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Statistical Analysis Plan

A Phase 2A Study of TRC105 (with Option to add Bevacizumab) in Patients with Refractory Gestational Trophoblastic Neoplasia (GTN)

Protocol 105GTN201

Version 1.0

Prepared for
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Approval Page

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STATISTICAL ANALYSIS PLAN

Table of Contents

1. Objectives

1.1. Primary Objective

To determine the objective response rate (ORR) of single agent TRC105 and of the combination of TRC105 and bevacizumab (in bevacizumab refractory patients) in patients with refractory GTN (including choriocarcinoma, placental site trophoblastic tumor [PSTT], and epithelioid trophoblastic tumor [ETT])

1.2. Secondary Objective(s)

- To determine PFS
- To determine ORR of single agent bevacizumab in patients with refractory GTN (including choriocarcinoma, PSTT, and ETT)
- To evaluate the formation of TRC105 anti-product antibodies
- To evaluate PK of TRC105 and bevacizumab
- To determine the frequency and severity of adverse events as assessed by NCI CTCAE (Version 4.03)

1.3. Exploratory Objective(s)

- To correlate efficacy endpoints with endoglin expression on tumor samples
- To explore the effects of TRC105 and bevacizumab on circulating angiogenic protein biomarkers
- To explore the effects of CD16 genotype on response to TRC105 therapy

2. Study Design

This is a multicenter, open-label, nonrandomized, single-arm phase 2 study to assess the response rate to treatment with single agent TRC105, single agent bevacizumab, and the combination of TRC105 and bevacizumab in patients with GTN that has progressed following treatment with at least one chemotherapy regimen that included two or more chemotherapy agents.

All patients will initially receive TRC105 as a single agent. Patients will receive TRC105 for two 28-day cycles at which time formal measurement for response will be made. The following scenarios are possible:

1. Single agent TRC105
    a. Complete response after 2 cycles: The patient will receive at least 3 cycles of consolidation therapy with single agent TRC105.
    b. Partial response after 2 cycles: The patient will continue single agent TRC105 for an additional 2 cycles and re-evaluate the response, unless the patient has clear progression any time after completing 2 cycles of treatment then add bevacizumab. If there is continued improvement in response after 4 cycles of

treatment, continue single agent TRC105. If there is no improvement in response, add bevacizumab for combination therapy. If there is a complete response any time after completing 2 cycles of treatment, the patient will receive at least 3 cycles of consolidation therapy.

c. Progression after 2 cycles or clear progression before 2 cycles: Transition to single agent bevacizumab after a 2 week washout period. Patients who have documented disease progression on a prior bevacizumab containing regimen will transition directly to TRC105 plus bevacizumab combination therapy.

2. Single agent bevacizumab
    a. Complete response after 2 cycles: The patient will receive at least 3 cycles of consolidation therapy with single agent bevacizumab.
    b. Partial response after 2 cycles: The patient will continue single agent bevacizumab for an additional 2 cycles are re-evaluate the response unless the patient has clear progression any time after completing 2 cycles of treatment then add TRC105. If there is continued improvement in response after 4 cycles of treatment, continue single agent bevacizumab. If there is no improvement in response, add TRC105 for combination therapy. If there is a complete response any time after completing 2 cycles of treatment, the patient will receive at least 3 cycles of consolidation therapy.
    c. Progression after 2 cycles or clear progression before 2 cycles: Add TRC105 and treat with combination therapy.
3. Combination therapy with TRC105 + bevacizumab
    a. Complete response after 2 cycles: The patient will receive at least 3 cycles of consolidation therapy with the combination.
    b. Partial response after 2 cycles: The patient will continue combination therapy for another 2 cycles to confirm partial response. Combination therapy will be continued until remission or progression.
    c. Progression after 2 cycles or clear progression before 2 cycles: The patient will come off study.

Improvement in response is defined as a continued decline in hCG and/or a continued decrease in tumor volume by RECIST 1.1 for patients with measurable disease. For patients with choriocarcinoma, efficacy will be assessed using weekly hCG central lab results, starting two weeks after initiation of treatment:

- Disease progression is defined as >20% increase (the absolute increase must be ≥10 IU/L) above nadir on consecutive measurements separated by at least two weeks;
- Partial response is defined as a hCG decrease of 50% or more from starting value on consecutive measurements separated by at least two weeks;
- Complete response is defined as normalization of hCG on consecutive measurements separated by at least two weeks;
- Stable disease is defined as the absence of response or progression on 3 consecutive measurements separated by at least two weeks.

Efficacy assessment of patients with PSTT and ETT will use standard RECIST 1.1 radiographic criteria integrated with weekly hCG assessment.

Regular safety and toxicity assessments are performed. Toxicities will be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0.

3. Sample Size Determination

The sample size of 30 patients is not based on statistical considerations. If five or more responses to TRC105 given as a single agent or when combined with bevacizumab (in a bevacizumab refractory patient) are detected among 30 patients, then the lower limit of the two-sided exact binomial 95% confidence interval will be greater than 5%. For example, with five responses, the 95% confidence interval would be (5.64%, 34.72%).

4. Analysis Population

The safety and efficacy populations include all patients who receive at least a portion of one dose of the study drug, TRC105.

5. General Analysis Comments

Summary statistics will consist of frequencies and percents of responses in each category for discrete measures; and of means, medians, standard deviations, minimum and maximum values for continuous measures. By-patient listings of data represented on the Case Report Form (CRF) will be provided.

Descriptive statistics (such as means, medians, standard deviations, and ranges for continuous data and percentages for categorical data) will be used to summarize patient characteristics, treatment administration/compliance, immunogenicity, efficacy, pharmacokinetic parameters, protein biomarkers, and archival tumor tissue. Data will also be displayed graphically, where appropriate.

SAS®, Version 9.0 or higher, or R v 3.23 or higher, or Python v 2.0 or higher or PostgreSQL v 9.2.14 or higher will be used to perform all statistical analyses.

6. Missing Data

All data collected, including unscheduled visits, will be presented in the data listings. Summary tables will generally be limited to planned visits.

In all analyses (except where partial dates are allowed), it is expected that only observed values will be presented; no imputation of missing data will be conducted. Where partial dates are allowed (i.e., medical history, adverse events, prior systemic therapy, prior radiation therapy, prior surgery, concomitant medications and concomitant treatments) the largest possible window for the event/item will be reported.

7. Patient Accountability and Patient Disposition

The number of patients enrolled and number of cycles completed will be presented. A summary of reasons for discontinuation will be provided. The number of patients in the safety population and the number of patients excluded from the safety population will also be presented. Study completion status, including reasons for discontinuation will be listed.

8. Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized. Demographic variables, including age, gender, race, and ethnicity will be summarized in a tabular form.

Primary diagnosis (histological classification), prior cancer surgery, prior radiotherapy, prior cancer therapy, and medical history will be listed and will also be summarized.

9. Concomitant Medications and Treatments

A listing of all concomitant medications and treatment will be provided by patient ID number, drug name, dosage, frequency of use, start and stop dates, whether the medication or treatment was ongoing. Concomitant medications will be coded by using WHO Drug Dictionary version September 2012.

10. Efficacy Analyses

10.1. Overall Response Rate (ORR)

ORR by hCG in cases of choriocarcinoma or by integrated radiologic and hCG assessments in cases of PSTT or ETT, will be calculated form the time of cycle 1 day 1 until the time of progression, and will include separate assessments while on TRC105, bevacizumab and while receiving both agents. hCG for purposes of calculating ORR (and overall treatment decisions) will be measured by the central laboratory. ORR to single agent TRC105 will include PR or CR. ORR to the combination of TRC105 and bevacizumab will include PR or CR. ORR for purposes of determining the co-primary endpoints will include the ORR to TRC105 given as a single agent and when combined with bevacizumab (in bevacizumab refractory patients) in each patient.

The point estimates and two-sided exact binomial 95% confidence intervals will be provided for ORR for each of the two co-primary populations.

10.2. Progression Free Survival (PFS) and Duration of Response (DR)

PFS is defined as the time from initial dosing until time of progression or death, with progression documented either hCG in cases of choriocarcinoma or by integrated radiologic and hCG assessments in cases of PSTT or ETT.

DR is defined as the time from initial documentation of response until time of progression or death, whichever occurs first. PFS and DR will include separate assessments while on TRC105, bevacizumab and while receiving both agents.

The distribution of PFS will be analyzed using the Kaplan-Meier method. Secondary endpoints defined as proportions will be summarized using point estimates and two-sided exact binomial 95% confidence intervals.

11. Safety Analyses

Safety will be assessed by examining vital signs, physical exams, clinical laboratory tests, and adverse events (AEs). These analyses will be conducted on the safety population. Baseline will be defined as the last available measurement prior to the first TRC105 dose. Where this definition does not apply, the definition for that analysis will be specified.

11.1. Extent of Exposure

The extent of exposure to TRC105 study drug and bevacizumab will be summarized by the number of doses completed, and the number of cycles completed and dose received in milligrams. A cycle is considered completed if the patient received all treatment infusions required during a given cycle. Actual extent of exposure versus expected extent of exposure will be provided for both TRC105 and bevacizumab.

11.2. Adverse Events

Adverse Events (AEs) and Serious Adverse Events (SAEs) will be coded by using the Medical Dictionary for Regulatory Activities (MedDRA Version 14.1) system organ class (SOC) and preferred term (PT). AEs and SAEs will be graded according to the CTCAE Version 4.0, where available.

All AEs and SAEs will be listed by patient ID number. TRC105 treatment-emergent AEs will be summarized. Treatment-emergent is defined as all events starting during or after the first dose of TRC105 study drug. The number and percentage of patients with AEs will be displayed by SOC and PT according to the worst severity experienced. Summaries will be provided of AEs by grade and of AEs by relationship to study medication. Serious AEs, AEs leading to study discontinuation, AEs resulting in dose delay, and AEs with an outcome of death will be summarized and listed.

11.3. Laboratory Evaluations

Quantitative laboratory test results will be summarized at each visit for hematology, coagulation, serum chemistry panel, and urinalysis.

The Investigator will determine whether abnormal lab values are clinically significant. Such results are to be reported as adverse events and CTCAE grading will be assigned (except for urinalysis) where applicable.

Laboratory results that are abnormal and clinically significant will be flagged. Abnormal and clinically significant results will be presented in listings with Investigator comments.

The number and percentage of patients who exhibit clinically significant abnormal laboratory results will be produced at each visit.

11.4. Physical Examination

The physical examination results will be displayed at each cycle. Listing of results of examinations will be provided by anatomical sites, assessment dates, and description of physical abnormalities.

11.5. Vital Signs

Vital signs will be summarized at each visit for systolic blood pressure, diastolic blood pressure, pulse, respiratory rate, temperature, and weight. Listing of vital signs will be provided.

11.6. Electrocardiogram

ECG results including ECG time, heart rate (bpm), PR interval (ms), QRS interval (ms), and QT interval (ms) (normal; abnormal, not clinically significant; abnormal, clinically significant), QTc, and comments for clinically significant abnormalities will be reported for each patient using Bazett's Formula as follows:

$$QT_B = \frac{QT}{\sqrt{RR}}$$

11.7. ECOG Performance Scale

The Eastern Cooperative Oncology Group (ECOG) performance grade scale will be used to measure patient ECOG performance status. Individual patient data at screening will be tabulated and individual patient data throughout the study will be displayed in a listing.

12. Pharmacokinetic Analysis

Serum samples will be assayed to measure the concentration of TRC105 and bevacizumab. Only concentrations greater than or equal to the limit of qualification (LOQ) from the assay will be used. The following parameters will be determined:

- C_{max} (ng/mL) [Maximal TRC105 or bevacizumab concentration]
- C_{min} (ng/mL) [Minimal TRC105 or bevacizumab concentration]

Descriptive statistics of C_{max} and C_{min}, following drug administrations will be calculated by time of treatment (baseline versus treatment completion Summary PK analyses will include all patients and also include only patients who develop positive APA titers.

Listings of individual patient serum concentrations, actual blood sampling times, and pharmacokinetic parameters will be provided.

13. Additional Analysis

14.1 Analysis of Protein Biomarkers

Angiogenic protein biomarker data for each patient who received at least one dose of TRC105 study drug will be listed.

14.2 Analysis of Immunogenicity

TRC105 anti-product antibody concentrations will be measured using validated ELISA methods at the timepoints specified in the Schedule of Assessments.

TRC105 anti-product antibody concentrations will be evaluated in the context of pharmacokinetic parameters and AE profiles.

14.3 Analysis of Serum and Urine Tumor Biomarkers

Urine and Serum hCG tumor marker data for each patient who received at least one dose of TRC105 study drug will be listed.

14.4 Analysis of CD16 Genotype

CD16 genotype for each patient who received at least one dose of TRC105 study drug will be listed.

14. Changes from the Protocol-Specified Analysis

The details of analysis as indicated in this plan are based on the specifications of the study protocol as amended on September 20th, 2016. Any later changes to the protocol may require consequential revision of this plan.

15. Programming Considerations

The format of listing and table shells should be followed as closely as possible during SAS or R programming, however, changes in format may be made due to space considerations and

abbreviation of labels etc. The number of decimal places for presentation of the data should be based on the actual data, not the format presented in the shells (i.e., xx.xx is only a place holder).

16. Appendices

Appendix 1: Planned 105GTN201 Tables
Appendix 2: Planned 105GTN201 Listings

17. References

1. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst 2000; 92:205-16.
2. NCI Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0. http://www.acrin.org/Portals/0/Administration/Regulatory/CTCAE_4.02_2009-09-15_QuickReference_5x7.pdf
3. MedDRA: Medical Dictionary for Regulatory Activities terminology. Version 14.1. Reston, VA: Northrop Grumman, MedDRA MSSO.

18. Appendix 1 Tables

1.1. Tables in Text:

- Protocol Versions under which Each Patient was Enrolled
- Individual Response Data
- Summary of Serum TRC105 Pharmacokinetic Parameters Following Multiple Intravenous Infusions of TRC105
- Treatment-Emergent Adverse Events by Maximum CTCAE Grade
- Treatment-Emergent TRC105 Drug-Related Adverse Events by Maximum CTCAE Grade
- TRC105 APA Results

1.2. Appended Tables:

- Serious Treatment-Emergent Adverse Events
- Adverse Events Leading to Discontinuation

2. Appendix 2 Listings

2.1. Appended Listings:

Listing 16.1.1 Listing of Informed Consent and Reconsent
Listing 16.2.1 Patient Disposition
Listing 16.2.2 Protocol Deviation
Listing 16.2.2.1 Inclusion and Exclusion Criteria
Listing 16.2.3 Patients Excluded from Efficacy Analysis
Listing 16.2.4.1 Demographics and Baseline Characteristics
Listing 16.2.4.3 Primary Diagnosis
Listing 16.2.4.4 Prior Cancer Therapy (Including Hormonal Therapy)
Listing 16.2.4.5 Prior Cancer Surgery
Listing 16.2.4.6 Prior Cancer Radiation Therapy
Listing 16.2.4.7 Medical History and Baseline Emergent Adverse Events
Listing 16.2.4.8 Concomitant Medications
Listing 16.2.4.9 Concomitant Treatments
Listing 16.2.4.10 TRC105 Pre-Medications
Listing 16.2.4.11 Drug Allergies
Listing 16.2.5.1 TRC105 Dosing Record
Listing 16.2.5.2 Bevacizumab Dosing Record
Listing 16.2.6.1 Investigator Response Assessment
Listing 16.2.6.3 Tumor Assessment - Target Lesions
Listing 16.2.6.4 Tumor Assessment - Non-Target Lesions
Listing 16.2.6.5 Scans
Listing 16.2.6.6 APA
Listing 16.2.6.7 Archival Tumor Specimens
Listing 16.2.6.9 Protein Biomarker Samples
Listing 16.2.6.10 Serum Tumor Markers
Listing 16.2.6.11 Urine Tumor Markers
Listing 16.2.7.1 All Adverse Events
Listing 16.2.7.3 Serious Adverse Events
Listing 16.2.7.4 Adverse Events Leading to Discontinuation
Listing 16.2.7.5 Adverse Events Leading to Death
Listing 16.2.8.1 Abnormal Laboratory Results – Hematology
Listing 16.2.8.2 Abnormal Laboratory Results – Coagulation
Listing 16.2.8.3 Abnormal Laboratory Results – Chemistry
Listing 16.2.8.4 Abnormal Laboratory Results – Urinalysis
Listing 16.2.9.1 Vital Signs
Listing 16.2.9.2 Abnormal Physical Exam Results
Listing 16.2.9.3 ECG Results
Listing 16.2.9.4 ECOG Performance Status
Listing 16.2.9.5 Pregnancy at Screening
Listing 16.2.9.6 24 Hr-Urine Collection
Listing 16.2.9.7 Microscopic Urinalysis
Listing 16.2.9.8 Urine Protein to Creatinine Ratio
Listing 16.2.9.9 Pre-Dose PK (TRC105 and bevacizumab)