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# ERK1/2 Phosphorylation Predicts Survival in Recurrent Glioblastoma Following Intracerebral and Adjuvant PD-1/CTLA-4 Immunotherapy: A REMARK-Guided Analysis

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## Abstract

**Purpose:** Evidence suggests that MAPK pathway activation, as measured by ERK1/2 phosphorylation (p-ERK), predicts overall survival (OS) in recurrent glioblastoma patients receiving anti-PD-1 therapy. We aimed to validate these findings in independent cohorts.

**Experimental design:** In a 24-patient clinical trial on recurrent glioblastoma and high-grade gliomas, we examined the link between p-ERK levels and overall survival (OS). Patients received intravenous nivolumab, followed by maximal safe resection and an intracerebral injection of either ipilimumab alone or combined with nivolumab. Bi-weekly adjuvant nivolumab was then administered up to five times (NCT03233152). Using REMARK criteria, we conducted independent analyses for p-ERK quantification and statistical evaluations. Additional comparative analysis included prior cohorts, totaling 65 patients. Cox proportional hazards models and meta-analysis were employed to assess p-ERK as a predictive biomarker post-immunotherapy.

**Results:** Lower median p-ERK+ cell density was observed compared to prior studies, likely due to tissue handling variances. Nonetheless, high p-ERK was associated with prolonged OS, particularly in IDH wild-type glioblastomas (P=0.036). Median OS for high and low p-ERK patients were 55.6 and 30 weeks, respectively. Multivariable analysis reinforced p-ERK's significance in survival prediction (P=0.011). Meta-analysis across three cohorts (n=65) supported the survival benefit of elevated tumor p-ERK levels (P=0.0424).

**Conclusions:** This study strengthens the role of p-ERK as a predictive biomarker for OS in glioblastoma patients on immune checkpoint blockade. Future research should focus on further validation in prospective trials and the standardization of preanalytical variables influencing p-ERK quantification.