Combination Immunotherapies

**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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**Background** Response to immune checkpoint inhibition (ICI) is encouraging for patients with progressive, DNA replication-repair deficient, high-grade glioma (RRD-HGG).1 However, the clinical outcomes and biological mechanisms for subsequent immune-directed salvage approaches after progression on anti-PD1 monotherapy remain unknown.

**Methods** The International RRD Consortium performed a registry study of patients managed using central molecular, genomic, radiological review and treatment recommendations between 2015–2021. Treatment after progression on anti-PD1 monotherapy included re-irradiation where feasible, and continuation of anti-PD1 with either anti-CTLA4 (ipilimumab), or a MEK-inhibitor (trametinib). Outcomes included radiological response (iRANO), toxicity, second progression-free (PFS2) and overall survival (OS2). Companion biomarkers were analyzed centrally.

**Results** Among 75 patients with RRD-HGG receiving PD-1 blockade, 20 remain progression-free at a median follow-up of 44.6-months. For 55 patients with 2nd-relapse/progressive tumors, continuation of ICI (n=38) resulted in median OS2 of 11.6-months (51% alive) versus 1.2-months when ICI was discontinued (n=17; no survivors, p<0.001). The combination of ipilimumab/nivolumab (n=24) resulted in response/stable disease in 75%, with median OS2 of 12.1-months. The addition of MEK-inhibitor led to response in 3/5 patients with prolonged survival. Re-irradiation improved OS2, especially for RRD-HGG with lower mutation burden (p=0.002), and those receiving ipilimumab (median OS2=33-months).

Several important insights were gained from the biomarker-analyses. Survival was impacted by extreme mutation burden, but not genomic microsatellite instability. Delayed, sustained responses were observed in ultra-hypermutant RRD-HGG, associated with changes in mutational spectra and immune microenvironment. RRD-HGG showed elevated CTLA4 expression over time, explaining the responses to ipilimumab. The remarkable sensitivity to re-irradiation was explained by an absence of deleterious post-radiation indel signatures (ID8; COSMIC),1 suggesting selective immune-editing. Early radiological immune ‘flare’ was observed in 33% of patients on combined immunotherapy and radiation who did not demonstrate flare on monotherapy, suggesting immune-synergism. Enrichment of RAS-MAPK mutations in genomically unstable RRD-HGG explained responses to MEK-inhibitors. Additionally, reinvigoration of peripheral immune response was observed. In all cohorts, immune adverse events were a major cause of treatment interruption, with higher prevalence in patients with bi-allelic mismatch-repair deficiency vis-à-vis Lynch syndrome.

**Conclusions** We provide mechanistic rationale for the sustained benefit in RRD-HGG from immune-directed/synergistic salvage. Our data suggest that the continuous mutagenesis renders hypermutant RRD-HGG susceptible to ICI beyond initial progression. The combination with re-irradiation and additional immune/targeted agents can maximize survival in these children and young adults. Future research should focus on biology-driven rational immunotherapy combinations that also result in lower toxicity to maximize patient benefit.

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**REFERENCES**


**Ethics Approval** The study was approved by the SickKids Research Ethics Board (REB number: 1000048813)

**Consent** Consent was obtained from study participants and/or their parents, as applicable.

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