The utility of pre-clinical trials in glioblastoma patient-derived xenograft (PDXs) models for informing clinical trial development of therapeutic strategies

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ABSTRACT

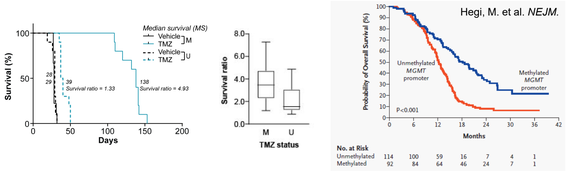
BACKGROUND
Large PDX collections provide broad representation of tumor genetics and are commonly used to evaluate the clinical potential of novel therapeutic strategies. In many solid malignancies, profound benefit in PDX preclinical studies has foreshadowed eventual FDA approval of clinically impactful therapeutics. With a lack of corresponding progress in glioblastoma (GBM), the value of PDX testing has been questioned. Mayo Clinic has developed 111 GBM PDXs from newly diagnosed (72 PDX) and recurrent (39 PDX) patients, and over the past 23 years, we have used this collection for extensive in vivo preclinical testing of 145 drugs in both orthotopic and heterotopic settings. As part of this work, the impact of standard of care therapy with temozolomide (TMZ) and bevacizumab was evaluated in orthotopic models using clinically relevant dosing regimens.

METHODS
For each animal study, the ratio of median survival for treated vs. control animals were used to define a 'survival ratio' as a normalized metric of benefit. TMZ efficacy was evaluated in 26 newly diagnosed GBM PDXs, with equal representation of MGMT methylated and unmethylated tumors.

RESULTS
As expected, MGMT methylated PDXs were much more sensitive to TMZ as compared to unmethylated PDXs (median survival ratio 4.47 vs 1.48, respectively), and similar to clinical experience, 2 MGMT unmethylated PDXs were markedly sensitive to TMZ. In a more limited study, dose-dense vs. standard TMZ dosing was compared in 7 PDXs (4 MGMT methylated, 3 MGMT unmethylated). In a pooled analysis of all lines, both standard (HR=0.09; 95% CI: 0.06–0.14) and dose-dense TMZ therapy (HR=0.09; 95% CI: 0.06–0.14) were superior to vehicle controls (p<0.001). Similar to the clinical results in the Phase III randomized RTOG 0525 trial, survival with the dose-dense TMZ was no different than standard dosing (p=0.88, HR=0.98; 95% CI: 0.72-1.32). In an analysis of bevacizumab across 32 PDXs, mice were dosed once a week until moribund, and a minimum overall median survival benefit of 20% was used to define 'responders'. Thirteen PDXs met this criterion, although the overall survival ratio among this subset was limited (range 1.21-1.65). Only 2 models had a 50% or greater survival benefit. Stratification by disease state (24 newly diagnosed vs 8 recurrent) showed equivalent performance (median survival benefit 1.13 for both). These results are consistent with the limited survival benefit observed with bevacizumab and the RTOG 0825 clinical trial.

CONCLUSION
In summary, the results from these relatively inexpensive PDX studies demonstrate the potential of pre-clinical PDX trials to evaluate the extent of benefit and fraction of responsive PDXs to a novel therapeutic. If analyzed across an 'adequate' number of PDXs, these results potentially can be used to identify predictive biomarkers or to compare various treatment regimens prior to clinical testing.

TMZ RESPONSE BY MGMT STATUS[1,2]



Methylated

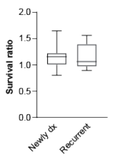
PDX	N	SR	PDX	N	SR
GBM5	3	2.42	GBM63	1	2.68
GBM8	4	3.73	GBM84	2	5.34
GBM12	10	2.63	GBM85	1	2.95
GBM15	1	4.68	GBM116	1	5.11
GBM16	1	6.85	GBM117	1	4.47
GBM22	2	5.16	**34 total experiments**		
GBM39	3	4.93			
GBM59	4	2.07			

Unmethylated

PDX	N	SR	PDX	N	SR
GBM6	2	1.14	GBM75	1	4.88
GBM26	1	1.21	GBM108	1	1.17
GBM28	4	1.48	GBM110	1	3.76
GBM34	1	4.13	GBM115	1	1.24
GBM38	3	3.00	GBM122	1	1.55
GBM43	6	1.74	**25 total experiments**		
GBM44	2	1.23			
GBM61	1	0.91			

Upper left. Mice bearing intracranial PDX tumors (n=9-10/group) were treated with vehicle or 50-66 mg/kg TMZ for days 1-5 every 28 days for up to three cycles and left on study until a moribund state was reached. 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. *Upper right.* Patient survival benefit stratified by MGMT status[2]. *Bottom.* Tables reporting all PDX data by individual PDX lines[1]. N = number of experiments, SR = survival ratio.

BEVACIZUMAB RESPONSE

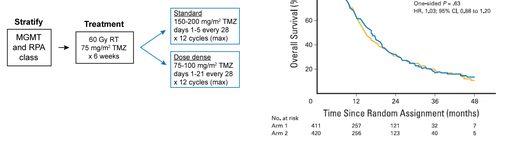


PDX	N	SR	Dx	PDX	N	SR	Dx	PDX	N	SR	Dx
GBM5	1	1.24	N	GBM61	1	1.06	N	GBM116	1	1.17	N
GBM6	2	1.04	N	GBM63	1	1.06	N	GBM117	2	0.99	N
GBM8	2	1.22	N	GBM64	1	0.95	R	GBM120	1	1.32	R
GBM10	6	1.56	R	GBM75	1	1.23	N	GBM122	1	0.99	N
GBM12	1	1.65	N	GBM76	1	1.02	R	GBM134	1	0.89	R
GBM15	1	1.11	N	GBM80	1	1.06	N	GBM150	1	0.97	N
GBM28	2	1.15	N	GBM84	1	1.21	N	**46 total experiments**			
GBM34	1	1.24	N	GBM85	1	0.91	N				
GBM39	3	1.21	N	GBM102	1	1.07	R				
GBM43	1	1.42	N	GBM108	2	1.16	N				
GBM44	1	0.9	N	GBM110	1	1.21	N				
GBM46	1	1.42	R	GBM114	1	1.05	R				
GBM59	3	1.46	N	GBM115	1	0.8	N				

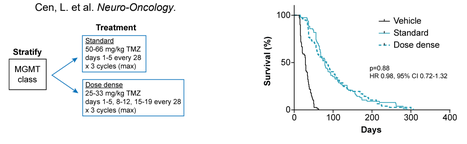
Highlighted models indicate responders (green >20% benefit, purple >50% benefit). N = number of experiments, SR = survival ratio, N = newly diagnosed GBM, R = recurrent GBM.

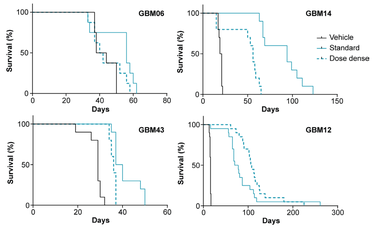
OPTIMAL ADJUVANT TMZ SCHEDULE[3,4]

Patient Gilbert, M. et al. *JCO.*



PDX Cen, L. et al. *Neuro-Oncology.*

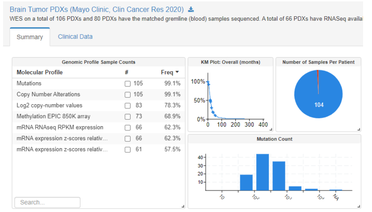




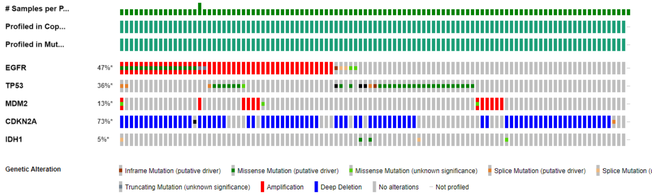
		Vehicle		Std			Dose dense			
PDX	MGMT	MS	N	MS	N	P-value	MS	N	P-value	Std vs DD
GBM6	U	41	8	56	8	0.02	41	8	0.44	0.09
GBM8	M	40	10	156	9	<0.001	176	9	0.003	0.1
GBM12	M	16	20	74	20	<0.001	107	20	<0.001	0.03
GBM14	U	20	10	94	10	<0.001	56	10	0.002	<0.001
GBM39	M	34	9	240	10	<0.001	200	10	<0.001	0.96
GBM43	U	29	10	38	10	<0.001	36	10	<0.001	0.0036
GBM59	M	42	11	79	10	<0.001	78	10	<0.001	0.98

Top. Adapted RTOG-0525 patient trial schematic and collective survival data from Gilbert et al. Treatments under evaluation are shown in blue boxes. *Middle and bottom.* PDX trial schematic highlights treatments under evaluation in blue boxes. Kaplan Meier plots from pooled and individual PDX lines are shown. Table reports all experimental data (7 PDX lines, 8 total experiments). Methylated PDX lines are shown in gray. U = Unmethylated, M = Methylated, MS = median survival (days), N = number of animals per group, Std = Standard TMZ dosing, DD = Dose dense TMZ.

MAYO CLINIC GBM PDX NATIONAL RESOURCE



- 100+ GBM models
  - Additional 49 brain metastasis models
- 150+ therapeutics evaluated
  - Standards of care
  - Targeted strategies
- 20+ years of experience in developing clinically relevant study plans
  - Efficacy
  - Tolerability
  - PKPD
- Since our R24 (NS092940) funding in 2016, 6500+ samples distributed and over 60 working relationships with industry



Platform	N
Whole exome sequencing	83
RNA sequencing	68
Methylation profiling	76
MGMT promoter methylation	103
TERT promoter sequencing	88

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CONCLUSIONS

- PDXs are clinically relevant preclinical models that can predict extent of benefit and fraction of responsive models to a given therapeutic.
  - Much more cost effective strategy
  - Limits the pursuit of agents that will not confer meaningful benefit to patients

REFERENCES

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2. Hegi, M et al. *New England Journal of Med* (2005) PMID 15758010.
3. Gilbert, M. et al. *Journal of Clinical Oncology* (2013) PMID 24101040.
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