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

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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. Preliminary results demonstrated anti-glioma effects and good blood-brain barrier penetration.

TMZ has proven efficacy in glioblastoma, but is limited by resistant 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/gliosarcoma.

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 high-grade astrocytoma,
- KPS ≥ 60
- Adequate organ functions,
- No more than 2 prior relapses,
- No prior treatment with bevacizumab,
- Tumor tissues available for review to confirm the histologic diagnosis and molecular profiling

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

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 TGO2.
- 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 progression free survival at 4 months (PFS4) 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 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

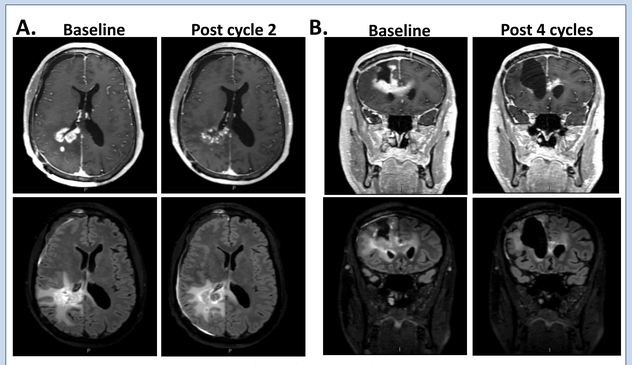

Figure 1. MRIs of a GBM patient from each treatment arm, DD arm (A) and MN arm (B) at baseline and post treatment.

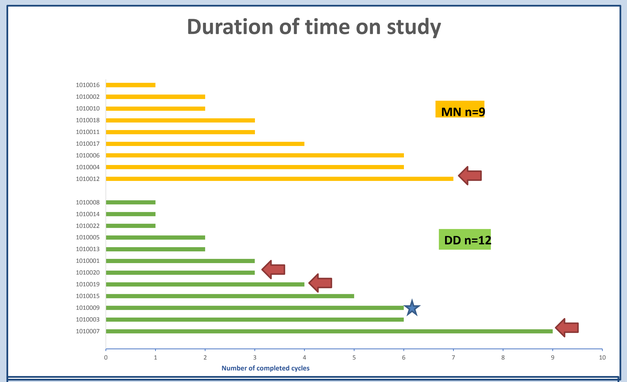

Figure 2. Bar graph representing the duration of the time on study for each subject in DD (green, n=12) and MN (yellow, n=9) arms. Arrows indicate patients currently on treatments. ★Patient on TG02 alone for more than 2 cycles.

Results

Table 1. Patient characteristics (n=21)

	DD Arm	MN Arm
No. Patient	12	9
Female/Male	3/10	0/9
Age (median)	54.8	50.6
KPS (median)	90	90
GBM/AA	8/5	7/2
No. 1 vs 2 prior relapses	10/2	7/2

Table 2. Patient disposition

Arm/dose level (mg)		Total patient	Active Patient	Patient off study		
				Progressive disease	Toxicity	withdraw
DD	**200**	6	1	4	1	0
	250	6	2	2	1	1
MN	**200**	3	0	3	0	0
	250	6	1	4	0	1

Table 3. Treatment related AEs

Description of AE (>15% in G1,2 & all G3,4)	No. (Percentage) of patient			
	AEs of all grades		AEs of grade3 and 4	
	DD	MN	DD	MN
Fatigue	8 (67)	8 (89)	-	-
Nausea	7 (58)	5 (56)	-	-
Vomiting	4 (33)	3 (33)	1 (8)	-
Diarrhea	9 (75)	5 (56)	1 (8)	-
Anorexia	-	2 (22)	-	-
Constipation	3(25)	3 (33)	-	-
Headache	2 (17)	3 (33)	-	-
ALT elevation	10 (83)	7 (78)	4(33)	2 (22)
AST elevation	6 (50)	5 (56)	-	1 (11)
Leukopenia	10 (83)	9 (100)	4 (33)	6 (67)
Neutropenia	6 (50)	5 (56)	5 (41)	5 (56)
Lymphopenia	9 (75)	9 (100)	6 (50)	7 (78)
Anemia	3 (25)	7 (78)	-	-
Thrombocytopenia	6 (50)	6 (67)	-	-

Table 4. DLT analysis

Arm/dose level		DLT	Description	Lead to off treatment
DD	**200**	1	G3 diarrhea	No
	250	2	G4 neutropenia G3 ALT elevation	Yes No
MN	**200**	0	-	
	250	3	G4 lymphopenia x 2 G3 ALT elevation	No No

Table 5. MTD Determination

Arm	TG02 mg On days 1, 12, 15, 26	TMZ
DD	250	125mg/m^2/d, 7on/7off
MN	200	50 mg/m^2 daily

Conclusions

- TG02 and TMZ are generally well-tolerated in combination in recurrent high grade gliomas.
- MTD of TG02 is 250mg with DD TMZ and 200mg with MN TMZ (Table 5).
- Six patients developed DLT. All DLT recovered and 5 patients continued on study treatment after dose reduction (Table 4).
- 67% and 38% of patients were stable or better at post-cycle 2 and 4 assessments, respectively. One of these patients is currently in cycle 9 treatment.
- 3 patients demonstrated tumor volume reduction on MRIs. Formal response assessment will be reported at the completion of the study.
- The safety and preliminary efficacy analysis suggest that the combination of TG02 and TMZ is a promising therapy in refractory high grade astrocytomas.

Future Directions

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