GE-19. GENOMICS GUIDED THERAPEUTIC APPROACH FOR THE TREATMENT OF GLIOBLASTOMA MULTIFORME (GBM) USING NEXT GENERATION SEQUENCING (NGS) TECHNOLOGIES

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BACKGROUND: The genomic heterogeneity of glioblastoma likely underlies the low response rates (8-24%) for targeted agents among unselected populations. We tested whether NGS would be useful in identifying therapeutically-actionable genetic alterations; we sought to test if this translated into improved tumor control in a patient-derived GBM model. METHODS: Tumor specimens from each patient (n = 11) that were used for analyte extraction contained between 70-80% viable tumor cellularity. Genome sequence coverage was more than 30X for both tumor and germline genomes; tumor RNA sequencing included over 100 million reads. NGS of paired tumor and germline DNA enabled detection of single nucleotide variations (SNVs), indels, translocations, intra-chromosomal rearrangements, and copy number alterations. A custom drug-matching workflow utilizing publicly available databases and curated literature on reported drug effects, pharmacokinetics, and blood-brain barrier (BBB) penetration was used to map individual gene alterations in tumors with associated drug-response relationships. One specimen was tested in vitro and in vivo using a matched, patient-derived xenograft model. RESULTS: NGS for the 11 tumor panel found ~30% of cases with EGFR amplification, p16, and/or PTEN deletion. Novel potentially actionable targets included a TRIM54-FGFR3 fusion, STAG2 mutation, KIF11 and KIF15 mutation, and BRAF amplification. One recurrent, MGMT-unmethylated GBM line with a TRIM54-FGFR3 fusion underwent chemovulnerability testing. Cyquant proliferation assays demonstrated sensitivity to the pan-FGFR1-3 inhibitor AZD4547 when compared to a line without FGFR alteration (IC50 3uM vs >10uM). Furthermore, a flank PDX study demonstrated significant activity by AZD4547 when compared with either placebo or temozolomide, resulting in near complete tumor stasis at 82+ days of dosing with AZD4547. CONCLUSIONS: These results support the notion that therapeutic planning for treatment of GBM can be individualized and predicted by genome- and transcription-based analysis on the primary tumor, with the ultimate goal to design individualized GBM therapy based upon genetic markers for treatment sensitivity.