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Investigation of Pharmacodynamic and Predictive Biomarkers to Define Response to Proteasome Inhibitor Marizomib in Glioma

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Introduction

Proteasome inhibitors (PIs) have been employed with clinical success in multiple myeloma, but have been much less effective in solid tumors, despite the central role of the proteasome in controlling cellular metabolism. Marizomib (MRZ) is a novel second generation proteasome inhibitor which binds irreversibly to and inhibits the enzymatic activity of all three subunits of the proteasome. The unique ability of MRZ among PIs to cross the blood-brain barrier, combined with its pan-proteasome activity, suggest that MRZ may have distinct therapeutic advantages over the approved PIs in the treatment of glioma. Preclinically, MRZ inhibits glioma cell proliferation and invasion and shows anti-tumor activity in intracranial glioma models (Di, 2015, Neuro Oncol.).

Here we present interim results of a Phase I clinical trial of MRZ in combination with bevacizumab (BEV) in WHO Grade IV recurrent glioma (NCT02330562) and preliminary pharmacodynamic and predictive biomarker data.

Results

MRZ-108 Study Objectives & Design

Primary: Determine the MTD and RP2D of the combination of MRZ and BEV

Secondary: Evaluate safety and activity of MRZ + BEV

Exploratory: Evaluate baseline proteasome activity, neurological coordination (SARA), and quality of life assessment (FACT-Cog/FACT-Br)

Cohort	MRZ IV (mg/m^2) – 10 min infusion Days 1, 8, 15 q 28 days	BEV IV (mg/kg) q 14 days
1	0.55	10
2	0.7	10
3	0.8	10
4	Expansion of RP2D	10

Key Eligibility Criteria

- ≥ 18 years
- Histological evidence of G4 malignant glioma in first or second relapse
- No prior proteasome inhibitor or anti-angiogenic therapies
- KPS ≥70

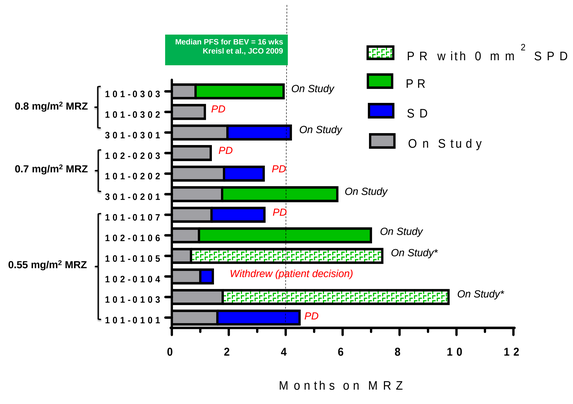
MRZ + BEV: All Related Grade 3 AEs (n=12)

Preferred Term	Cohort 1 (n=6)		Cohort 2 (n=3)		Cohort 3 (n=3)		Total	
	MRZ	BEV	MRZ	BEV	MRZ	BEV	MRZ	BEV
Hypertension	0	0	0	1	0	1	0	2
Headache	0	1	0	0	0	0	0	1
Fatigue	1	1	0	0	0	0	1	1
Confusional State	1	0	0	0	0	0	1	0
Hallucination	1	0	0	0	0	0	1	0

Unaudited data through 29 Jan 2016

- No Grade 4 or 5 AEs reported

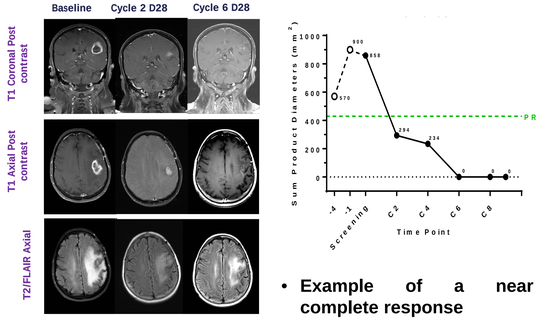
MRZ Clinical Activity



**2 of 4 PR with 0 mm² SPD on at least 2 consecutive MRIs*

Unaudited data through 29 Jan 2016

Patient 101-0103 MRI

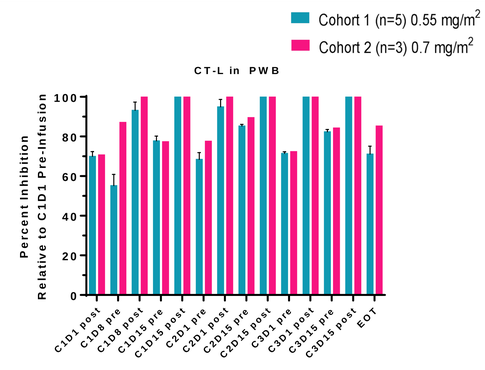


- Example of a near complete response

MRZ PK Parameters

Parameter (Units)	0.55 mg/m^2 SE (n)	0.7 mg/m^2 SE (n)	0.8 mg/m^2 SE (n)
$T_{1/2}$ (min)	8.8 ± 0.8 (3)	32.0 (1)	7.6 ± 0.9 (2)
T_{max} (min)	4.0 ± 0.6 (6)	11.3 ± 9.3 (3)	0.0 ± 0 (3)
C_{max} (ng/ml)	23 ± 11 (6)	65 ± 31 (3)	26 ± 8 (3)
AUC_{last} (min*ng/ml)	236 ± 108 (6)	193 ± 85 (2)	243 ± 77 (3)
V_{ssobs} (mL/m^2)	12971 ± 7600 (3)	7377 (1)	12379 ± 8698 (2)
CL_{obs} (mL/min/m^2)	2665 ± 1063 (3)	162 (1)	3822 ± 1798 (2)

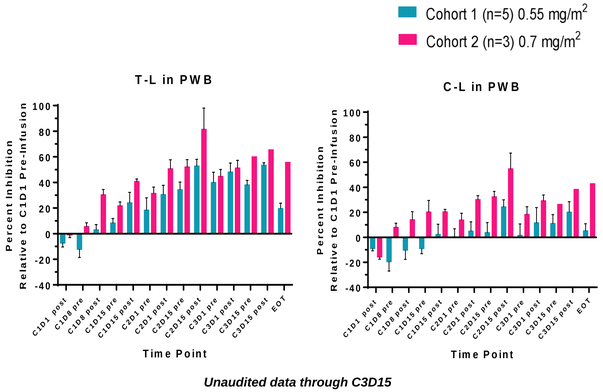
MRZ results in complete and persistent inhibition of CT-L proteasome activity



Unaudited data through C3D15

Data not yet available for Cohort 3

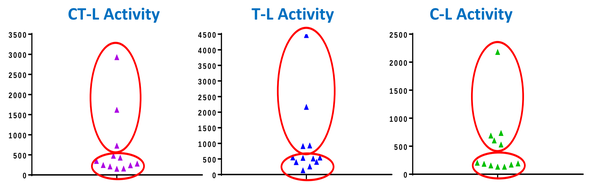
MRZ inhibits compensatory hyperactivation of T-L and C-L proteasome activities



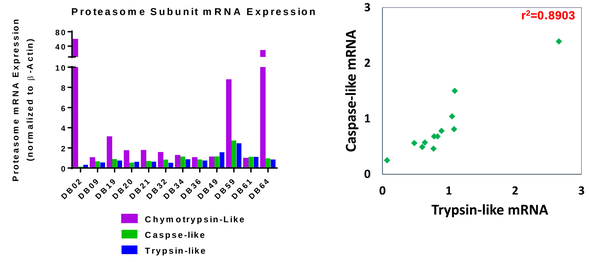
Unaudited data through C3D15

- T-L and C-L inhibition more significant in Cohort 2 suggesting possible dose dependent inhibition of T-L and C-L activities

Proteasome activity is elevated in a subset of glioma patient samples



- Two subpopulations of proteasome enzymatic activity exist in archival glioma tumor bank samples; high and low proteasome activities were identified in high grade glioma (HGG) samples (circled in red)



- Proteasome catalytic subunit mRNA expression was analyzed in the same archival HGG tumor bank samples and was also shown to be variably expressed and elevated in a subset of samples. No correlation was observed between samples with high enzymatic activity and high mRNA expression
- A linear correlation was observed between T-L and C-L mRNA expression

Summary & Conclusions

- In this study we demonstrate that MRZ + BEV is well tolerated up to 0.8 mg/m^2 MRZ in G4 malignant glioma patients
- MRZ + BEV demonstrated 42% (5/12) PR rate, with durable responses in some patients
- MRZ-108 study is currently being expanded at 0.8 mg/m^2 MRZ to further evaluate safety and efficacy
- MRZ has a short $T_{1/2}$ and large V_d
- Significant inhibition of all three proteasome subunits was observed
- Compensatory hyperactivation of T-L and C-L was observed, followed by subsequent inhibition
- More effective inhibition of T-L and C-L subunits was observed with a higher MRZ dose, suggesting PD activity in PWB may be utilized to determine maximal pharmacological proteasome inhibition
- Variable and elevated proteasome activity was detected in HGG tumor bank samples suggesting that there may be potential for variable response to proteasome inhibition in glioma
- No correlation between proteasome enzymatic activity and mRNA expression was observed
- Current preclinical studies are evaluating whether there is a correlation between MRZ sensitivity and proteasome catalytic subunit mRNA levels