Glioblastoma Multiforme
Clinical Trial Landscape Analysis

Comprehensive Assessment of ClinicalTrials.gov Data,
Therapeutic Modalities, and Strategic Opportunities

Analysis Date: January 22, 2026

Data Source: ClinicalTrials.gov API v2

Total Trials Analyzed: 1,913 interventional studies

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Generated using K-Dense Web (k-dense.ai)

Graphical Abstract

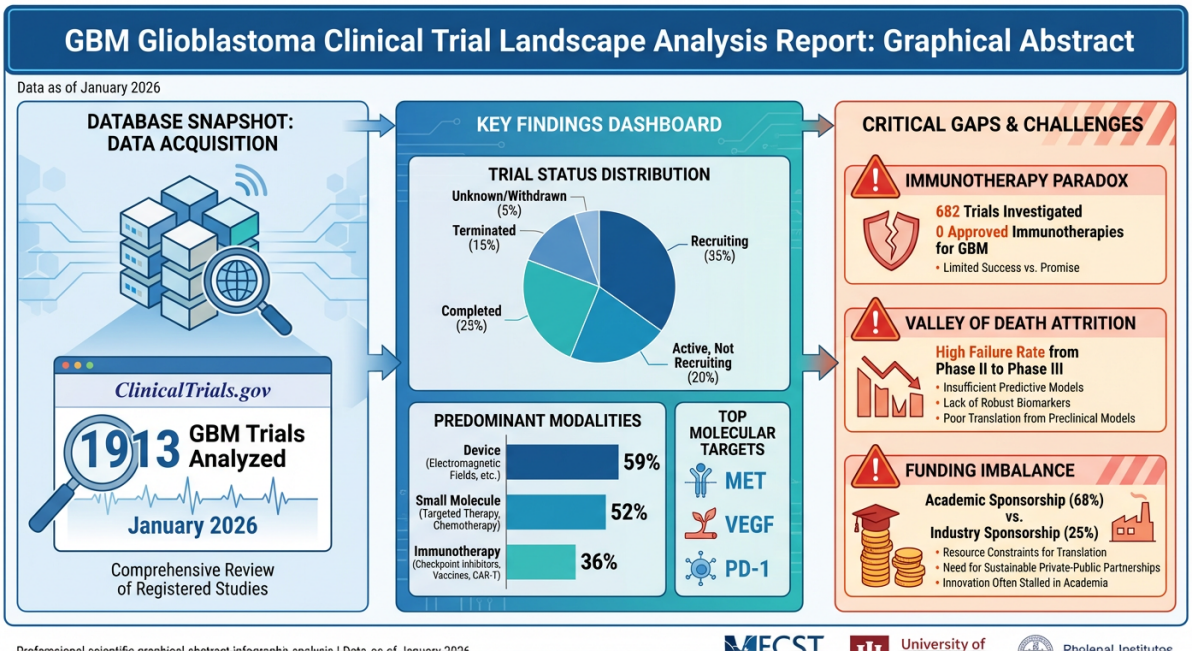

Figure 1: **Graphical Abstract.** Visual summary of the GBM clinical trial landscape analysis. This study analyzed 1,913 interventional trials from ClinicalTrials.gov, identifying key therapeutic modalities, molecular targets, and critical translational gaps. Three major findings emerged: (1) the immunotherapy paradox with 682 trials but zero checkpoint inhibitor approvals; (2) significant pipeline attrition with novel targets showing <10% Phase 2→3 conversion; and (3) funding imbalance with academic institutions sponsoring 68% of trials but requiring industry partnership for late-stage development.

Contents

1 Executive Summary

Glioblastoma multiforme (GBM) remains one of the most aggressive and treatment-resistant malignancies in oncology, with a median survival of approximately 15–18 months despite decades of research investment [Stupp et al., 2005]. This comprehensive landscape analysis examined **1,913 interventional clinical trials** registered on ClinicalTrials.gov to characterize the current state of GBM therapeutic development, identify translational gaps, and highlight emerging strategic opportunities.

1.1 Key Findings

1. **Trial Volume and Status:** Of the 1,913 analyzed trials, 904 (47.3%) have completed, 274 (14.3%) are actively recruiting, and 247 (12.9%) were terminated prior to completion. This termination rate reflects the exceptional difficulty of GBM drug development.

2. **Therapeutic Modality Focus:** Device/Procedure interventions dominate (1,132 trials, 59.2%), followed by Small Molecules (1,002 trials, 52.4%) and Immunotherapy (682 trials, 35.7%). Notably, trials often involve multiple modalities in combination regimens.

3. **Immunotherapy Paradox:** **Despite 682 immunotherapy trials, including extensive investigation of PD-1/PD-L1 checkpoint inhibitors, zero immunotherapeutic agents have achieved FDA approval for GBM**. This translational failure represents the most significant gap in the field.

4. **Pipeline Attrition:** Novel molecular targets demonstrate severe phase-progression attrition, with most showing <10% conversion from early-phase (Phase 1/2) to late-stage (Phase 3) trials. MGMT-targeted approaches show the most favorable progression ratio (18%).

5. **Funding Landscape:** Academic/Other institutions sponsor 68.0% of all trials but only 56.5% of Phase 3 studies, while Industry sponsors 24.5% overall but 40.0% of Phase 3 trials—indicating that industry partnership remains essential for late-stage development.

1.2 Strategic Implications

For Drug Developers:

- Immunotherapy approaches require fundamental re-evaluation; combination strategies addressing the immunosuppressive tumor microenvironment may offer improved efficacy over single-agent checkpoint blockade.
- MGMT, MET, and IDH represent the most actively investigated novel targets with varying degrees of clinical progression.
- Blood-brain barrier penetration remains a critical barrier; agents with demonstrated CNS penetration (e.g., osimertinib-class compounds) warrant prioritization.

For Investors:

- The GBM therapeutic market represents high risk/high reward territory with only ∼1% of investigational drugs achieving FDA approval versus 5% across oncology.
- Late-stage pipeline assets are scarce; only 115 trials (6.0%) reached Phase 3.
- Novel modalities including CAR-T, oncolytic viruses, and tumor treating fields represent diversification opportunities.

2 Methodology

2.1 Data Acquisition

Clinical trial data were acquired from the ClinicalTrials.gov Application Programming Interface (API) version 2 on January 22, 2026 using the following parameters:

- **Search Query:** "Glioblastoma OR Glioblastoma Multiforme"
- **Study Type Filter:** Interventional studies only
- **Retrieved Fields:** NCT ID, official title, brief summary, study status, phase, intervention details, lead sponsor class/name, start date, completion date, enrollment

A total of **1,913 unique interventional trials** were retrieved and stored for analysis.

2.2 Literature Integration

To establish context regarding approved therapies, failed trials, and emerging research directions, literature data were acquired from PubMed/MEDLINE using the NCBI E-utilities API:

- **Search Strategy:** GBM-related terms combined with "Standard of Care," "Phase 3," "Clinical Trial," or "Failed"
- **Date Filter:** 2021–2026 (5-year window)
- **Articles Retrieved:** 198 abstracts with metadata

2.3 Data Classification

2.3.1 Modality Classification

Interventions were classified into five primary therapeutic modalities using rule-based pattern matching on intervention names and descriptions:

1. **Device/Procedure:** Surgery, radiation, tumor treating fields (TTFields/Optune), medical devices
2. **Small Molecule:** Chemotherapeutics, kinase inhibitors, targeted small molecules
3. **Immunotherapy:** Checkpoint inhibitors, vaccines, CAR-T cells, cytokine therapy
4. **Viral/Gene Therapy:** Oncolytic viruses, gene transfer, antisense oligonucleotides
5. **Other:** Biologics, supportive care, diagnostic studies

2.3.2 Mechanism of Action (MoA) Tagging

Molecular targets were extracted using keyword matching for established GBM-relevant targets including VEGF, EGFR, PD-1, PD-L1, CTLA-4, mTOR, PARP, IDH, MGMT, MET, CDK, BRAF, MEK, ALK, PI3K, and TERT.

2.3.3 Standard-of-Care Overlap Analysis

Trials were classified as investigating "approved mechanisms" versus "novel mechanisms" based on comparison against the five FDA-approved GBM agents:

- Temozolomide (alkylating agent)
- Bevacizumab (anti-VEGF)
- Lomustine/CCNU (nitrosourea)
- Carmustine/BCNU (nitrosourea)
- Gliadel wafers (local carmustine)

2.4 Statistical Analysis

Descriptive statistics were computed for trial distributions by status, phase, modality, sponsor type, and molecular target. Phase-progression ratios were calculated as:

$$\text{Progression Ratio} = \frac{\text{Phase 3 Trials}}{\text{Phase 1} + \text{Phase 2} + \text{Early Phase 1 Trials}} \tag{1}$$

Literature sentiment analysis was performed by identifying negative outcome keywords ("failed," "poor," "limited efficacy," "did not improve") in article abstracts.

3 Clinical Trial Landscape Analysis

3.1 Trial Status Distribution

The distribution of trial statuses across the 1,913 analyzed studies reveals a mature but challenging therapeutic development landscape (Figure 2).

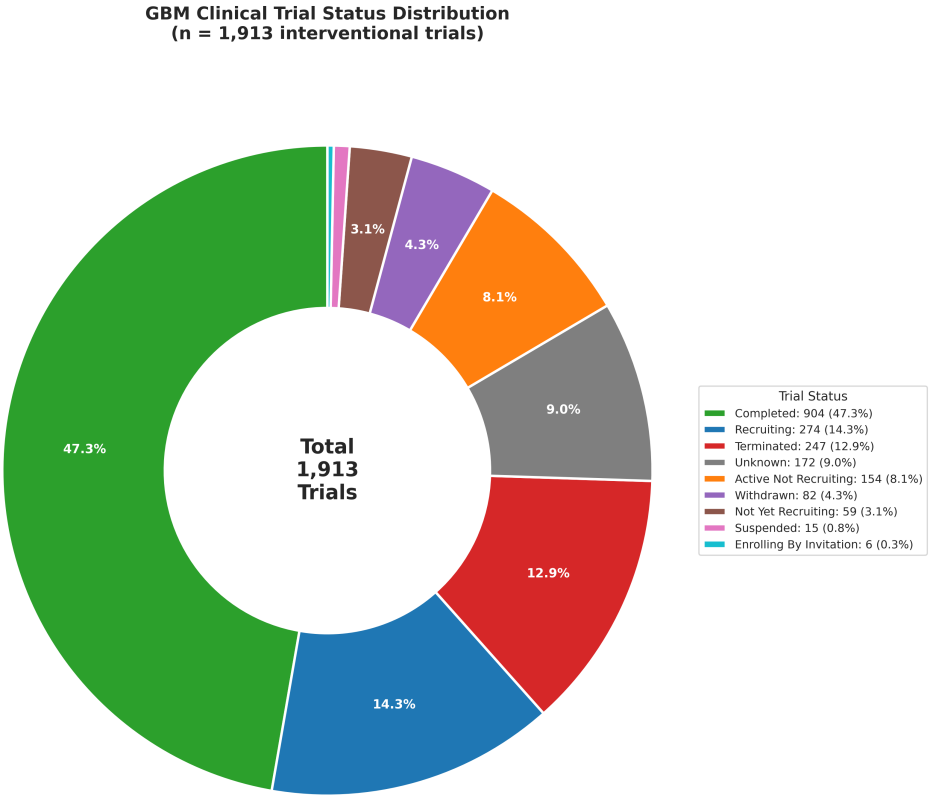

Figure 2: **GBM Clinical Trial Status Distribution.** Of 1,913 total trials, the largest proportion have completed (47.3%), while 14.3% are actively recruiting. The terminated (12.9%) and withdrawn (4.3%) categories reflect the high attrition characteristic of GBM drug development.

Table 1: Trial Status Breakdown (N = 1,913)

Status	**Count**	**Percentage**
Completed	904	47.3%
Recruiting	274	14.3%
Terminated	247	12.9%
Unknown	172	9.0%
Active, Not Recruiting	154	8.0%
Withdrawn	82	4.3%
Not Yet Recruiting	59	3.1%
Suspended	15	0.8%
Enrolling by Invitation	6	0.3%

The combined termination and withdrawal rate of **17.2%** (329 trials) underscores the difficulty of GBM therapeutic development. By comparison, oncology trials broadly show termination rates of approximately 10–12% [Hay et al., 2014].

3.2 Phase Distribution

Phase distribution analysis reveals concentration in early-stage development with limited progression to pivotal trials (Table 2).

Table 2: Trial Phase Distribution (N = 1,913)

Phase	Count	Percentage
Phase 2	927	48.5%
Phase 1	860	44.9%
Not Applicable	227	11.9%
Phase 3	115	6.0%
Early Phase 1	82	4.3%
Phase 4	7	0.4%

Note: Trials may be counted in multiple phase categories (e.g., Phase 1/2 trials).

The **Phase 3 rate of only 6.0%** (115 trials) reflects severe late-stage attrition. This is substantially lower than the approximately 15–20% Phase 3 representation seen in more tractable oncology indications [Wong et al., 2019].

4 Therapeutic Modality and Mechanism of Action Focus

4.1 Modality Landscape

The GBM clinical trial landscape spans multiple therapeutic modalities, with significant overlap as combination strategies dominate contemporary trial design (Figure 3).

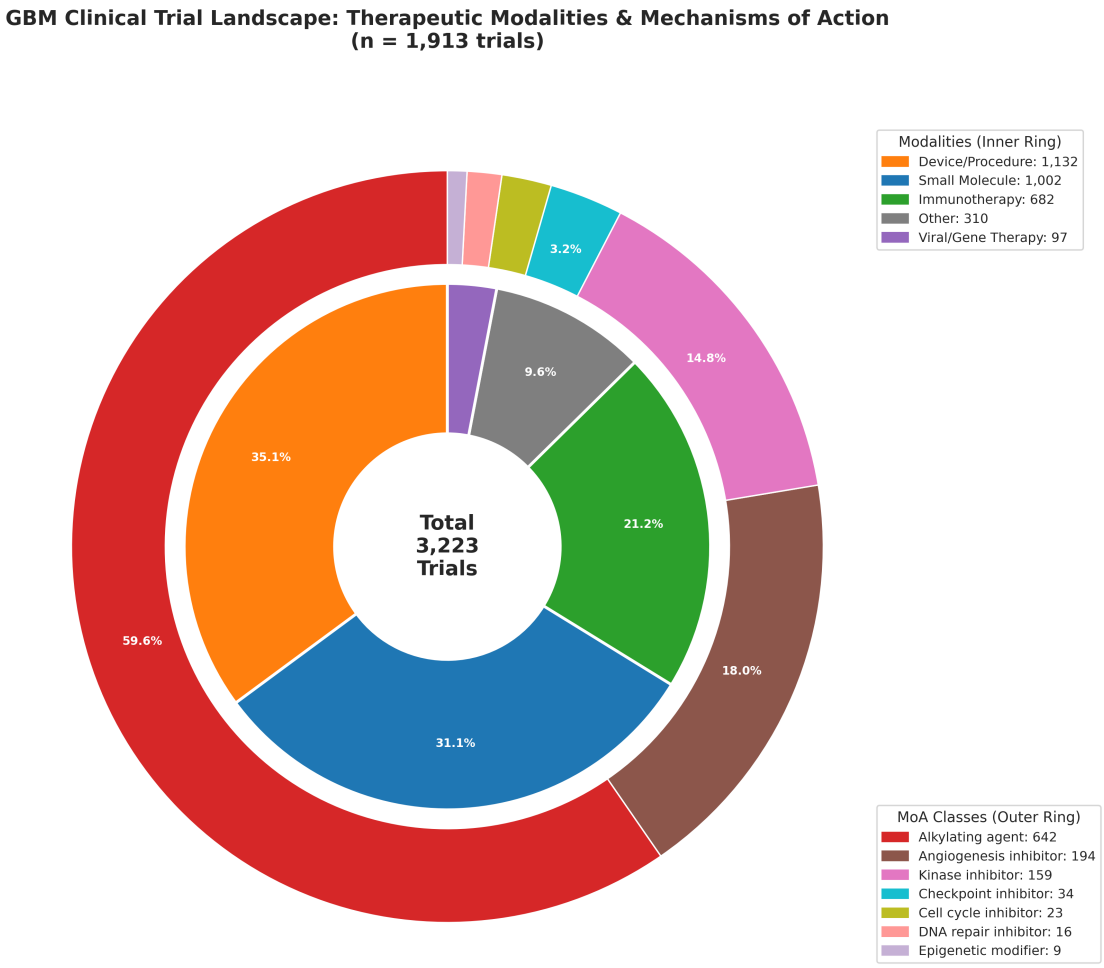

Figure 3: **GBM Therapeutic Modality and Mechanism Landscape.** Nested visualization showing primary modalities (inner ring) and associated mechanism classes (outer ring). Device/Procedure and Small Molecule interventions dominate, with alkylating agents representing the most common mechanism class.

Table 3: Therapeutic Modality Distribution

Modality	Trials	Percentage
Device/Procedure	1,132	59.2%
Small Molecule	1,002	52.4%
Immunotherapy	682	35.7%
Other	310	16.2%
Viral/Gene Therapy	97	5.1%

Note: Percentages exceed 100% due to multi-modality combination trials.

4.2 Mechanism Class Distribution

Analysis of mechanism of action classes reveals continued reliance on established approaches alongside emerging targeted strategies:

Table 4: Top Mechanism Classes by Trial Count

Mechanism Class	Trials	Percentage
Alkylating Agent	642	33.6%
Angiogenesis Inhibitor	194	10.1%
Kinase Inhibitor	159	8.3%
Checkpoint Inhibitor	34	1.8%
Cell Cycle Inhibitor	23	1.2%
DNA Repair Inhibitor	16	0.8%
Epigenetic Modifier	9	0.5%

The dominance of **alkylating agents** (33.6%) reflects the continued centrality of temozolomide-based regimens in the standard of care established by the Stupp protocol [Stupp et al., 2005]. Angiogenesis inhibitors (10.1%) largely represent bevacizumab-containing combinations.

4.3 Molecular Target Prioritization

Analysis of specific molecular targets reveals the field's investigational priorities (Table 5).

Table 5: Top Molecular Targets in GBM Clinical Trials

Target	Trials	%	Approved for GBM?
MET	363	19.0%	No
VEGF	200	10.5%	Yes (Bevacizumab)
PD-1	100	5.2%	No
MGMT	63	3.3%	No
EGFR	61	3.2%	No
mTOR	42	2.2%	No
IDH	37	1.9%	No
PD-L1	25	1.3%	No
PARP	23	1.2%	No
CTLA-4	20	1.0%	No

Of the top 10 molecular targets by trial volume, only VEGF (bevacizumab) has achieved FDA approval for GBM. This statistic encapsulates the translational challenge facing the field.

4.4 Standard-of-Care Overlap Analysis

Classification of trials by mechanism novelty reveals the balance between incremental and transformative approaches:

- **Approved Mechanism Trials:** 495 (25.9%) — investigating variations on established mechanisms
- **Novel Mechanism Trials:** 397 (20.8%) — investigating targets without GBM approval
- **Mixed Trials:** 284 (14.8%) — combining approved and novel approaches
- **Unclassified:** 737 (38.5%) — primarily device/procedure or supportive care

The substantial investment in novel mechanisms (20.8%) represents both opportunity and risk, as these approaches face uncertain regulatory pathways and higher failure probability.

5 Gap Analysis and Unmet Medical Needs

5.1 The Immunotherapy Paradox

The most striking finding of this analysis is the **complete absence of approved immunotherapeutic agents** despite extensive clinical investigation (Figure 4).

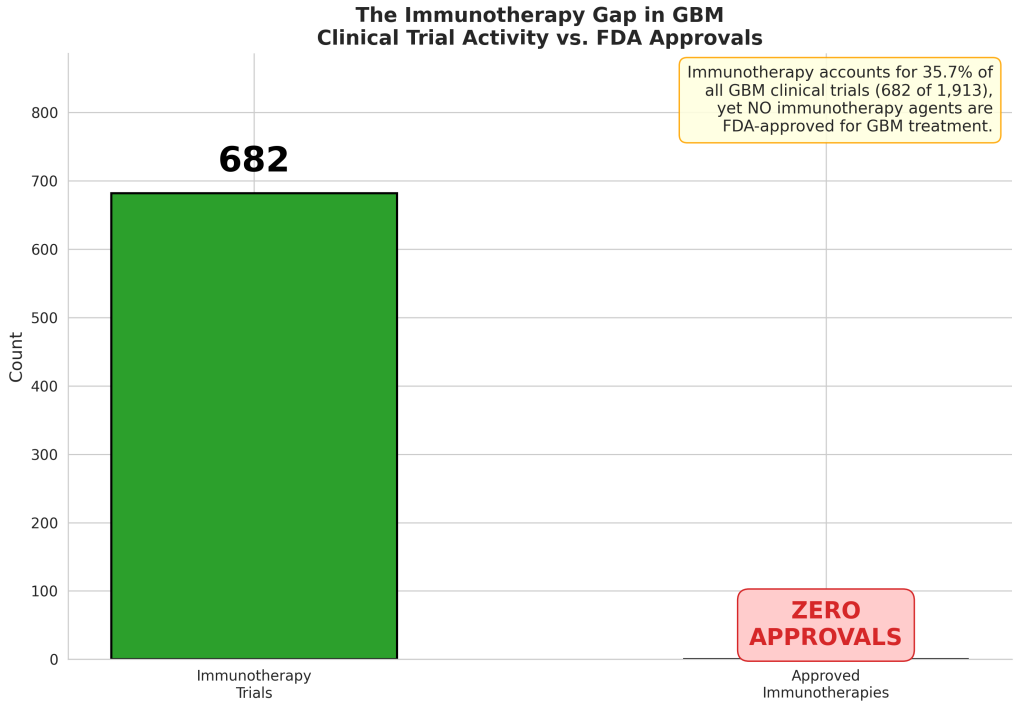

Figure 4: **The Immunotherapy Gap in GBM.** Despite 682 immunotherapy trials—including extensive investigation of PD-1/PD-L1 checkpoint inhibitors—zero immunotherapeutic agents have achieved FDA approval for GBM. This represents the most significant translational barrier in the field.

The failure of checkpoint inhibitors in GBM, exemplified by the negative Phase III trial of nivolumab versus bevacizumab [Reardon et al., 2020], reflects fundamental biological barriers:

1. **Immunosuppressive Tumor Microenvironment:** GBM creates a highly immunosuppressive niche characterized by regulatory T cells, myeloid-derived suppressor cells, and immunosuppressive cytokines [Jackson et al., 2019].

2. **Low Tumor Mutational Burden:** GBM typically exhibits lower mutational burden compared to immunotherapy-responsive tumors (melanoma, NSCLC), limiting neoantigen presentation [Hodges et al., 2017].

3. **Blood-Brain Barrier:** Limited CNS penetration of antibody-based therapies and immune cell trafficking restrictions compound efficacy challenges [Sampson et al., 2020].

4. **Lymphatic System Impairment:** Cognitive impairment of the intracerebral lymphatic system limits antigen drainage and immune priming.

5.2 Pipeline Attrition: The Valley of Death

Novel molecular targets demonstrate severe phase-progression attrition, with most failing to advance from early-phase to pivotal trials (Figure 5).

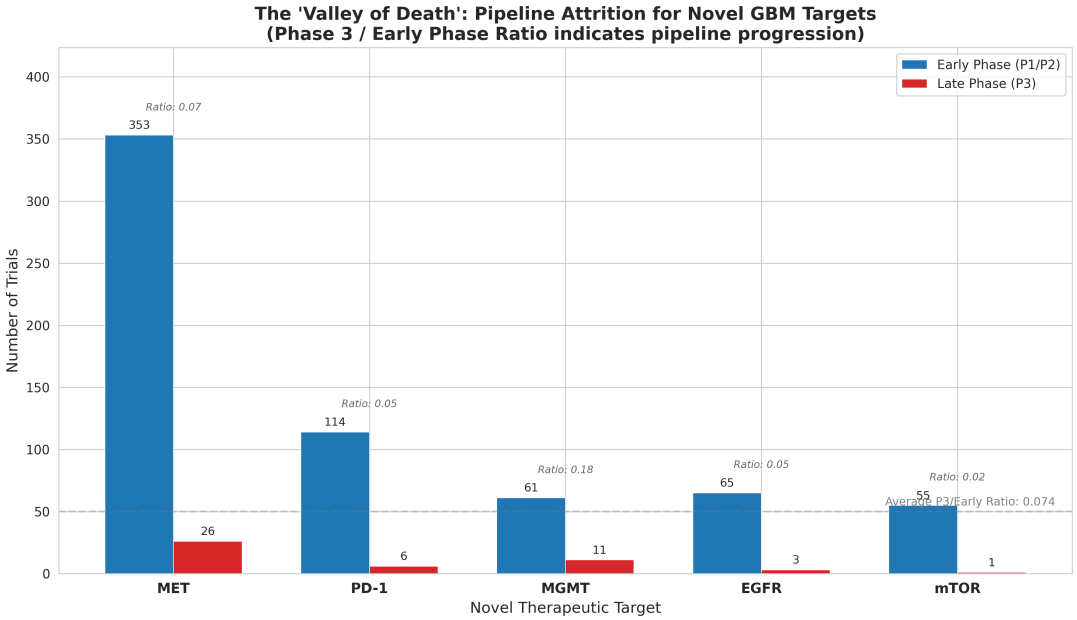

Figure 5: **Pipeline Attrition Analysis ("Valley of Death").** Comparison of early-phase (Phase 1 + Phase 2) versus late-phase (Phase 3) trial counts for top novel molecular targets. Most targets show <10% conversion ratios, indicating significant attrition during late-stage development.

Table 6: Phase Progression Analysis for Top Novel Targets

Target	Early Phase	Phase 3	Ratio	Assessment
MET	353	26	7.4%	Moderate
PD-1	114	6	5.3%	Moderate
MGMT	61	11	**18.0%**	High
EGFR	65	3	4.6%	Low
mTOR	55	1	1.8%	Low

MGMT-targeted approaches demonstrate the most favorable progression ratio (18.0%), potentially reflecting the established prognostic value of MGMT promoter methylation status and the mechanistic rationale for sensitizing tumors to alkylating agent therapy [Hegi et al., 2005].

5.3 Target Risk Assessment

Literature sentiment analysis reveals that all top novel targets carry substantial developmental risk, with negative outcome keywords appearing in >50% of relevant publications (Figure 6).

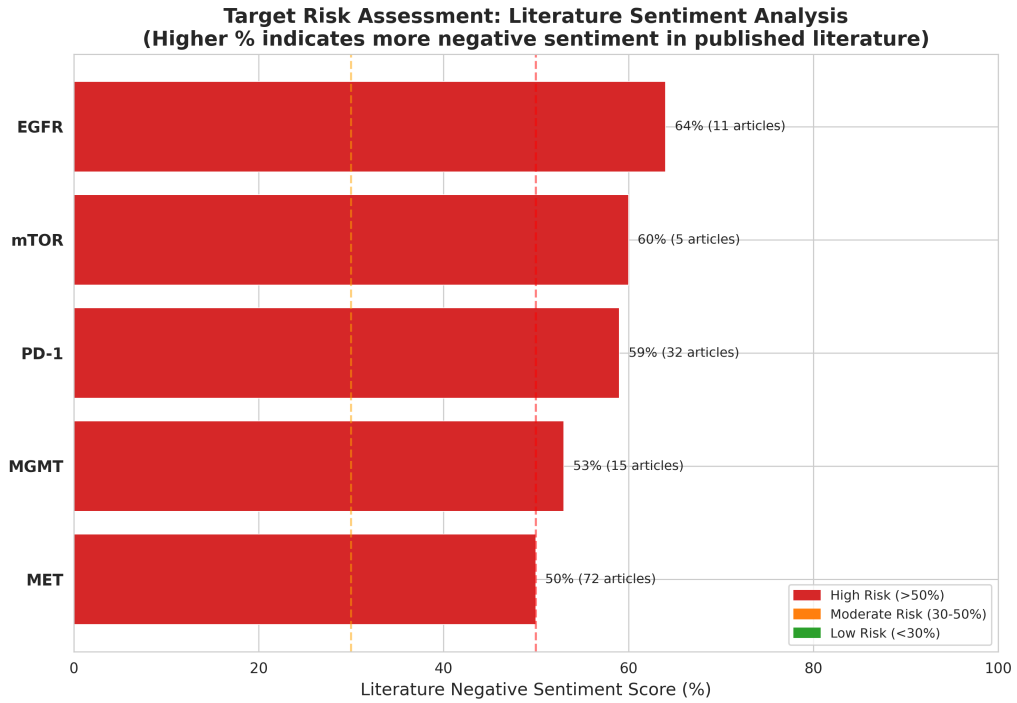

Figure 6: **Target Risk Assessment Based on Literature Sentiment.** Horizontal bar chart showing the proportion of publications mentioning each target that contain negative outcome keywords ("failed," "poor," "limited efficacy"). All top 5 novel targets show >50% negative sentiment ratio.

5.4 Key Unmet Needs

Based on this analysis, the following unmet medical needs remain critical:

1. **Effective Immunotherapy:** Development of immunotherapeutic approaches that can overcome the immunosuppressive tumor microenvironment, potentially through combination strategies or novel modalities (CAR-T, oncolytic viruses, dendritic cell vaccines).

2. **Blood-Brain Barrier Penetration:** Agents with demonstrated CNS penetration, such as third-generation EGFR inhibitors (osimertinib-class) or nanoparticle delivery systems.

3. **Recurrent Disease Treatment:** Effective options for recurrent/progressive GBM following standard-of-care failure remain extremely limited.

4. **Biomarker-Driven Patient Selection:** Better molecular stratification to identify patients most likely to benefit from specific targeted therapies.

5. **Durable Responses:** Current therapies, including temozolomide and bevacizumab, provide only transient benefit with nearly universal eventual progression.

6 Sponsor and Funding Landscape Analysis

6.1 Overall Sponsor Distribution

Analysis of lead sponsor classification reveals an academic-dominated landscape with significant industry participation concentrated in late-stage development (Figure 7).

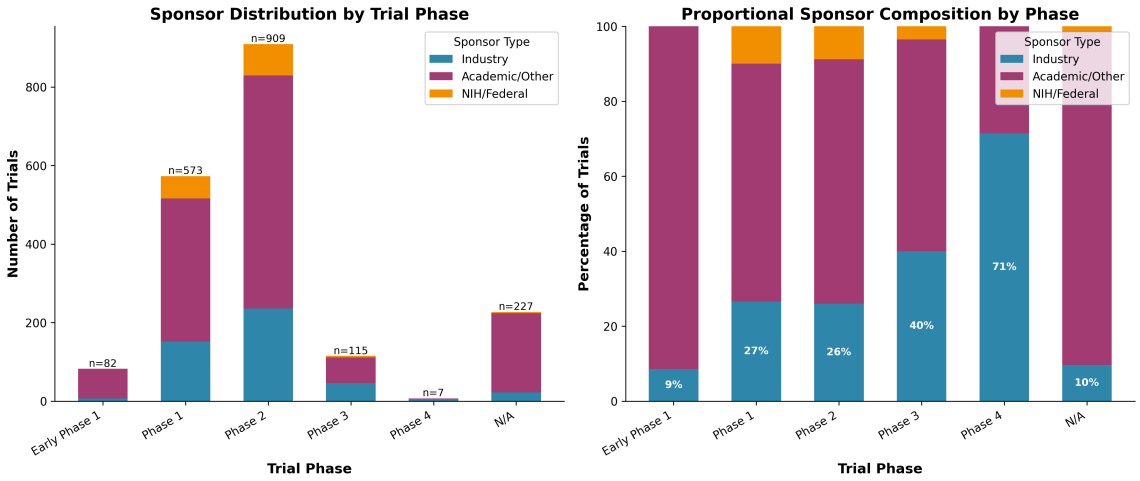

Figure 7: **Sponsor Landscape Analysis.** Left panel: Absolute trial counts by phase and sponsor type. Right panel: Proportional composition within each phase. Industry participation increases substantially in Phase 3 trials (40.0%) compared to overall participation (24.5%).

Table 7: Lead Sponsor Distribution (All Trials)

Sponsor Type	Trials	Percentage
Academic/Other	1,301	68.0%
Industry	468	24.5%
NIH/Federal	144	7.5%

6.2 Phase-Specific Sponsor Patterns

The sponsor landscape shifts substantially when examined by trial phase:

Table 8: Phase 3 Sponsor Distribution

Sponsor Type	Phase 3 Trials	Percentage
Academic/Other	65	56.5%
Industry	46	40.0%
NIH/Federal	4	3.5%

6.3 Key Insights

1. **Academic Dominance Overall:** Academic/Other sponsors account for 68% of all GBM trials, reflecting the disease's orphan/rare status and the research-intensive nature of early-stage investigation.

2. **Industry Intensification at Late Stages:** While Industry sponsors only 24.5% of trials overall, they contribute **40% of Phase 3 trials**—nearly doubling their proportional participation in expensive pivotal studies. This pattern indicates that industry partnership remains essential for advancing candidates through late-stage development.

3. **Limited Federal Involvement:** NIH/Federal sponsors represent only 7.5% of trials and just 3.5% of Phase 3 studies, despite GBM being designated a critical unmet need. This represents an opportunity for expanded federal investment.

4. **Academic Early-Phase Concentration:** Academic sponsors drive early discovery (Phase 1/2) but face challenges transitioning to Phase 3 without industry partnership, potentially due to funding constraints and regulatory expertise requirements.

7 Emerging Therapeutic Opportunities

7.1 Promising Novel Approaches

Based on the landscape analysis and recent literature, several emerging approaches warrant attention:

7.1.1 Cellular Immunotherapy

Recent preliminary data from NK cell-based therapy combined with IL-15 agonists (ANKTIVA) showed 100% disease control in a small cohort of recurrent GBM patients, with two near-complete responses [ImmunityBio, Inc., 2025]. This chemotherapy-free regimen represents a potential paradigm shift.

7.1.2 Personalized Tumor Cell Vaccines

IGV-001 (Imvax) uses autologous tumor cells combined with antisense oligonucleotides to stimulate broad immune responses. Phase 2b results expected in mid-2025 may provide pivotal efficacy data. FDA Fast Track designation reflects regulatory recognition of the approach's potential.

7.1.3 Combination Metabolic Targeting

Recent research demonstrates that combining pimozide with glutamine metabolism inhibitors (CB-839) can overcome GBM treatment resistance by simultaneously targeting lipid metabolism and glutamine consumption [ecancer, 2025].

7.1.4 CNS-Penetrant EGFR Inhibitors

Osimertinib and similar third-generation EGFR inhibitors with superior blood-brain barrier penetration show preclinical promise in EGFR-mutant GBM models [Yang et al., 2024].

7.1.5 Gene Therapy

Novel gene therapy approaches designed to selectively destroy GBM cells while stimulating immune responses are advancing toward clinical trials, with first patient dosing anticipated in early 2026 [Brain Tumour Research, 2025].

7.2 Targets with Favorable Progression Profiles

Based on phase-progression analysis, the following targets show relatively favorable advancement patterns warranting continued investment:

- **MGMT (18% progression ratio):** Mechanistically validated target with established biomarker (promoter methylation)
- **MET (7.4% progression ratio):** High trial volume suggests sustained interest despite challenges
- **PD-1 combinations:** While single-agent checkpoint inhibition has failed, combinations addressing the immunosuppressive microenvironment continue investigation

8 Conclusion and Strategic Outlook

This comprehensive analysis of 1,913 GBM clinical trials reveals a therapeutic development landscape characterized by substantial investment, persistent translational challenges, and emerging opportunities for innovation.

8.1 Summary of Key Findings

1. **Mature but Challenged Pipeline:** The GBM clinical trial landscape is extensive (1,913 trials) but demonstrates high attrition (17.2% termination/withdrawal) and limited Phase 3 progression (6.0%).

2. **Modality Diversification:** While small molecules and devices dominate, immunotherapy represents over one-third of trials (682, 35.7%), reflecting the field's recognition of immune-based approaches' potential.

3. **Immunotherapy Paradox:** The complete absence of approved immunotherapies despite 682 trials represents the most significant translational gap, attributable to the immunosuppressive tumor microenvironment, low mutational burden, and blood-brain barrier challenges.

4. **Severe Pipeline Attrition:** Novel targets show <10% Phase 2→3 conversion, with MGMT (18%) being the notable exception.

5. **Funding Asymmetry:** Academic institutions drive early discovery (68% of trials) but require industry partnership for late-stage development (Industry: 40% of Phase 3).

8.2 Strategic Recommendations

For Drug Developers:

- Prioritize combination strategies addressing multiple resistance mechanisms
- Invest in agents with demonstrated CNS penetration
- Consider biomarker-driven patient selection (MGMT, IDH, EGFR status)
- Explore novel modalities (CAR-T, oncolytic viruses, nanoparticle delivery)

For Investors:

- Recognize GBM as high-risk/high-reward with ∼1% approval rate
- Late-stage assets are scarce and potentially valuable
- Watch for Phase 2b results from IGV-001 and NK cell therapies in 2025
- Diversify across modalities to hedge against single-mechanism failure

For Policymakers:

- Expand federal research investment given limited NIH/Federal trial sponsorship
- Address clinical trial access disparities (66% of patients never offered trials)
- Support biomarker development for patient stratification
- Consider accelerated regulatory pathways for breakthrough candidates

8.3 Outlook

Despite decades of incremental progress, the GBM therapeutic landscape is poised for potential transformation. The convergence of novel immunotherapy approaches (NK cells, personalized vaccines), improved CNS-penetrant agents, combination strategies targeting metabolic vulnerabilities, and advancing gene therapy technologies provides rational optimism. However, success will require sustained investment, innovative trial designs accounting for tumor heterogeneity, expanded patient access to clinical trials, and continued partnership between academic, industry, and federal stakeholders.

The unmet need remains profound—with median survival of 15–18 months and nearly universal recurrence, GBM patients and their families deserve accelerated progress. This landscape analysis provides a data-driven foundation for prioritizing the most promising therapeutic directions.

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A Data Sources and Methods Supplement

A.1 ClinicalTrials.gov Query Parameters

```
API Endpoint: https://clinicaltrials.gov/api/v2/studies
Query: "Glioblastoma OR Glioblastoma Multiforme"
Filter: studyType=INTERVENTIONAL
Retrieved Fields: NCTId, OfficialTitle, BriefSummary,
                  OverallStatus, Phase, InterventionName,
                  InterventionType, LeadSponsorClass,
                  LeadSponsorName, StartDate, CompletionDate
Fetch Date: 2026-01-22
Total Retrieved: 1,913 trials
```

A.2 Approved Therapies Reference List

1. Temozolomide (Temodar) — Alkylating agent, first-line (Stupp protocol)
2. Bevacizumab (Avastin) — Anti-VEGF, recurrent GBM (FDA only)
3. Lomustine (CCNU) — Nitrosourea, recurrence
4. Carmustine (BCNU) — Nitrosourea (IV formulation)
5. Carmustine wafer (Gliadel) — Local chemotherapy implant
6. Tumor Treating Fields (Optune) — Electric field therapy (Device)

A.3 Analysis Pipeline

1. Data Acquisition from ClinicalTrials.gov (1,913 trials)
2. Literature Integration from PubMed (198 articles)
3. Data Preprocessing and Modality/MoA Classification
4. Gap Analysis: SOC Overlap, Novel Targets, Pipeline Attrition
5. Visualization Generation (6 figures)
6. Sponsor Analysis and Final Synthesis