Evaluation of novel therapeutics using the Mayo Clinic GBM Patient-Derived Xenograft (PDX) collection

#2495

Danielle M. Burgenske[1], Ann C. Mladek[1], Shulan Tian[2], Mark A. Schroeder[1], Zeng Hu[1], Brett L. Carlson[1], Paul A. Decker[2], Jeanette E. Eckel-Passow[2], Rachael Vaubel[3], Jann N. Sarkaria[1]
[1]Department of Radiation Oncology, Mayo Clinic, 200 First St. SW, Rochester, MN 55905, USA
[2]Department of Biostatistics, Mayo Clinic, 200 First St. SW, Rochester, MN 55905, USA
[3]Laboratory Genetics and Genomics, Department of Laboratory Medicine and Pathology, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA

ABSTRACT

Background

The Mayo Clinic collection of patient-derived xenograft (PDXs) has been developed from the direct implantation of glioblastoma (GBM) samples into immunodeficient mice. Over 105 models have been extensively characterized with regards to histology, invasion, flank and orthotopic growth rates, and molecular profiling.

Results

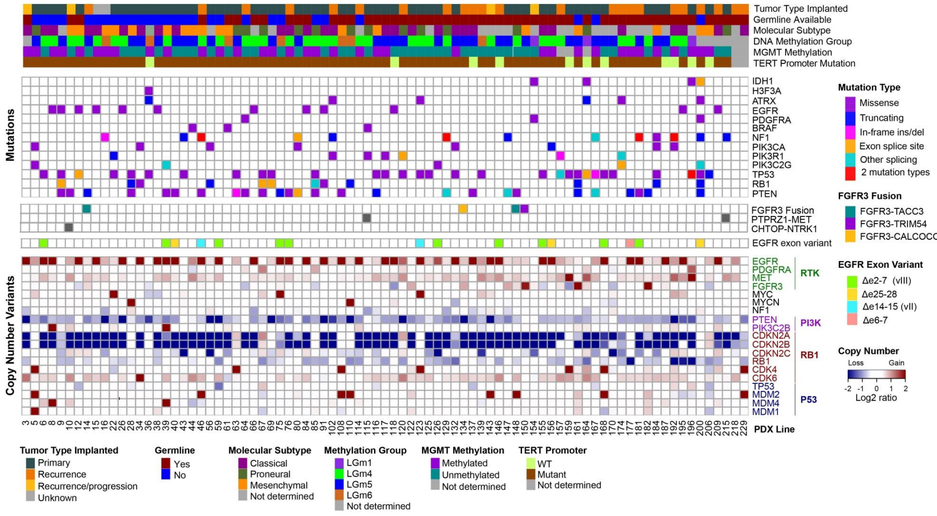
Evaluation of orthotopic tumors demonstrated infiltration of tumor cells into the brain parenchymal in 90% of models with contralateral hemisphere involvement in 64%. Extensive molecular profiling confirmed the PDX collection captures the genetic heterogeneity of GBM, with the majority of typical molecular alterations seen at a frequency similar to the TCGA including gain of chromosome 7 and loss of chromosome 10. *TERT* promoter mutations (86%) and homozygous deletion of *CDKN2A* (70%) were the most frequent. Additional alterations in the p53 pathway included *TP53* mutations (36%) and *MDM2/4* amplification (10%/2%). *IDH* mutations were found in three models while *MGMT* promoter methylation was observed in 45% of PDXs. The available molecular sequencing results are viewable on cBioPortal.

These genetically diverse models are extremely useful for biomarker discovery and efficacy evaluations. Using an innovative 1x1x1 PDX preclinical trial design[2,3], we are establishing a workflow to evaluate control and drug treatment in an individual animal across PDX lines in the flank. As our first use of this strategy, a small molecule MDM2 inhibitor was evaluated in 17 PDX lines with variable *MDM2* and *TP53* statuses. Tumors harboring *MDM2* amplification without *TP53* mutation (n=5) showed profound response, with 4 PDXs showing a complete response that lasted >150 days. Response in *TP53* wild-type tumors lacking *MDM2* amplification was variable, with a 1.9 to 4.8 fold longer time to endpoint (mean 3; median 2.7). A more traditionally powered intracranial efficacy study performed with one *MDM2* amplified (GBM108) and two non-amplified (GBM14, GBM10) PDX lines confirmed these findings of reduced and more variable response to therapy in *MDM2* non-amplified *TP53* wild-type tumors.

Future Directions

Future studies will aim to examine novel biomarkers indicative of therapeutic response to better understand molecular features associated with MDM2 inhibitor efficacy.

ORTHOTOPIC PDX CHARACTERIZATION



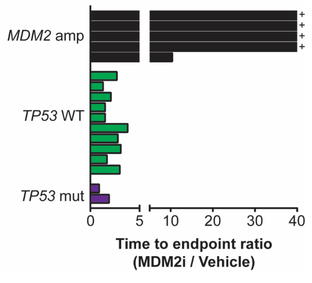
Mutations and CNVs from WES (n=83 PDX models) are shown for core glioma genetic drivers[1]. When available (n=55), patient germline variants were subtracted. Molecular gene expression subtype was determined from RNAseq, DNA methylation group was determined from genome-wide methylation profiling according to TCGA pan-glioma classification. *MGMT* promoter methylation was assessed by quantitative methylation-specific PCR performed at Mayo Clinic (Rochester, MN). *TERT* promoter mutations (C228T and C250T) were detected by Sanger sequencing.

OVERALL STUDY DESIGN

Site	n/grp	Treatment	Dose	Schedule
Flank	1	Vehicle	0 mg/kg	QD PO Weekly x 4
		MDM2i	10 mg/kg	
Intracranial	10	Vehicle	0 mg/kg	QD PO until moribund
		MDM2i	10 mg/kg	

Above. A subcutaneous tumor was transplanted from a colony mouse, either directly into the subcutaneous flank or intracranially after short-term explant culturing, into experimental mice.

1x1x1 FLANK RESULTS



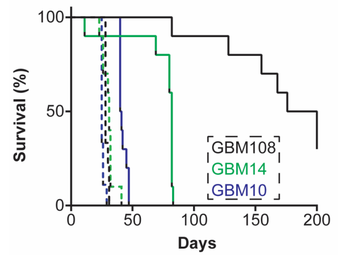
Above right. Athymic nude mice bearing subcutaneous flank tumors were treated with vehicle or MDM2i as indicated once tumors reached approximately 250 mm^3. Animals were followed until endpoint which was defined as a tripling in tumor volume from dosing start. + indicates specific PDX model never reached this endpoint. Tumor volumes were captured three times per week.

1x1x1 FLANK RESULTS

PDX	*TP53*	*MDM2*	Survival Ratio
8	WT	Non-amp	3.0
10			1.7
14			3.1
39			2.8
40			4.1
76			1.5
84			1.5
174			1.3
242			2.7
46		Amp	*CR
108			*CR
143			*CR
148			10.4
280			*CR
228	Mutant		2.4
12		Non-amp	2.5
120			0.9

Responses in gray were verified in intracranial studies (data below). *CR = complete response, Non-amp = non-amplified, Amp = amplified. Survival ratio = (MDM2i survival / vehicle survival).

INTRACRANIAL RESULTS



Athymic nude mice bearing intracranial tumors were treated as indicated with vehicle (dashed) or MDM2i (solid) and followed for survival.

CONCLUSIONS

- Our PDX models recapitulate genetic heterogeneity and invasive nature of GBM.
- A 1x1x1 preclinical trial design[2,3] whereby one mouse was treated to ascertain therapeutic benefit of a MDM2 inhibitor successfully predicted the sensitivity observed in a more traditionally powered intracranial study across a small subset of PDX models.
- *TP53* WT, *MDM2* amplified GBM PDX models derived the best overall survival benefit from MDM2 inhibition.

POTENTIAL COLLABORATIONS

- With over 20 years of experience, our group has extensive expertise in development of clinically relevant study designs focused on examining efficacy, tolerability, and pharmacokinetic/pharmacodynamic assessments. Our diverse collection of clinically relevant GBM PDX models provides a highly sought-after resource which has been utilized by the pharmaceutical community with approximately 60 working relationships to date. Through these collaborations, we aim to expand the use of our highly characterized GBM PDX panel for biomarker discovery using similar strategies.
- Our models have also been utilized in 40+ NIH funded grants and featured in over 134 peer-reviewed published manuscripts.
- 6100+ samples distributed since 2016 across 280+ MTAs.

REFERENCES

1. Vaubel RA et al. Genomic and Phenotypic Characterization of a Broad Panel of Patient-Derived Xenografts Reflects the Diversity of Glioblastoma. Clin Cancer Res. 2020 Mar 1;26(5):1094-1104. PMID: 31852831.
2. Gao H et al. High-throughput screening using patient-derived tumor xenografts to predict clinical trial drug response. Nat Med. 2015 Nov;21(11): 1318-1325. PMID: 26479923.
3. Townsend EC et al. The Public Repository of Xenografts Enables Discovery and Randomized Phsae II-like Trials in Mice. Cancer Cell. 2016 Apr11;29(4): 574-586. PMID: 27070704.