Defining critical features for successful preclinical use of glioblastoma patient-derived xenograft (PDX) models for therapeutic assessment and clinical trial development

6897

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ABSTRACT

Mayo Clinic has developed 111 GBM PDXs from newly diagnosed (72 PDX) and recurrent (39 PDX) patients. This large collection of PDXs provides a broad representation of genetic heterogeneity seen in patients. GBM PDXs that perform well in both *in vitro* and *in vivo* settings can be extensively utilized in the preclinical setting for downstream analysis. Based on 20 years of experience, we have defined the attributes that best enable preclinical use of our GBM PDX models. Among them are short-term *in vitro* culturing performance, large scale genomic evaluation data, benchmarked responses to standards of care, and median time to moribund for untreated orthotopic tumors.

PDXs with prolonged survival timelines delay study readouts and, in some situations, confound efficacy results due to age-related animal decline. Setting median survival thresholds as part of the upfront experimental design allows for more timely study readouts that are unaffected by these confounding variables. Our preferred cutoff for the Mayo GBM PDX collection is 70 days median survival (n=64). Using this 64 PDX line panel, regimens expected to double survival would produce results within 4-5 months. This timeframe is well within the range of robust health for athymic nude mice. This 64-line collection features both newly diagnosed (nGBM; n=42) and recurrent (rGBM; n=22) tumors. MGMT promoter methylation status was determined by qMS-PCR (25 methylated, 37 unmethylated, 2 indeterminate). Available WES (n=62) and RNAseq (n=42) data, along with our tissue microarray (n=42), are critical resources for biomarker-based evaluations aimed at defining patient populations that are most likely to benefit from a given therapeutic. From these data, the molecular subtypes available include 26 classical, 14 proneural, and 3 mesenchymal. Twenty-seven of these 64 PDX models have also been successfully cultured from fresh as well as cryopreserved cell stocks to further expand their experimental value. Correlative clinical data including diagnosis and treatments are also available (n=61).

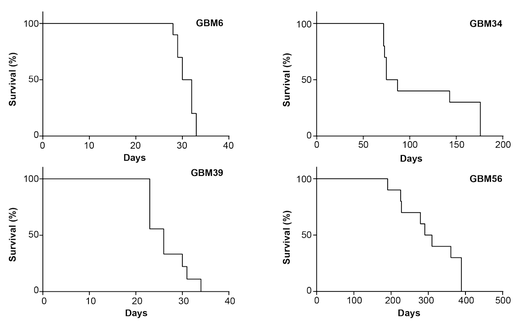
Current standards of care (SOC) for GBM include radiation, temozolomide, and bevacizumab. Defining sensitivity to these therapies is an important first step for evaluating the integration of novel therapeutics with these standards. Since the creation of our GBM PDX collection, efficacy of these therapies has been evaluated as follows: RT 26 PDXs, TMZ 20 PDXs, and Avastin 23 PDXs.

The Mayo Clinic GBM PDX collection provides an important platform for preclinical evaluation of novel therapeutics. Through careful selection of PDX lines with favorable growth characteristics and known genetic features, researchers can select the most relevant models for their study. This approach will enable more meaningful preclinical work in the hopes of providing more tangible clinical benefits for GBM patients.

PDX CHARACTERISTICS

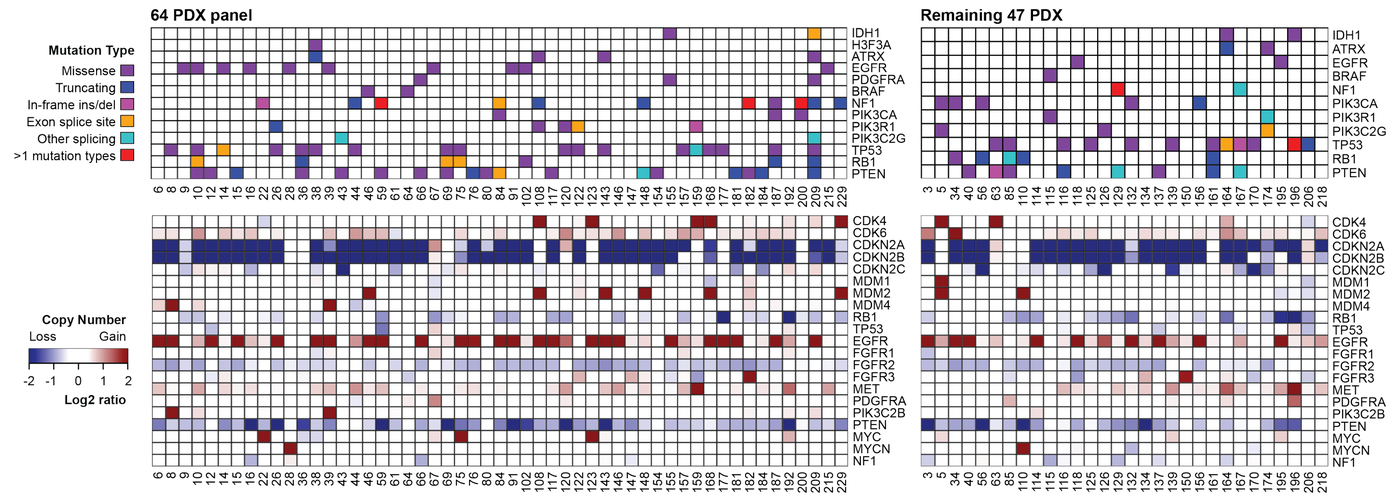
64 PDX panel	N (%)
Diagnosis	
Primary	42 (66%)
Recurrent	22 (34%)
MGMT status	
Methylated	25 (39%)
Unmethylated	37 (58%)
Indeterminate	2 (3%)
Subtyping	
Classical	26 (41%)
Proneural	14 (22%)
Mesenchymal	3 (4%)
Unknown	21 (33%)
Known SOC (PDX) responses	
RT	26 (41%)
TMZ	20 (31%)
Avastin	23 (36%)
Good culture performance	
Fresh cells	27 (42%)
Cryopreserved cells	27 (42%)
Not determined	36 (56%)
Available large-scale data	
WES	62 (97%)
RNAseq	42 (66%)

Remaining 47 PDX	N (%)
Diagnosis	
Primary	30 (64%)
Recurrent	17 (36%)
MGMT status	
Methylated	22 (47%)
Unmethylated	23 (49%)
Indeterminate/Unknown	2 (43%)
Subtyping	
Classical	10 (21%)
Proneural	12 (26%)
Mesenchymal	0
Unknown	24 (51%)
Known SOC (PDX) responses	
RT	12 (26%)
TMZ	3 (6%)
Avastin	10 (21%)
Good culture performance	
Fresh cells	8 (17%)
Cryopreserved cells	10 (21%)
Not determined	34 (72%)
Available large-scale data	
WES	42 (89%)
RNAseq	26 (55%)



Representative survival plots of favorable (left) and suboptimal (right) PDX models.

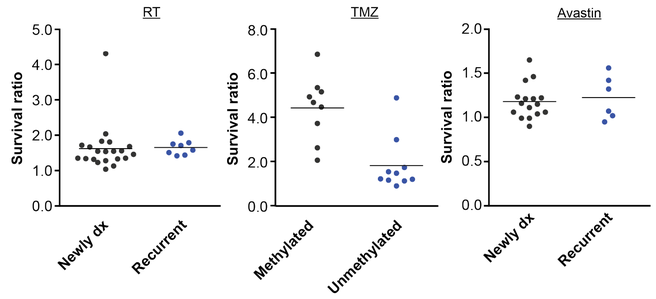
MAYO CLINIC GBM PDX NATIONAL RESOURCE



Mutations and copy number variations from WES are shown for core glioma genetic drivers. Adapted from Vaubel RA et al. Clin Can Res. PMID 31852831.

SOC RESPONSES

Mice bearing intracranial PDX tumors (n=9-10/group) were treated with 18-20 Gy RT (left), 50-66 mg/kg TMZ for days 1-5 every 28 days for up to three cycles (middle), or 5 mg/kg Avastin until moribund (right).



Median survival ratios were calculated from 57 (RT), 50 (TMZ), and 25 (Avastin) total experiments. Survival benefit is shown as ratios and defined as the ratio of median survival for treated mice versus the median survival for control mice for each treatment within a PDX line. If more than 1 experiment was performed, the mean was calculated for each treatment for a given GBM line.

OUR OTHER WORK

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Aberrant ATM signaling and homology-directed DNA repair as a vulnerability of p53-mutant GBM to AZD1390-mediated radiosensitization.

Heterogenous delivery across the blood-brain barrier limits the efficacy of an EGFR-targeting antibody drug conjugate in glioblastoma.

FUNDING

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