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A new paradigm for immunotherapy in glioblastoma

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A detailed case report shows that neoadjuvant combination immunotherapy can activate antitumor immunity and drive clinical benefit in newly diagnosed glioblastoma, revealing avenues for further research that could shift the treatment landscape to improve survival.

Glioblastoma remains one of the most difficult cancers to treat, with limited progress in improving survival outcomes having occurred over the past few decades. The current standard of care includes maximal safe surgical resection followed by radiotherapy and temozolomide, which offers patients a median overall survival of 18 months. Immune-checkpoint inhibitors (ICIs) have revolutionized outcomes in cancers such as melanoma and non-small-cell lung cancer; however, glioblastoma has not yet benefited from these therapies. Resistance to immunotherapy may be driven by the brain's unique biological barriers as well as by tumor-specific characteristics (such as low mutational burden) — resulting in low immunogenicity and a highly immunosuppressive microenvironment owing to limited antigen presentation and infiltration of suppressive immune cells. As a result, phase 3 trials using adjuvant ICIs in glioblastoma have largely failed to demonstrate a survival benefit[1]. In this issue of *Nature Medicine*, Long et al.[2] provide insights into how ICI might be harnessed to benefit patients with glioblastoma, when used in a neoadjuvant setting and in combination with other immunomodulation such as personalized peptide vaccination[2].

Long et al.[2] describe a single patient with newly diagnosed, treatment-naive, biopsy-confirmed glioblastoma who received a single dose of neoadjuvant triplet ICI therapy (nivolumab, anti-PD-1; ipilimumab, anti-CTLA-4; and relatlimab, anti-LAG3) followed by surgical resection 12 days later. The patient subsequently received adjuvant ICIs and a novel, personalized peptide vaccine along with adjuvant radiation. After 17 months of follow-up, the patient remained free from disease progression or recurrence. Analysis of the resected tumor revealed a robust expansion of tumor-infiltrating lymphocytes (TILs) and a high level of T cell receptor diversity. Importantly, TILs showed evidence of nivolumab binding, confirming the penetrance of the ICI to the tumor site.

The treatment regimen used in this single case has not been studied in clinical trials, but the results are broadly in alignment with findings of studies that investigated ICI as a single agent in the neoadjuvant setting in glioblastoma[3,4]. A randomized prospective study of adjuvant ($n = 19$) versus neoadjuvant ($n = 16$) pembrolizumab (PD-1 blockade) in patients with recurrent glioblastoma found that neoadjuvant delivery

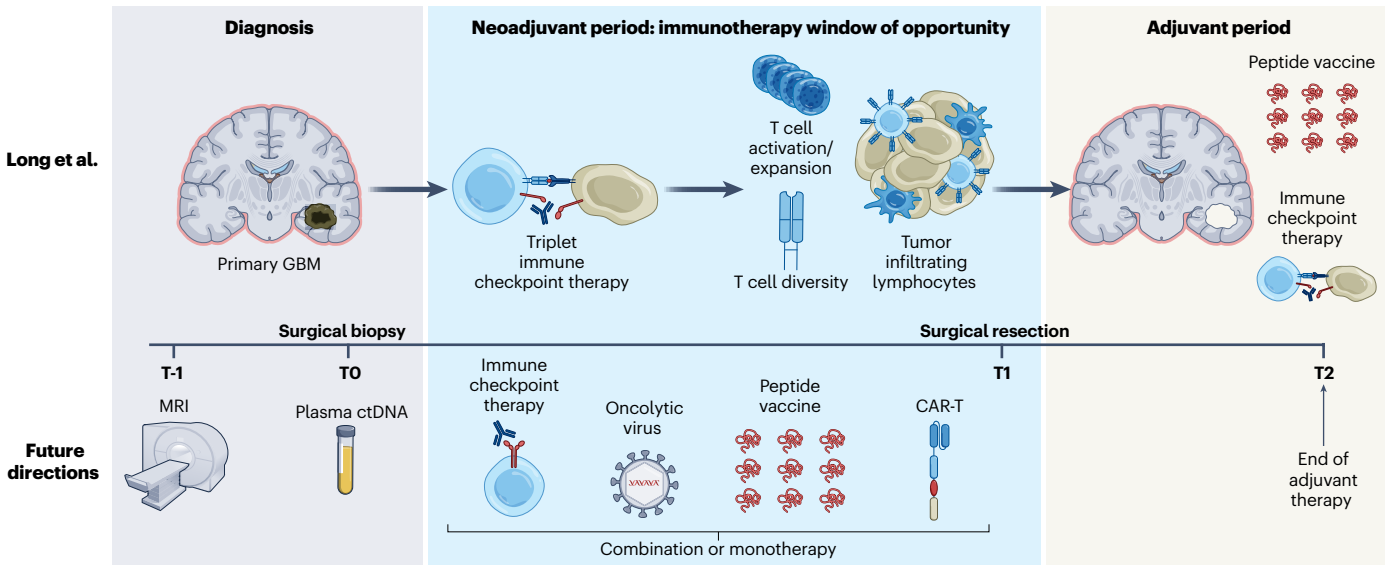

Fig. 1 | Neoadjuvant immunotherapy window of opportunity in glioblastoma. Schematic representation of a neoadjuvant immunotherapy approach for brain tumors. The timeline highlights key treatment milestones, emphasizing the role of immunotherapy in modifying the tumor microenvironment before surgical intervention. The top panel outlines the treatment timeline from Long et al.[2], including diagnosis, surgical biopsy, neoadjuvant therapy and adjuvant therapy. The bottom panel parallels these stages while highlighting future areas of exploration, including non-invasive diagnostics (such as circulating tumor DNA (ctDNA)) and additional neoadjuvant therapies (such as oncolytic virotherapy).

improved overall survival (13.7 months versus 7.5 months) as well as progression-free survival (3.3 month versus 2.4 months)[3]. More compelling is a phase 2 clinical trial of neoadjuvant nivolumab in which 27 patients with recurrent glioblastoma showed no benefit, whereas 2 of 3 patients with newly diagnosed glioblastoma who received the same therapy had ongoing disease-free survival at 33 and 28 months, respectively[4]. The case described by Long et al.[2] extends the concept of neoadjuvant ICI further, exploring whether triplet ICI therapy, targeting multiple immune checkpoints simultaneously in combination with a personalized peptide vaccine, can generate a robust and durable antitumor immune response.

The study prompts several critical questions about how to advance the care of patients with glioblastoma in novel directions. First, the role of tumor mutational burden (TMB), although suggested to be a predictor of response to ICI in other settings, remains an unknown in glioblastoma. Previous case reports have highlighted the benefit of ICIs in glioblastomas with a high TMB or mismatch-repair deficiency; however, most cases of glioblastoma do not fit this profile[5]. Contrary to the current understanding, in the report from Long et al.[2], the patient had a low TMB (2 mutations per megabase) yet still experienced substantial immune activation and antitumor responses. This challenges the assumption that low TMB precludes effective immune responses and opens new avenues for research to explore other potential predictors, such as the immune signatures of the untreated tumor microenvironment, the drug delivery method, or the combination of multiple ICIs. Corticosteroids, particularly dexamethasone, are used to manage peritumoral edema but are potent immunosuppressants and have been shown to induce an immunosuppressive environment in glioma[6]. In this case, avoiding corticosteroids may have contributed to the promising antitumor immune response observed; this highlights the potential benefit of withholding corticosteroids to enhance the efficacy of ICI when clinically feasible, a strategy worth further exploration. Similarly, temozolomide and radiation can also have immunosuppressive effects, and therefore treatment with ICI prior to chemotherapy and radiation may enhance the antitumor immune response.

A key challenge inherent to neoadjuvant therapies in CNS tumors is the reliance on surgical tissue biopsies for patient selection. Although the patient in this case underwent a pre-treatment open biopsy to confirm eligibility, this approach carries risks of infection and surgical complications. As neoadjuvant therapies gain traction in newly diagnosed or primary glioblastomas, there is a need to develop non-invasive biomarkers, such as liquid biopsies or imaging-based markers, to streamline patient selection and reduce the need for multiple surgical interventions. Advances in the detection of circulating tumor DNA, functional imaging and immune profiling could have a pivotal role in optimizing patient selection and response monitoring in future trials[7,8].

The report of single cases with exceptional responses, such as that described by Long et al.[2], certainly has value to inform the field about how to shift treatment paradigms and stimulate research into alternative, novel approaches to managing glioblastoma. Clinical trials investigating neoadjuvant treatment in primary glioblastoma are at a critical turning point, and there are opportunities to explore strategies to prime the tumor microenvironment and develop antitumor immunity with various methods including ICI, oncolytic viral therapy, peptide vaccines, chimeric antigen receptor T (CAR-T) cell therapy and combinatorial approaches, some of which have shown promising results in patients with recurrent glioblastoma[9–12]. The phase 0 'window-of-opportunity' design provides a structured approach to identifying the optimal immunotherapy regimens for larger clinical trials. This involves administering an immunotherapy regimen prior to surgical resection and assessing molecular readouts, including immune response, to refine treatment selection. If the neoadjuvant phase proves pivotal for establishing robust antitumor responses, these findings should prompt a shift toward a neoadjuvant phase 0 clinical trials, focusing particularly on combinatorial oncolytic virotherapy and immune-checkpoint blockade as neoadjuvant strategies for primary glioblastoma (Fig. 1). Such a transformation in management paradigms requires a multidisciplinary approach with input from neurosurgeons, medical oncologists, neuropathologists, neuroradiologists and radiation oncologists. Overall, the work from Long et al.[2] represents a considerable step forward and could drive further research to ultimately reshape the therapeutic landscape for glioblastoma.

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Competing interests

The authors declare no competing interests.