response)
- Patients with MR (minor response) and Decrease in Abscopal Lesions
- Patients with PD at Study Entry
- Patients with Guided Injection of G100
- Patients with Not Guided Injection of G100

MR (minor response) is defined as more than 25% decrease in tumor burden but less than the 50% that would make it a PR.

5.6.3 Duration of Response (DOR) and Duration of Clinical Benefit

Duration of response (DOR) is defined as the time interval between the date of the earliest qualifying confirmed/unconfirmed response using irRC and the date of disease progression (PD) or death for any cause, whichever occurs first. DOR in months is calculated as: (date of PD or death – date of first confirmed/unconfirmed irCR/CR or irPR/PR + 1)/30.4375. DOR analysis will include only patients with confirmed/unconfirmed response of irCR/irPR using irRC.

For patients who are alive without documentation of disease progression following the qualifying response, duration of response will be censored following the same rule defined for PFS.

Duration of clinical benefit is defined as the time interval between the date of the earliest qualifying confirmed/unconfirmed best response using irRC and the date of progression disease (PD) or death for any cause, whichever occurs first. Duration of clinical benefit in months is calculated as: (date of PD or death – date of first confirmed/unconfirmed irCR/irPR or irSD + 1)/30.4375. Duration of clinical benefit will include only patients with confirmed/unconfirmed response of irCR/irPR or irSD using irRC.

For patients who are alive without documentation of disease progression following the qualifying response, duration of clinical benefit will be censored following the same rule defined for PFS.

Median DOR and duration of clinical benefit with the corresponding two-sided 95% CI will be estimated using the Kaplan-Meier method in each treatment group. The Kaplan-Meier curves will be presented.

DOR and duration of clinical benefit data will be presented in listing.

5.6.4 Progression-free Survival (PFS)

PFS is defined as time from date of first study treatment to date of first disease progression by irRC criteria, symptomatic deterioration, or death due to any cause, whichever occurs first. Progression-free survival (PFS) in months is calculated as: (date of first progression, symptomatic deterioration, or death (any reason) – date of first dose +1)/30.4375. The irRC modification requires a PD confirmation no less than 4 weeks from first documentation of progressive Disease (PD); once confirmed, the date of progression is defined as date of the first PD. In case of unconfirmed PD followed by symptomatic deterioration, the date of unconfirmed PD will be the date of progression. Patients without progression, symptomatic deterioration, or death are censored at the date of the last tumor assessment. If a patient begins a new anti-cancer therapy or has radiotherapy or surgery at a lesion site prior to confirmed progression (or death), the patient will be censored at the last assessment where the patient is documented as progression free prior to the intervention. Patients with two or more missing response assessments prior to a visit with progression (or death) will be censored at the last visit where the patient is documented to be progression free. Patients without disease assessment post-baseline will be censored at the first dose date. Table 7 below provides further details on how date of PFS event and date of PFS censoring are assigned.

Table 7 Progression-Free Survival

Situation	Date of Progression or Censoring	Outcome
No baseline tumor assessments	Date of first dose	Censored

Situation	Date of Progression or Censoring	Outcome
Progression documented between scheduled visits	Date of last radiological assessment of measured lesions (if progression is based on increase in sum of measured lesions)	Progressed
Symptomatic deterioration before first PD assessment	Date of Symptomatic deterioration	Progressed
Symptomatic deterioration between adequate assessment visits	Date of Symptomatic deterioration	Progressed
Symptomatic deterioration after two or more missed visit	Date of last tumor assessment	Censored
Death before first scheduled assessment	Date of death	Progressed
Death between adequately scheduled assessment visits	Date of death	Progressed
Death or progression after two or more missed visit	Date of last tumor assessment	Censored
New anti-cancer therapy or radiotherapy or surgery at a lesion site prior to confirmed progression (or death)	Date of last tumor assessment where the patient was documented as progression free prior to the intervention	Censored
No progression or death	Date of last tumor assessment	Censored

Summary of PFS including median, 95% CI, 25th and 75th percentiles, range, PFS rate at 3-month, 6-month, 9-month and 12-month will be estimated using the Kaplan-Meier method. The corresponding 95% CI for median will be calculated using the Brookmeyer and Crowley method. The Kaplan-Meier curve and swimmer plot will be displayed.

PFS analysis for the following subgroups will be presented:

- Relapsed/Refractory Patients
- Treatment Naïve Patients
- MR Patients
- MR and Abscopal Decrease Patients

PFS data will be presented in a data listing.

5.6.5 Overall Survival (OS)

Overall Survival (OS) is defined as the time from date of first study treatment to death due to any cause. Overall survival in months is calculated as: (date of death – date of first dose) +1)/30.4375. Patients who are alive at the end of study will be censored at the last date the patient is known to be alive or data analysis cutoff date, whichever is earlier.

Summary of OS including median, 95% CI, 25th and 75th percentiles, and range will be estimated using the Kaplan-Meier method. The corresponding 95% CI for median will be calculated using the Brookmeyer and Crowley method. The Kaplan-Meier survival curve will be displayed.

OS data will be presented in a data listing.

5.6.6 Time to Response for CR or PR Patients

Time to Response for CR/PR Patients is defined as time from date of first study treatment to the date of CR or PR response first documented. Time to response in months is calculated as: (date of first CR or PR – date of first dose +1)/30.4375.

Summary of Time to Response including median, 95% CI, 25th and 75th percentiles, and range will be estimated using Kaplan-Meier method. The Kaplan-Meier survival curve and swimmer plot will be displayed.

5.6.7 Time to Next Treatment and Duration of All Subsequent Therapies

Time to next treatment is defined as the time from the date of first study treatment to the start date of subsequent therapy after PD. Patients who did not receive subsequent therapy after PD are censored at the date of last contact or death.

Duration of all subsequent therapies after PD in week is calculated as (date of subsequent therapies last administered – date of subsequent therapies first administered + 1)/7. If one patient has multiple consecutive systemic therapies, the duration will be summarized per patient. If the start and end dates of multiple systemic therapies overlap, then duration = (date of last systemic therapy last administered – date of first systemic therapy first administered + 1)/7.

Summary of time to next treatment including median, 95% CI, 25th and 75th percentiles, and range will be estimated using the Kaplan-Meier method. The corresponding 95% CI for median will be calculated using the Brookmeyer and Crowley method. Descriptive statistics using PROC UNIVARIATE of time to next treatment and duration of all subsequent therapies including only patients with subsequent anti-cancer therapies will also be reported.

<u>Partial Dates for Subsequent Therapy</u>

Incomplete subsequent therapy dates will be imputed. Imputed dates will be used to determine Study Day.

Partial start dates will be imputed as follows:

1. Only the year is reported, with month and day missing: If the subject's last study treatment and subsequent therapy are in the same year, then the date of the last dose of study treatment will be used to impute the start date of the subsequent therapy.
2. The month and year are reported, with day missing: The first day of the month will be used to impute the start of the subsequent therapy.

Partial end dates will be imputed for non-ongoing therapies as follows:

1. Only the year is reported, with month and day missing: the earlier of December 31 or analysis cut-off date will be used to impute the end of the therapy.
2. The month and year are reported, with day missing: The last day of the month will be used to impute the end of the therapy.

End dates for ongoing therapies will be imputed to analysis cut-off date.

If an imputation results in an imputed start date after the stop date, set the date with more imputation to the one with less imputation.

Subsequent anti-cancer therapies will be summarized by part, treatment and will be presented in a listing.

- Any subsequent anti-cancer therapy
- Type of therapy
- Subsequent systemic therapy regimen/agents
- Best response
- Reason for discontinuation

Subsequent procedures and surgeries will be presented in a separate listing.

5.6.8 Immune Response and Biomarker Analyses

All patients who have received at least one injection of G100 and have available immunohistochemistry (IHC), nanostring, or T cell receptor (TCR) data will be included in the biomarker analysis.

Anti-tumor cellular immunity (CD4, CD8 T cell, CD20, CD68, NKp46, FoxP3, CD8/CD4 ratio, CD8/FoxP3 ratio) by immunohistochemistry (IHC) will be explored. Post/pre treatment ratio will be summarized by treatment, and by subgroups of interest (irPR vs non-responder, pre-TLR4>=50% vs <50%, treatment naïve, relapsed/refractory patients, prior line of therapy 0-2 vs >=3). Post and pre treatment values will be compared using signed-rank test to identify significant changes post treatment. Association between clinical endpoints (irPR, irPR+MR, irPR+MR+SD, abscopal best % change better than -25%) and cellular immunity by immunohistochemistry will be explored using a logistic regression model for all dosed patients, and by treatment. Association between response (irPR) and pre-treatment TLR4 using different cutoffs will be presented in 2x2 tables and the proportion of response will be compared between TLR4 high and TLR4 low patients using Barnard's unconditional exact test. Comparison of post treatment change in immunohistochemistry will be explored between G100 monotherapy 10 μg and G100 monotherapy 20 μg patients.

Association between clinical response and nanostring genes (NK, M1 Markers, M2 Markers, and other genes of interest) using PBMC and tumor samples will be explored using a logistic regression model that includes $\log_2$ transformed nanostring data. Post/pre mean expression ratio (as antilogarithm of the means of ($\log_2$ post – $\log_2$ pre)) for responder and non-responder, odds ratio, and nominal and adjusted p-values will be presented. Adjusted p-value is adjusted using False Discovery Rate (FDR) method. Ten most upregulated and ten most downregulated immune-related genes will be presented, with post/pre mean expression ratio and p-value from signed-rank test. Further, ten most highly differentially induced immune-related genes in clinical responders versus non-responders will be explored.

T cell receptor (TCR) clones not detectable at baseline in tumor/PBMC but become detectable or increased post-treatment in tumor/PBMC will be explored.

5.7 Safety Evaluation

Safety evaluation will be based on safety population.

5.7.1 Treatment Exposure

Local radiation therapy received will be summarized by frequency. Number of radiation doses (for Part 1, 2, and 3), number of G100 doses in first course, number of G100 doses modification in first course, number of G100 doses in second course, number of G100 doses modification in second course, cumulative pembrolizumab dose (mg), treatment duration of pembrolizumab (weeks), and number of pembrolizumab infusion interruptions will be reported.

Treatment duration of pembrolizumab (weeks) will be calculated as (date of last pembrolizumab dose administered – date of first pembrolizumab dose administered + 21) / 7. Pembrolizumab treatment interruption, if any, will be removed from treatment duration of pembrolizumab.

In addition, duration from first course to second course in month, calculated as (first dose date of G100 in second course – last dose date of G100 in first course + 1)/30.4375, will be reported. Treatment site for irradiated lesions, type of imaging used for G100 injection will be reported.

G100, pembrolizumab administration, and low dose radiation treatment (Part 1, 2, and 3) will be displayed in listings.

5.7.2 Adverse Events

A Treatment-Emergent Adverse Event (TEAE) is an AE with onset date on or after the initiation of study treatment, or a pre-existing condition that worsens after initiation of study treatment (i.e., increase in severity), up to 30 days after the date of last dose of study treatment. AEs that occur more than 30 days after last dose, if deemed as related to study treatment, will also be included as TEAEs.

If the AE start date is partial or missing, then:

- If AE start date is completely missing, then the AE is considered treatment-emergent.
- If both AE start month and day are missing, if the year is in the same year as the first study treatment, then the AE is considered treatment-emergent. Otherwise, 01Jan will be used to impute month and day. If the imputed AE start day is more than 30 days after the date of last study treatment, then the AE will not be a TEAE.
- If AE start day is missing and AE start year and month are the same or after the first dose year and month, then the AE is considered as treatment-emergent, unless the imputed AE start day using day 01 is more than 30 days after the date of last study drug.

The summaries will be based on TEAEs by part, treatment, and overall. A separate summary by treatment will be provided. All adverse events will be included in patient listings.

The incidence of a TEAE will be defined as the number and percent of patients experiencing an event. TEAEs will be summarized by system organ class, preferred term, and further by severity. Adverse events will be coded using Medical Dictionary for Regulatory Activities (MedDRA 20.1 or newer). A patient with more than one different adverse event in a system organ class (SOC) will be counted only once in the total number of patients experiencing adverse events in that particular SOC. A patient having experienced the same event (AE preferred term) more than once during the study will be counted only once under the worst grade or relationship.

The following adverse events summaries will be reported:

- Overall summary of TEAEs, including TEAEs, treated-related TEAEs, serious TEAEs, treatment-related serious TEAEs, TEAEs of grade 3 and above, treatment-related TEAEs of grade 3 and above, TEAEs leading to treatment interruption, TEAEs leading to treatment discontinuation, TEAEs leaing to treatment interruption or discontinuation, TEAEs leading to death reported during the study, dose limiting toxicities (DLTs)
- Incidence of TEAEs by system organ class, preferred term, and severity
- Incidence of TEAEs related to study drug by system organ class, preferred term, and severity
- Incidence of TEAEs related to G100 by system organ class, preferred term, and severity
- Incidence of TEAEs related to pembrolizumab by system organ class, preferred term, and severity
- Incidence of TEAEs related to study drug by preferred term and severity
- Incidence of TEAEs related to G100 by preferred term and severity
- Incidence of TEAEs related to pembrolizumab by preferred term and severity
- Incidence of dose limiting toxicities (DLTs) by system organ class, preferred term, and severity
- Incidence of TEAEs leading to study drug discontinuation by system organ class, preferred term, and severity
- Incidence of medical events of interest (MEOIs) by system organ class, preferred term, and severity
- Incidence of TEAEs by system organ class and preferred term
- Incidence of TEAEs related to study drug by system organ class and preferred term
- Incidence of TEAEs related to G100 by system organ class and preferred term
- Incidence of TEAEs related to pembrolizumab by system organ class and preferred term
- Incidence of serious TEAEs by system organ class and preferred term
- Incidence of serious TEAEs related to study drug by system organ class and preferred term
- Incidence of serious TEAEs related to G100 by system organ class and preferred term
- Incidence of serious TEAEs related to pembrolizumab by system organ class and preferred term
- Incidence of TEAEs leading to study drug discontinuation by system organ class and preferred term
- Incidence of TEAEs related to study drug leading to study drug discontinuation by system organ class and preferred term
- Incidence of TEAEs related to G100 leading to study drug discontinuation by system organ class and preferred term
- Incidence of TEAEs related to pembrolizumab leading to study drug discontinuation by system organ class and preferred term
- Incidence of TEAEs leading to death by system organ class and preferred term
- Incidence of TEAEs related to study drug leading to death by system organ class and preferred term

5.7.3 Death

Deaths (and cause of death) will be provided in table and listing.

5.7.4 Clinical Laboratory Evaluation

Hematology and blood chemistry are assessed at baseline visit (Visit 2), Visit 10 and Visit 11. Urinalysis is assessed at baseline visit (Visit 2). Laboratory assessments included the following:

- Hematology: WBC with differential count, RBC count, hemoglobin, hematocrit, platelet count, PT, PTT and INR (PT, PTT and INR for baseline only)
- Serum chemistry: sodium, chloride, potassium, random glucose, blood urea nitrogen (BUN), creatinine, calcium, AST/SGOT, ALT/SGPT, total bilirubin, alkaline phosphatase, lactic acid dehydrogenase (LDH), total protein, albumin

- Urinalysis (baseline only): protein, glucose, blood, leukocytes, nitrites, urobilinogen, bilirubin, pH, specific gravity, ketones
- Thyroid function (Visit 2 (Parts 1-4), Visit 11 (Part 2 - Pembro arm), Visit 9 (Part 4), FU (Parts 1-4)): T3, T4 and TSH

All local laboratory data will be stored in the database with the units in which they are originally reported. Laboratory data in summary tables and patient data listings will be presented in the SI Units. Laboratory data not reported in SI units will be converted to SI units before further processing or data analysis.

Summary statistics (mean, median, standard deviation, and range) of laboratory values for hematology tests and chemistry tests and their changes from baseline values will be tabulated for each visit, by part, treatment, and overall. Baseline is defined as the last value prior to first study treatment dosing.

Laboratory tests will be graded using NCI-CTCAE v4.03 toxicity grading (see Appendix 1).

Worst change from baseline in toxicity grade for selected laboratory parameters will be presented in shift tables. For each patient, baseline grade will be cross-tabulated by the patient's maximum post-baseline grade. Data from both scheduled and unscheduled visits will be used for maximum post-baseline NCI-CTCAE grade of laboratory values.

All laboratory measurements will be presented in a listing.

5.7.5 Vital Signs

Vital sign measurements include temperature, pulse (heart rate), respiratory rate, resting systolic and diastolic blood pressure, height and weight. Temperature, pulse (heart rate), respiratory rate, resting systolic and diastolic blood pressure will be collected from baseline visit (Visit 2) through end of study visit (Visit 12) and continued throughout follow-up visits. Height and weight will be collected at baseline visit only.

Summary statistics (mean, median, standard deviation, and range) of baseline and post-baseline vital signs measurements (temperature, pulse, respiratory rate, resting systolic and diastolic blood pressure), as well as the changes from baseline, will be tabulated for each visit, by part, treatment, and overall. Baseline is defined as the last value prior to first study treatment dosing.

All vital signs measurements will be presented in a listing. Clinically significant abnormalities in vital sign measurements will be flagged in listing.

5.7.6 Electrocardiogram (ECG)

12-Lead ECG measurements collected in both scheduled and unscheduled visits will be presented in data listings.

5.7.7 Physical Examination

Physical examination abnormalities will be included in the adverse event (abnormalities after the start of study drug) or medical history (abnormalities before the start of study drug) summaries and listings.

5.7.8 Pregnancy Test

Pregnancy test results will be presented in a listing.

5.7.9 ECOG Performance Status

ECOG performance status will be summarized by visit and presented in a listing.

5.7.10 Prior and Concomitant Medications

Verbatim terms of prior and concomitant medications will be coded using the most current version of the World Health Organization (WHO) Drug Dictionary (3Q 2018 or newer).

All concomitant medications will be summarized by ATC class and preferred name and all prior and concomitant medications will be presented in a listing. A patient with more than one medication in a medication class will be counted only once in the total number of patients in that medication class. A patient having the same medication more than once during the study will be counted only once in the number of patients with that medication.

Prior medication is defined as any medication with start date on or before the first dose date, or medication with start date missing.

Concomitant medication/treatment will be any medication/treatment with start date on or after the initial dosing of study treatment. Any medication/treatment that cannot be identified as prior or concomitant will be considered as prior and concomitant.

Prior and concomitant medications will be presented in a listing.

6 Interim Analysis and Data Monitoring

For the purposes of safety monitoring, key safety analyses are performed quarterly. The DMC have evaluated available data and made necessary recommendations to the study. Details are outlined in the DMC charter.

7 Adjustment for Covariates

In exploratory analyses comparing post treatment change in immunohistochemistry immune infiltrate between G100 monotherapy 10 µg and G100 monotherapy 20 µg patients, pre-treatment TLR4 and pre-treatment CD8/CD4 ratio are included as covariates in the analysis of variance model.

8 Multiplicity

In analysis of nanostring data, adjusted p-value using False Discovery Rate (FDR) method is presented, as footnoted on summary tables. Nominal p-values are presented otherwise in this early phase study of exploratory nature.

9 Changes in the Protocol Planned Analysis

Clinical response by Lugano criteria for lymphomas (Cheson 2014), and independent radiology review of response by Immune-related Response Criteria (irRC) and Lugano criteria for Part 4 will not be assessed due to study termination by the sponsor.

10 References

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.

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.

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.

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

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.

Appendix 1: NCI CTCAE V4.03 Grades for Laboratory Parameters

Panel: Chemistry

Lab Test	Unit	Grade 1	Grade 2	Grade 3	Grade 4
Albumin	g/L	[30, LLN)	[20, 30)	[0, 20)	Life-threatening consequences; urgent intervention indicated
Alkaline Phosphatase	U/L	(ULN, 2.5*ULN]	(2.5*ULN, 5*ULN]	(5*ULN, 20*ULN]	>20*ULN
ALT (increased)	U/L	(ULN, 3.0*ULN]	(3.0*ULN, 5.0*ULN]	(5*ULN, 20*ULN];	>20*ULN
AST (increased)	U/L	(ULN, 3.0*ULN]	(3.0*ULN, 5.0*ULN]	(5*ULN, 20*ULN];	>20*ULN
Bilirubin	umol/L	(ULN, 1.5*ULN]	(1.5*ULN, 3*ULN]	(3*ULN, 10*ULN]	>10*ULN
Calcium high (Hypercalcemia)	mmol/L	(ULN, 2.9]	(2.9, 3.1]	(3.1, 3.4]	>3.4
Calcium low (Hypocalcemia)	mmol/L	[2.0, LLN)	[1.75, 2.0)	[1.5, 1.75) ; hospitalization indicated	[0, 1.5); life threatening consequences
Creatinine (increased)	umol/L	(1 – 1.5*baseline]; (ULN, 1.5*ULN]	(1.5 – 3.0* baseline]; (1.5*ULN, 3*ULN]	>3.0*baseline; (3*ULN, 6*ULN]	>6*ULN
Glucose high (hyperglycemia)	mmol/L	(ULN, 8.9]	(8.9, 13.9]	(13.9, 27.8] ; hospitalization indicated	>27.8; life threatening consequences
Glucose low (hypoglycemia)	mmol/L	[3.0, LLN)	[2.2, 3.0)	[1.7, 2.2)	[0, 1.7); life threatening consequences; seizures
Potassium high (hyperkalemia)	mmol/L	(ULN, 5.5]	(5.5, 6]	(6, 7]; hospitalization indicated	>7; life-threatening consequences
Potassium low (hypokalemia)	mmol/L	[3, LLN)	[3, LLN); symptomatic; intervention indicated	[2.5, 3) ; hospitalization indicated	[0, 2.5); life-threatening consequences
Sodium high (hypernatraemia)	mmol/L	(ULN, 150]	(150, 155]	(155, 160]; hospitalization indicated	>160; life-threatening consequences
Sodium low (hyponatraemia)	mmol/L	[130, LLN)	UNDEFINED	[120, 130)	[0, 120); life-threatening consequences

Panel: Hematology

Lab Test	Unit	Grade 1	Grade 2	Grade 3	Grade 4
Hemoglobin (decreased)	g/L	[100, LLN)	[80, 100)	[0, 80); transfusion indicated	Life-threatening consequences; urgent intervention indicated
Platelet count (decreased)	10^9/L	[75, LLN)	[50, 75)	[25, 50)	[0, 25)
WBC (decreased)	10^9/L	[3, LLN)	[2, 3)	[1, 2)	[0, 1)
Lymphocytes (decreased)	10^9/L	[0.8, LLN)	[0.5, 0.8)	[0.2, 0.5)	[0, 0.2)
Neutrophil count (decreased)	10^9/L	[1.5, LLN)	[1, 1.5)	[0.5, 1)	[0, 0.5)
Activated Partial Thromboplastin Time	sec	(ULN, 1.5*ULN]	(1.5*ULN, 2.5*ULN]	>2.5*ULN; hemorrhage	
Prothrombin Intl. Normalized Ratio	Ratio	(ULN, 1.5*ULN]; >1 - 1.5 times above baseline if on anticoagulation	(1.5*ULN, 2.5*ULN]; >1.5 - 2.5 times above baseline if on anticoagulation	>2.5*ULN; >2.5 times above baseline if on anticoagulation	

Reference:

http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf