A Multi-Targeted Approach to Evaluate Therapeutic Selection and Efficacy in Preclinical GBM Models


ABSTRACT (NUMBER EXTH–61)
Glioblastoma (GBM) is a devastating primary brain cancer with approximately 10,000 new US diagnoses annually. The current standard of care (SOC) for GBM includes surgical resection followed by radiation therapy (RT) and temozolomide (TMZ); however, there is near universal recurrence and development of resistance after treatment. Relapse in disease is tightly linked with dynamic changes in gene expression during tumor evolution, highlighting the need for more practical preclinical GBM models. Here, we report developing a pair of patient-derived xenograft (PDx) models from surgical resections obtained from initial GBM incidence in a patient (Barney® Cancer Model CRT00433) and subsequent recurrence following treatment (Barney® Cataract Model CRT00435) to study disease progression and novel treatment strategies. Recent studies have suggested the utilization of combination therapy approaches for GBM patients to address TMZ resistance. To this end, Certis has developed a personalized, AI-based approach to predict and test combination therapies in preclinical cancer models. Accuracy of the predicted sensitivities to treatment was evaluated in vivo with both subcutaneous (SC) and orthotopic (OT) mouse models. Luciferase-tagged CRT00433 and CRT00435 spheroid cell lines were transduced with freely luciferase and implanted intracranially by stereotactic surgery for OT monitoring. Optical biomimicness imaging (BMI) and mouse-scale MRI from Aspect Imaging were used to assess therapeutic response of AI-predicted combination therapies and SOC treatment.

METHODS
For in vitro assays, PDx cell lines were plated in 384-well plates (1,000 cells/well) and compounds were added as single agents or in combination. Plates were read at D4 or D7 with CalFluor-Orn (CTG). Synergy analysis was determined using SynergyFinder®. For subcutaneous PDx studies, 3-10® cells were implanted into the right rear flank of female NOG mice. For OT PDx studies, CRT00433 and CRT00435 cell lines were transplanted with freely luciferase and 3.5-6.0 cells were implanted intracranially (X:1.5, Y:0.5, Z:2.03mm from Bregma) into female NOG mice. To monitor tumor growth, SC tumors were measured via caliper every weekly, and OT tumors were imaged using biomimicness weekly with the维克 Newton 7.0 FT300. Therapeutics were formulated and administered per manufacturer’s instructions or based on peer-reviewed, published literature. CertisTM-pretrained cancer models are a set of proprietary machine learning models trained on experimental high-throughput monotherapy and combination experiments, encompassing over 4,500 investigational and FDA-approved drugs tested against 110 major indications. Normalized transcripts per million (TPM) values from a set of predictive biomarker signatures for CRT00433 were used as input into a pre-trained CertisAI (brain) machine learning model to obtain monotherapy and combination therapy predictions. Drugs were additionally screened for predicted blood-brain barrier (BBB) permeability using a custom BBB prediction model trained on a curated diverse molecular database of over 7,800 small molecules.

RESULTS

Figure 1. In vitro and in vivo assessment of SOC and synthetic compounds in a selected pair of GBM models: CRT00432 and CRT00433. A. In vitro IC50 response in TMZ (CTG). B-C. In vivo dose response of Certis and Venturis in CRT00432 (B) and CRT00433 (C). D. Single and combination pharmacodynamic results of Venturis and certis. E. Sensitivity analysis using the CertisAI platform. F. In vitro sensitivities for combination therapy.

CONCLUSIONS
These results demonstrate a novel, combinatorial platform with which to more efficiently identify therapeutic candidates and assess efficacy in GBM. Combining expression profiling, predictive biomarker analysis, machine learning, and functional in vitro and in vivo testing, represents a promising new approach in overcoming this deadly disease’s overall ability to adapt to an ever-changing molecular and genomic landscape that leads to therapy resistance.

CITATIONS

Figure 2. In vitro assessment of synthetic compounds in a patient-matched, native to SOC treated, recurrent model of GBM. A. ZIP synergy analysis of Certis and Venturis in CRT00432 (A rebreathing necessary secondary selectivity of this model). B. Synergy analysis with combinational Venturis and Certis in the nonrebreathing model (CRT00433) for the assessment of synergistic effects observed in the native-patient derived model shown in Figure 2A.