Expression on tumor cells (PD-L1TC) in 33 (35%) cases was associated with tumor recurrence and median follow-up was 6.97 years. PD-L1 expression was higher in men (58%) compared to women (35%). WHO grade I (41%), II (43%), and III (9%) had 42 (47%) cases with positive PD-L1 expression in validation cohorts. We analyzed a total of 93 meningioma cases: 81 (87.4%) were positive for PD-L1 expression, and 9 (9.7%) were positive for NFKB2 protein. These results indicate that PD-L1TC expression is an independent prognostic factor for tumor recurrence after adjusting for extent of resection (EOR), WHO grade, and maximum tumor diameter (p<0.0001). Analysis of RNAseq data of two GEO meningioma studies demonstrated prominent expression of NFKB activation associated with PD-L1 expression. IHC analysis confirmed increased expression of NFKB2 protein in 26 (30%) cases, which correlated with PD-L1TC expression (p<0.02). Furthermore, GSEA on RNAseq data of 88 sporadic meningiomas using Hypoxia gene signature of HUVEC cells showed that hypoxic sporadic meningiomas have significantly elevated PD-L1 expression (p=0.001). Our data strongly suggest that PD-L1TC expression serves as a significant prognostic marker for tumor recurrence. We found that hypoxia and NFKB2 activation are potential underlying mechanisms. These results also provide a rationale for potential adjuvant therapeutic role for PD-L1 inhibitors in meningioma.

Gliaioblastoma is inherently resistant to radiation and drug treatments. This is mediated by the most common forms of cell death that are often actively inhibited. Identifying and exploiting alternative cell death pathways is essential for overcoming or bypassing drug resistance. Ferroptosis, a newly described, morphologically and biochemically distinct cell death mechanism, is characterized by iron-dependent cellular accumulation of reactive oxygen species. The combination of sirolimus, a lysosome disruptor, and lapatinib, a dual tyrosine kinase inhibitor (TKI), synergistically induces death in glioma cancer cells. This cell death mechanism involves ferroptosis: it is blocked by the ferroptosis inhibitor ferrostatin-1 and the iron chelator defereroxamine. In addition, the amount of ROS and lipid peroxidation was increased in glioma cells. Iron transport protein remained unchanged but reactive iron levels increased. One target for kinase inhibitors is protein bisulfate isomerase (PDI). Knockdown of PDI in combination with sirolimus increased cell death that was blocked by ferrostatin-1. Taken together, drug combinations that alter reactive iron and ROS levels might induce ferroptosis and overcome drug resistance in glioma cells.

Glioblastoma is the most common adult malignant glioma, with poor prognosis and adverse neurological sequelae. Physical activity improves outcomes in patients with other cancers, but has not been evaluated in GBM. This prospective, single-arm intervention trial examines feasibility and preliminary efficacy of exercise on PFS, cognition and QOL in newly diagnosed GBM patients. Method: Participants are English-speaking GBM patients scheduled for concurrent chemoradiation at PMH, 18-65 years old, ECOG ≤ 2. The 3-month home-based exercise program includes aerobic and resistance training, tailored to prior fitness level, current physical status, and individual interests. Assessments of physical and neuropsychological functions, mood, fatigue, sleep, and QOL, occur within 2 weeks of starting chemoradiation, and approximately 3, 6, 12, and 18 months later, or until tumor progression. Feasibility will be assessed by accrual, retention, and adherence rates. Outcomes include PFS (RANO criteria), change in cognition (reliable change index method), physical activity and sleep (actigraphy, self-report questionnaires). Time-to-event outcomes will be estimated (Kaplan-Meier), and mixed modelling will explore individual and disease variables that contribute to outcomes. Results: During the first five months of recruitment, 13 of 19 eligible patients consented. Nine completed the exercise program. One patient died after the intervention and none of the others progressed. No exercise-related serious adverse events occurred. Preliminary results will be presented at the meeting. Discussion: Exercise appears feasible for GBM patients. Effects on survival, performance status, cognition, sleep, mood, and QOL are ongoing. Results may guide physical activity recommendations in GBM and generate avenues for translational research.