Background: TTFields induce anti-tumor immunity via simultaneous activation of type-1 interferon (T1IFN) pathways of the STING and AIM2 inflammasomes and immunogenic cell death. Thus, TTFields-treated GBM cells may provide a complete in situ vaccination platform and synergize with immune checkpoint inhibitors to prolong survival in GBM patients.

Methods: We enrolled 26 newly diagnosed GBM patients in a pilot phase 2 study combining TTFields, pembrolizumab and maintenance temozolomide (TMZ). To distinguish immune effects of TTFields from those of pembrolizumab, TTFields was started at cycle 1 of TMZ while pembrolizumab (200 mg IV every 3 weeks) at cycle 2 of TMZ. Primary endpoints were progression-free survival (PFS) versus case-matched controls treated with TTFields plus TMZ only in the EF-14 study. Secondary endpoints included overall survival (OS), toxicity, signature and mechanism of response by multiomics analyses of PBMCs and tumors.

Results: The median age was 60.5 years. Fourteen (54%) had biopsy only or partial resection. Nineteen (73%) had unmethylated MGMT and 3 (11.5%) had an IDH mutation. Median PFS was 12.0 months versus 5.8 months in a case-matched control cohort of 26 patients (HR = 0.377; 95% CI: 0.217–0.653; P = 0.0026). Median OS was 24.8 months versus 14.6 months in controls (HR = 0.522; 95% CI: 0.301–0.905; P = 0.047). Importantly, residual tumor size positively correlated with the objective response and survival. Six of 15 (40%) patients with measurable disease achieved partial to complete response. The most common serious adverse events were thromboses, seizures, and metabolic disturbances in 4 (15%), 3 (11.5%), and 2 (7.7%) patients, respectively. Molecular analyses prior to the addition of pembrolizumab confirmed robust T cell activation by TTFields via the T1IFN trajectory, as evidenced by a high correlation between TCRab clonal expansion and T1IFN responsive plasmacytoid dendritic cells (Spearman coefficient = -0.8; P = 0.014) and defined a T cell-based gene signature of TTFields effects. Subsequently, the ability of the top expanded TCRab clones to adapt to the everchanging tumor microenvironment through successful clonal switching by 2 months after the addition of pembrolizumab strongly predicted response to the triple combination in a Cox HR fit model for OS with a concordance rate of 0.876, P = 0.031.

Conclusions: The triple combination was well tolerated and demonstrated promising efficacy in ndGBM. Bulky residual disease was associated with better outcomes, consistent with the in-situ immunizing properties of TTFields, which synergize with pembrolizumab. Additional molecular analysis will be updated.

REFERENCES:

Ethics Approval: The study was approved by USC’s and UF’s IRBs, approval numbers USC#HS-23–00020 and UF#IRB201702270, respectively.

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