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# Re-irradiation plus pembrolizumab: Phase II study for recurrent glioblastoma patients

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## Abstract

**Purpose:** Radiation therapy may enhance anti-tumor immune responses by several mechanisms including induction of immunogenic cell death. We performed a phase 2 study of pembrolizumab with re-irradiation in patients with recurrent glioblastoma.

**Methods:** Sixty recurrent glioblastoma patients received pembrolizumab with re-irradiation alone (cohort A, bevacizumab-naïve; n=30) or with bevacizumab continuation (cohort B, n=30). Dual primary endpoints including overall response rate (ORR) and overall survival at either 12 (OS-12; cohort A) or six months (OS-6; cohort B) were assessed per cohort relative to historical benchmarks. Paired paraffin-embedded formalin-fixed tumor samples were assessed for immunologic biomarkers by immunohistochemistry using digital quantification and Co-Detection-by-InDEXing (CODEX).

**Results:** Study therapy was well tolerated with most toxicities being grade ≤ 3. For cohort B, the primary endpoint of OS-6 was achieved (57%), however survival was not improved for cohort A patients. The ORR was 3.3% and 6.7% for cohorts A and B, respectively. CODEX analysis of paired tumor samples from 5 patients revealed an increase of activated T cells in the tumor microenvironment after study therapy.

**Conclusions:** Compared to historical controls, re-irradiation plus pembrolizumab appeared to improve survival among bevacizumab-refractory patients but not among bevacizumab-naïve patients. CODEX revealed evidence of intratumoral infiltration of activated immune effector cells. A randomized, properly controlled trial of PD-1 blockade plus re-irradiation is warranted to further evaluate this regimen for bevacizumab refractory patients, but alternative approaches are needed for bevacizumab-naïve patients.