Phase I trial of TG02 plus dose-dense or metronomic temozolomide for recurrent anaplastic astrocytoma and glioblastoma in adults

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Background

Most therapies for recurrent high grade gliomas are not successful, largely due to the complexity of the disease.

TG02 is a multi-kinase inhibitor with the primary effect on CDK9 activity, inhibiting transcriptional progress. TG02 has been investigated preclinically and clinically in hematologic malignancy, suggesting anti-glioma effects and good blood-brain barrier penetration.

TMZ has proven efficacy in glioblastoma, but is limited by resistance mechanisms. Our preclinical studies have demonstrated the anti-glioma effects of TG02 and the synergy with TMZ through modulation of transcription and metabolism.

We hypothesize that given the multiple mechanisms of TG02 and established efficacy of TMZ, combined treatment may be effective for malignant gliomas. A phase I/II trial was launched and herein we report the results of the MTD finding part of the phase I trial.

Objectives

Primary Objectives

To determine the maximum tolerated dose (MTD) of TG02 plus TMZ using both Dose-dense (DD) and metronomic (MN) TMZ in adult with recurrent anaplastic astrocytoma or glioblastoma.

Secondary Objectives

- To select the treatment regimen with better PFS4 between TG02 plus dd TMZ or mn TMZ at each of the MTDs following cohort extension.
- To perform pharmacokinetic and pharmacogenomic studies of TG02 once the MTD is determined in each cohort.

Eligibility Criteria

- Adults with recurrent anaplastic astrocytoma (AA) or glioblastoma
- KPS ≥ 60
- Adequate organ functions
- No more than 2 prior relapses for phase I part
- No prior treatment with bevacizumab as tumor treatment
- Tumor tissues available for review to confirm the histologic diagnosis and molecular profiling

Study Design

- Phase I study is designed to be conducted in two stages: **MTD finding** and **cohort extension, in two treatment arms:** Dose-dense (DD) and metronomic (MN) ; with dose escalation of TG02. The maximum number of cycle is 12.
- MTD finding part: TMZ with two alternate schedules (DD and MN) in combination with TG02 will be administered.
  - A Bayesian Optimal Interval design was employed to determine the MTD and the toxicity profile of treatments.
- A cohort extension of both arms will be performed at each MTD and the treatment arm with a better response will be selected for the combination treatment arm for Phase II.
- Pharmacokinetic, pharmacogenetic studies and neutrophil analysis will be performed during the cohort extension of both arms.

Study treatment 28-day cycles

TG02:
Dose-escalation, starting dose 200mg PO
On days -3, 1, 12, 15, and 26 in cycle 1, and
On days 1, 12, 15, and 26 in cycle 2 and after

TMZ:
DD arm: 125mg/m^2/day 7on/7off
MN arm: 50mg/m^2 daily

Dose escalation

Level	TG02 (mg)	DD-TMZ (mg/m2)	MN-TMZ (mg/m2)
-1	150	125	50
0	200	125	50
1	250	125	50
2	300	125	50

Results

Table 1. Patient characteristics (n=40)

	DD Arm	MN Arm
No. Patient	19	21
Female/Male	6/13	6/15
Age (median)	50.8	50.6
KPS (median)	90	90
GBM/AA	10/9	17/4

Table 2. Patient disposition

Arm/dose level (mg)		Total patient	Active Patient	Reasons for off-study			
				Progressive disease	Toxicity	Withdraw	Completed
DD	**200**	6	0	4	1	0	1
	250	13	0	10	1	1	1
MN	**200**	6	0	6	0	0	0
	250	13	1	8	0	3	1
	300	2	0	1	0	0	1

Table 3. MTD Determination

Arm	TG02 mg On days 1, 12, 15, 26	TMZ
DD	250	125mg/m^2/d, 7on/7off
MN	250	50 mg/m^2 daily

Table 4. DLT analysis

Arm/dose level		No. pt with DLT/pt. at each level	Description
DD	**200**	1/6	G3 diarrhea
	250	3/12	G4 neutropenia G3 ALT elevation G3 fatigue
MN	**200**	1/6	Recurrent G3 neutropenia
	250	5/12	G3 ALT elevation G3 fatigue G4 neutropenia
	300	1/2	G4 febrile neutropenia G4 ALT elevation G4 AST elevation

Acknowledgement: We thank our patients and their families for participating in the study. We thank Adastra Pharmaceuticals for providing TG02.

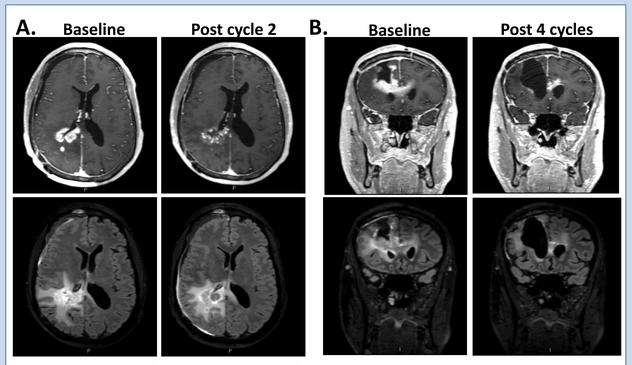

Figure 1. MRIs of a GBM patient from each treatment arm, DD arm (A) and MN arm (B) at baseline and post treatment.

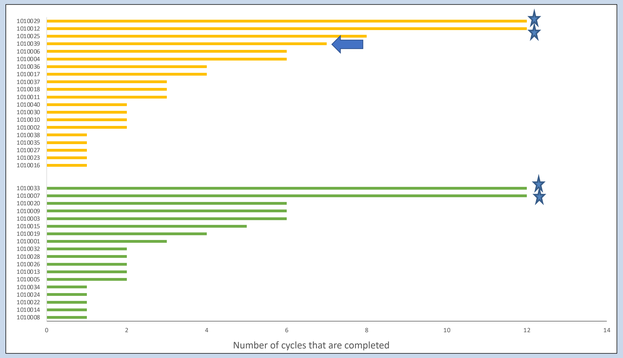

Figure 2. Bar graph representing the numbers of cycles that were completed by each subject in DD (green, n=18) and MN (yellow, n=20) arms. Arrow indicates a patient currently on treatments. Stars indicate the patients completed study treatments.

Conclusions

- Combined therapy with TG02 and TMZ are tolerable and feasible in recurrent AA and glioblastoma.
- MTD of TG02 is 250mg with DD TMZ or MN TMZ (Table 3).
- All patients with DLT recovered and continued on study treatment after dose reduction (Table 2).
- Four patients (10%) have completed 12 cycles of treatments with prolonged disease control.
- Ten percent of patients demonstrated tumor volume reduction on MRIs.
- **These results demonstrated the safety and treatment efficacy of the TG02/TMZ combination in refractory AA and glioblastoma and prompting creation of the name zotiraciclib and plans for a randomized clinical trial.**

Future Directions

- Cohort extension at MTD for both arms is now enrolling.
- Neutrophil analysis will be perform to study the transient neutropenia that was observed in study patients.