COVER PAGE

OFFICIAL PROTOCOL TITLE:	**A Multi-Center Phase III, Randomized, Open-Label Trial of Vigil (bi-shRNAfurin and GMCSF Augmented Autologous Tumor Cell Immunotherapy) in combination with Irinotecan and Temozolomide as a Second-Line Regimen for Ewing's Sarcoma**
PROTOCOL NUMBER:	**CL-PTL-130**
IND NUMBER:	**014205**
NCT NUMBER:	**NCT03495921**
STATISTICAL ANALYSIS PLAN VERSION DATE:	**December 5, 2018**

STATISTICAL ANALYSIS PLAN

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PROTOCOL NUMBER:	**CL-PTL-130**
STUDY AGENT(S):	**Vigil** **bi-shRNA^{furin} and GMCSF Augmented Autologous Tumor Cell Immunotherapy**
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ABBREVIATIONS

Abbreviation	Term
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
CBC	Complete blood count
CD	Cluster of differentiation
CRF	Case report form
CT	computerized tomography
CTCAE	Common Toxicity Criteria for Adverse Events
ctDNA	Circulating tumor DNA
CTM	Clinical Trial Material
ELISPOT	Enzyme-Linked ImmunoSorbent Spot
ESFT	Ewing's Sarcoma Family of Tumors
EWS	Ewing's Sarcoma
GMCSF	Granulocyte Macrophage-Colony Stimulating Factor
HR	Hazard Ratio
IDMC	Independent Data Monitoring Committee
IFN	Interferon
ITT	Intent to Treat
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
ORR	Objective Response Rate
OS	Overall Survival
PBMC	Peripheral Blood Mononuclear Cells
PFS	Progression Free Survival
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event
STD	Standard Deviation
TEAE	treatment-emergent adverse event
WHO	World Health Organization

1.0 INTRODUCTION

This document describes the statistical methods and data presentations to be used in the summary and analysis of safety and efficacy data from Gradalis Protocol CL-PTL-130. Background information is provided for the overall study design and objectives. The reader is referred to the study protocol and case report forms (CRFs) for details of study conduct and data collection.

2.0 STUDY RATIONALE

The results from the Phase I Vigil trial show product safety (both short-term and long-term through 3+ years), confirm effective transgene expression (GMCSF) and RNAi [furin] silencing, and support the rationale of the immunotherapeutic triad, i.e., autologous tumor cell therapy with increased GMCSF expression and decreased TGFβ production shown to effectively modulate immunogenicity as evidenced by the correlation of IFNγ-ELISPOT responsiveness with overall survival and the elicitation of the CD4+ mediated circulating antibody responses against CT47 in two of the Phase 1 Ewing's sarcoma patients. The preliminary evidence of safety, immune stimulation and clinical benefit from Vigil in patients with Ewing's sarcoma treated in the Phase I setting supports evaluation of this therapy in a larger and randomized study and at earlier stage of recurrence (first recurrence). A lower tumor burden is typically associated with greater delay in progression with other immunotherapies. Mathematical modeling supports the concept of better control of disease progression with the combined use of effective chemotherapy (e.g., temozolomide/irinotecan as second line treatment in Ewing's sarcoma) and immunotherapy (i.e., Vigil) in first relapse patient population (de Pillis, Gu et al. 2006). The utilization of the standard of care temozolomide/irinotecan regimen at investigator consensus defined dose and schedule appears to be minimally immunosuppressive and thus a reasonable option for combination with Vigil. Moreover, the temozolomide and irinotecan regimen at effective dose levels has low myelosuppressive toxicities (irinotecan 50mg/m^2/dose and temozolomide 100mg/m^2/dose) and may increase the tumor antigen release and surface exposure of calreticulin (part of the specific danger-signaling system) as well as reduce the frequency of CD4+ CD25+ regulatory T-cells (Kim, Kim et al. 2010). In addition, given that Ewing's sarcoma expression levels of type-1 associated chemokine ligands CXCL9, CXCL10, and CCL5 correlate with TIL expression chemokine receptors (CXCR3 and CCR5) (Berghuis, Santos et al. 2011) it is notable that temozolomide has been shown to enhance tumor matrix presentation of CXCL9 and CXCL10 in certain tumor models (Tan, Evrard et al. 2015). Temozolomide and irinotecan in combination have shown benign safety profiles without any Grade 3 treatment-related adverse events in seven combination treated Ewing's Sarcoma patients of Part 2 of CL-PTL-121. Furthermore, clinical antitumor activity was demonstrated in 4 of the 7 combination treated patients, all of whom had previously failed temozolomide and irinotecan, as evidenced by 2 partial responses, one histological CR (autopsy) and one prolonged SD currently near 1 year in duration. Thus, the combination of Vigil, irinotecan and temozolomide may not only increase anti-tumor responses but also prolong time to progression and improvement of quality of life in Ewing's sarcoma patients.

3.0 OBJECTIVES

3.1 Primary objective(s)

- To compare the progression free survival of subjects dosed with Vigil immunotherapy in combination with irinotecan and temozolomide vs. irinotecan and temozolomide.

3.2 Secondary objective(s)

- To determine and compare the overall survival of subjects with relapsed or refractory Ewing's sarcoma dosed with Vigil immunotherapy in combination with irinotecan and temozolomide.
- To determine the objective response rate (RECIST 1.1) of patients with metastatic Ewing's sarcoma refractory or intolerant to 1 prior line of systemic chemotherapy treated with Vigil immunotherapy or dosed with Vigil immunotherapy in combination with irinotecan and temozolomide.
- To determine the Vigil manufacturing success rate by gathering data from tumor tissue collection, Vigil construction, and test procedures.

4.0 END POINTS

4.1 Primary Endpoint

The primary endpoint of PFS is the time from randomization to progression according to RECIST version 1.1 or death. Incomplete data resulting from patients who terminate the study for reasons other than disease progression or death will be censored in time-to-event analyses on the last assessment date at which a RECIST 1.1 evaluation of disease status was made. The distributions of PFS in the two arms will be compared using a two-sided log-rank test.

4.2 Secondary Endpoint

The secondary endpoint of OS is defined as time from randomization to death or to the date of last follow-up. The date of last follow-up confirming survival will be used as the censoring date for subjects who are alive and/or do not have a known date of death. The analysis of OS will be conducted using the two-sided log-rank test. Kaplan-Meier OS curves will be displayed by treatment arm. Median OS and percent OS at fixed time points will be estimated.

The secondary endpoint of ORR will be analyzed using Pearson's chi-square test.

All secondary analyses will be conducted using two-sided tests at the alpha=0.05 level of significance.

5.0 STUDY DESIGN

This is a multicenter, 1:1 randomized Phase III study of intradermal autologous Vigil immunotherapy (1.0 x 10^6 cells/injection cells/injection; minimum of 4 to a maximum of 12 administrations) in combination with irinotecan and temozolomide in subjects with metastatic Ewing's sarcoma Family of Tumors (ESFT) refractory/intolerant or recurrent to 1 prior line of chemotherapy. Participants undergoing a standard surgical procedure (e.g., tumor biopsy or palliative resection) may have tumor tissue harvested for manufacture of investigational product.

Subjects meeting eligibility criteria including manufacture of a minimum of 4 immunotherapy doses of Vigil will receive:

Group A

(i) oral temozolomide 100 mg/m^2 daily (Days 1 – 5, total dose 500 mg/m^2/cycle),
(ii) oral irinotecan 50 mg/m^2 daily (Days 1 – 5, total dose 250mg/m^2/cycle), and
(iii) Vigil 1.0 x 10^6 cells/injection, intradermally on Day 15.

OR

Group B

(i) oral temozolomide 100 mg/m^2 daily (Days 1 – 5, total dose 500 mg/m^2/cycle), and
(ii) oral irinotecan 50 mg/m^2 daily (Days 1 – 5, total dose 250mg/m^2/cycle)

If chemotherapy study drugs cannot be administered orally (i.e. size of capsule, nausea, etc.) it is physician's discretion to request iv administration of temozolomide at 100 mg/m^2 daily and/or irinotecan 20 mg/m^2 daily intravenously.

One cycle = 21 days. Screening for the main portion of the study may occur as early as one week but no later than 8 weeks following tumor procurement. Vigil is typically released approximately 3 weeks after the completion of the two-day manufacturing process. At the time of analysis the subjects will be stratified by initial response to frontline treatment (recurrent versus refractory (progressive)).

Participants will be managed in an outpatient setting. Hematologic function, liver enzymes, renal function and electrolytes will be monitored. Blood for immune function analyses including IFNγ-ELISPOT analysis of cytotoxic T cell response to autologous tumor antigens will be collected at tissue procurement, post-procurement screening and prior to chemotherapy administration on Day 1 of Cycles 2, 4, and 6, end of treatment (EOT), 3 months after EOT and every 6 months thereafter. Blood for exploratory ctDNA analysis will be collected at tissue procurement, prior to chemotherapy administration at baseline, prior to chemotherapy administration on Day 1 of Cycles 2, 3, 4, and 6, and EOT.

6.0 SCHEDULE OF ASSESSMENTS

Procedure	Prestudy	Screening	Day 1 of each Cycle[1] (unless otherwise noted)	End of TX	Response Follow-Up (q 3mo±7 days) Until Progression
Informed consent	X	X			
Medical History	X				
Physical Examination	X	X	X	X	X
Toxicity (adverse events)		from time of procurement	X	X	
Concomitant medications		X	X	X	X
Performance Status		X	X	X	X
Radiological Tumor Assessment (chest/abdomen/pelvis)		within 4 weeks (must be post-procurement)	every 6 weeks ± 7 days from Cycle 1	Within 45 days	X
CBC with differential	X[2]	X	X	X	X
HIV testing, if applicable		X			
Hepatitis testing, if applicable		X			
Serum Chemistry	X[3]	X	X	X	X
PBMC collection for Immune Function Analysis	≤ 1 week of tumor procurement	X	Cycles 2, 4, and 6 Day 1prior to chemotherapy administration	X	3 months post EOT and q 6 months thereafter
Plasma collection for ctDNA	≤ 1 week of tumor procurement	X	(Cycles 2, 3, 4, and 6 Day 1 prior to chemotherapy administration	X	
Pregnancy Test (if applicable)		X			
Vigil administration *depending on randomization*			Day 15 q 21±3 days[4]		
Injection Site Assessment			Day 16 only (may be conducted at home)[5]		
Temozolomide			Days 1 – 5, q21 days		
Irinotecan			Days 1 – 5, q21 days		

[1] Subjects who are stable at the end of Cycle 4, with prior approval by the Sponsor may conduct evaluations on Day 15 of each cycle (1 Cycle = 21 days ±3 days)

[2] Obtain from medical records from standard preoperative hematology and chemistry panels.

[3] Obtain from medical records from standard preoperative hematology and chemistry panels.

[4] Cross-over subjects will receive Vigil on Day 1

[5] Cross-over subjects will have assessment on Day 2

Procedure	Prestudy	Screening	Day 1 of each Cycle[1] (unless otherwise noted)	End of TX	Response Follow-Up (q 3mo±7 days) Until Progression
Survival Status	X				Long Term Follow Up[6]
Immunohistochemistry		X[7]			

7.0 SAMPLE SIZE JUSTIFICATION

This is an open label randomized controlled Phase III clinical trial. Information concerning the predicted survival of the control group is limited, based on rarity of disease and few published reports. However expert advisors in the EWS field estimate a conservative one-year survival rate of 25% in the chemotherapy control group. The one-year survival rate of 60% in the Vigil treated group is estimated from EWS patients treated on the Vigil phase 1 protocol. These estimates correspond to a hazard ratio (HR) of 0.383 favoring Vigil over control.

Assuming 1:1 randomization and the use of a two-sided log rank test at the alpha=0.0476 level of significance, 67 events will provide 90% power to detect an PFS HR of 0.45. Assuming a Group B (control group) median PFS of 6 months, a one-year accrual period, and a six-month follow-up period after randomization of the last subject, it is estimated that the total sample size (number of subjects) required to achieve 67 events is 114 (57 patients in each arm).

An unblinded interim analysis will be conducted by an independent data monitoring committee (IDMC) when 40 PFS events have occurred. Based on the results of this interim analysis, the planned sample size may be increased to 120 events. If the sample size is increased to 120 events, then the study will have approximately 90% power to detect a true HR of 0.55. Note that if the sample size is increased to 120 events, then the accrual period will be extended to 24 months, with a 6-month follow-up period after randomization of the last patient. Under these assumptions, it is estimated that approximately 164 patients will need to be randomized in order to achieve 120 events. Section 16.6 provides further details.

7.1 Definition of Progression Free Survival (PFS)

- Progression free survival (PFS) is defined as the time from randomization to the event of disease recurrence/progression or death due to any cause.
- Radiographic disease recurrence/progression will be assessed using the RECIST 1.1 criteria. If the disease recurrence/progression assessment involves more than one date, the earliest date will be used as the event date.

[6] After progression, subjects will be contacted by phone quarterly for documentation of survival status.

[7] These slides should correlate with tumor procured for vaccine manufacture.

- Patients who are alive and recurrence free at the time of analysis data cut-off, or who terminate the study for reasons other than disease progression or death, or who receive non-protocol treatment for Ewing's Sarcoma, will be censored on the last assessment date at which a RECIST 1.1 evaluation of disease status was made.
- Patients missing baseline disease assessment will be censored at date of randomization.
- For equivocal findings of recurrence (e.g., very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If recurrence is confirmed at the next scheduled assessment, the date of recurrence should be the earlier date when recurrence was suspected.

8.0 ANALYSIS POPULATIONS

The intent-to-treat (ITT) population will include all randomized subjects. All efficacy analyses will be completed in the ITT population.

The Safety population will include all patients who receive study treatment and patients will be analyzed according to actual treatment received. All safety analyses will be completed in the Safety population.

8.1 Efficacy Analyses

8.1.1 Primary Efficacy Analysis

The primary endpoint of PFS is the time from randomization to progression according to RECIST version 1.1 or death. The distributions of PFS in the two arms will be compared using a two-sided log-rank test at the alpha=0.0476 level of significance.

8.1.2 Secondary Efficacy Analyses

A fixed sequence testing procedure will be used to control the overall level of significance for the analysis of the secondary endpoints of OS and ORR. If the primary analysis of PFS is statistically significant ($p<0.0476$), then OS will be analyzed using a two-sided test at the alpha=0.0476 level of significance. In addition, if the analysis of OS is statistically significant ($p<00476$), then ORR will be analyzed using a two-sided test at the alpha=0.0476 level of significance. However, if an earlier analysis is not statistically significant, the remaining analyses will be exploratory rather than confirmatory.

The secondary endpoint of OS is defined as time from randomization to death or to the date of last follow-up. The date of last follow-up confirming survival will be used as the censoring date for subjects who are alive and/or do not have a known date of death. The analysis of OS will be conducted using the log rank test. Kaplan-Meier OS curves will be displayed by treatment arm. Median OS and percent OS at fixed time points will be estimated.

The secondary endpoint of ORR will be analyzed using Pearson's chi-square test. Overall response rate (ORR) is defined as the proportion of patients who have prolonged stable disease or a partial or complete response to therapy according to RECIST 1.1. ORR will be reviewed 6 months after treatment with Vigil.

The secondary analysis of all secondary endpoints will be conducted using two-sided tests at the alpha=0.05 level of significance.

8.1.3 Sensitivity Analyses of the Primary Endpoint

Five sensitivity analyses of the primary endpoint will be conducted using each of the following modifications to the definition of PFS:

- If the disease recurrence/progression assessment involves more than one date, the latest date will be used as the event date.
- If disease recurrence or death occurs right after missing data for a scheduled radiographic disease assessment (including missing the assessment or assessment results in an unevaluable status for overall response per RECIST 1.1), the patient will be censored at the date of the last radiographic disease assessment.
- If a patient receives non-protocol treatment for Ewing's Sarcoma, the patient will be treated as having progression at the date of the last radiographic disease assessment.
- Patients missing baseline disease assessment will be treated as having progression at the date of randomization.
- For equivocal findings of recurrence (e.g., very small and uncertain new lesions; cystic changes or necrosis in existing lesions) for whom treatment continues until the next scheduled assessment, and if recurrence is confirmed at the next scheduled assessment, the date of recurrence should be the earlier date when recurrence was suspected.

8.1.4 Sensitivity Analysis of Overall Survival

A sensitivity analysis of OS will be conducted in which subjects who are crossed over to Vigil therapy will be censored at the time of crossover.

8.1.5 Subgroup Analyses of the Primary (PFS) and Key Secondary Endpoints (OS, ORR)

Subgroup analyses will be conducted in the following subsets of the ITT population:

- Race / ethnicity
- Study site / region

- Age group (<15 years (low), ≥15 years (high))
- Gender
- Number of doses received (≤median number of doses administered, >median number of doses administered)
- Number of lines of prior treatments including chemotherapy and radiation
- At time of diagnosis: localized vs. metastatic disease
- At time of diagnosis: skeletal vs. extraskeletal
- At time of diagnosis: tumor volume/burden (<100ml or 8cm vs >100ml or 8cm)
- Response to frontline therapy (CR vs. PR vs. SD vs. progressive disease)
- Time to first recurrence: <2 years, > 2 years

8.2 Safety Analyses

Safety endpoints include all adverse events (CTCAE version 5.0), laboratory safety assessments, and physical examination findings.

8.3 Interim Analysis

An interim analysis for efficacy, futility, and potential sample size re-estimation will be conducted by an independent data monitoring committee (IDMC) when 40 PFS events have been achieved (60% information fraction). Based on the Lan-DeMets method for group sequential trials using O'Brien-Fleming boundaries (Reboussin, DeMets et al. 2000), the levels of significance for the interim and final analyses are alpha=0.00762 and alpha=0.0476, respectively.

Based on the results of the interim analysis, the IDMC will make one of the following four recommendations to the sponsor:

- Terminate the study for efficacy (p<0.00762 at the interim analysis);
- Continue the study as planned;
- Increase the sample size to 120 events;
- Terminate the study for futility.

Provided that the IDMC does not recommend terminating the study early for efficacy, the conditional power of the planned final analysis at 67 events will be computed using the methodology of (Harrington 2001) (Jennison and Turnbull 2000), under the assumption that the observed hazard ratio at the interim analysis represents the true effect. In terms of the HR observed at the interim analysis, these rules can be translated (approximately) as follows:

- If the HR is less than 0.43, terminate for efficacy
- If the HR is in the range from 0.43 to 0.51, continue as planned.
- If the HR is in the range from 0.51 to 0.61 (i.e., conditional power in the range from 50% to 80%), increase the sample size to 120 events.
- If the HR is greater than 0.61 (i.e., conditional power less than 50%), terminate for futility.

9.0 CONSIDERATIONS FOR DATA ANALYSIS

9.1 Programming Environment

All analyses will be conducted using SAS® version 9.0.

9.2 Statistical Notation and Methodology

Unless stated otherwise, the term "descriptive statistics" refers to the number of subjects (n), mean, median, standard deviation (STD), minimum (min), and maximum (max) for continuous data and frequencies and percentages for categorical data. Min and max values will be rounded to the precision of the original value, means and medians will be rounded to 1 decimal place greater than the precision of the original value, and STDs will be rounded to 2 decimal places greater than the precision of the original value. Percentages will be rounded to the nearest whole number (zeros are not displayed) with values of "< 1%" and "> 99%" shown as necessary for values falling near the boundaries. P-values will be presented with 3 decimal places and values less than 0.001 will be presented as < 0.001.

Unless otherwise noted, all data collected during the study will be included in data listings and will be sorted by cohort, subject number and then by date/time for each subject number.

10.0 DATA HANDLING METHODS

10.1 Missing Data

10.1.1 Date Values

In cases of incomplete dates (e.g., pertaining to AE, concomitant medication, medical history, etc.), the missing component(s) will be assumed as the most conservative value(s) possible. For example, if the start date has a missing day value, the first day of the month will be imputed for study day computations (i.e., treatment-emergent status, etc.). If day is missing for an end date, the last day of the month will be imputed. Similar logic will be assumed for missing month and year components.

Date imputation will only be used for computational purposes e.g., treatment-emergent status, etc. Actual data values as they appear in the original CRFs will be shown in the data listings.

10.1.2 Non-Date Values

Every effort will be made to obtain the protocol-required data for all study assessments that are scheduled for each scheduled visit for all subjects who have been enrolled. The primary endpoint is progression free survival, survival models (Kaplan-Meier estimates and Cox model) which take into account censored observations will be used. There will be no imputation for missing data for the primary endpoint.

10.2 Visit Windows

Study visit periods will be windowed as applicable as shown in Section 6.0.

Values will be presented for all scheduled study visits according to the nominal visit obtained from the CRF. If an unscheduled visit falls in a visit window with an existing nominal visit assessment, the nominal assessment will be used for summary presentation. If no nominal visit assessment exists for a visit window with unscheduled visit(s), then the latest unscheduled visit within the visit window will be used. If multiple nominal assessments are collected within the same visit, the latest value and corresponding date will be used for summary presentation.

All values will be included in the data listings.

10.3 Data Derivations and Definitions

The following definitions and derivations will be used for this study:

Baseline for all assessments will be considered as the last non-missing assessment prior to the first administration of clinical trial material (CTM).

Change from baseline will be calculated as:

Change = observed value – baseline value.

Study days on or after the initial dose of CTM will be computed as:

Study Day = Date – Study Drug Start Date + 1.

For pre-dosing dates, Study Day = Date – Study Drug Start Date.

Age will be calculated from the date of birth to informed consent date.

Treatment-emergent events will be considered as any event occurring after the first dose of treatment drug and prior to a subject's termination, withdrawal or completion of the study.

Prior medications will be those ended before the first study treatment.

Concomitant medications are those used on or after the date of first study treatment.

11.0 STUDY POPULATION

Unless otherwise stated, all study population analyses will be performed on the Safety Population.

11.1 Subject Disposition

Subject disposition will be presented for all subjects. The composition of the analysis populations and those who enrolled, completed or discontinued from the study will be summarized by dose cohort and overall with descriptive statistics. Reasons for early discontinuation will be presented with frequencies and percentages for all categories.

11.2 Demographic and Baseline Characteristics

Demographics and baseline characteristics listing will include date of birth, age, gender, ethnicity, race, and height and weight and BMI at screening. Each of these variables except date of birth will also be summarized with descriptive statistics.

11.3 Prior Disease medications/therapy and Concomitant Medications

Concomitant medications will be coded with the World Health Organization (WHO) drug dictionary. Concomitant medications will be summarized with descriptive statistics by drug Anatomical Therapeutic Chemical (ATC) Classification System (level one), generic name, and cohort. A data listing will be included that shows all medications by generic name and verbatim name. Prior medications/therapy will be excluded from the summary but be included in the listing.

11.4 Concomitant procedures

Concomitant procedures will be summarized by indication type, treatment arm, and time point and also will be included in the listing.

11.5 Medical and Surgery History

Medical history will be summarized with descriptive statistics by medical history code and treatment group. A comprehensive data listing will also be included.

11.6 Inclusion/Exclusion Criteria

Inclusion and exclusion criteria failures will be included in a data listing.

11.7 Protocol Violations/Deviations

Protocol violations will be summarized with descriptive statistics by category. A listing of all events will also be included.

Major protocol deviations include, but are not limited to the following:

- Non-fulfillment of all inclusion criteria or fulfillment of at least one exclusion criteria;
- No consent form found;
- Other relevant deviations, to be judged on an individual basis.

Minor protocol deviations include, but are not limited to:

- Measurements obtained outside the visit window to a limited degree;
- Other deviations will be judged on an individual basis.

12.0 EFFICACY ANALYSIS

12.1 Tumor Assessment

Disease recurrence will be evaluated in this study using the Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 (Eisenhauer, Therasse et al. 009). RECIST response will be summarized with descriptive statistics.

Local and central radiology tumor assessment will be performed in this study, summary of the tumor assessment will be presented.

12.1.1 Radiology Tumor Assessment

Radiology tumor assessment will be performed within 4 weeks of the registration.

If the study agent is completed or discontinued before disease recurrence the subject will be followed for recurrence on the following schedule. Radiological assessment of disease status until disease recurrence (i.e., chest X-ray, (chest CT or MRI is acceptable), pelvic/abdominal CT or MRI) performed quarterly (every 3 months ±7 days). The methods used for prestudy assessments (e.g., CT or MRI) should be used throughout the study and if possible, the same equipment should be used each time.

Radiology tumor assessment will be summarized with descriptive statistics in a summary table. A detailed listing will be provided.

13.0 SAFETY

The safety population will be used for all the analyses of safety data.

13.1 Exposure to Study Drug

Study treatment dosing compliance will be summarized with descriptive statistics by treatment group. All exposure and compliance data will be provided in data listings.

13.2 Adverse Events

All reported terms (investigator descriptions) for AEs will be coded using the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA) and summarized with frequencies and percentages by treatment group, system organ classification, and preferred term.

A treatment-emergent adverse event (TEAE) is an event that emerges during treatment, having been absent pretreatment, or worsens relative to the pretreatment state.

The following summaries will be presented with frequencies and percentage by treatment group, system organ classification, and preferred term:

- All AEs
- All TEAEs
- TEAEs leading to discontinuation from the study
- TEAEs by relation to study treatment
- TEAEs by CTCAE severity
- All serious TEAEs
- Serious TEAEs by relation to study drug
- TEAEs with fatal outcome

For all AE summaries, events will be counted only once for a given subject by primary SOC and preferred term. When an adverse event occurs more than once for a subject, the maximum severity and causality will be used.

All AEs will be included in comprehensive data listings. A separate listing will be included for AEs leading to discontinuation from study and AEs with fatal outcome.

13.3 Serious Adverse Events and Death

Separate data listings and summaries will be presented for all SAEs and deaths.

13.4 Laboratory Evaluations

Laboratory assessments and change from baseline will be summarized with descriptive statistics by panel, test, treatment group, and time point. Additionally, abnormal results will be summarized with frequencies and percentages by clinical significance, panel, test, treatment group, and time point.

A data listing will display all laboratory test results and findings.

13.5 Vital Signs

The results of change from baseline of vital signs will be summarized with descriptive statistics by treatment group and time point. A data listing of all data will also be included.

13.6 Physical Examinations

The results of physical examinations will be summarized with frequencies and percentages by category, treatment group, and time point. A data listing of all results will also be included.

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