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Pilot report of an anti-PD-1/VEGF bispecific antibody for treating recurrent H3K27M-mutant diffuse midline gliomas

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Background: H3K27M-mutant diffuse midline gliomas (DMGs) are highly aggressive, immunosuppressive tumors that are resistant to conventional therapies. Median overall survival is typically 8–11 months after diagnosis; fewer than 10% of patients survive beyond 2 years, and the 5-year survival rate is generally below 1%. Ivonescimab, a novel bispecific antibody that simultaneously targets PD-1 and VEGF, may help overcome this resistance by restoring T-cell immunity and normalizing tumor vasculature. We report the first use of ivonescimab as salvage therapy for recurrent DMG. Methods: Two patients with recurrent H3K27M-mutant DMG who experienced rapid progression after standard first-line chemoradiotherapy received off-label ivonescimab (10 mg/kg) plus chemotherapy intravenously every 3 weeks for 5–6 cycles. Results: After only three cycles, MRI revealed marked tumor shrinkage and substantial improvement in Karnofsky Performance Status (KPS). At treatment completion, both patients achieved partial remission (PR, tumor volume decreased at 66.7% and 68.7%, respectively). Both patients-maintained progression-free survival (PFS) of more than 8 months and overall survival (OS) of more than 16 months, and both were alive more than 10 months after recurrence. Furthermore, treatment was well tolerated, the most common adverse event was fatigue, hematology toxicity and nausea vomiting, and no grade 3 or higher adverse events were observed. Conclusions: These preliminary findings demonstrate the tolerability of concurrent anti-PD-1/VEGF bispecific antibody with chemotherapy for recurrent DMG, who do not fit for reRT, and suggests that combination therapy may offer survival benefit. However, larger and more rigorous studies are needed to validate these initial observations and to define the efficacy and safety of this strategy in the clinical management of DMG.

Keywords: H3K27M, recurrent diffuse midline glioma, anti-PD-1/VEGF, immunotherapy

Introduction

Diffuse midline gliomas (DMGs) are WHO grade 4 tumors associated with a dismal prognosis in children and young adults. Median overall survival (mOS) is typically 8-11 months after diagnosis; fewer than 10% of patients survive beyond 2 years, and the 5-year survival rate is generally 2.2%[1, 2]. These tumors arise in midline structures, including the thalamus, brainstem, particularly in diffuse intrinsic pontine glioma (DIPG), and spinal cord. They are characterized by H3K27M mutations in histone H3 genes (H3F3A and HIST1H3B/C) and are associated with epigenetic dysregulation and treatment resistance. The H3K27M mutation leads to a global reduction in H3K27 trimethylation, thereby contributing to epigenetic dysregulation and tumor proliferation.

Accordingly, DMGs are biologically distinct from other gliomas[3]. These tumors are resistant to chemotherapy and exhibit low immunogenicity[4, 5]. Despite advances in molecular profiling, targeted therapies alone have not substantially improved outcomes, and radiotherapy remains the only treatment with established, albeit temporary, benefit. Therefore, novel therapeutic strategies beyond surgery, radiotherapy, and chemotherapy are urgently needed to improve patient outcomes (Fig. 1). Although IDH inhibitors such as vorasidenib have been used in patients with low-grade glioma (LGG) and high-grade glioma (HGG), DMGs generally lack IDH mutations[6]. Current evidence suggests that immunotherapy may represent a promising alternative therapeutic modality for DMG[7, 8]. Despite the critical need to elucidate the tumor immune microenvironment (TIME) of DMG to enable the development of effective therapies, research in this area remains limited. Ongoing clinical studies are evaluating a range of immunotherapeutic strategies, including GD2-CART therapy, B7-H3 target therapy, pembrolizumab, IL-12 adenoviral vectors, and cemiplimab combined with radiotherapy[8-11]. A deeper understanding of TIME dynamics and the development of novel immunotherapies will likely be critical to advancing the future treatment landscape of DMG[5, 12-14] (Table 1).

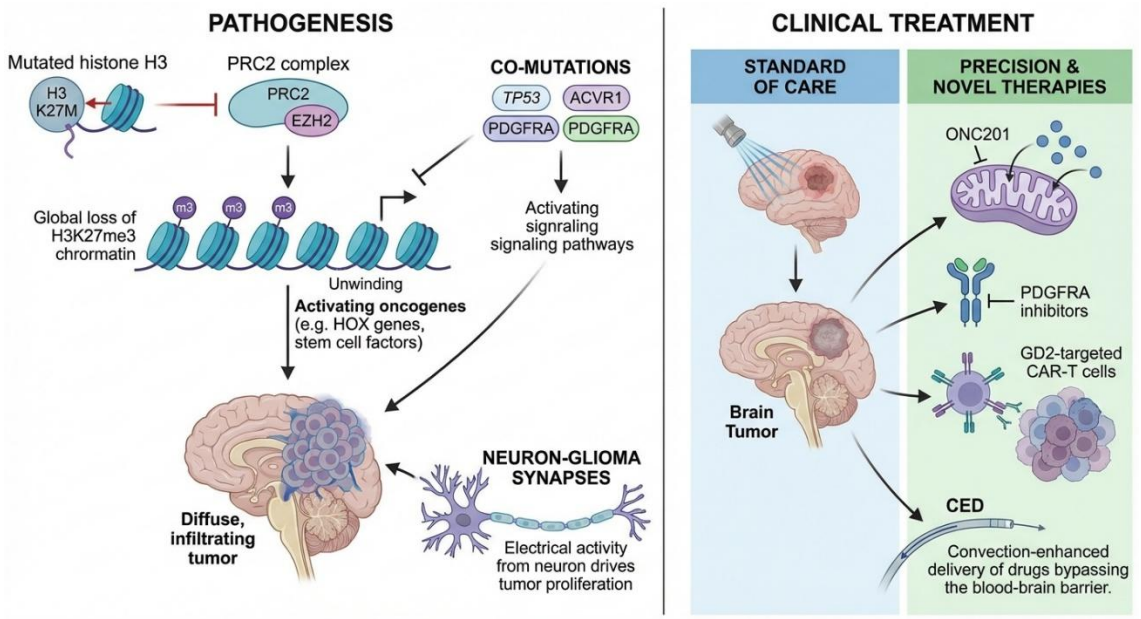

Fig. 1. Molecular pathogenesis and therapeutic landscape of DMG. **A:** Epigenetic mechanism of DMG. Over 80% of DMGs harbor a missense mutation in histone H3 genes (most commonly H3F3A for H3.3 or HIST1H3B for H3.1), resulting in an H3K27M substitution. The mutant H3K27M protein acts as a dominant-negative inhibitor that binds and sequesters the Polycomb Repressive Complex 2 (PRC2), specifically inhibiting its catalytic subunit, EZH2. Consequently, PRC2 is unable to catalyze the repressive trimethylation of histone H3 (H3K27me3). This global loss of the repressive H3K27me3 mark leads to the aberrant transcription of oncogenes, trapping the tumor cells in a highly proliferative, undifferentiated stem-like state. **B:** Current and emerging treatment modalities. Standard-of-care therapies, including radiotherapy and chemotherapy, historically yield unsatisfactory clinical outcomes. Consequently, novel targeted approaches are under active investigation. Emerging therapies include the DRD2/ClpP modulator ONC201 and GD2-directed CAR-T cell therapy, both of which have demonstrated clinical efficacy. Additionally, kinase inhibitors targeting secondary signaling pathways driven by PDGFRA or ACVR1 mutations are being evaluated. Epigenetic modifiers, such as HDAC and EZH2 inhibitors, aim to directly reverse the downstream effects of the H3K27M mutation; however, clinical application is currently limited by systemic toxicity and poor blood-brain barrier (BBB) penetrance.

Table 1 Summary of immunotherapy clinical trials in glioma

Therapy	Clinical Trials	Outcome	Status/Remarks
Checkpoint Inhibitors (ICIs)	• CheckMate 143/498/548 • NCT05580562	No survival benefit Recruiting	Not recommended as monotherapy Recruiting
Vaccines	• DCVax-L	Mixed results	Under review
CAR-T	• EGFRvIII/IL13Rα2	Shown efficacy	Ongoing research
Oncolytic Viruses	• DNX-2401	Durable responses in rGBM	Ongoing research

Furthermore, combinatorial strategies, improved patient selection, and a deeper understanding of the brain tumor immune microenvironment are critical for therapeutic progress[15-17]. These approaches include combining immune checkpoint inhibitors (ICIs) with radiotherapy, oncolytic viruses, vaccines, or anti-angiogenic agents such as bevacizumab[18-20]. Promising outcomes may also be achieved by combining ICIs with other targeted therapeutic strategies[10, 21-24]. Remodeling the glioma tumor microenvironment is a key determinant of immunotherapy efficacy. In particular, low-dose vascular endothelial growth factor (VEGF) inhibitors may promote vascular normalization within the tumor microenvironment, thereby enhancing antitumor immune responses. Therefore, emerging agents such as ivonescimab (Akeso Biopharma), a novel bispecific antibody targeting PD-1 and VEGF-A, may help overcome these limitations. By blocking PD-1, ivonescimab may restore T-cell function, while inhibition of VEGF-A may suppress tumor angiogenesis and reprogram the tumor microenvironment to promote immune infiltration. Preclinical studies further suggest that the presence of VEGF-A increases the binding affinity of ivonescimab for PD-1 by more than 18-fold, with a reciprocal effect observed for VEGF-A binding, indicating cooperative binding and potential synergistic antitumor activity[25, 26]. This dual mechanism may be particularly advantageous in tumors characterized by both vascular abnormalities and an immune-desert phenotype, such as DMG.

In this report, ivonescimab was used as salvage therapy. To date, no clinical trial has evaluated ivonescimab in DMG.

Treatment Methods

Two Chinese patients of Han ethnicity with DMG received salvage therapy at West China Hospital, Sichuan University. This clinical observation was approved by the Ethics Committee of West China Hospital, Sichuan University. The treatment regimen consisted of ivonescimab (10 mg/kg administered intravenously every 3 weeks for 5–6 cycles) combined with temozolomide (100 mg once daily for 21 days in each 28-day cycle, for a total of 6 cycles). Baseline assessments included thyroid function tests,

cardiac biomarker measurements, electrocardiography, and thyroid ultrasonography. Treatment-related adverse events were assessed according to the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0 (Supplementary).

Results

Both patients derived significant clinical benefit (Fig. 2). Notably, compared with chemotherapy alone, the combination of ivonescimab and chemotherapy did not appear to increase the incidence of adverse events. The most common adverse event was fatigue, hematology toxicity and nausea vomiting, which was predominantly grade 1 or 2, and no immune pneumonia and autoimmune myocarditis were observed.

After recurrent, patient 1 received ivonescimab plus temozolomide. At week 9, MRI showed a marked reduction in tumor size, and the patient's Karnofsky Performance Status (KPS) improved from 40 to 80, and partial remission (PR, tumor volume decreased 67.7%) was achieved with good tolerability according to RECIST criteria. By week 18, the patient was recurrent again. The patient tolerated therapy well, and no immune-related adverse events above grade 2 were observed. The patient achieved a progression-free survival (PFS) of 6 months, measured from recurrence to second recurrence, and an OS of 16 months, measured from diagnosis to death. Post-recurrence survival exceeded 8 months (Supplementary Fig. 4&5).

After recurrent, patient 2 received ivonescimab plus temozolomide and cisplatin for 6 cycles. At week 9, MRI showed a marked reduction in tumor size, and the patient's KPS improved from 30 to 90. By week 21, PR (tumor volume decreased 68.8%) was achieved according to RECIST criteria. The patient achieved a PFS of 8 months and remained alive at the time of last follow-up. Post-recurrence survival exceeded 10 months, and OS was more than 17 months (Supplementary Fig. 6&7).

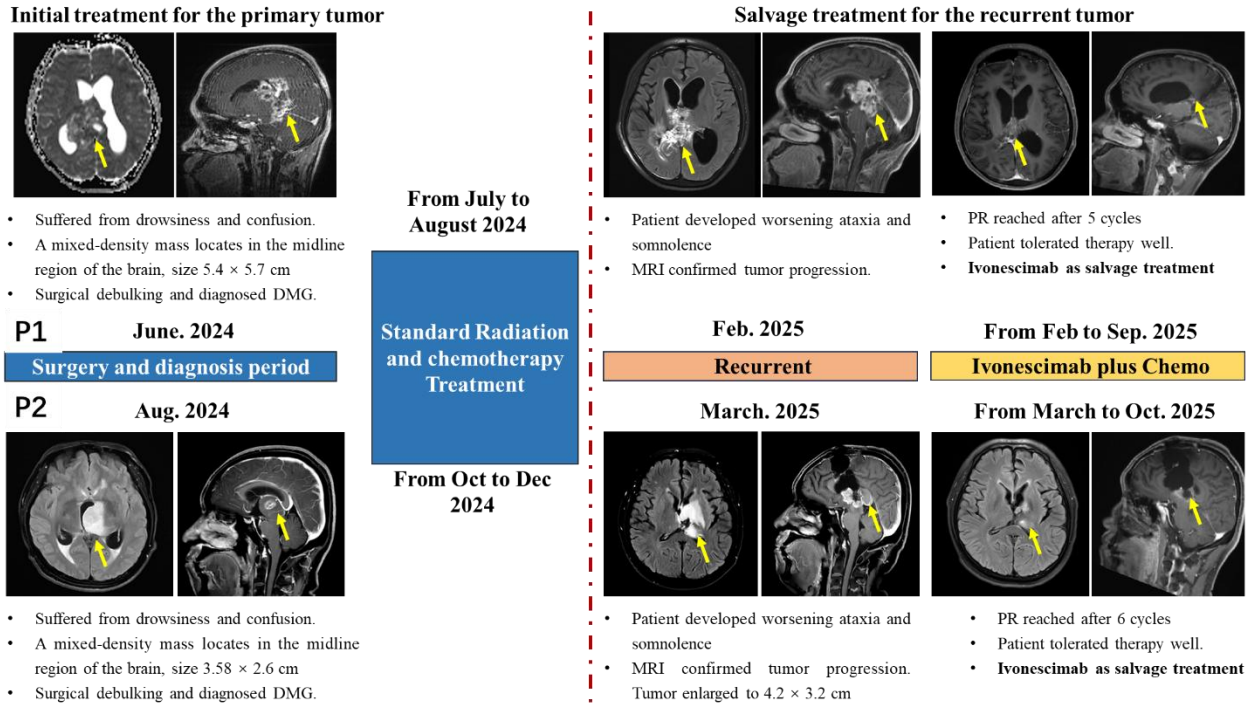

Fig. 2 Treatment timetable. **P1:** A patient diagnosed with DMG (June 2024) initially presented with a 5.4 × 5.7 cm heterogeneous mass. Following surgical resection, the patient received standard focal radiotherapy (60 Gy/30 fractions) with concurrent temozolomide (TMZ). Eight months post-surgery (Feb 2025), MRI confirmed tumor progression. The patient was initiated on salvage therapy with ivonescimab and TMZ. By week 9, imaging demonstrated significant tumor shrinkage, correlating with an improvement in Karnofsky Performance Status (KPS) from 40 to 80, and PR was achieved. By week 18, the patient was recurrent again. For the salvage regimen, post-recurrence progression-free survival (PFS) was 6 months, and post-recurrence survival reached 8 months. Overall survival (OS) from initial diagnosis to death was 16 months. **P2:** A patient diagnosed with a 3.58 × 2.6 cm left thalamic DMG (Aug 2024) underwent resection followed by focal radiotherapy (60 Gy/30 fractions) with concurrent TMZ and teniposide (6 cycles). Seven months post-surgery (March 2025), MRI confirmed disease progression, with the tumor enlarging to 4.2 × 3.2 cm. The patient received 6 cycles of ivonescimab, TMZ, and cisplatin. At week 9, MRI revealed a marked reduction in tumor burden, accompanied by a dramatic clinical recovery (KPS improved from 30 to 90). PR was achieved by week 21. At the time of last follow-up, the patient remained alive with a post-recurrence PFS of 8 months, post-recurrence survival exceeding 10 months, and an ongoing OS of >17 months.

Discussion

H3K27M-mutant DMG is a highly aggressive primary malignancy arising in the midline structures of the central nervous system. Mortality is exceptionally high, with a 5-year survival rate of only 2.2% in

newly diagnosed patients and a mOS of approximately 1 year[2].

As shown in Table 2, numerous clinical trials are currently investigating DMG. Despite major advances in immunotherapy across many cancer types, outcomes in glioma remain disappointing because of its immunosuppressive microenvironment and unique biology, particularly with ICIs[27]. In a previous clinical trial, pediatric patients with recurrent DIPG who received re-irradiation (reRT) combined with a PD-1 inhibitor achieved a mOS of 22.9 months. These findings suggest a potential survival benefit of combining reRT with PD-1 blockade in recurrent DIPG[28]. However, given the limited immune infiltration in DMG, PD-1/PD-L1 inhibitors used as monotherapy may have limited efficacy and may provide only modest survival benefit[5]. Although numerous studies have evaluated PD-1/PD-L1-targeted immunotherapy in gliomas, the CheckMate 143, CheckMate 498, and CheckMate 548 trials showed that checkpoint inhibitors failed to demonstrate significant survival benefits in patients with newly diagnosed or recurrent glioblastoma (GBM), regardless of MGMT methylation status[29-35]. However, a recent study suggested that nivolumab plus ipilimumab and relatlimab may be effective as neoadjuvant triplet immune checkpoint blockade in newly diagnosed GBM[15].

Meanwhile, anti-angiogenic agents used alone have also produced suboptimal results. In the AVF3708g (BRAIN) study, the 6-month progression-free survival rate (PFS-6) and objective response rate (ORR) in the bevacizumab monotherapy group were 42.6% and 28.2%, respectively, and the median duration of response was 5.6 months. Similarly, in the NCI 06-C-0064E trial, bevacizumab monotherapy achieved a PFS-6 rate of 29%, a 6-month OS rate of 57%, and a mOS of 31 weeks. Angiogenesis is a defining feature of GBM and a major driver of tumor growth, invasion, edema, and treatment resistance. Hypoxia, persistent VEGF signaling, and interactions among tumor, endothelial, stromal, and immune cells promote the formation of abnormal, highly permeable vasculature that supports tumor progression. Emerging evidence indicates that non-coding RNAs (ncRNAs) further regulate this process through epigenetic, transcriptional, and post-transcriptional mechanisms that control angiogenesis-related genes. These mechanisms provide a strong rationale for the use of anti-angiogenic therapy in GBM. By inhibiting VEGF-dependent and related pathways, anti-angiogenic therapy can reduce neovascularization, transiently normalize tumor vasculature, decrease vascular permeability, and alleviate peritumoral edema, thereby potentially enhancing the efficacy of radiotherapy, chemotherapy, and combination regimens. However, these benefits are often limited by adaptive resistance and compensatory angiogenic signaling. A better understanding of GBM vascular biology, including ncRNA-mediated regulation, is therefore essential for the development of more durable and effective therapeutic strategies[36].

Table 2 Key clinical research data on immunotherapy for DMG/DIPG

Therapy	Target	Clinical Trials	Clinical Data
CAR-T	• GD2	NCT04196413	Radiographic response and symptom improvement.
	• B7-H3	NCT04185038	Disease stabilization and potential bioactive signals
	• IL-13Rα2	NCT04003649	
	• HER2	NCT03500991	Shown efficacy.
	• EGFR806	NCT03638167	
Vaccines	• H3.3K27M	NCT02960230	Specific T-cell responses can be observed.
	• Peptide Vaccine	NCT03923769	/
ICI	• PD-1 / PD-L1	NCT03638169	PD-1/PD-L1 inhibitor monotherapy is ineffective.

Improving therapeutic efficacy remains an urgent clinical challenge. Here, we report a novel dual-targeted therapeutic strategy combining PD-1 blockade with VEGF inhibition, which demonstrated promising efficacy. Ivonescimab is a bispecific antibody targeting both PD-1 and VEGF-A. It has been approved in China for selected NSCLC indications and is under regulatory review for additional uses. Multiple global phase III trials are currently underway to evaluate its efficacy and safety across diverse patient populations and tumor types. The U.S. Food and Drug Administration has granted Fast Track designation to Ivonescimab in combination with chemotherapy for patients with EGFR-mutant NSCLC who have progressed after tyrosine kinase inhibitor (TKI) therapy. In the phase III HARMONi-2 trial, Ivonescimab monotherapy significantly improved PFS compared with pembrolizumab in treatment-naïve patients with PD-L1-positive advanced NSCLC. Among treatment-naïve patients with PD-L1-positive tumors (tumor proportion score, TPS ≥1%), those treated with Ivonescimab at doses >10 mg/kg every 3 weeks achieved an ORR of 60.0% and a disease control rate (DCR) of 97.1%. In patients with high PD-L1 expression (TPS ≥50%), the ORR was 76.9% and the DCR reached 100%. These findings suggest that Ivonescimab has favorable efficacy across different levels of PD-L1 expression. Beyond its approved indication in lung cancer, Ivonescimab is also being evaluated in phase II clinical trials for cervical cancer, ovarian cancer, triple-negative breast cancer (TNBC), small cell lung cancer (SCLC), and hepatocellular carcinoma (HCC). However, no clinical trials have yet evaluated ivonescimab in GBM or DMG.

As shown in Fig. 3, the synergy between VEGF inhibition and PD-1/PD-L1 blockade arises from their complementary effects on the tumor microenvironment. VEGF-driven angiogenesis creates abnormal, hypoxic vasculature that restricts effector T-cell infiltration and impairs dendritic cell maturation. It also recruits immunosuppressive populations, such as regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs), induces FasL expression on tumor endothelium that

selectively eliminates $CD8^+$ T cells, and upregulates inhibitory checkpoints, including PD-1, CTLA-4, TIM-3, and LAG-3, on T cells[37, 38]. VEGF blockade can normalize tumor vasculature, reduce hypoxia, restore dendritic cell function, diminish Treg and MDSC accumulation, and downregulate inhibitory receptor expression, thereby converting the tumor into a more immunologically active or 'immune-hot' state[39-42]. In parallel, PD-1/PD-L1 blockade can more effectively reinvigorate exhausted T cells, sustain antitumor activity, and enhance cytotoxic responses. This mechanistic synergy has translated into clinical benefit, as demonstrated in the IMbrave150 trial, in which atezolizumab plus bevacizumab significantly improved OS and PFS compared with sorafenib in hepatocellular carcinoma, establishing this combination as a standard first-line therapy[43].

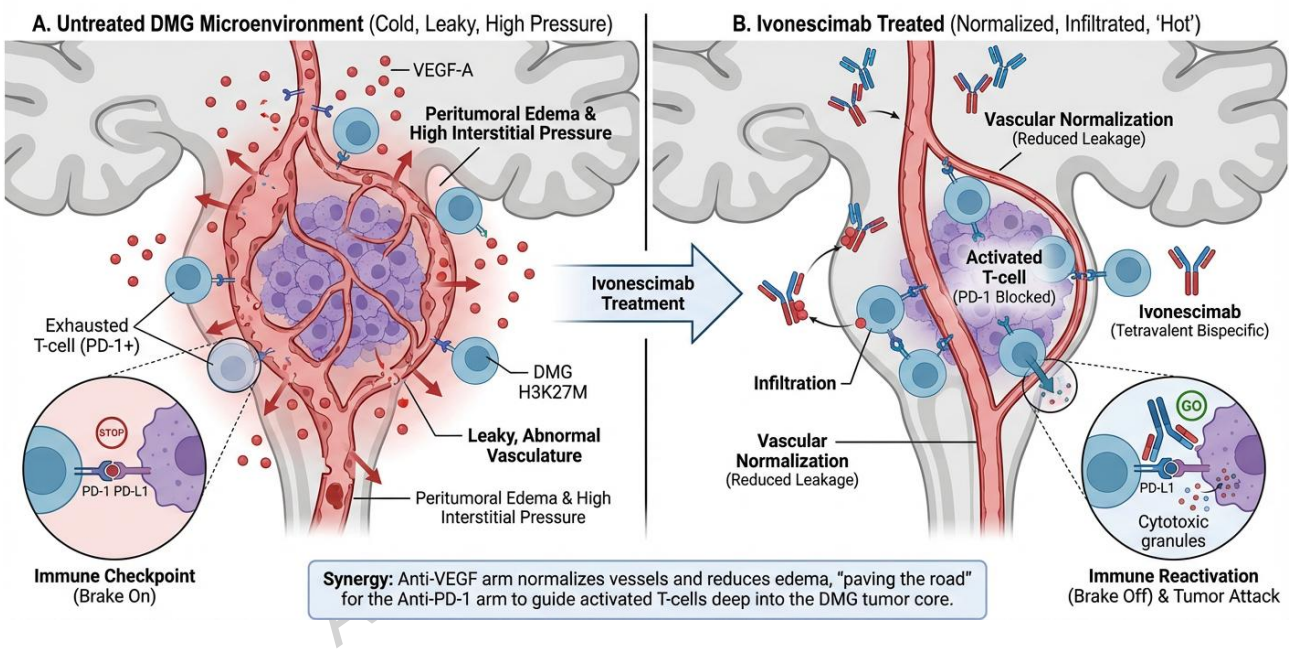

Fig. 3 Potential mechanism of ivonescimab in DMG, acting through synergistic vascular normalization and immune activation. **A:** Anti-VEGF-mediated vascular normalization. In the anatomically confined pons, tumor-derived VEGF induces disorganized, leaky blood vessels and peritumoral edema. This generates high interstitial fluid pressure, creating a physical barrier that restricts the entry of drugs and immune cells. By sequestering VEGF, ivonescimab normalizes the tumor vasculature, reducing fluid leakage and lowering interstitial pressure. This structural repair paradoxically enhances local blood perfusion, facilitating the efficient delivery of T-cells and the therapeutic antibody into the tumor core. **B:** Anti-PD-1-mediated immune reactivation. DMGs are characteristically 'immunologically cold' tumors with sparse, exhausted T-cell populations. Ivonescimab overcomes this via a targeted 'hitchhiking' mechanism. The anti-VEGF arm concentrates the molecule at the tumor vasculature, delivering the anti-PD-1 arm directly to the site of action. Once localized in the tumor

microenvironment, the antibody blocks the PD-1/PD-L1 checkpoint, successfully reversing exhaustion and reactivating infiltrating T-cells to mount an anti-tumor response.

Thus, combined blockade of VEGF-A and PD-1 may enhance antitumor activity, suggesting that ivonescimab may represent a promising therapeutic option. In combination therapy with PD-1 inhibitors and bevacizumab, the two agents act as independent molecules with distinct pharmacokinetic profiles. Bevacizumab neutralizes VEGF-A to promote vascular normalization and facilitate T-cell infiltration, whereas PD-1 antibodies independently reinvigorate T cells. However, because these agents function separately, they may lack direct spatial synergy and may achieve suboptimal intratumoral colocalization. In contrast, ivonescimab functions as a single molecular entity capable of simultaneously engaging both PD-1 and VEGF-A, thereby linking anti-angiogenic and immune-activating effects within the same spatial niche. Mechanistically, binding to intratumoral VEGF may serve as a molecular 'anchor', enriching the drug within tumor tissue and increasing its local concentration. Through cooperative binding, this anchoring may optimize molecular interactions with PD-1, thereby enhancing blockade efficiency in local tumor-infiltrating lymphocytes. Furthermore, by modulating the immunosuppressive microenvironment and reversing VEGF-mediated immune suppression, ivonescimab may promote the conversion of immunologically 'cold' tumors into 'hot' tumors, thereby potentiating antitumor efficacy.

For the proper dose, in a multicenter phase Ib/II clinical trial (AK112-202), four dose cohorts were evaluated: 10 mg/kg, 20 mg/kg, 20 mg/kg, and 30 mg/kg administered every 3 weeks. Based on dose-escalation results, the recommended phase II dose (RP2D) was established as 20 mg/kg every 3 weeks. However, given the immunologically cold tumor microenvironment characteristic of DMG, the optimal dose for this disease remains to be defined. In the present report, a dose of 10 mg/kg was selected for safety considerations.

In addition, this report describes patients with DMG who experienced recurrence within 1 year after standard Stupp therapy. Although this patient population may not be suitable for re-irradiation, chemotherapy combined with bevacizumab together with re-irradiation may be considered in patients with DMG recurrence more than 1 year after standard treatment. The underlying mechanism may involve vascular normalization, which could improve intratumoral delivery of temozolomide while alleviating tumor hypoxia, thereby enhancing radiosensitivity. In addition, radiotherapy and temozolomide-induced tumor cell death may release tumor antigens that stimulate antitumor immunity, thereby generating a stronger and more sustained immune response.

According to the results, despite the promising clinical outcomes observed, several important limitations of this pilot study must be acknowledged. First, the sample size was extremely small, comprising only two patients. Consequently, these findings are preliminary and should be interpreted strictly as hypothesis-generating. We strongly caution against overinterpreting either the efficacy or the generalizability of this regimen. The robust responses observed in these two patients may not be representative of outcomes in the broader DMG population, particularly given the profound biological heterogeneity of DMGs. Moreover, two cases are insufficient to establish a definitive safety profile. Although this dual PD-1/VEGF-targeting strategy plus chemotherapy represents a compelling therapeutic avenue, robust large-scale prospective clinical trials are urgently needed to validate these findings and determine its true clinical value.

Conclusion

This brief report suggests a potential synergistic effect between anti-angiogenic therapy and PD-1 blockade plus chemotherapy in recurrent DMG. These preliminary findings suggest that this treatment strategy is well tolerated and may improve patient outcomes. However, larger and more rigorous studies are needed to validate these initial observations and to define the efficacy and safety of this strategy in the clinical management of DMG.

Ethics approval and consent to participate

Informed consent was obtained from the patient for the present report, and this study was approved by Ethics Committee of West China hospital.

Consent for publication

All authors have read and approved the manuscript for publication.

Availability of data and material

All relevant data is included within the manuscript. Figures 1 and 3 were designed by the authors, with drawing assistance provided by Nano-Banana AI.

Competing interests

The authors declare that the research was conducted in the absence of any commercial or financial

relationships that could be construed as a potential conflict of interest.

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Authors' Contributions

Prof. Li Yanchu, Dr. Wang Hongbin, Prof. Yuan Xiaoli and Dr. Wang Jun conducted histological investigations, reviewed the literature, and wrote the manuscript. Prof. Wang Feng and Prof. Liu Lei edited the manuscript. and Prof. Li Yanchu, Dr. Zhang Li, Dr. Wang Jun, and Dr. Ren Meiling collected clinical data.

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Supplementary

Case 1

A 24-year-old male patient presented with drowsiness and confusion, and MRI scan show that a mixed density mass shadows were observed in the midline area of the brain, presenting cystic and solid changes. The lesions mainly involved the brainstem, the third ventricle, the posterior Angle of the right ventricle, the septum pellucidum and the compression part of the corpus callosum. The size of the mass was approximately 5.4×5.7cm. As shown in time table (Fig. 3), surgery was performed, and immunohistochemistry showed strong nuclear positivity for H3K27M mutant protein, and GFAP (+), ATRX (-), p53(+), Oligo-2(+), Ki-67(MIB-1) (+ 30%), EMA (-), CD34(-), SMA (-). H3F3A gene mutation (+) was detected: codon 27 mutation (K27M). HIST1H3B gene mutation was not detected. MGMT promoter methylation was positive, and IDH1/2 and TERT were negative. Histopathological morphology and immunophenotype confirmed DMG. After surgery, the patient underwent focal radiotherapy (60 Gy in 30 fractions) with concurrent temozolomide. Initial follow-up MRI showed stable disease, and clinical symptoms improved moderately. Five months after the surgery, bilateral lateral ventricle effusion occurred. While VP drainage was performed, and the bilateral lateral ventricle effusion of the patient improved (Fig. 4).

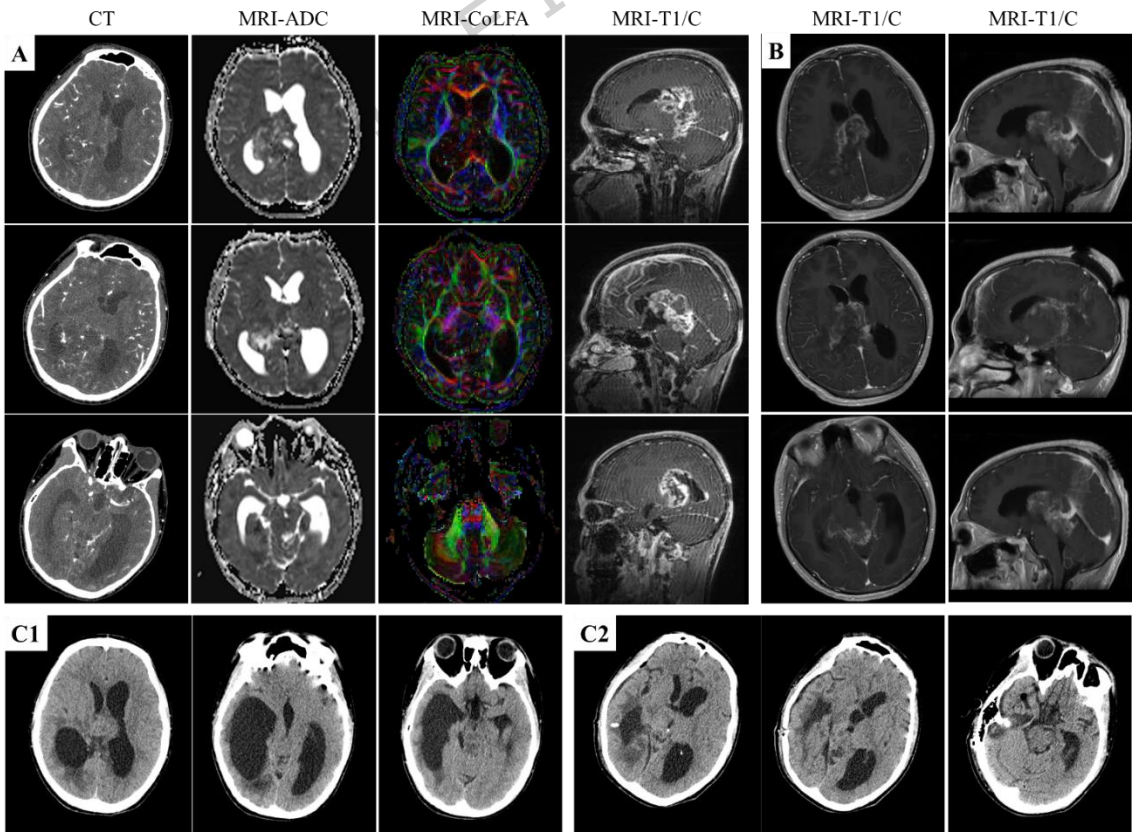

Fig. 4 Radiology test of patient 1 before recurrent. **A**: Before surgery: CT and MRI scan were test. CT scan shows a mixed-density mass in the midline region of the brain, exhibiting cystic-solid features. High-density calcifications are visible within the lesion. The mass primarily involves the brainstem, third ventricle, posterior horn of the right lateral ventricle, septum pellucidum, and splenium of the corpus callosum. MRI scan by T1/C and ADC shows the largest cross-sectional area of the tumor measures approximately 5.4 × 5.7 cm, and there is supratentorial ventricular enlargement. **B**: 72 hours after surgery: MRI scan shows a patchy mixed-signal area in the surgical region, with localized uneven diffusion restriction. Contrast-enhanced imaging reveals multiple areas of enhancement along the lesion margins and adjacent brain tissue. Short T1 signal areas are seen in the bilateral ventricles, third ventricle, and some sulci of the right cerebral hemisphere. Mild dilation of the bilateral ventricles and third ventricle is also noted. **C:** Five months after the surgery, bilateral lateral ventricle effusion was found. C1: Before VP drainage surgery, the anterior horn of the right lateral ventricle is compressed and narrowed, while the temporal horn of the right lateral ventricle and the posterior horns of both lateral ventricles are markedly dilated. The midline structures are slightly shifted to the left, and there is severe supratentorial hydrocephalus. C2: After VP drainage surgery, the hydrocephalus was significantly relieved.

However, eight months after surgery, the patient developed worsening ataxia and somnolence, and MRI confirmed tumor progression. Because of rapid progression and lack of alternative therapies, the patient received Ivonescimab and temozolomide. At 9 weeks, MRI revealed a major reduction in tumor size, and the patient's KPS improved from 40 to 80, and PR was achieved according to RECIST criteria. After 18 weeks, tumor was recurrent again. The patient tolerated therapy well, and no immune-related adverse events over grade 2 were observed (Fig. 5).

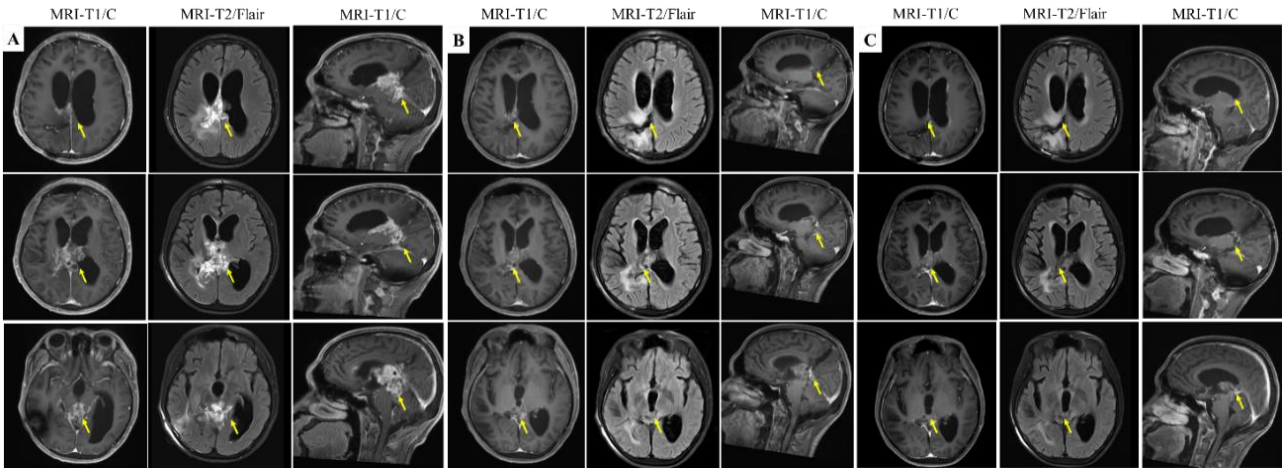

Fig. 5 Radiology test of patient 1 after recurrent. **A:** Eight months after the surgery, the lesion recurred. An irregularly shaped, heterogeneously enhancing mass is observed in the corpus callosum region,

compressing the adjacent cerebral aqueduct. There is enlargement of the supratentorial ventricles, along with marked enhancement on the surface of the brainstem. **B:** After three-cycles treatment. Compared to before treatment, the area of abnormal enhancement has significantly decreased. **C:** After five-cycles treatment, and the area of abnormal enhancement has significantly decreased.

Case 2

In August 2024, a 40-year-old male patient presented with dizziness without any obvious trigger, in the form of vertigo of long duration, with double vision, with persistent tinnitus, with unsteady and assisted walking, with occasional involuntary shaking of the lower limbs during sleep, with slightly slower reaction time, and with memory loss. Head MRI diagnosed left thalamic glioma (Fig. 6), and as shown in time table (Fig. 2), surgical treatment was performed. Postoperative pathology diagnosed diffuse midline glioma, H3K27M mutant, and GFAP (+), ATRX (-), p53(+), 0ligo-2(+), Ki-67(MIB-1) (+ 25%). H3F3A gene mutation (+) was detected: codon 27 mutation (K27M). HIST1H3B gene mutation was not detected. MGMT promoter methylation, IDH1/2 and TERT were negative. Histopathological morphology and immunophenotype confirmed DMG. After surgery, the patient underwent focal radiotherapy (60 Gy in 30 fractions) with concurrent temozolomide and teniposide for six cycles.

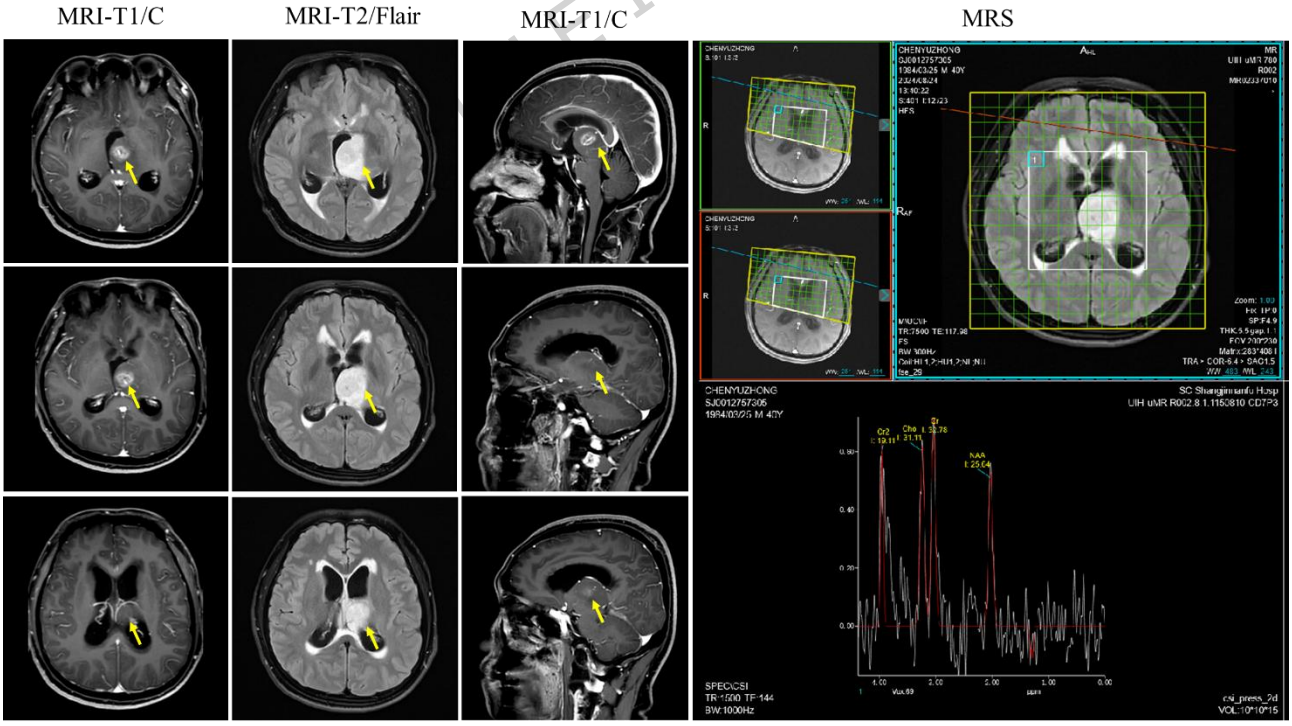

Fig. 6 Radiology test of patient 2 before recurrent. MRI scan before surgery. Several punctate and patchy areas of slightly prolonged T2 signal were observed in the bilateral frontal lobes and

periventricular white matter, showing high signal intensity on FLAIR sequences. A mass was seen in the left thalamus, exhibiting slightly prolonged T1 and T2 signal intensity, and slightly high signal intensity on FLAIR sequences. Diffusion was mildly restricted, with significant internal enhancement upon contrast administration. The ventricles were compressed and narrowed, and multiple small blood vessels were observed within the mass. DTI showed discontinuous fiber tracts. No paramagnetic material was observed on SW. MRS showed an elevated Cho peak and a decreased NAA peak in the lesion, with an inverted Cho/NAA ratio and a local ratio >2. PWI showed slightly increased CBV and CBF in the lesion, a slightly shortened MTT, and no significant abnormalities in TTP. The tumor mass was approximately 3.58 × 2.6cm.

However, seven months after the surgery, the patient developed worsening ataxia and somnolence, and MRI confirmed tumor progression. MRI scan showed tumor recurrence in the brainstem and left thalamus region, with an irregular mass measuring 4.2×3.2cm in cross-section. Because of rapid progression and lack of alternative therapies, the patient received Ivonescimab plus temozolomide (dose at 75mg/m^2 d1-21, every 3 weeks) and cisplatin (dose at 120mg every 3 weeks) for six cycles. At 9 weeks, MRI revealed major reduction in tumor size, and the patient's KPS improved from 30 to 90. After 21 weeks, PR was achieved according to RECIST criteria. The patient tolerated therapy well, and no immune-related adverse events over grade 3 were observed (Fig. 7).

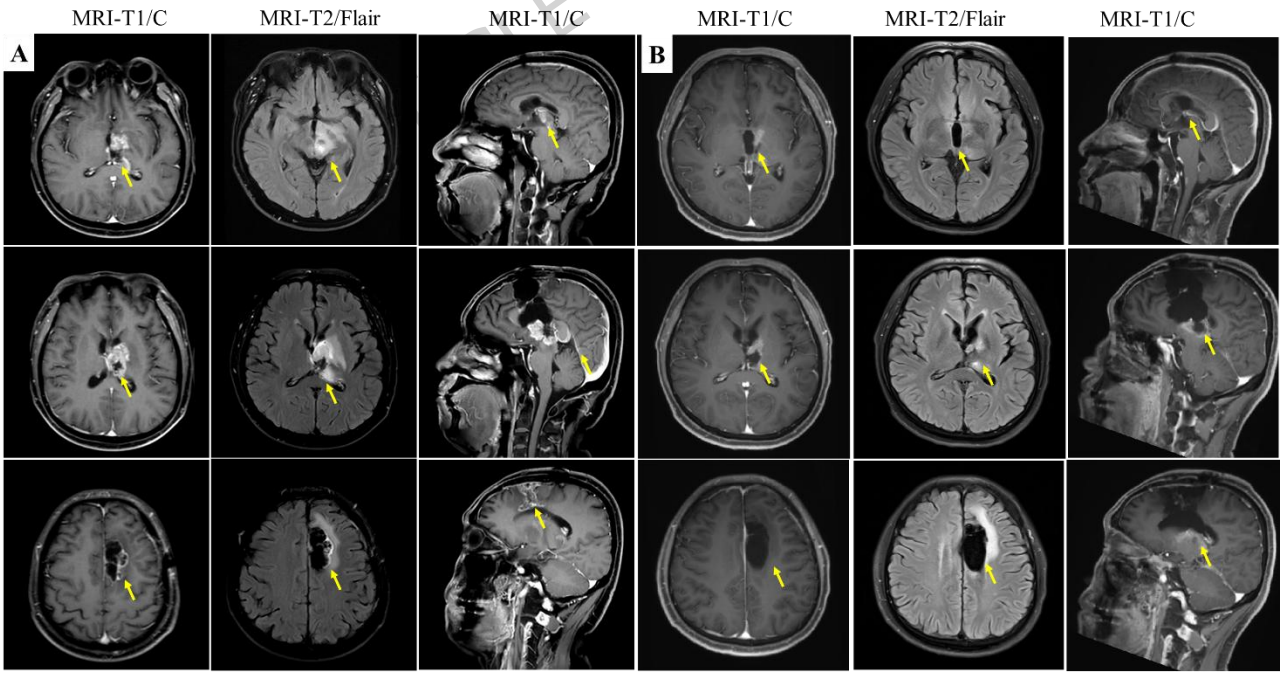

Fig. 7 Radiology test of patient 2 after recurrent. **A:** On March 21st,2025, MRI scan showed irregular enhancement with mild cerebral edema was observed at the edge of the surgical remnant cavity in the genu of the corpus callosum in the left frontal lobe. Irregular and significant enhancement with

restricted diffusion was seen next to the basal ganglia and thalamus remnant cavity, with a maximum cross-section of approximately 4.2×3.2cm. The lesion involved the left fornix, pineal region, superior colliculus, left part of the midbrain, and crossed the midline to involve the right thalamus and right part of the midbrain. **B:** On August 19th,2025, MRI scan showed a surgical cavity remnant was observed in the left cerebral region of the left corpus callosum genu in the left frontal lobe. The cavity margins showed irregular enhancement with mild cerebral edema. Especially, an irregular, significantly enhancing lesion with restricted diffusion was observed adjacent to the basal ganglia and thalamus cavity remnant. The lesion involved the left fornix, pineal region, superior colliculus, and left midbrain region. Patchy edema was observed in the surrounding brain parenchyma. The lesion area was significantly smaller than before, and the enhancement intensity was reduced.