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a través del abordaje multiciplinar

White Paper on the

Multidisciplinary Management of Glioblastoma

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MED-ES-GBM-2500010 September 2025

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First edition: April 2026

ISBN: 978-84-09-84593-4

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This document has been funded by Novocure Spain SL ("Novocure"). The authors have been engaged as consultants and have received appropriate compensation for their participation in the preparation of this White Paper. The content of this document reflects the personal opinions and experience of the authors. It does not necessarily represent the official position of Novocure, nor does it replace any official clinical guidelines. This document is intended exclusively for healthcare professionals residing in Spain. The information contained herein should be interpreted in accordance with the intended use of Novocure products.

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NEUROONCOLOGÍA

Avalado por:
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Index

Preface

This White Paper has been developed with the aim of providing a practical, concise, and multidisciplinary guide for the management of patients with glioblastoma. Thanks to the collaboration of a broad and carefully selected group of specialists from across the country, this document tries to bring together the best available evidence and current clinical guidelines to support decision-making in real-world clinical settings. It covers the full spectrum of specialties involved in the diagnosis and treatment of glioblastoma —including neurosurgery, neurology, medical oncology, radiation oncology, neuropathology, and neuroradiology— ensuring a comprehensive and coordinated approach.

Contributors were selected based on their recognized experience and active involvement in the care of these complex patients, representing institutions from all regions of the national healthcare system.

White Papers are designed to distill expert knowledge into accessible and actionable recommendations. Glioblastoma remains one of the greatest challenges in oncology, due to its aggressiveness, heterogeneity, and the urgent need for timely, individualized management. In this context, the goal of this publication is to serve as a quick-reference resource for clinicians —particularly those with less experience in this field— offering clear, practical information to facilitate optimal patient care from diagnosis through treatment and follow-up.

We hope this initiative contributes to improving the consistency and quality of care for all patients affected by this devastating disease.

Juan Manuel Sepúlveda and María Martínez García

Coordinators of the White Paper on the Multidisciplinary Management of Glioblastoma

1. Introduction to glioblastoma

Glioblastoma (GB) is the most prevalent type of malignant primary brain tumor in adults, with an estimated incidence of 3 per 100,000 people.[1] Its incidence increases with age, with a peak incidence between 75 and 84 years, and it occurs more frequently in males. Despite recent advancements in deciphering the molecular pathogenesis of these tumors, the overall survival (OS) remains poor.[1]

The current standard treatment for newly diagnosed GB is based on the Stupp protocol, which combines radiotherapy with concomitant daily temozolomide (TMZ) following maximal safe surgical resection, and then maintenance TMZ for six months.[2] In appropriate patients, this regimen may be used together with Tumor Treating Fields (TTFields).[3]

GB is characterized by a poor prognosis and a rapid progression. Therefore, **close multidisciplinary collaboration is essential to ensure appropriate patient care and management**.[4]

This document presents a detailed analysis of the multidisciplinary management of GB. It discusses clinical, therapeutic, and follow-up aspects, emphasizing the importance of a collaborative approach in the treatment of this aggressive disease.

2. Anatomical pathology, molecular biology, and WHO classification

(Section authors: Cristina Carrato and Eloy Rivas)

Before addressing the clinical management of GB, it is essential to first understand how these tumors are currently classified. This section reviews the **latest World Health Organization (WHO) classification and the biological and pathological characteristics** that guide diagnosis and treatment decisions.

2.1 Current classification of infiltrating gliomas

The current WHO classification of central nervous system tumors, published in 2021, represents a paradigm shift in the categorization of diffuse gliomas, also known as infiltrating gliomas.[5] This fifth edition consolidates the histomolecular classification introduced in 2016, which is based on an **integrated diagnosis** that considers not only the **histological features** of the tumors but also their **molecular characteristics**.[5,6]

For the first time, age-related criteria are also included in the classification, distinguishing between "pediatric-type" diffuse gliomas (both low- and high-grade) and "adult-type" diffuse gliomas (**Table 1**).[6]

The classification of "adult-type" diffuse gliomas has been simplified in this new edition, being reduced to three unique entities: 1) astrocytoma with a mutation in the isocitrate dehydrogenase enzyme (IDH-mutant, IDH-m), 2) oligodendroglioma IDH-mutant and with codeletion of the short arm of chromosome 1 and the long arm of chromosome 19 (1p/19q), and 3) GB without IDH mutation (IDH-wildtype, IDH-wt) (**Table 1**).[6]

On the other hand, the tumor grade is now integrated within each histological type, eliminating the term "anaplastic" from the nomenclature. Furthermore, **the concept of "GB" is exclusively restricted to "adult-type" astrocytomas that do not have mutations in IDH or histone H3 (GB, IDH-wt) and meet grade 4 (G4) criteria**. Consequently, IDH-mutant astrocytomas that were previously included in this group are now called "astrocytomas IDH-m, grade 4" (**Table 1**).[6] IDH-wt astrocytomas of grades 2 (G2) and 3 (G3) have also disappeared as diagnostic entities (see below).

Table 1. Categories of diffuse gliomas according to the 2021 WHO classification.[6]

"Adult-type" diffuse gliomas
• Astrocytoma, IDH-mutant (G2, G3, G4) • Oligodendroglioma, IDH-mutant and 1p/19q-codeleted (G2, G3) • Glioblastoma, IDH-wt (G4)
"Pediatric-type" diffuse low-grade gliomas (G1)
• Diffuse astrocytoma, MYB- or MYBL1-altered • Angiocentric glioma • Diffuse low-grade glioma, MAPK pathway-altered • Polymorphous low-grade neuroepithelial tumor of the young (PLNTY)
"Pediatric-type" diffuse high-grade gliomas (G4)
• Diffuse midline glioma, H3 K27-altered • Diffuse hemispheric glioma, H3 G34-mutant • Diffuse pediatric-type high-grade glioma, H3-wt and IDH-wt • Infant-type hemispheric glioma

G: grade; IDH: isocitrate dehydrogenase; wt: wild-type.

Within the classification of high-grade "pediatric-type" diffuse gliomas, which can also occur in adult patients, are included gliomas associated with histone H3 alterations (such as diffuse midline glioma H3 K27-altered and diffuse hemispheric glioma H3 G34-mutant), diffuse pediatric-type high-grade glioma H3-wt and IDH-wt, and infant-type hemispheric glioma. None of these are currently termed as GB (**Table 1**).[6]

2.2 Histological and molecular criteria of GB

The 2021 WHO classification defines GB as a diffuse, IDH-wt, H3-wt G4 astrocytoma that exhibits **one or more of the following molecular characteristics: microvascular proliferation, necrosis, mutation in the telomerase reverse transcriptase promoter (TERTp), amplification of the epidermal growth factor receptor (EGFR), or a combined gain of chromosome 7 with loss of chromosome 10 (+7/-10 signature)**.[6]

Histological criteria such as microvascular proliferation and necrosis have been used for years to establish a diagnosis. However, as mentioned above, the new 2021 WHO classification also incorporates for the first time molecular criteria for tumor grading. Thus, a G2 or G3 IDH-wt/H3-wt astrocytoma that presents any of these molecular alterations (TERTp, EGFR, or +7/-10 signature) should be classified as G4 malignancy.[6,7] Some authors refer to these types of GB tumors as molecular subtype, as opposed to the traditional histological subtype.

Although the WHO does not specify which techniques should be used to define the molecular profile of these tumors, the most common are PCR techniques to determine TERTp alterations and fluorescence in situ hybridization (FISH) techniques to evaluate EGFR amplification, gain of chromosome 7, and loss of chromosome 10. However, the increasingly widespread use of next-generation sequencing (NGS) techniques allows for the analysis of all these alterations with a single assay.

Most diagnostic protocols recommend the **use of an immunohistochemistry (IHC) panel with antibodies to define, from the beginning, the molecular profile** of an "adult-type" diffuse glioma. This panel should include, at least, the **study of IDH1 (p.R132H mutation) and ATRX**, as IDH-mutant astrocytomas frequently exhibit ATRX mutations (characterized by loss of nuclear expression on IHC). In addition, **H3 K27M and H3 K27me3 should be evaluated when the tumor is located in the midline**.[8] **Figure 1** illustrates the recommended algorithm for the integrated diagnosis of GB.

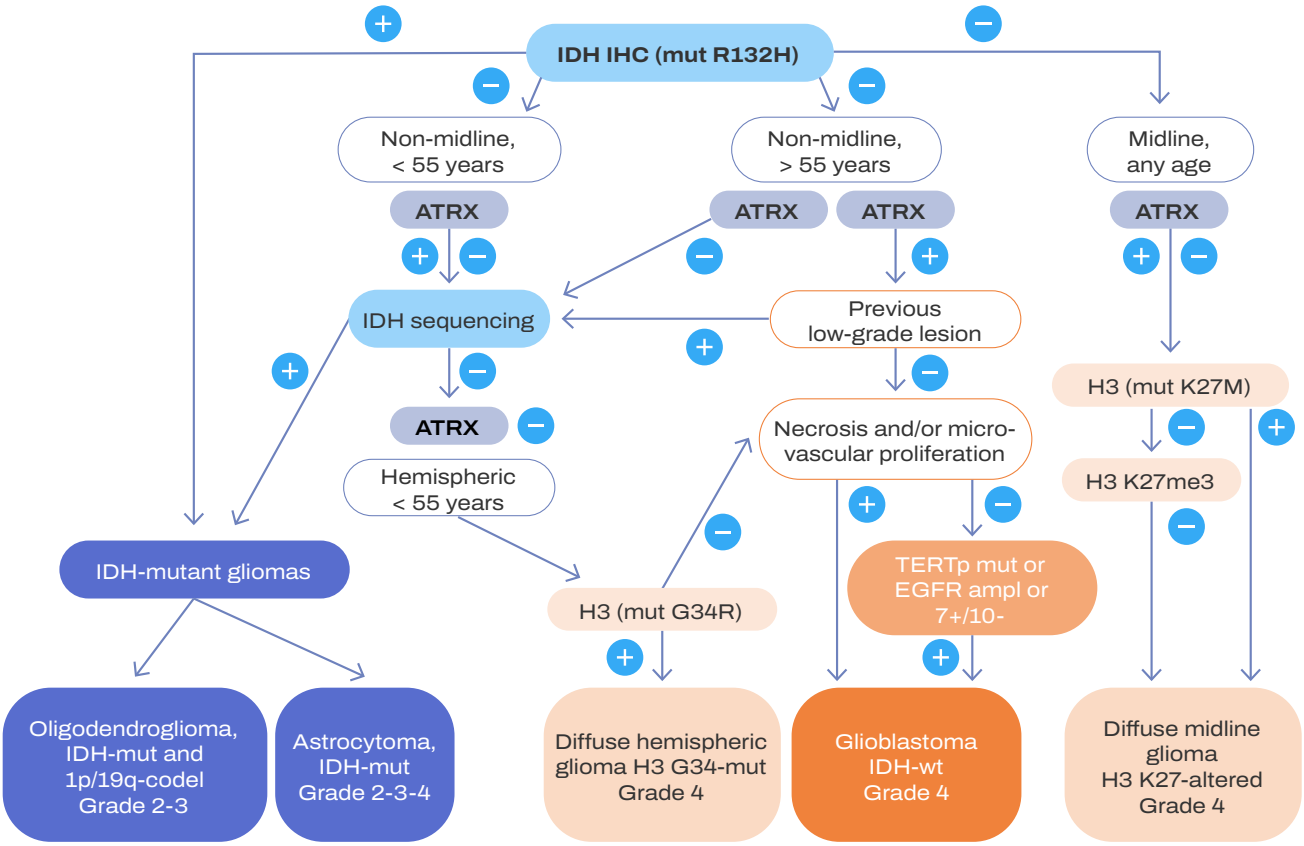


Figure 1. Proposed algorithm for the integrated diagnosis of GB. The IHC analysis includes the study of IDH1-R132H (positive in case of mutation), ATRX (negative in case of mutation), and, in certain cases, H3K27M (positive in case of mutation), H3K27me3 (negative in case of H3K27M alteration), and H3G34R (positive in case of mutation). In ATRX-positive gliomas without a prior lower-grade lesion and lacking necrosis or microvascular proliferation, in addition to the study of TERTp, EGFR, and chromosomes 7/10, IDH should be studied through sequencing as indicated in **Table 2**. Figure created by the authors based on clinical evidence.

The use of IHC is sufficient to determine the IDH mutation status in most cases, since the antibody specific for the canonical IDH1 p.R132H mutation can identify up to 90% of IDH-mutant gliomas. In patients aged 55 and older, with G4 diffuse gliomas not located in the midline and without a history of a prior low-grade glioma, a negative IHC result for IDH1 p.R132H is sufficient to diagnose them as IDH-wt GBs.[8] However, in patients who are either younger than 55 years, whose tumors show loss of ATRX expression by IHC, or do not present histological criteria for G4, the study should be completed by sequencing the IDH1 and IDH2 genes in order to detect other less frequent mutations, different from the canonical IDH1 p.R132H mutation (**Table 2**).[8]

Table 2. Situations requiring further IDH sequencing after a negative IHC for IDH-p.R132H.[8]

Situations requiring further IDH sequencing after a negative IHC for IDH-p.R132H
Patients younger than 55 years old
Patients with a history of prior low-grade glioma
Diffuse gliomas without microvascular proliferation or necrosis
Diffuse gliomas with loss of ATRX expression.

IDH: isocitrate dehydrogenase; IHC: immunohistochemistry.

Similarly, most authors recommend an IHC study of H3 G34 in patients younger than 50 years with hemispheric tumors, especially if they show loss of ATRX expression, a p53 mutational pattern (more than 10% of positive tumor nuclei), or loss of Olig2 expression.[8,9] In contrast, evaluating the H3 G34 status in patients older than 55 years is not considered necessary to establish GB diagnosis.[9]

For a G2 or G3 diffuse glioma exhibiting negative IHC result for IDH1, the recommended procedure is: 1) verify the absence of IDH mutation by sequencing. If the tumor is IDH-wt, then: 2) continue the molecular analysis (either in-house or at reference centers) by studying the TERTp mutation, EGFR amplification, and/or +7/-10 signature. **If any of these alterations are present, the case should be classified as GB**. If none of these alterations are found, other diagnostic possibilities should be considered, such as the possibility of a "pediatric-type" glioma or a circumscribed glioma.

Regarding this point, the recommendations of the cIMPACT-NOW expert group (The Consortium to Inform Molecular and Practical Approaches to CNS Tumor Taxonomy – Not Official WHO) have been published very recently.[10] These recommendations address the refinement of diagnostic criteria for IDH-wt, H3-wt gliomas (including GB and diffuse pediatric-type high-grade glioma, IDH-wt and H3-wt).

With respect to GB, the **cIMPACT-NOW recommendations** are as follows:

- The presence of a TERTp mutation should not be considered a diagnostic criterion for GB when it is the only molecular finding in a histologically low-grade glioma (as not all such cases behave aggressively).
- The presence of EGFR amplification or the +7/–10 cytogenetic pattern should not be considered diagnostic criteria for GB when they are the only GB-related findings in a patient younger than 40 years (since these alterations are not specific to GB and may also be observed in pediatric-type gliomas, which are more frequent in this age group).

In such situations, the differential diagnosis should be broadened, taking into account all clinical, radiological, and molecular findings. In case of uncertainty, a descriptive diagnosis should be issued rather than designating the tumor as GB.

These recommendations do not represent formal changes to the WHO definition until they are officially approved by the WHO editorial committee and published in a future edition.

2.3 GB subtypes

The WHO recognizes three subtypes of GB: 1) giant cell GB, 2) gliosarcoma, and 3) epithelioid GB.[5] These subtypes present histological characteristics, different from conventional GB, and are often observed as better-defined and superficially located lesions on imaging tests, which generally facilitates their surgical resection. However, the prognosis does not differ significantly from conventional GB.

2.4 Prognostic and predictive molecular markers of response in GB

The **most relevant prognostic and predictive molecular marker of response to treatment in GB is the methylation status of the MGMT promoter** (MGMTp). Patients with MGMTp methylation show longer survival and a better response to TMZ treatment.[11,12]

However, other molecular markers with prognostic value have been identified, as well as molecular markers of response to targeted therapies, including BRAF mutations, which are especially prevalent in the epithelioid subtype of GB.[13] In this context, the increasingly widespread use of NGS panels in the diagnosis of diffuse gliomas allows for the identification of potential therapeutic targets, such as a high tumor mutational burden and NTRK or FGFR3 fusions, which could be accessible within the framework of clinical trials.[13]

3. Neuroimaging of gliomas

(Section authors: Stela Asadurova and Ana Ortiz de Mendívil)

Neuroimaging is indispensable in the comprehensive management of GB, playing a pivotal role from the initial diagnosis and tumor characterization to guide therapeutic planning, including surgical resection and radiation therapy.[14] Furthermore, advanced neuroimaging techniques are crucial in the post-treatment monitoring of GB to accurately assess therapeutic response and to distinguish true tumor progression from treatment-related effects.[15] The sensitivity of these techniques in the early detection of tumor recurrence allows for timely intervention, which is critical in managing GB.[14]

3.1 Imaging tests used in the management of GB

Magnetic resonance imaging (MRI)

MRI is the gold standard imaging test for the diagnosis and monitoring of GB. In current clinical practices, both conventional and advanced sequences are used.[14] **Conventional sequences** include: T1-weighted imaging (3D T1 pre- and post-contrast), T2-weighted imaging, 2D or 3D fluid-attenuated inversion recovery (FLAIR), and susceptibility-weighted imaging (SWI). These sequences are primarily used to assess brain anatomy and characterize peritumoral edema.[14] SWI is capable of detecting intratumoral susceptibility signals (ITSS) which reflect underlying processes such as neoangiogenesis, microbleeds, necrosis, and calcification. According to the Park classification (2009), ITSS are graded as follows: grade 0, no ITSS; grade 1, 1–5 dot-like or fine linear foci; grade 2, 6–10 foci; and grade 3, more than 11 foci.[16] On the other hand, **advanced MRI sequences**, which are useful for assessing tumor extent, cellularity, and vascularization, include diffusion-weighted imaging (DWI); dynamic susceptibility contrast perfusion-weighted imaging (DSC-PWI); arterial spin labelling (ASL); dynamic contrast-enhanced perfusion-weighted imaging (DCE-PWI); and magnetic resonance spectroscopy (MRS). DWI is used to evaluate hypercellularity of the tumor.[14,15,17] DSC-PWI, ASL and DCE-PWI enable the quantification of cerebral blood volume (CBV), cerebral blood flow (CBF), and the volume transfer constant (K_{trans}), reflecting neoangiogenesis and capillary permeability.[14,15,17] MRS enables the biochemical assessment of the tumor through the analysis of metabolites such as choline, N-acetylaspartate, and lactate, facilitating the differentiation between tumor and post-treatment changes.[14,15]

It is essential to maintain technical consistency during follow-up, ensuring that sequences are always acquired in the same order. In particular, post-contrast 3D T1 imaging should be performed with a constant delay after contrast administration, ideally between 4 and 8 minutes. All studies should be conducted using the same protocol and, whenever possible, on the same scanner.

Combined positron emission tomography/computed tomography (PET/CT)

PET/CT with ^{18}F-Fluorodeoxyglucose (^{18}F-FDG) has limited utility in neurooncology due to the low contrast between the tumor and surrounding brain tissue, as well as the high physiological uptake of FDG by the cerebral cortex.[18,19] However, the use of **PET/CT with amino acids tracers**, such as ^{11}C-methionine (^{11}C-MET), ^{18}F-fluoroethyltyrosine (^{18}F-FET), and ^{18}F-dihydroxyphenylalanine (^{18}F-DOPA), or with ^{18}F-choline has significantly **increased in recent years as a complementary modality to MRI**.[18-21]

3.2 Diagnosis and characterization of GB

GB typically presents as an **infiltrative lesion with heterogeneous contrast enhancement, central necrosis, and irregular margins**. **Advanced MRI sequences are essential for distinguishing GB from other brain tumors and non-neoplastic processes**. On T2-weighted and FLAIR sequences, non-enhancing infiltrative areas may be observed in association with edema, making differentiation between the two entities challenging. In some cases, this non-enhancing infiltrative pattern may represent the initial form of presentation.[22]

Key imaging techniques for the diagnosis of GB or other high-grade gliomas include several modalities, each with specific diagnostic contributions (**Table 3**).[14,15,17-19]

Table 3. Key imaging techniques for the diagnosis of GB.

Imaging modality	Diagnostic application
MRI	Differential diagnosis (peritumoral infiltration); tumor grading; prognosis; biopsy guidance; monitoring
Contrast-enhanced T1-weighted MRI	Detection of necrosis
DWI	Identification of hypercellular tumor regions
DSC-PWI/DCE-PWI/ ASL	Quantification of CBV/permeability/CBF to highlight neoangiogenesis
SWI	Quantification of ITSS: Intratumoral Susceptibility Signal
MRS	Tumor grading and differentiation of peritumoral infiltration (especially in differential diagnosis with solitary metastases)
^{18}F-FDG PET/CT	Differentiation between high-grade and low-grade gliomas; distinction between GB, metastases, and central nervous system lymphoma; prognostic value; biopsy guidance
Amino acid PET/CT	Differentiation of tumors from non-neoplastic lesions; delineation of non-enhancing regions for biopsy and surgical guidance

^{18}F-FDG: fluorodeoxyglucose; ASL: arterial spin labelling; CBF: cerebral blood flow; CBV: cerebral blood volume; DCE-PWI: dynamic contrast-enhanced perfusion-weighted imaging; DSC-PWI: dynamic susceptibility contrast perfusion-weighted imaging; DWI: diffusion-weighted imaging; GB: glioblastoma; ITSS: intratumoral susceptibility signals; MRI: magnetic resonance imaging; MRS: magnetic resonance spectroscopy; PET/CT: positron emission tomography/computed tomography; SWI: susceptibility-weighted imaging; T1: T1-weighted imaging.

Importantly, certain MRI features have been associated with longer survival, including the presence of non-enhancing infiltrative tumor tissue; and the absence of edema, satellite lesions, and multifocal disease.[23]

However, **GB shows signi icant variability**. Some molecular subtypes, such as those with TERTp and EGFR mutations, may lack necrosis and exhibit no or only minimal contrast enhancement, and fail to display the typical perfusion or diffusion imaging patterns seen in high-grade gliomas, thereby mimicking low-grade tumors. In addition, some GBs also demonstrate gyriform cortical infiltration and a tendency toward multifocality, particularly those with EGFR or TERTp mutations.[24] Given this heterogeneity, **a multimodal diagnostic approach is therefore essential for achieving an accurate diagnosis**.

3.3 Neuroimaging in surgical planning and intraoperative guidance

Advanced neuroimaging plays a pivotal role in surgical planning, a crucial component in the management of GB. Diffusion tensor imaging (DTI) allows for white matter tractography, enabling tumor resections that preserve critical motor and language functions.[18,25] Functional MRI identifies eloquent cortical areas through neural activation mapping.[26] DSC-PWI delineates highly vascularized tumor regions, guiding biopsy or surgical approach, especially in partially resectable or unresectable tumors.[14,15,17] DWI helps target hypercellular tumor areas, even when contrast enhancement is absent.[14,15,17] Additionally, PET/CT with amino acid tracers can delineate non-enhancing regions, assisting also in surgical planning.[21]

In addition to preoperative imaging, **intraoperative image-guided techniques** such as ultrasound, intraoperative MRI, and fluorescence-guided surgery using 5-aminolevulinic acid (5-ALA) or fluorescein **have**

proven valuable in optimizing GB resections.[27] Intraoperative ultrasound provides real-time visualization of the tumor and its relationship to critical structures, while intraoperative MRI helps to identify residual tumor not detected by other methods. 5-ALA fluorescence improves the distinction between tumor and healthy tissue, thereby increasing the rate of complete resections.[27]

3.4 Treatment monitoring and response evaluation

Routine MRI follow-up plays a critical role in the early detection of tumor recurrence and in evaluating treatment efficacy.[14] In clinical trials, the Response Assessment in Neuro-Oncology (RANO) 2.0 criteria are commonly employed, while the Brain Tumor Reporting and Data System (BT-RADS) is commonly used in clinical practice (**Tables 4 and 5**).[28]

Table 4. RANO 2.0 criteria for glioma evaluation.[29]

Criterion	Description
Measurable lesion	Lesions with well-defined margins on MRI, at least 10 mm in both perpendicular diameters
Non-measurable lesion	Lesions with unclear margins or less than 10 mm in maximum diameter
Selection of target lesion	Select 2 to 3 measurable lesions, prioritizing the largest or those with reproducible measurements
Basal MRI for newly diagnosed glioma	Use post-radiotherapy MRI (3-5 weeks after radiotherapy completion) as the reference
Basal MRI for recurrent glioma	Use pre-treatment MRI as the reference (≤ 14 days prior to treatment initiation)
Basal MRI for low-grade glioma or no radiotherapy	Use post-operative MRI (3 months after surgery) or pre-treatment MRI as the reference (≤ 14 days prior to treatment initiation)
Tumor components to evaluate	Evaluate enhancing component (for IDH-wildtype GB); include non-enhancing component when assessing IDH-mutant gliomas, and after treatments affecting vascular permeability
Confirmation of MRI for progression	Mandatory within 12 weeks post-radiotherapy or if pseudoprogression is suspected
Evaluation based on corticosteroid use	Clinically stable or improved, without an increase in corticosteroid dose compared to baseline

GB: glioblastoma; IDH: isocitrate dehydrogenase; MRI: magnetic resonance imaging.

Table 5. Comparison of tumor response evaluation criteria: RANO 2.0[29] versus BT-RADS.[30]

Evaluation Criterion	RANO 2.0	BT-RADS
Complete Response (CR)	• Disappearance of all measurable and non-measurable lesions • No new lesions • No corticosteroids or only in physiological replacement doses • Stable or improved clinical condition • Requires confirmation MRI at 4 weeks	**No distinction between complete and partial response** **1a - Improvement** • Decreased enhancing component + • Unchanged or decreased FLAIR component + • No new enhancing or FLAIR lesions + • Unchanged or decreased mass effect + • Clinically stable or improved **Or** • All of the above + • On bevacizumab with response confirmed by 4-week MRI **1b – Medication effect** • Decreased enhancing component + • Unchanged or decreased FLAIR component + • No new enhancing or FLAIR lesions + • Unchanged or decreased mass effect + • Clinically stable or improved + • On increasing doses of steroids or first post-bevacizumab imaging with decreased enhancement only
Partial Response (PR) or minor	• **PR under same conditions as CR:** ≥50% reduction in the sum of products of perpendicular diameters or ≥65% in volume (of all measurable enhancing target lesions). Infiltrative component should be stable or reduced • Patients with non-measurable disease only at baseline cannot have PR; the best response possible is stable disease (SD) • **Minor response for non-enhancing disease:** reduction ≥25%-50% or ≥40%-65% in volume (under the same conditions) Enhancing component should be stable	
Stable disease (SD)	• Does not meet criteria for CR, PR, or PD • Stable imaging (enhancing) • No new lesions • Stable or decreased corticosteroid doses • Clinically stable or improved	**2 – No changes** • Unchanged enhancing or FLAIR component + • No new lesions + • Unchanged mass effect + • Clinically stable

Evaluation Criterion	RANO 2.0	BT-RADS
Progression (PD)	• ≥25% increase in sum of products of perpendicular diameters or ≥40% in volume of enhancing target lesions • New enhancing lesions ≥10 mm x 10 mm or definitive leptomeningeal disease • Progression of non-measurable (at least 5 x 5 mm to ≥10 x 10 mm) or non-target lesion (should be added to the sum of the target lesions). • Definite clinical deterioration not attributable to decrease in corticosteroid dose or other causes • Confirmation MRI (at least two sequential scans separated by ≥4 weeks both exhibiting ≥25% increase in sum of products of perpendicular diameters or ≥40% increase in total volume of enhancing lesions compared with the most recent previous scan) will be required.	**4 – Progression** • Progressive increase in enhancing or FLAIR component over multiple studies over time + increased mass effect + progressive clinical deterioration **Or** • Increased enhancing and FLAIR component >25% + increased mass effect + clinically worse **Or** • New definitive lesions outside of XRT treatment zone
Worsening/Possible pseudoprogression/ Treatment-induced changes	**Stable disease (SD)** • Considered when initial images show progression (increase in enhancement), but subsequent images show stability or response • Therapy can continue • Confirmation with repeated MRI (every 4-8 weeks), especially within the first 12 weeks post-treatment	**3a – Favor treatment effect** • Imaging worsening **<12 weeks post-RT** + • One of the following: - Increased enhancing component - Increased FLAIR component + • No new enhancing or FLAIR lesions outside of XRT treatment zone + • Increased mass effect + • Clinically stable
Worsening/ Indeterminate	**Stable disease (SD)**	**3b - Indeterminate** • Worsening of images **>12 weeks post-RT** + • One of the following: - Increased enhancing component - Increased FLAIR component and increasing mass effect + • No new enhancing or FLAIR lesions outside of XRT treatment zone + • Clinically stable
Worsening/ Favorable to progression	**Stable disease (SD)**	**3c – Favor Tumor Progression** • Increased enhancing and FLAIR component <25% + increased mass effect • No new lesions (enhancing or FLAIR) outside XRT treatment zone + • Clinically worse **Or** • New indeterminate lesion (FLAIR without enhancement) outside of XRT treatment zone

CR: complete response; FLAIR: fluid-attenuated inversion recovery; MRI: magnetic resonance imaging; PD: progression disease; PR: partial response; SD: stable disease; XRT: radiation therapy.

The recommended timing and purpose of MRI scans throughout the treatment course of GB are summarized below (**Figure 2**).

A **postoperative MRI should be performed within 24–72 hours after surgical resection** to assess the extent of resection and to differentiate residual tumor from postoperative inflammatory changes, with the first **24–48 hours considered ideal** for optimal interpretation.[31,32] It also helps to identify postoperative infarction and prevents its misinterpretation as early tumor recurrence on subsequent MRI scans.[33] Later on, a **pre-radiotherapy MRI can be considered 2 to 4 weeks post-surgery**.[29,34] While not mandatory, it is highly valuable for accurately delineating the residual tumor volume and defining the radiation fields. This scan also helps to detect early recurrence prior to radiotherapy (which may lead to adjustments in the radiotherapy plan) and helps to prevent overestimation of pseudoprogression or misinterpretation of post-treatment changes as true tumor progression.[34] After radiotherapy, **another MRI is recommended 3 to 5 weeks after radiotherapy completion**, as it reduces the confounding effect of contrast enhancement related to pseudoprogression induced by chemoradiotherapy. This timing also enables better correlation with OS and progression-free survival (PFS) outcomes.[29] Finally, a long-term surveillance involves **serial MRI scans every 2–4 months during the initial 3 years**, followed by intervals of **3–6 months indefinitely**.[8,35]

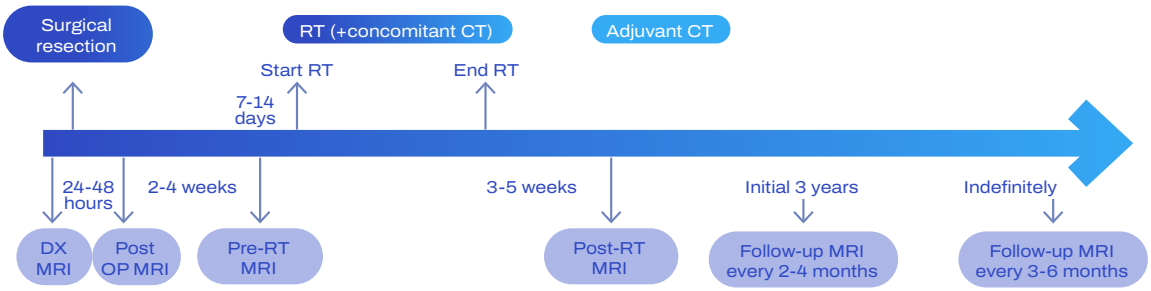


Figure 2. Schematic representation of radiological follow-up in clinical practice. Adapted from Pineda Ibarra C, et al., 2024.[36] CT: chemotherapy; MRI: magnetic resonance imaging; OP: operation; RT: radiotherapy.

In addition to MRI, **amino acid PET/CT imaging** (^{11}C-MET, ^{18}F-FET, ^{18}F-DOPA) is increasingly recognized for its **utility in evaluating treatment response**. Increased tracer uptake may indicate tumor progression or treatment failure, while decreased uptake is suggestive of a positive response. Likewise, FET and DOPA can help identifying pseudoresponse in patients undergoing antiangiogenic therapy.[18,19,21] Recently, the **PET RANO 1.0 criteria were introduced to standardize response assessment**, primarily in clinical trials, although systematic validation is still needed (**Table 6**).[37]

Table 6. PET RANO 1.0 criteria for response assessment.

PET-positive lesion	SUVmax ≥ 1.6 x the mean background activity	
Measurable lesion	PET-positive lesion with a volume ≥ 0.5 mL	
Non-measurable lesion	Visible lesions with TBRmax < 1.6 or lesions with PET-positive volume < 0.5 mL	
Target lesion	Lesion(s) with the highest uptake intensity or the largest PET-positive volume	
	PET-positive measurable lesion	**PET-negative lesion or non-measurable PET-positive lesion**
Progressive disease (PET-PD)	At least one of the following: • ≥30% increase in TBRmax of at least one target lesion • ≥10% increase in TBRmean of at least one target lesion • ≥40% increase in PET volume of at least one target lesion • Appearance of one or more new measurable lesions	Appearance of one or more new PET-positive measurable lesions
Stable disease (PET-SD)	Absence of criteria for PET-PD, PET-PR, or PET-CR	No appearance of new PET-positive measurable lesions
Partial response (PET-PR)	At least one of the following and no criteria for PET-PD, PET-SD, or PET-CR (in case of multiple lesions, each lesion must meet at least one criterion): • ≥30% decrease in TBRmax • ≥10% decrease in TBRmean • ≥40% decrease in PET volume Or resolution of all target lesions except one, with no criteria for PET-PD or PET-SD	**n/a**
Complete response (PET-CR)	Complete resolution of PET-positive disease	**n/a**

Adapted from Albert, N. L. et al., (2024).[37] PET: positron emission tomography; PET-CR: PET complete response; PET-PD: PET progressive disease; PET-PR: PET partial response; PET-SD: PET stable disease; SUVmax: maximum standardized uptake value; TBRmax: maximum tumor-to-background ratio; TBRmean: mean tumor-to-background ratio.

3.5 Advanced imaging for evaluating pseudoprogression and pseudoresponse

What is pseudoprogression?

Pseudoprogression is defined as a transient increase in the size of the contrast-enhancing lesion within the irradiated zone, followed by subsequent improvement or stabilization. It affects approximately one in three patients.[20] **The period of stabilization after pseudoprogression typically ranges from 3 to 6 months**. Pseudoprogression **mimics true tumor progression but is instead caused by inflammation or**

treatment-induced necrosis. Although it most often occurs within the first 12 weeks after completion of chemoradiation, some cases occur later, particularly after TMZ in combination with lomustine.[20] The risk is 3.5 times higher in patients with MGMTp methylation and lower in cases with total resection.[38] According to RANO 2.0, within the first 3 months post-radiotherapy, new enhancement is only considered progression if located outside the radiation field.[29]

How to differentiate pseudoprogression from the true tumor progression?

Differentiating pseudoprogression from true progression involves several imaging techniques. DWI shows lower ADC values in true progression due to restricted water diffusion.[39] DSC-PWI distinguishes pseudoprogression, which typically exhibits low perfusion, from tumor progression, which generally presents elevated relative CBV values.[40,41] MRS aids in distinguishing tumor metabolism from post-radiation changes.[14] Additionally, PET/CT imaging with amino acid tracers (^{11}C-MET, ^{18}F-FET, ^{18}F-DOPA) or ^{18}F-choline provides high accuracy in detecting tumor recurrence, with reported sensitivity ranging from approximately 80% to 95% and specificity from 80% to 90%, through visual and semi-quantitative analyses, utilizing tumor-to-background ratios (TBR) specific to each compound and contrasting with healthy brain tissue[19,21,42].

What is pseudoresponse?

Pseudoresponse **occurs in patients treated with antiangiogenic agents**, where the anti-vascular effect reduces enhancement, edema, and permeability as early as one day after the initiation of therapy. However, there may be an increased tumor extent observed on FLAIR/T2 sequences.[42]

4. Surgical treatment of GB

(Section authors: Francisco Martínez and Irene Iglesias)

Surgical intervention is crucial for the treatment of GB, with a dual objective: **1)** to obtain tissue for histopathological and molecular diagnosis, and **2)** to achieve maximal safe resection of the tumor while preserving the patient's neurological function.[27] **Multiple studies confirm that the extent of resection (EOR) directly impacts OS and quality of life (QoL)**, highlighting the importance of a **personalized surgical approach** based on good anatomical and functional knowledge, advanced planning tools, and intraoperative imaging systems.[43,44]

4.1 Stereotactic biopsy and surgical resection

Stereotactic biopsy is a minimally invasive neurosurgical procedure **indicated for patients with deep-seated brain lesions, bilateral involvement, or lesions in eloquent brain regions** where complete resection poses a significant risk of neurological morbidity.[45] Neuronavigation and intraoperative ultrasound are the most commonly used systems to perform the surgery.[46] The acquired tumor tissue is used for its histopathological, immunohistochemical, and molecular analysis, thus allowing a comprehensive characterization of the tumor and its mutational profile.[47]

Surgical resection is the treatment of choice for patients with accessible tumors and good functional status. Removing neoplastic tissue not only improves OS but also reduces tumor burden, thereby optimizing the effectiveness of adjuvant therapies.[2] Furthermore, it allows for better local disease control and decreases intracranial pressure, which can improve neurological symptoms and QoL.[45]

4.2 Fundamental role of surgical resection in GB: impact on OS and QoL

The positive impact of surgical resection on OS and QoL has been extensively documented. Postoperative volumetric analyses have evidenced that **subtotal resection (<90%) is associated with shorter OS compared to total resection (>90%)**.[48] Moreover, it has been described that **supramaximal resection** (which involves removing both the contrast-enhancing tumor and infiltrated peritumoral tissue) **might offer**

additional benefit in certain patients.[49] Additionally, a recent meta-analysis showed no statistically significant difference in OS between patients who underwent partial resection and those who only had a biopsy.[44]

In patients with GB, QoL depends not only on OS, but also on functional status after surgery. **Tumor resection must be carefully balanced with preservation of neurological function** to avoid deficits that could compromise the patient's autonomy.[48] Some studies have shown that patients who underwent supramaximal or maximal resections experienced better postoperative QoL compared to those who had submaximal resections or biopsies (as long as they did not develop severe neurological deficits).[50,51]

Additionally, **pre- and postoperative neurocognitive evaluation tools, early rehabilitation, and multidisciplinary follow-up** help mitigate the negative impact of surgery and **improve the QoL** of these patients.[52]

4.3 The EOR concept: RANO resection categories and prognostic value

The EOR, also referred to as the tumoral resection grade, has been identified as **an independent predictor of OS in patients with GB**. The classification proposed by the RANO Resect Group provides a standardized framework for evaluating the EOR and its impact on patient outcomes.[49,53] This classification includes four main categories, as shown in **Table 7**.

Table 7. RANO Resect Group classification of resection types and corresponding predicted OS rates.[49,53]

Class	Resection types	Description	OS
1	**Supramaximal resection**	Resection of all contrast-enhancing tumor visible on postoperative MRI, along with the removal of peritumoral infiltrated tissue identified on T2/FLAIR sequences. The aim is to eliminate the macroscopic tumor burden and part of the infiltrative component, thereby achieving the longest OS and a lower recurrence rate.	18-24 months
2	**Maximal resection**	Complete resection of all contrast-enhancing tumor visible on postoperative MRI, without removing the non-enhancing tissue visible on FLAIR sequences. This is the standard approach in most cases, maximizing tumor removal without significantly increasing the risk of neurological deficits. It is associated with prolonged OS compared to submaximal resection.	14-18 months
3	**Submaximal resection**	Incomplete resection of all contrast-enhancing tumor (>1 cm^3 of residual tumor) on postoperative MRI. It is associated with less benefit in OS compared to Class 1 and 2, but it still provides better tumor control than biopsy alone. It may be the only feasible option for tumors located in highly eloquent brain areas.	10-14 months
4	**Biopsy**	Obtaining tumoral tissue without the intention of significant resection. It is used when aggressive surgery is not feasible due to the tumor's location or the patient's functional status. While it allows for histopathological and molecular diagnosis, it does not significantly impact OS.	6-10 months

FLAIR: fluid-attenuated inversion recovery; MRI: magnetic resonance imaging; OS: overall survival.

4.4 Importance of preoperative planning and intraoperative guidance

As mentioned in section 2, **preoperative planning is a key element in GB surgery**, as it allows for the definition of optimal strategies to maximize resection while minimizing neurological risks. The integration of advanced neuroimaging techniques, such as functional MRI and tractography, facilitates the identification of critical neural pathways and their relationship to the tumor, enabling a safer and more effective surgical approach.[54] Similarly, **preoperative evaluation of the patient's functional status and multidisciplinary discussion** with neurooncologists and neuroradiologists **contribute to individualized surgical decision-making**.

Intraoperative image-guided techniques such as ultrasound, intraoperative MRI, and fluorescence-guided surgery using 5-ALA or fluorescein also **play an important role in optimizing GB resections** (see **section 3** for more detail).[27] However, these tools do not replace the need for a thorough understanding of surgical anatomy and brain physiology. This fundamental knowledge is essential to minimize the risk of neurological deficits and to maximize the safety of the procedure.[55]

Additionally, the combination of these technologies with **intraoperative neurophysiological monitoring** helps to reduce morbidity during the resection of tumors located near eloquent brain areas.[56] Accurate interpretation of intraoperative findings, together with precise surgical planning, remains a fundamental pillar for achieving an effective and functionally safe resection.

5. Treatment indications and clinical decision

(Section authors: Izaskun Valduvieco, Aurea Molina and Regina Gironés)

5.1 The importance of multidisciplinary committees

GB is the most aggressive brain tumor, requiring a comprehensive and coordinated therapeutic approach.[57] In this context, **multidisciplinary committees represent a key strategy in the management of GB**, as they are **essential for designing personalized treatment strategies and improving patient care**.[58,59] Their implementation, supported by clinical guidelines and international consensus, optimizes therapeutic outcomes and improves patients' QoL.[58-61]

Implementation of these committees is essential in centers specialized in neuro-oncology, where the complexity of cases demands a detailed and coordinated evaluation.[59,62] Treatment guidelines emphasize that **each patient should be individually assessed by a multidisciplinary team composed of neurosurgeons, medical and radiation oncologists, neuroradiologists, neuropathologists, and other healthcare professionals**.[58,60]

This interdisciplinary collaboration allows for improving the quality of care by standardizing protocols, thus reducing variability in clinical practice and ensuring that decisions are based on uniform and updated criteria. It also enables a comprehensive evaluation of both the tumor and the patient, and supports evidence-based decisions. Moreover, it ensures efficient coordination of treatment through optimal planning, which improves therapeutic response, reduces risks, and facilitates the selection of more effective and safer therapies based on updated knowledge and clinical experience. Finally, it facilitates access to clinical trials, as specialized committee acts as a reference within the research network to open new clinical trials and to identify eligible patients, thereby expanding access to innovative therapies.[58,60,63]

The success of a committee depends on having an organized structure and effective communication. To this end, the authors recommend:

1) **holding regular meetings** to discuss new cases and reassess patients undergoing treatment;

2) **maintaining detailed documentation**, including accurate records of decisions made and the follow-up of each patient;

3) ensuring efficient coordination by assigning a designated person to facilitate communication between specialties; and

4) promoting ongoing training through continuous updates on scientific and therapeutic advancements.

5.2 Clinical prognostic factors

Clinical prognostic factors in patients with GB can be grouped based on three key aspects: 1) **patient-related factors**, 2) **tumor-related factors**, and 3) **molecular alterations** (**Table 8**). The combined consideration of these factors is essential for **predicting the course of the disease and guiding therapeutic decision-making**, which must be individualized.[8]

Table 8. Classification of clinical prognostic factors in patients with GB.

Category	Prognostic factor	Description
Patient-related factors[8,64,65]	Age	• Older age is associated with worse prognosis. • Treatments for older patients tend to be less aggressive due to increased vulnerability and comorbidities, which may negatively impact prognosis.
	Functional Status (Karnofsky Performance Status, KPS)	• KPS is a widely used index that measures the functional status of a patient to perform ordinary tasks and their level of care needs. • A low KPS is associated with a worse prognosis. • Patients with a very low KPS may not be candidates for standard treatments.
	Neurological presentation	• Patients with more pronounced neurological deficits, especially those causing functional disability, have a worse prognosis. • Patients with fewer neurological symptoms tend to have a better prognosis.
Tumor-related factors[65]	Size and location	• Larger tumors or those located in critical areas of the brain can negatively impact prognosis.
	Extent of surgical resection	• A greater degree of tumor resection is associated with a better prognosis.
	Growth pattern (unifocal versus multifocal)	• Multifocal GBs have a worse prognosis compared to unifocal ones.
Molecular alterations[66]	MGMT	• MGMTp methylation is associated with a better response to alkylating agents such as TMZ, and therefore, with a better prognosis.
	EGFR	• Overexpression or amplification of the EGFR gene has been linked to a greater tumor aggressiveness and a worse prognosis.
	TP53	• Mutations in TP53 are associated with an increased resistance to treatments.
	PTEN	• Mutations or deletions in PTEN are also associated with greater aggressiveness and a worse prognosis.

EGFR: epidermal growth factor receptor; GB: glioblastoma; KPS: Karnofsky Performance Status; TMZ: temozolomide.

5.3 Clinical decision in elderly patients

More than half of the patients diagnosed with GB are over 65 years, with a peak incidence between 75 and 85 years.[67] However, age has traditionally been an exclusion criterion in clinical trials, so the scientific evidence regarding elderly patients with GB is subject to interpretation biases,[67,68] and **OS in the elderly population is lower** compared to the adult population, primarily due to undertreatment.[69] Moreover, it has been described that MGMTp methylation in this population has prognostic and therapeutic implications.[70]

In this context, it is **recommended that older patients (approximately 70 years or older) diagnosed with IDH-wt GB be evaluated by multidisciplinary teams**, including a comprehensive **geriatric assessment**, to guide **personalized therapeutic decisions**.[67,71,72] Thus, special care should be taken in the elderly population, as their poor disease prognosis, limited functional status, and increased risk of adverse events may limit the therapeutic benefit.

Geriatric assessment allows for analyzing the performance or functional status of the patient, independently of the neoplasm, helping to determine whether they belong to a fit, vulnerable, or frail population. It also facilitates the detection of age-associated deficits, not related to the neoplasm, which may be reversed in order to increase treatment tolerance. Moreover, it helps **identify patients who are eligible for the same treatment as the non-geriatric** adult population, as well as **those who are vulnerable and may benefit from adjusted treatment plans** or modified clinical protocols, such as hypofractionated radiotherapy (HFRT) schemes. Finally, it enables the identification of frail patients for whom active treatment may offer no benefit and instead increase the risks of toxicity and functional decline.[73-76]

Scientific evidence in the elderly population

Given the increasing incidence of GB in elderly patients, it is essential to investigate how this population should be managed and which treatment options provide the greatest benefit. In this regard, two **phase III clinical trials have evaluated TMZ versus radiotherapy in elderly patients**: the NOA-08 and the NORDIC studies.

The **NOA-08 study** included patients aged 60 years or older. It showed that TMZ alone was not inferior to radiotherapy (median OS was 8.6 months in the TMZ group and 9.6 months in the radiotherapy group). Additionally, a significant increase in OS was observed in patients with methylated MGMTp treated with TMZ (11.9 months versus 8.2 months with radiotherapy), while in patients with unmethylated MGMTp, radiotherapy appeared to provide better OS than TMZ alone.[77]

The **NORDIC study** included 291 patients aged 60 years or older and compared standard radiotherapy, HFRT and TMZ alone. In the subgroup of patients aged 70 years or older, both TMZ and HFRT were associated with higher OS compared to standard radiotherapy. The greatest benefit from TMZ was observed in patients with methylated MGMTp, with a median OS of 9.7 months versus 6.8 months in unmethylated patients.[78]

Additionally, the **EORTC 26062-22061 study** evaluated patients aged 65 years or older who received HFRT with concomitant TMZ followed by adjuvant TMZ, compared to HFRT alone (40 Gy in 15 fractions). This study demonstrated improved OS with the combined treatment (9.3 versus 7.6 months).[79]

Despite this evidence in elderly patients, treatment regimens and median OS remain inferior to those reported in the Stupp study (which led to the definition of the current first-line treatment standard, explained in more detail in Section 6), as it did not include this population.[2] However, a post-hoc subgroup analysis of the **EF-14** trial showed that **elderly patients (≥65 years) (*n* = 136) benefit from the addition of TTFields to maintenance TMZ**, showing **significantly improved OS (17.4 months versus 13.7 months) and PFS (6.5 months versus 3.9 months)**, with no increase in severe adverse events (see Section 7 for more information).[3,80] Additionally, the National Comprehensive Cancer Network (NCCN) guidelines **recommend standard treatment with or without TTFields** as a therapeutic option **in elderly patients with good functional status**[81].

Management of elderly patients with GB presents significant challenges, as treatment decisions must

carefully **balance extending survival and preserving QoL**. **Chronological age alone should not determine therapeutic decisions**; instead, assessment of functional status, comorbidities, and patient preferences is essential to personalize treatment strategies.

6. First-line treatment for GB

(Section authors: Virginia Martínez, Larraitz Egaña and Sara Garduño)

6.1 The STUPP protocol: standard first-line therapy

The STUPP protocol, first proposed by Stupp et al. in 2005,[2] remains the **standard first-line adjuvant treatment** for GB. It **combines radiotherapy with concomitant and adjuvant TMZ**.[2,82] Following maximal safe surgical resection, patients receive fractionated focal radiotherapy of 60 Gy in 30 fractions of 2 Gy each, administered five days a week for six weeks. Concomitantly, TMZ is administered orally at a daily dose of 75 mg/m² throughout the radiotherapy period. After a four-week break, patients continue with six adjuvant cycles of TMZ monotherapy (150-200 mg/m²/day for five days in 28-day cycles).[2,82]

This protocol has demonstrated a **significant improvement in OS compared to radiotherapy alone**. With a median follow-up of 28 months, OS was 14.6 months in the combination group versus 12.1 months with radiotherapy alone, and the two-year survival rate was 26.5% compared to 10.4%. In addition, grade 3–4 hematological toxicity related to concomitant treatment with radiotherapy and TMZ was minimal, occurring in only 7% of patients.[2]

The STUPP protocol is considered the cornerstone of new therapeutic approaches, including TTFields and novel molecular therapies.[3]

6.2 Hypofractionated radiotherapy

HFRT is an **effective alternative** to conventional fractionated radiotherapy **for the treatment of GB in elderly or frail patients**. Unlike the standard regimen, HFRT reduces the treatment duration by using shorter fractionation schedules, such as 40 Gy in 15 fractions over three weeks or 25 Gy in 5 fractions over one week.[84,85]

HFRT is associated with reduced toxicity and better preservation of QoL, making it a suitable option for patients with a poor prognosis or significant functional limitations.[84,85] Furthermore, this approach has been shown to be **non-inferior to conventional radiotherapy in terms of OS and PFS**, facilitating treatment adherence in patients with comorbidities or impaired performance status.[85]

According to Yuen et al. (2022), in elderly patients with GB and g**ood performance status, the combination of HFRT and TMZ is recommended**, especially in the presence of MGMTp methylation. Conversely, in patients with poorer performance status and in the absence of MGMTp methylation, HFRT alone is a viable therapeutic option.[86]

6.3 Adjuvant treatment

As previously described, once concomitant treatment is completed, the original STUPP protocol continues with six adjuvant cycles of TMZ monotherapy.[2]

Since the publication of the STUPP protocol in 2005, there has been controversy about whether extending treatment with TMZ beyond six cycles could provide additional survival benefit. The **GEINO 1401 study**, presented at the ASCO 2019 congress, evaluated this question by comparing two groups of 159 patients

who had completed the standard STUPP regimen: one group received six additional TMZ cycles (a total of 12) and the other ended treatment after six cycles. The results showed that **extending treatment to 12 cycles did not provide a significant benefit in either OS or PFS**. Consequently, the current standard continues to **recommend six cycles of adjuvant TMZ**.[87]

On the other hand, the **use of TTFields** (described in more detail in **Section 7**) **during the six cycles of TMZ and for up to 24 months thereafter** has been shown to i**mprove clinical outcomes**. In the EF-14 study,[3] the concomitant use of these therapies was associated with increased PFS and OS compared to TMZ monotherapy. These results have been confirmed in subsequent real-world studies and a meta-analysis.[3,88]

Based on the available peer-reviewed evidence, **the first-line treatment algorithm for GB shown in Figure 3**—tailored to patient profiles—may be considered.

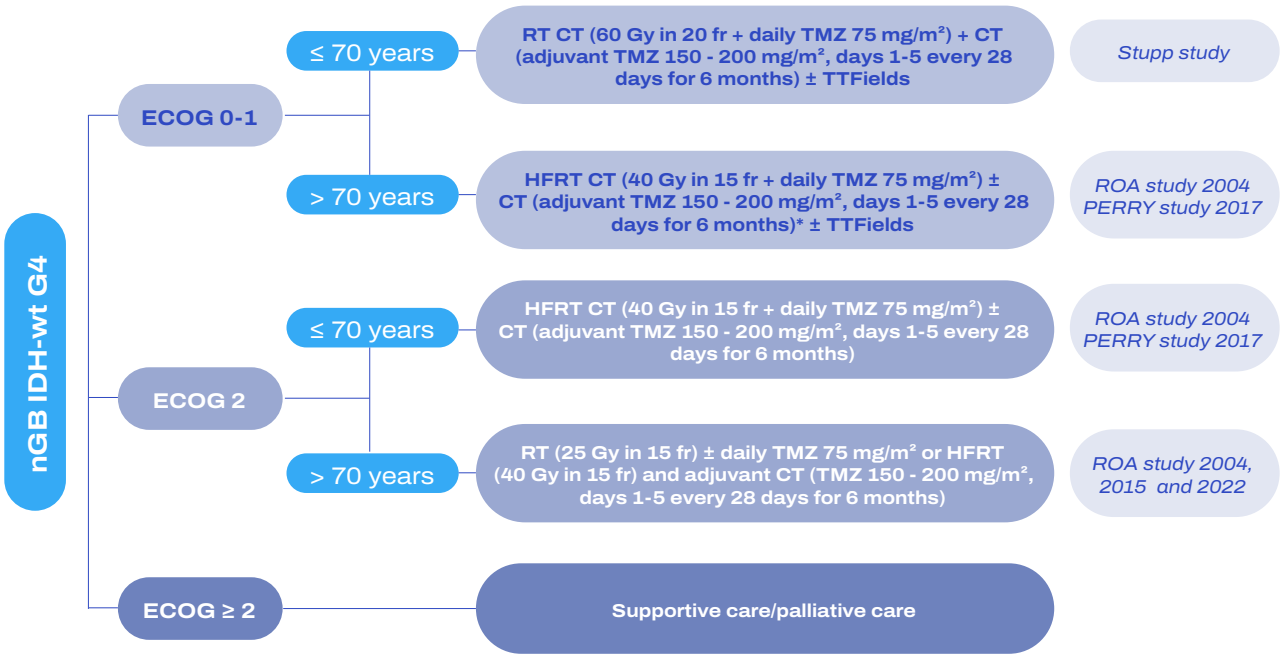


Figure 3. First-line treatment algorithm for GB, stratified by patient profile and based on available peer-reviewed evidence.

*In some centers, the Stupp protocol may still be considered for selected patients aged 70-76 with excellent performance status and favorable scores on geriatric assessment scales. CT: chemotherapy; ECOG: Eastern Cooperative Oncology Group; GB: *de novo* glioblastoma; Gy: gray; Fr: fractions; HFRT: hypofractionated radiotherapy; IDH: isocitrate dehydrogenase; RT: radiotherapy; TMZ: temozolomide; wt: wild type.

6.4 Treatment response follow-up

Neurological and radiological follow-up is essential in the management of GB. Currently, **2D MRI sequences** constitute the basis of radiological monitoring. To evaluate treatment response, it is recommended to follow the recently updated **RANO criteria**,[29] consistently **integrating clinical and radiological criteria**, **temporal disease progression**, and the perspectives of various specialists within **multidisciplinary committees**.

As previously described in section 3, in routine clinical practice, the first follow-up MRI is recommended 3 to 5 weeks after the completion of radiotherapy.[89] During the first three years, MRI should be repeated every 2 to 4 months, and subsequently every 3 to 6 months (**Figure 2**).[36]

In addition, the incidence of **pseudoprogression** is high during the first 12 weeks after radiotherapy. If it occurs, a **confirmatory MRI** should be performed **4 to 8 weeks later** (**Figure 2**). In the meantime, **the**

planned treatment should continue.[29,36,89] In IDH-mutant GB, pseudoprogression can occur beyond this period; therefore, the decision to repeat MRI will depend on clinical and radiological criteria.[29,36]

7. TTFields in the treatment of GB

(Section authors: Noelia Vilariño and Santiago Cabezas)

7.1 Innovative therapeutic approach: description and mechanism of action

In the treatment of adults with GB, TTFields are a **non-invasive** therapeutic modality in which alternating **electric fields at an intermediate frequency** (200 kHz) **and low intensity** (1-3 V/cm) are delivered through transducer arrays placed on the shaved scalp.[90-92] The device is designed for portable use and can operate on rechargeable batteries —with an approximate battery life of 2 or 3 hours— or it may be connected to a standard wall outlet. The device weighs 1.2 kg and has dimensions comparable to a medium-sized tablet. It can be carried in a backpack or shoulder bag (**Figure 4**).[93,94]

Figure 4. TTFields treatment kit and its components.[95] Refer to the device's user manual here.

Preclinical studies* have shown that TTFields act by **interfering with tumor cell mitosis and the proper assembly of organelles during cell division**, leading to cell death.[99,100]

7.2 Clinical evidence: main results

The efficacy of TTFields in the treatment of GB was demonstrated in the **phase III EF-14 clinical trial**, which included 695 patients with newly diagnosed GB who had completed standard treatment consisting of maximal safe debulking surgery or biopsy followed by concomitant radiotherapy with adjuvant TMZ. Patients were randomized to receive maintenance chemotherapy with TMZ alone or together with TTFields.[3]

Treatment with **TTFields plus TMZ significantly improved PFS** (**6.7 months** versus 4.0 months) **and OS** (**20.9 months** versus 16.0 months) compared to TMZ alone. Furthermore, the 5-year OS rate was higher in patients receiving the combination therapy (13% versus 5%).[3] Post-hoc subgroup analyses showed that the

*Preclinical models suggest that TTFields impact other pathways involved in tumor pathogenesis, including cell invasion and migration, DNA damage response, increased cell membrane permeability, and autophagy induction. TTFields also exert immunomodulatory effects, such as activation of the STING pathway and promotion of immunogenic cell death.[92,96-98]

addition of TTFields to TMZ was similarly associated with improved OS accorss all the patient subgroups according to MGMTp region methylation status (unmethylated, methylated); resection (biopsy, partial, gross total); region (outside United States, United States); age (<65 years, ≥65 years); Karnofsky performance score (90-100, ≤80); and sex (women, men).[3]

In terms of **safety**, the frequency of adverse events was similar between the two groups (48% versus 44%, respectively; **Table 9**). The only notable difference was a higher incidence of skin irritation in the combination arm (mild to moderate in 52% of patients and severe in 2%).[3] Regarding **QoL**, no significant differences were observed between the two groups.[101]

Table 9. Grade 3-4 adverse events reported in the EF-14 trial study.[3]

Grade 3-4 events	Nº (%) of patients	
	TTFields + TMZ (n=456)	TMZ (n=229)
≥1 Adverse event	218 (48)	94 (44)
Blood and lymphatic system disorders	59 (13)	23 (11)
Thrombocytopenia	39 (9)	11 (5)
Gastrointestinal disorders	23 (5)	8 (4)
Asthenia, fatigue, and gait disturbance	42 (9)	13 (6)
Infections	32 (7)	10 (5)
Injury, poisoning, and procedural complications	24 (5)	7 (3)
Metabolism and nutrition disorders (anorexia, dehydration, and hyperglycemia)	16 (4)	10 (5)
Musculoskeletal and connective tissue disorders	21 (5)	9 (4)
Nervous system disorders	109 (24)	43 (20)
Seizures	26 (6)	13 (6)
Respiratory, thoracic, and mediastinal disorders (pulmonary embolism, dyspnea, and aspiration pneumonia)	24 (5)	11 (5)

Nº: number; TMZ: temozolomide; TTFields: Tumor Treating Fields.

A secondary analysis of the EF-14 clinical trial showed that **adherence to the TTFields plus TMZ combination for more than 50%** of the time was associated with **improvements in both PFS and OS** compared to TMZ alone. Additionally, treatment adherence of 75% or higher was an independent predictor of OS, and with an **adherence rate above 90%, median OS reached 24.9 months** (compared to 16 months with TMZ alone), with a 5-year OS rate of 29.3% (**Table 10**).[102]

Table 10. Median overall survival according to treatment compliance with TTFields plus TMZ.

TTFields compliance (% of adherence time)	Median OS (months) TTFields/TMZ	Median OS (months) TMZ alone
>90	24.9	16
80–90	21.5	16
70–80	21.7	16
60–70	19.9	16
50–60	18	16
30–50	17.9	16
≤30	18.2	16

Adapted from Toms SA, et al., 2019.[102] OS: overall survival; TMZ: temozolomide; TTFields: Tumor Treating Fields.

7.3 Indications and integration with standard treatment

The use of TTFields has been approved by the FDA and holds CE marking for clinical use in the European Economic Area, the UK, and Switzerland for the treatment of newly diagnosed GB in adult patients*. TTFields treatment **should be initiated during the maintenance phase with TMZ , following clinical trial protocol, and can be continued beyond first progression**, potentially in combination with a second local or systemic therapeutic intervention.[3,89,103,104]

Clinical data indicate that **higher daily use of TTFields is associated with improved treatment outcomes**, measured by gains in PFS and OS (**Table 10**).[102]

7.4 Patient education

It is important for the patient to **receive adequate information** to ensure **proper use of TTFields**. Patients must shave their scalp with an electric shaver before placing the transducer arrays to ensure optimal contact.[94,95]

The placement of the transducer arrays must follow the instructions of the placement "map", which is generated based on the tumor location of each patient. However, in cases where MRI is delayed, a standard arrangement suitable for all patients may be employed temporarily. Once MRI results are available, it is important to **adapt the array positioning to the specific tumor location**. A total of **four arrays** are used —two pairs placed opposite each other to generate the electric fields— and are typically **changed every 3 or 4 days**. On average, about 34 transducers are used per month.[94,95]

TTFields therapy **can be paused for personal activities**, such as bathing or showering (in this case they must disconnect from the battery and cover their head with a shower cap to prevent the transducer arrays from getting wet), exercising, or performing other activities where using the device is uncomfortable. Patients should also consider the need to remove the transducer arrays for the corresponding follow-up MRI examinations. To ensure optimal use, patients are advised to plan ahead for these daily periods when the device will be paused. The head may be covered with a breathable light wig or a hat while using the device.[94,95]

*Optune Gio is intended for the treatment of adult patients (18 years of age or older) with newly diagnosed WHO grade 4 glioma, following maximal debulking surgery or biopsy, radiation therapy and/or chemotherapy, concomitant with maintenance Temozolomide with or without Lomustine, and after systemic therapy is stopped.

7.5 Periodic evaluation

Regular clinical follow-up by the treating physician is necessary to **evaluate treatment efficacy**, **monitor potential side effects**, and **adjust the placement of the transducer arrays** or their usage duration if needed.[94,95]

It is essential to **review the patient's adherence** to the device, ensuring daily compliance of **at least 75% of the time**, as indicated in the device's user manual. To facilitate this evaluation, the device records daily activity, and usually every month, the collected data is sent to the physician to monitor treatment adherence.[94,95]

7.6 Management of toxicities

As previously mentioned, prolonged use of transducer arrays and adhesives during TTFields treatment can lead to **localized skin reactions**.[3,105,112] Nevertheless, early prophylaxis and proper patient management can help reduce the risk and severity of skin-related adverse events.[105-107] The use of **prophylactic topical agents**, such as **silicone-based barriers** compatible with TTFields, **low-potency topical steroids**, or **calcineurin inhibitor creams**, may help prevent skin-related adverse events or reduce their severity. Moreover, the continuous use of prophylactic measures, combined with **early identification and appropriate management** of dermatologic adverse events, can help ensure treatment tolerability and adherence.[105-107]

The most common toxicities associated with the device include **skin irritation, headache, and fatigue**, which are generally **mild and easily managed**. For skin irritation, the use of topical creams is recommended, including corticosteroids or topical antibiotics in cases of ulceration and/or infection, as well as regularly changing the position of the transducer arrays. **Zinc-based creams should be avoided**, as their viscosity can form barriers and potentially reduce the efficacy of TTFields.[107] Headache may be managed with first-line analgesics, such as acetaminophen or NSAIDs.[3,95]

General clinical information on the management of dermatologic adverse effects related to TTFields in patients with GB is provided in **Figure 5**.[95,105]

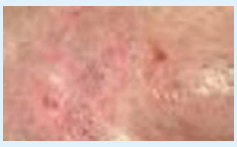
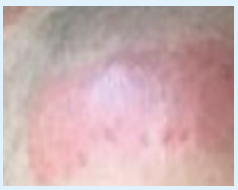
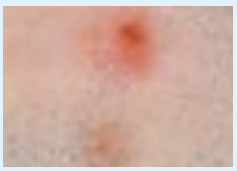
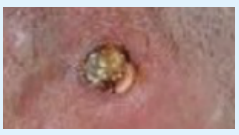
	**Hyperhidrosis** • Treat with aluminum chloride antiperspirant* or topical glycopyrrolate at every array exchange • Advise patients to avoid using ointments and medications that may cause sweating • Consider referral to a dermatologist for botulinum toxin injection
	**Pruritus** • Advise patients to use fragrance-free or anti-dandruff shampoo • Although part of the standard array change protocol, limit skin contact with alcohol-based products • Topical corticosteroids may be prescribed if inflammation is present (e.g., betamethasone, clobetasol, fluocinonide) • Identify cause and, if possible, reduce/eliminate
	**Contact dermatitis** • Immediate removal of the irritant/allergen • Transducer array removal from irritation/allergen site • Topical corticosteroid (e.g., betamethasone, clobetasol, fluocinonide) application • Apply a barrier film • Consider trimming adhesive/surgilast if reaction exists to tape/adhesive • If blistering develops, old, moist compress application (20 min; 3 times/day) is recommended • Consider systemic corticosteroids/treatment breaks if condition persists
	**Erosion/ulceration** • Transducer array removal from site of erosion/ulcer: consider re-placement to avoid hardware exposure • Wound dressing with gauzes, hydrogels, or hydrocolloids • Assess wound and treat with topical antibiotic (e.g., clindamycin, gentamicin) • Consider wound culture • Keep clear of excess discharge and dead skin (severe cases may require surgical debridement) • Return to clinic in 2 weeks; if condition persists, consider oral antibiotic/treatment break
	**Dermatitis + infections** • Assess wound and treat with topical antibiotic (e.g., clindamycin or gentamicin) • Warm compresses with saltwater or Burow's solution (5% aluminum subacetate) • Take wound culture and potentially refer to dermatologist • Return to clinic in 2 weeks; if condition persists, consider oral antibiotic/treatment break

Figure 5. Management strategies for skin adverse events associated with TTFields.

Adapted from Lacouture et al., 2020, *JAMA Dermatology*, under Creative Commons Attribution License (CC BY 4.0).[105]
*In some patients, chloride-containing formulations may cause skin irritation; a chloride-free alternative is recommended.[107]

8. Treatment of recurrent GB

(Section authors: Natalia Luque, Alba Moratiel and Irene Moya)

8.1 Definition and assessment of recurrent GB

As described above, MRI is considered the key tool for monitoring GB; however, in certain cases, it may need to be complemented by other imaging techniques, such as PET, despite its still limited validation, to help differentiate tumor progression from pseudoprogression.[108]

Tumor progression is assessed using distinct criteria for enhancing and non-enhancing disease. According to the RANO 2.0 criteria, **progression in enhancing tumors is defined by a ≥25% increase in the sum of perpendicular diameters** or a **≥40% increase in the total volume of target lesions**. This is especially important when corticosteroid treatment is stable or increasing. Confirmation scans, typically performed at least 4 weeks apart, may be necessary, especially post-radiotherapy or with treatments prone to pseudoprogression. **If subsequent imaging shows improvement**, the **initial progression is reclassified as pseudoprogression**. Other indicators of progression include new measurable lesions (≥10 mm x 10 mm), definite leptomeningeal disease, progression of non-measurable lesions, or clinical deterioration not attributable to corticosteroid changes. Failure to return for follow-up due to clinical worsening is also considered progression. An increase in corticosteroid dose alone is not considered progression unless accompanied by tumor-related clinical decline.[29]

For **non-enhancing disease**, progression is defined by a **≥25% increase in the sum of the perpendicular diameters** or a **≥40% increase in lesion volume on T2/FLAIR sequences**, excluding radiation, edema, or comorbidities. The appearance of new lesions (>10 mm x 10 mm) or new contrast enhancement also indicates progression. Criteria for leptomeningeal disease, progression of non-measurable lesions, and clinical deterioration are consistent with those used for enhancing tumors.[29]

8.2 Treatment options in recurrent GB

Currently, there is **no standardized approach for recurrent GB** (rGB) management. Therefore, all potential treatment options should be **evaluated by a multidisciplinary committee**. The optimal treatment for each patient should be selected **based on individual prognostic factors**, and whenever possible, patients should be offered the opportunity to **participate in a clinical trial**.[89,103]

Surgery

Rescue surgery may be considered in cases of rGB, particularly when the tumor causes mass effect (i.e., for symptomatic and/or large lesions). The main predictive factors for survival after rescue surgery include patient age, functional status (ECOG), time since initial surgery, and tumor location.[109] However, to date, there are **no prospective studies analyzing the impact of rescue surgery on OS**. In this regard, the randomized clinical trial **RESURGE** (NCT02394626) aims to compare survival outcomes between patients undergoing rescue surgery followed by second-line adjuvant treatment and those receiving second-line therapy without surgery. The trial will also evaluate survival outcomes based on the EOR (complete versus incomplete resection).

Additionally, the implantation of biodegradable carmustine polymers during surgery for rGB has been associated with a modest survival benefit versus placebo, according to a randomized clinical trial published in the 1990s.[110]

Radiotherapy

Currently, there are no prospective studies analyzing the role of reirradiation in the treatment of rGB. However, it **may be considered in patients who responded well to initial radiotherapy** and/or in **those where at**

least 6 months have passed since the first treatment. According to retrospective series, fractionated stereotactic radiotherapy may be a suitable option **for patients with good general condition and small-volume recurrence**.[111-113]

TTFields

The use of TTFields has also been approved by the Food and Drug Administration (FDA) and holds CE marking for clinical use in the European Economic Area, the UK, and Switzerland for the treatment of rGB in adults, based on the results of the randomized **clinical trial EF-11**. This study assigned patients with rGB to receive either TTFields or chemotherapy. Although no statistically significant differences were observed in OS or PFS, **TTFields demonstrated efficacy comparable to chemotherapy**, with a **better adverse event profile and improved QoL**.[114] Additionally, for those patients who start maintenance therapy with TTFields plus TMZ, the possibility of using TTFields together with other treatments, such as rescue surgery, reirradiation, and second-line systemic therapies, could represent an opportunity to improve outcomes in patients with rGB.[115]

Systemic Treatment

There is **no established standard treatment for rGB**, and the systemic therapies used to date have shown only modest benefits.[89,103]

Nitrosoureas

Treatment with nitrosoureas is typically **used in patients with diffuse rGB that do not cause mass effect or** for those with tumors that **exhibit MGMTp methylation**, as they may have a higher likelihood of benefiting from nitrosoureas.[89,103]

Lomustine is the most commonly used treatment for rGB, although **its efficacy is limited**, with a **6-month PFS rate of approximately 20%**. The EORTC 26101 study evaluated the combination of lomustine and bevacizumab versus lomustine monotherapy, showing an improvement in PFS but no significant impact on OS, with median OS of 9.1 months versus 8.6 months, respectively.[116] Similarly, the BELOB study demonstrated that the combination of bevacizumab and lomustine did not improve OS but increased hematological toxicity.[117]

Fotemustine has been evaluated in several phase II trials, showing a **6-month PFS rate ranging from 39%[118] to 51.5%**.[119] The most commonly used treatment regimens are those described by Addeo and Fabrini.[118,119]

Antiangiogenics

Bevacizumab is the most widely studied antiangiogenic drug in rGB. It has been shown to be effective in **reducing cerebral edema and relieving related symptoms**, allowing for a **reduction in corticosteroid doses**.[103] Its efficacy has been evaluated in multiple trials, including combinations with irinotecan or nitrosoureas, showing an **objective response rate of around 30% and an improvement in PFS**, although without benefit in OS.[89] These results led to its approval by the FDA, though it has not been approved by the European Medicines Agency (EMA). Patients with rGB should ideally be **considered for clinical trials before receiving bevacizumab**, as most trials exclude those with prior use of bevacizumab. Its use is primarily recommended for recurrences causing mass effect.[89,103]

TMZ

Retreatment with TMZ can be considered **in patients with a progression-free interval of at least 4 to 6 months** since the completion of initial therapy, especially in those **with MGMT-methylated tumors**.[89] In these favorable patients, a **6-month PFS rate of 40%** has been observed. Although extended administration schedules have been investigated, these have not demonstrated superiority over the standard dose.[120]

Immunotherapy and targeted therapies

Programmed cell death protein 1 **(PD-1)** and programmed death-ligand 1 **(PD-L1) inhibitors** have not shown significant benefits as monotherapy for the treatment of rGB. However, their neoadjuvant use **in combination with surgery and adjuvant treatments may improve OS**.[121,122]

Tumor peptide vaccination and chimeric antigen receptor T-cell **(CAR-T) therapies** have demonstrated **therapeutic potential**, although efficacy remains limited due to tumor heterogeneity, including resistant clones, and tumor-induced immunosuppression.[123]

In addition, molecular analysis is recommended to **identify BRAFV600E mutations or NTRK gene fusions**, as patients presenting these alterations may benefit from **targeted therapy**.[124,125]

Palliative Care

Early palliative care in patients with rGB **improves QoL, controls symptoms** such as pain and neurological deficits, **and optimizes emotional and family support**, ensuring comprehensive and dignified care until the end of life.[126]

Figure 6 illustrates **a proposed treatment algorithm for rGB**, based on peer-reviewed evidence, to guide treatment decisions using clinical and molecular factors.

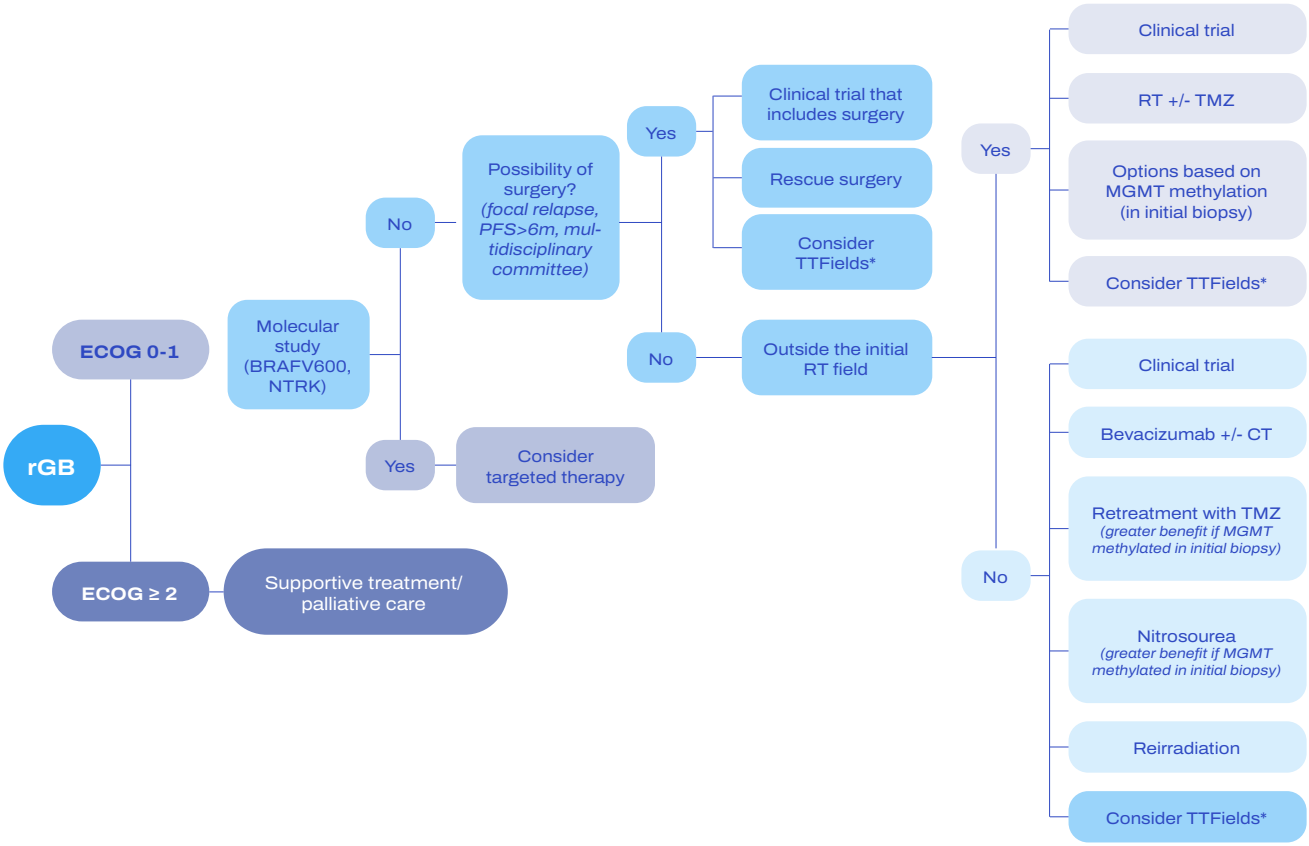


Figure 6. Proposal for a treatment algorithm for rGB based on peer-reviewed evidence.

*Consider continuing TTFields together with the selected second-line therapy following progression on first-line TMZ plus TTFields.
CT: chemotherapy; ECOG: Eastern Cooperative Oncology Group; PFS: progression-free survival; rGB: recurrent glioblastoma; RT: radiotherapy; TMZ: temozolomide; TTFields: tumor treating fields.

9. Symptomatic treatment of GB

(Section authors: Roser Velasco and Alberto Garrido)

Clinical manifestations of primary brain malignancies are **related to the location of the tumor** and may include **seizures, headache, focal neurological deficits, fatigue, edema and cognitive impairments**. These neurological symptoms, which may progress over time, should be addressed to ensure proper management of symptomatic patients with GB.

9.1 Management of seizures in patients with GB

Seizures are common in patients with GB, presenting as the **starting symptom in 25-50%** of cases and occurring **during the course of the disease in 20-30%** of patients.[127] Epilepsy in GB is related to the epileptogenesis of the tumor, peritumoral alterations, and adjacent brain damage.[127] The seizures are focal in nature, although they can rapidly generalize.[127] **Their initial presentation is associated with longer survival**,[128-130] while their **late onset or recurrence is usually indicative of rGB or progression**.[131] Management of seizures frequently requires the administration of antiepileptic drugs (AEDs) simultaneously with other treatments.[127] However, **the prophylactic use of AEDs is not recommended**,[132] **except for the postoperative period**, during which they should be discontinued 1–2 weeks after surgery.[131] It has been shown that surgery, chemotherapy, and radiotherapy can also contribute to seizure control. Furthermore, TTFields therapy has not been associated with an increased risk of seizures.[3] Corticosteroids can act as adjunctive therapy and help in seizure control; however, due to their unpredictable interaction with enzyme-inducing AEDs, close monitoring of their plasma levels is required.[127]

Any patient with GB who has experienced a seizure should receive treatment with AEDs, **prioritizing monotherapy with non-enzyme-inducing drugs** such as levetiracetam.[133] In cases of psychiatric comorbidity or the need for combination therapy, lacosamide, valproate, perampanel, or brivaracetam are considered (**Table 11**). Between 10 and 40% of patients with GB may develop **refractory epilepsy**, which **often requires the use of more than one AED** to achieve adequate seizure control.[127]

Table 11. Main AEDs, dosage, and adverse effects.

AED	Administration route	Dosage	Adverse effects
Brivaracetam[&]	IV O	Initial: 50-100 mg/24 h Escalation: 100 o 150 mg, or without escalation Maintenance: 50-200 mg/24 h	Drowsiness, fatigue, dizziness
Carbamazepine	O	Initial: 200 mg/12 h Escalation: 200 mg weekly Maintenance: 600-1800 mg/24 h	Frequent: drowsiness, dizziness, diplopia, hyponatremia Infrequent: rash (Stevens-Johnson syndrome and toxic epidermal necrolysis), bone marrow aplasia, hepatotoxicity, hypersensitivity reactions
Eslicarbazepine	O	Initial: 400 mg/24 h Escalation: 400 mg, or without escalation Maintenance: 1200-1600 mg/24 h	Hyponatremia, rash

AED	Administration route	Dosage	Adverse effects
Phenytoin[##]	IV O	Initial: 100 mg/8 h Escalation: 50-100 mg weekly Maintenance: 300-600 mg/24 h	Frequent: dizziness, diplopia (double vision), drowsiness, tremor Infrequent: rash (Stevens-Johnson syndrome and toxic epidermal necrolysis), agranulocytosis, hypersensitivity reactions (DRESS syndrome)
Phenobarbital[##]	IV IM O	Initial: 100 mg/24 h Escalation: 100 mg weekly Maintenance: 100-300 mg/24 h	Frequent: sedation, drowsiness, osteoporosis Infrequent: rash (Stevens-Johnson syndrome and toxic epidermal necrolysis), agranulocytosis, hypersensitivity reactions
Lacosamide	IV O	Initial: 50 mg/12 h Maintenance: 100-400 mg/24 h	Frequent: dizziness, headache, diplopia, nausea Infrequent: AV block
Lamotrigine	O	Initial: 25 mg/24 h (50% of dose if associated with VPA) Escalation: 25-50 mg weekly (with VPA ½) Maintenance: 200-600 mg/24 h (reduce dose to 30-50% if associated with VPA)	Infrequent: rash (Stevens-Johnson syndrome and toxic epidermal necrolysis), agranulocytosis, hypersensitivity reactions
Levetiracetam	IV O	Initial: 500 mg/24 h Escalation: 500-1000 mg weekly Maintenance: 100-3000 mg/24 h	Drowsiness, asthenia, irritability, neuropsychiatric
Oxcarbazepine[#]	O	Initial: 300 mg/24 h Escalation: 300-600 mg weekly Maintenance: 900-2400 mg/24 h	Frequent: dizziness, headache, diplopia, nausea, drowsiness, hyponatremia Infrequent: rash (Stevens-Johnson syndrome and toxic epidermal necrolysis), agranulocytosis, hypersensitivity reactions
Perampanel[&]	O	Initial: 2 mg/24 h Escalation: 2mg every 2-4 weeks Maintenance: 4-12 mg/24 h	Dizziness, drowsiness, irritability, aggressiveness
Valproic acid (VPA)*	IV O	Initial: 200 mg/8 h Escalation: 200-500 mg weekly Maintenance: 1000-3000 mg/24 h	Frequent: tremor, weight gain, alopecia, thrombocytopenia Infrequent: hyperammonemic encephalopathy, acute pancreatitis, immunoallergic hepatitis, agranulocytosis, teratogenicity (also in males)*
Zonisamide	O	Initial: 25 mg/24 h Escalation: 100 mg weekly Maintenance: 300-600 mg/24 h	Frequent: photosensitivity, weight loss, irritability, fatigue, drowsiness, mood changes Infrequent: nephrolithiasis, language disorders, suicidal ideation

[&]added therapy; [##]enzyme inducer: potent; [#]enzyme inducer: moderate. *Current recommendations advise informing male patients currently receiving VPA of the potential risk of neurodevelopmental disorders in their children conceived during treatment or up to three months after discontinuing it.[134] IV: intravenous; IM: intramuscular; O: oral.

In the terminal phase of GB, it is recommended to maintain the treatment with AEDs due to the increased risk of seizures, even in the presence of swallowing difficulties or impaired level of consciousness. In these cases, alternative formulations may be considered, such as oral suspensions, intravenous formulations, or rectal administrations.[127,135]

The **discontinuation of AEDs** in patients with GB should be evaluated very carefully and **only considered after at least 24 months without seizures**, no evidence of tumor progression **or significant edema**, and in the absence of additional risk factors, such as recent surgery or extensive cortical involvement.[131] It is recommended to withdraw AEDs **gradually and under close monitoring**, always respecting the patient's decisions. The recurrence of seizures can increase morbidity and mortality by increasing intracranial pressure, the risk of falls, or the occurrence of complications such as status epilepticus. It can also negatively affect QoL and limit daily activities, such as driving. In this regard, it should be noted that in cases with good seizure control, **the use of AEDs alone should not be a contraindication for driving**. However, in patients with GB, other possible associated conditions should be considered, such as neurological deficits and cognitive impairment.

In cases of a **prolonged seizure**, the immediate administration of benzodiazepines is recommended, preferably **intravenous diazepam** (10–20 mg) administered at a rate of 2 mg/min. For use in the out-of-hospital setting, rectal formulations of diazepam are also available.[136]

9.2 Management of cerebral edema in GB

Cerebral edema in GB occurs due to an accumulation of fluid in the brain parenchyma, leading to an **increase in tissue volume and intracranial pressure**. These events are associated with headache, nausea, vomiting, seizures, focal neurological deficits, decreased level of consciousness, ischemic events, and even brain herniation and death.[137] This edema has a vascular origin, caused by the disruption of the blood-brain barrier, related to the production of vascular endothelial growth factor and the abnormal vascularization of the tumor.[138]

Depending on the clinical severity of the edema, an urgent or non-urgent management will be considered. **Urgent management** is indicated in cases of **increased intracranial pressure with deterioration of the level of consciousness or signs of herniation**.[139] In the absence of **immediate surgical options**, treatment with **high-dose steroids** should be initiated, for example, dexamethasone 10–20 mg IV bolus, followed by a maintenance regimen of dexamethasone 8–16 mg/day divided into 2–4 doses.[140] Hypertonic saline and osmotic diuretics such as 20% mannitol may also be used (1 g/kg bolus, followed by 0.25 to 0.5 g/kg every 3–5 h, in a rapidly tapering regimen).[141]

Non-urgent treatment is based on the **administration of dexamethasone**. Its initial dose should be adapted to the severity of the symptoms, always aiming for the minimum effective dose.[140] It should be started with a minimum of 4 mg and a maximum of 16 mg daily, divided into one or two doses, avoiding nighttime administration.[142] The maximum benefit is achieved between 24 and 72 hours after the start of treatment,[143] and after reaching it, a progressive dose reduction (tapering) should be performed. Although there is no fixed established regimen, it is considered that the tapering should be carried out over 2 to 4 weeks, or for longer periods in symptomatic patients.[144] **Close monitoring should always be performed**, adapting the rate of tapering according to the appearance or evolution of symptoms.

Prolonged use of dexamethasone and other corticosteroids can lead to multiple adverse effects, such as Cushing's syndrome, impaired fasting glucose, muscle weakness, increased risk of infections, gastric ulcers and gastrointestinal bleeding, skin changes, and hematological and psychiatric disturbances.[145]

It is essential to establish **preventive measures against the most common adverse effects**. Furthermore, these **adverse effects should be systematically monitored**, as they constitute a significant cause of morbidity and have a significant impact on the QoL of patients. For example, the use of **proton pump**

inhibitors should be considered in elderly patients or those receiving nonsteroidal anti-inflammatory drugs (**NSAIDs**) concomitantly with corticosteroids,[146] as well as regular monitoring of blood glucose levels.

In patients receiving **prednisone ≥20 mg/day** (or equivalent) for ≥4 weeks, it is recommended **prophylaxis against *Pneumocystis jirovecii*** with trimethoprim 160 mg/sulfamethoxazole 800 mg (strong formulation), three times per week,[147] preferably on alternate days.

9.3 Rehabilitation and support for GB patients

In addition to all of the above, rehabilitation in **patients** with GB **contributes to improving functional prognosis and QoL**.[148] It should address both **motor deficits** (with strength and body awareness therapy) and **cognitive deficits** (with attention and memory exercises), with the aim of achieving greater independence in daily activities.[149]

Occupational therapy and the **support from a multidisciplinary team**, including psychologists and social workers, are essential. Furthermore, it is crucial to **address the emotional needs** of the patient and to provide **adequate support to caregivers**. In this regard, it is important to actively assess the psychological and support needs of caregivers,[150] which are often underestimated, as the family and social environment play a fundamental role in the patient's treatment process.

10. Other high-grade gliomas

(Section authors: Eva Corrales and Jairo Legaspi)

High-grade gliomas represent a **significant therapeutic challenge due to their aggressiveness, poor prognosis, and biological heterogeneity**. As previously discussed, the current WHO classification categorizes gliomas based on IDH mutation status, histological grade, and molecular profile.[6,151]

10.1 Oligodendrogliomas and astrocytomas

High-grade non-GB gliomas are IDH-mutant and are broadly classified into two main entities or "types": oligodendrogliomas and astrocytomas. Those classified as high-grade correspond to G3 and G4:[151]

- Astrocytoma IDH-mutant, G2
- Astrocytoma IDH-mutant, G3
- Astrocytoma IDH-mutant, G4
- Oligodendroglioma IDH-mutant and 1p/19q codeleted, G2.
- Oligodendroglioma IDH-mutant and 1p/19q codeleted, G3.

Oligodendrogliomas are defined by the presence of IDH mutation and 1p/19q codeletion, whereas the absence of this codeletion supports the diagnosis of astrocytoma.[152] These tumors **frequently exhibit TERTp mutations**; however, unlike in GB, these alterations do not appear to affect prognosis.[6,151] In **astrocytomas**, **alterations in p53** (mutation or >10% nuclear positivity by IHC, mutually exclusive with 1p/19q codeletion) **and in ATRX** (mutation or nuclear loss by IHC) **are considered diagnostic**.[152] However, recurrent oligodendrogliomas may acquire TP53 mutations following treatment with radiotherapy and TMZ.[152]

In **astrocytomas**, **assessment of CDKN2A/B gene status is essential**, as **homozygous deletion directly classifies the tumor as G4**, regardless of its micromorphological features, due to the associated worse prognosis.[152]

10.2 Other high-grade astrocytomas

Furthermore, there are other less frequent high-grade astrocytomas, which are briefly described below:[152]

Infratentorial astrocytoma

These tumors are rare and poorly described in the literature. They are **located in the brainstem or cerebellum** and exhibit a non-canonical IDH mutation profile. The DNA methylation profile indicates that they are epigenetically different from those located at the supratentorial level. The prognosis of infratentorial astrocytomas is intermediate between that of diffuse midline glioma H3 K27-altered and high-grade supratentorial IDH-mutant astrocytomas.[152,153]

Primary mismatch repair-deficient IDH-mutant astrocytoma (PMMRDIA)

This entity is associated with **microsatellite instability** due to a germline mismatch repair alteration. Its **prognosis is similar to that of GB**, with lower level of MGMTp methylation.[152,154]

Oligosarcoma

This is a rare entity with features of both oligodendroglioma (IDH mutation and 1p/19q codeletion) and sarcoma, but with a distinct DNA methylation profile. It **frequently arises as a secondary tumor** after recurrence and **tends to be aggressive**.[152] Recently, it has been proposed as a distinct entity, but further studies are needed to confirm its classification.[155]

Pediatric astrocytomas (children and young adults)[156]

H3 K27-altered diffuse midline glioma

This is a **rare but highly aggressive** tumor that affects midline structures such as the **brainstem** (predominantly the pontine region), **thalamus, and spinal cord**. It is more prevalent in the pediatric population and in young adults. The name derives from a characteristic alteration in histone 3 (most commonly **H3K27M**, although other variants such as **H3F3A** and **HIST1H3B** also exist), which leads to hypomethylation and repression of tumor suppressor genes.[157] It is frequently **associated with mutations in ACVR1, TP53**, and alterations in the **PRC2 complex**. Specifically, the H3 mutation inhibits the PRC2 suppressor complex through its interaction with the protein EZH2 (Enhancer of Zeste Homolog 2).[158] Recent studies suggest the existence of potential subtypes within this entity, with a progressively expanding role for DNA methylation profiling.[157]

Diffuse H3G34-mutant glioma

These tumors, located in the cerebral hemispheres, exhibit the **H3G34** mutation and **commonly show alterations in TP53 and ATRX**. The **prognosis is poor**. Treatment typically involves surgery, radiotherapy, and alkylating agents.[159]

High-grade diffuse glioma, H3-wt and IDH-wt

These tumors frequently present **alterations in PDGFRA, EGFR, and TERT** genes, as well as **MYCN amplification**. Their **prognosis is equally poor**, and treatment is similar to that for diffuse H3G34-mutant gliomas.[159]

Infantile-type hemispheric glioma

This tumor is characterized by abnormalities in **NTRK, ROS, ALK, and MET**. It has a **better prognosis** than the previously mentioned gliomas due to the **possibility of using targeted therapies**.[159]

10.3 Therapeutic management of the most relevant tumors

The diagnostic, molecular, and therapeutic characteristics of the most relevant high-grade gliomas are summarized in **Table 12**.

Table 12. Summary of the diagnostic, molecular, and therapeutic characteristics of the most relevant high-grade gliomas (other than GB).

Characteristics	Astrocytoma (WHO 2021)	Oligodendroglioma	H3-K27-altered diffuse midline glioma
WHO Grade	III-IV	III	IV
IDH	Mutated	Mutated	Wild-type
1p/19q codeletion	Not present	Present	Not present
Associated mutations	ATRX loss (90%), p53 mutation (90%), homozygous deletion of CDKN2A/B*	TERT (90%), CIC, NOTCH1, FUBP1, CDKN2A/B	H3-K27M, TP53, ACVR1
Treatment	Post-surgery RT (± concurrent TMZ) + extended TMZ**	Post-surgery RT + PCV (extended TMZ** as alternative)	Post-surgery RT ± CT (TMZ / clinical trial)
OS	2–8 years	10–15 years	12–18 months

*The presence of a homozygous deletion of CDKN2A/B specifically classifies this entity as G4. **Temozolomide for 12 cycles, CATNON trial.[160] CT: chemotherapy; IDH: isocitrate dehydrogenase; OS: overall survival; PCV: procarbazine, lomustine (CCNU), and vincristine; TMZ: temozolomide.

Grade 3 astrocytoma IDH-mutant

Therapeutic management of grade 3 astrocytoma IDH-mutant includes maximal surgical resection, when possible, followed by **radiotherapy** (59.4-60.0 Gy in fractions of 1.8-2.0 Gy), combined with **concurrent TMZ** (75 mg/m^2), and subsequent **extended adjuvant TMZ** for up to 12 cycles, based on the results of the CATNON trial.[160] However, a subanalysis showed no beneficial effect from the addition of concurrent chemoradiotherapy, suggesting that it could potentially be omitted during the radiotherapy course.[161]

Currently, there are ongoing studies **evaluating the use of IDH inhibitors** (vorasidenib and ivosidenib) due to their promising results in low-grade tumors.[162,163]

The median OS for astrocytoma IDH-mutant is around 5 to 7 years.[164,165]

Grade 3 oligodendroglioma IDH-mutant and 1p/19q codeleted

The pivotal studies RTOG 9402[166] and EORTC 26951[167] compared the addition of procarbazine, lomustine and vincristine (PCV) chemotherapy to radiotherapy in grade 3 oligodendrogliomas. They concluded that **surgery followed by radiotherapy** (59.4 Gy in 33 fractions, 1.8 Gy per fraction)[168] **and posterior PCV chemotherapy** (4 to 6 cycles) produced a **significant benefit** in patients (**Table 13**).

The use of TMZ is also accepted because of lower toxicities, although PCV is the chemotherapy of choice in patients who tolerate this regimen.[35,169] Results of the CODEL study will demonstrate whether radiotherapy

plus PCV is more effective than radiotherapy plus TMZ in patients with newly diagnosed 1p/19q codeleted oligodendroglial tumors.[170]

These tumors have better OS, with a median of 10-15 years.[171,172]

Table 13. PCV chemotherapy regimen for grade 3 IDH-mutant, 1p/19q-codeleted oligodendroglioma.

Drug	Standard dose*	Route of administration	Days of administration	Cycle frequency	Remarks
Lomustine	110 mg/m² (single doses)	Oral	Day 1	Every 6 weeks	-Hepatotoxicity -Neurotoxicity *empty stomach
Procarbazine	60 mg/m²/day	Oral	Days 8 to 21	Every 6 weeks	-Hematologic -Gastrointestinal
Vincristine	1.4 mg/m² (max 2 mg)	Intravenous	Days 8 and 29	Every 6 weeks	-Accumulative neurotoxicity

*Dose adjustment is recommended for patients over 70 years of age or with comorbidities.

H3 K27-altered diffuse midline glioma

There is insufficient scientific evidence for these tumors; therefore, it is recommended to **enroll the patients in a clinical trial whenever possible**. Tumor location in the thalamus may confer a prolonged disease course compared to pontine gliomas, with a median OS of 12-18 months.[173,174]

Due to their location in critical brain regions and their diffuse nature, **surgical resection is often very limited**. Consequently, **radiotherapy is recommended as the primary treatment** (54-60 Gy in 27-30 fractions).[173,175] These doses vary according to the site and adjacent organs at risk. Accelerated fractionation radiotherapy can be considered in selected patients without compromising disease control or survival. Moreover, the use of **concurrent or adjuvant systemic treatments** should be **evaluated individually**, as no standard regimen has yet been defined.[173]

Currently, there are ongoing phase II and III clinical trials exploring the use of **EZH2 inhibitors**, **ONC201 therapy** (a dopaminergic receptor DRD2 antagonist and mitochondrial caseinolytic protease P [ClpP] agonists), the use of **vaccines** and **CAR-T therapies**.[173,175,176] Preliminary clinical evidence suggests that **ONC201 may offer therapeutic benefit** in patients with H3K27M-mutant diffuse midline gliomas, showing durable responses and manageable toxicity profiles.[177]

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