Clinical Trial 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

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Investigational Agent:
Indoximod (1-methyl-D-tryptophan, D-1MT)

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Principal Investigators and Participating Sites

Multiple institutions throughout the United States will be conducting this study. For a full list of participating institutions please refer to the Clinicaltrials.gov website listing for this study (NCT02052648).

PROTOCOL SYNOPSIS

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

Primary Objective:

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

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

Population: Adult patients (16 years and older) with histologically proven intracranial glioblastoma or gliosarcoma (phase 2) or any high-grade glioma (phase 1). There must be imaging confirmation of tumor progression or regrowth. Patients must have completed a course of radiation therapy and at least 2 adjuvant cycles of temozolomide (phase 2).

Sample Size:

Phase 1: 12-18 subjects (depending on dose escalation)

Phase 2: Up to 132 subjects
Cohort 2a: 68 subjects who will receive indoximod with temozolomide (for those that are naïve to bevacizumab)
Cohort 2b: 24 subjects who will receive indoximod with temozolomide and bevacizumab in patients currently receiving or having previously received and failed bevacizumab
Cohort 2c: 40 subjects who will receive indoximod with temozolomide and stereotactic radiosurgery

Investigational Drug: Indoximod (1-methyl-D-tryptophan, D-1MT)

Dosage/Treatment:

Phase 1: Table below summarizes dose levels of indoximod and temozolomide for the Phase 1 portion of the study.

Dose Level	Indoximod DOSE (oral)	Temozolomide Dose (oral)
1	600 mg BID x 28 days	150 mg/m^2 x 5 days
2	1000 mg BID x 28 days	150 mg/m^2 x 5 days
3	1200 mg BID x 28 days	150 mg/m^2 x 5 days

Phase 2:

During Phase 2 portion of study, Indoximod will be administered at RP2D. The dose of indoximod will be determined in the phase 1 portion of the trial.

Patients will be separated into three different cohorts, based on their prior therapy (bevacizumab-naïve or bevacizumab-failure) and current potential indication for stereotactic re-irradiation.

Cohort 2a: Indoximod with temozolomide (for patients naïve to bevacizumab)

Cohort 2b: Indoximod with temozolomide and bevacizumab (for patients currently receiving or having previously received and failed bevacizumab)

Cohort 2c: Indoximod with temozolomide and stereotactic radiosurgery

This protocol will be conducted in the adult population and children age 16 years or older. A companion study for a pediatric population (brain tumors) will be opened after the completion of the Phase 1 portion of this study.

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1.0 OBJECTIVES

1.1 Primary Objectives

Phase 1b component: To determine the recommended phase 2 doses of indoximod and temozolomide in combination for treatment of progressive high-grade glioma (including glioblastoma multiforme) 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 SRS) in patients with progressive glioblastoma multiforme (GBM)

1.2 Secondary Objectives

Phase 1b:

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

Phase 2:

1. To determine efficacy as measured by objective 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.

2.0 BACKGROUND

2.1 Introduction

Glioblastoma is a diffusely infiltrating tumor that spreads microscopically throughout the brain. Therefore, all local therapies, such as surgery and radiation, are inherently palliative. Long-term disease control requires therapies targeting tumor cells throughout the brain, such as chemotherapy and small molecule pathway inhibitors.

The present standaid of core for newly diagnosed plioblastoino involves inoxiniN surgical resection followed by concun'ent radiotherapy with telnozolomide, on orolly available DNA alkylatinp agent followed by at least 6 months of adjiivant temozolomide.

Several clinical tiials foi recurrent plioblastoina tested the efficacy of different strategies that include EGFR inhibitors, the PDGFR/KIT inhibitor, the PDGFR and VEGFR inhibitor, and the lnTOR inhibitor CCI-779 (telnsuolimus) as suigle apents. Despite initial enthiisiosln, treatment of recurrent glioblastoma with these single pathway inhibitors has penei'ally been disappointing. without response or survival 1'ates superior *10* traditional cheniothei'apies. Combination studies with telnozolomide are ongoing.

A data set froln the North American Brain Tumor Consortiiun pooled data froln multiple phase 2 clinical trials for 1'eciuxent/progressive plioblastonm. all of which were consideied negative. This lneta-analysis denionstiated an overall 6-month pi'ogiession-free survival rate of 15% foi' patients with recurrent/piogiessive glioblastoina treated with small molecule inhibitors as sinple ogents[1] . Thus, novel therapies are needed in this disease.

Recently, bevacizuinab has been approved os a standard thelapy foi ieciuient GBM based on single arm oi iandoinized phase 2 sttidies. Cun'ent clinical practice varies, tailored to individiml patients, so not all patients receive bevacizuinab. In the ciurent study, patients who me akeady receiving bevaciziunab and hove progressed on theiapy will not stop bevacizuiuob.

Key cellular and molecular immune system mediators in the context of bi'ain tumors have been identified end include TGF-§, cytotoxic T cells, T1'egs, CTLA-4, PD- I and IDO. New and promising inununotheropeiitic drugs as well as conibinotoriol strategies that focus on the simultaneous inhibition of inununosuppi'essive checkpoints, both in innnune and brain tulnor cells: will open new avenues fo1 the ti'eatment of hiph grade glio s.

In this study, we will conduct o phose 1/2 trial in recurrent (teinozoloinide resistant) glionia patients. The overall poal of this study is to provide a foimdation for fittue sttidies with indoximod tested in newly diagnosed glioblostoma patients with iadiotion and telnozolomide, or in combination with vaccine theiapies.

2.2 Indoximod [-Methyl-D-tryptophan, hSC-[redacted]; IND#[redacted], IND#[redacted], IND#[redacted])

Indoximod was developed to inhibit the indoleomine 2, 3 dioxygenase (IDO) enzymatic pathway, which is important in the natural ie ilotion of immune responses. This potent immune suppi'essive mechanism hos been implicated in preserving tissue allografts, most dramatically in preventing T cell-mediated iejection of pateioally-derived fetal silo-antigens in pregnancy[2]. IDO also repulotes iininime responses in infection, autoiininime syndromes, and malignant states (reviewed in ref 3)[3]. Indoximod inhibits the IDO pathway end inipi'oves onti-tiunor T cell responses, slowing the m'owth of tuinoï s[4] '. This IDO-pathway inhibitor wcs subsequently developed for clinical rise via NCI's RAID program md is currently on the list of priority agents for continued development by the Concer Therapy Evaluation Program (CTEP) [6]. Initial work showed that the D-enantiomer was more effective in shrinking hunols than either the L-

enantiomer or the racemic mixture. Indoximod has very good oral bioavailability and favorable pharmacokinetics with twice daily dosing. In addition, the drug was well tolerated in preclinical animal studies.

Phase 1 trials of indoximod (IND#78060 and #78189) have been conducted and enrolled 65 patients with various solid malignancies, including breast, colon, melanoma, sarcoma, pancreatic, and lung cancer. The maximum dose of indoximod administered was 2000 mg PO BID given for 28 day cycles. No maximum tolerated dose was established because the drug demonstrated good tolerability. Five patients achieved prolonged stabilization of their disease (longer than six months), and other patients experienced mixed responses during the trial. No objective responses were achieved by patients on the study. Three patients, who had been previously treated with experimental immunotherapy, experienced autoimmune hypophysitis when started at the lowest dose level of indoximod. Subsequently, similar patients were excluded from the study, and no additional cases of hypophysitis were documented. Correlative studies showed elevations in serum C-reactive protein levels and tumor-specific autoantibodies. In conclusion, indoximod was well tolerated, showed biological activity, and had modest anti-tumor activity as monotherapy.

2.3 Temozolomide (Temodar®)

Temozolomide, an oral alkylating agent with good penetration of the central nervous system, has been evaluated in patients with glial malignancies. Initial studies evaluated the efficacy of temozolomide in patients with recurrent glioblastoma and anaplastic glioma. A large, randomized phase 2 study by Yung and colleagues[7] treated patients with recurrent glioblastoma with either temozolomide (200 mg/m2 days 1-5 of a 28-day cycle) or procarbazine (150 mg/m2 28 day- on, 28-day off schedule). The study demonstrated only a modest objective response rate for both regimens (approximately 5%), but a superior 6-month progression-free survival rate for temozolomide (21% vs. 9%) was found.

In a phase 3 trial performed by the EORTC and the NCIC, patients with newly diagnosed glioblastoma were randomized to receive either radiation therapy alone or concurrent radiation and temozolomide followed by 6 months of adjuvant temozolomide[8]. The study demonstrated a statistically significant improvement in median survival for the combination treatment arm (12.1 vs. 14.6 months) as well as a significant increase in 2-year survival (10% vs. 26%). This chemo-radiation regimen has been widely accepted as the new standard of care for patients with newly diagnosed glioblastoma. However, Temozolomide has demonstrated limited efficacy in recurrent glioma patients who previously have received adjuvant therapy with temozolomide[9].

2.4 Recurrent glioblastoma

The standard of care for recurrent glioblastoma multiforme (GBM) has not been clearly established. GBMs are highly vascularized brain tumors and growth has been shown to be angiogenesis dependent, thus stimulating interest in developing antiangiogenic therapeutic strategies.

Antiangiogenic agents are one of the most promising novel agents in development for GBM but to date have not substantially changed overall survival. The development of targeted therapy based on tumor vascular blockade led to the approval of bevacizumab for recurrent or progressive glioblastoma, since it was proven that this offers a new opportunity for patients suffering from this malignancy. Bevacizumab is a recombinant antivascular monoclonal antibody binding to circulating Vascular Endothelial Growth Factor (VEGF) preventing this cytokine from reaching its receptors (VEGFR1 and VEGFR2) on endothelium. This results in an inhibition of endothelial cell proliferation and vessel sprouting. In addition to its role as a regulator of angiogenesis, VEGF has been found to mediate immunosuppression. VEGF impairs maturation of dendritic cells, resulting in diminished antigen-presenting function, but also suppresses T cell function through a number of proposed mechanisms[10]. In vivo, inhibition of VEGF after the administration of bevacizumab with adoptive cell transfer results in a significant infiltration of T cells, presumably due to normalization of tumor vasculature, as well as significant tumor growth inhibition[11].

Recent intriguing data have been obtained by vaccinating patients with the epidermal growth factor receptor variant III (EGFRvIII) peptide, reproducing a specific epitope arising because of large deletion of the EGFR gene.

Survival in patients with recurrent GBM is poor regardless of which treatment strategy is employed. Median progression free survival is 2.5 months in adults with bevacizumab-refractory GBM[12]. The ongoing effort to identify effective strategies for the treatment of recurrent GBM includes combination strategies with agents that target complementary or redundant pathways. Incorporation of novel trial designs that permit simultaneous evaluation of several agent combinations and allow for rapid discontinuation of ineffective regimens can accelerate the clinical evaluation of such candidate regimens.

3.0 RATIONAL FOR COMBINING INDOXIMOD AND TEMOZOLOMIDE

Chemotherapy and immunotherapy can have additive or synergistic effects. A number of current trials combine early-phase immunomodulatory agents with standard chemotherapy regimens. Indoximod is a potent and selective inhibitor of IDO in phase 1/2 development in solid tumors. Temozolomide is FDA approved for the treatment of front line and recurrent glioblastoma and forms the basis for the combination therapies in GBM. Development of a well-tolerated and active combination of these two drugs has the potential for further improvement in the treatment of refractory GBM. Substantial preclinical data support using this combination.

Indoximod (1-Methyl-D-Tryptophan) synergizes with a number of different chemotherapy drugs in multiple tumor models[4, 5]. Recent animal studies conducted at GRU Cancer Center in Dr. Theodore Johnson's laboratory suggest a survival benefit in mice with glial tumors using either D-1MT or DL-1MT in combination with a standard treatment platform of alkylator chemotherapy (cyclophosphamide or temozolomide) plus radiation. These studies also suggest enhanced inflammatory effects (intratumoral complement activation) when 1MT is added to chemotherapy (temozolomide) or chemo-radiation treatments. In addition, widespread target IDO expression has been documented in both the glioma tumor cells and in surrounding host astrocytes using this model[13]. In other studies, a low-dose metronomic TMZ regimen reduced the number of circulating Tregs *in vivo*[14].

IDO as a therapeutic target in glioblastoma:
IDO is expressed by tumor cells in a large proportion (50-90%) of primary glioblastoma biopsy samples[15] (and unpublished data, Johnson and Munn). In human glioma patients, IDO expression appears to be an independent prognostic factor, as its upregulation is associated with poor prognosis[16]. In addition, Wainwright et al have recently used an in vivo mouse glioma model (GL261) to demonstrate the critical role of IDO in promoting GBM survival and progression[16]. In this study they also showed the importance of IDO in recruiting regulatory T cells into brains of tumor-bearing mice[16]. Thus, in this preclinical model, the IDO-pathway appears to play a pivotal role in suppressing T cell responses against glial tumors and promoting their progression.

Immunologic effect of stereotactic radiation:
Hypofractionated stereotactic radiation plus concomitant TMZ followed by TMZ is a feasible treatment option associated with potential survival benefits and low risk of complications in selected patients with recurrent malignant glioma. The potential advantages of combined chemo-radiation schedules in patients with recurrent malignant gliomas is currently under evaluation. Recent reports of stereotactic radiation in combination with immune-modulatory drug ipilimumab (anti-CTLA-4) describe systemic tumor regression following local irradiation of single lesions[17, 18]. This effect is consistent with an immune-activating effect of stereotactic radiosurgery, which has been predicted from preclinical models.

Study rationale:

The aim of this study is to identify the safety profile and the recommended dose for phase 2 study of the combination of indoximod (portion 1, phase 1b study). We will then evaluate the tolerability and the preliminary activity in patients with recurrent GBM in three different situations:

- Combination of indoximod and temozolomide (bevacizumab-naïve patients)
- Combination of indoximod and temozolomide in patients currently receiving or having received and failed bevacizumab
- Combination of indoximod and temozolomide with stereotactic radiation.

Ancillary studies will be conducted to assess the correlation between intra-tumoral IDO expression or serum biomarkers (immune monitoring) and treatment efficacy.

If the current study shows an acceptable safety profile and suggests preliminary evidence of activity, this will provide the justification for subsequent randomized phase 2 studies in refractory GBM.

This study conducted in adults will be expanded to include pediatric patients in a linked companion protocol that will be initiated after the completion of the phase 1 portion in adults.

4.0 PATIENT SELECTION AND ELIGIBILITY

4.1 Inclusion Criteria

- Histologically proven intracranial glioblastoma multiforme (WHO grade IV glioma) or gliosarcoma. In addition, the Phase 1b cohort will include patients with progressive WHO

grade III glioma. There must be imaging confirmation (with and without gadolinium contrast) of tumor progression or regrowth.

- Patients will be eligible if the original histology was lower grade glioma and a subsequent diagnosis of glioblastoma or gliosarcoma is made.

- Unequivocal radiographic evidence for tumor progression by MRI. It is understood that some patients may be resected prior to enrolling onto protocol.

- Patients must have completed a course of radiation therapy and at least 2 adjuvant cycles of temozolomide for the phase 2 component.

- Patients enrolling onto Cohort 2b who have been taken off bevacizumab must have had at least a 28 day washout from any previous administration of bevacizumab. It is preferred that patients who fail bevacizumab prior to trial entry remain on bevacizumab in the trial.

- Prior temozolomide is not required for the phase 1 component; prior radiation is required for the phase 1 arm. It is suggested (but not required) that patients be at least 3 months post radiation to reduce the chances of pseudoprogression.

- Patients must be on a steroid dose $\leq$ 2 mg of dexamethasone daily (or equivalent), and this dose must not have increased for at least 14 days prior to obtaining the enrollment.

- ECOG performance status $\leq$1 or Karnofsky $\geq$70% (Appendix A).

- Age $\geq$ 16 years

- Normal organ functions, which includes adequate:
  Bone marrow function as defined by the following laboratory values:
  - Absolute Neutrophil Count (ANC) $\geq 1.0 \times 10^9$/L
  - Platelets $\geq 100 \times 10^9$/L
  - Hemoglobin $\geq$ 9.0 g/dL

- Renal function (creatinine level within normal institutional limit, or creatinine clearance $\geq$60 mL/min/1.73 m^2 for patients with creatinine levels above institutional normal).

- Liver function (AST/ALT $\leq$2.5 X institutional upper limit of normal, Total bilirubin $\leq$ 1.5 times ULN, INR within 1.5 times ULN (or if receiving anticoagulant therapy an INR of $\leq$ 3.0 is allowed with concomitant increase in PT or an aPTT $\leq 2.5 \times$ control).

- Must be 28 days from the administration of any investigational agent or prior cytotoxic therapy with the following exceptions:
  - Must be 14 days from administration of non-cytotoxic agents (e.g., bevacizumab (except COHORT 2b), interferon, tamoxifen, thalidomide, cis-retinoic acid, tyrosine kinase inhibitor, etc.).

- Patients with prior therapy that included interstitial brachytherapy, Gliadel wafer, or stereotactic radiosurgery must have confirmation of progressive disease, rather than radiation necrosis, by PET scanning, Thallium scanning, MRI spectroscopy, or surgical documentation.

- The effects of indoximod on the developing human fetus are unknown. For this reason and because indoximod may affect maternal immune tolerance of the fetus, sexually active women of child-bearing potential must agree to use two forms of contraception (hormonal and barrier method of birth control or abstinence) prior to study entry and for the duration of study participation. Use of contraception or abstinence should continue for a minimum of 1 month after completion of the study. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should discontinue the study drug and inform her treating physician immediately. Also men should be discouraged from fathering children while on treatment.

4.2 Exclusion Criteria

- Prior invasive malignancy that is not low-grade glioma, high-grade glioma, glioblastoma, or gliosarcoma (except non-melanomatous skin cancer or carcinoma in situ of the cervix) unless the patient has been disease free and off therapy for that disease for a minimum of 3 years.

- Patients on the phase 2 portion of the study may not have more than 2 prior regimens for recurrent disease for glioblastoma/gliosarcoma. Patients on the phase 1 portion of the study may not have had more than 3 prior regimens.

- Active systemic infection requiring treatment, including any HIV infection or toxoplasmosis.

- Systemic corticosteroid therapy > 2 mg of dexamethasone daily (or equivalent) at study enrollment.

- Patients with baseline QTc interval of >470 msec at study entry and patients with congenital long QT syndrome.

- Patients with significantly altered mental status that would prohibit the understanding or rendering of informed consent and compliance with the requirements of this protocol must have a legally authorized representative (LAR) willing to participate and support the patient throughout the trial. Such situations will be handled as discussed in Appendix C. Affected patients without a LAR are excluded from participation.

- Other severe acute or chronic medical or psychiatric condition, or laboratory abnormality that may increase the risk associated with study participation or study drug administration,

or may interfere with the interpretation of study results, and in the judgment of the investigator would make the patient inappropriate for entry into this study.

- Active or history of autoimmune disease

- Pregnant women are excluded from this study, where pregnancy is confirmed by a positive serum hCG laboratory test (> 5 mIU/mL); breastfeeding should be discontinued.

- Patients with known autoimmune thyroid disease or positive anti-TPO antibodies (anti-Thyroid Peroxidase) at time of screening.

4.3 Inclusion of Women and Minorities

No exclusion is made on the basis of sex, race or ethnic background.

4.4 Baseline Tests

- Baseline and Eligibility Tests will include (See Section 11.0, Table 5 for details)

- Pre-Study Tests to be completed within **14** days prior to proposed treatment start include:

  - Baseline MRI performed within 14 days prior to initiating therapy

  - Upon approval of the Version 3 protocol amendment, 12 consecutive patients will receive Baseline ECG (also to be repeated at 3 hours after first (cycle 1, day 1) indoximod dose administration, again on Cycle 2, Day 1 after morning indoximod dose administration, as clinically indicated, and at the end of therapy).

- Pre-Study Tests to be completed within **7** days prior to proposed treatment start include:

  - Baseline history and complete physical examination (to include height and weight) within 7 days prior to initiating therapy.

  - Serum chemistries including BUN, creatinine, albumin, and glucose; electrolytes including sodium, potassium, and calcium; INR; liver function tests including total bilirubin, AST (SGOT), ALT (SGPT), and alkaline phosphatase to be done within 7 days prior to initiating therapy.

  - HCG pregnancy test (serum or urine) to be done within 7 days prior to first treatment for all women with child-bearing potential

  - LH, FSH and ACTH to be drawn at baseline and then monthly while on active treatment. Full endocrine analysis will be done if clinical suspicion and/or MRI data is suggestive of pituitary inflammation.

- TSH, T3 and Free T4 to be drawn ct baseline and then monthly while on octive treatment. If abnormal. complete anti-TPO antibodies (anti-Th 'Oid Peroxidase). If abnormal. iuonitoi clinically for thyroid dysfunction and supplement with thyioid hoonones as needed.

- CBC with platelets and 5-part differential (to include neutrophils, lymphocytes, eosinophils, bosophils, end inonocytes) to be done within 7 days prior to initiating theiapy.

- Blood (appi'oxiinotely 4 inL) for lneosiuement of [redacted] ratio ct baseline (con be obtained on lust day of treatment prioi to drup aAninistrotion)

5.0 REGISTRATION PROCEDL'RES

5.1 **Registration** Process

All patients lnust be registered on s0idy before begiiming therapy.

All subjects must have a: (1) sigaed Informed Consent Docimient md, (2) a completed Eligibility Checklist Form befoi'e iepisti'ation on the study. To iepistei o subject for this protocol, an autho1'ized physician or their designee must FAX or EMAIL the subject infoixuotion to the NewLink Genetics Registiation Office or the site's desipnoted CRA between the hours of 8:30 A.M. and 5:00 P.M. Centi'al Standaid Time. Monday thi'ough Friday. (FAX: (515) 296-3556; EMAIL: PotientRepisti'ations@1inkp.coin). No evening, weekend or holiday iegistrations will be peimitted. Once eligibility is confused, NewLink will FAX or EMAIL a confirmation of iegistration to the site.

A file of copies of all leports, laboiatoiy sttidies end other pertinent infornmtion docimienting the subject's eligibility fo1 sttidy will be maintained in the Clinical Research Office of NewLink Genetics Corpoiation.

6.0 TREATMENT PLAN

6.1 Experimental Design Synopsis

The sttidy is designed as a prospective Phase lb/2 trial of the combination of indoximod and temozolomide in odult patients with progressive glioblastolna iniiltifoime (WHO grade IV glionia) or pliosoicolno. In addition, the Phase lb cohort will include patients with progressive WHO grode III plioiuo. There must be imaging confMxuation of tumor progression or regiowth aftei' completing a standard coiuse of radiation theiapy and at least 2 adjuvant cycles of temozolomide.

The triol will be performed in two cohol4s:

Cohort 1 (phase lb):

[redacted]

Cohort 2 (phase 2):

[redacted]

Patients will be followed both clinically and radiopraphically every 8 weeks fo1 evidence of tiunor progression. Post-treatment scans will be colnpoi'ed to the baseline MRI scan and iesponses will be assessed based using RANO ciiteiia (see Section 12.2.1).

Safety will be evaliuited by following the giudelines piovided in the National Cancel Instittite Common Terminology Criteria for Adverse Events (NCI-CTCAE) Veision 4.03.

6.2 Phase lb Treatment Plan (Portion 1)

[redacted]

[redacted]

The standard i'epimen with temozoloinide is one of the backbone regimens into which new agents will be integrated for patients with GBM. To establish the safety and the RP2D of the new agent indoximod in combination with teiuozolomide, it is necessary to determine the attiibiition of all toxicities. Howevel, when telnozolomide is administered as standard regimen, it is associated with sipnificont toxicities that may confound efforts to define the tiue toxicity of new agents added to this backbone. The danper is thot the high iate of toxicity of the backbone iepimen will iesult in an unacceptably high rate of rejecting oll dose levels of new ogents. It has been recommended in these situations thot a 'yiapiuotic" approach be adopted foi determining dose limiting toxicities. In this approach only grade 3 and 4 toxicities thot are attributable to the test apent and iesult in the delay of the adininisti'ation of the backbone iepimen temozoloinide will be considered as iepinien limiting. Thus for purposes of the dose escNation in this trim definition of Regimen Limiting Toxicities will be defined as the following toxicities occiurinp divine the first cycle (28 days) of the treatment (which includes the combination of teiuozoloniide with indoximod)

- O Any m'ade 4 non-heiuotologica1 toxicity thot is treatment-ielated with the exception of alopecia, nausea and vomiting or lyiuphopenia.
- O Any grade 3 non hernatolopical toxicity that is treatment related that results in delay of backbone regimen (teinozoloinide) by greatei than 4 weeks.
- O Giade 4 thronibocytopenio (<25,000/ inin^3) attributable to indoximod that results in delay of backbone chemotheiapy for greater than 4 weeks
- O Gi'ade 4 (<500/ nun^3) neutropenia lasting lnore than 7days, or Giade 3 (<l000/ nun') febrile neiiti'openio.
- O Delay in starting second cycle by more than 2 weeks due to toxicity attributable to test agent indoximod

AEs **not known and expected from ternozolornide and not seen in phase 1 indoximod will be considered regimen toxicities initially. Any grade 3 or higher regimen toxicity mandates a conference** call **next business day between investigators anil** sponsor to discuss **attribution** and response.

In the presence of clinical neuro-deterioration, a brain MRI **will be performed to evaluate the presence of tumor progression** versus **tumor necrosis (and brain edema). If the diagnosis remains questionable,** MR **Spectroscopy will be performed,** as **usually recommended.**

If temozolomide is discontinued due to toxicity, patients may continue to receive indoximod alone.

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.

Table1. Dose levels (Phase 1 portion).

[redacted]

Patients will be assigned in cohorts of three.

Dose escalation will occur according to the following schema:

Number of Patients with RLT at a Given Dose Level	Escalation Decision Rule
0 out of 3	Enroll next three patients at the next higher dose level.
≥2 out of 3	Dose escalation will be stopped. Next lower dose will be declared MTD. If only three patients were enrolled at lower dose level, an additional three patients will be enrolled.
1 out of 3	3 more patients are enrolled at this dose. • If 0 of 3 of these experience a RLT, escalate to next level • If 1 or more of these experience RLT, dose escalation is stopped and next lower dose is declared MTD

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.

6.3 Phase 2 Treatment Plan (Cohort 2)

Indoximoil with temozolomide (cohort 2a):

This group of patients will receive fixed doses of indoximod and temozoloinide deteonined in the phase I port, based on toleiability.

Indoximod with temozolomide and bevacizumab or previous bevacizumab (Cohort 2b):

This group of patients who are currently on bevacizuinab (the usiml dose for plioblastonia 10 Ing/kg every 2 weeks) and have become bevacizuinab-refractory will be continued on bevacizumob (some dose) along with fixed dose of indoximod end temozolomide. Patients who are not ciuTently being tieated with bevacizuinob, having demonstrated progression on bevocizumab end been taken off bevacinunab by theu treating physician will be treated as in cohort 2a but accounted for as to analysis of results in Cohort 2b. In this cohoi4, stei'eotoctic radiation (oi i'e-radiation) will not be allowed.

Indoximod with temozolomide and stereotactic radiosurgery (Cohort 2c):

Patients who are suitable fo1 re-iadiotion with steieotoctic iadiosiugeiy (SRS) or hypofiactionated stereotactic i'adiotion treatment (SRT) will be enrolled in Cohort 2e. SRS or SRT will be combined with fixed doses of indoximod and telnozolomide deteixuined in phase 1. SRS and SRT will be adnunistei'ed 2 weeks after the initiation of indoxñnod end teniozolomide. The dose and volume of radiation will be described in detail in section 6.7.

Cycle length and duration:
Eoch cycle is 28 days. Patients will continue imtil they experience disease piogiession oi toxicity (as defined in Section 6.7).

[redacted]

6.4 Study Agent Administration and Pharmacokinetic considerations

Treatment will be administered on an outpatient basis.

All patients in the phose 1 poi4ion of the trial will have pharmacokinetics performed on day 1 of the first cycle. Patients will be adniinisteied o sinple dose of indoximod at the appropriate dose level. They will also take their lust dose of temozoloinide as well as the fu'st dose of prophylactic Bactrini end anti-elnetic in the morning of day I with the indoximod. Phainmcokinetics for indoximod will be evaluated ovei the next 48 horns md patients will begin twice daily indoximod on day 3. Patients will resume telnozolomide on the evening of day 3 and complete the remaining four doses of the lust cycle of temozoloinide on days 3-6. The cycle will refrain 28 days in length.

Reported adveise events and potential risks are described in Section 7.1. A]31'O]31'iate dose lnodificotions are described in Section 7. No investigationol oi' commercial agents or therapies othei than those desci ibed below may be adininisteied with the intent to treat the patient's malignancy.

6.5 Indoximod Adininistration

[redacted]

6.7 Administration of Radiation (SRS or SRT)

SRS oi SRT will be adininistrated for Cohol4 2c patients 2 weeks aftel the initiation of indoximod and temozoloinide. The use of single fraction SRS o1 5 fractions of SRT will depend on the ttunor voliune. Sinple fraction SRS will be given to patients with the target volimie of less than 4 cc, while 5-fiaction SRT will be given to patients with the tarpet voliune loi ge than 4 cc.

Foi single fiaction SRS, piescription dose will be 16 Gy when the toiget volume is loiger then 1.5 cc. The presciiption dose con go up to 20 Gy when the torget volume is less than 1.5 cc.

Foi 5-fiaction SRT, the presciiption dose will be genei'ally 5.5 Gy/fiaction with a totol dose of 27.5 Gy. The prescription dose may be reduced if the critical no 1 stluc0ne constiains connot be met.

The tai get voliune is defined as the contrast enhanced lesion in MRI. A margin of 0-2 min lnay be added to the planning tnget volume (PTV). The piescription dose should be cover at least 95% of the toiget volume. The presciiption isodose line could be os low as 50%. The FLAIR enhanced area in the FLAIR MRI may be defined os the sub-toiget volimie and a dose of 70-80% of prescription dose niay be given to this sub-tarpet voliune.

The constiaints of the ciitical stiuc0nes mainly includes the optical apparatus and the bi'ain stem. Foi single-fraction SRS, Moxiiniun dose of the optical apparatus (0.03 cc of the voliune) should receive less than 8 Gy, the maximimi dose of the brain stem (0.03 cc of the voliune) should be less

than 12 Gy. For 5-fraction SRT, the maximum dose of the optical apparatus (0.03 cc of the volume) should receive less than 15 Gy total dose, and the maximum dose of the brain stem (0.03 cc of the volume) should be less than 23 Gy.

Any FDA cleared external beam radiation delivery system, including conventional linear accelerators, cyberknife, tomotherapy, or gamma knife may be used for the treatment delivery.

6.8 General Concomitant Medication and Supportive Care Guidelines

All standard of care anti-emetics, anti-diarrheals, antibiotics or hematopoietic growth-factors are permitted if clinically indicated. Patients on temozolomide should be treated per standard institutional practices for pneumocystis carinii (PCP) prophylaxis.

6.9 Duration of Therapy

In the absence of treatment delays due to adverse event(s), treatment may continue until one of the following criteria applies:

- Disease progression.
- Intercurrent illness that prevents further administration of treatment.
- Unacceptable adverse event(s).
- Patient decides to withdraw from the study
- Patient inability to be compliant with study treatment in opinion of investigator defined as missing treatments or study visits for non-medical reasons or complying with oral treatments below an 85% threshold on two sequential study visits
- General or specific changes in the patient's condition that render the patient unacceptable for further treatment in the judgment of the investigator.

At the discretion of the treating physician, if it is thought to be the best possible course of treatment, subjects may be able to stay on indoximod alone after temozolomide/bevacizumab treatment if they do not go on to other treatment regimens.

6.10 End of Treatment and Premature Withdrawal Visit

Once a participant discontinues study therapy for any reason, the participant will be asked to return to the clinic within 30 days for the assessments listed below.

- Update medical history including prior and concomitant medications.
- Physical examination including vital signs, height, and weight, and a review of body systems.
- ECOG performance status
- CBC with differential and platelets.
- Serum chemistries.
- ECG
- [redacted].
- Concurrent medications and adverse events assessed at end of treatment.

6.11 Duration of Follow-up

After the End of Treatment Visit, Follow up visits will be conducted every 3 months for 2 years, to include the following:

- Update medical history including current cancer therapy receiving every 3 months.
- Physical examination including vital signs, height, and weight, and a review of body systems every 3 months.
- CBC with differential and platelets per SOC practices.
- Serum chemistries per SOC practices.
- Serum kynurenine and tryptophan levels every 6 months.

Patients will be followed for survival and possible long-term toxicity from this treatment. Follow-up visits will continue for 2 years as per Section 11 (and as stated above). For those surviving longer than 2 years, follow-up will be performed using telephone contact, correspondence with treating physicians, and death records as necessary to update vital status at least every 6 months until death or lost to follow-up. Further therapy will be at the discretion of the treating physician.

6.12 Criteria for Removal from Study Therapy

Patients will be removed from study therapy when any of the criteria listed in Section 6.9 applies. If rapid life-threatening disease progression happens, or unacceptable adverse event(s) occur, or patient decides to discontinue the study, or patient becomes pregnant or starts breast-feeding, the patient will be removed from the study therapy. The reason for study removal and the date the patient was removed must be documented on the Case Report Form.

7.0 DOSING DELAYS/DOSE MODIFICATIONS

7.1 Temozolomide (Temodar®)

First Cycle: Temozolomide will be started at a dose of 150 mg/m^2/day. Patients that had already been on temozolomide pre-study at a dose of 100 mg/m^2/day due to temozolomide toxicity (i.e., neutropenia, thrombocytopenia, etc.) can start the study at 100 mg/m^2/day at the discretion of the treating physician.

Second Cycle: If patients tolerate the first cycle of combination therapy without any temozolomide related toxicities, the patient may be dose escalated up to 200 mg/m^2/day at the discretion of the treating physician. The dose of temozolomide will be modified according to: (1) non-hematologic AE during the preceding treatment cycle, as well as (2) the worst ANC and platelet counts. Recalculation of BSA and temozolomide doses is required if the patient has a 10% or greater weight change (+/-) from baseline or from the last weight used to calculate BSA and drug doses.

Delay: On day 1 of each cycle (within the prior 72 hours), ANC 1.5 x 10^9/L, platelet count 100 x 10^9/L and all grade 3 or 4 non-hematologic AEs (except for alopecia, nausea, and vomiting) must have resolved (to grade 1).

If AEs persists, treatment should be delayed by 1 week for up to 4 consecutive weeks. If, after 4 weeks of delay, all AEs have still not resolved: then any further treatment with temozolomide should be stopped.

Dose Reductions: If, during the first cycle, all non-hematologic AEs observed were grade 2 (except alopecia, nausea and vomiting) and with platelets > 100 x 10^9/L and ANC > 1.5 x10^9/L: then the temozolomide dose should remain the same.

Dose reductions: If any non-hematologic AE observed was grade > 2 (except alopecia, nausea and vomiting) and/or if platelets < 50 x 10^9/L and/or ANC < 1 x 10^9/L, then the dose should be reduced by one dose level (table 2). Patients who require more than two dose reductions will have treatment stopped.

If any treatment-related non-hematologic AE observed was grade 4 (except alopecia, nausea and vomiting) then temozolomide treatment should be stopped.

Subsequent cycles: Any dose reductions of temozolomide will be determined according to: (1) non-hematologic AE during the preceding treatment cycle, as well as (2) the lowest ANC and platelets observed. No dose escalation should be attempted. The same dose reductions as for the second cycle should be applied. Important: If the dose was reduced or delayed for AEs, there will be no dose escalation in subsequent treatment cycles.

Table 2.Dose Adjustment Table

Dose level	Dose mg/m^2	Remarks
-2	100	Reduction if prior AE
-1	125	Reduction if prior AE
0	150	Starting dose for cycle 1

Table 3: Worst Treatment-Related Hematologic AE During the Previous Cycle

Worst Treatment-Related Hematologic AE During the Previous Cycle

Worst AE		Platelets		
		≥100 x 10^9/L	50 – 99 x 10^9/L	< 50 x 10^9/L
ANC	≥ 1.5 x 10^9/L	Dose unchanged	Reduce by 1 dose level	Reduce by 2 dose levels
	≥1 & <1.5 x 10^9/L	Dose unchanged	Reduce by 1 dose level	Reduce by 2 dose levels
	< 1 x 10^9/L	Reduce by 1 dose level	Reduce by 2 dose level	Remove from study

Note: A complete blood count must be performed on days 14, 21 and 28 (± 48 hours) after the first daily dose of each treatment cycle.

Hematologic AE on Day 1 of Each Cycle (within the prior 72 hours before Day 1)	
AE	**Delay**
ANC< 1.5 x 10^9/L and/or Platelet count < 100 x 10^9/L	Delay up to 4 weeks until all resolved. If unresolved after 4 weeks then stop. If resolved, dose delay/reductions based on non-hematologic AEs are applicable. If treatment has to be delayed for AEs, then no escalation is possible.

Non-Hematologic AE (except for alopecia, nausea, and vomiting) On Day 1 of Each Cycle (within the prior 72 hours)	
Grade	**Delay**
2-3	Delay up to 4 weeks until all resolved (to grade ≤ 1). If unresolved after 4 weeks, then stop. If resolved, dose delay/reductions based on ANC and platelets are applicable. If treatment has to be delayed for AE, then no escalation is possible.

Table 4. Summary of Dose Modifications or Discontinuation for Temozolomide-Related Adverse Events

Summary of Dose Modifications or Discontinuation for Temozolomide-Related Adverse Events

Worst Treatment-Related Non-Hematologic AE (except for alopecia, nausea, and vomiting) During the Previous Cycles	
Grade	**Dose Modification**
0-2	No dose modifications for non-hematologic AEs. Dose reductions based on ANC and platelet counts are applicable.
3	Reduce by one dose level (except alopecia, nausea, and vomiting).
4	Stop (except alopecia, nausea, and vomiting). Dose modifications based on ANC and platelet counts are not applicable.

7.2 Indoximod

In general, indoximod was very well tolerated in previous phase 1 trials and seldom required any dose reductions. If a dose reduction is deemed necessary due to intolerance from taking the required number of pills or grade 3-4 nausea, one dose reduction by 200 mg is permitted. Indoximod will not be restarted at full dose after a dose reduction. If this dose reduction is not tolerated then discontinuation of the study treatment is required.

7.3 Bevacizumab:

In cohort 2b, the dose of bevacizumab will be 10 mg/kg every 2 weeks

Per the drug insert of bevacizumab, there are no recommended dose reductions.

Bevacizumab will be temporarily suspended for:

- At least 4 weeks prior to elective surgery.
- Severe hypertension not controlled with medical management.
- Severe infusion reactions.

Bevacizumab will be discontinued for the following:

- Gastrointestinal perforations (gastrointestinal perforations, fistula formation in the gastrointestinal tract, intra-abdominal abscess)
- Wound dehiscence and wound healing complications requiring medical intervention.
- Serious hemorrhage (i.e., requiring medical intervention)
- Severe arterial thromboembolic events.

At the discretion of the treating physician if it is thought to be the best possible course of treatment, subjects may be able to stay on temozolomide plus indoximod or indoximod alone after temozolomide/bevacizumab treatment if they do not go on to other treatment regimens.

8.0 ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of AEs (Section 7.1) and the characteristics of an observed AE (Section 7.2) will determine whether the event requires expedited reporting in addition to routine reporting.

8.1 Most Common Adverse Events

8.1.1 Adverse Events for Indoximod

The most common adverse reactions (≥ 10% incidence) are: fatigue, nausea, anorexia, anemia, diarrhea, lymphopenia, neutropenia, abdominal pain, shortness of breath, rash, vomiting, constipation, thrombocytopenia, headache, and alopecia.

The most common Grade 3 to 4 hematologic laboratory abnormalities that have developed during treatment with indoximod are: thrombocytopenia, neutropenia, leukopenia, and lymphopenia.

8.1.2 Adverse Event List(s) for Temozolomide

- The most common adverse reactions (≥10% incidence) are: alopecia, fatigue, nausea, vomiting, headache, constipation, anorexia, convulsions, rash, hemiparesis, diarrhea, asthenia, fever, dizziness, coordination abnormal, viral infection, amnesia, and insomnia.

- The most common Grade 3 to 4 hematologic laboratory abnormalities (≥ 10% incidence) that have developed during treatment with temozolomide are: lymphopenia, thrombocytopenia, neutropenia, and leukopenia.

- Allergic reactions have also been reported.

8.2 Adverse Event Reporting

Subject data accrued on this study will be reported in accordance with Code of Federal Regulations Title 21 (21CFR) 312.32.

This study will utilize the descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 for grading all adverse events. All appropriate treatment areas should have access to a copy of the CTCAE version 4.03. A copy of the CTCAE version 4.03 can be downloaded from the CTEP web site (http://ctep.cancer.gov).

The Site P.I. will notify the IRB and NewLink Genetics (Study Sponsor) who in turn will notify the FDA and other regulatory agencies of all serious adverse events as required by law or regulation. All participating investigators will be notified of IND Safety Reports by Investigator Alerts sent through email. Serious Adverse Event (AE) Reporting by investigators will be done as outlined below.

An ***adverse event*** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

Related/Attribution to the use of the drug: There is a reasonable possibility (more likely than not) that the experience may have been caused by the investigational drug.

Attribution Categories:

Unrelated	The AE *is clearly NOT related* to the intervention.
Unlikely	The AE *is doubtfully related* to the intervention.
Possible	The AE *may be related* to the intervention.
Probable	The AE *is likely related* to the intervention.
Definite	The AE *is clearly related* to the intervention.

A ***serious adverse event*** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity

- a congenital anomaly or birth defect
- an important medical event

Reporting Requirements for **Serious Adverse Events** (21CFRPart312)

Investigators MUST immediately report to the sponsor ANY serious adverse events within 24 hours of learning of the SAE, whether or not they are considered related to the investigational agent(s)/intervention (21CFR312.64)

An adverse events is considered SERIOUS if it results in ANY of the following outcomes:

1. Death
2. A life-threatening adverse event
3. An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4. A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5. A congenital anomaly/birth defect
6. Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA21CFR312.32; ICHE2A and ICHE6).

SAE reporting timelines are defined as:

- "24 Hour; 5 Calendar Days" – The SAE must initially be reported within 24 hours of learning of the SAE, followed by a complete SAE report within 5 calendar days of the initial 24 hour report.

Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and are considered related to the investigational drug require reporting on the same timelines as noted above.

Deaths clearly due to progressive disease should **NOT** be reported expeditiously but rather should be reported via routine reporting (death report).

Hospitalization, Prolonged Hospitalization or Surgery

Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for and adverse event.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should ***not*** be reported as an outcome of an adverse

event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.
- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

SAE Reporting Form and Content: For those events that meet the criteria for serious as listed above, please complete a Serious Adverse Event Reporting Form. This form will be provided by NewLink Genetics. Please send to NewLink Genetics within the time frames listed above. Please FAX to (515) 296-3556 or EMAIL to **SAE_Reporting@linkp.com**. Please call (515) 598-2935 with any reporting questions. You may also contact and send this form to the CRA designated for your site.

8.3 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions. AEs reported through expedited SAE reports must also be reported in routine study data submissions (CRFs).

8.4 Reporting Requirements for Baseline Adverse Events

A pertinent positive finding identified on baseline assessment is to be documented as a Baseline Adverse Event using CTCAE terminology and grade on the provided Baseline CRF. An expedited AE report is not required if a patient is entered on to the study with a pre-existing condition (e.g., elevated laboratory value, diarrhea). The baseline AE must be re-assessed throughout the trial and reported if it fulfills expedited AE reporting guidelines.

1) If the pre-existing condition worsens in severity, the investigator must reassess the event to determine if an expedited report is required.
2) If the AE resolved and then recurs, the investigator must re-assess the event to determine if an expedited report is required.
3) No modification in grading is to be made to account for abnormalities existing at baseline.

8.5 Adverse Event Case Report Form

All adverse events (regardless of grade and attribution) observed while on study and for 30 days after last dose of treatment, must be recorded on the adverse event case report form. After 30 days from last dose of treatment, only adverse events that are attributed to the study drug/combination (possible, probable, or definite) are required to be recorded on the adverse event forms.

8.6 Pregnancy

The teratogenic potential of indoximod is unknown. During the course of the study, all women of childbearing potential who are participants and all spouses of participants must be instructed to contact the Principal Investigator immediately if pregnancy is suspected. Pregnancy in a participant or partner of a participant who is receiving treatment will be reported following

procedui'es for a SAE (olthoiiph it will not be coded as a SAE). The event will be i'ecorded in the pregnancy CRF. If pregnancy is suspected in a participant or partnei of a participant prioi' to study drup administiation, the sttidy drug will be withheld until the b-hCG test result is available. If pregnancy is confirmed. the patient will not ieceive study drug and will be withdrawn fiom the stridy. If pregnancy is suspected while the patient is ieceiving sttidy drug, the study tip will be immediately withheld until the result of a §-hCG test result is available. If pi'epnmcy is confirmed, the patient will be permanently discontinued from the study in an appropriate manner. Protocol-required procediues foi study discontiniwtion will be performed imless contiaindicated by pregnancy (e.p., x-iay studies). Other appropriate follow-up procedures should be conside1'ed, if indicated. In addition, the Principal Investipatoi will repoit pregnancy-related follow-up information, including perinotol and neonatal outcomes to the IRB. Infants will be monitored for a nuniniuni of eight weeks.

[redacted]

How supplied: Indoximod is supplied by NewLink Genetics os 200 Ing capsules. The capsules contain the inactive ingredients lactose nionohydiate, microcrystalline cellulose, sodiimi croscoiniellose, colloidal silicon dioxide, and nmgnesiiun stearate. The capsules are packaged 175 capsules/bottle in white opoque HDPE bottles.

The 200 nip capsules are white opaque hard gelatin capsules.

Storage: Stored at contiolled ioom teiupeiattue (59-77°F).

Stability: Shelf-life surveillance of the intoct bottles is on-goinp. Initial lots have been stable at 48 months.

Route of Administration: Oral

Agent Ordering and Agent Accountability: Indoximod is supplied and shipped by NewLink Genetics Corporation to the study site. Each shipment is accompanied by a Clinical Investigational Material Shipment Receipt Form. Upon receipt, at the clinical site, the product is stored in the clinical site's Investigational Pharmacy or designated area.

As required by FDA regulations for all drug storage, procurement and usage are carefully monitored and documented. The Principal Investigator will oversee this process and delegate responsibility as needed to conduct the trial under Good Clinical Practices. A careful inventory is maintained at each of the clinical sites.

9.2 Temozolomide (Temodar®)

Please refer to the package insert for comprehensive information.

Formulation Other Names: Methazolastone; Temozolomide is supplied in white opaque, preservative-free, two-piece, hard gelatin capsules of the following p.o. dosage strengths: 5 mg, 20 mg, 100 mg, 140 mg, 180 mg, and 250 mg. Dose is rounded to the nearest 5 mg based on surface area. Each capsule contains drug substance in combination with lactose, anhydrous NF, colloidal silicon dioxide NF, sodium starch glycolate NF, tartaric acid NF, and stearic acid NF. The capsule shells contain gelatin NF, titanium dioxide USP, and sodium lautyl sulfate NF.

Mode of Action: Alkylating agent of imidazotetrazinone class.

Storage and Stability: The capsules are packaged in amber glass bottles and should be stored at 25°C. Temperature excursions between 15 and 30°C are permissible. Refer to the commercially labeled bottles for expiration dating.

Pharmacokinetics: Temozolomide is rapidly and completely absorbed after oral administration; peak plasma concentrations occur in 1 hour. Food reduces the rate and extent of temozolomide absorption. Mean peak plasma concentration and AUC decreased by 32% and 9%, respectively, and Tmax increased 2-fold (from 1.1 to 2.25 hours) when temozolomide was administered after a modified high-fat breakfast.

Temozolomide is rapidly eliminated with a mean elimination half-life of 1.8 hours and exhibits linear kinetics over the therapeutic dosing range. Temozolomide has a mean apparent volume of distribution of 0.4 L/kg (%CV=13%). It is weakly bound to human plasma proteins; the mean percent bound of drug-related total radioactivity is 15%.

Metabolism and Elimination: Temozolomide is spontaneously hydrolyzed at physiologic pH to the active species, 3-methyl- (triazen-1-yl) imidazole-4-carboxamide (MTIC) and to temozolomide acid metabolite. MTIC is further hydrolyzed to 5-amino-imidazole-4-carboxamide (AIC), which is known to be an intermediate in purine and nucleic acid biosynthesis and to methylhydrazine, which is believed to be the active alkylating species. Cytochrome P450 enzymes play only a minor role in the metabolism of temozolomide and MTIC.

Relative to the AUC of temozolomide, the exposure to MTIC and ACI is 2.4% and 23%,

respectively. About 38% of the administered teniozolonude tots radioactive dose is iecovered over 7 days; 37.7% in urine and 0.8% in feces. The majority of the 1'ecoveiy of radioactivity in urine is os unchanged temozoloinide (5.6%), AIC (12%), temozolomide acid metabolite (2.3%), and unidentified polai metabolites(s) (17⁰/»). Oveiall clearance of teinozoloinide is about 5.5 L/In/m2.

10.0 CORRELATIYE/SPECIAL STLWIES

The following sttidies will be performed as part of this study

- Phaonacokinetics
- Assessment of prinwiy ttmioi biopsy/resection samples (foixuolin-fixed, paiaffin-embedded) stained for: (1) IDO and TDO expression
- Evaluation of blood for bioinoikers of IDO activity (kyniuenine and tiyptophan). beforeand after initiation of therapy
- Evaluation of seoun for C-reactive protein ct diagnosis end duiinp thelapy
- Banking of blood for fittue studies

10. 1 [redacted]

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[redacted]

[redacted]

11.0 STUDY CALENDAR

Baseline evaluations including lobolatory exaiiiinations, and history and physical exam conducted within 7 days prior to initiation of piotocol therapy. Baseline MRI and ECG must be performed within 14 days prior to the start of therapy. In the event that the patient's condition is detei ioratinp, laboiatory evaluations should be repented within 48 horus piior to initiation of the next cycle of theiapy.

Study calendar for phase 1 comporient (escalation phase)

Evaluation	Pre Study	Cycle I				Cycle 2 and subsequent cycles.				End of Therapy Visit	FoBow-Up Visits to 2 yea s
		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		
Infomied consent	X										
Verify elipibzlity 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
Perfomiaiice Status	X	X		X		X		X		X	Q3mo
CBC'D**	X			X		X		X		X	SOC
CMP**	A			A		A		A		X	SOC
INR	X										
C-Reactire Protein	X			X		X		X			
TSH, T3, T4 (and anti-TPO antiboAes if)	X					X					
LH. FSH, ACTH***	X					X					
Pregnancy test for wolnen of childbeai ing potential**	X	Patient will be asked about contraceptive every time beiiip eraluated by study staff (Prouder. RN) if they are iii childbearing age.									
[redacted]		[redacted]		[redacted]		[redacted]		[redacted]			o
PK		PK									
Blood fo1 fiitui e testiiig		X				X					
MRI	X	MRI will be repeated every 8 weeks.									SOC
Indoxnnod		→									
leinozoloinide		T				T					
DLT Assessment				X		X		X			

A: Albumin. alkaline phosphatase. total bilirubin. blCarbDnate. BUN. calcium. chloride, creatinine, glucose, phosphonis. potassium, total protein. SGOT [AST]. SGPT [ALT], sodium.
*history and physical exam will be performed by physician aud"or niidlevel proiJdei Dr designated fellDU.
** Will be done within 7 deys before the staid of the study drop.
*** The endocrine tests should be drawn around 7 a m. due to the natural circadiaii fluctuations of ACTH [redacted].
T: Temozolomide miven first 5 days of each cycle (except Cycle 1, see section 6.4)
PK Time Points (Single Dose of Indoximod) — Cvcle 1 of PhRse 1

D.BY	Time Point	D.44'	Time Point
Day 1	Pre- a.m. dose	Day 1	6 hours s/p a.m. dose
Day 1	15 minutes s/p a.m. dose	Day 1	8 hnurs s/p a.m. dose
Day 1	30 minutes s/p a.in. dose	Day 1	12 horns s/p a.m. dose
Day 1	60 minutes s/p a.in. dose	Day2	24 hours s/p Day 1 s.m. dose
Day 1	120 minutes s/p a.in. dose	Day3	48 horns s/p Day l a.m. dose
Day 1	4 hoitrs s/p a.m. dose		

Stud y calendar for phase 2 com prient.

Evaluation	Ple-Slid	Cycle I				Cycle 2 and subsequent cycles.				End of Therapy Visit	FU Visits for 2 years
		Wk 1 Day 1	in 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 eligibzlity critei ia	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
Perfomiaiice 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 antiboAes if needed)	X					X					
LH, FSH, ACTH***	X					X					
INR	X										
Pregnancy test for women of childbealinp potential**	X	Patient null be asked about coirtraceptive erery time belnp eralimted by soidy staff (R ovidei. RN) if they ale Mr childbearing age									
[redacted]		[redacted]		[redacted]		[redacted]				[redacted]	[redacted]
Blood fo1 fiitui e testing		X				X					
Indoxuiiod + Temozolomide		T				T					
Indoxnnod + Temozolouiide + Bevacizimiab		T B		B		T B		B			
Indoxuiiod + Temozolomide + SRT		T		SRT		T					
MRI	X	MRI wd1 be rp eated es ery 8 w'eeks o1 ever 2 cycles.									SOC
Vital States Check										Q6ino for 1 years	

*Hzstolj and physical exam will be perfomied by physician anAol midlevel pioiuder or designated fellow.
** *i11 be done within 7 days before the start of the study dms.
*** The eiidocruie tests should be drawn around 7 a m. due to the natural circadian fliictriations of ACTH
E: ECG to be completed pre-study and 1 hour after fast indominod dose on the first 9 subjects enrolled in Phase 2. Upon approval of the 4"elsioii 3 plotocol auienAneut. 12 consecutive patients will Ieceive Baseline ECG (also to be repeated at 3 horns after lust indoximod dose administration (Cycle 1. Day 1), agani on Cycle 2. Day 1 after inoriuiip indommod dose administration. as clinically Indicated. and at the end of therapy).
A: Albumin. alkaline phosphatase. total bilirubin, bicarbonate, BUN. calcivnm chloride, creatinine, glucose, phosphorus. potassiimi. total protein SGOT [AST], SGPT [ALT], so‹1iuin.
B: Bevacizimiab T: Teinozolomide Indomlnod
SRT: Stereotactic radiation theiapy to start 2 weeks after indoximod and teuiozolouiide.

12.0 MEASUREMENT OF EFFECT

In addition to a baseline scan, patients should be re-evaluated every 8 weeks (or every 2 cycles) after starting study treatment until response is noted.

12.1 Criteria for Evaluation of Therapy Effectiveness

Tumor response and regrowth can frequently be difficult to measure directly. Serial neurological exams and MRI scans may provide a guide to the actual course. Time interval to progression will be measured from registration until deterioration is documented by the individual investigator using these guides.

- **Overall survival** will be measured from the start of GBM treatment on protocol until death.
- **Progression-free survival** will be measured from the start of GBM treatment on protocol until the first occurrence of progression on protocol or death.
- The quality of survival will be measured by neurological functional classification and performance status.
- Toxicities will be measured using the CTCAE criteria, version 4.03

12.2 Response Criteria

For this study we will be utilizing the RANO criteria (See Table 7):

Complete Response
Complete response requires all of the following: complete disappearance of all T1 gadolinium enhancing measurable and nonmeasurable disease sustained for at least 8 weeks; no new lesions; stable or improved nonenhancing (T2/FLAIR) lesions; and patient must be off corticosteroids or on physiologic replacement doses only, and stable or improved clinically. In the absence of a confirming scan at least 8 weeks after first indication of an objective response is noted, this response will be considered only stable disease.

Partial Response
Partial response requires all of the following: > 50% decrease, compared with baseline, in the sum of products of perpendicular diameters of all measurable T1 gadolinium enhancing lesions sustained for at least 4 weeks; no progression of nonmeasurable disease; no new lesions; stable or improved nonenhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared with baseline scan; and patient must be on a corticosteroid dose not greater than the dose at time of baseline scan and is stable or improved clinically. In the absence of a confirming scan at least 8 weeks after first indication of an objective response is noted, this response will be considered only stable disease.

Stable Disease
Stable disease occurs if the patient does not qualify for complete response, partial response, or progression (see next section) and requires the following: stable nonenhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared with baseline scan and clinically stable status. In the event that the corticosteroid dose was increased for new symptoms and signs without confirmation of disease progression on neuroimaging, and subsequent follow-up imaging shows that this increase in corticosteroids was required because of disease progression, the last scan

considered to show stable disease will be the scan obtained when the corticosteroid dose was equivalent to the baseline dose.

Progression
Progression is defined by any of the following: >25% increase in sum of the products of perpendicular diameters of enhancing lesions (compared with baseline if no decrease) on stable or increasing doses of corticosteroids; a significant increase in T2/FLAIR nonenhancing lesions on stable or increasing doses of corticosteroids compared with baseline scan or best response after initiation of therapy, not due to comorbid events; the appearance of any new lesions; clear progression of nonmeasurable lesions; or definite clinical deterioration not attributable to other causes apart from the tumor, or to decrease in corticosteroid dose. Failure to return for evaluation as a result of death or deteriorating condition should also be considered as progression.

The apparent increases in tumor burden that sometimes precede responses (pseudo-progression) in patients receiving immune therapy may reflect either continued tumor growth until a sufficient immune response develops or transient immune-cell infiltrate with or without edema (Wolchok CCR 2009). In the absence of overt clinical deterioration, patients with apparent radiographic disease progression in the first two months of therapy will be re-scanned 8 weeks later to evaluate progression, as long as they remain clinically stable (Taal et al, Cancer 113:405-410, 2008). In addition, a brain Magnetic Resonance Spectroscopy (MRS) may be performed (per investigator's decision) to differentiate tumor progression versus tumor necrosis/inflammation.

Nonmeasurable enhancing lesion increased to measurable enhancing disease
Patients with non-measurable enhancing disease whose lesions have significantly increased in size and become measurable (minimal bidirectional diameter of $\geq$ 10 mm and visible on at least two axial slices that are preferably, at most, 5 mm apart with 0-mm skip) will also be considered to have experienced progression. Ideally, the change should be significant (>5 mm increase in maximal diameter or >25% increase in sum of the products of perpendicular diameters of enhancing lesions). In general, if there is doubt about whether the lesion has progressed, continued treatment and close follow-up evaluation will help clarify whether there is true progression.

12.3 Special circumstances

Non-target lesions
All other lesions (or sites of disease) should be identified as **non-target lesions** and should also be recorded at baseline. Non-target lesions include measurable lesions that exceed the maximum numbers per organ or total of all involved organs as well as non-measurable lesions. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

Steroid dose:
Increase in corticosteroid dose alone, in the absence of clinical deterioration related to tumor, will not be used as a determinant of progression. Patients with stable imaging studies whose corticosteroid dose was increased for reasons other than clinical deterioration related to tumor do not qualify for stable disease or progression. They should be observed closely. If their corticosteroid dose can be reduced back to baseline, they will be considered as having stable

disease; if further clinical deterioration related to tumor becomes apparent, they will be considered to have progression. The date of progression should be the first time point at which corticosteroid increase was necessary.

Clinical deterioration
Determination of clinical deterioration is left to the discretion of the treating physician, it is recommended that a decline in the KPS from 100 or 90 to 70 or less, a decline in KPS of at least 20 from 80 or less, or a decline in KPS from any baseline to 50 or less, for at least 7 days, be considered neurologic deterioration unless attributable to comorbid events or changes in corticosteroid dose. Similarly, a decline in the Eastern Cooperative Oncology Group and WHO performance scores from 0 or 1 to 2 or 2 to 3 would be considered neurologic deterioration.

Uncertainty regarding progression
The patient may continue on treatment and remain under close observation (e.g., evaluated at 4-week intervals). If subsequent evaluations suggest that the patient is in fact experiencing progression, then the date of progression should be the time point at which this issue was first raised.

Multifocal Tumors

Progressive disease is defined as $\geq$ 25% increase in the sum of products of perpendicular diameters of all measurable lesions compared with the smallest tumor measurements after initiation of therapy. The appearance of a new lesion or unequivocal progression of nontarget lesions will also be considered progression.

Partial response is defined as $\geq$50% decrease, compared with baseline, in the sum of products of perpendicular diameters of all measurable lesions sustained for at least 4 weeks with stable or decreasing corticosteroid doses.

Table 7: Summary of RANO criteria

Criterion	CR	PR	SD	PD
T1 gadolinium enhancing disease	None	≥ 50% ↓	< 50% ↓ but < 25% ↑	≥ 25% ↑*
T2/FLAIR	Stable or ↓	Stable or ↓	Stable or ↓	↑*
New lesion	None	None	None	Present*
Corticosteroids	None	Stable or ↓	Stable or ↓	NA†
Clinical status	Stable or ↑	Stable or ↑	Stable or ↑	↓*
Requirement for response	All	All	All	Any*

Abbreviations: RANO, Response Assessment in Neuro-Oncology; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; FLAIR, fluid-attenuated inversion recovery; NA, not applicable.
*Progression occurs when this criterion is present.
†Increase in corticosteroids alone will not be taken into account in determining progression in the absence of persistent clinical deterioration.

12.4 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria (see table 8 and section 12.2).

Table 8: Summary of evaluation of best overall response

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Incomplete response/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration." Every effort should be made to document the objective progression, even after discontinuation of treatment. In some circumstances it may be difficult to distinguish residual disease from normal tissue.

12.5 Confirmatory Measurement/Duration of Response

Confirmation
To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed four weeks after the criteria for response are first met. In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry and at a minimum interval of eight weeks (see section 12.2).

Duration of Overall Response
The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

Duration of Stable Disease
Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started.

12.6 Response Review

Patients with measurable disease will be assessed by standard criteria. The purpose of tumor measurements will be to assess benefit to the patients from treatment and to determine appropriateness for continuing on study. For the purposes of this study, patients should be re-evaluated according to the study guidelines and undergo imaging studies as highlighted in the study calendar. Following documentation of an objective response, confirmatory scans will also be obtained a minimum of eight weeks later.

Time to progression: The time between the first day of treatment to the day of disease progression as described in section 12.2.

13.0 DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 8.0 (Adverse Events: List and Reporting Requirements).

13.1 Regulatory Compliance/Good Clinical Practices

This study will be conducted in accordance with the following regulations and guidelines, to include but not limited to:

- Declaration of Helsinki (October 2000)
- Current ICH Guideline for Good Clinical Practice
- 21 CFR 50: Protection of Human Subjects
- 21 CFR 54: Financial Disclosure by Clinical Investigators
- 21 CFR 56: Institutional Review Boards
- 21 CFR 312: Investigational New Drug Application

13.2 Regulatory Documentation

Prior to study start-up, investigators will submit the following documents to NewLink Genetics Corporation, as outlined in the Essential Documents Section 8.0 of the ICH Guidelines for Good Clinical Practice to include but not limited to:

- Signed Confidentiality Agreement
- Signed Clinical Trial Agreement, if applicable
- Up-to-date signed and dated Curriculum vitae and copies of medical licenses for Principal and one sub/co-investigator with CVs for all investigators to be submitted promptly
- Financial Disclosure form for Principal and one sub/co-investigator with financial disclosure forms for all investigators to be submitted promptly
- FDA Form 1572
- IRB approval to conduct the study: IRB-approved informed consent form,
- Name and address of the IRB with the statement that it is organized and operates according to GCP and the applicable laws and regulations
- IRB membership roster
- Local laboratory certifications, its name and address
- Local laboratory normal ranges (a dated copy for tests to be performed during the study).
- Financial agreement, if applicable.
- Signed and dated Investigator Agreement page of the final protocol and amendments, where applicable.

13.3 Institutional Review Board (IRB)

This Trial will be undertaken only after full approval of the protocol and addenda has been obtained from a local IRB and a copy of this approval has been received by the sponsor. The IRB must be informed of all subsequent protocol amendments issued by the sponsor. Reports on and reviews of, the trial and its progress will be submitted to the IRB by the investigator at intervals set force in its guidelines.

13.4 Informed Consent

Each subject must give written consent and sign other locally required documents after the nature of the study has been fully explained. The informed consent form must be signed prior to performance of any study-related activity with the exception of baseline imaging (if already obtained within 14 days prior to starting study treatment) and baseline lab studies (if already obtained within 7 days prior to starting study treatment). The informed consent form that is used must be approved both by the sponsor and by the reviewing IRB. The Informed Consent should be in accordance of the Declaration of Helsinki, current International Conference on Harmonization (ICH) and Good Clinical Practices (GCP) guidelines.

13.5 Administrative Requirements

Protocol modifications
The investigator will not modify this protocol without obtaining permission from the sponsor. All protocol amendments must be issued by the sponsor, signed and dated by the investigator, and should not be implemented without prior IRB approval, except where necessary to eliminate immediate hazards to the subjects or when the change(s) involves only logistical or administrative aspects of the trial (e.g., change in monitor(s), change of telephone number(s).

In situations requiring a modification, the investigator or other physician in attendance will contact the medical monitor by fax or telephone (see Contact Information page). This contact must be made prior to implementing any departure from protocol. Contact with the sponsor must be made as soon as possible in order to outline an appropriate course of action.

Record Retention
In compliance with the ICH/GCP guidelines the investigator/institution will maintain all CRFs and all source documents that support the data collected from each patient, and all trial documents as specified in Essential documents for the Conduct of a Clinical Trial and as specified by the applicable regulatory requirement(s).

The investigator/institution will take measures to prevent accidental or premature destruction of these documents. Essential documents must be retained until at least two years after the last approval of a marketing application in an ICH region or at least two years have elapsed since the formal discontinuation of clinical development of the investigational product.

These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

Case Report Forms (CRF)
CRFs are provided for each patient. Data must be entered onto CRFs in English. All forms must be filled out in black ball-point pen. CRFs must be signed by the investigator where indicated.

All CRF corrections are to be made by the investigator or other authorized study center personnel as instructed on the CRF title page. The investigator must authorize changes to the recorded safety and efficacy data.

The Case Report Forms (CRF) will be designed for the capture of all relevant clinical data for this study. The CRFs are to be completed as soon as possible after the subject's visit, so that they always reflect the latest observations on the subjects participating in the trial. All finalized data will be reviewed and authorized by the Investigator. Copies of CRF data will be retained by the site and Sponsor in accordance with FDA regulations.

Monitoring
All clinical and standard laboratory data specified in this study will be collected and recorded by the nurse coordinator under the supervisions of the Principal Investigator and physician co-investigator

NewLink Genetics (sponsor) will perform on-site monitoring visits as outlined in the Monitoring Plan for this clinical trial. The dates of the visits will be recorded by the monitor in a trial center monitor visit log to be kept at the site. The first routine monitoring visit will usually be made approximately 4 weeks after enrollment has begun at that site. At these visits the monitor will verify the data entered onto the CRFs with the hospital or clinic records (source documents).

At a minimum, source documentation must be available to substantiate patient eligibility and participation, proper informed consent procedures, adherence to protocol procedures, record of safety and efficacy parameters, adequate reporting and follow-up of adverse events, administration of concomitant medication, drug receipt/dispensing/return records, study medication administration information, and date of completion and reason.

Specific items required as source documents will be reviewed with the investigator prior to the study. Findings from this review of CRFs and source documents will be outlined in a Site Visit Report and discussed with the investigator. The sponsor expects that, during monitoring visits, the investigator (and as appropriate the study coordinator) will be available, the source documents will be available, and a suitable environment will be provided for review of study-related documents.

Safety Monitoring
The NewLink Genetics Medical Monitor and Safety Department will review accrual information and safety data such as listings and nature of adverse events. Individual SAEs are monitored by the Safety Department and Medical Monitor as they are received. All aggregate safety data is reviewed at least quarterly by the Safety Department and Medical Monitor.

This study will use a Data Safety Monitoring Committee (DSMC) during phase 2. The DSMC will meet quarterly.

Use of Information and Publication
All information on indoximod, NewLink operations, patent application, manufacturing process and basic scientific data supplied by the sponsor to the investigator and not previously published is considered confidential and remains the sole property of NewLink Genetics. The investigator agrees to use this information only to accomplish this study and will not use it for other purposes without the sponsor's written consent. The investigator understands that the information developed in the clinical study will be used by NewLink in connection with the continued development of indoximod and thus may be disclosed as required to other clinical investigators or government regulatory agencies. To permit the information derived from the clinical studies to be used, the investigator is obligated to provide the sponsor with all data obtained in the study.

Any publication or other public presentation of results from this study requires prior review of NewLink Genetics. Draft abstracts, manuscripts and materials for presentation at scientific meetings should be provided to the sponsor as outlined in the clinical trial agreement.

13.6 Human Subjects Protection

Rationale for subject selection
Advanced glioblastomas affect men and women from all racial/ethnic groups. Subjects from all racial/ethnic groups are eligible for this study if they meet the eligibility criteria. We will make an attempt at enrolling representative proportions of minorities on this study.

Efforts will be made to extend accrual to a representative population, but in this phase 1/2 study, a balance must be struck between subject safety considerations and limitations on the number of individuals exposed to potentially toxic and/or ineffective treatments on the one hand and the need to explore gender and ethnic aspects of clinical research on the other hand.

Participation of Children
A study to evaluate the efficacy of indoximod in children (< 16 years of age) is planned once part 1 of this study is completed.

Evaluation of Benefits and Risks
Advanced glioblastomas have a very poor overall prognosis. After failing currently available regimens, the chance of cure is rare if at all. The benefits of this approach are theoretical and it is hoped that the inhibition of IDO will lead to an effective anti-tumor immune response. By generating an immune response against the subject's tumor, their overall survival might be improved.

Given the safety demonstrated by indoximod in several clinical studies, and the poor prognosis of this patient population, it is believed that the possible benefits from improved survival probability far outweigh the risk to the patient. The information obtained in this study may be extremely valuable in the treatment of malignancies in the future. The chance of this experimental treatment to provide clinical benefit is unknown. All possible benefits and risks will be carefully explained to all subjects and the Informed Consent Document will be signed by the subject prior to entrance into the protocol.

There are no new anticipated severe adverse side effects to the treatment approach technique employed in this study. Theoretical risks may include the induction of unanticipated autoimmune disease and/or liver, kidney, lung, heart and CNS damage and/or coagulopathy and bleeding as a result of excessive activation of the complement system. Expected risks and discomforts to the

subjects are minimal and will be those of needle sticks for phlebotomy. Subjects will be treated as deemed medically appropriate for any immediate or delayed adverse event related to the treatment.

Blood and tissue specimens collected in the course of this research project may be banked and used in the future to investigate new scientific questions related to this study.

Consent and Assent Processes and Documents
All subjects will be thoroughly screened prior to admission onto this study. During this time, the subject, along with family members, will be presented with a detailed description of the protocol treatment. The specific requirements, objectives, advantages and disadvantages will be presented. The Informed Consent document is given to the subject (and parent(s) / guardian if patient < 18 years of age) and they are asked to review it and ask questions prior to agreeing to participate in this protocol. The subject will be reassured that participation on this trial is entirely voluntary and that they can withdraw or decide against treatment at any time without adverse consequences. The Principal Investigator or their designee is responsible for completing the consent process and a copy of the completed Consent Document is offered to the subject.

Recruitment Strategy
Patients, their physicians or family members may contact the clinical sites directly. Information about the clinical trial can be obtained at clinicaltrials.gov. Given the number of patients with glioblastoma and the limited therapy available, we believe enrollment for this trial will be completed in less than 1 year.

Patient Confidentiality
Strict patient confidentiality is standard policy at clinical research sites. Standard practices will be followed.

14.0 STATISTICAL METHODS

14.1 General statistical considerations

This is an open-label phase 1b/2 clinical trial of indoximod with temozolomide. Descriptive statistics will be presented for primary and secondary endpoints employed to analyze the data. Summary statistics for continuous variables will include the mean, standard deviation, median, and range (minimum/maximum); categorical variables will be presented as frequency counts and percentages; and time-to-event variables will be summarized by Kaplan-Meier medians and survival plots. Data listings will be created to support each table and to present all data.

The data will be tabulated and analyzed with respect to patient enrollment and disposition, demographic and baseline characteristics, prior and concomitant medications, efficacy and safety measures on a per cohort basis for phase 2, and on a per dose level for phase 1. The efficacy analysis will be conducted on the Efficacy Evaluable Population and safety analysis will be performed on the Safety Population as described in section 14.5.

Maximum tolerable dose for indoximod with temozolomide will be estimated based on the data by using a formal statistical inference procedure based on the percentage of RLT per dose. RP2D will then be determined based on the estimated MTD, which should not exceed 1/6 of RLT.

In the phase 2 trial, the observed 6-month progression free survival (PFS), overall survival, overall response rate, duration of response, toxicity and tolerability will be summarized and compared with those reported in the literatures for standard-of-care treatment. PFS and OS will be calculated starting at the initiation of indoximod. Historical control was chosen in place of active control for

low incidence of the malignant brain tumor. Chi-squared test or Fisher Exact test when appreciate, will be used to compare the observed 6-month PFS rate, ORR between the experiment group and the historical control. The detected overall survival and duration of response will be compared with previous published counter parts via log-rank test, separately.

The correlation of risk factors pertinent to patients' outcome or response will be assessed in an exploratory fashion when sample size allows.

14.2 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 MDT as described in in Section 6.2.

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 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 (SOC) and experimental combination therapy (ECT) of percent of patients with 6-month progression free survival:

Cohort 2a: 0.25 for SOC vs. 0.44 for ECT [22]
Cohort 2b: 0.42 for SOC vs. 0.65 for ECT [23]
Cohort 2c: 0.40 for SOC vs. 0.58 for ECT [24]

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.

14.3 STATISTICAL ANALYSIS

Phase 1b portion

- Primary endpoint:
  The recommended phase 2 dose will be based on dose escalation method provided in section 6.2, Table 1.

- Secondary endpoints:
  - The adverse events will be listed along with identification of the regimen-limiting toxicities (RLT) of indoximod plus temozolomide in combination therapy

- The overall dose of temozolomide delivered and timing of administration will be compared to historical control using T-test.

Phase 2 portion

- Primary endpoint

The primary endpoint is defined as the rate of 6-month progression free survival (PFS) starting at the initiation of indoximod among all participants. The study has three cohorts of patients (2a, 2b, and 2c).

The following definitions of the parameters apply to all the cohorts:
P_0 = the maximum proportion of the 6-month PFS under SOC.
P_1 = the minimum response proportion of PFS under the new Combination Therapy.
If the number of responses $\geq R+1$, P_0 is rejected
If the number of responses $\leq R$, P_1 is rejected.

Table 9 summarizes the sample size and stopping rules for cohort 2a, 2b and 2c.

Cohort	P_0	P_1	Alpha	Power	Cut-off R+1	N
2a	0.25	0.44	0.025	0.90	25	68
2b	0.42	0.65	0.10	0.80	14	24
2c	0.40	0.58	0.10	0.80	21	40

Cohort 2a:
A total of up to sixty-eight (68) evaluable patients with intracranial glioblastoma or gliosarcoma and not currently on bevacizumab will be enrolled into cohort 2a of phase 2. By the end of the 6-months follow up period, a decision will be made if the proportion of patients with PFS, P, is ≤ 0.25 or ≥ 0.44. If the number of patients with PFS is 25 or more, the hypothesis that $P \leq 0.25$ is rejected with a target error rate of 0.025. If the number of patients with PFS is 10 or less, the hypothesis that $P \geq 0.44$ is rejected with a target error rate of 0.10 (beta =1-power).

Cohort 2B:
A total of up to twenty-four (24) patients with previous bevacizumab treatment will be enrolled into cohort 2b and receive bevacizumab in addition to indoximod with temozolomide. If a patient has been taken off bevacizumab after progressing on bevacizumab prior to entry into the study, the patient will be considered with Cohort 2b but may receive temozolomide / study drug alone. By the end of the 6-months follow up period, a decision will be made if the proportion of patients with PFS, P, is ≤ 0.42 or ≥ 0.65. If the number of patients with PFS is 14 or more, the hypothesis that $P \leq 0.42$ is rejected with a target error rate of 0.10. If the number of patients with PFS is 13 or less, the hypothesis that $P \geq 0.65$ is rejected with a target error rate of 0.20 (beta=1-power).

Cohort 2C:
A total of up to forty (40) patients with current potential indication for stereotactic re-irradiation will be enrolled into cohort 2c and be treated with indoximod with temozolomide and stereotactic

radiosurgery. By the end of the 6-months follow up period, a decision will be made if the proportion of patients with PFS, P, is ≤ 0.40 or ≥ 0.58. If the number of patients with PFS is 21 or more, the hypothesis that $P \leq 0.40$ is rejected with a target error rate of 0.10. If the number of patients with PFS is 20 or less, the hypothesis that $P \geq 0.58$ is rejected with a target error rate of 0.20 (beta =1-power).

- Secondary endpoints:
  - The Overall Response Rate (ORR), overall survival, and tolerability of indoximod plus temozolomide will be evaluated for patients with progressive GBM using methods listed in the section 14.1.

  - The Overall Response Rate (ORR) and tolerability of indoximod plus temozolomide and bevacizumab will be evaluated, for patients with GBM, whose disease progressed during therapy with a bevacizumab-based regimen, using methods listed in the section 14.1.

  - The Overall Response Rate (ORR) and tolerability of indoximod plus temozolomide and stereotactic radiotherapy will be evaluated, for patients with GBM patients who may reasonably benefit from tumor debulking, using methods listed in the section 14.1.

14.4 Treatment Randomization and Blinding

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

14.5 Study Populations and analysis datasets

The definitions of study populations are as follows:

1) Enrolled (Intent-to-Treat): This population will comprise all patients who were enrolled in the study whether or not the study drug was administered.
2) Safety: This population will comprise all patients who receive at least one infusion of indoximod and temozolomide. This population will be analyzed for safety.
3) Efficacy Evaluable - This population will comprise all patients who receive at least one dose of study drugs, indoximod with temozolomide, and either undergo at least one post-baseline assessment or die before any evaluation. For sensitivity, analyses the efficacy endpoints may be repeated in subsets of this population.

   No adult group (except patients with cognitive impairment) is being excluded from participation. Patients of both genders, from all racial and ethnic groups are eligible for this study. There is no information suggesting differences in absorption, metabolism, or disposition or disease response to the study drug among racial or ethnic groups or between the genders. Efforts will be made to extend the accrual to a representative population, but, in a study accruing small numbers of patients such as this one, the enrollment diversity may not be optimal.

   Pediatric patients (<16 years of age) are excluded from evaluation in this study for safety considerations.

14.6 Study Endpoints

14.6.1 Safety Endpoints

Safety analyses will be peifoisted using the safety population os defined in Section 14.5.

- All adverse events (AE's) will be presented in incidence tables coded by MedDRA Pi'eferred Teim (PT), Body System Class (SOC). and NCICTC. Additionally, separate AE incidence tables. coded by MedDRA PT end NCICTC, will be presented by: 1) toxicity grade (severity) groded by the CTCAE and 2) ielotionship to indoximod with teiuozolomide treatment as deteimined by the Investigator (tieatinent related end treatment emergent adverse events).
- All selious adverse events, discontinuations due to adverse event, o1 deaths occurring after the lust administration of sttidy drug imtil 4 weeks following termination from the triol will be siiininarized on a pe1-patient basis.
- Fo1 laboratory tests, siuninary tables describing the fieqiiency with which laboratory parameters are outside the normal i'anpe (ct baseline and at any time post-baseline) will be displayed. Complete listings of all laboratory data will be provided end values with CTCAE Giade > 3 will be identified with flags. A list of all nolxuol laboratory ranges will also be plovided.
- Vitol sigas (blood pressure, pulse, temperature) over time will be siunniarized usinp descriptive statistics md data listings.
- Percent of patients experiencing dose modifications, inteiniptions, and/or premattu'e discontiniiations fiom stridy tip.

[redacted]

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15.0 APPENDICES

APPENDIX A

Performance Status Criteria

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.

Appendix B: Study Medication Diary

Study Medication Diary **Subject Initials:**_____ **Subject #: NLG2102 -** _____
Cycle:_____ **Cycle Start Date:**_____/_____/_____ **Subjects planned daily dose:**_____**mg**

# of capsules dispensed:_____**by:**_____**on**_____/_____/ _____

# of capsules returned:_____**to:**_____ **on**_____/_____/ _____

INSTRUCTIONS TO THE PATIENT:

1. **Complete one form for each Cycle.**
2. **You will take**_____**capsules each morning and evening. No food should be taken for at least 2 hours before and at least 1 hour after administration of the morning and evening doses. Take the capsules whole with a full glass of water.**
3. **Record the date, the number of capsules you took, and when you took them.**
4. **If you have any comments or notice any side effects, please record them in the Comments column.**
5. **Please bring your medication bottle and this form to your physician at each return visit.**

Date	Day #	#Capsules	AM Dose (time HH:MM)	#Capsules	PM Dose (time HH:MM)	Comments

Subject Initials (Signed by Subject):_____Date:____/_____/ _ _____

To be completed by site staff upon return of study medication diary:

Total Number of Capsules taken this cycle:_____Percent of Compliance:_____

Comments on capsules taken, capsules not taken as planned, capsules lost, or other discrepancies: _____
Signature of Study Nurse or Study Designee:
_____Date:____/_____/ _____

Appendix C: Neuro-Oncology Consent Process

Neuro-Oncology Consent Process

Our program offers clinical trials for patients with brain tumors at different stages of disease. We offer clinical trials to patients who are newly diagnosed with a brain tumor, as well as patients who had disease progression or recurrent brain tumors. We believe that these clinical trials are a good option for patients with incurable cancer and strive to offer a clinical trial as a treatment option for each of our patients. Furthermore, many patients with recurrent disease have no FDA approved effective therapies available, so the opportunity to participate in a clinical trial for these patients provides an important therapeutic option. Typically, the majority of brain tumor patients with sufficiently good performance status to participate in clinical trials will have the cognitive capacity to understand and provide consent to participate in a clinical trial and sign the appropriate consent documents. However, some patients are capable of understanding and providing consent, yet they have a neurologic deficit as a result of disease or treatment that causes the inability to write or sign their name to a document. Occasionally, there are patients who are not capable of providing consent independently due to cognitive impairment or communication deficits related to disease or treatment that they have received for their disease. Our process for obtaining consent is as follows:

1. Patients with a brain tumor with full cognitive and physical ability will independently provide consent with a signature of the consent documents following the entire consent process.
2. Patients with a brain tumor with full cognitive ability, but neurologic impairment who cannot provide a signature, will provide full consent verbally using the consent document, make a mark if they can, and then have a witness sign the consent attesting that the patient consented willingly after a full consent process. A family member can act as a witness in this situation or anyone outside of the study team can witness this process. A witness signature block will be included in the consent document.
3. If the investigator has determined that the patient has significant cognitive impairment and cannot independently provide consent, an LAR will be required. Verbal assent will be obtained, but written assent may not be possible depending on the level of physical and/or cognitive impairment. If written assent is possible, the participant will provide assent by signing the full consent document along with an LAR. The LAR will be informed of their obligation as a surrogate decision maker to determine the patient's wishes or what is in the best interest of the patient. The entire consent process will be well documented in the research records and include the Investigator's assessment of the participant's ability to provide consent independently or the need for an LAR.

The investigators will assess each patient and determine if the patient is competent to independently consent to a clinical trial based on their ability to express understanding of the information presented regarding the treatment options and expression of their desire to participate in the clinical trial. In some cases, use of a patient advocate or neuro-cognitive testing may be included in the process to help determine if patient is able to give consent themselves or if the LAR

is more appropriate. In situations in which patients' ability to give consent themselves is not clear, the LAR process will be utilized. The investigator's assessment will be documented in the consent documentation notes that are kept in the research chart along with the original consent forms. (See attached).

Justification for Including Cognitively Impaired Individuals

Our target population is patients with brain tumors. Not all patients who have brain tumors are cognitively impaired. However, for those individuals who are cognitively impaired, we would like to offer them the same opportunity to participate in our clinical trials and to do it in a way that is consistent with the regulations for obtaining consent in human subjects. Exclusion of cognitively impaired patients would be discriminatory, and as described above, many of these patients have no proven effective therapies available, so participation in a clinical trial is the best opportunity they have for treatment with potentially effective novel therapies.

Greater than Minimal Risk/Risk and Benefit

The clinical trials that are being conducted for the treatment of primary brain tumors are more than minimal risk trials. Participation in a clinical trial for an incurable brain tumor offers the prospect of direct benefit to an individual.

Cognitively impaired individuals may be at greater risk for non-compliance on a clinical trial and may not be able to completely report adverse events or side-effects of treatment. All cognitively impaired individuals must have a LAR who acts as a caregiver to ensure compliance, including drug administration and reporting of toxicities in some cases. The benefit for including these patients is that they may have an opportunity to receive a treatment on a clinical trial that would not otherwise be available to them.

Additional Consent Considerations

As it is expected that some brain cancer patients will have cognitive impairment, it is appropriate to include adults with impaired decision making capacity.

Patients may be able to provide consent independently at the time of enrollment, but may have cognitive decline while on a study. If there is noticeable decline that includes loss of ability to understand or communicate effectively, and patient is going to continue on trial, then consent from an LAR may be appropriate to continue participation in a clinical trial.

Neuro-Oncology Consent Process Note

Please select one of the following consent processes that will be followed for the above patient.

- ☐ The patient has full cognitive and physical ability to independently provide consent with a signature to participate in this clinical trial.

- ☐ The patient has full cognitive ability and is able to provide verbal consent to participate in this clinical trial; however, s/he is not physically able to provide a signature due to a neurologic impairment. If possible, the participant will "make their mark" on the consent document. I, as the investigator, attest that the patient has provided verbal consent to participate in this trial, and the process has been witnessed by the patient's family member or a representative outside of the study team.

- ☐ The patient has significant cognitive impairment and is unable to independently provide consent. I, as the investigator, believe that participation in the clinical trial is a good treatment option for this patient. I attest that this has been discussed with the patient's Legally Authorized Representative (LAR), who understands his/her obligation as a surrogate decision maker. The LAR has agreed to participation in the clinical trial.

_____ _____

Investigator's Signature Date

Appendix D: Sample Informed Consent Form

The use of 'you' throughout this document refers to the research subject as an adult or child. If the research subject is less than 18 years old, the subject's parent or legal guardian must provide written consent for the child to participate in this study.

INTRODUCTION

Before agreeing to participate in this research study, it is important that you read and understand the following explanation of the proposed procedures. This document describes the purpose, procedures, benefits, risks, discomforts and precautions of the study. It also describes the alternative procedures that are available to you and your right to withdraw from the study at any time. No guarantees or assurances can be made as to the results of the study. You must be completely truthful with your study doctor regarding your health history, including past and present usage of both prescription and non-prescription medications, including herbals. If you are not completely truthful with your study doctor you may harm yourself by participating in this study. This form tells you about a research study. Research studies are voluntary and include only those who wish to participate. We may learn about new things that make you want to stop being in the study. If this happens, you will be informed. You can then decide if you want to continue to be in the study.

The study doctor may remove you from this study for any reason. Any new information about the study medicine will be given to you so you may decide to continue in the study or leave it.

You may be taken out of the study if:

1. Staying in the study would be harmful.
2. You need treatment not allowed in this study.
3. You fail to follow instructions.
4. The study is cancelled.
5. Your disease progresses.

If you should decide to leave the study, you should tell the study doctor or study staff. They will make sure that proper procedures are followed and a final visit is made for your safety

Why is this research study being done?

This study is being done to test the feasibility of combining the approved drug therapy temozolomide (Temodar) with an experimental drug called indoximod. "Experimental" means the drug has not been approved by any Authority that regulates new medicines, including the US Food and Drug Administration (FDA).

Temozolomide is an oral medicine that is approved for commercial use as a prescribed drug by the FDA for the treatment of brain cancer. The experimental (study) drug, indoximod, is an oral medication that blocks an enzyme (a type of protein that affects other proteins in the body) called IDO. Doctors think that tumors use IDO to escape attack by your body's immune system. By blocking this IDO enzyme, indoximod may help your body attack the tumor cells more effectively. Indoximod given along with various chemotherapy agents such as temozolomide may increase the effectiveness of the chemotherapy.

Why am I being asked to take part in this study?

You are being asked to take part in this research study because you have brain cancer.

How many people will take part in the study?

This study will have two parts, a dose-escalation phase (the first part of the study) and then later, a dose-expansion part (the second part of the study). Enrollment for the first part of the study is now complete and

12 people were asked to participate. In the second part, approximately 132 additional people will be asked to participate.

Do I have to take part?
It is up to you to decide whether or not to take part. If you decide not to participate in the research study, your decision will not affect the medical treatment and care you are entitled to receive. If you do decide to take part after reading this Informed Consent Form, you will be asked to indicate your consent to participate in this study by signing and dating this Informed Consent Form.

If you decide to take part, you are still free to withdraw from study procedures and/or study treatment at any time. If you do not want to take part in the study, your study doctor will discuss different options that are available to you. These options may include:

- Treatment with other chemotherapy drugs such as temozolomide alone;
- Treatment with medications that will make you feel more comfortable, but have no effect on your cancer;
- Other experimental treatments;
- No treatment

What will happen if I take part in this study?
Indoximod will be given to you orally twice a day for 28 day cycles. You will be asked to visit the clinic during weeks 1 and 3 of the first cycle. In Cycle 2 and subsequent cycles, you will attend the clinic every other week as long as you are receiving the treatment. Your doctor will tell you the dose of Indoximod before you begin study treatment.

Subjects will be treated in one of the two phases of this study: dose-escalation or dose-expansion. The dose-escalation phase occurs first and enrollment has been completed for this portion of the study. You are being asked to participate in the dose expansion phase of the study.

Screening

The screening period is held within 14 days before starting the study treatment to find out if you can be in the study. During this period, you will need to come to the clinic or study site for multiple tests. More than one screening visit may be required. If these tests show that you can be in the study and you choose to take part, then you will be entered in the study. The following screening examinations, tests, or procedures will be performed after you have given consent to participate in this study:

- Medical history, including information about you and your cancer, previous treatments for your cancer and other medications you are taking or have taken. Certain medications are not allowed to be taken during the study treatment.
- Complete physical exam including vital signs (heart rate, temperature, breathing rate, blood pressure, height and weight)
- Performance Status (questions about your ability to perform everyday activities)
- Your tumor size will be measured by MRI [Magnetic Resonance Image; combines a series images taken from many different angles and computer processing to create cross-sectional images of the brain].
- Standard blood tests, using up to 6 teaspoons of blood, to measure your liver and kidney function, white blood cells, red blood cells and platelets, your blood sugar and blood electrolytes and if you are female and able to become pregnant, to confirm you are not pregnant. You will not be allowed to enter the study of you are pregnant or lactating.

- Research blood tests will be taken to monitor how your body will be affected by the drug. These initial tests will serve as a guide to see how your body reacts after you have received the study drug throughout the study.
- An ECG to determine if your heart is healthy enough for treatment.
- Additionally, 3 ½ teaspoons of blood will be drawn and stored for future testing of an enzyme that is released in tumors, called IDO enzyme (this is an immune suppressing enzyme released by the tumor and indoximod seems to block this enzyme). This is an optional test that may help us better understand who will respond to study treatment with indoximod. You will sign a separate consent for this testing.

On Study Procedures

- Approximately 1 teaspoon of blood will be taken for an analysis of white blood cells at weeks 1, and 3, and then on the first day of each cycle for the time you are receiving study drug. After that time this test will be performed once every 6 months during your follow up visits.
- At week 1 of each Cycle, approximately 3 ½ teaspoons of blood will be drawn and stored for future testing of an enzyme that is released in tumors, called IDO enzyme (this is an immune suppressing enzyme released by the tumor and indoximod seems to block this enzyme). This is an optional test that may help us better understand who will respond to study treatment with indoximod. You will sign a separate consent for this testing.
- ECG – An electrocardiogram will be taken 1 hour after the first dose of indoximod for the first 9 subjects enrolled in phase II. Twelve additional patients will receive an electrocardiogram 3 hours after first dose of indoximod and again on Cycle 2, Day 1 after morning indoximod dose administration, and at the end of therapy visit. These tests are used to confirm there are no changes to the activity of your heart after taking the study medication for short and longer periods of time. The research staff will let you know if you are participating in this portion of the trial.

Additionally, a biopsy of your tumor is usually done as part of routine care to make the diagnosis of cancer prior to starting this course or most courses of treatment. If there is any extra preserved tissue from the biopsy remaining after it has been used to make a diagnosis, a small portion of the tissue will be requested as part of this study to look for the presence of the IDO/TDO enzyme. A separate biopsy will not be done for research purposes alone. It is not required for participation in this study, and you do not have to agree to provide the tumor sample. If you say no, you can still participate in the main study. This testing will not benefit you directly or change how your disease is treated.

I agree to have left over tumor tissue provided for this study to test for IDO and TDO expression.

_____ YES _____NO _____Initials

Treatment regimen

If you continue to be eligible for study participation after screening, you will begin taking 6 capsules of indoximod (study drug) two times per day. Indoximod comes in 200mg capsules. No food should be taken for at least 2 hours before and at least 1 hour after taking the morning and evening doses. You must swallow the capsules whole with a full glass of water and not chew them. It is very important that you follow these instructions listed above because they could change the safety and how well the study drug works.

Bottles containing indoximod capsules will be given to you periodically. It is very important that you take this medicine just as the doctor tells you. Do not miss any capsules. It is important to tell the study staff about any other medications you are taking during the study, including prescription drugs, over-the-counter medicines and vitamins. You will be asked to complete dosing diaries while you are taking the study medication and it will be distributed to you at the start of the study. You must bring your dosing diary and indoximod bottle(s) back to the clinic at regular intervals so the study staff can make sure you are taking your indoximod as you should. The study staff will review the dosing diary with you to ensure accuracy and assess compliance.

Temozolomide (Temodar) will be taken orally for 5 days and this will be repeated every 28 days. Temozolomide will be started at bedtime on an empty stomach. Anti-nausea medication is recommended approximately 1 hour prior to the oral dose. Your doctor will discuss this with you. If vomiting occurs after a dose is administered, you should wait until the next scheduled dose. Capsules should not be opened or chewed.

If you have any side effects during the treatment period, you and your doctor will decide if you should continue in the study.

DOSE-EXPANSION PHASE:
Subjects participating in this phase of the study will receive one of the dose levels of indoximod determined from the dose-escalation phase plus additional treatment as outlined below. This was determined to be 1200mg twice daily. There are 3 groups in this part of the study.

1- Indoximod and Temozolomide: In this group you will be getting temozolomide and indoximod (at 1200 mg twice daily)
2- Indoximod, Bevacizumab and Temozolomide: If you are getting a standard brain tumor medication called bevacizumab (Avastin) and your disease progresses, you will continue to take the Avastin, along with temozolomide and indoximod (at 1200 mg twice daily). If you have previously taken bevacizumab and your disease progressed and your physician stopped the bevacizumab, you will only take the temozolomide and indoximod.
3- Indoximod, temozolomide and radiation: If you are a candidate for radiation, you will be getting it along with temozolomide and indoximod (at 1200 mg twice daily).

You will return to your doctor's office at regular intervals so that your disease can be monitored and routine blood tests and safety evaluations can be carried out. Please tell your study doctor or study staff if you have any unusual symptoms. You will be closely monitored for any side effects and you should report any changes in the way you feel to your study doctor. If you experience any side effects, your study doctor may instruct you to stop the study drug temporarily and restart at the same or lower dose after the side effect has resolved.

How long will you be asked to be on the study?

You may continue to receive the study treatment as long as your cancer does not get worse. Your participation in the study may end at any time if your doctor thinks it is in your best interest to stop or you decide you do not wish to receive any more study treatment. Even if you decide to stop study treatment you may continue to be followed by routine office visits every 3 months for up to 2 years and telephone calls every 6 months to check on the status of your disease for up to 5 years.

COSTS
This is a treatment study. There will be no cost to you for the supply of the study drug (indoximod) during your participation in the study. You will not be charged for any of the tests and procedures performed solely

for research purposes. All study-related testing (tests performed for research purposes only) will be provided to you by the study at no charge. Tests and procedures that are standard of care for your disease (not part of this research study) will be billed to your insurance or Medicare. Tests and standard procedures that are routine care for your disease that are not paid for by the study, and will be charged to your insurance or Medicare, if applicable. This includes medications that are typically given to patients receiving treatment for your disease (such as temozolomide and/or bevacizumab). You will be responsible for all co-pays. You or your insurance company will be charged for standard medical care and for any hospitalizations. It is possible that your insurance or Medicare will not pay routine care charges because the treatment is taking place within a research study. If this happens, you will be responsible for these charges. A member of the research team will contact your insurance company to determine the additional costs you may be responsible for paying. Your study doctor will inform you of the potential cost to you.
You will not be paid to take part in this research study**.**

Even though it probably won't happen, it is possible that the manufacturer may not continue to provide the indoximod to the study site for some reason. If this would occur, other possible options are:

- You might be able to get the indoximod from the manufacturer or your pharmacy, but you or your insurance company may have to pay for it.

- If there is no indoximod available at all, no one will be able to get more and the study would close.

If a problem with getting indoximod occurs, your study doctor will talk to you about these options.

What are the potential benefits if you take part in the study?

We do not know if you will get any health benefits by taking part in this study. We do not know if the experimental study treatment will help you. That is why we are doing this study. We hope that what we may learn can benefit you and others in the future.

What are the risks if you take part in the study?

INDOXIMOD
The following may be related risks and side effects of the indoximod therapy that have been observed in patients that have received it:

Likely: Likely to happen to 20% or more of patients
- Fatigue or feeling tired
- Nausea
- Anorexia or loss of appetite
- Decrease in red blood cells (anemia)
- Diarrhea

Less Likely: Likely to happen to 10 to 19% of patients
- Decrease in white blood cells (neutrophils and lymphocytes)
- Abdominal pain
- Shortness of breath (dyspnea)
- Rash
- Vomiting
- Constipation
- Decrease in platelets

- Headache
- Hair loss (alopecia)

Rare**:** Likely to happen to less than 10%

- Dizziness
- Lung Infections
- Increase in blood potassium, glucose and creatinine
- Sleeplessness (insomnia)
- Low blood levels of sodium (hyponatremia)
- Multi-organ failure
- Low Blood Pressure (Hypotension)
- Dehydration
- Ringing in ears
- Fever associated with low white blood cells (febrile neutropenia)
- Mouth sores
- Redness, pain, numbness, and possible peeling of the skin of the hands and feet

Autoimmune Events

Autoimmunity is a term that describes when your immune system begins to attack normal cells in your body. Two patients out of 48 in a completed indoximod study developed an autoimmune reaction in their pituitary gland called hypophysitis. Both of these patients received prior experimental immune therapies which may have increased the risk of this occurring, but there is a distinct possibility that this may occur with indoximod alone.

One of the two hypophysitis patients were on low dose steroids and thyroid hormone as long as they were alive, and one of the patients was able to stop the steroids but remained on thyroid hormone for the rest of her life. To date, none of the patients who did not receive prior immune therapies have developed this side effect. The pituitary gland is considered the "master gland" which coordinates the function of your other glands such as your thyroid, adrenals, and gonads (ovaries/testicles). If it does function properly (pituitary insufficiency) you may experience symptoms of

- weakness
- fatigue
- loss of libido (lack of interest in sex)
- You may need to take hormone replacement therapy to treat these or other symptoms.

Another hormone called ACTH (a hormone secreted by the pituitary gland), excites the adrenal gland (a gland situated above the kidneys) to make steroids, particularly cortisol. If there is a decline in ACTH (ACTH deficiency) you may experience

- weight loss
- lack of appetite (anorexia)
- weakness
- nausea
- vomiting
- low blood pressure (hypotension).

Stopping the study drug and using steroids to calm the immune system are effective in many cases of autoimmune disease, but there is a risk of chronic autoimmune disease requiring treatment for longer periods of time. We will monitor you closely for any signs of autoimmune conditions and treat you for them if necessary. Prior experience with other immunotherapy agents seems to indicate those who do develop

these autoimmune events may have a higher likelihood of their cancers responding to treatment, but it is not known if this is the case with indoximod.

Note: Indoximod in combination with other agents could cause an exacerbation (worsening) of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

Possible Side Effects and Risks of the Temozolomide (Temodar)

During the study you will receive an anti-cancer drug called temozolomide (Temodar). This drug is approved by the FDA. This drug is also given orally for 5 days every 28 days. This drug, like many other anti-cancer drugs, has side effects which include:

Most common side effects (occur in 10% or more of patients):

- Low white blood cell levels – increases risk of infection (Pneumocystis jirovecii pneumonia)
- Low platelet levels – increases risk of bleeding
- Nausea/ Vomiting
- Diarrhea
- Generalized fatigue or weakness
- Hair loss
- Fluid retention in ankles or abdomen
- Headache

Less common side effects (occur in <10% of patients):

- Allergic-type reaction, may include flushing, rash, itching.
- Abnormalities in liver function levels as determined by blood tests
- Muscle pain
- Joint pain
- Low red blood cell levels – increases risk of anemia and the need for blood transfusions
- Sleeping disturbance
- Upper respiratory tract infection.

Rare side effects (<1% of patients):

- Elevated liver enzymes.
- Secondary malignancies like leukemia.

To avoid the problem of pneumocystis jirovecii pneumonia, your study doctor may ask you to take an antibiotic while taking temozolomide.

Unknown Risks

You might have side effects or discomforts that are not listed in this form. Some side effects may not be known yet. New ones could happen to you. Tell the study doctor or study staff right away if you have any problems.

<u>Risks associated with standard care and alternative treatment:</u>

As with any medication or chemotherapy treatment, there may be risks, known or unknown. The most common temporary side effects for **some** chemotherapy drugs may include:

- Nausea and vomiting
- Loss of appetite
- Hair loss
- Mouth sores
- Higher risk of infection (due to decreased white blood cells)
- Bruising or bleeding
- Fatigue (feeling tired)
- Changes in your menstrual cycle if you are female (e.g. irregular periods to symptoms of menopause [end of menstruation])

A more complete listing of side effects for other therapies may be available for you to review if you wish. Please talk with your study doctor about the risks of both this experimental therapy and any alternative methods of treatment that are available.

We will tell you as soon as we can, if we find out more information about the side effects that are caused by the experimental drug. During the course of this study, we may find out more information that could be important to you. This includes information that, once learned, might cause you to change your mind about your willingness to be in this study. We will notify you as soon as possible if such information becomes available.

Is there any risk to your unborn children if you take part in this study?

For Females:
If you are pregnant, you may not participate in this study, because there may be risks to you and your unborn baby. Breastfeeding (nursing) mothers will not be included in this study, since it is not known whether the drugs in this study will be passed on to the baby in the mother's milk. If you are currently breastfeeding and wish to continue, your study doctor may recommend another treatment.

If you are a female of childbearing potential (able to become pregnant), you will be given a pregnancy test at no cost to you before beginning any study treatment.

Tell one of the study doctors right away if:

- You are pregnant
- You get pregnant
- You are breastfeeding

If you are male:
We do not know what the study drug will do to your sperm. Should you get a woman pregnant, there could be harm to the unborn baby. You and your partner should use at least one effective birth control method (two are preferable when possible) if you are having sexual intercourse with a woman of childbearing potential.

For males and females:
Whether you are male or female, there may be risks to your unborn children. If you take part in this study, you must use at least one effective birth control method (two are preferable when possible) as discussed with your study doctor. Examples of acceptable birth control methods include:

- Oral birth control pills

- Birth control patch
- Implanted (injectable contraceptive hormones or mechanical products such as intrauterine device)
- Barrier methods (diaphragm, condoms, spermicidal)
- Tubal ligation or vasectomy
- Abstinence

Certain birth control methods may not be a good choice for you (for example some patients with breast cancer should not use birth control methods that contain hormones). You should discuss the method of birth control which is best for you to use both during study treatment and for a period of time after study treatment. Also, if you are a sexually active male or premenopausal female, the study staff will review your birth control use at each study visit. Use of contraception or abstinence should continue for a minimum of one month after completion of the study.

Please place your **initials** in the appropriate box below:

☐ I am surgically sterile (hysterectomy, tubal ligation or vasectomy) or have gone through menopause (no period for 24 consecutive months).

☐ I understand and agree to use contraception during study treatment and for the time recommended by my study doctor and for at least one month after study treatment is over.

Whether you are female or male, you should tell your study doctor immediately if you become pregnant or if your partner becomes pregnant. The long-term effects of the study treatment on fertility are unknown. This means that it is unknown if study treatment with these medications will affect your ability to have children in the future.

Compensation for injury

If you become ill or are hurt while you are in the study, get the medical care that you need right away.

Sponsor Compensation

Your safety is the major concern of every member of the research team. If you experience physical injury or illness as a result of participating in this research study, the sponsor will reimburse you for reasonable and necessary medical expenses when the injury is found to be the result of the study drug used as indicated in the research plan and is not the result of negligence or misconduct of any agent or employee of <<CLINICAL INSTITUTION>>>. Financial compensation for lost wages or other non-medical costs will not be provided. Agreeing to participate in this study and signing this document does not waive your rights in the event of negligence on the part of the Hospital or research staff.

You still have the right to seek compensation for injury related to malpractice, negligence, fault, guilt or blame of those involved in the research.

VOLUNTARY PARTICIPATION/STUDY WITHDRAWAL

Your participation in this study is voluntary. You may refuse to take part and/or decide to withdraw consent and stop participating in the study at any time. You will not have any penalties and you will not lose any benefits that you currently have at this site.

Your decision will not affect your usual medical care. Your decision will not affect your relationship with the study doctor or this institution in any way. If you choose not to take part, you will still be offered all available care that meets your needs and disease. If you choose to stop the study, you will still have all available care that meets your needs and disease.

Your taking part in this study may be stopped at any time without your consent. Your study doctor or someone authorized by the sponsor may stop you from taking part in this study:

- If you do not follow the study doctor's instructions
- If we find out you should not be in the study
- If the study is limited or stopped
- For medical reasons, such as if it becomes harmful to your health to continue

If you decide to withdraw consent and stop your part in the study, please contact <<<PRINCIPAL INVESTIGATOR>>> or one of the study staff who will tell you what you should do before leaving the study. You may be asked to return to the clinic for follow-up care. You may be asked to have laboratory tests, or physical examinations that the study doctor feels are necessary. Until you withdraw your permission, additional information may continue to be taken from your medical records for study follow-up purposes.

Privacy Notice

The researchers are asking for your written authorization before using your health information or sharing it with others in order to conduct the research as described. However, under certain circumstances, the researchers may use and disclose your health information without your written authorization if they obtain approval through a special process to ensure that research without your written authorization poses minimal risk to your privacy. Under no circumstances, however, would the researchers allow others to use your name or identity publicly.

The researchers may also disclose your health information without your written authorization to people who are planning a future research project, so long as any information identifying you does not leave our facility.

Information about people who have died may be shared with researchers using the information of deceased persons, as long as the researchers agree not to remove from our facility any information that identifies these individuals.

Confidentiality

Only the investigator, the members of the research team, the sponsor (NewLink Genetics Corporation), authorized officials from state and federal governments such as the Food and Drug Administration (FDA) or the Office of Human Research Protections (OHRP), governmental agencies in other countries where the study drug may be considered for approval, and authorized representatives of the <<<CLINICAL INSTITUTION>>> will have access to confidential data which would identify you, unless specifically required to be disclosed by state or federal law.

Because of the need to release information to these parties, absolute confidentiality cannot be guaranteed. The results of this study may be presented at meetings or in publications. However, you will not be identified in any reports or publications resulting from the study. All reasonable steps will be taken to ensure confidentiality.

Description of the right to access medical records

You will not be able to review your study-related records while the study is in progress. However, you will be able to review your medical records after the research study has been completed. This authorization has no expiration date.

Who to contact during the study for questions
<<<PRINCIPAL INVESTIGATOR>>> or one of the other study doctors can be reached at XXX-XXX-XXXX, 24 hours a day, seven days a week and will answer any further questions you may have at any time concerning the study or any problems you may be having.

If you have any questions or concerns about the "rights of research subjects", you may contact the <<<CLINICAL INSTITUTION>>> of Human Research Protection at XXX-XXX-XXXX.

Authorization to Use or Disclose (Release) Health Information that Identifies You for a Research Study

Use and Sharing of Study Data That Identify You: HIPAA Authorization to Use and Disclose Your Protected Health Information
By signing this form, you authorize <<<CLINICAL INSTITUTION, PRINCIPAL INVESTIGATOR>>> and their study staff to use and disclose your Protected Health Information in connection with this Study as further described in this authorization. This authorization is designed to comply with the Health Insurance Portability and Accountability Act of 1996 (HIPAA) and its implementing regulations; namely, the Privacy Rule.

What is Protected Health Information? Protected Health Information or "PHI" are records that identify you which are created or collected in the course of this study. This PHI may include, but is not limited to, your name, address, telephone number, date of birth, government-issued identification number, and medical records and charts, including the results of all tests and procedures performed during this study.

For what purposes can your PHI be used or disclosed by the study doctor or staff? Your PHI may be used or disclosed by the study doctor or staff in order to conduct this study, as necessary for your study-related treatment or payment for such treatment, to allow the Institution to conduct its normal business operations, and to ensure that information relating to this study is available to the parties that need it for study purposes. Another type of disclosure may be to regulatory authorities (e.g., the U.S. Food and Drug Administration [FDA]), Institutional Review Boards or other persons required by law to properly conduct and monitor this study, including those verifying the proper collection of study data. PHI may also be used by the study doctor or staff to determine your health, vital status or contact information should you withdraw from treatment or are lost to follow-up.

With whom will the study doctor and staff share your PHI? Your PHI may be shared with the following persons or organizations:

- Domestic and foreign regulatory/health authorities, e.g., the U.S. Food and Drug Agency (FDA)
- Affiliated Institutional Review Boards or Independent Ethics Committees and privacy boards
- NewLink Genetics Corporation (the sponsor)
- Health care providers who provide services to you in connection with this study
- Other individuals and organizations that analyze or your health information in connection with this study, such as laboratories and other study sites participating in this study
- Other individuals and organizations that assist in determining your health, vital status or contact information should you withdraw from treatment or are otherwise lost to follow-up

Will the PHI disclosed per this authorization be re-disclosed? Please be aware that after disclosure by the Institution, study doctor, or study staff, there is the possibility that your PHI may be shared with other entities and may no longer be protected by applicable privacy laws and regulations.

What rights do you have to review your PHI? You have the right to request access to your PHI from the study doctor named above, but to ensure proper evaluation of test results your access to these records may not be allowed until after this study has been completed.

Does this authorization expire and can you revoke authorization for the use and disclosure of your PHI? This authorization does not expire. However, you may revoke it by providing written notice to the study doctor that you are revoking the Institution's, study doctor's and study staff's authorization to use or disclose your protected health information/PHI. If you revoke this authorization, you will not be allowed to continue your participation in this study and neither the Institution, the study doctor, nor the study staff will be able to use or disclose your PHI generated from this study except to the extent that they or the study sponsor has already relied on this information to conduct the study.

Can you refuse to sign this authorization? You have the right to refuse to sign this consent, but you will not be allowed to participate in this study. In addition, while your doctor and other treatment providers cannot require you to sign this authorization as a condition of providing general treatment, they may require it for study-related treatment.

Please note that you may change your mind and revoke (take back) this Authorization in writing, at any time. Even if you revoke your Authorization, <<<PRINCIPAL INVESTIGATOR>>> and the study staff may still use or disclose your information they already have obtained about you as necessary to maintain the integrity or reliability of the current research. To revoke this Authorization, you must write to: <<<PRINCIPAL INVESTIGATOR, INSTITUTION, ADDRESS>>>

This Authorization does not have an expiration date.

STATEMENT OF SUBJECT CONSENT

I have read this form and its contents were explained to me. I agree to be in this research study for the purposes listed above. All of my questions were answered to my satisfaction. I will receive a signed and dated copy of this form for my records. I am not giving up any of my legal rights by signing this form.

_____
Printed Name of Research Subject

_____ ____/____/_____
Signature of Research Subject Date

STATEMENT OF SUBJECT CONSENT/PARENTAL PERMISSION

This study has been explained to me. I voluntarily agree to allow my child to take part in this study. I have had the opportunity to ask questions. I understand that the doctors listed in this form can answer future questions I may have about this study and my child's rights. By signing this form I understand that I am not giving up any of the patient rights. I understand that signing this consent does not take the place of any other consents I have signed. I understand that I will be given a copy of this consent to keep.

_____ _____

Parent/Guardian Signature (if patient < 18 yrs) (Date)

_____ _____
Parent/Guardian Printed Name (if patient < 18 yrs) (Date)

Witness Statement (required for all subjects)

My signature indicates that I was present during the entire informed consent process interview and that the information in the form was presented and reviewed with the subject and that informed consent was freely given by the subject or the subject's legally authorized representative.

My signature also indicates that I was present when the subject signed this form.

_____ ____/____/_____
Signature of Witness Date

_____
Printed Name of Witness

STATEMENT OF PERSON EXPLAINING CONSENT

I have carefully explained to the subject the nature and purpose of the above study. There has been an opportunity for the subject to ask questions about this research study. I have been available to answer any questions that the subject has about this study.

_____ ____/____/_____
Signature of Person Explaining Consent Date

_____
Printed Name of Person Explaining Consent

INVESTIGATOR STATEMENT
I acknowledge that I have discussed the above study with this participant and answered all of his/her questions. They have voluntarily agreed to participate. I have documented this action in the subject's medical record source documents or research chart source documents, as applicable. A copy of this signed document will be placed in the subject's medical record or research chart, as applicable. A copy of this document will be given to the subject or the subject's legally authorized representative.

_____
Printed name of Investigator obtaining consent

_____ ____/____/_____
Signature of Investigator obtaining Consent Date

Appendix E: Sub-Study Consent Form Template

Addendum to the Consent
Consent to take and store additional blood samples

The use of 'you' throughout this document refers to the research subject as an adult or child. If the research subject is less than 18 years old, the subject's parent or legal guardian must provide written consent for the child to participate in this study.

We are asking you to allow us to take and store an additional sample of your blood. This is an optional test that may help us better understand who will respond to treatment with indoximod.

This means we will take an additional 18 mL (about 3½ teaspoons) of blood to be stored for subsequent (later) genetic analysis of an enzyme that is released in tumors, called IDO enzyme. The IDO enzyme is an immune suppressing enzyme released by the tumor and indoximod seems to block this enzyme.

These samples may be stored at NewLink Genetics Corporation within a climate controlled, restricted access area requiring key cards for entry. These samples will be used for future research to help us better understand who may respond to treatment with indoximod.

These samples will only have subject identifiers consisting of your initials followed by your study subject number (XX-111). No one except your physician or clinical research team will be able to connect your coded health information to you.

You can decide if you want us to store and use your samples for this future analysis of the IDO enzyme.

You do not have to agree to these optional samples of blood in order to take part in the study that has been previously explained to you.

Please initial your choice below:

____ I give my consent to provide an additional 18 mL of blood for that purpose on the first day of each treatment cycle.

____ I do not give my consent to provide an additional 18 mL of blood for that purpose.

Even if you sign this consent, you have the right to withdraw your samples at any time. To do so, please submit a written request to Dr. XXXXXXX at:

Attn: Principal Investigator, MD
Institution Name
Address
City, State Zip

STATEMENT OF SUBJECT CONSENT

I have read this form and its contents were explained to me. I agree to be in this research sub-study for the purposes listed above. All of my questions were answered to my satisfaction. I will receive a signed and dated copy of this form for my records. I am not giving up any of my legal rights by signing this form.

_____
Printed Name of Research Subject

_____ ____/____/_____
Signature of Research Subject Date

STATEMENT OF SUBJECT CONSENT/PARENTAL PERMISSION

This study has been explained to me. I voluntarily agree to allow my child to take part in this study. I have had the opportunity to ask questions. I understand that the doctors listed in this form can answer future questions I may have about this study and my child's rights. By signing this form I understand that I am not giving up any of the patient rights. I understand that signing this consent does not take the place of any other consents I have signed. I understand that I will be given a copy of this consent to keep.

_____ _____
Parent/Guardian Signature (if patient < 18 yrs) (Date)

_____ _____
Parent/Guardian Printed Name (if patient < 18 yrs) (Date)

STATEMENT OF PERSON EXPLAINING CONSENT

I have carefully explained to the subject the nature and purpose of the above sub-study. There has been an opportunity for the subject to ask questions about this research sub-study. I have been available to answer any questions that the subject has about this sub-study.

_____ ____/____/_____
Signature of Person Explaining Consent Date

_____
Printed Name of Person Explaining Consent