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Combined immunotherapy improves outcome for replication repair deficient (RRD) high-grade glioma failing anti-PD1 monotherapy: A report from the International RRD Consortium

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Abstract

Immune-checkpoint inhibition (ICI) is effective for replication-repair deficient, high-grade gliomas (RRD-HGG). Clinical/biologic impact of immune-directed approaches after failing ICI-monotherapy are unknown. We performed an international study on 75 patients treated with anti-PD1; 20 are progression-free (median follow-up: 3.7-years). After 2nd-progression/recurrence (n=55), continuing ICI-based salvage prolonged survival to 11.6-months (n=38; p<0.001), particularly for those with extreme mutation burden (p=0.03). Delayed, sustained responses were observed, associated with changes in mutational spectra and immune-microenvironment. Response to re-irradiation was explained by an absence of deleterious post-radiation indel signatures (ID8). Increased CTLA4-expression over time, and subsequent CTLA4-inhibition resulted in response/stable disease in 75%. RAS-MAPK-pathway inhibition led to reinvigoration of peripheral immune and radiological responses. Local (flare) and systemic immune adverse events were frequent (biallelic mismatch-repair deficiency > Lynch syndrome). We provide mechanistic rationale for the sustained benefit in RRD-HGG from immune-directed/ synergistic salvage therapies. Future approaches need to be tailored to patient and tumor biology.