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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INTRODUCTION

The standard of care for recurrent glioblastoma multiforme (GBM) has not been clearly established. 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 [1].

The main function of the IDO pathway is the regulation of acquired local and peripheral immune tolerance in normal and pathological conditions, particularly in the tumor microenvironment [2]. IDO is expressed in a large proportion of solid tumors that includes 50 to 90% of glioblastomas and is correlated with poor prognosis [3]. The IDO pathway mediates an acquired immune tolerance towards tumors, allowing tumors to thwart an immune response by the host. Therefore, the IDO pathway is an attractive target for cancer drug development.

IDO is an enzyme that catalyzes the initial and rate limiting step in the conversion of tryptophan to kynurenine. Tryptophan depletion and kynurenine metabolites enhance the number and function of the Tregs (suppressive arm of the immune system) and inhibits the effector T cell (stimulatory arm).

IDO inhibitors such as indoximod (1-methyl-D-tryptophan / D-1MT) can improve anti-tumor T cell response slowing the tumor growth in vivo [ref 4, 5]. The current standard of care for newly diagnosed glioblastoma involves maximal surgical resection followed by concurrent radiotherapy with temozolomide (TMZ), an orally available DNA alkylating agent, followed by at least 6 months of adjuvant TMZ.

The antiangiogenic monoclonal antibody bevacizumab is also used in treatment regimens to target the highly vascularized brain tumors [6].

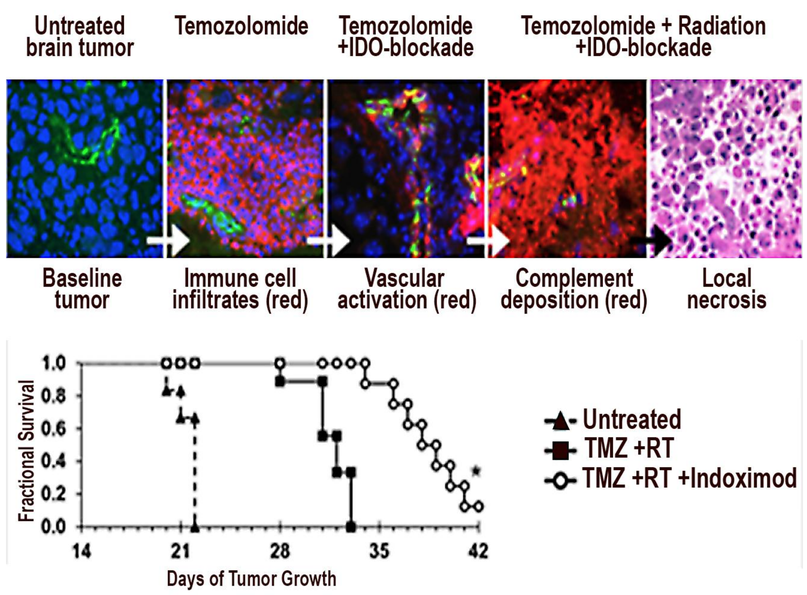
We have demonstrated a synergistic effect of indoximod when combined with TMZ and radiation in a syngeneic orthotopic brain tumor model [7].

The purpose of this ongoing phase I study is to determine maximum tolerated dose (MTD) of indoximod in combination with TMZ in GBM followed by phase 2 studies testing the preliminary activity of the combination in several relevant situations including the addition of bevacizumab or stereotactic radiosurgery (SRS).

MURINE GLIAL TUMOR MODEL

Preclinical Animal Data:

- IDO inhibitors such as indoximod (1-methyl_D-tryptophan / D-1MT) can improve anti-tumor T cell responses, slowing the tumor growth *in vivo.*
- In a murine glioblastoma model, we used a backbone therapy consisting of a singe dose of TMZ plus a single 500cGy fraction of radiation.
- Adding indoximod triggered a fundamentally different anti-tumor response to chemo-radiotherapy characterized by:
  - Widespread vascular activation
  - Complement deposition
  - Tumor necrosis with improved survival



Effect of treatment in the murine glioblastoma model

OVERVIEW

- The study is designed as a prospective phase 1b/2 trial of the combination of oral indoximod and temozolomide in adult patients with progressive glioblastoma multiforme (WHO grade IV glioma) or gliosarcoma.
- In addition, the phase 1b cohort is designed to include patients with progressive WHO grade III glioma.

Eligibility

- 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 of tumor progression or regrowth
- Patients must have completed a course of radiation therapy (phases 1 and 2) and at least 2 adjuvant cycles of temozolomide (phase 2)

PHASE 1 OBJECTIVES

Study Design

- The study uses a 3+3 dose escalation design, until reaching the MTD or the maximal specified dose.

Primary Objective

- Recommended phase 2 doses of indoximod and temozolomide in combination

Secondary Objective

- Adverse event profile and regimen-limiting toxicities (RLT) of indoximod plus temozolomide in combination therapy
- PK profile of indoximod in the setting of this treatment regimen.

PHASE 1 STUDY SCHEMA

After progression to standard front-line therapy, patients with glioblastoma are currently being enrolled in a dose escalation study of indoximod (600, 1000 or 1200 mg twice daily given orally) with a standard fixed dose of TMZ.

DOSE LEVEL (COHORT)	INDOXIMOD DOSE (ORAL)	TMZ 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 OBJECTIVES

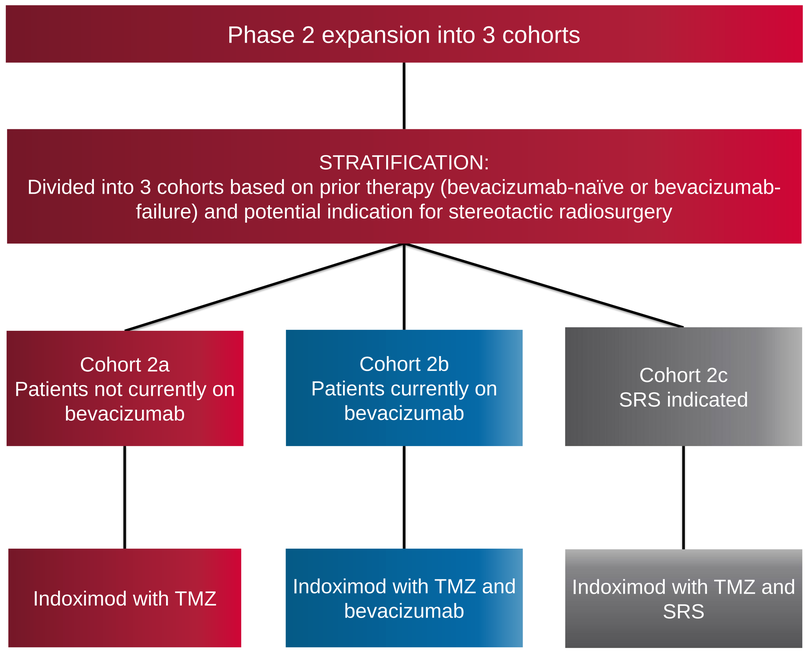
Primary Objective

- Efficacy as measured by six-month progression-free survival with indoximod plus temozolomide (+/- bevacizumab or SRS)

Secondary Objectives

- Efficacy as measured by ORR, OS, safety, and tolerability of indoximod plus temozolomide in patients with progressive GBM
- ORR, safety, and tolerability of indoximod plus temozolomide and bevacizumab in GBM patients whose disease progressed during therapy with a bevacizumab-based regimen
- ORR, safety, and tolerability of indoximod plus temozolomide and SRS in GBM patients who may reasonably benefit from tumor debulking

PHASE 2 STUDY SCHEMA



CORRELATIVE STUDIES

Assessment of primary tumor samples for:

- IDO expression
- Evaluation of plasma for biomarkers of IDO activity (kynurenine and tryptophan)
- Pharmacokinetic analysis

SUMMARY

- Chemotherapy and immunotherapy can have additive or synergistic effects
- Indoximod is a potent inhibitor of the IDO pathway 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
- Trial is currently open and enrolling dose escalation cohorts

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CLINICAL TRIALS IDENTIFIER

ClinicalTrials.gov Identifier: NCT02052648

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