Abstract #2070

A Phase 1b/2 Study of the Combination of the IDO Pathway Inhibitor Indoximod and Temozolomide for Adult Patients With Temozolomide-Refractory Primary Malignant Brain Tumors: Safety Analysis and Preliminary Efficacy of the Phase 1b Component

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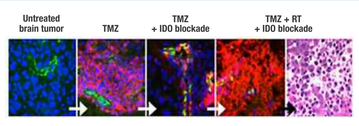
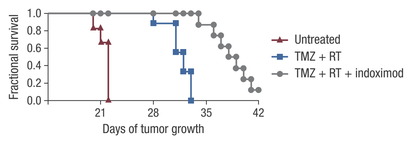
INTRODUCTION

- Recurrent glioblastoma multiforme (GBM) is associated with poor survival; a standard of care has not been clearly established
  - Treatment for newly diagnosed glioblastoma typically involves maximal surgical resection followed by concurrent radiotherapy with temozolomide (TMZ), an oral DNA-alkylating agent, followed by ≥6 months of adjuvant TMZ
  - Bevacizumab, an anti-angiogenic monoclonal antibody, is also used to target highly vascularized brain tumors[1]
    - Median progression-free survival (PFS) is 2.5 months in adults with bevacizumab-refractory GBM[2]
- Indoleamine 2,3-dioxygenase (IDO) is a key immunomodulatory enzyme of acquired immune tolerance in normal and pathologic conditions, particularly in the tumor microenvironment, that allows tumors to thwart the host immune response[3]
  - IDO inhibits CD8+ T cells, and enhances the suppressor activity of regulatory T cells
- IDO is expressed in a large proportion of solid tumors, including 50% to 90% of GBM, and high IDO expression is correlated with poor prognosis in GBM[4]
  - Therefore, the IDO pathway is an attractive target for cancer drug development
- This phase 1b/2 study is designed to determine the safety profile and maximal tolerated dose (MTD) of the IDO inhibitor indoximod (1-methyl-D-tryptophan/D-1MT) in combination with TMZ in recurrent refractory malignant brain tumors, with subsequent expansion into a phase 2 portion to evaluate the efficacy of the combination
  - Here, we present the safety analysis and preliminary efficacy of the phase 1b component

Murine Glial Tumor Model

- IDO inhibitors, such as indoximod, can improve antitumor T cell response, which slows the tumor growth in vivo[5,6]
  - In a murine glioblastoma model, antitumor response was measured at baseline, after a single dose of TMZ plus 500 cGy fraction of radiation, and with the addition of indoximod to TMZ and radiation therapy (**Figure 1**)





TMZ, temozolomide; RT, radiation therapy; IDO, indoleamine 2,3-dioxygenase.

Figure 1. The antitumor response of indoximod plus chemoradiotherapy in a murine glioblastoma model.

  - The antitumor response triggered with indoximod was fundamentally different than that of chemoradiotherapy and characterized by the following:
    - Widespread vascular activation
    - Complement deposition
    - Tumor necrosis with improved survival
- A synergistic effect of indoximod was demonstrated when combined with TMZ and radiation therapy in a syngeneic orthotopic brain tumor model[7]

METHODS

- This is a prospective, phase 1b, dose-escalation study in adult patients with progressive GBM or gliosarcoma that is refractory to TMZ
- 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
- Indoximod was administered at 3 dose levels in combination with a fixed dose of TMZ (**Table 1**)
  - Twelve patients were required to fully enroll all 3 dose cohorts with no regimen-limiting toxicities (RLTs) that required cohort expansion at lower doses

Table 1. Phase 1 Study Schema of Indoximod Dose Escalation

Dose level (cohort)	Indoximod (oral)*	TMZ (oral)
1	600 mg BID × 28 days	150 mg/m^2 × 5 days
2	1,000 mg BID × 28 days	150 mg/m^2 × 5 days
3	1,200 mg BID × 28 days	150 mg/m^2 × 5 days

TMZ, temozolomide; BID, twice daily.
*Indoximod is administered in 200-mg capsules (ie, 3, 5, and 6 capsules, respectively, for each dose level), and should be taken with water 1 hour before breakfast and 1 hour before dinner.

OBJECTIVES

- To determine the MTD of indoximod in combination with TMZ in recurrent TMZ-refractory malignant brain tumors for use in the phase 2 study
  - MTD was defined as the dose of indoximod that does not induce RLT in >1 of 6 patients who were treated with TMZ
- To evaluate the adverse event (AE) profile, including type, incidence, severity, duration, causality, and treatment intervention, and identify RLTs of combination therapy with indoximod plus TMZ

RESULTS

Patients

- Twelve patients received escalating doses of indoximod in combination with TMZ
  - Three patients received indoximod 600 mg BID, three patients received indoximod 1,000 mg BID, and six patients received indoximod 1,200 mg BID
- Baseline demographic characteristics are summarized in **Table 2**

Table 2. Patient Demographic and Baseline Characteristics

Characteristic	Indoximod + TMZ (N = 12)
Gender, n (%)	
Female	5 (41.7)
Male	7 (58.3)
Race, n (%)	
White	9 (75.0)
Black/African American	3 (25.0)
Median age (range), years	48.5 (27-62)
Diagnosis	
GBM	10 (83.3)
Oligodendroglioma	1 (8.3)
Anaplastic astrocytoma	1 (8.3)

TMZ, temozolomide; GBM, glioblastoma multiforme.

Safety and Tolerability

- The MTD of indoximod in combination with TMZ was 1,200 mg BID
- A summary of AEs is presented in **Table 3**; the most frequently (>25%) reported AEs were headache, diarrhea, vomiting, nausea, fatigue, and dizziness
- No patients have experienced a reduction or delay in TMZ dosing due to the addition of indoximod
- Six (50%) of 12 patients experienced ≥1 treatment-related AE
  - Only 1 treatment-related AE was grade 3 (fatigue); the remainder were either grade 1 or grade 2 events

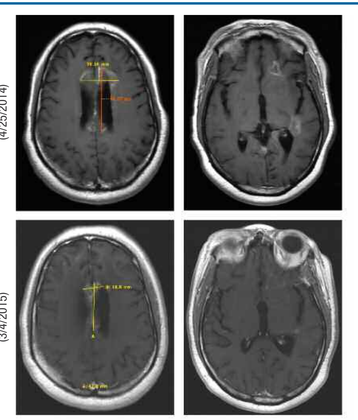
Table 3. Summary of AEs for Indoximod + TMZ (N = 12)

	Number of patients, n (%)		Number of patients, n (%)
Grade ≥3 AEs			
Fatigue	2 (17)	Vomiting	1 (8)
Hyperglycemia	1 (8)	Insomnia	1 (8)
Seizure	1 (8)	Extremity pain	1 (8)
Arm pain	1 (8)		
Treatment-related AEs*			
Nausea	4 (33)	Pruritus	1 (8)
Fatigue	2 (17)	Vomiting	1 (8)
Edema	1 (8)		

AE, adverse event; TMZ, temozolomide.
*All treatment-related AEs were grade 1 or 2 events except for fatigue, in which 1 patient had a grade 3 event.

Antitumor Activity

- Four (33%) patients remain on the study, and 9 (75%) patients are alive at the time of this analysis
- One (8%) patient is showing an ongoing partial response after having exhibited stable disease for 10 months
  - This patient is a 42-year-old African American woman who was initially diagnosed with a left fronto-parietal GBM in September 2012
  - The patient underwent surgical biopsy in September 2012, but definitive surgical resection was not performed due to tumor extension that involved corpus callosum and contralateral lesions
  - The patient received standard chemoradiotherapy (60 Gy over 6 weeks with TMZ [75 mg/m^2/day]) followed by maintenance TMZ
  - However, after 5 cycles of maintenance TMZ, disease progression occurred in June 2013
  - Subsequently, the patient received single-agent bevacizumab, but demonstrated disease progression again in January 2014; the patient was then taken off bevacizumab
  - Upon starting indoximod + TMZ in March 2014, the patient experienced stable disease with slow but modest reduction in tumor size from March 2014 to January 2015
  - By March 2015, the patient demonstrated a partial response by Response Assessment in Neuro-Oncology (RANO) criteria, as demonstrated on selected MRI images (**Figure 2**)
- Four (33%) additional patients have shown stable disease ranging from 4 to 11 months
- Among the 5 patients with responses better than progressive disease, 4 (80%) have a diagnosis of GBM

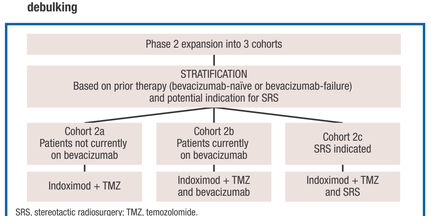


TMZ, temozolomide.

Figure 2. MRI images demonstrating partial response in 1 patient following treatment with indoximod + TMZ.

CONCLUSIONS

- **The combination of chemotherapy and immunotherapy can have additive or synergistic effects in preclinical models**
- **Indoximod is a potent inhibitor of the IDO pathway, and is currently in phase 1/2 development for the treatment of solid tumors**
- **The MTD for indoximod in combination with TMZ was 1,200 mg BID**
- **No patients have experienced an indoximod-related serious AE or a reduction or delay in TMZ dosing due to the addition of indoximod**
- **The clinical data, although preliminary, are encouraging with 4 stable disease patients (4-11 months) and an objective response on a previously TMZ-refractory patient**
- **Expansion into the phase 2 portion of the study is proceeding according to the schema shown in Figure 3**
- **The primary objective of the phase 2 study is to assess the efficacy of indoximod + TMZ in TMZ-refractory patients with or without bevacizumab or stereotactic radiosurgery (SRS), as measured by 6-month PFS**
- **Secondary objectives include overall response, overall survival, safety, and tolerability in the various cohorts:**
  - **Indoximod + TMZ in patients with progressive GBM**
  - **Indoximod + TMZ and bevacizumab in patients with GBM who progressed during therapy with a bevacizumab-based regimen**
  - **Indoximod + TMZ and SRS in patients with GBM who may benefit from tumor debulking**



SRS, stereotactic radiosurgery; TMZ, temozolomide.

Figure 3. Phase 2 study schema.

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