ABSTRACT

Background

The Mayo Clinic collection of patient-derived xenograft (PDX) models has been developed from the direct implantation of glioblastoma (GBM) samples into immunodeficient mice. Over 100 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 parenchyma in 90% of models with contratransfer 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. TEPT promoter mutations (86%) and homozygous deletion of CDKN2A (76%) were the most frequent. Additional alterations in the P53 pathway included TP53 mutations (38%) and MDM4 amplification (10%). CDH1 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 preclinical trial design, we are establishing a workflow to evaluate control and drug treatments 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=3) showed profound response, with 4 PDXs showing a complete response that lasted >60 days. Response to 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=43 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. MDM2 promoter methylation was assessed by quantitative methylation-specific PCR performed at Mayo Clinic (Rochester, MN). TEPT promoter mutations (C228T and C250T) were detected by Sanger sequencing.

OVERALL STUDY DESIGN

1x1x1 FLANK RESULTS

1x1 FLANK RESULTS

Site n/group 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

1x1 FLANK RESULTS

A 1x1 preclinical trial design whereby one mouse was treated as a non-amputated 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.

REFERENCES


CONCLUSIONS

• Our PDX models recapitulate genetic heterogeneity and invasive nature of GBM.

• A 1x1 preclinical trial design whereby one mouse was treated as a non-amputated 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.

• 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.

• 600+ samples distributed since 2016 across 280+ MTAs.

POTENTIAL COLLABORATIONS

1 FLANK RESULTS

Responses in gray were verified in intracranial studies (data below). CR = complete response, Non-amp = non-amplification, 39 = amplified. Survival ratio = (MDM2 survival / vehicle survival).

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

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