NewLink Genetics Corporation

STATISTICAL ANALYSIS PLAN

Protocol Title: A Phase 1/2 Study of the Combination of Indoximod and Temozolomide for Adult Patients with Temozolomide-Refractory Primary Malignant Brain Tumors

Protocol Number: NLG-2102

Phase: Phase 1/2

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SUMMITANALYTICAL

Statistical Analysis Plan Approval Form

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The statistical analysis plan has been reviewed and approved.

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9/18/2019
Date

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2. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Below is a list of abbreviations used in this statistical analysis plan (SAP).

Abbreviation/Term	Definition
ADaM	Analysis Data Model
AE	Adverse event
ATC	Anatomical therapeutic chemical
BID	Twice a day
BMI	Body mass index
BOR	Best overall response
CR	Complete response
CRF	Case Report Form
CSR	Clinical Study Report
CTCAE	Common Toxicity Criteria for Adverse Events
DSMC	Data Safety Monitoring Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EE	Efficacy evaluable
GBM	Glioblastoma multiforme
ICH	International Council for Harmonization
ICF	Informed Consent Form
ITT	Intent-to-treat
MedDRA	Medical Dictionary for Regulatory Activities
MTD	Maximum tolerated dose
NCI	National Cancer Institute
OR	Overall response
ORR	Overall response rate
OS	Overall survival
PD	Progressive Disease
PFS	Progressive-free survival
PFS6	6 – month PFS
PK	Pharmacokinetic
PR	Partial response
PT	Preferred Term
RANO	Response Assessment in Neuro-Oncology

Abbreviation/Term	Definition
RLT	Regimen-limiting toxicity
RP2D	Recommended Phase 2 dose
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Stable disease
SDTM	Study Data Tabulation Model
SOC	System organ class
SRS	Stereotactic radiosurgery
SRT	Stereotactic Radiation Treatment
TEAE	Treatment-emergent adverse event
TFL	Tables, Figures, Listings
WHO	World Health Organization
WHODDE	WHO Drug Dictionary Enhanced

3. INTRODUCTION

3.1. Preface

This SAP describes the analysis and data presentation for NewLink Genetics Corporation. Protocol NLG-2102 (*A Phase 1/2 Study of the Combination of Indoximod and Temozolomide for Adult Patients with Temozolomide-Refractory Primary Malignant Brain Tumors*). This SAP will provide the details and methods for analysis and reporting of the patient characteristics, safety and efficacy information.

The SAP described hereafter is an *a priori* plan. The SAP will be finalized and approved prior to database lock. Statistical programming may occur as study data accumulate in order to have analysis programs ready at the time the study finishes.

The conduct of the study in the field is considered to be independent of any study outcome that might materialize upon enactment of the currently proposed statistical plan. The documents used to develop this SAP include the study protocol, version 3 date 8/27/15, and the case report form (CRF) printout named NLG 2102 Project_crfPrintout_2019-Sep-06.

3.2. Purpose of Analyses

The purpose of the planned analyses described in this SAP are to assess the safety and efficacy profiles of indoximod plus temozolomide for adult patients with temozolomide-refractory primary malignant brain tumors. Results from the analyses will be included in the final clinical study report, and may also be utilized for regulatory submissions, manuscripts, or other clinical development activities.

Post-hoc exploratory analyses not identified in this SAP may be performed to further examine the study data. These analyses will be clearly identified, where appropriate, in the final clinical study report.

Additional analyses not prospectively identified in this SAP may also be performed for publications, regulatory or funding inquiries. These analyses, if performed, may not be reported in the clinical study report, but will be fully documented in the document containing additional analyses.

3.3. Summary of Statistical Analysis Changes to the Protocol

Protocol specifies that historical control will be used for phase 1 secondary endpoint analysis for study drug administration analysis in Section 1.2.

"To test the hypothesis that the addition of indoximod will not reduce the overall dose of temozolomide delivered or delay the timing of administration, compared to historical controls."

However, historical control is not available. This SAP will not make comparison between study data and historical control, and that specific secondary endpoint will be removed.

Protocol specifies that the Efficacy Evaluable population is the population to be used for efficacy analysis, and this SAP adds the ITT population as another population for efficacy analyses. Further, this SAP refines the definition of Efficacy Evaluable population as subjects who have received at least one dose of study drug and at least one post-baseline RANO assessment.

4. STUDY OBJECTIVES AND ENDPOINTS

Study objectives and endpoints defined in the protocol include safety and efficacy. Objectives and pre-specified endpoints are as follows:

4.1. Study Objectives

4.1.1. Primary Objective

Phase 1 component: To determine the recommended Phase 2 doses (RP2D) of indoximod and temozolomide in combination for treatment of progressive high-grade glioma (including glioblastoma multiforme (GBM)) or gliosarcoma.

Phase 2 component: To evaluate efficacy as measured by six-month progression-free survival (PFS) of indoximod plus temozolomide (with or without bevacizumab or stereotactic radiation therapy) in patients with progressive GBM.

4.1.2. Secondary Objectives

Phase 1:

1. To determine the adverse event (AE) profile and identify regimen-limiting toxicities (RLT) of indoximod plus temozolomide in combination therapy.
2. To determine the pharmacokinetic profile of indoximod in the setting of this treatment regimen.

Phase 2:

1. To determine efficacy as measured by overall response rate (ORR), overall survival, safety, and tolerability of indoximod plus temozolomide in patients with progressive GBM.
2. To determine ORR, safety, and tolerability of indoximod plus temozolomide and bevacizumab in GBM patients whose disease progressed during therapy with a bevacizumab-based regimen.
3. To determine ORR, safety, and tolerability of indoximod plus temozolomide and stereotactic radiosurgery (SRS) in GBM patients who may reasonably benefit from tumor debulking.

4.2. Study Endpoints

Phase 1 Primary Endpoint:

The primary endpoint of Phase 1 is Regimen Limiting Toxicity for the purpose of the [redacted] will be based on the dose escalation method.

Phase 1 Secondary Endpoints:

The secondary endpoints of Phase 1 include:

- Incident rates of AEs
- Incident rates of SAEs
- Incidents of RLTs
- Frequency with which laboratory tests are out of normal ranges
- Vital Signs including blood pressure, pulse and temperature.
- Total dose of temozolomide delivered
- Number of patients with grade 3 non-hematological toxicity that is treatment related that results in
  - the delay of temozolomide treatment by greater than 4 weeks.
  - a delay in starting the second cycle by more than 2 weeks due to toxicity attributable to test agent indoximod.
- Number of subjects experiencing dose modification in each of the prescribed study drugs.
- Pharmacokinetics (PK) (specified in a separate document).

Phase 2 Primary Endpoint:

The primary endpoint of Phase 2 is 6-month PFS.

Phase 2 Secondary Endpoints:

The secondary efficacy endpoints for Phase 2 include

- Best overall response,
- Proportion of subjects who reached stable disease (SD) and maintained as such,
- Overall survival (OS).
- Incident rates of AEs
- Incident rates of SAEs
- Frequency with which laboratory tests are out of normal ranges
- Vital Signs including blood pressure, pulse and temperature.
- Total dose of temozolomide delivered
- Number of subjects experiencing dose modification in each of the prescribed study drugs.

5. STUDY METHODS

5.1. Overall Study Design

As background for the statistical methods presented below, this section provides an overview of the study design and plan of study execution. The protocol is the definitive reference for all matters discussed in what follows.

The study is designed as a prospective Phase 1/2 trial of the combination of indoximod and temozolomide in adult patients with progressive glioblastoma multiforme (WHO grade IV glioma) or gliosarcoma. In addition, the Phase 1 cohort will include patients with progressive WHO grade III glioma. There must be imaging confirmation of tumor progression or regrowth after completing a standard course of radiation therapy and at least 2 adjuvant cycles of temozolomide.

This trial will be performed in two phases:

Phase 1:
The primary objective of the Phase 1 dose escalation is to determine the recommended Phase 2 doses (RP2D) of indoximod and temozolomide combination therapy for progressive high-grade glioma (including GBM) or gliosarcoma.

The different dose-levels are defined in Table 1. Each cycle is 28 days. Pharmacokinetic study will be performed for each patient in Phase 1 portion after a single dose of indoximod. Patients will continue until they experience disease progression or toxicity.

[redacted]

[redacted]

The maximum tolerated dose (MTD) will be declared to be the highest dose at which ≤ 1 out of 6 patients experiences a RLT. MTD in this context is considered a function of indoximod in this combination and not a MTD for indoximod in any other context / combination.

The period for determination of dose-limiting toxicities will be the initial 28 days of treatment. The recommended Phase 2 dose will include an assessment of toxicities that occur at later time points.

The initial dose of indoximod will be 600 mg BID. If a RLT is reported at Dose Level 1, a lower dose may be added after consultation between the Investigators, Medical Monitor and Sponsor, depending on the cumulative safety data. The protocol will be amended at that time accordingly.

Phase 2:
The primary objective of Phase 2 is to determine the efficacy (using 6-month progression-free survival) of indoximod with temozolomide in combination for treatment of progressive GBM or gliosarcoma. Phase 2 patients will be assigned to one of three cohorts:

Cohort 2A: indoximod with temozolomide
Cohort 2B: indoximod with temozolomide and bevacizumab or previous bevacizumab
Cohort 2C: indoximod with temozolomide and stereotactic radiosurgery

Patients will be treated with 28-day cycles of study treatment until disease progression or toxicity.

Patients will be followed both clinically and radiographically every 8 weeks for evidence of tumor progression. Post-treatment scans will be compared to the baseline MRI scan and

responses will be assessed based using Response Assessment in Neuro-Oncology (RANO) criteria.

Safety will be evaluated by following the guidelines provided in the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 4.03.

Table 3. Study Calendar

Study calendar for phase 1 component (escalation phase)

Evaluation	Pre Study	Cycle 1				Cycle 2 and subsequent cycles.				End of Therapy Visit	Follow-Up Visits to 2 years
		Wk 1 Day 1	Wk 2 Day 8	Wk 3 Day 15	Wk 4 Day 22	Wk 1 Day 1	Wk 2 Day 8	Wk 3 Day 15	Wk 4 Day 22		
Informed consent	X										
Verify eligibility criteria	X										
Medical History*	X			X		X		X			Q3mo
Concurrent medication	X	X		X		X		X		X	
Vital signs	X	X		X		X		X		X	Q3mo
Physical exam*	X	X		X		X		X		X	Q3mo
Performance Status	X	X		X		X		X		X	Q3mo
CBCD**	X			X		X		X		X	SOC
CMP**	A			A		A		A		X	SOC
INR	X										
C-Reactive Protein	X			X		X		X			
TSH, T3, T4 (and anti-TPO antibodies if needed)	X					X					
LH, FSH, ACTH***	X					X					
Pregnancy test for women of childbearing potential**	X	Patient will be asked about contraceptive every time being evaluated by study staff (Provider, RN) if they are in childbearing age.									
[redacted]											
PK		PK									
Blood for future testing		X				X					
MRI	X	MRI will be repeated every 8 weeks.									SOC
Indoximod		→									
Temozolomide		T				T					
DLT Assessment				X		X		X			

A: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium.
*History and physical exam will be performed by physician and/or midlevel provider or designated fellow.
** Will be done within 7 days before the start of the study drug.
*** The endocrine tests should be drawn around 7 a.m. due to the natural circadian fluctuations of ACTH

[redacted]

Study calendar for phase 2 component.

Evaluation	Pre-Study	Cycle 1				Cycle 2 and subsequent cycles.				End of Therapy Visit	FU Visits for 2 years
		Wk 1 Day 1	Wk 2 Day 8	Wk 3 Day 15	Wk 4 Day 22	Wk 1 Day 1	Wk 2 Day 8	Wk 3 Day 15	Wk 4 Day 22		
Informed consent	X										
Verify eligibility criteria	X										
Medical History *	X			X		X		X			Q3mo
Concurrent medication	X			X		X		X		X	
Vital signs	X	X		X		X		X		X	Q3mo
Physical exam*	X	X		X		X		X		X	Q3mo
Performance status	X	X		X		X		X		X	Q3mo
ECG	E	E				E				E	
CBCD**	X			X		X		X		X	SOC
CMP**	A			A		A		A		X	SOC
C-Reactive Protein	X			X		X		X			
TSH, T3, T4 (and anti-TPO antibodies if needed)	X					X					
LH, FSH, ACTH***	X					X					
INR	X										
Pregnancy test for women of childbearing potential**	X	Patient will be asked about contraceptive every time being evaluated by study staff (Provider, RN) if they are in childbearing age.									
[redacted]											
Blood for future testing		X				X					
Indoximod + Temozolomide		T →				T →					
Indoximod + Temozolomide + Bevacizumab		T B →		B		T B →		B			
Indoximod + Temozolomide + SRT		T →		SRT		T →					
MRI	X	MRI will be repeated every 8 weeks or every 2 cycles.									SOC
Vital Status Check										Q6mo for 5 years	

*History and physical exam will be performed by physician and/or midlevel provider or designated fellow.
** Will be done within 7 days before the start of the study drug.
*** The endocrine tests should be drawn around 7 a.m. due to the natural circadian fluctuations of ACTH
E: ECG to be completed pre-study and 1 hour after first indoximod dose on the first 9 subjects enrolled in Phase 2. Upon approval of the Version 3 protocol amendment, 12 consecutive patients will receive Baseline ECG (also to be repeated at 3 hours after first indoximod dose administration (Cycle 1, Day 1), again on Cycle 2, Day 1 after morning indoximod dose administration, as clinically indicated, and at the end of therapy).
A: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium.
B: Bevacizumab **T:** Temozolomide → Indoximod
SRT: Stereotactic radiation therapy to start 2 weeks after indoximod and temozolomide.

5.2. Randomization and Blinding

This is an open-label, single arm, Phase 1/2 study and randomization and blinding are not a part of the study design.

5.3. Analysis Variables

Variables to be analyzed include demographics, baseline characteristics, efficacy, and safety variables as described throughout this SAP.

6. SAMPLE SIZE

Phase 1
Up to 18 evaluable patients with high-grade glioma will be enrolled in the trial. The actual number of patients will depend on the RLT and MTD.

Phase 2
The sample size will be based on the primary end point of 6-month PFS. PFS will be calculated starting at the initiation of indoximod therapy. A modified Fleming procedure by A'Hern (2001) for a single stage phase-II clinical trial will be used and implemented by PASS12 software (NCSS, LLC). The sample sizes for Cohorts 2A, 2B, and 2C are based the following information of standard of care and experimental combination therapy (ECT) of percent of patients with 6-month progression free survival:

[redacted]

Due to differences in expected rates of enrollment between the Phase 2 cohorts (Cohort 2A being expected to enroll more readily) as well as the desire to more accurately inform a potential randomized trial focusing on the patients eligible for inclusion in Cohort 2A, the statistical stringency for Cohort 2A will be higher than that for 2B and 2C.

The minimum required sample sizes estimated are 68, 24, and 40 for Cohort 2A, 2B, and 2C, respectively.

The sample size for each cohort is estimated to provide 90% power at significance level 2.5% for Cohort 2A and 80% power at significance level 10% for Cohorts 2B and 2C.

7. GENERAL CONSIDERATIONS

7.1. Analysis Populations

7.1.1. Safety

The Safety population will include all patients who receive at least one dose of indoximod and temozolomide. The Safety population will be used for all safety data analyses. The Safety population will be used for Phase 1 and Phase 2.

7.1.2. Intent-to-Treat

The Intent-to-Treat (ITT) population will include all patients who signed an Informed Consent Form (ICF) and were enrolled (assigned a study number) into the study whether or not the study drug was administered. The ITT population will be used for all efficacy data summaries and analyses. The ITT population will be used for Phase 2 only.

7.1.3. Efficacy Evaluable (EE)

The Efficacy Evaluable (EE) population will include all patients who receive at least one dose of study drugs, indoximod with temozolomide, and either undergo at least one post-baseline RANO assessment or die before any evaluation. The EE population will be used for all efficacy data summaries and analyses. The EE population will be used for Phase 2 only.

7.2. Covariates and Subgroups

No covariates or subgroup analyses are planned for this study.

7.3. Management of Analysis Data

7.3.1. Data Handling

Laboratory, vital signs and ECG results that are collected during unscheduled visits will not be analyzed for the by visit summary but will be included in the shift tables. Unscheduled visits will be included with the time of the nearest scheduled test. If there is a scheduled test and one or more unscheduled tests assigned to the same time point, the most conservative test (i.e., most extreme test result from a safety standpoint) will be used. All data recorded on the electronic case report form (eCRF) and in third party lab transfer will be provided in patient listings. Test results collected but not pre-specified in the protocol, regardless of whether they occurred during scheduled or unscheduled visits will not be included in analysis.

7.3.2. Missing Data

Every effort will be made to collect all data. However, despite best efforts, missing or incomplete data may be reported. All missing or partial data will be presented in patient data listings, as they are recorded on the eCRF, as long as the patient is in the population of interest.

Patients lost to follow-up or withdrawn will be included in statistical analyses up to the point of their last evaluation. Unless otherwise specified, as noted below, in general, no imputation of values for missing data will be performed.

7.3.2.1. Handling of Missing Date Values

Partial dates are not permitted for Adverse Events and Concomitant Medications. Rules for data entry used by the sites for partially known dates are provided below.

Partially known date	Instruction
Date is missing – UNK-UNK-UNK	Enter the date as **Not available** and add a comment indicating the date is missing.
Only year is known – e.g. UNK-UNK-1989	If day and month are unable to be left blank please enter the date as **01-07**-1989 (1st of July). A comment indicating day and month not known should be entered.
Exact date not known – e.g. UNK-03-1989	If day is unable to be left blank please enter the date as **15**-03-1989 (15th day of the month). A comment indicating that the exact day is not known should be entered.

7.3.2.2. Imputation Methods

All data will be observed cases, without imputation.

7.3.3. Handling of Early Termination Visit Information

In the event that a patient is terminated early from this study, the early termination visit data will be analyzed at the closest scheduled visit. If the closest visit has valid data, the early termination data will be assigned to the next available visit.

Unless otherwise specified, date of contact will be set as the date of last valid vital signs measure or end date of last Adverse Event.

7.3.4. Pooling of Investigational Sites

In general, the data from all study centers will be pooled together for analyses, as all sites follow the same study protocol.

7.3.5. Coding Conventions for Events and Medications

Table 4. Coding Conventions for Events and Medications

Event/Medication	Coding/Mapping Convention
Adverse Events Coding	Mapped by MedDRA version 20.0
Adverse Events Intensity/RLT	Assess intensity by NCI CTCAE version 4.03
Medical History	Mapped by MedDRA version 20.0
Prior and Concomitant medications	Coded by WHO-DDE version Sep 17, 2017

7.3.6. Baseline

Baseline is defined as the last measurement taken prior to first exposure to study drug, including Day 1 measurements taken pre-dosing.

7.3.7. Analysis Software

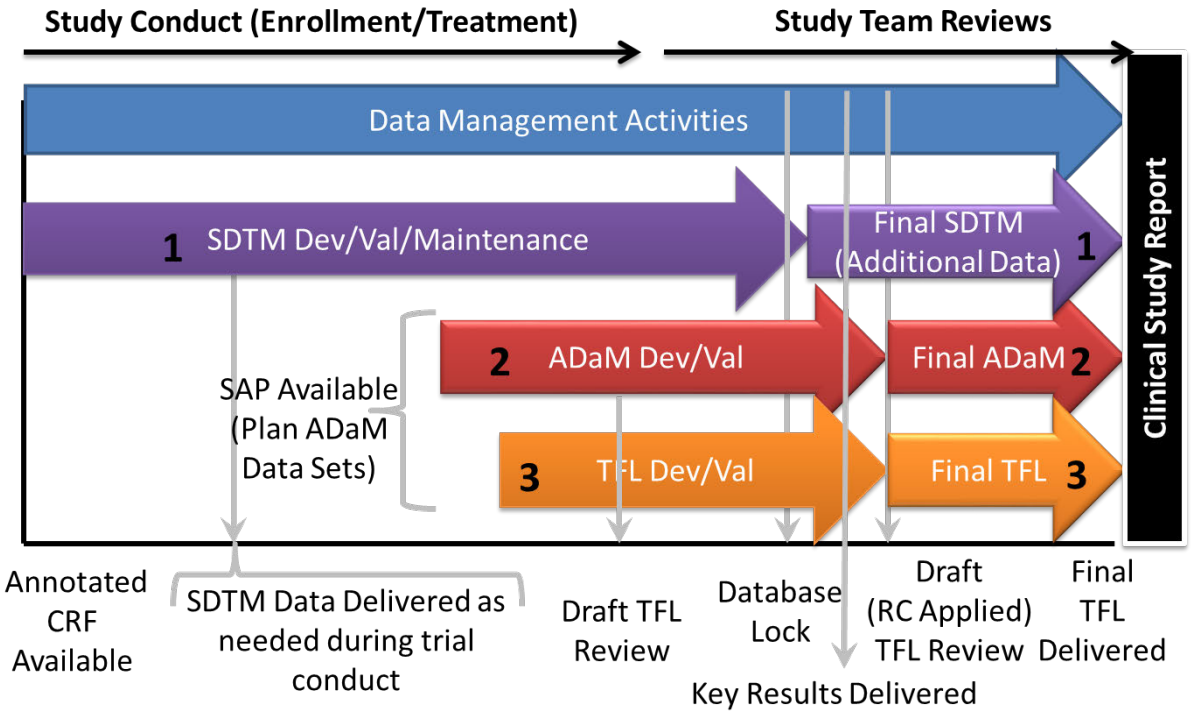
Data manipulation, tabulation of descriptive statistics, calculation of inferential statistics, and graphical representations will be performed primarily using SAS® (release 9.4 or higher) for Windows. If the use of other software is warranted, the final clinical study report will detail what software was used and for what purposes.

7.3.8. Study Data

Study data identified in the Study Calendar in Table 3 of Section 5.1 are collected and source verified on the electronic data capture tool: Clincase. Local Lab results will be in the database. PK data are captured and reported separately.

Observed study data will be mapped to the CDISC Study Data Tabulation Model (SDTM) and serve as the source data from the trial. All study analyses will be completed using analysis data sets that are derived from the SDTM and follow the CDISC Analysis Data Model (ADaM) architecture. The methods for programming the CDISC SDTM and ADaM data sets are described in Figure 1.

Figure 1 SDTM, ADaM, and TFL Development and Validation



Where:

1. Development, Validation, and Maintenance of SDTM domains.
2. Development and Validation of Analysis Data Sets (ADaM), with input source the appropriate SDTM domains.
3. Development and Validation of draft and then final Tables, Figures, and Listings (TFL), with input data source the SDTM domains and analysis specific ADaM data sets.

7.4. Planned Study Analyses

7.4.1. Statistical Summaries: Descriptive and Inferential

In general, inferential statistical analyses will be two-sided, and a difference resulting in a p-value of less than or equal to 0.05 will be considered statistically significant. All p-values will be rounded to and displayed in four decimals. If a p-value less than 0.0001 occurs, it will be shown in tables as <0.0001.

Descriptive summaries of variables will be provided where appropriate. In general, for continuous variables, the number of non-missing values (n) and the mean, median, standard deviation, minimum, and maximum will be tabulated. For categorical variables, the counts and proportions of each value will be tabulated.

All collected data will be presented in listings. Data not subject to analysis according to this plan will not appear in any tables or graphs but will be included in the data listings.

7.4.2. Interim Analyses and Data Safety Monitoring

No interim analysis is planned for this study. This trial will use a Data Safety Monitoring Committee (DSMC) during Phase 2. The DSMC will meet quarterly.

7.4.3. Final Analysis

The final study analysis will be completed after all patients have completed their end of therapy visit days and the database has been locked.

7.5. Multiple Testing Procedures

There will be no adjustments for multiplicity and no formal multiple testing procedures are to be implemented with this analysis plan.

8. SUMMARY OF STUDY DATA

8.1. Patient Summary Grouping

All tables and listings will be presented by actual dose level administrated and overall for Phase 1 dose escalation. The planned dose cohorts are starting at 600 mg BID for up to 6 patients, then followed by 1000 mg BID and 1200 mg BID if needed. Screen failure patients are not included in analysis sets. Patients who withdraw from the study prior to dosing may be replaced but will not be replaced after dosing. Phase 1 and Phase 2 will be presented separately. In addition, as each cohort in the Phase 2 expansion is enrolled separately and has potentially different expected rates of PFS, each cohort in Phase 2 will also be reported separately.

8.2. Patient Disposition

Patient disposition will be summarized and will include the number and percentage of patients included in the Safety, ITT and EE populations. The reasons for withdrawal for the patients who discontinue treatment and discontinue the study will also be summarized. All results will be presented for each phase, dose and cohort.

Data on study completion information, including the reason for treatment discontinuation and study discontinuation will be presented in a patient listing.

8.3. Protocol Deviations

All subject-level protocol violations will be presented in a patient listing.

8.4. Demographics and Baseline Cancer Characteristics

Descriptive summaries of patient demographics will be provided including age, sex, race, and ethnicity baseline ECOG score, weight, height, body mass index (BMI), defined as weight (kg) / height(m)^2. All demographic and baseline cancer characteristics will be summarized for each phase, dose and cohort using the ITT and EE populations.

All demographic and baseline information will be presented in a patient listing.

8.5. Medical History and Cancer Status

Patient medical history along with their cancer status will be collected during the screening period.

The number and percentage of patients with any medical history will be summarized overall and for each system organ class (SOC) and preferred term (PT). Details on cancer status will also be summarized.

Baseline cancer status including current tumor type, location and grade, time from initial brain tumor diagnosis to date of ICF, number of prior tumor relapses and resection, radiation type and duration, site radiated, total radiation dose, prior treatment with interstitial brachytherapy, stereotactic radiosurgery or implanted chemotherapy sources, progression/recurrence after this treatment, method to confirm progressive disease and surgery data

Medical history, as well as cancer status, will be summarized for each phase, dose and cohort using the ITT and EE populations.

Patient medical history and cancer status data will be presented in a patient listing.

8.6. Concomitant Medications

All medications taken by subjects at the time of enrollment or then after will be reported. The number and percentage of patients who take concomitant medications will be summarized in tables by Anatomical Therapeutic Chemical (ATC) level IV and preferred term.

For all medication tables, medications will be counted once for a patient using it, regardless of the number of times it was reported on the eCRF.

A concomitant medication is defined as any medications taken or ongoing on or after first dose date up to last visit after the last dose..

Concomitant medications will be summarized for each phase, dose and cohort using the ITT and EE populations.

All Concomitant medications will be presented in patient listings.

8.7. Corticosteroid Administration

All corticosteroid use reported will be summarized and listed by Preferred Term and by cohort for the ITT and EE Populations.

8.8. Treatment Exposure and Compliance

[redacted]

9. EFFICACY ANALYSES

9.1. Phase 1

Safety is the focus of Phase 1; efficacy analyses are not applicable to Phase 1.

[redacted]

PFS6 will be estimated using Kaplan-Meier methods. Then progression by 6 months will be defined as any occurrence within 6 months of either death or a RANO score of 4 or 5 for the

[redacted]

Primary efficacy for Phase 2 will be summarized for the ITT and EE populations.

Cohort 2C (Had Radiation):
Subjects who have any treatment entries in the SRS/SRT CRF will be summarized separately for the PFS and overall response tables, in order to examine if radiation therapy makes difference in survival.

9.3. Secondary Efficacy for Phase 2

The secondary efficacy endpoints for Phase 2 include best overall response, SD and OS.

Best Overall Response

The best overall response will be summarized by Cohort 2A, 2B, 2C, and for all cohorts combined. The patient's best overall response will depend on the achievement of both measurement and confirmation based on RANO criteria. The best overall response is the best response recorded from ICF until disease progression/recurrence/death.

Duration of Best Overall Response (BOR)

For duration of BOR for each subject described in the previous section, only patients who meet OR of CR or PR criteria based on RANO are included in the assessment. Duration of response is the time from the date of the first overall RANO response of CR or PR for the BOR to progression of disease of the target lesion or death, whichever comes first. Those who did not progress or die will be censored and the time will be defined as the time from the start of the BOR to either early termination or to the last known date without progression defined as the last date in the vital signs dataset, whichever comes first.

Note that other periods of responses that is not the BOR may occur but not summarized in this analysis. If there are multiple independent periods of BOR in a given subject, the first period will be used.

Duration of response will be summarized overall and by Cohort 2A, 2B, 2C and 2C who had radiation, using Kaplan-Meier estimates and 95% confidence intervals for the 25th, 50th (median), and 75th quantiles.

Stable Disease

Stable disease (RANO of CR, PR or SD) is measured from the date of ICF until the criteria for progression are met.

Duration of SD

Similar analysis as Duration of BOR above, will be performed for Duration of SD.

Overall Survival

OS will be measured from the date of ICF until death. Those who did not die will be censored at the last known date alive defined as the last date in the vital signs dataset.

OS will be summarized overall and by Cohort 2A, 2B, 2C and 2C who had radiation, using Kaplan-Meier estimates and 95% confidence intervals for the 25th, 50th (median), and 75th quantiles.

Secondary efficacy for Phase 2 will be summarized for the ITT and EE populations by cohorts.

10. SAFETY ANALYSES

Safety analyses will be performed using the Safety Analysis Set by dose level at 600, 1000, 1200 mg BID and overall for Phase 1, by dose Cohort 2A, 2B, 2C for Phase 2.

All safety data will be presented in listings.

10.1. Analyses for Phase 1 Only

Safety analyses in Phase 1 include assessment of AEs, RLTs, dose of temozolomide delivered, and PK parameters.

AEs are defined in Section 10.2, RLTs are defined in Section 10.3. AEs and RLTs for patients in Phase 1 will be presented in patient listings.

The dose of temozolomide delivered will be captured overall for each patient in milligrams.

A pharmacokinetic study will be performed for each patient in the Phase 1 portion of the study after a single dose of indoximod. PK summaries will be documented outside of this SAP.

10.2. Adverse Events

Treatment-emergent adverse events (TEAEs) are defined as any AEs occurred on or after first dose date or worsening of existing events up to 30 days post last dose.

TEAEs are summarized by frequency and percentage of patients and tabulated by SOC and PT, by greatest relationship to indoximod, to temozolomide, to bevacizumab, and to SRS/SRT respectively, by maximum Severity grade. Serious adverse events (SAEs), TEAEs leading to treatment discontinuation and death are summarized. Patients with multiple TEAEs are only counted once within a summary category.

AE Severity grade will be assessed using the CTCAE grading.

The following summary tables and patient level listings will be presented for TEAE data:

- Overall Summary of AEs
- TEAEs by SOC and PT
- TEAEs by SOC and PT, and Relationship to indoximod, temozolomide, bevacizumab and SRS/SRT separately.
- TEAEs by SOC and PT, and Maximum Severity Grade
- SAEs by SOC and PT

All AEs including both treatment-emergent and non-treatment-emergent events will be presented in patient listings.

10.3. Regimen Limiting Toxicity

RLTs, which are only reported for Phase 1, are defined as toxicities that delay the planned administration of the next cycle of the backbone chemotherapy. Toxicity grades are evaluated according to NCI CTCAE version 4.03.

RLTs will be presented in a patient listing.

10.4. Vital Signs, ECG, Laboratory Tests and Physical Examinations

Vital signs, ECG, laboratory results, ECOG, physical examination will be summarized by visit, overall and by phase, dose and cohort.

10.4.1. Vital Signs

Descriptive statistics of observed vital sign data and change from baseline will be presented by visit, including systolic blood pressure, diastolic blood pressure, temperature, heart rate and respiration rate.

All vital sign data will be summarized using the Safety population and will be presented in patient listings.

10.4.2. ECG

ECG observed data and change from baseline including heart rate, PR interval, QRS duration, QTc interval will be presented by visit, overall and by phase, dose and cohort.

All ECG data will be summarized using the Safety population and will be presented in patient listings.

10.4.3. Clinical Laboratory Evaluations

Clinical laboratory results including hematology, blood chemistry will be summarized by visit, overall and by phase, dose and cohort for the observed value as well as for change from baseline value. Other parameters such as c-reactive protein, endocrine functions, thyroid evaluation and TSH, T3, T4 evaluation will only be listed and not summarized.

Patient listings of individual laboratory parameters with normal ranges and abnormality assessments will also be presented by patient. Laboratory listings will include date collected, study day and observed laboratory values with low/normal/high or abnormal/normal flags.

All laboratory will be presented using the Safety population.

10.4.4. Physical, and ECOG Scale

Anthropometrics data including height and weight and BSA, and their change from baseline will be summarized by visit, overall and by phase, dose and cohort. ECOG scores will be summarized by using actual scores and changes from baseline, by visit, overall and by phase, dose and cohort.

All physical, ECOG data will be summarized using the Safety population and will be presented in patient listings.

10.5. Other Safety Measures

All other safety data will be presented in listings.

If additional safety measures not described herein are requested after study results are reviewed, these additional safety parameters and/or analyses will be completed and will be fully described and documented as post-hoc in the final clinical study report (CSR). The SAP will not be amended to complete any other safety measures identified as post-hoc.

11. PHARMACOKINETIC ANALYSES

PK summaries will be captured in a separate SAP.

12. REPORTING CONVENTIONS

The following reporting conventions will be adopted for the presentation of study data. These conventions will enhance the review process and help to standardize presentation with common notations

11.1 General Reporting Conventions

- All tables and data listings will be developed in Landscape Orientation, unless presented as part of the text in a CSR, where they may be in Landscape or Portrait Orientation.
- Figures will be presented in Landscape Orientation, unless presented as part of the text in a CSR, where they may be in Landscape or Portrait Orientation.
- Legends will be used for all figures with more than one variable or item displayed.
- Figures will be in presented in color with dose cohorts distinguished by different symbols and colors. Lines in figures should be wide enough to view the line after being photocopied.
- Specialized text styles, such as bolding, italics, borders, shading, superscripted and subscripted text will not be used in tables, figures, and data listings unless they add significant value to the table, figure, or data listing.
- Only standard keyboard characters should be used in tables and data listings. Special characters, such as non-printable control characters, printer-specific, or font-specific characters, will not be used on a table, figure, or data listing. Hexadecimal character representations are allowed (e.g., μ, α, β).
- All titles will be centered on a page. The International Council for Harmonization (ICH) numbering convention is to be used for all tables, figures, and data listings.
- All footnotes will be left justified and at the bottom of a page. Footnotes must be present on the page where they are first referenced. Footnotes should be used sparingly and must add value to the table, figure, or data listing. If more than four footnote lines are planned, then a cover page may be used to display footnotes.
- Missing values for both numeric and character variables will be presented as blanks in a table or data listing. A zero (0) may be used if appropriate to identify when the frequency of a variable is not observed.
- All date values will be presented as YYYY-MM-DD (e.g., 2013-05-17) ISO

8601 format.

- All observed time values will be presented using a 24-hour clock HH:MM:SS format (e.g., 01:35:45 or 11:26). Seconds should only be reported if they were measured as part of the study, also in ISO 8601 format.
- Time durations will be reported in mixed HH MM SS notation (e.g., 5h 32m, or 27h 52m 31s). The use of decimal notation to present (display) time durations should be avoided (e.g. 0.083h = 5m) unless it is necessary to show the computation of time differences in a table, figure, or data listing, in which case both notations may be used to display the time duration.
- All tables, figures, and data listings will have the Table, Listing, or Graph status (DRAFT, FINAL), and a date/time stamp on the bottom of each output.
- All analysis programs developed for a table, figure, or data listing display will be self-contained to facilitate transfer of programs to multiple computing environments and transfer to a regulatory agency (if requested).

11.2 Population Summary Conventions

- Population(s) represented on the tables or data listings will be clearly identified in the last title of the Table as "<name of population>" and will be identical in name to that identified in the protocol or SAP.
- Consistent terminology will be used to define and identify a population.
- Sub-population(s) or special population(s) descriptions will provide sufficient detail to ensure comprehension of the population (e.g., FAS Females, Per-Protocol Males >60 years of age) used for analysis in a table or figure.
- Population sizes may be presented for each treatment or dose cohort as totals in the column header as (N=xxx), where appropriate.
- Population sizes shown with summary statistics are the samples sizes (n) of patients with non-missing values.
- All population summaries for categorical variables will include all categories that were planned and for which the patients may have had a response.
- All population summaries for continuous variables will include: N, mean, standard deviation, minimum, and maximum. Other summaries (e.g. number missing, median, quartiles, 5%, 95% CIs, CV or %CV) may be used as appropriate.

  Unless otherwise noted, the estimated mean and median for a set of values are printed out to one more significant digit than the original values, and Standard Deviations are printed out to 2 more significant digits than the original values. The minimum and maximum will be reported the same significant digits as the original values. For example, for age:

N	XX
Mean	XX.X
Standard Deviation	X.XX
Median	XX.X
Minimum	XX
Maximum	XX

- All percentages are rounded and reported to xx.x%. A percentage of 100% will be reported as 100%. No value of 0% will be reported. Any computation of percent that results in 0% is to be presented as a blank.
- Population summaries that include p-values will report the p-value to four decimal places with a leading zero (0.0001). All p-values reported on default output from statistical software (i.e., SAS® Software version 9.4 or later) may be reported at the default level of precision. P-values <0.0001 should be reported as <0.0001 not 0.0000.

12 REFERENCES

A'Hern, R. P, 'Sample size tables for exact single-stage phase II designs.' Statistics in Medicine, 20; 859-866 (2001).

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Kong et al. Cancer. 2008;112(9):2046.

Perry et. al J Clin Oncol. 2010 Apr 20;28(12):2051-7

APPENDIX A PLANNED TABLES, LISTINGS, AND FIGURES

Tables

Listings

Figures

APPENDIX B ECOG PERFORMANCE STATUS SCALE

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.