The current plan has successfully collected comprehensive data across all required dimensions; a Generate-Summary step will synthesize these results into a cohesive forward-looking research analysis addressing the user's query.

Based on a comprehensive analysis of the provided tool use results, here is a forward-looking summary of the glioblastoma multiforme (GBM) immunotherapy landscape in the United States (US) and European Union (EU).

**Executive Summary**

As of late 2025, the glioblastoma multiforme (GBM) immunotherapy landscape is characterized by intense innovation and a rapidly evolving pipeline, despite the significant challenge that no immunotherapy has yet secured FDA or EMA approval for this indication [[4](https://www.biospace.com/dnatrix-inc-awarded-fda-orphan-products-development-grant-for-dnx-2401)][[24](https://www.aptitudehealth.com/oncology-news/most-fda-and-ema-oncology-drug-approvals-in-q1-2025-were-new-indications-for-biologics-and-biosimilars/)]. The field is moving decisively away from single-agent checkpoint inhibitors, which have largely failed in late-stage trials, toward sophisticated, multi-modal strategies. Key forward-looking trends include the rise of personalized cell therapies and vaccines, the use of oncolytic viruses as immune-priming agents, the development of multi-antigen targeting constructs to overcome resistance, and novel strategies to breach the blood-brain barrier (BBB) and remodel the immunosuppressive tumor microenvironment (TME).

Financially, the GBM treatment market is projected to grow from $2.48 billion in 2024 to $2.73 billion in 2025, with a 10.5% CAGR forecasted through 2029, creating a significant opportunity for the first successful immunotherapies [[48](https://www.futuremarketinsights.com/reports/glioblastoma-treatment-drugs-market)][[49](https://www.thebusinessresearchcompany.com/report/glioblastoma-multiforme-gbm-treatment-global-market-report)]. Venture capital continues to fund promising mid-to-late-stage assets, signaling sustained investor confidence in the field's potential [[50](https://braintumorinvestmentfund.org/news/diakonos-oncology-closes-20-million-financing-to-accelerate-phase-2-glioblastoma-clinical-development-program-and-expand-use-of-innovative-dendritic-cell-platform-for-studies-in-other-indications/)][[51](https://www.imvax.com/imvax-announces-completion-of-29-million-financing-and-confirms-timing-for-topline-results-of-phase-2b-trial-of-igv-001-in-newly-diagnosed-glioblastoma/)].

**1. Regulatory Status and Market Outlook**

Currently, there are no FDA or EMA-approved immunotherapies specifically for GBM [[4](https://www.biospace.com/dnatrix-inc-awarded-fda-orphan-products-development-grant-for-dnx-2401)]. However, regulatory agencies are providing support through expedited pathways, indicating a willingness to accelerate promising candidates.

* **Regulatory Designations:**
  + **DNX-2401 (tasadenoturev):** This oncolytic adenovirus has received FDA Orphan Drug and Fast Track designations, as well as EMA PRIME designation, positioning it as a leading candidate [[4](https://www.biospace.com/dnatrix-inc-awarded-fda-orphan-products-development-grant-for-dnx-2401)].
  + **MB-108:** This second-generation oncolytic HSV-1 virus was granted FDA Orphan Drug designation in November 2024 [[71](https://www.onclive.com/view/fda-grants-orphan-drug-designation-to-mb-108-for-malignant-glioma)].
  + **LP-184:** A synthetic lethal agent intended for combination with immunotherapies, received FDA Fast Track designation [[54](https://www.onclive.com/view/fda-grants-fast-track-designation-to-lp-184-for-glioblastoma)].
* **Market and Financial Outlook:**
  + **Market Size:** The total GBM treatment market was valued at approximately $2.48 billion in 2024 and is expected to grow, providing substantial headroom for novel, premium-priced immunotherapies [[49](https://www.thebusinessresearchcompany.com/report/glioblastoma-multiforme-gbm-treatment-global-market-report)].
  + **Investment:** The field is primarily driven by venture capital. Recent financing rounds include $20 million for Diakonos Oncology's dendritic cell vaccine (June 2025) and $29 million for Imvax's whole-tumor immunotherapy (July 2024) to fund Phase II trials [[50](https://braintumorinvestmentfund.org/news/diakonos-oncology-closes-20-million-financing-to-accelerate-phase-2-glioblastoma-clinical-development-program-and-expand-use-of-innovative-dendritic-cell-platform-for-studies-in-other-indications/)][[51](https://www.imvax.com/imvax-announces-completion-of-29-million-financing-and-confirms-timing-for-topline-results-of-phase-2b-trial-of-igv-001-in-newly-diagnosed-glioblastoma/)]. This demonstrates that investors are willing to fund de-risked assets with strong mid-stage data.

**2. Comprehensive Competitive Landscape and Pipeline Analysis**

The GBM immunotherapy pipeline is robust, with over 118 active programs in the US and EU across various modalities [[47](https://www.noahai.co/tool/drug-compete/?search_param=%7B%22indication_name%22%3A%20%5B%22Brain%20neoplasm%20malignant%22%2C%20%22Central%20nervous%20system%20neoplasms%20malignant%20NEC%22%5D%2C%20%22drug_modality%22%3A%20%7B%22data%22%3A%20%5B%22Cell-based%20Therapies%22%2C%20%22Vaccine%22%2C%20%22Gene%20Therapy%22%5D%2C%20%22logic%22%3A%20%22or%22%7D%2C%20%22location%22%3A%20%5B%22USA%22%2C%20%22European%20Union%22%2C%20%22Germany%22%2C%20%22France%22%2C%20%22Italy%22%2C%20%22Spain%22%2C%20%22UK%22%5D%2C%20%22top_n%22%3A%201000%7D)]. The US is the dominant player, hosting approximately 75% of these programs [[47](https://www.noahai.co/tool/drug-compete/?search_param=%7B%22indication_name%22%3A%20%5B%22Brain%20neoplasm%20malignant%22%2C%20%22Central%20nervous%20system%20neoplasms%20malignant%20NEC%22%5D%2C%20%22drug_modality%22%3A%20%7B%22data%22%3A%20%5B%22Cell-based%20Therapies%22%2C%20%22Vaccine%22%2C%20%22Gene%20Therapy%22%5D%2C%20%22logic%22%3A%20%22or%22%7D%2C%20%22location%22%3A%20%5B%22USA%22%2C%20%22European%20Union%22%2C%20%22Germany%22%2C%20%22France%22%2C%20%22Italy%22%2C%20%22Spain%22%2C%20%22UK%22%5D%2C%20%22top_n%22%3A%201000%7D)].

**Cell-Based Therapies: The Most Promising Modality**

Cell-based therapies, particularly personalized dendritic cell vaccines and advanced CAR-T constructs, have shown the most encouraging clinical signals.

| Drug/Platform | Company | Phase | Modality | Key Highlights |
| --- | --- | --- | --- | --- |
| **murcidencel (DCVax-L)** | Northwest Biotherapeutics | BLA/NDA | Autologous Dendritic Cell Vaccine | Most advanced immunotherapy for GBM; regulatory submission filed in the US and UK [[47](https://www.noahai.co/tool/drug-compete/?search_param=%7B%22indication_name%22%3A%20%5B%22Brain%20neoplasm%20malignant%22%2C%20%22Central%20nervous%20system%20neoplasms%20malignant%20NEC%22%5D%2C%20%22drug_modality%22%3A%20%7B%22data%22%3A%20%5B%22Cell-based%20Therapies%22%2C%20%22Vaccine%22%2C%20%22Gene%20Therapy%22%5D%2C%20%22logic%22%3A%20%22or%22%7D%2C%20%22location%22%3A%20%5B%22USA%22%2C%20%22European%20Union%22%2C%20%22Germany%22%2C%20%22France%22%2C%20%22Italy%22%2C%20%22Spain%22%2C%20%22UK%22%5D%2C%20%22top_n%22%3A%201000%7D)]. |
| **CARv3-TEAM-E** | Mass General Cancer Center | Phase I | Dual-mechanism CAR-T | Showed rapid, near-complete tumor regressions (up to 61%) within days in recurrent GBM patients [[61](https://www.massgeneral.org/news/press-release/clinical-trial-results-show-dramatic-regression-of-glioblastoma-after-next-generation-car-t-therapy)]. |
| **AV-GBM-1** | AIVITA Biomedical | Phase III | Autologous Dendritic Cell Vaccine | Phase II showed a 50% improvement in Progression-Free Survival (PFS) over standard of care [[17](https://pmc.ncbi.nlm.nih.gov/articles/PMC12310467/)][[46](https://www.noahai.co/tool/clinical-result/?search_param=%7B%22indication_name%22%3A%20%5B%22Malignant%20ascites%22%2C%20%22Brain%20tumor%22%2C%20%22Traumatic%20brain%20injury%22%2C%20%22Central%20nervous%20system%20tumor%22%5D%2C%20%22phase%22%3A%20%5B%22I%22%2C%20%22II%22%2C%20%22III%22%5D%2C%20%22drug_modality%22%3A%20%7B%22data%22%3A%20%5B%22Monoclonal%20Antibodies%22%2C%20%22Bi-specific%20Antibodies%22%2C%20%22Cell-based%20Therapies%22%2C%20%22Vaccine%22%5D%2C%20%22logic%22%3A%20%22or%22%7D%2C%20%22top_n%22%3A%20150%7D)]. |
| **taniraleucel (CYNK-001)** | Celularity | Phase II | Allogeneic NK Cell Therapy | An "off-the-shelf" approach being tested in the US [[47](https://www.noahai.co/tool/drug-compete/?search_param=%7B%22indication_name%22%3A%20%5B%22Brain%20neoplasm%20malignant%22%2C%20%22Central%20nervous%20system%20neoplasms%20malignant%20NEC%22%5D%2C%20%22drug_modality%22%3A%20%7B%22data%22%3A%20%5B%22Cell-based%20Therapies%22%2C%20%22Vaccine%22%2C%20%22Gene%20Therapy%22%5D%2C%20%22logic%22%3A%20%22or%22%7D%2C%20%22location%22%3A%20%5B%22USA%22%2C%20%22European%20Union%22%2C%20%22Germany%22%2C%20%22France%22%2C%20%22Italy%22%2C%20%22Spain%22%2C%20%22UK%22%5D%2C%20%22top_n%22%3A%201000%7D)]. |
| **ERC-1671 (Gliovac)** | Epitopoietic Research | Phase II | Allogeneic DC Vaccine | Uses lysate from allogeneic tumor tissue to stimulate an immune response [[47](https://www.noahai.co/tool/drug-compete/?search_param=%7B%22indication_name%22%3A%20%5B%22Brain%20neoplasm%20malignant%22%2C%20%22Central%20nervous%20system%20neoplasms%20malignant%20NEC%22%5D%2C%20%22drug_modality%22%3A%20%7B%22data%22%3A%20%5B%22Cell-based%20Therapies%22%2C%20%22Vaccine%22%2C%20%22Gene%20Therapy%22%5D%2C%20%22logic%22%3A%20%22or%22%7D%2C%20%22location%22%3A%20%5B%22USA%22%2C%20%22European%20Union%22%2C%20%22Germany%22%2C%20%22France%22%2C%20%22Italy%22%2C%20%22Spain%22%2C%20%22UK%22%5D%2C%20%22top_n%22%3A%201000%7D)]. |

**Cancer Vaccines: A Resurgence Driven by New Platforms**

Vaccine approaches are diverse, ranging from peptide-based to next-generation mRNA and personalized neoantigen platforms.

| Drug/Platform | Company | Phase | Target/Approach | Key Highlights |
| --- | --- | --- | --- | --- |
| **SurVaxM** | MimiVax | Phase IIb | Survivin Peptide Vaccine | The randomized SURVIVE trial passed a futility analysis in May 2025 and continues to enroll [[18](https://www.mimivax.com/survaxm/)][[62](https://www.cancernetwork.com/view/phase-2b-trial-for-cancer-vaccine-in-newly-diagnosed-glioblastoma-will-continue)]. |
| **CVGBM** | CureVac | Phase I | mRNA Vaccine | Induced de-novo CD8+ T-cell responses in 77% of patients in an early study [[16](https://www.curevac.com/en/curevacs-cvgbm-cancer-vaccine-induces-promising-immune-responses-in-phase-1-study-in-glioblastoma-presented-at-the-esmo-2024-congress/)]. |
| **VBI-1901** | VBI Vaccines | Phase II | CMV Antigens | Targets cytomegalovirus antigens expressed on GBM cells [[47](https://www.noahai.co/tool/drug-compete/?search_param=%7B%22indication_name%22%3A%20%5B%22Brain%20neoplasm%20malignant%22%2C%20%22Central%20nervous%20system%20neoplasms%20malignant%20NEC%22%5D%2C%20%22drug_modality%22%3A%20%7B%22data%22%3A%20%5B%22Cell-based%20Therapies%22%2C%20%22Vaccine%22%2C%20%22Gene%20Therapy%22%5D%2C%20%22logic%22%3A%20%22or%22%7D%2C%20%22location%22%3A%20%5B%22USA%22%2C%20%22European%20Union%22%2C%20%22Germany%22%2C%20%22France%22%2C%20%22Italy%22%2C%20%22Spain%22%2C%20%22UK%22%5D%2C%20%22top_n%22%3A%201000%7D)]. |
| **GAPVAC** | BioNTech / Immatics | Phase II | Personalized Neoantigen Vaccine | A highly personalized approach tailored to individual tumor mutations [[47](https://www.noahai.co/tool/drug-compete/?search_param=%7B%22indication_name%22%3A%20%5B%22Brain%20neoplasm%20malignant%22%2C%20%22Central%20nervous%20system%20neoplasms%20malignant%20NEC%22%5D%2C%20%22drug_modality%22%3A%20%7B%22data%22%3A%20%5B%22Cell-based%20Therapies%22%2C%20%22Vaccine%22%2C%20%22Gene%20Therapy%22%5D%2C%20%22logic%22%3A%20%22or%22%7D%2C%20%22location%22%3A%20%5B%22USA%22%2C%20%22European%20Union%22%2C%20%22Germany%22%2C%20%22France%22%2C%20%22Italy%22%2C%20%22Spain%22%2C%20%22UK%22%5D%2C%20%22top_n%22%3A%201000%7D)]. |

**Oncolytic Viruses (OVs) and Gene Therapy: Priming the Immune System**

OVs are increasingly viewed as agents to convert "cold" GBM tumors into "hot," T-cell-inflamed environments, making them ideal for combination with checkpoint inhibitors.

| Drug/Platform | Company | Phase | Mechanism | Key Highlights |
| --- | --- | --- | --- | --- |
| **DNX-2401 + pembrolizumab** | DNAtrix / MSD | Phase II | Oncolytic Adenovirus + PD-1 Inhibitor | Showed a 12-month Overall Survival (OS) of 52.7-56%, tripling historical controls [[4](https://www.biospace.com/dnatrix-inc-awarded-fda-orphan-products-development-grant-for-dnx-2401)][[19](https://www.nature.com/articles/s41591-023-02347-y)]. |
| **vocimagene amiretrorepvec** | Denovo Biopharma | Phase III | Retroviral Vector + Prodrug | A suicide gene therapy approach in late-stage development [[47](https://www.noahai.co/tool/drug-compete/?search_param=%7B%22indication_name%22%3A%20%5B%22Brain%20neoplasm%20malignant%22%2C%20%22Central%20nervous%20system%20neoplasms%20malignant%20NEC%22%5D%2C%20%22drug_modality%22%3A%20%7B%22data%22%3A%20%5B%22Cell-based%20Therapies%22%2C%20%22Vaccine%22%2C%20%22Gene%20Therapy%22%5D%2C%20%22logic%22%3A%20%22or%22%7D%2C%20%22location%22%3A%20%5B%22USA%22%2C%20%22European%20Union%22%2C%20%22Germany%22%2C%20%22France%22%2C%20%22Italy%22%2C%20%22Spain%22%2C%20%22UK%22%5D%2C%20%22top_n%22%3A%201000%7D)]. |
| **lerapolturev (PVS-RIPO)** | Istari Oncology | Phase II | Modified Poliovirus | Directly infused into the tumor to induce a potent inflammatory response [[47](https://www.noahai.co/tool/drug-compete/?search_param=%7B%22indication_name%22%3A%20%5B%22Brain%20neoplasm%20malignant%22%2C%20%22Central%20nervous%20system%20neoplasms%20malignant%20NEC%22%5D%2C%20%22drug_modality%22%3A%20%7B%22data%22%3A%20%5B%22Cell-based%20Therapies%22%2C%20%22Vaccine%22%2C%20%22Gene%20Therapy%22%5D%2C%20%22logic%22%3A%20%22or%22%7D%2C%20%22location%22%3A%20%5B%22USA%22%2C%20%22European%20Union%22%2C%20%22Germany%22%2C%20%22France%22%2C%20%22Italy%22%2C%20%22Spain%22%2C%20%22UK%22%5D%2C%20%22top_n%22%3A%201000%7D)]. |
| **GLIX1** | Hemispherian | IND-Ready | DNA-Repair Targeting OV | IND cleared by the FDA in April 2025, representing a new class of OVs [[20](https://www.targetedonc.com/view/fda-clears-ind-for-glix1-in-glioblastoma-phase-1-study-to-proceed)]. |

**Antibody-Based Therapies: A Shift to Novel Targets**

While first-generation checkpoint inhibitors have failed, the pipeline includes novel antibody constructs.

| Drug/Platform | Company | Phase | Target | Key Highlights |
| --- | --- | --- | --- | --- |
| **Nivolumab (Opdivo)** | Bristol-Myers Squibb | Phase III (Failed) | PD-1 | Multiple Phase III trials (CheckMate 143, 498, 548) failed to improve survival [[5](https://www.cancer.gov/news-events/cancer-currents-blog/2018/immunotherapy-glioblastoma)][[46](https://www.noahai.co/tool/clinical-result/?search_param=%7B%22indication_name%22%3A%20%5B%22Malignant%20ascites%22%2C%20%22Brain%20tumor%22%2C%20%22Traumatic%20brain%20injury%22%2C%20%22Central%20nervous%20system%20tumor%22%5D%2C%20%22phase%22%3A%20%5B%22I%22%2C%20%22II%22%2C%20%22III%22%5D%2C%20%22drug_modality%22%3A%20%7B%22data%22%3A%20%5B%22Monoclonal%20Antibodies%22%2C%20%22Bi-specific%20Antibodies%22%2C%20%22Cell-based%20Therapies%22%2C%20%22Vaccine%22%5D%2C%20%22logic%22%3A%20%22or%22%7D%2C%20%22top_n%22%3A%20150%7D)]. |
| **Ivonescimab** | Akeso / Summit | Phase II | PD-1 / VEGF Bispecific | Combines immune activation with anti-angiogenic effects [[1](https://www.noahai.co/tool/drug-compete/?search_param=%7B%22indication_name%22%3A%20%5B%22Central%20nervous%20system%20neoplasms%20malignant%20NEC%22%2C%20%22Erythema%20multiforme%22%5D%2C%20%22phase%22%3A%20%5B%22Preclinical%22%2C%20%22IND%22%2C%20%22I%22%2C%20%22II%22%2C%20%22III%22%2C%20%22BLA%2FNDA%22%5D%2C%20%22drug_modality%22%3A%20%7B%22data%22%3A%20%5B%22Monoclonal%20Antibodies%22%2C%20%22Bi-specific%20Antibodies%22%5D%2C%20%22logic%22%3A%20%22or%22%7D%2C%20%22location%22%3A%20%5B%22USA%22%2C%20%22European%20Union%22%2C%20%22EU%22%2C%20%22Germany%22%2C%20%22France%22%2C%20%22United%20Kingdom%22%2C%20%22Italy%22%2C%20%22Spain%22%2C%20%22UK%22%5D%2C%20%22top_n%22%3A%201000%7D)]. |
| **Bavituximab** | OncXerna Therapeutics | Phase II | Phosphatidylserine (PS) | Met its primary endpoint with a 12-month OS of 73% in a Phase II study [[46](https://www.noahai.co/tool/clinical-result/?search_param=%7B%22indication_name%22%3A%20%5B%22Malignant%20ascites%22%2C%20%22Brain%20tumor%22%2C%20%22Traumatic%20brain%20injury%22%2C%20%22Central%20nervous%20system%20tumor%22%5D%2C%20%22phase%22%3A%20%5B%22I%22%2C%20%22II%22%2C%20%22III%22%5D%2C%20%22drug_modality%22%3A%20%7B%22data%22%3A%20%5B%22Monoclonal%20Antibodies%22%2C%20%22Bi-specific%20Antibodies%22%2C%20%22Cell-based%20Therapies%22%2C%20%22Vaccine%22%5D%2C%20%22logic%22%3A%20%22or%22%7D%2C%20%22top_n%22%3A%20150%7D)]. |

**3. Clinical Efficacy and Safety Data**

Clinical trial results have clearly stratified immunotherapy modalities, with cell therapies showing the most promise and checkpoint inhibitors showing the least.

**Summary of Clinical Outcomes by Modality**

| Modality | Key Positive Results | Key Negative Results | Safety Profile |
| --- | --- | --- | --- |
| **Cell-Based Therapies** | **DCVax-L (Phase III):** mOS 19.3 vs. 16.5 months (p=0.002) [[46](https://www.noahai.co/tool/clinical-result/?search_param=%7B%22indication_name%22%3A%20%5B%22Malignant%20ascites%22%2C%20%22Brain%20tumor%22%2C%20%22Traumatic%20brain%20injury%22%2C%20%22Central%20nervous%20system%20tumor%22%5D%2C%20%22phase%22%3A%20%5B%22I%22%2C%20%22II%22%2C%20%22III%22%5D%2C%20%22drug_modality%22%3A%20%7B%22data%22%3A%20%5B%22Monoclonal%20Antibodies%22%2C%20%22Bi-specific%20Antibodies%22%2C%20%22Cell-based%20Therapies%22%2C%20%22Vaccine%22%5D%2C%20%22logic%22%3A%20%22or%22%7D%2C%20%22top_n%22%3A%20150%7D)]. **INCIPIENT (Phase I):** Rapid, deep tumor regressions [[61](https://www.massgeneral.org/news/press-release/clinical-trial-results-show-dramatic-regression-of-glioblastoma-after-next-generation-car-t-therapy)]. | **ALECSAT (Phase II):** No improvement in PFS or OS [[46](https://www.noahai.co/tool/clinical-result/?search_param=%7B%22indication_name%22%3A%20%5B%22Malignant%20ascites%22%2C%20%22Brain%20tumor%22%2C%20%22Traumatic%20brain%20injury%22%2C%20%22Central%20nervous%20system%20tumor%22%5D%2C%20%22phase%22%3A%20%5B%22I%22%2C%20%22II%22%2C%20%22III%22%5D%2C%20%22drug_modality%22%3A%20%7B%22data%22%3A%20%5B%22Monoclonal%20Antibodies%22%2C%20%22Bi-specific%20Antibodies%22%2C%20%22Cell-based%20Therapies%22%2C%20%22Vaccine%22%5D%2C%20%22logic%22%3A%20%22or%22%7D%2C%20%22top_n%22%3A%20150%7D)]. | Excellent; very few serious adverse events attributed to therapy. No cytokine release syndrome (CRS) with DCVax-L [[46](https://www.noahai.co/tool/clinical-result/?search_param=%7B%22indication_name%22%3A%20%5B%22Malignant%20ascites%22%2C%20%22Brain%20tumor%22%2C%20%22Traumatic%20brain%20injury%22%2C%20%22Central%20nervous%20system%20tumor%22%5D%2C%20%22phase%22%3A%20%5B%22I%22%2C%20%22II%22%2C%20%22III%22%5D%2C%20%22drug_modality%22%3A%20%7B%22data%22%3A%20%5B%22Monoclonal%20Antibodies%22%2C%20%22Bi-specific%20Antibodies%22%2C%20%22Cell-based%20Therapies%22%2C%20%22Vaccine%22%5D%2C%20%22logic%22%3A%20%22or%22%7D%2C%20%22top_n%22%3A%20150%7D)]. |
| **Cancer Vaccines** | **Gliovac (Phase II):** mOS 19.63 months [[46](https://www.noahai.co/tool/clinical-result/?search_param=%7B%22indication_name%22%3A%20%5B%22Malignant%20ascites%22%2C%20%22Brain%20tumor%22%2C%20%22Traumatic%20brain%20injury%22%2C%20%22Central%20nervous%20system%20tumor%22%5D%2C%20%22phase%22%3A%20%5B%22I%22%2C%20%22II%22%2C%20%22III%22%5D%2C%20%22drug_modality%22%3A%20%7B%22data%22%3A%20%5B%22Monoclonal%20Antibodies%22%2C%20%22Bi-specific%20Antibodies%22%2C%20%22Cell-based%20Therapies%22%2C%20%22Vaccine%22%5D%2C%20%22logic%22%3A%20%22or%22%7D%2C%20%22top_n%22%3A%20150%7D)]. **ITI-1000 (Phase I/II):** 5-year OS rates of 33-36% [[46](https://www.noahai.co/tool/clinical-result/?search_param=%7B%22indication_name%22%3A%20%5B%22Malignant%20ascites%22%2C%20%22Brain%20tumor%22%2C%20%22Traumatic%20brain%20injury%22%2C%20%22Central%20nervous%20system%20tumor%22%5D%2C%20%22phase%22%3A%20%5B%22I%22%2C%20%22II%22%2C%20%22III%22%5D%2C%20%22drug_modality%22%3A%20%7B%22data%22%3A%20%5B%22Monoclonal%20Antibodies%22%2C%20%22Bi-specific%20Antibodies%22%2C%20%22Cell-based%20Therapies%22%2C%20%22Vaccine%22%5D%2C%20%22logic%22%3A%20%22or%22%7D%2C%20%22top_n%22%3A%20150%7D)]. | In the searched materials, most vaccine trials are ongoing or have shown positive signals. | Generally mild, with injection-site reactions and flu-like symptoms being most common [[5](https://www.cancer.gov/news-events/cancer-currents-blog/2018/immunotherapy-glioblastoma)][[46](https://www.noahai.co/tool/clinical-result/?search_param=%7B%22indication_name%22%3A%20%5B%22Malignant%20ascites%22%2C%20%22Brain%20tumor%22%2C%20%22Traumatic%20brain%20injury%22%2C%20%22Central%20nervous%20system%20tumor%22%5D%2C%20%22phase%22%3A%20%5B%22I%22%2C%20%22II%22%2C%20%22III%22%5D%2C%20%22drug_modality%22%3A%20%7B%22data%22%3A%20%5B%22Monoclonal%20Antibodies%22%2C%20%22Bi-specific%20Antibodies%22%2C%20%22Cell-based%20Therapies%22%2C%20%22Vaccine%22%5D%2C%20%22logic%22%3A%20%22or%22%7D%2C%20%22top_n%22%3A%20150%7D)]. |
| **Oncolytic Viruses** | **DNX-2401 + Pembro (Phase II):** 12-month OS of 56%; 3 durable complete responses >3 years [[4](https://www.biospace.com/dnatrix-inc-awarded-fda-orphan-products-development-grant-for-dnx-2401)]. | No major negative trial results found in the searched materials for lead candidates. | Mostly grade 1-2 headaches and fever; manageable safety profile [[4](https://www.biospace.com/dnatrix-inc-awarded-fda-orphan-products-development-grant-for-dnx-2401)]. |
| **Checkpoint Inhibitors** | None in late-stage trials. | **CheckMate 143, 498, 548 (Phase III):** All failed to meet primary survival endpoints [[5](https://www.cancer.gov/news-events/cancer-currents-blog/2018/immunotherapy-glioblastoma)][[46](https://www.noahai.co/tool/clinical-result/?search_param=%7B%22indication_name%22%3A%20%5B%22Malignant%20ascites%22%2C%20%22Brain%20tumor%22%2C%20%22Traumatic%20brain%20injury%22%2C%20%22Central%20nervous%20system%20tumor%22%5D%2C%20%22phase%22%3A%20%5B%22I%22%2C%20%22II%22%2C%20%22III%22%5D%2C%20%22drug_modality%22%3A%20%7B%22data%22%3A%20%5B%22Monoclonal%20Antibodies%22%2C%20%22Bi-specific%20Antibodies%22%2C%20%22Cell-based%20Therapies%22%2C%20%22Vaccine%22%5D%2C%20%22logic%22%3A%20%22or%22%7D%2C%20%22top_n%22%3A%20150%7D)]. | Manageable but includes risk of grade ≥3 immune-related adverse events, often requiring steroids which can blunt efficacy [[5](https://www.cancer.gov/news-events/cancer-currents-blog/2018/immunotherapy-glioblastoma)]. |

**4. Key Challenges and Mechanisms of Resistance**

The failure of many immunotherapies in GBM is attributed to a combination of biological hurdles. Emerging research is focused on understanding and overcoming these barriers.

* **Blood-Brain Barrier (BBB):** Large molecules like antibodies and CAR-T cells show erratic penetration. Current strategies to bypass this include:
  + **Direct Delivery:** Intratumoral, intracavitary, or intraventricular infusion is now standard for cell therapies and OVs [[8](https://www.sciencedirect.com/science/article/pii/S1525001625001789)][[4](https://www.biospace.com/dnatrix-inc-awarded-fda-orphan-products-development-grant-for-dnx-2401)].
  + **Neoadjuvant Dosing:** Administering immunotherapy before surgery to take advantage of a transiently open BBB and study the immune response in resected tissue [[7](https://www.nature.com/articles/s41423-024-01226-x)].
  + **Novel Delivery Systems:** Preclinical work on nanocapsules and stem-cell carriers aims to enable systemic (IV) delivery of OVs across the BBB [[37](https://patents.google.com/patent/US20230265392A1/en)][[64](https://advanced.onlinelibrary.wiley.com/doi/10.1002/adhm.202404965)].
* **Immunosuppressive Tumor Microenvironment (TME):** GBM is an immunologically "cold" tumor, rich in M2 macrophages, regulatory T-cells (Tregs), and myeloid-derived suppressor cells (MDSCs). High steroid use further exacerbates this immunosuppression [[5](https://www.cancer.gov/news-events/cancer-currents-blog/2018/immunotherapy-glioblastoma)].
* **Mechanisms of Resistance:**
  + **Antigen Loss:** Tumors can stop expressing the target antigen to evade therapy. This is well-documented for EGFRvIII, which is lost in ~50% of recurrent tumors, driving resistance to targeted CAR-T cells [[8](https://www.sciencedirect.com/science/article/pii/S1525001625001789)].
  + **Adaptive Resistance:** Tumors upregulate alternative immune checkpoints like TIM-3, LAG-3, and TIGIT following PD-1 blockade [[7](https://www.nature.com/articles/s41423-024-01226-x)].
  + **Wnt/β-catenin Signaling:** The Wnt7b pathway was recently identified as a key driver of resistance to anti-PD-1 therapy. Blockade of this pathway with a porcupine inhibitor (WNT974) restored immune response in preclinical models [[67](https://bioengineer.org/breakthrough-study-highlights-potential-of-combination-therapy-to-combat-treatment-resistance-in-glioblastoma/)].

**5. Forward-Looking Analysis: Emerging Trends (2025-2026)**

The future of GBM immunotherapy lies in multi-faceted, rationally designed approaches that address the core challenges of the disease.

**1. Multi-Antigen Targeting to Preempt Resistance:**  
To combat antigen loss, next-generation therapies are designed to target multiple antigens simultaneously.

* **Bivalent/Trivalent CAR-T:** Constructs targeting EGFR + IL13Rα2 ± HER2 are in development to prevent antigen escape [[9](https://www.nature.com/articles/s41591-024-02893-z)][[32](https://patents.google.com/patent/US20220125847A1/en)].
* **Dual-Mechanism CAR-T:** The CARv3-TEAM-E platform combines a CAR targeting one antigen (EGFRvIII) with a secreted bispecific T-cell engager targeting another (EGFR), effectively broadening the attack [[61](https://www.massgeneral.org/news/press-release/clinical-trial-results-show-dramatic-regression-of-glioblastoma-after-next-generation-car-t-therapy)].

**2. "Heating Up" the Cold TME:**  
Strategies are focused on turning the immunosuppressive TME into an inflamed one that is responsive to immunotherapy.

* **Viral Priming:** Using OVs like DNX-2401 or MB-108 to induce local inflammation, release tumor antigens, and upregulate PD-L1, thereby synergizing with checkpoint inhibitors [[4](https://www.biospace.com/dnatrix-inc-awarded-fda-orphan-products-development-grant-for-dnx-2401)][[13](https://www.mustangbio.com/pipeline/)].
* **Vaccine Adjuvants:** Personalized vaccines are being combined with potent adjuvants (e.g., TLR agonists) to enhance dendritic cell priming and T-cell activation [[35](https://patents.google.com/patent/US20230054318A1/en)].

**3. Advanced Biomarker Integration:**  
Patient stratification is moving beyond MGMT methylation status to more sophisticated, multi-parameter profiling.

* **Immune Profiling:** Trials now routinely incorporate analysis of PD-L1, TMB, LAG-3, and the CD8/Treg ratio to identify potential responders [[6](https://www.sciencedirect.com/science/article/pii/S2405844024007606)].
* **Novel Biomarkers:** CLDN9 has been identified as a negative prognostic marker associated with reduced immune infiltration, offering a new tool for patient selection [[68](https://cancerci.biomedcentral.com/articles/10.1186/s12935-025-03852-5)].
* **Immuno-PET:** Non-invasive imaging tracers are being developed to quantify T-cell engagement in the brain, allowing for real-time monitoring of therapeutic effect [[75](https://medicalxpress.com/news/2024-10-imaging-technique-glioblastoma-patients-benefit.html)].

**4. Next-Generation Engineering and Technology (from Patents):**  
The patent landscape reveals the next wave of innovation.

* **Systemic OV Delivery:** Calidi Biotherapeutics' CAVES platform uses stem cells to shield OVs from the immune system, enabling IV delivery for brain tumors [[37](https://patents.google.com/patent/US20230265392A1/en)].
* **Upgraded CAR-T Designs:** Patents describe "short-spacer" CARs for better synapse formation, "DuoCAR" platforms for flexible multi-antigen targeting, and armored CARs that secrete cytokines to resist exhaustion [[31](https://patents.google.com/patent/US20240025961A1/en)][[33](https://patents.google.com/patent/US12365718B2/en)][[69](https://www.sciencedirect.com/science/article/pii/S0304383525001053)].
* **Targeting Metabolic Checkpoints:** Patents for anti-CD73 and TGF-β blockade show a pivot toward targeting metabolic pathways like the adenosine axis that drive immunosuppression in the TME [[42](https://patents.google.com/patent/US11530273B2/en)][[43](https://patents.google.com/patent/US11685775B2/en)].

**Conclusion**

While the path to an approved immunotherapy for glioblastoma remains arduous, the field is at a critical inflection point. The era of relying on single-agent checkpoint inhibitors is over, replaced by a paradigm of **personalization, combination, and rational design**. The most promising forward-looking strategies involve:

1. **Personalized cell therapies (DCVax-L, AV-GBM-1)** that leverage the patient's own tumor antigens.
2. **Combination therapies using OVs (DNX-2401)** to prime the immune system for a subsequent checkpoint inhibitor attack.
3. **Multi-targeted CAR-T cells (CARv3-TEAM-E)** engineered to overcome antigen escape.

The potential regulatory approval of a first-in-class agent like DCVax-L in the near future could serve as a landmark achievement, validating the entire therapeutic category and energizing a field that is closer than ever to delivering meaningful clinical benefits for patients with this devastating disease.