PROTOCOL SYNOPSIS

Title of Study: A Retrospective Observational Study for H3 K27M-mutant Glioma

Study Centers: Approximately 50 centers in the United States & other regions (country selection based on feasibility results).

Number of Patients: Available data from all eligible patients from each study center will be collected. Target enrollment is ~50 evaluable patients in Cohort A and ~1500 evaluable patients in Cohort B.

Rationale: There is limited published information about prognostic factors and the progression of H3 K27M-mutant glioma. Therefore, this natural history study aims to better define the response to treatment, natural disease progression, outcomes, and prognostic factors in patients with H3 K27M-mutant and/or midline glioma.

Overall Design:

This is a multicenter, retrospective, descriptive, observational study in patients with H3 K27M-mutant and/or midline glioma to describe the response to treatment, natural disease progression, outcomes, and prognostic factors. Data will be collected via retrospective chart reviews across selected centers.

The study will present data and outcomes for 2 cohorts of patients:

- Cohort A will include patients with diffuse midline glioma, H3 K27M-mutant that is intended to match selection criteria for patients included in an analysis of efficacy in a planned new drug/marketing application for the Sponsor.
- Cohort B is intended to evaluate prognostic factors for survival in a broader group of patients with H3 K27M-mutant and/or midline glioma.
- A patient who meets eligibility criteria for both Cohort A and Cohort B will be included and analyzed in both (i.e., the cohorts are not mutually exclusive).

Primary Objectives with Endpoints:

Cohort A: To determine recurrent diffuse midline glioma, H3 K27Mmutant glioma objective response to treatment intervention determined by overall objective response rate (ORR) by RANO-HGG criteria as assessed by BICR.

Cohort B: To identify prognostic factors for survival determined by OS, measured from diagnosis and from each instance of recurrence

Key Inclusion criteria:

1. Medical records (including clinic notes and/or electronic databases) relating to glioma diagnosis and treatments received are available for review. (Minimum information includes demographics, disease characteristics, histology, disease history [diagnosis, tumor location, recurrences], radiation and other treatment history, survival status and death date if applicable.)
2. Glioma:
    a. Cohort A
        i. Pathology-proven diffuse glioma with a known H3 K27M mutation AND
        ii. Tumor involvement in a midline structure of the brain (thalamus, hypothalamus, basal ganglia, brainstem, cerebellum, cerebellar peduncle, midline cortex, corpus collosum, pineal region, optic tract, optic chiasm.
    b. Cohort B
        i. Pathology-proven diffuse glioma with a known H3 K27M mutation OR
        ii. Tumor involvement in a midline structure of the brain (including DIPG or a primary spinal tumor).
3. Initial diagnosis was in 2012 or later.

Additional inclusion criteria for Cohort A:

4. Age ≥2 years at start of treatment intervention.
5. At least one second-line, or later, therapy for glioma that did not involve radiation, bevacizumab, Sponsor's study drugs, or related compounds (e.g., biosimilars).
6. Availability of MRI files ([DICOM] format) and corticosteroid dose from baseline of treatment intervention through progression (if applicable), with associated KPS/LPS.
7. Prior therapy with at least radiation and an interval of at least 90 days from completion of the most recent prior radiation to start of treatment intervention.
8. Evidence of progressive and measurable contrast-enhancing disease on brain MRI according to Response Assessment in Neuro-Oncology (RANO) high-grade glioma (HGG) criteria before treatment intervention was initiated.
9. The following time periods must have elapsed prior to the start of treatment intervention: 23 days for temozolomide, 6 weeks from antibodies including bevacizumab, and 4 weeks from other anti-tumor therapies.
10. Corticosteroid dose that was stable or decreasing for at least 3 days prior to MRI scan that occurred before initiation of treatment intervention.
11. KPS/LPS ≥60 at the start of treatment intervention. [If a patient meets all other eligibility criteria, but the KPS/LPS score is not specified in the medical records, a score may be inferred by the investigator based on physical examination chart notes.]

Additional inclusion criteria for Cohort B:

Known date of death or survival follow-up of at least 6 months from initial diagnosis.

Key Exclusion criteria:

A potential patient who meets any of the following criteria will not be eligible for inclusion in the study:

1. Unknown H3 K27M mutation status.

Additional exclusion criteria for Cohort A:

2. DIPG or a primary spinal tumor.
3. Evidence of leptomeningeal spread of disease or cerebrospinal fluid dissemination.

Additional exclusion criteria for Cohort B:

Prior treatment with Sponsor's study drugs at any time.