Statistical Analysis Plan (SAP)

Protocol Title: A Phase II, Open-Label Study of ONC201 in Adults with Recurrent High-Grade Glioma

Protocol Number: ONC013 (NCT03295396)

Protocol Date: 19 November 2019 (Version 4.0)

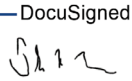
SAP Date: 01 December 2023 (Version 1.0

Statistical Analysis Plan

ONC013

A phase II, open-label study of ONC201 in adults with recurrent high-grade glioma

I confirm that I have reviewed this document and agree with the content.

APPROVALS	
Approved by: Tom Brundage Vice President, Biostatistics Chimerix	Signature/Date: DocuSigned by:  Signer Name: Thomas M. Brundage Signing Reason: I approve this document Signing Time: 01 December 2023 | 12:11:46 PST BC6C67E7107342EDA191F4AD84A2F915

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1. Introduction

This abbreviated Statistical Analysis Plan (SAP) describes the statistical analyses to be conducted for the Study ONC013. For simplicity, reference is made to existing Integrated Summary of Safety (ISS) and Integrated Summary of Efficacy (ISE) SAPs when approaches are the same.

Study ONC013 is a Phase II, open-label, multi-center clinical trial of ONC201 in adult recurrent glioma with two arms. All subjects receive oral ONC201 at 625 mg every week. All subjects remain on study until progressive disease, unacceptable toxicity or withdrawal of consent. For other study details, refer to the study protocol.

2. General Conventions

The All Treated Analysis Set includes all patients who receive at least one dose of ONC201. This will be used for all analyses.

Unless otherwise specified, continuous variables will be summarized using descriptive statistics [number of observations, mean, standard deviation (SD), median, 1st (Q1) and 3rd (Q3) quartiles, minimum and maximum]. Categorical variables will be summarized as number (percent) of patients.

Day 1 is defined as the date of the first dose of study drug. For events that occur on or after Day 1, study day is defined as (date of event - date of Day 1 + 1). For events that occur prior to Day 1, study day is defined as (date of event - date of Day 1). There is no Day 0. Baseline is defined as the last observed measurement on or before the date of the first dose of study drug.

In general, other than for partial dates, missing data will not be imputed and will be treated as missing. Unless otherwise specified, partial dates will be imputed using the following rules:

- If year is missing, do not impute.
- If only day is missing, impute day as 1st of the month for start dates, end of the month for end dates, and 15th of the month for other dates.
- If day and month are missing, impute as January 1st for start dates, December 31st for end dates, and July 1st for other dates.

3. Analyses

All analyses will be presented by Arm and for All Patients. Otherwise, specified patient disposition, study drug usage, prior/concomitant/post-ONC201 medications, demographic and baseline characteristics, adverse events, and laboratories will use methods and summaries defined in the ISS SAP.

Laboratory boxplots will be presented for all tests with at least 60 patients having numeric baseline results: one plot per test, time on the x-axis, value on the y-axis. The plots will not be broken out by arm (i.e. only the All Patients group). Only Baseline and Cycles 2-12 will be presented. For Cycles 2-12, nominal visits will be used; if multiple values are associated with a visit, the highest value will be used for chemistry tests and lowest value will be used for hematology tests.

The following efficacy analyses will be performed: best overall response, overall response rate, disease control rate, duration of response, progression-free survival, and overall survival. All analyses will be based on the investigator-assessed overall RANO response. Discontinuation of treatment due to progressive disease will also be considered. All analyses, aside from overall survival, will be censored at

the earlier of: (1) last disease assessment or (2) last assessment prior to initiation of other anticancer therapy.

Cycle 1 (2hr, 24hr, 48hr, 72hr) ONC201 plasma concentrations will be summarized descriptively, including geometric mean and %CV. BLQ results will be imputed as zero.

Collected data contributing to presented tables and figures will be listed.

Other analyses specified in the protocol will either not be completed, or will be defined outside the scope of this plan.

Following is a complete list of the tables, figures, and listings to be prepared (with clarifying notes in parentheses).

Number	Description
Table 1.1	Patient Disposition
Table 1.2	Demographics and Baseline Characteristics
Table 1.3	Study Drug Usage
Table 1.4.1	Prior Medications
Table 1.4.2	Concomitant Medications
Table 1.4.3	Post-ONC201 Medications
Table/Figure 2.1	Progression-free Survival
Table/Figure 2.2	Overall Survival
Table 2.3	Response Rate (includes ORR, BOR, and DCR)
Table/Figure 2.4	Duration of Response
Table 3.x.1*	Treatment-emergent Adverse Events (TEAE)
Table 3.x.2*	TEAE Grade 3 and Above
Table 3.x.3*	Serious TEAE
Table 3.x.4*	TEAE Leading to Death
Table 3.x.5*	TEAE Leading to Study Drug Discontinuation, Reduction, or Interruption
Table 3.x.6*	Study Drug Related TEAE
Table 3.x.7*	Study Drug Related TEAE Grade 3 and Above
Table 3.x.8*	Study Drug Related Serious TEAE
Table 3.x.9*	Study Drug Related TEAE Leading to Death
Table 3.x.10*	Study Drug Related TEAE Leading to Study Drug Discontinuation, Reduction, or Interruption
Table 3.x.11*	TEAE by Maximum Severity (overall only)
Table 3.x.12*	Study Drug Related TEAE by Maximum Severity (overall only)
Table 4.x.1*	Graded Laboratory Results (maximum post-baseline)
Table 4.x.2*	Graded Treatment-emergent Laboratory Results (maximum on-treatment, result only counted if > Baseline Grade)
Table 5.1	Plasma Concentrations
Figure 4.1	Boxplot of Laboratory Results
Listing 1.1	Patient Disposition
Listing 1.2	Demographics and Baseline Characteristics
Listing 1.3	Study Drug Usage
Listing 1.4	Other Medications
Listing 2.1	Efficacy Outcomes
Listing 3.1	Adverse Events
Listing 3.2	AE Leading to Death
Listing 3.3	AE Leading to Study Drug Discontinuation, Reduction, or Interruption
Listing 4.1	Listing of Graded Laboratory Results (includes all results for a patient/test where at least one on-treatment result is ≥ Grade 1)
Listing 5.1	Plasma Concentrations
x=1: all post-baseline, x=2: prior to initiation of other anticancer therapy	