Clinical application of a functional 3D *ex vivo* test to predict therapeutic response in patients with HGG: A progression free survival analysis

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Background

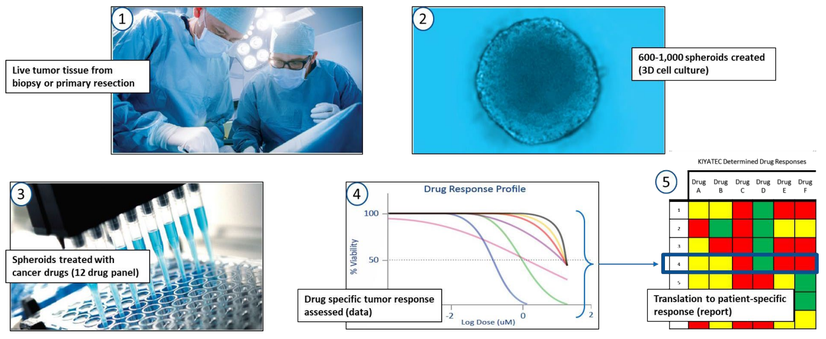
High grade gliomas (HGG) including glioblastoma (GBM) are among the most aggressive brain cancers, with patients exhibiting highly variable treatment responses in both newly diagnosed (ND) and recurrent disease. Temozolomide (TMZ) + radiation therapy is the guideline directed standard of care (SOC) in the ND setting[1], having remained relatively unchanged for > 15 years, despite variable patient responses.

MGMT promoter methylation testing is recommended for high grade gliomas[2]. Patients with *MGMT* promoter methylation have shown association with longer survival and benefit from TMZ treatment[3]. Methods to assess *MGMT* methylation vary between institutions, while most clinical trials utilize PCR-based assays to assess promoter status.

KIYATEC's 3D Predict™ Glioma test utilizes live tissue taken from a biopsy/resection to assess response of an individual patient's tumor tissue to commonly prescribed therapeutics in HGG. Analytical and clinical validation of 3D Predict Glioma has been previously published[4]. Drug concentration ranges and optimal drug exposure times were evaluated and optimized using both cell lines and primary patient specimens. In a cohort of ND HGG patients, TMZ test-predicted response as determined by the assay was associated with improved Overall Survival (OS) compared to patients with test-predicted non-response to TMZ (p=0.0376).

Here we present data in an expanded cohort of ND GBM patients using Progression Free Survival (PFS) as a surrogate endpoint. PFS by *MGMT* promoter methylation status is also reported.

3D Predict Platform



3D Predict Glioma starts with fresh tissue acquired as part of standard of care diagnostics. *Fresh, live* tissue (1) is digested and reformed into 600 – 1,000 individual 3D spheroids (2) and exposed to TMZ and up to 11 other compounds commonly used in HGG treatment (3). Therapeutic response assessment is evaluated using KIYATEC's proprietary algorithms (4), with patient specific results delivered to physicians within 7-10 business days (5).

Test repeatability has been previously demonstrated along with an 85% accuracy rate of predicting response to TMZ in SOC management of HGG patients. Similar test accuracy was also observed in ovarian cancer, showing broader applicability of the platform[5].

Patient Population

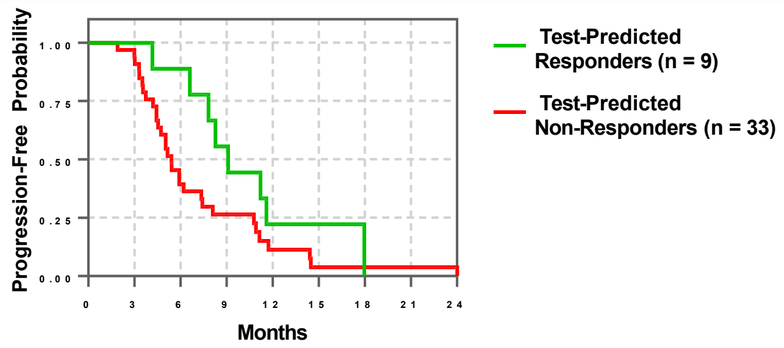
Patients with HGG were enrolled into 3D PREDICT (NCT03561207), a prospective observational registry. 56 ND patients having ≥ 6 months follow up post-surgery and ≥ 6 months follow up data, OR < 6 months follow-up but experiencing progression/death post-tissue collection were identified as of December 31, 2021.

Patient demographics are shown with the majority of patients having GBM, wild-type (WT) *IDH*, and an unmethylated *MGMT* promoter. PFS analysis is presented for the ND GBM, WT *IDH* cohort only (N=42).

	N=56	Percentage
Histology		
GBM	49	87.5%
AA	6	10.7%
Other*	1	1.7%
IDH Status		
Wild-Type	47	83.9%
Mutated	6	10.7%
Unknown	3	5.3%
MGMT Methylation Status†		
Methylated	19	33.9%
Unmethylated	31	55.4%
Unknown	6	10.7%

* Gliosarcoma; †Methylation data provided by site

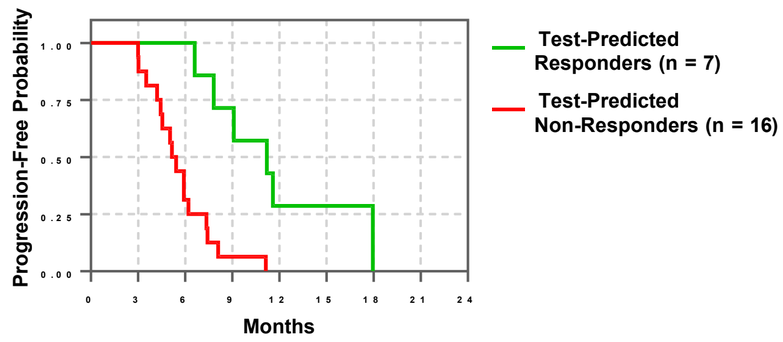
PFS—Test Predicted Responders vs. Non-Responders



	n, total	Test Responders PFS, months	Test Non-Responders PFS, months	p-value (Wilcoxon)
PFS (median)	42	9.1 (n=9)	5.4 (n=33)	**0.039**

PFS Analysis of ND GBM, WT *IDH* Cohort. Test predicted responders had a relative PFS advantage of 3.7 months compared to test predicted non-responders. Methylation status was known in 90.4% (38/42) of the patient population with both methylated and unmethylated patients being represented in both test predicted responder and non-responder categories.

PFS—**Unmethylated** *MGMT* Cohort



	n, total	Test Responder PFS, months	Test Non-Responder PFS, months	p-value (Wilcoxon)
PFS (median)	23	11.2 (n=7)	5.3 (n=16)	**0.0018**

PFS Analysis of ND GBM, WT *IDH* Patients with Unmethylated *MGMT* Promoter. In 23 patients with unmethylated *MGMT* promoter, test predicted responders had a relative PFS advantage of 5.9 months compared to test predicted non-responders.

Limitations

- Limitations of the current study include:
  - Small sample size
  - Observational registry compared to a randomized, blinded, controlled study
  - PFS as a surrogate endpoint for OS
  - PFS was locally assigned by site and not centrally verified
  - *MGMT* methylation status determined via varying diagnostic methods

Conclusions

The data presented here suggests that 3D Predict Glioma testing of patient specific tumor tissue in ND GBM could be helpful in the following clinical scenarios:

- TMZ Non-responders:
  - Identification of patients who may be better suited for clinical trials evaluating novel therapeutics
  - Rationale for early therapeutic switching from TMZ to another compound (or therapeutic combination) that might provide greater clinical outcomes
  - Upfront treatment with TMZ combination therapy
- *MGMT* Unmethylated Patients:
- Prediction of TMZ response to stratify patients to 1) receive SOC therapy or 2) identify patients for clinical trial participation Functional response testing has the potential to inform effective therapy selection in ND GBM, thus advancing functional precision oncology.

References

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