16.1.9. Documentation of Statistical Methods

Statistical Analysis Plan, Version 1.1, 14 April 2019

STATISTICAL ANALYSIS PLAN

PRODUCT UNDER INVESTIGATION:

OTL38 Injection: folate analog ligand conjugated with an indole cyanine-like green dye as a solution in vials containing 1.6 mL at 2 mg/mL

TITLE:

A Phase 2, Single dose, Open-Label, Exploratory Study to Investigate the Safety and Efficacy of OTL38 Injection for Intraoperative Imaging of Folate Receptor Positive Lung Nodules

STUDY NUMBER
OTL-2016-OTL38-005

STUDY SPONSOR
On Target Laboratories, LLC.
[redacted]

PREPARED BY
[redacted]

DATE AND VERSION
April 14th, 2019 (Final Version 1.1)
(Based on version 5.0 of the protocol dated June 14, 2018)

STATISTICAL ANALYSIS PLAN

APPROVALS

Name and Title	Signature	Date
[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]

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1. LIST OF ABBREVIATIONS

Abbreviation or Specialist Term	Explanation
AE	Adverse event
ANC	Absolute neutrophil count
CSE	Clinically Significant Event
CTCAE	Common Terminology Criteria for Adverse Events
eCRF	Electronic Case Report Form
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
OTL	On Target Laboratories, Inc.
PP	Per Protocol
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAS	Safety Analysis Set
TEAEs	Treatment-emergent adverse events

2. INTRODUCTION

The purpose of this plan is to prospectively (*a priori*) outline the types of analyses and presentations of the safety and efficacy data that will form the basis for conclusions regarding this clinical investigation. The analysis defined in this plan should answer the study objectives outlined in the protocol and explain in detail how the data will be handled or analyzed.

This document contains information to support the generation of the efficacy and safety section for the Clinical Study Report (CSR) for Clinical Protocol OTL38-005. This plan contains the detailed descriptions of the statistical methodologies to be applied, as well as the analysis summaries to present the analysis results. Consistently, OTL38 will be referred to as the ***study drug***.

2.1. Responsibilities

[redacted] will perform the statistical analyses for all clinical data collected. [redacted] is responsible for production and quality control of all datasets, tables, figures, and listings.

2.2. Timing of Analyses

There will be one final analysis for this study after the database lock.

3. STUDY OBJECTIVES AND ENDPOINTS

3.1. Study Objectives

The primary objectives of this study are as follows:

- To estimate the Sensitivity and False Positive rate of OTL38 for malignancy detection during Near Infrared Imaging (NIR).
- To assess the safety and tolerability of single intravenous doses of OTL38.

There are 2 secondary objectives defined for this study.

- To assess the safety of the Fluorescence Imaging Systems for intraoperative imaging when used with OTL38.
- To estimate the efficacy of OTL38 and NIR with respect to the identification of Clinically Significant Events (CSEs).

There are 2 exploratory objectives defined for this study.

- [redacted]

3.2. Endpoints

Primary

Sensitivity or True Positive Rate (TPR) [redacted]

False positive rate (FPR) [redacted]

Secondary

The secondary efficacy endpoint is proportion of patients with at least one CSE as a result of utilizing OTL-38 and Near Infrared Imaging.

[redacted]

Exploratory

1. [redacted]

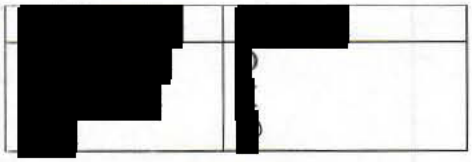
Safety

1. Incidence rates of all treatment-emergent AEs (TEAEs), adverse device effects (ADEs), and SAEs, from the time of OTL38 administration through follow-up Visit 4.
2. Laboratory parameters (chemistry and hematology) and vital signs collected at: screening, during day of surgery and 7-day follow-up
3. Electrocardiograms (ECG) and physical examinations will be collected at screening, day of infusion, and within 24 hours prior to discharge.

4. STUDY OVERVIEW

4.1. Study Design

This is a phase 2, multi-center, single dose, open-label, exploratory study in patients with folate receptor positive lung nodules scheduled to undergo endoscopic or thoracic surgery per CT/PET imaging based on standard of care.



[redacted]

[redacted]

4.2. Sample Size Justification

The primary objective of the study is estimation of the sensitivity and false positive rate of OTL38 and NIR. [redacted]

4.3. Schedule of assessments

5. ANALYSIS POPULATIONS

The efficacy results will be generated for 3 populations:

Safety Analysis Set (SAS): The safety analysis set will include all patients exposed to OTL38 and/or the imaging system.

Full Analysis Set (FAS): [redacted]

- [redacted]
- [redacted]

Per Protocol Analysis Set (PPAS): [redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]

6. GENERAL ASPECTS OF THE STATISTICAL ANALYSIS

The following general rules will be followed for the analysis specified in this SAP. In addition, Section 10 further detailed analysis presentation conventions.

Continuous data will be summarized using the following descriptive summary statistics: the number of observations (n), mean, SD, median, minimum value (min), and maximum value (max).

Categorical data will be summarized using counts and percentages.

Baseline value will be defined as the most recent non-missing scheduled measurement before the administration of the first dose of study drug.

Change from baseline value will be calculated as postbaseline value minus baseline value.

Unscheduled visits: Patient data obtained during unscheduled visits/assessments will not be summarized but will be included in patient data listings only; except for the analysis of maximum values and maximum changes from baseline.

Incomplete and/or missing data will not be imputed, [redacted]

7. DEMOGRAPHIC AND BASELINE CHARACTERISTICS

7.1. Subject Disposition

Subject disposition will be presented for all screened subjects, including number of subjects screen failed and number of subjects enrolled (all subjects).

Summary tables for subject disposition will be presented for all subjects.

Number and percentage of subjects in the following categories will be summarized as appropriate:

- Enrolled (All Subjects, number only)
- Safety Analysis Set
- Full Analysis Set
- Per Protocol Analysis Set

For the summary of the following, the percentage will be based on the Safety Analysis Set:

- Surgery Performed
- Imaging Performed
- Completed study
- Prematurely discontinued the study and the reasons for discontinuations

In addition, total duration of the study will be summarized based on the Safety Set by race and by dose cohort.

Two listings will be presented for Subject Disposition and Major Protocol Deviations.

7.2. Demographic and Baseline Characteristics

All patients in the Safety Analysis Set will be used to summarize the demographic and baseline characteristics with respect to height (cm), weight (kg), gender, age (years) at dosing, race, and ethnicity. Age will be calculated as:

[Date of dosing – Date of Birth] / 365.25 rounded down to the nearest integer.

Age will be reported in years and summarized with descriptive statistics: n, arithmetic mean, standard deviation, median, range (ie, minimum and maximum values). The number and percent of each gender, race, and ethnicity category will be presented using counts and percentages.

7.3. Disease History

Disease history will be coded according to the latest version of MedDRA and presented in listings. Baseline disease characteristics will also be summarized by tumor type and histological grade.

7.4. Prior and Concomitant Medication/Systemic Therapy

Prior systemic therapy for lung cancer and medications used in this study will be coded by using the World Health Organization Drug Dictionary Enhanced. Medications will be categorized as follows:

- **Prior medication** is any recorded medication or supplement that started and ended before initial dosing of study drug,
- **Concomitant medication** is any medication received at or after the dose of study drug, as well as any medication that was received before initial dosing and continued after initial dosing of study drug.

If a medication has a missing or partial missing start/end date or time and it cannot be determined whether it was taken before initial dosing or concomitantly, it will be considered as concomitant.

Concomitant medication will be summarized. Prior medication will be listed. A separate listing will also be provided for any prior radiation therapy and prior surgeries.

7.5. Study Drug Exposure

Study drug exposure will be described using an individual patient data listing to indicate whether the study drug was taken.

OTL38 will be administered intravenously over approximately 60 minutes, the infusion will be completed at least 1 hour prior to initiation of intraoperative imaging.

[redacted]

A summary of study drug administration will be presented via number and percentage of patients who receive the complete dose of OTL38, and also via summary statistics of arithmetic mean, standard deviation, median, range (ie, minimum and maximum values) of the actual OTL38 dose. The individual dosing data will be listed.

7.6. Camera/Imaging System Exposure

A camera/imaging system will be used to identify tumor lesions under fluorescence prior to surgical excision of lesions, and again after surgical excision of lesions to identify persistent lesions. The Investigator will record the start and stop time for each exposure to fluorescence (pre-resection, post-initial resection, other [give reason]) in the eCRF. The total time of fluorescence will be calculated automatically. The camera exposure data will be listed for each patient.

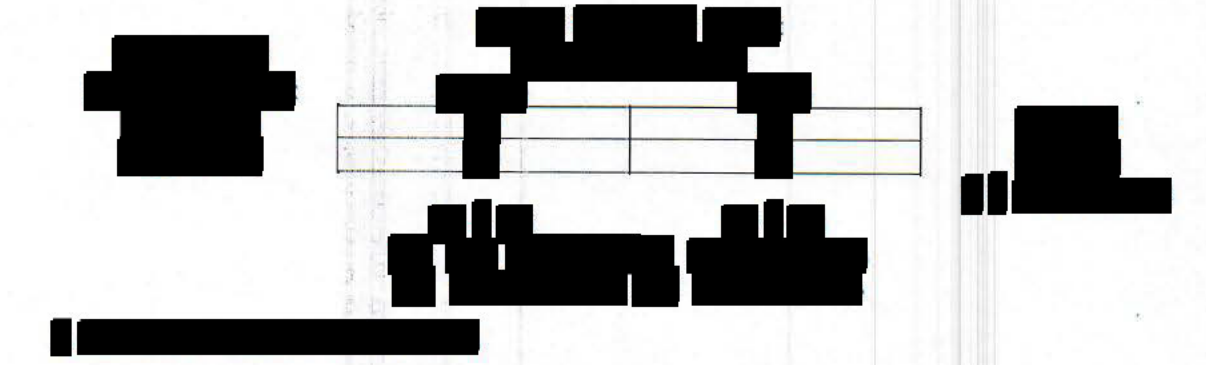
8. EFFICACY

The primary and secondary efficacy analyses will be based on the Full Analysis Set (FAS). The Per Protocol Analysis Set (PPAS) will be used for sensitivity analyses.

8.1. Primary Efficacy Endpoint

The sensitivity and false positive rate of OTL38 to identify lung cancer will be analyzed [redacted]

- **Sensitivity:** Sensitivity or True Positive Rate (TPR) [redacted]
- **False Positive Rate (FPR):** False positive rate (FPR) [redacted]



[redacted]

8.2. Secondary Efficacy Endpoint

The secondary efficacy endpoint is the proportion of patients with at least 1 Clinically Significant Event (CSE) as a result of utilizing OTL-38 and Near Infrared Imaging. [redacted]

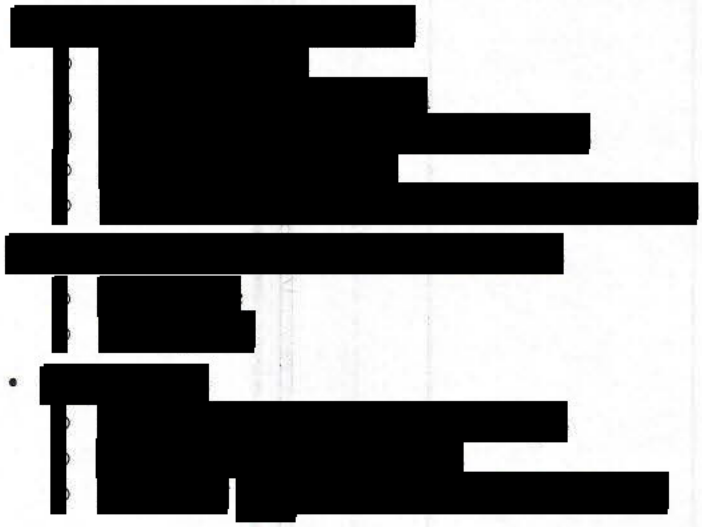
8.3. Exploratory Analyses

[redacted]

8.4. Subgroup Analysis

Using the FAS, point estimates and 95% confidence intervals for the sensitivity and FPR will be provided for the following subgroups:

- Age: < 65 Yrs. Vs. ≥ 65 Yrs.
- Race/Ethnicity
- [redacted]
- Study Center
- [redacted]



9. SAFETY

The safety of all patients enrolled in this study will be recorded from the time of study drug administration and throughout the course of the study that will end with Visit 4 (Day 32).

Safety will be evaluated using the safety analysis set and will include treatment emergent adverse events (TEAEs), adverse device effects (ADEs), serious adverse events (SAEs), vital signs, physical examinations, clinical laboratory measurements, electrocardiograms, and concomitant medications.

For all safety assessments, the baseline value will be the last non-missing value recorded for a particular safety parameter before exposure to study drug. Treatment emergent adverse events are adverse events occurring during or after study drug exposure. Adverse device effects occur during or after exposure to the imaging device and classified as device effects by the Investigator. In general, the analysis of safety will be descriptive. No data will be imputed except for partial dates if required to determine if an adverse event is treatment emergent or a medication concomitant with exposure to study drug.

9.1. Adverse Events and Adverse Device Effects

Adverse events occurring after the signing of informed consent but prior to exposure to OTL38 administration will be provided in line listings. Treatment emergent adverse events (TEAEs) will be summarized via the MedDRA system organ class and preferred term using subject incidence rates. Data will be tabulated by severity, physician assessment of the relationship to study drug, serious TEAEs, and TEAEs leading to death or study withdrawal. Further description of TEAEs may be defined by temporal onset to study drug infusion. Additional summaries of TEAEs identified as potential ADEs will also be provided.

9.2. Clinical Laboratory Assessments

Summary statistics will be presented for each laboratory parameter by visit for hematology, biochemistry, and urinalysis, for both actual values and changes from Baseline.

Shift tables of laboratory data from baseline to post-baseline value, will be presented based on the upper and/or lower limits of normal.

All laboratory data will be listed and values outside of normal ranges will be flagged.

9.3. Electrocardiogram (ECG)

Electrocardiogram results will be provided in patient listings only, sorted by patient, and visit.

9.4. Vital Signs

Vital signs (including the assessments of systolic and diastolic blood pressure, heart rate, respiration rate, and body temperature), and their change from baseline will be summarized each scheduled visit.

All data, including unscheduled visits will be listed.

9.5. Physical Examination

Physical exam results will be presented in a listing that will be sorted by patient number, parameter, and study visit.

[redacted]

11. APPENDIX: ANALYSIS PRESENTATION CONVENTIONS

Post-text tables and listings will be prepared in accordance with the current ICH Guidelines. The information and explanatory notes to be provided in the "footer" or bottom of each table and listing will include the following information:

1. Date and time of output generation;
2. SAS® program name, including the path that generates the output;
3. Any other output specific details that require further elaboration.

In general, tables will be formatted with a column displaying findings for all patients combined. Zeros will be displayed if no data exists for a cell in a count table. The summary tables clearly indicate the number of patients to which the data apply and unknown or not performed are distinguished from missing data.

The study dose level and patient number will be included in all data listings. All listings will be sorted by patient number, and visit date, as applicable. Patient listings will also include the number of days relative to the initial exposure to the study drug, if applicable.

This section details general conventions to be used for the statistical analyses. The following conventions will be applied to all data presentations and analyses.

- Summary statistics will consist of the number and percentage of responses in each level for categorical variables, and the sample size (n) mean, median, standard deviation (SD), minimum, and maximum values for continuous variables.

- All mean and median values will be formatted to one more decimal place than the measured value. Standard deviation values will be formatted to two more decimal places than the measured value. Minimum and maximum values will be presented with the same number of decimal places as the measured value.

- The number and percentage of responses will be presented in the form XX (XX.X%) or XX (XX.X) if % is in the header.

- All summary tables will include the analysis set sample size (ie, number of patients).

- Date variables will be formatted as DDMMMYYYY for presentation.

- SAS® Version 9.4 will be the statistical software package used for all data analyses.

12. REFERENCES

1. SAS Institute Inc., SAS® Version 9.4 software, Cary, NC.