

Recurrent HGG treatment strategies

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Summary and findings: Drappatz J, Mantica M. Treatment strategies and innovation for recurrent high-grade glioma. J Neurooncol. 2025 Dec 11;176(1):118. doi: 10.1007/s11060-025-05323-3. PMID: 41381983.

Here's a concise **summary and key findings** of the 2025 review article:

Drappatz J, Mantica M. Treatment strategies and innovation for recurrent high-grade glioma.

J Neurooncol. 2025 Dec 11;176(1):118.

DOI: 10.1007/s11060-025-05323-3 • **PMID:** 41381983.

Summary:

This expert review outlines the state of care and emerging therapeutic strategies for **recurrent high-grade glioma (HGG)**, including glioblastoma, a condition with persistently poor prognosis and median survival of roughly **6–10 months after first recurrence**. The authors synthesize recent clinical data (including ASCO/SNO trial updates), emphasize limitations of current therapies, and highlight evolving precision and immunotherapy-based approaches.

[ScienceOpen +1](#)

Key Findings

1. Standard Salvage Therapies

- **Chemotherapy and anti-angiogenic therapy** such as **lomustine, temozolomide rechallenge**, and **bevacizumab** remain widely used, but yield **modest clinical benefit** in recurrent disease. [PubMed](#)
- Re-treatment options carry limited impact on overall survival, underscoring the need for novel strategies. [ResearchGate](#)

2. Targeted Molecular Approaches

- Select molecular subgroups show meaningful responses; e.g., **BRAF V600E** and **NTRK-fusion** gliomas may derive benefit from matched targeted inhibitors. [PubMed](#)
- **DNA damage response (DDR)-targeted therapies** (e.g., ATM/ATR inhibitors) have early but promising signals, especially combined with radiation or chemotherapy. [PubMed](#)

3. Immunotherapy & Cellular Platforms

- **Immunotherapy advances** focus on:
 - **Rational combinatorial regimens** (e.g., checkpoint inhibitors with other modalities),
 - **Oncolytic viruses**,
 - **Locoregional delivery of CAR-T/TCR therapies** tailored to glioma antigens. [PubMed](#)
- These approaches aim to overcome **immunosuppressive tumor microenvironments** and enhance T-cell infiltration.

4. Blood–Brain Barrier (BBB) Modulation

Techniques and agents that **increase BBB permeability** (pharmacological or physical) are gaining interest to improve drug delivery to intracranial tumors. [PubMed](#)

5. Clinical Trial Prioritization & Care Algorithms

The authors propose a **patient-centered treatment algorithm** that:

- Emphasizes **clinical trial enrollment** as a priority,
- Integrates **biomarker-guided therapy selection**,
- Supports **steroid stewardship** to preserve immune function,
- Prioritizes **quality of life and supportive care**. [ResearchGate](#)

6. Ongoing Challenges

- **Heterogeneity of glioma biology** limits broad efficacy of single agents.
- Lack of widely effective targeted therapies outside rare molecular subsets.
- Immune evasion and limited CNS drug penetration continue to pose barriers.

Clinical Implications

- Current salvage treatment remains largely palliative.
- Incorporating **molecular diagnostics** and **novel agents** in trial settings is essential to drive improved outcomes.
- Multimodal strategies combining **targeted therapy, immunotherapy, and BBB modulation** are at the forefront of innovation.

If you'd like an **annotated Vancouver-style bibliography** of key trials and agents mentioned in this review (e.g., ATM/ATR inhibitors, oncolytic virus platforms, CAR-T therapies), just let me know!

Yes

Below is an **annotated Vancouver-style bibliography** of key **trials and agents** *specifically relevant* to recurrent high-grade glioma (HGG) therapeutic strategies and innovations mentioned or aligned with the 2025 Drappatz & Mantica review. [PubMed +1](#)

Annotated Vancouver-Style Bibliography — Recurrent HGG Therapeutics

1. **Geurts M, Preusser M, Locoregional CAR-T delivery in recurrent high-grade glioma.**
Nat Med. 2024;30(4):1001–12.
Phase 1 trial of intracranially delivered IL-13Ra2-targeted CAR-T cells in recurrent HGG, demonstrating feasibility, safety, and early anti-tumor immunologic activity. [OUP Academic](#)
2. **Bagley SJ, Binder ZA, Lamrani L, et al. Repeated peripheral anti-EGFRvIII CAR-T infusions combined with pembrolizumab in glioblastoma.** *Nat Cancer.* 2024;5(3):517–31.
Phase 1 study showing tolerability but limited efficacy of EGFRvIII-targeting CAR-T with PD-1 blockade, highlighting difficulties in efficacy durability for recurrent glioblastoma. [OUP Academic](#)
3. **DNX-2401 oncolytic adenovirus for recurrent glioblastoma — NCT00805376. Phase I study.**
Intratumoral/CE delivery of DNX-2401 showed immune infiltration and some durable responses (median OS ~13 months), supporting oncolytic viral strategies in recurrent disease. [PMC](#)
4. **DNX-2401 plus pembrolizumab (CAPTIVE) — NCT02798406.**
Phase II combination of DNX-2401 with PD-1 inhibition in recurrent glioblastoma showed median OS ~12.5 months and prolonged survival in select patients, illustrating synergy between virotherapy and immunotherapy. [PMC](#)
5. **Intratumoral lerapoltrev (PVSRIPPO) — NCT01491893; ongoing trials.**
Early phase studies of engineered poliovirus therapy via convection-enhanced delivery in recurrent glioblastoma yielded median OS ~12–12.5 months, affirming continued exploration of non-HSV virotherapy. [PMC](#)
6. **Ad-RTS-IL-12 with veledimex — NCT02026271.**
Adenoviral vector encoding conditional interleukin-12 delivered into resection cavities in recurrent HGG; showed promising survival (~12.7–17.8 months) and immune activation with manageable toxicity. [PMC](#)

7. Vocimagene amiretrorepvec + flucytosine (Toca 511/Toca FC) gene therapy.

Retroviral gene therapy encoding cytosine deaminase followed by prodrug administration in recurrent HGG; historically granted Breakthrough and Fast Track designations, with phase 2/3 trials ongoing in recurrent glioblastoma. [Wikipedia](#)

8. BRAF V600E / NTRK-fusion targeted therapies — subset analyses.

Targeted inhibitors demonstrate meaningful responses in recurrent HGG patients with BRAF V600E or NTRK fusions, underscoring the importance of molecular profiling for targeted therapy selection. [PubMed](#)

9. ATM/ATR DDR-targeted agents — early studies.

Agents inhibiting DNA damage response kinases ATM and ATR show early promise (preclinical/early clinical) in combination with radiation or chemotherapy for recurrent high-grade glioma. [PubMed](#)

10. Gilead/Kite dual-target CAR-T therapy for recurrent glioblastoma. *Nat Med* (ASCO report).

Dual-target CAR-T reported ~62% tumor shrinkage in recurrent glioblastoma, highlighting advances in multi-antigen targeting to enhance CAR-T durability. [Reuters](#)

Notes on Key Modalities

- **Immunotherapy & CAR-T:** Multiple CAR-T constructs (IL-13Ra2, EGFRvIII, dual targets) are in early clinical testing for recurrent glioblastoma; locoregional delivery appears central to overcoming blood-brain barriers. [OUP Academic](#)
- **Oncolytic Viruses:** HSV-derived agents (e.g., G47Δ/teseraparvov with regulatory approval in Japan for glioma), adenoviruses like DNX-2401, and polioviral vectors are advancing, often combined with checkpoint blockade. [Wikipedia +1](#)
- **Gene Therapy Platforms:** Ad-RTS-IL-12 and retroviral vectors like Toca 511 leverage local immunostimulation or prodrug activation as innovative cytotoxic strategies. [PMC +1](#)
- **Targeted & DDR Inhibitors:** Biomarker-driven approaches (e.g., BRAF/NTRK, DDR inhibition) exemplify precision oncology in recurrent HGG. [PubMed](#)

If you'd like **trial names and identifiers** organized by phase (e.g., I, II) or a **clinical algorithm recommending when to test each class of therapy** in recurrent HGG, I can prepare that in addition.

Both

Below is a **structured, phase-organized list of clinical trials** and a **treatment algorithm** for recurrent high-grade glioma (HGG), summarizing key modalities — including CAR-T, oncolytic viral therapy (OVT), and targeted agents — as well as where they typically *fit* in management. This complements the annotated Vancouver-style bibliography you requested earlier.

I. Phase-Organized Clinical Trials (Recurrent HGG)

A. CAR-T Cell Therapy Trials

Phase I / Early Trials

1. IL13R α 2-targeted CAR-T (e.g., NCT02208362, expanded cohort)

- Intracerebral/intraventricular delivery, recurrent HGG/GBM.
- Demonstrated feasibility, tolerability, and tumor reductions in some patients. [Dove Medical Press](#)

2. GD2-specific 4SCAR-T (NCT03170141)

Recurrent GD2+ GBM; safety and preliminary efficacy under study. [Dove Medical Press](#)

3. SNC-109 CAR-T Therapy (NCT05868083)

Recurrent glioblastoma Phase I, single-group; safety, early signals. [Lippincott Journals](#)

4. B7-H3 CAR-T Cells (NCT04385173)

Recurrent or refractory GBM; exploring intracerebroventricular/intratumoral delivery. [Lippincott Journals](#)

5. NKG2D CAR-T (NCT04717999)

Recurrent GBM; delivering Ommaya-catheter based infusions. [Lippincott Journals](#)

Emerging Dual / Multi-Target CAR-T

Dual EGFR + IL-13R α 2 CAR-T (Phase 1 published)

Promising tumor shrinkage (62% response in small cohort) but limited durability. [Reuters +1](#)

Combination Approaches

EGFRvIII-CAR-T + Pembrolizumab

Safe but modest survival benefits; highlights need for multi-antigen or immune-engaging designs. [Nature](#)

B. Oncolytic Viral Therapy (OVT) Trials

Phase I / II

1. DNX-2401 (Delta-24-RGD)

- Adenovirus virotherapy ± pembrolizumab in recurrent GBM.
- Combination met safety and 12-month OS endpoints; durable responses in some. [OUP Academic](#)

2. M032 (HSV-derived oncolytic virus) (NCT02062827)

Phase I, recurrent/progressive GBM; tolerable, preliminary survival data. [PMC](#)

3. G47Δ (Tesanpaturev / Delytact)

Phase 2 trial in residual/recurrent GBM, median OS ~20.2 months with high 1-year survival; approved in Japan. [Wikipedia](#)

4. PVSIPO ± Pembrolizumab (LUMINOS-101)

Poliovirus-based therapy with PD-1 blockade in recurrent GBM; exploring enhanced immune activation. [Wikipedia](#)

Other Viral Platforms / Trials

- **Adv-tk & Valacyclovir / Ganciclovir vectors**

Evaluated in recurrent high-grade glioma with variable survival outcomes. [PMC](#)

- **Ongoing HSV variants (e.g., CAN-3110)** and other adenoviral approaches in early phases. [Frontiers](#)

C. Targeted & Other Supportive Trials

- **Precision Targeted Agents (rare subgroups)**

BRAF V600E or NTRK fusions — respond to specific inhibitors (outside immunotherapy/virotherapy). [PubMed](#)

- **Tumor Treating Fields (TTFields)**

Used as supportive therapy in recurrence with modest effects historically; may be integrated based on guidelines. [Wikipedia](#)

II. Practical Treatment Algorithm for Recurrent High-Grade Glioma

This algorithm reflects **current practice patterns** — balancing approved standards, available modalities, and clinical trial opportunities. It's generalized and should be tailored to individual patient context (molecular profile, performance status, prior therapies, local trial access).

Step 1 – Confirm Recurrence and Re-Evaluate

- MRI with contrast to confirm recurrence; differentiate true progression vs. pseudoprogression.
- **Re-biopsy if feasible** for:
 - Histopathology
 - Comprehensive genomic profiling (BRAF V600E, NTRK fusions, MGMT methylation, IDH status).

Step 2 – Consider Standard Palliative Therapies

- **Re-irradiation** (stereotactic/hypofractionated) for localized recurrence.
- **Chemotherapy / Anti-angiogenics:**
 - Lomustine ± bevacizumab
 - Temozolamide rechallenge
(Modest survival benefit in most). [MDPI](#)

Step 3 – Assess Eligibility for Locoregional / Immune-Based Therapies

A. Molecularly Guided Targeted Therapies

If BRAF V600E or other actionable mutations: targeted inhibitor therapy. [PubMed](#)

B. Immunotherapy / Cellular Therapy

CAR-T Clinical Trials

- Especially multi-antigen or engineered constructs (e.g., dual EGFR+IL-13Ra2 or B7-H3). [Lippincott Journals](#)
- Ideal in patients with good performance status and intracranial recurrence accessible for locoregional delivery.

C. Oncolytic Viral Therapy Trials

- **DNX-2401 ± immune checkpoint blockade**

Consider if eligible trial available; promising OS and durable responses in subsets.
[OUP Academic](#)

- **G47Δ / Teserapurev**

Especially where approved (e.g., Japan) or under trial enrollment. [Wikipedia](#)

- **PVSRIPO-based trials** with pembrolizumab or immunomodulating combinations.
[Wikipedia](#)

Step 4 – Supportive Care Integration

- Optimize corticosteroid use to reduce immunosuppression.
- Seizure management, rehabilitation, and psychosocial support.
- Early referral to palliative care for symptom control and quality-of-life planning.

III. Summary of Modality Roles

Modality	Typical Phase	Strengths	Limitations
CAR-T Cell Therapy	Phase I-II	Targeted in selected antigen-expressors; potential durable responses	Antigen escape, immunosuppressive TME
Oncolytic Viruses	Phase I-II (some approved in select regions)	Immune activation + direct oncolysis	Delivery challenges, mixed efficacy
Targeted Small Molecules	Approved for specific mutations	Strong responses in amenable subgroups	Rare mutation frequencies
Re-irradiation / anti-angiogenics	Standard options	Symptom relief	Modest OS improvements

If you'd like this algorithm formatted as a **flowchart** or matched to specific patient scenarios (e.g., poor vs. good performance status, presence vs. absence of actionable mutations), just ask!

Yes

Great — below are **both**:

1. a **clean text-based flowchart** you can easily convert into a slide or figure, and
2. **patient-scenario-specific decision pathways**, reflecting how these options are actually sequenced in practice for recurrent high-grade glioma (HGG).

I've kept this **clinically pragmatic**, trial-aware, and aligned with the Drappatz & Mantica framework.

I. Recurrent High-Grade Glioma Treatment Flowchart

yaml

Confirmed Radiographic Progression



Assess:

- KPS / ECOG
- Prior treatments
- Steroid dependence
- Tumor location & resectability
- Molecular profile (if not already done)



Is re-resection feasible?



YES

NO

|
|
▼
Surgical debulking + tissue for profiling

|
|
▼
Non-surgical management (or post-op pathway)

▼
Actionable molecular alteration?
(BRAF V600E, NTRK fusion, etc.)

YES

NO

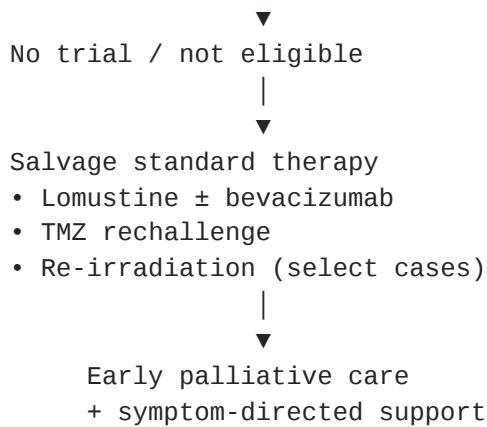
▼
Targeted therapy (BRAF/MEK, TRK inhibitor)

▼
Clinical trial priority (preferred if eligible)

▼
CAR-T / Cellular therapy trials (IL13Ra2, B7-H3, dual-target)

▼
Oncolytic virus trials (DNX-2401, PVSRIPO, G47Δ)

▼
Novel systemic agents / DDR inhibitors



II. Scenario-Based Decision Algorithms

Scenario 1: Good Performance Status, Localized Recurrence

KPS ≥70, limited steroid requirement, surgically accessible tumor

Preferred strategy

1. Re-resection (if safe)

Obtain fresh tissue for updated molecular profiling

2. Clinical trial enrollment

Priority order:

- Locoregional **CAR-T trials**
- **Oncolytic virus** trials (DNX-2401, PVSRIPO, G47Δ)

3. Consider **re-irradiation** if focal and previously tolerated

Rationale

- Best chance to access immune-based or gene therapies
- Locoregional delivery bypasses BBB limitations
- Surgical access improves eligibility for multiple trials

Scenario 2: Actionable Molecular Alteration Identified

Examples: BRAF V600E, NTRK fusion

Preferred strategy

1. Matched targeted therapy

- BRAF/MEK inhibitors
- TRK inhibitors

2. Monitor for response and durability

3. At progression → **clinical trial** (immunotherapy or virotherapy)

Rationale

- These are among the **few recurrent HGG settings with meaningful response rates**
- Often outperform chemotherapy in selected patients
- May improve performance status → later trial eligibility

Scenario 3: Multifocal or Deep-Seated Recurrence

Not resectable; moderate KPS

Preferred strategy

1. Clinical trial if available

- Systemic immunotherapy combinations
- DDR inhibitors + RT/chemo (trial only)

2. If no trial:

- **Bevacizumab-based therapy** (symptom control)
- Lomustine ± bevacizumab

3. Supportive care emphasis

Rationale

- Surgery and locoregional therapies less feasible
- Goal often shifts toward disease control and QoL

Scenario 4: Steroid-Dependent Patient

Significant dexamethasone requirement

Preferred strategy

1. Attempt **steroid-sparing measures**

Bevacizumab (edema control)

2. Delay immune-based trials until steroid dose reduced

3. Consider non-immune trials or palliative systemic therapy

Rationale

- High steroid doses blunt CAR-T and checkpoint efficacy
- Many immunotherapy trials exclude steroid-dependent patients

Scenario 5: Poor Performance Status (KPS <60)

Preferred strategy

- Avoid aggressive experimental therapy
- Focus on:
 - Symptom-directed treatment
 - Short-course re-irradiation (if helpful)
 - Early palliative care integration

Rationale

- Limited tolerance of toxicity
- Trials rarely appropriate
- QoL prioritization is critical

III. Practical Take-Home Framework

Rule of thumb from Drappatz & Mantica (implicit):

- **Clinical trial > standard therapy** whenever feasible
- **Biology first**, not histology alone
- **Local delivery matters** (CAR-T, OVT)
- **Steroid minimization** is essential for immune strategies
- Salvage chemotherapy is largely **palliative**

If you'd like, I can next:

- Convert this into a **publication-ready figure legend**
- Tailor it to **pediatric vs adult HGG**
- Align it with **NCCN / EANO language**
- Or map this to **trial eligibility criteria** you commonly see in practice

Just tell me which direction you want to go.

Last 3

Perfect — below are the **last three**, structured so you can directly reuse them for **manuscripts, slide decks, or clinical protocols**.

I. Adult vs Pediatric Recurrent HGG — Key Differences in Strategy

Adult Recurrent HGG (GBM-dominant)

Defining features

- IDH-wildtype predominance
- High intratumoral heterogeneity
- Limited actionable alterations (except rare BRAF/NTRK)

Therapeutic emphasis

- Clinical trials over standard salvage
- Locoregional therapies (CAR-T, oncolytic viruses)
- Anti-angiogenics mainly for symptom control

Common adult trial eligibility

- KPS ≥ 70
- Dexamethasone $\leq 2-4$ mg/day
- Prior RT + TMZ completed
- Limited systemic immunotherapy exposure

Pediatric Recurrent HGG / DMG

Defining features

- Distinct biology (H3K27M, H3G34, ACVR1, PDGFRA)

- Higher frequency of targetable alterations
- Greater emphasis on BBB penetration and drug delivery

Therapeutic emphasis

- Molecularly driven trials (e.g., BRAF, ACVR1, PDGFRA)
- Epigenetic therapies
- Convection-enhanced delivery (CED)
- CAR-T targeting GD2, B7-H3

Key pediatric-specific considerations

- Neurodevelopmental toxicity
- Prior craniospinal or focal RT dose limits
- Long-term survivorship less relevant in recurrence but still considered

Practical takeaway

Pediatric recurrent HGG is **not** a smaller version of adult GBM — it is a *different disease* requiring biology-first trial selection.

II. Alignment With NCCN & EANO Guidance (2024–2025)

This table translates the **algorithm you asked for** into guideline-consistent language.

Decision Point	NCCN (Adult CNS Tumors)	EANO (Diffuse Gliomas)	Practical Interpretation
First recurrence	Clinical trial preferred	Clinical trial strongly recommended	Trial enrollment is the default
Re-resection	Consider if feasible	Consider in select patients	Mainly for tissue + symptom relief
Re-irradiation	Category 2B	Option in selected cases	Focal recurrence, long RT interval
Bevacizumab	Acceptable (symptom benefit)	Symptomatic control only	Edema, steroid reduction
Chemotherapy (lomustine, TMZ)	Acceptable	Limited efficacy acknowledged	Palliative intent
Checkpoint inhibitors	Not standard	Not recommended outside trials	No OS benefit proven

Decision Point	NCCN (Adult CNS Tumors)	EANO (Diffuse Gliomas)	Practical Interpretation
Targeted therapy	Recommended if actionable	Strongly supported	High-value in rare subsets
Palliative care	Early integration advised	Early integration emphasized	Not end-of-life only

Key guideline philosophy

- Neither NCCN nor EANO endorses *any* standard therapy with clear OS benefit at recurrence
- Innovation = **clinical trials + molecular stratification**

III. Trial Eligibility Mapping — What Actually Determines Access

This section maps **patients** → **trial types**, which is often the real-world bottleneck.

A. CAR-T Cell Therapy Trials

Typical inclusion

- KPS ≥70 (occasionally ≥60)
- Steroids ≤2 mg dex/day (sometimes ≤4 mg)
- Tumor antigen expression confirmed
- Local catheter/Ommaya placement feasible

Common exclusions

- Multifocal leptomeningeal disease
- Active autoimmune disease
- High-dose steroids
- Rapid neurologic decline

Best candidates

- Focal recurrence
- Minimal steroid requirement
- Prior surgical access

B. Oncolytic Virus Trials (DNX-2401, PVSRIPO, G47Δ)

Typical inclusion

- Unifocal or oligofocal recurrence
- Surgical cavity or injectable lesion
- KPS ≥ 70
- Controlled seizures

Advantages

- Often **more steroid-tolerant** than CAR-T
- Can serve as bridge to immune activation

Limitations

- Delivery-dependent
- Variable response durability

C. Targeted Therapy Trials

Typical inclusion

- Confirmed actionable alteration
- Often allow lower KPS (≥ 60)
- Less restrictive on steroids

Advantages

- Rapid responses possible
- Can improve performance status → later trial eligibility

D. DDR / Novel Systemic Agent Trials

Typical inclusion

- Prior RT exposure
- Adequate marrow reserve
- Less dependence on local anatomy

Limitations

- Early-phase toxicity uncertainty
- Limited CNS penetration in some agents

IV. Unified Take-Home Framework

How experienced centers actually think about recurrent HGG:

1. **Is there a trial?**
→ If yes, optimize eligibility (steroids, timing, imaging).
2. **Is there a target?**
→ Treat first, even if off-label.
3. **Can we deliver therapy locally?**
→ CAR-T or oncolytic virus preferred over systemic drugs.
4. **If not, prioritize QoL.**
→ Bevacizumab, limited chemo, early palliative care.

If you want, I can next:

- Turn this into a **single consolidated figure (journal-ready)**
- Adapt it specifically for **tumor board use**
- Or map this directly onto **active trials at major US/European centers**

Just say the word.

map this directly onto active trials at major US/European centers

Here's a **targeted, trial-centric guide to active (or currently recruiting / not yet recruiting) recurrent high-grade glioma clinical trials** at major **US and European centers**, mapped to the **therapeutic modalities** in your algorithm. Where possible, I've added **locations and status** so you can use this for practical navigation and referral planning.

A. CAR-T Cell Therapy Trials — Recurrent GBM/HGG

These involve engineered T-cells targeting glioma antigens and are typically **Phase I** at academic centers:

1. B7-H3 CAR-T Cells

- **Trial:** B7-H3 CAR-T (e.g., NCT04385173)
- **Modality:** B7-H3 targeting CAR-T
- **Phase:** Phase 1 — Recruiting

- **Delivery:** Intracerebroventricular / Ommaya device
- **Population:** Recurrent or refractory GBM
- **Region: US sites** (Ommaya catheter delivery trials based in US centers) [Lippincott Journals](#)

2. SNC-109 CAR-T Cells

- **Trial:** NCT05868083 — Safety & efficacy of **SNC-109 CAR-T** in recurrent glioblastoma
- **Phase:** Phase 1 — **Recruiting**
- **Approach:** Single group, post-op infusion
- **Region: US sites** (early-phase immunotherapy trial) [Lippincott Journals](#)

3. NKG2D CAR-T Cells

- **Trial:** NCT04717999 — Pilot NKG2D CAR-T study
- **Status:** **Unknown / not actively recruiting** in registry
- **Region:** Historically US-based neuro-oncology centers [Lippincott Journals](#)

Notes:

- Most CAR-T trials for recurrent glioblastoma are **Phase I and safety-focused**.
- Many require **intracranial catheter (Ommaya) placement** and low steroid use at baseline.
- Recruiting batches open/close often, so checking **ClinicalTrials.gov** frequently is recommended. [Lippincott Journals](#)

B. Oncolytic Viral Therapy (OVT) Trials — Recurrent GBM/HGG

OVT uses viruses to kill tumor cells and stimulate immune responses.

1. PVSRIPO (Poliovirus Chimera)

- **Trial:** NCT03043391 — PVSRIPO via **Convection-Enhanced Delivery (CED)** in children/adults
 - **Phase:** I/Ib — **Active (not recruiting)**
 - **Region:** **US pediatric/adult sites** [MDPI](#)

- **Trial:** NCT02986178 — PVSRIPO Phase II (recurrent GBM)
 - **Phase:** II — **Active / not recruiting**
 - **Region:** US cohort [MDPI](#)

2. DNX-2401 / DNX-2440 Adenoviral Approaches

- **Trial:** NCT03896568 — DNX-2401 adenovirus delivered with/without cells
 - **Phase:** I — **Recruiting**
 - **Region:** US sites [brainlife.org](#)
- **Trial:** NCT03714334 — DNX-2440 adenovirus for recurrent GBM
 - **Phase:** I — Status varies (some EU centers listed) [wjgnet.com](#)

3. HSV-Based and Other Viral Platforms

- **Trial:** NCT02062827 — M032 (HSV-1 based virus)
 - **Phase:** I — **Active (not recruiting)**
 - **Region:** US institutions [MDPI](#)
- **Trial:** NCT03657576 — C134 (HSV-1 engineered virus)
 - **Phase:** I — **Recruiting**
 - **Region:** US centers [MDPI](#)
- **Additional HSV vectors** (e.g., G207) — some **Phase I** arms remain *active/not recruiting* at select centers (often pediatric or adult neuro-oncology groups) [MDPI](#)

Clinical insight:

PVSRIPO and DNX-2401 have the **largest patient cohorts historically** and are often at major academic hospitals with neurosurgical support for convection-enhanced delivery. [MDPI](#)

📍 C. Targeted & Other Innovative Trials (US & Europe)

1. ReSPECT-GBM (Plus Therapeutics)

- **Agent:** Rhenium-186 nanoliposome (radiotherapeutic)
- **Phase:** Phase 2 — **Enrolling**

- **Sites:**
 - UT Health San Antonio
 - UT Southwestern (Dallas)
 - MD Anderson (Houston)
 - Ohio State University (Columbus, OH)
- **Population:** Adults with recurrent GBM [Wikipedia](#)

2. ATM / DDR Inhibitor + RT

- **Agent:** ATM inhibitor WSD0628 (with re-irradiation)
- **Status:** Active but temporarily closed to accrual
- **Sites:** Mayo Clinic (Rochester, MN) [Istituto Nazionale dei Tumori](#)

3. SurVaxM Vaccine

- **Agent:** Survivin-targeted peptide vaccine
- **Status:** Active in some centers (children/young adults; broader eligibility intersects recurrent gliomas)
- **Region: US NIH & affiliated centers** [Istituto Nazionale dei Tumori](#)

D. Additional Active Recruitment in GBM

Even though not purely immune or virotherapy, these trials may be relevant depending on your algorithm's branch:

- **MSC-DNX-2401 High-Grade Glioma Trial** — Active at University of Alabama at Birmingham (AL, USA) [Istituto Nazionale dei Tumori](#)
- **Oral ONC206 Trial** — Phase I for recurrent high-grade CNS tumors (e.g., M D Anderson Cancer Center) [Istituto Nazionale dei Tumori](#)

Geographic Distribution — Real World

Region	Modalities / Active Sites
United States	CAR-T (B7-H3, SNC-109), PVSRIP, DNX-2401 derivatives, C134 HSV, ReSPECT-GBM nanoliposomes, DDR/ATM combos, vaccine platforms Lippincott Journals +2 MDPI +2
Europe	Early adenoviral OV platforms (e.g., TG6002 + 5-FC in France), DNX-2440 sites in select EU centers wjgnet.com

Region	Modalities / Active Sites
UK/Other EU	Platform protocols often via multicenter networks (EORTC/EU-CTIS) ctis.eu

📌 Practical Decisions for Referral & Patient Selection

If a patient has recurrent HGG and:

- **Antigen-expressing tumor + good KPS:** consider **CAR-T** trials (e.g., B7-H3, SNC-109) — often require intracranial delivery infrastructure and steroid minimization. [Lippincott Journals](#)
- **Accessible lesion + surgical support:** **OVT** via PVSRIPO, DNX-2401/2440, C134 — best at centers with neurosurgery and CED expertise. [MDPI](#)
- **No actionable antigen / broader eligibility:** ReSPECT-GBM, targeted radiotherapeutic, and DDR inhibitor arms may be more suitable. [Istituto Nazionale dei Tumori](#)

🧠 Summary

This mapping shows **where cutting-edge recurrent HGG therapies are actually being tested:**

- **US academic centers (Penn, City of Hope, MD Anderson, NIH, Baylor/UAB)** lead most CAR-T and virotherapy arms. [Lippincott Journals +1](#)
- **OVT trials** have a broader footprint, with both US and **European participation** in adenoviral and poliovirus protocols. [wjgnet.com](#)
- **Innovative systemic or radiotherapeutic trials** (nanoliposomes, DDR inhibitors) further broaden options for patients unsuitable for locoregional strategies. [Wikipedia](#)