Phase 2 Combination Study of the IDO Pathway Inhibitor Indoximod with 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 glioblastoma. IDO high expression is correlated with poor prognosis in GBM [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 Treg (suppressive) arm of the immune system and inhibits the effector T cell (stimulatory) arm.

IDO pathway inhibitors such as indoximod 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].

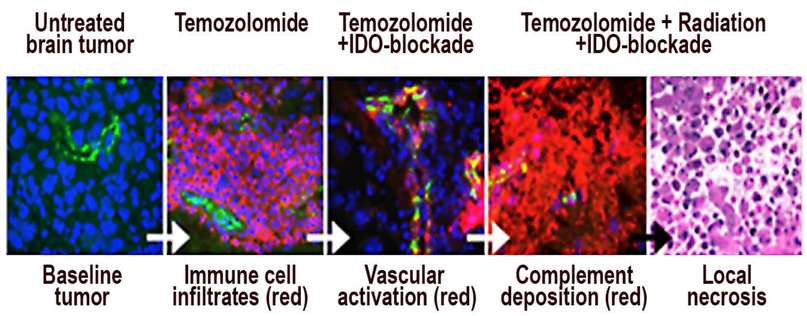
The phase 1b portion of this study concluded successfully and established the initial safety of the combination necessary to proceed into phase 2.

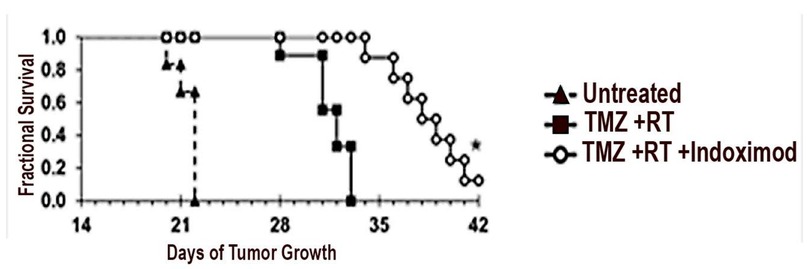
The phase 2 portion of the study is ongoing.

MURINE GLIAL TUMOR MODEL

Preclinical Animal Data:

- IDO inhibitors such as indoximod (1-methyl_D-tryptophan / D-1MT) can improve anti-tumor T cell response 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

This is a Phase 2 study intended to determine the preliminary efficacy of adding the IDO pathway inhibitor indoximod to standard treatment of recurrent, temozolomide-refractory malignant brain tumors.

Patients must have completed surgery and concurrent temoxolomide / radiation therapy. Patients must have recurred / progressed while on adjuvant temozolomide therapy or after completion of adjuvant temozolomide therapy.

The Phase 2 design includes 3 pre-defined cohorts

- Bevacizumab naïve patients; N=68 patients
- Patients currently on or recently taken off bavacizumab therapy; N=24 patients
- Patients in whom additional stereotactic radiotherapy may be utilized; N=40 patients

Results will be determined using standard RANO criteria

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

STUDY CRITERIA

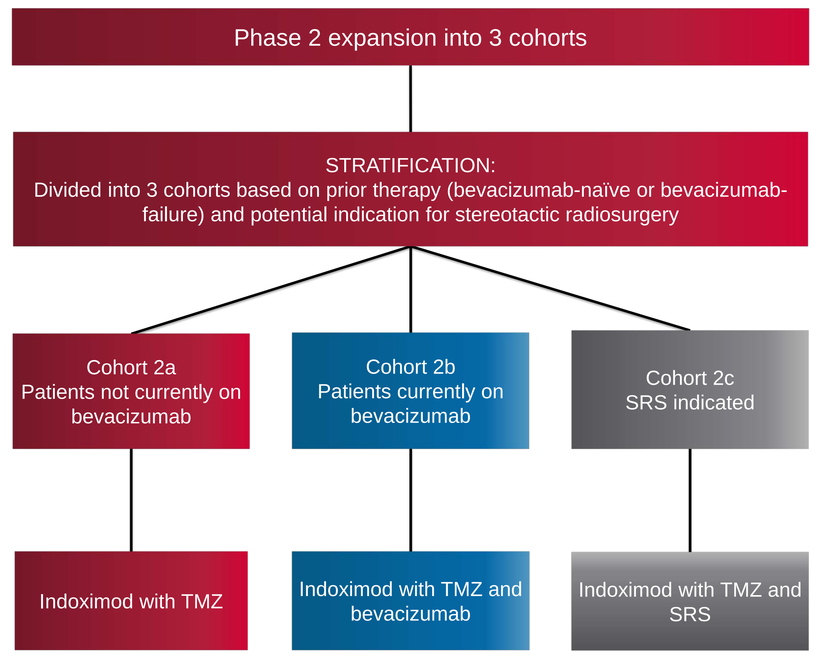
Inclusion Criteria

- Patients 16 to 70 years of age with histologically proven intracranial GBM (World Health Organization grade III-IV glioma) or gliosarcoma
- Confirmation of tumor progression or regrowth on imaging, with and without gadolinium contrast
- Patients must have completed a course of radiation therapy
- Corticosteroid dose <2 mg of dexamethasone daily (or equivalent)
- Eastern Cooperative Oncology Group performance status of 0 or 1, Karnofsky performance status ≥70%, and life expectancy >6 months

Exclusion Criteria

- >3 prior regimens for recurrent GBM or gliosarcoma
- Active systemic infection requiring treatment
- Active or history of autoimmune disease

PHASE 2 STUDY SCHEMA



CURRENT STATUS

- Phase 1b completed and data reported at ASCO 2015
- Combination therapy well tolerated with no increase in treatment limiting toxicities over historic norms for backbone therapy alone in Phase 1b
- Phase 2 study has fully enrolled cohorts 2a and 2b
- Cohort 2c still open to enrollment

REFERENCES

1. Chamberlain, M.C. Expert Rev Neurother 12, 929-936 (2012)
2. Johnson, T.S. & Munn, D.H. Immunol Invest 41, 765-797 (2012)
3. Mitsuka K et al. Neurosurgery (2013), 72(6)1031-8.
4. Hou, D.Y. et al. Cancer Res 67, 792-801 (2007)
5. Muller, A.J. et al. Nat Med 11, 312-319 (2005)
6. Shrimali, R.K. et al. Cancer Res 70, 6171-6180 (2010)
7. Li, M. et al. #701 26th Annual Soc of Ped Hem/Onc (2013) .

CLINICAL TRIALS IDENTIFIER

ClinicalTrials.gov Identifier: NCT02052648

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