**STATISTICAL ANALYSIS PLAN**

# Phase II Trial of Niraparib in Patients with Recurrent Glioma

**Version 2.0**

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| **Investigational Product:** | Niraparib |
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**Abbreviations**

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| cOR | Clinical response |
| CR | Complete response |
| DLT | Dose limiting toxicity |
| EOS | End of study |
| iCRS | Interval cyto-reduction surgery |
| MTD | Maximum tolerated dose |
| NACT | Neoadjuvant chemotherapy |
| OS | Overall survival |
| pCR | Pathological complete response |
| PFS | Progression free survival |
| PK | Pharmacokinetics |
| PR | Partial response |
| Q BIW | Twice a week |
| SAP | Statistical analysis plan |

**Contents**

1. **Objectives**
    a. **Primary Objectives**
        i. For safety lead-in phase: To evaluate the safety and tolerability of niraparib using RADAR-based dosing in patients with recurrent brain tumor.
        ii. For Phase II Dose Expansion Cohorts: To evaluate the efficacy of niraparib in patients with recurrent brain tumor using Response Assessment in Neuro-Oncology Criteria (RANO); and to evaluate the safety of niraparib in patients with recurrent brain tumor at safety lead-in dose.

    b. **Secondary Objectives**
        i. To evaluate Progression free survival (PFS) and overall survival (OS) time for patients enrolled in dose expansion cohorts
        ii. To evaluate the duration of disease control (DDC) in patients enrolled on study.
    c. **Exploratory Objectives**
        i. To identify potential biomarkers associated with tumor response to niraparib based on the molecular profile of tumor tissue biomarkers.
        ii. To correlate homologous recombination deficiency (HRD) score obtained via myChoice test (Myriad Genetics) with other biomarkers such as IDH1/IDH2 mutation and with treatment outcomes.

2. **Study Endpoints**
    a. **Primary End points**
        i. For safety lead-in dose and expansion cohorts, monitor safety and tolerability of niraparib with individualized starting dose (ISD) in patients with recurrent brain tumor. Determination of safety will utilize adverse event occurrence monitoring and grade using CTCAE v5.0.
        ii. For Phase II dose expansion cohorts, define the anti-cancer efficacy of niraparib in patients with recurrent brain tumor by disease control rate (DCR; complete and partial response, and stable disease) as assessed by the RANO. DCR is the percentage of patients with a SD or better from start of treatment (cycle 1, day 1) to 3 months, 6 months, 9 months, and 12 months per RANO.

    b. **Secondary Endpoints**
        i. Anticipate to have prolonged PFS and OS for patients enrolled in dose expansion cohorts
        ii. DDC is elapsed time from the first documented CR, PR, pathological CR, or SD until first documentation of disease progression or death, whichever comes first.

    c. **Exploratory Endpoints**
        i. Obtain preliminary data about the molecular profile of tumor tissue biomarkers and their association with tumor response to niraparib.
        ii. Obtain preliminary data about the association of HRD status with other biomarkers and with the anti-cancer effect of niraparib.

## 3. Design information

### a. General statistical considerations

This is a single arm phase II trial of niraparib in patients with recurrent gliomas. Three to six patients will be enrolled in the safety lead-in phase with RADAR dosing. If no SAEs are observed in the first 3 patients, then the study will move on to the dose expansion. If 1/3 patients experience an SAE that is determined to be significant by the PI and medical monitor, the same dose will be expanded to 3 more patients. A safety review will be conducted following the treatment of the first three or all six patients to determine the niraparib dose for the dose expansion phase. Patients enrolled in the safety lead-in phase will be included in the dose-expansion phase. The starting dose of niraparib for the safety lead-in phase will depend on baseline platelet count and weight.

### b. Sample Size and Power

This phase II study consists of a safety lead-in and a dose-expansion phase. In the safety lead-in phase, three or six patients will be enrolled depending on the safety profile. A total of 45 evaluable patients (including those from the safety lead-in phase), evenly distributed among 3 gliomas including GBM, Astrocytoma, and Oligodendroglioma, will be enrolled into dose-expansion phase. The sample sizes were not computed based on formal statistical power calculation.

## 4. Study Populations

Inclusion and exclusion criteria are sometimes modified during the duration of the protocol. Before beginning analysis, the statistical team will review the criteria in the SAP to confirm it is up to date with the current criteria.

### a. Inclusion Criteria

i. Patients must be able to understand and willing to sign the informed consent form.
ii. Patients must be ≥ 18 years of age.
iii. Patients must have histologically proven high grade gliomas - GBM, Astrocytoma, or Oligodendroglioma (glioma WHO Grade III or IV) that is now recurrent by MRI or surgical pathology. If there is clinical evidence (such as MRI contrast enhancement) that supports a Grade 3 diagnosis of the glioma, the patient will be eligible for the study (even if the initial diagnosis was a Grade 2).
iv. Patients must have measurable or evaluable lesions by RANO.
v. Eastern Cooperative Oncology Group (ECOG) performance status of 0-2tients must be able to understand and willing to sign the informed consent form.
vi. Patient has archival tumor tissue available; or a fresh biopsy of recurrent or persistent tumor must be obtained for molecular assay by myChoice test (Myriad Genetics) prior to study treatment initiation. Patient will be requested to share reports from any prior genetic testing with the study investigators.
vii. Participants have systolic BP< 140 mmHg or diastolic BP <90 mmHg that has been adequately treated or controlled.
viii. Have adequate organ function defined by ANC > 1500 cells/mcl, platelets > 100,000/mcl, Hemoglobin ≥ 9 g/dL, calculated creatinine clearance ≥ 50 mL/min (by Cockcroft-Gault formula); total bilirubin < 1.5 times ULN, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels < 2.5 x ULN.
ix. Be able to take oral medications

x. Life expectancy ≥ 3 months, allowing adequate follow up of toxicity evaluation and antitumor activity;
xi. Female patient, if of childbearing potential, has a negative serum pregnancy test within 72 hours of taking study medication and agrees to abstain from activities that could result in pregnancy from enrollment through 180 days after the last dose of study treatment or is of nonchildbearing potential. Nonchildbearing potential is defined as follows (by other than medical reasons):
    1. ≥45 years of age and has not had menses for >1 year
    2. Patients who have been amenorrhoeic for <2 years without history of a hysterectomy and oophorectomy must have a follicle stimulating hormone value in the postmenopausal range upon screening evaluation
    3. Post-hysterectomy, post-bilateral oophorectomy, or post-tubal ligation. Verbal confirmation of hysterectomy, oophorectomy, or tubal ligation from the patient of non-childbearing potential to study staff is sufficient in lieu of records from actual procedure and/or confirmation by ultrasound. In this case, the patient must be willing to use two adequate barrier methods throughout the study, starting with the screening visit through 180 days after the last dose of study treatment. This information must be captured appropriately within the site's source documents. Note: Abstinence is acceptable if this is the established and preferred contraception for the patient.
xii. Male participant agrees to use an adequate method of contraception starting with the first dose of study treatment through 180 days after the last dose of study treatment. Note: Abstinence is acceptable if this is the established and preferred contraception for the patient.
    1. In addition, men must not donate sperm during niraparib therapy and for 90 days after receiving the last dose of niraparib.
xiii. Patient must agree to not breastfeed during the study or for 30 days after the last dose of study treatment.
xiv. Participant must agree to not donate blood during the study or for 90 days after the last dose of study treatment.
xv. Participant receiving systemic corticosteroids may continue as long as their dose is stable for at least 4 weeks prior to initiating protocol therapy. Topical and nasal steroids are not considered contraindicative and may be used.

**b. Exclusion Criteria**

i. Patient has a known additional malignancy that progressed or required active treatment within the last 3 years (exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin that has undergone potentially curative therapy, or in situ cervical cancer).
ii. Prior treatment with a known poly(ADP-ribose) polymerase (PARP) inhibitor
iii. Participants with human immunodeficiency virus (HIV) with detectable viral load. Participants with HIV on effective anti-retroviral therapy with documented undetectable viral load and CD4 count ≥ 350 within 6 months of the first dose of study treatment are eligible for this trial.
iv. Known active hepatitis B or hepatitis C.
v. Known history of myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML).

vi. Participant is pregnant or expecting to conceive while receiving study treatment and/or for up to 180 days after the last dose of study treatment.
vii. Patient currently participating and receiving study therapy or has participated in a study of an investigational agent and received study therapy or used an investigational device within 4 weeks, or within a time interval less than at least 5 half-lives of the investigational agent, whichever is longer, prior to the first dose of study drug.
viii. Received prior anticancer therapy (chemotherapy, targeted therapies, radiotherapy, or immunotherapy) within 4 weeks.
ix. Patients must not have a known hypersensitivity to the components of niraparib or the excipients (lactose monohydrate and magnesium stearate).
x. Patients must not have had major surgery within 4 weeks (including craniotomy) of starting the study and patient must have recovered from any effects of any major surgery. Stereotactic biopsy by burr hole is considered a minor surgery, and those patients undergoing this surgery will be eligible for the study 2 weeks post-procedure.
xi. Patients must not have had radiotherapy encompassing > 20% of the bone marrow within 2 weeks; or any radiation therapy within 1 week prior to Day 1 of protocol therapy.
xii. Patients must not have received a transfusion (platelets or red blood cells), colony stimulating factors (eg, granulocyte colony-stimulating factor, granulocyte macrophage colony stimulating factor, or recombinant erythropoietin) ≤ 4 weeks of the first dose of study treatment.
xiii. Patient has had any known Grade 3 or 4 anemia, neutropenia or thrombocytopenia due to prior chemotherapy that persisted > 4 weeks and was related to the most recent treatment.
xiv. Participants have any clinically significant gastrointestinal abnormalities that may alter absorption such as malabsorption syndrome or major resection of the stomach and/or bowels.
xv. Participants have received live vaccine within 30 days of planned start of study randomization.
xvi. Patients have medical risk due to a serious, uncontrolled medical disorder, nonmalignant systemic disease, or active, uncontrolled infection. Examples include, but are not limited to, uncontrolled ventricular arrhythmia, recent (within 90 days) myocardial infarction, uncontrolled major seizure disorder, unstable spinal cord compression, superior vena cava syndrome, or any psychiatric disorder that prohibits obtaining informed consent
xvii. Any medical condition not yet specified above that is considered to possibly, probably or definitely interfere with study procedures, including adequate follow-up and compliance and/or would jeopardize safe treatment.

## 5. Analysis Populations

The safety lead-in and dose-expansion phases will be statistically analyzed separately. The safety lead-in phase analysis population will include all patients who have received at least one dose of niraparib.

The analysis populations in the dose-expansion phase are defined as below.

• **Safety population:** All patients who receive at least one dose of niraparib will be included in the analyses of compliance and safety.
• **Biomarker population:** For biomarker analysis, the biomarker population will comprise all patients who have sufficient baseline measurements.
• **Efficacy Evaluable population:** For tumor response analysis, the evaluable population will comprise all patients who have sufficient baseline and on-study measurements of tumor response parameters.

**6. Summary of Study Population**

**a. Patient Disposition**

i. Patient disposition will be summarized and include the number dosed, the number in each patient population for analysis, the number who withdrew prior to completing the study and reason(s) for withdrawal.

**b. Demographic and Baseline Characteristics**

i. Patient demographic and characteristics at study entry will be summarized with frequency tables for categorical variables, and with descriptive statistics such as the mean, standard deviation, median, and range as appropriate, for quantitative variables.

**c. Medical History and Cancer History**

i. Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 18 or higher. The count and percentage of subjects under each history term, coded by system organ class (SOC) and preferred term (PT), will be summarized.

ii. Cancer history data will also be summarized, including the primary site of cancer, the stage and grade of cancer at study entry, time from initial diagnosis of cancer to Day 1 of the study in days, duration of metastatic disease in days (first dose date – date of diagnosis of metastatic disease + 1), the extent of metastatic disease, and the histology.

**d. Study Drug Administration and Compliance**

i. Study drug administration will be summarized in terms of the actual doses administered and the proportion of drug actually taken relative to the amount that should have been taken; these data will be summarized in frequency distributions by cycle and dose level. The total number of cycles administered; the median (range) of cycles administered; dose modifications, dose delays, and dose omissions; and reasons for deviations from planned therapy will be summarized by dose level.

**7. Safety Analyses**

**a. Adverse Events**

i. Adverse events will be tabulated using MedDRA v20.1. The severity of the AE will be graded by the Investigator using the NCI CTCAE, version 5.0. The frequency of patients experiencing a specific AE will be tabulated by dose level, cycle, system organ class, preferred term, seriousness, worst severity, timing of occurrence, outcome, and relationship to study drug. In addition, the number and percentage of patients experiencing a specific AE will be tabulated similarly.

**b. Laboratory Abnormalities**

i. The severity of laboratory abnormalities will be graded using the NCI CTCAE, version 5.0, whenever possible. The frequency of patients experiencing a specific laboratory abnormality will be tabulated by dose level, cycle, worst severity, and timing of occurrence. In addition, the number and percentage of patients experiencing a specific laboratory abnormality will be summarized similarly.

**c. Other Safety Assessments**

i. The results of vital sign measurements, body weight assessments, ECOG performance status determinations and physical examinations will be summarized by cycle and dose level, using appropriate descriptive statistics.

**8. Biomarkers**

i. Data of molecular profile from myChoice test will be collected. The tumor biomarkers from tumor biopsies, such as HRD, IDH1 /IDH2 mutation and PARP in tumor, will be summarized for each patient.

**9. Antitumor Evaluation**

i. The statistical analysis for the dose-expansion phase will be performed by the types of gliomas. The objective tumor response (complete and partial response) will be summarized as the proportion (and 95% exact Clopper-Pearson CI) of patients with a tumor response. The duration of response by RANO will be summarized descriptively using Kaplan-Meier method. Results will be presented in tabular and graphic form, as appropriate. The response rate will be compared between biomarker status using the chi-squared test or Fisher's Exact were appropriate.

ii. Progression-Free Survival (PFS) time is defined as the time from date of study entry to the earliest date of progression based on RANO, death (due to tumor progression) or date of last contact. Patients who are still alive without progression at End of Study (EOS) will be censored on the date of the last evaluable response assessment that is not progressive disease (PD). Six-month PFS rate is defined as the percentage of patients who are alive and progression-free at 6-month from the start of study treatment; with tumor response including CR, PR and SD (estimated by the Kaplan-Meier method). PFS will be compared between biomarker status using the log-rank test.

Survival curve for PFS will be generated using the Kaplan-Meier method. Median PFS with 95% CI will be computed.

iii. Overall survival (OS) time is defined as the time from date of study entry to death by any cause. Patients who are still alive at EOS are censored on the date they were last known to be alive. Patients who are still alive at EOS or whose vital status is unknown, will be censored at the last date of contact. An exploratory analysis to determine 6 months or 9 months OS rate will be estimated by the Kaplan-Meier method. OS will be compared between biomarker status using the log-rank test.

Survival curve for OS will be generated using the Kaplan-Meier method. Median OS with 95% CI will be computed.

**10. Handling of Missing Data**

Every effort will be made to collect information at all defined visits including at early withdrawal or dropout. Reasons for missing data will be summarized. However, there will be no imputation of missing data.