STATISTICAL ANALYSIS PLAN

Phase 1b & 2 Study with GL-ONC1 (aka Olvi-Vec) in Patients with Recurrent or Refractory Ovarian Cancer (VIRO-15)

PROTOCOL:	GL-ONC1-015
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1. INTRODUCTION

This document describes the statistical analyses and data presentations to be performed for the clinical study report (CSR) of Genelux Corporation protocol GL-ONC1-015 "Phase 1b & 2 Study with GL-ONC1 (aka Olvi-Vec) in Patients with Recurrent or Refractory Ovarian Cancer (VIRO-15)."

This statistical analysis plan (SAP) provides a comprehensive and detailed description of the strategy, rationale, and statistical techniques to be used to assess the efficacy and safety of GL-ONC1 (aka Olvi-Vec) with or without platinum doublet +/- bevacizumab in patients with Platinum-resistant, platinum-refractory and intermediate platinum-sensitive ovarian cancer and peritoneal carcinomatosis.

The purpose of the SAP is to ensure the credibility of the study findings by specifying the statistical approaches to the analysis of study data.

2. OVERALL STUDY DESIGN, OBJECTIVES, AND ENDPOINTS

2.1 Study Objectives and Endpoints Outlined in Original Protocol

Primary Objective:

Phase 1b: Investigate the safety and tolerability.
Phase 2 (Cohorts A, B & D): Investigate Progression-free Survival (PFS) with therapeutic intent.
Phase 2 (Cohort C & D): Overall Response Rate (ORR) by RECIST1.1 and by GCIG CA-125 criteria with therapeutic intent.

Secondary Objectives:

Phase 1b & Phase 2 Cohorts A & B: Response to treatment with therapeutic intent will be determined based on Response Evaluation Criteria in Solid Tumors (RECIST) 1.1, by the Immune-related Response Criteria (irRC) as an exploratory endpoint, and by CA-125 according to the Gynecologic Cancer Intergroup (GCIG) CA-125 response criteria in patients with measurable disease. Patients who enter with non-measurable disease will be evaluated for response to treatment by PET/PET CT scan, physical examination and CA-125 levels. Antitumor

activity (if evaluable by CT, PET/PET-CT scans) will be evaluated by progression-free survival (Phase 1b only), Clinical Benefit Rate (CBR: CR + PR + SD), best overall response (BOR), duration of response (DoR), objective overall response rate (ORR), disease control rate (DCR = CR + PR + SD≥15 weeks). Additionally, overall survival (OS) and time to treatment failure (TTF) will be assessed. In the Phase 2 study, safety assessment will continue.

Phase 2 Cohort C & D:

- Progression-free Survival by RECIST1.1 (Ch C)
- Duration of Response
- Clinical Benefit Rate
- Disease Control Rate
- Overall Survival

Exploratory Objectives (optional):

All cohorts:

(1) To evaluate the immune response to treatment, immune assays will be performed to study immune activation and antitumor immune response in blood, ascites and tumor biopsies;
(2) To evaluate antitumor activity at the tissue/cellular levels (proliferation index, apoptosis, etc.);
(3) To confirm the presence of GL-ONC1 within the tumor by viral plaque assay (VPA), immunohistochemistry (IHC), and/or quantitative polymerase chain reaction (qPCR).
(4) To determine the possible prognostic value (e.g., as a predictive value of survival outcome) of circulating tumor cells (CTCs) in patients diagnosed with ovarian cancer. In addition, to demonstrate the correlation of CTC number with radiological outcome as early pharmacodynamic and response rate indicators in the context of GL-ONC1 treatment.

2.2 Trial Design

This is an open-label, non-randomized Phase 1b & 2 study evaluating the effect of the oncolytic virus GL-ONC1 (aka Olvi-Vec) as a monotherapy or as a combination therapy with carboplatin doublet +/- bevacizumab. GL-ONC1 is administered via an intraperitoneal catheter or as an intravenous bolus infusion in patients diagnosed with recurrent or refractory ovarian cancer and peritoneal carcinomatosis. Eligible patients must have histologically confirmed (from prior treatment(s)) non-resectable ovarian, fallopian tube or primary peritoneal cancer who are platinum-resistant, platinum-refractory or intermediate platinum-sensitive with good performance status (ECOG of 0 or 1). Patients with platinum-resistant disease (i.e., recurrence or progression < 6 months) or platinum-refractory disease (progression while on platinum-based therapy) must have either (1) failed at least two consecutive therapies, or (2) are not eligible for additional cytotoxic therapies. Intermediate platinum-sensitive patients (recurrence of disease 6 to 12 months from last platinum compound) have recurrent ovarian carcinoma with at least four prior individual treatment regimens including at least two separate platinum-based therapies with recurrence from the last platinum-based regimen less than 12 months, who are unwilling or unable to undergo additional platinum-based cytotoxic therapy. Patients treated with

chemotherapy, radiotherapy or any anti-cancer biologic therapies will require a 4-week washout period prior to administration of first GL-ONC1 dose.

2.3 Sample Size

PHASE 1B STATISTICAL CONSIDERATIONS AND SAMPLE SIZE

This study is descriptive in nature. The sample size is based on clinical and regulatory considerations and has no formal statistical basis. The anticipated sample size is 12 to 18 patients. Descriptive statistics will be used to summarize all baseline patient characteristics and changes of the efficacy variables. All patients who receive GL-ONC1 will be included in the safety analysis. Incidence of serious and non-serious adverse events, including those that are dose limiting, will be tabulated by system organ and preferred term. Patients, who have at a minimum one imaging time point following the initiation of treatment, will be assessed for efficacy objectives.

PHASE 2 COHORTS A, B & C STATISTICAL CONSIDERATIONS AND SAMPLE SIZE

Data (see *Section 2.6 Overview of Clinical Trial Experience with Oncolytic Viruses*, updated summary for **GL-ONC1-015** trial) from the Phase 1b part of this trial have demonstrated clinically significant results in this heavily pretreated patient population, including (1) evidence of anti-tumor activities, e.g., stabilized and/or reduced CA-125 tumor biomarker, tumor shrinkage by RECIST 1.1 (including objective response), reduction in circulating tumor cells (CTC), and encouraging Disease Control Rate (DCR = OR + SD≥15 weeks) = 55 % in 6/11 evaluable pts (4 in Ch1, 2 in Ch2). The Phase 2 portion of this trial is to further investigate anti-tumor response of GL-ONC1 monotherapy or combination therapy to observe trend of clinical benefits in a larger number of patients. PFS, ORR, CBR, and continued safety evaluation will be documented. Patients from corresponding cohorts at equivalent dose levels in the Phase1b and 2 portions will be evaluated together. To evaluate PFS as compared to historical data or to a patient's own treatment history, for a study with 80% power at 1-sided level of significance of 10%, we anticipate 21 evaluable patients (6 from Phase 1b, and 15 from Phase 2; up to 26 patients total to account for any non-evaluable patients). Therefore, the proposed number of patients in Phase 2 (Cohorts A & B) at each dose level is 20.

The study analysis is designed to evaluate ORR with 90% power using a 1-sided level of significance of 5%. The proposed number of subjects in added cohort (Ch C) is up to 35, with 28 evaluable.

Published data from the AURELIA Phase 3 study in subjects with platinum-resistant recurrent ovarian cancer with ≤ 2 prior lines of therapy and treated with bevacizumab and chemotherapy report an ORR = 27.3% by RECIST; and ORR = 31.8% by GCIG CA-125 criteria. Data from the VIRO-15 study will be evaluated in the context of these results, even though the VIRO-15 trial has enrolled subjects with significantly more prior lines of therapy (median ≥ 5). The statistical analysis is designed to provide evidence of a response that is either likely to be similar to that seen in Aurelia, or potentially a more robust improvement of ORR

above the AURELIA trial, e.g., a doubling of ORR by RECIST from 27% to 54% (Using a Simon 2-stage design, Stage 1: Immediately proceed to stage 2 when reach 5 or more responders in up to 15 evaluable subjects; Stage 2: Enroll up to an additional 13 subjects; the null is rejected if there are 12 or more responders of up to 28 evaluable). Part of the 28 evaluable subjects could be from Chs A & B if they received further chemo +/- bev after treatment with GL-ONC1. If Chs A and/or B subjects are included together with Ch C subjects, the number of evaluable subjects needed to be enrolled into Ch C could be fewer than 28. The ORR for subjects in Chs A & B will be evaluated independently from Ch C, regardless of whether it is considered acceptable to include Chs A & B subjects with those in Ch C.

PHASE 2 COHORT D STATISTICAL CONSIDERATIONS AND SAMPLE SIZE

Cohort D is designed to evaluate ORR as one of the Primary Objectives with 90% power using a 1-sided level of significance of 5%. Using a Simon 2-stage design, Stage 1: Immediately proceed to Stage 2 when reach 5 or more responders in up to 15 evaluable subjects. Therefore, the initial number of subjects in Ch D is 15 (expandable to an additional 13 subjects in Stage 2, with 28 subjects total).

3. GENERAL ANALYSIS CONVENTIONS

3.1 Populations Definitions

Safety Population: The safety population will consist of all patients who received at least one dose of protocol-specified treatment.

3.2 Baseline Platinum Status Definitions

Platinum-resistant (Response to therapy, but recurrence or progression 1-6 months after completion of last platinum-based therapy)

Platinum-refractory (Lack of response including persistent disease, or progression while receiving or within 1 month after completion of last platinum-based therapy)

Intermediate platinum-sensitive patients (Response to therapy, but recurrence of disease 6-12 months after completion of last platinum-based therapy)

Platinum status may be further divided into *primary* or *secondary*, with *primary* based on results from front-line platinum-based therapy in previously untreated patients, and *secondary* based on results from subsequent platinum-based line of therapy in previously treated patients.

4. PROTOCOL DEVIATIONS

Major protocol deviations will be identified via site monitoring and EDC data. The categories for major protocol deviations are in accordance with the ICH E3 guidelines and will be identified prior to database lock. The deviations that will be deemed major fall under the following categories:

- Incorrect IP treatment
- Significant deviation of inclusion or exclusion criteria
- Over-dose or under-dose of study drug
- Prohibited medications as specified in the protocol
- Any other significant deviation that had the potential to affect the primary efficacy or safety of the patients

A listing with all the major protocol deviations if any will be presented.

5. DEMOGRAPHICS AND BASELINE CHARACTERISTICS

The demographic variables will be summarized with frequency tabulations that will focus on identifying differences between subpopulations. Descriptive statistics may also be used to summarize the quantitative variables. The demographic variables will include analysis of the following exemplary baseline characteristics:

Baseline Characteristics	**Patients (n=xx)**
Age, median (range)	xx (xx-xx)
Race	
White or Caucasian	x (xx%)
Black or African American	x (xx%)
Asian	x (xx%)
Unknown or Not Reported	x (xx%)
Histology	
High-grade serous	xx (xx%)
Intermediate-grade serous	xx (xx%)
Mixed	xx (xx%)
ECOG performance status	
0	xx (xx%)
1	xx (xx%)
Prior number of lines, median (range)	xx (xx-xx)
Prior platinum lines, median (range)	xx (xx-xx)
Platinum status at enrollment	
Platinum-resistant	xx (xx%)
Platinum-refractory	xx (xx%)
Intermediate platinum sensitive	xx (xx%)
Prior anti-angiogenic therapy with bevacizumab	
Yes	xx (xx%)
No	xx (xx%)
Prior PARP inhibitor therapy	
Yes	xx (xx%)
No	xx (xx%)
Baseline genetic profiles	
Tumor PD-L1 expression	
Positive	xx (xx%)

Negative	xx (xx%)
Unknown	xx (xx%)
BRCA1/2 mutations	
Positive	xx (xx%)
Negative	xx (xx%)
Unknown	xx (xx%)
Microsatellite instability status	
Stable	xx (xx%)
High	xx (xx%)
Unknown	xx (xx%)
Tumor mutational load	
Low	xx (xx%)
Intermediate	xx (xx%)
High	xx (xx%)
Unknown	xx (xx%)
Response & PFS from last prior line before enrollment into VIRO-15 trial	
ORR by RECIST	x/xx (xx%)
ORR by CA-125	x/xx (xx%)
PFS (mos), median (95% CI)	xx (xx-xx)
PFS-6-month	xx%

Medical History
Medical history events will be classified using the Medical Dictionary for Regulatory Activities (MedDRA) classification system version 19.1. Medical history data will be summarized using frequency tabulations by System Organ Class (SOC) and Preferred Term (PT).

Past treatment and response history are to be documented when available, which may include baseline platinum status, number (regimen and cycles) of lines of therapy, number (regimen and cycles) of platinum-based lines, best overall response by RECIST1.1, changes of target lesion diameters, CA-125 values, date of disease progression (to assess PFS and DOR), adverse events, etc.

6. STUDY DRUG EXPOSURE AND COMPLIANCE

The following variables will be summarized:

- Date & dose of GL-ONC1 (aka Olvi-Vec) treatment; number of cycles if applicable
- If applicable, date, regimen & dose of subsequent chemotherapy +/- bevacizumab; number of cycles.

7. PRIOR AND CONCOMITANT MEDICATIONS

All concomitant treatments documented during the study period will be summarized in frequency tabulations. Prior/concomitant medication coding will utilize the World Health Organization (WHO) Drug Dictionary version 2016SEP01DDE (Enhanced).

Prior medications will only be presented in listings. Prior medications will be defined as those medications with both a start and a stop date that is before the day of the first dose of study drug administration. If either the start date and/or the stop date of the medication is missing so that it is unclear whether the medication was stopped prior to first dose of study drug administration then the medication will be included in the summary of the concomitant medications.

8. SAFETY & EFFICACY VARIABLES

Primary variables:

Phase 1b: adverse events.
Phase 2 (Cohorts A, B & D): Progression-free Survival (PFS) with therapeutic intent.
Phase 2 (Cohort C & D): Overall Response Rate (ORR) by RECIST1.1 and by GCIG CA-125 criteria with therapeutic intent.

Secondary Objectives:

Phase 1b & Phase 2 Cohorts A & B: Response to treatment with therapeutic intent will be determined based on Response Evaluation Criteria in Solid Tumors (RECIST) 1.1, by the Immune-related Response Criteria (irRC) as an exploratory endpoint, and by CA-125 according to the Gynecologic Cancer Intergroup (GCIG) CA-125 response criteria in patients with measurable disease. Patients who enter with non-measurable disease will be evaluated for response to treatment by PET/PET CT scan, physical examination and CA-125 levels. Antitumor activity (if evaluable by CT, PET/PET-CT scans) will be evaluated by progression-free survival (Phase 1b only), Clinical Benefit Rate (CBR: CR + PR + SD), best overall response (BOR), duration of response (DoR), objective overall response rate (ORR), disease control rate (DCR = CR + PR + SD≥15 weeks). Additionally, overall survival (OS) and time to treatment failure (TTF) will be assessed. In the Phase 2 study, safety assessment will continue.

Phase 2 Cohort C & D:

- Progression-free Survival by RECIST1.1 (Ch C)
- Duration of Response
- Clinical Benefit Rate
- Disease Control Rate
- Overall Survival

9. EFFICACY ANALYSIS

Since VIRO-15 is a non-randomized single-arm study, efficacy analysis will be conducted in comparison to historical data or in comparison to patients' own past treatment history.

For GL-ONC1 (aka Olvi-Vec) monotherapy patients, baseline is at enrollment prior to start of virotherapy.

For GL-ONC1 (aka Olvi-Vec) followed by chemotherapy +/- bevacizumab patients, baseline for PFS, ORR, DoR, CBR, DCR and TTF evaluations is the timepoint immediately prior to starting post-Olvi-Vec carboplatin doublet +/- bevacizumab in evaluable patients to allow direct comparison to historical data or patients' own previous line of therapy. Alternatively, baseline from prior to virotherapy will also be studied for the primary and secondary endpoints.

Progression-free Survival

PFS assessment follows the FDA's published guidelines: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics Guidance for Industry (2018): https://www.fda.gov/media/71195/download.

PFS is defined as the time from enrollment before virotherapy or from start of subsequent chemotherapy to first documentation of progressive disease, death due to any cause, or receipt of subsequent anticancer chemotherapy other than components of the protocol specified treatment regimen (PARP inhibitor as maintenance after subsequent chemotherapy +/- bevacizumab is allow). A combined PFS (i.e. PFS1 from viral monotherapy and PFS2 from subsequent chemotherapy +/- bevacizumab) will also be presented if applicable. Disease progression is determined based on radiological evidence of progression per RECIST1.1, and is not by clinical symptom or rise of CA-125. Patients are censored if there is no documented progression, lost to follow up, withdrawal of consent, or other reasons.

Tumor scans will continue to be performed during follow up for patients who discontinue treatment without a documented disease progression event by RECIST1.1. As such, a sensitivity analysis will be performed in which all tumor scans or death events will be included for assessment of PFS even if the patient discontinued study treatment or initiated a subsequent anticancer therapy that is not part of the protocol.

Kaplan-Meier curves depicting PFS will be generated for each study part. Additionally, median PFS and probability of PFS at a defined time point (such as PFS-6-month) will be reported. If able to be estimated, the 50th (median) together with a 95% CI, will be presented.

Overall Response Rate by RECIST1.1

The ORR by RECIST will be analyzed in the subgroup of patients who have measurable disease (i.e., measurable target lesions) at baseline. Patients are considered as evaluable if they have had at least 1 measurable target lesion and at least 1 post-chemo CT scan. Both unconfirmed and confirmed response rate by RECIST1.1 will be summarized. The confirmed response rate is defined as the proportion of patients with a confirmed CR or PR on subsequent tumor assessment at least 28 days after first response documentation. The ORR will be summarized with frequencies and proportion together with 95% confidence interval (CI). In addition, the frequency and proportion of patients will be summarized for each of the unconfirmed and confirmed response categories:

- Complete response (CR)
- Partial response (PR)
- Stable disease (SD)
- Progressive disease (PD)

• Not evaluable (for example, discontinuation or death before first tumor assessment)

Change from Baseline in Sum of the Diameters of Target Lesions

The change from baseline (before virus or before first dose of subsequent chemotherapy) in sum of longest diameters (SLD) of target lesions will be analyzed in the subgroup of patients who have measurable disease (i.e., measurable target lesions) at baseline (such as shown in a spiderplot). The largest percent decrease from baseline in the SLDs of target lesions as identified by RECIST1.1 will be displayed graphically using a waterfall plot. This analysis will be presented for patients with measurable disease at baseline and one valid post-baseline evaluation of the target lesions. Additionally, changes of individual target lesions from each patient will also be presented using a waterfall plot to investigator potential systemic antitumor efficacy against multiple target lesions.

When available, comparative CT scan images showing before and after treatment of target lesion changes in the same patients will be presented.

Overall Response Rate by GCIG CA-125 criteria

Analyses of changes and/or percent changes from baseline (before virus or before first dose of subsequent chemotherapy) for CA-125 measured by clinical laboratories will be analyzed for each post-baseline visit, if feasible. Patients who do not have both a baseline measurement and at least one post-baseline measurement will not be included in this analysis. CA-125 response is determined by GCIG criteria (Rustin *et al*., 2011) https://www.ncbi.nlm.nih.gov/pubmed/21270624. Dynamic change of CA-125 from baseline until progression (and beyond) will be plotted *vs.* time as spider plots. The largest percent decrease from baseline will be displayed graphically using a waterfall plot. This analysis will be in evaluable patients per GCIG criteria. If able to be estimated, the 50th (median) together with a 95% CI, will be presented.

Duration of Response per RECIST 1.1

The Duration of Response (DOR) will be analyzed in the subgroup of patients who have measurable disease (i.e., measurable target lesions) at baseline and have confirmed/unconfirmed response by RECIST 1.1. DOR for any confirmed/unconfirmed RECIST CR or PR will be measured from the date of the first response until the first date that PD is documented. DOR will be summarized as a time to event variable. Time-to-response (from baseline to first response) will also be documented.

For patients who continue treatment post-progression, the first date of progression will be used for the analysis. Any patients with an ongoing response will be censored at the date of the last post-baseline scan. The Kaplan-Meier methodology will be used to summarize DOR. If able to be estimated, the 50th (median) together with a 95% CI, will be presented.

Overall Survival

The time to overall survival will be calculated in months as the time from enrollment (or from before starting subsequent chemotherapy) to date of death (1) due to any cause. Patients who are still alive will be censored (0) on the date of their last available visit or last date known to be alive. Kaplan-Meier curves depicting OS will be generated for each study part. Additionally,

median OS and probability of OS at a defined time point (such as OS-12-month) will be reported.

Median Follow-up Time
Schemper and Smith (A note on quantifying follow-up in studies of failure time. Controlled clinical trials (1996)17 (4)343-346) devised a method to obtain the median follow-up time by conducting 'reverse' Kaplan-Meier analysis of overall survival, with the meaning of the status indicator reversed, where loss of follow-up is the event (1) being followed, and a death (0) is treated as censoring the data.

Clinical Benefit Rate (CBR)
CBR is assessed based on RECIST, which is the percentage of patients with objective responses and patients with stable diseases (i.e., CBR = OR + SD).

Disease Control Rate (DCR)
DCR is assessed based on RECIST, which is the percentage of patients with objective responses and patients with stable diseases lasting ≥15 weeks (i.e., DCR = OR + SD ≥15 weeks).

Time to Treatment Failure (TTF)
TTF is defined as the time from baseline to treatment discontinuation for any reason, including disease progression, treatment toxicity, patient preference, or death.

Examination of Efficacy in Subgroups
Subgroup analyses of the endpoints are to be conducted in the following exemplary groups if relevant and feasible:

- Age
- FIGO stage
- Histology at diagnosis
- Number of prior chemotherapy lines
- Number of prior platinum-based lines
- Gap between last Olvi-Vec virus dose to first dose of subsequent chemotherapy
- Body mass index (BMI)
- Prognostic nutritional index (PNI)
- Baseline CA-125 values (ideally on the day before first dose of Olvi-Vec)
- Baseline LDH
- LDH/PNI ratio
- Baseline absolute lymphocyte counts
- Highest post virus treatment anti-vaccinia neutralizing antibody levels (shown as dilution factor)
- Platinum status (resistant, refractory, intermediate platinum-sensitive; primary or secondary)
- ECOG
- BRCA status
- PD-L1 status
- MSI status

- Tumor mutation load (number of mutations, and low/intermediate/high status)
- Prior exposure to bevacizumab
- Prior exposure to PARP inhibitor
- Prior exposure to immune checkpoint inhibitor
- Best change of CA-125 post virotherapy
- Best change of CA-125 post chemotherapy (after virotherapy)
- Baseline tumor burden (presented as SLDs of target lesion(s) in millimeters) before virotherapy or before subsequent chemotherapy
- Best change of tumor size, either after virotherapy or after start of subsequent chemotherapy
- Best response to virotherapy, or to subsequent chemotherapy +/- bevacizumab
- Baseline platinum-free interval (time from last dose of last prior line of platinum until PD)
- Gap of platinum-free time (last dose of last platinum until first dose of platinum in VIRO-15)
- Best Overall Response by RECIST of last prior line, or last platinum-based line
- PFS from enrollment, or from before starting subsequent chemotherapy after virus
- PFS of last prior line, and of last platinum-based line (e.g., for Von Hoff ratio analysis; *J. Clin. Oncol*. 2010;28(33):4877-83)
- Overall survival

10. ADVERSE EVENTS (AES) AND SAFETY ANALYSIS

The safety analyses will be performed using the safety population.

All AEs will be classified using the MedDRA version 19.1 classification system. The severity of the toxicities will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) whenever possible. Treatment-related adverse events (TRAEs) are defined as AEs with onset date on or after the date of first dose of study medication (GL-ONC1, aka Olvi-Vec) until within 28 days after the last GL-ONC1 treatment that are determined to have a degree of attribution to GL-ONC1 (i.e., probably, possibly or definitely).

The number and percentage of patients who experienced AEs/TRAEs will be presented. Multiple instances of the AEs/TRAEs in each SOC and multiple occurrences of the same PT are counted only once per patient with the higher degree of severity included in safety analysis. The number and percentage of patients with at least one AE/TRAE will also be summarized.

Separate tables will be presented as follows, if relevant:

- All AEs/TRAEs;
- AEs/TRAEs by CTCAE grade;
- Grades 1 or 2 AEs/TRAEs (in all, a %, or a number of patients, such as ≥ 20% of patients);
- Grade 3 or greater AEs/TRAEs (in all, a %, or a number of patients, such as ≥ 2 patients);
- AEs/TRAEs with an outcome of death;
- AEs/TRAEs leading to discontinuation of study medication;
- AEs/TRAEs resulting in reduction study medication;

- AEs/TRAEs resulting in interruption of study medication;
- AEs/TRAEs resulting in reduction or interruption of study medication;
- Time to the first AEs/TRAEs that results in a reduction or interruption of study drug.

The incidence of AEs/TRAEs will be summarized by relationship to study drug according to the following categories: "treatment-related," or "not treatment-related". If a patient experiences multiple occurrences of the same AE with different relationship categories, the patient will be counted once, as a relationship category of treatment related.

If a patient experiences multiple occurrences of the same AEs/TRAEs with different toxicity grades, the patient will be counted once for the maximum (most severe) toxicity grade. AEs with a missing toxicity grade will be presented in the summary table with a toxicity grade of "Missing." For each toxicity grade, the number and percentage of patients with at least one AEs/TRAEs of the given maximum grade will be summarized.

11. Clinical & Translational Laboratory Evaluations

Clinical laboratory evaluations include the continuous variables for hematology, serum chemistry, and urinalysis. Translational laboratory evaluations are listed in the optional *Exploratory Objectives*, including immune cell analyses by multiplex IHC of pair tumor biopsies, tumor-specific T-cell response analysis by ELISPOT, tumor gene expression analysis using NanoString RNA analysis, anti-vaccinia neutralizing antibody, etc. The laboratory values will be presented in SI units if applicable. The summary of laboratory data will include descriptive statistics, e.g., N, mean, SD, minimum, median, and maximum. Laboratory data including normal ranges and flagged abnormal laboratory findings will be provided using by-patient listings. Graphic results will also be presented when applicable.