Key findings immunotherapy CNS tumours

> Key findings of: Mahdi J, Trivedi V, Monje M. The promise of immunotherapy for central nervous system tumours. Nat Rev Immunol. 2025 Oct 6. doi: 10.1038/s41577-025-01227-5. Epub ahead of print. PMID: 41053233.

Here's a structured summary of the **key findings and insights** from **Mahdi J, Trivedi V, Monje M. "The promise of immunotherapy for central nervous system tumours"** (Nat Rev Immunol, 2025) Nature +1

Background & Rationale

- CNS tumours (primary brain tumours, gliomas, diffuse midline gliomas, etc.) reside in a **unique immunological environment** shaped by interactions between neurons, glia, vasculature, barrier systems (e.g. blood–brain barrier, blood–cerebrospinal fluid barrier), and immune cells. Nature +2 ResearchGate +2
- Conventional immunotherapies (checkpoint inhibitors, CAR T cells, oncolytic viruses, cancer vaccines) that work well in peripheral solid tumours have faced special challenges in the CNS setting (low antigenicity, immunosuppressive microenvironment, neurotoxicity risk, limited infiltration). Nature +1
- Recent advances in our understanding of **neural–immune crosstalk** provide new levers to tailor immunotherapy strategies for brain tumours. Nature +2 ResearchGate +2

Major Themes & Findings

1. CNS Immune Landscape & Barriers

- The CNS is not "immunologically inert" — it has resident immune populations (microglia, perivascular macrophages), meningeal lymphatics, and dynamic interactions with peripheral immunity. Nature +2 ResearchGate +2
- Barriers (BBB, perivascular niche) limit immune cell trafficking, antibody delivery, and immune surveillance. Strategies that modulate or transiently open these barriers are critical for enabling immunotherapy efficacy in CNS. ResearchGate +1
- Neural activity, neurotransmitters, synaptic connections, and neuromodulators can influence immune cell behavior (e.g. T cell trafficking, microglial activation) and tumour-immune interactions. The tumour may hijack neural circuits (via e.g. neuron-glioma synapses) to promote growth and immune evasion. Cell +1

2. Lessons from Clinical and Preclinical Trials

- Some early trials with immune checkpoint inhibitors (e.g. anti-PD1, CTLA4) in glioblastoma have shown limited efficacy, likely due to low tumour mutational burden, immune exhaustion, or suppressive myeloid environment. Nature +1
- CAR T cells targeting CNS-expressed antigens (e.g. GD2 in H3K27M-mutant diffuse midline glioma) have shown promising regressions when delivered intracranially or via cerebrospinal fluid pathways. ResearchGate +1
- Oncolytic viruses and vaccines face challenges in achieving sufficient penetration and overcoming local immunosuppression, but combinatorial approaches (e.g. virus + checkpoint blockade) are under active exploration. Nature +1

3. Challenges Specific to CNS Tumours

- **Tumour heterogeneity and antigen specificity**: Many candidate antigens are expressed in normal CNS cells, raising risk of off-tumour toxicity.
- **Immune suppression by myeloid cells & microglia**: CNS-resident myeloid populations can adopt immunosuppressive phenotypes, limiting T cell activity.
- **Neurotoxicity / neuroinflammation risk**: Inflammatory responses must be balanced carefully to avoid damage to normal neural tissue.
- **T cell exhaustion / persistence**: Sustaining functional, non-exhausted T cells in the CNS tumour microenvironment is a major barrier.
- **Limited trafficking / penetration**: Efficient delivery to the tumour site (especially deep midline structures) remains a key barrier.

4. Proposed Strategies & Future Directions

The authors propose several promising strategies to overcome the above hurdles:

- Engineering CAR T cells (or other immune effectors) with **resistance to exhaustion** (e.g. via transcriptional rewiring, metabolic programming).
- Use of **multimodal delivery routes** (intratumoral, intraventricular, intrathecal) to bypass systemic barriers.
- **Modulation of neural–immune interactions**, e.g. leveraging neuromodulators, altering neurotransmitter signaling, or disrupting neuron–tumour synapses to weaken tumour advantage.
- **Combinatorial therapies**: pairing immunotherapies with radiotherapy, small molecules, epigenetic modulators, or other agents that modulate the microenvironment.

- Use of **spatial and temporal control systems** (e.g. inducible systems, local release) to limit off-target effects.
- Biomarker development (e.g. imaging, immune signatures) to stratify patients likely to benefit and monitor response.

Take-Home Messages & Outlook

- Immunotherapy for CNS tumours holds real promise, but its success will depend not simply on porting approaches from peripheral solid tumours — it requires deep integration of neuroscience and immunology. Nature +2 ResearchGate +2
- A key enabling insight is that tumours in the brain don't just lie passively in an "immune-privileged" niche — they actively engage and co-opt neural circuits and immune elements.
- The field is moving toward **rational design**: combining mechanistic understanding, biomarker-guided patient selection, precise delivery, and engineered immune effectors.
- There is optimism that in the coming years, advances in neural-immune biology, delivery methods, and cell engineering will begin to translate into durable immunotherapy strategies for gliomas, diffuse midline gliomas, and other CNS malignancies.

If you like, I can also pull up a more detailed bullet-pointed annotated summary or even project the implications for ongoing or upcoming trials. Would you like me to do that?

Implications for ongoing or upcoming trials

Great — here are focused, trial-relevant **implications** drawn from Mahdi et al. (Nat Rev Immunol 2025) plus recent clinical signals (GD2 CAR-T, neoadjuvant ICI, oncolytic viruses, multi-target CAR-T). I'll keep each implication actionable for investigators, sponsors or data-safety teams and cite the most relevant recent evidence.

1) Prioritize route-of-delivery questions in trial design

- **Why:** Systemic delivery often fails to achieve durable intratumoural exposure in deep midline or poorly vascularized CNS sites; intratumoural, intraventricular/ intrathecal or convection-enhanced delivery (CED) can improve local exposure and reduce systemic toxicity.
- **Actionable trial design:** add dedicated arms or dose-escalation cohorts testing intracranial/intraventricular/intrathecal versus IV delivery; prespecify pharmacodynamic (PD) sampling (CSF, on-treatment biopsy when safe). (Mahdi et al.; GD2 CAR-T experience). Life Science Network +1

2) Build biomarker-rich, adaptive early-phase protocols (PD + spatial

profiling)

- **Why:** Response depends on local immune context (TILs, myeloid states, neural-immune interactions). Early PD readouts let you stop futile arms and escalate promising combos.
- **Actionable trial design:** mandatory baseline and early on-treatment tissue/CSF for single-cell, TCR clonality, myeloid signatures and spatial transcriptomics; predefine biomarker-guided expansion rules. (Mahdi et al.). Life Science Network

3) Enrich or stratify by biology — not only histology

- **Why:** Antigen expression (e.g., GD2, B7-H3, HER2, EGFRvIII), mutation signatures and immune profiles strongly influence benefit and off-tumour risk. Trials that lump heterogeneous GBM/DMG cohorts risk diluting signals.
- **Actionable trial design:** require central molecular testing for target expression / H3K27M / IDH / TMB; prespecified subgroup analyses or biomarker-selected cohorts. (Mahdi et al.; GD2 work). Life Science Network +1

4) Use rational combinations and sequencing (local therapy, radiation, epigenetic or myeloid-modulating agents)

- **Why:** Radiation and some epigenetic drugs can increase antigen presentation or effector infiltration; myeloid suppression is a dominant resistance axis in CNS tumours. Early clinical data show biological activity when immunotherapy is combined with other modalities.
- **Actionable trial design:** include combination cohorts (e.g., CAR-T or oncolytic virus + anti-myeloid agent, RT + ICI). Use safety lead-in cohorts for combinations and monitor neuroinflammation closely. Life Science Network +1

5) Measure and prespecify neurotoxicity/neurologic safety endpoints and management algorithms

- **Why:** CNS inflammation can cause devastating neurologic morbidity; neurotoxicity phenotypes differ from systemic CRS/ICANS.
- **Actionable trial design:** prespecify neurologic AE grading, distinct management algorithms (steroids, intrathecal rescue, IL-6 blockade escalation rules), mandatory neurologic baseline/function scales and early MRI/EEG triggers; separate DSMB for neuro events. (Mahdi et al.). Life Science Network

6) Consider multi-antigen or multi-target strategies to overcome antigen loss

- **Why:** Single-antigen relapse is common; early reports with dual-target CARs show higher initial response rates but varying durability.

- **Actionable trial design:** evaluate bispecific CARs or sequential multi-target approaches, and plan molecular monitoring for antigen loss (IHC/CSF ctDNA) to trigger salvage strategies. (Recent CAR-T reports). Reuters +1

7) Leverage neoadjuvant windows where possible to study immune pharmacodynamics

- **Why:** Neoadjuvant ICI in GBM produced clear intratumoural immune activation signatures—useful as a Proof-of-Biology even if survival benefit is uncertain.
- **Actionable trial design:** embed single-dose neoadjuvant arms (ICI or other immunomodulator) with pre-op biopsy and post-resection tissue for PD endpoints and to choose combos for expansion. Nature

8) For pediatric / DMG trials, expect different risk–benefit and regulatory paths

- **Why:** Pediatric tumours (H3K27M DMG) have distinct antigens (e.g., GD2) and a high unmet need; regulators and ethics boards often accept different safety tradeoffs. Early GD2 CAR-T data show promising regressions in children/young adults.
- **Actionable trial design:** include pediatric-specific endpoints, neurodevelopmental follow-up, and pediatric formulation/manufacturing plans; engage regulators early for accelerated pathways. Nature +1

9) Endpoint selection — include functional/neurologic and patient-reported measures

- **Why:** Traditional radiographic endpoints (RANO/PFS) can be confounded by immunotherapy-related inflammation; survival and neurologic function matter equally.
- **Actionable trial design:** co-primary or hierarchical endpoints combining OS or durability, steroid-sparing, and validated neurologic function / quality-of-life metrics; prespecify immune-related response criteria and radiographic adjudication. (Mahdi et al.). Life Science Network

10) Manufacturing, logistics and access: plan for complex supply chains and equity

- **Why:** Intracranial or intrathecal cell products, rapid manufacturing, or repeat dosing raise operational hurdles. Trial success depends on feasible manufacturing timelines and geographic access.

- **Actionable trial design:** build regional manufacturing capacity or cryopreservation/back-up plans; include pragmatic criteria for referral and support for travel/CSF sampling; consider allogeneic “off-the-shelf” arms if safety allows. (Field trends / CAR-T programs). Reuters +1

Short checklist investigators can copy into protocols

1. Central molecular/target expression testing + biomarker stratification.
2. PD sampling plan (CSF, pre/post tumor tissue, blood) and analytic plan.
3. Delivery route cohorts (IV vs intratumoural/intraventricular/CED).
4. Safety DSMB with neurology expertise + prespecified neuro-AE management.
5. Built-in expansion/stop rules tied to early PD signals (adaptive design).
6. Prespecified imaging/response adjudication for immune-related pseudoprogression.
7. Pediatric-specific cohorts and long-term neurodevelopment follow-up when relevant.
8. Plan for combination arms targeting myeloid suppression / RT / epigenetics.

Quick evidence anchors (selected)

- Mahdi J et al., 2025 — state-of-the-field review discussing neural–immune interactions and delivery/engineering implications. Life Science Network
- GD2 CAR-T in H3K27M DMG — strong biologic rationale and early clinical activity supporting intraventricular/intravenous delivery exploration. Nature +1
- Neoadjuvant anti-PD-1 work in glioblastoma shows clear intratumour PD signals; useful as a screening/PD platform. Nature
- DNX-2401 and other oncolytic approaches show direct oncolysis + immune priming — supports trials combining OVs with ICI or cell therapy. PMC
- Multi-target CAR-T early results (industry academic reports) show higher response rates but durability and relapse mechanisms are active questions. Reuters +1

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