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Dynamic signature for the effectiveness of anti-PD-1 therapy combined with vascular normalization therapy in recurrent glioblastoma: A randomized phase 2 trial

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Abstract

Background: This study evaluated tislelizumab combined with low-dose bevacizumab in recurrent glioblastoma (rGBM), assessing efficacy, safety, and mechanisms of immune escape.

Methods: This randomized phase 2 trial divided patients into treatment arms with distinct strategies. Longitudinal tumor in situ fluid (TISF) samples were collected for molecular analysis to monitor genome evolution. Immunohistochemical markers in paired primary and recurrent tumor specimens were analyzed to assess therapy-induced immune resistance.

Results: A total of 109 patients were included, with 59 in the control group and 50 in the experimental group. No grade 4 adverse events or treatment discontinuations occurred in the experimental group. The experimental group demonstrated a median overall survival of 13.3 months, compared to 6.6 months in the control group. The objective response rate and disease control rate were 32.6% and 79.1%, respectively. Post-treatment TISF analysis revealed a 68.4% reduction in detectable genomic alterations. Immunophenotypic analysis of paired tumor samples showed increased infiltration of $CD163^{+}$ macrophages and elevated GDF-15 expression in recurrent tumors.

Conclusion: This study shows that combining tislelizumab and low-dose bevacizumab improves survival in rGBM patients with good safety and tolerability. Dynamic changes in TISF-based molecular markers reflect genomic evolution and predict prognosis. Increased $CD163^{+}$ cell infiltration in recurrent tumors may activate M2 macrophages, promoting tumor growth and immune evasion. Elevated GDF-15 levels may further suppress antitumor immunity, facilitating immune escape.

Keywords: CD163; GDF-15; PD-1 inhibitor; TISF-ctDNA; recurrent glioblastoma; treatment response; vivo genetic evolution.