



# Multidisciplinary consensus recommendations for the management of IDH-mutant grade 2 gliomas in Spain: a Delphi study

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## Abstract

**Purpose** Management of IDH-mutant grade 2 gliomas is challenging due to tumor heterogeneity and uncertainties arising from new imaging modalities, diagnostic advances, and emerging targeted therapies. This study aimed to develop multidisciplinary consensus recommendations to standardize the diagnosis, treatment, and follow-up of these gliomas in Spain.

**Methods** A multidisciplinary scientific committee drafted 85 clinical statements based on literature and expert experience. These were independently rated through two rounds of an online Delphi survey by a panel of 18 experts, including three representatives from each of six Spanish scientific societies involved in neuro-oncology, neurosurgery, neuropathology, radiation oncology, neuroradiology, and medical oncology.

**Results** After two rounds, consensus was achieved on 74 statements (87.1%). Key agreements included magnetic resonance imaging (MRI) with gadolinium and advanced imaging as preferred diagnostics; mandatory molecular testing for IDH1/2 mutations and 1p/19q codeletion; individualized risk stratification guiding treatment; maximal safe surgical resection as first-line management; and combined chemoradiotherapy for high-risk patients. The IDH1/2 inhibitor vorasidenib is recognized as an emerging therapy for patients with grade 2 glioma. Areas without consensus involved liquid biopsy and specific clinical scenarios for vorasidenib. Emphasis was placed on multidisciplinary decision-making and long-term toxicity monitoring.

**Conclusions** This work delivers multidisciplinary consensus recommendations to standardize care in IDH-mutant grade 2 gliomas, integrating advances in molecular diagnostics, imaging, and therapeutics. It also identifies key knowledge gaps and clinical uncertainties, underscoring the critical need for ongoing research and expert collaboration to continually refine personalized management approaches and improve patient outcomes.

**Keywords** Neuro-oncology · Glioma · Isocitrate dehydrogenase · Vorasidenib · Delphi technique

## Introduction

Isocitrate dehydrogenase (IDH) mutations are a defining molecular feature that has reshaped the classification and understanding of diffuse gliomas [1, 2]. They occur most often in IDH1 and less commonly in IDH2, arise early in gliomagenesis, and drive accumulation of the oncometabolite 2-hydroxyglutarate (2-HG). Elevated 2-HG disrupts epigenetic regulation by inhibiting enzymes involved in DNA and histone demethylation, promoting tumor initiation and progression [3]. Clinically, IDH-mutant gliomas constitute a distinct subgroup with better prognosis and distinct treatment responses compared with IDH-wildtype tumors.

Grade 2 gliomas account for 5–10% of primary brain tumors, and ~70–85% harbor IDH mutations; adult-type diffuse gliomas comprise >90% of gliomas diagnosed in adults [2, 4, 5]. Adult-type diffuse grade 2 gliomas harboring IDH mutations are classified by the World Health Organization (WHO) 2021 into IDH-mutant astrocytomas and IDH-mutant, 1p/19q-codeleted oligodendrogliomas [1]. In contrast, central nervous system (CNS) WHO grade 1 gliomas are typically circumscribed, biologically less aggressive entities with distinct molecular profiles and are generally outside the diffuse IDH-mutant glioma spectrum. In diffuse IDH-mutant gliomas, grades 2 and 3 share IDH mutations, whereas grade 3 reflects increased histologic proliferative/anaplastic activity (most commonly higher mitotic activity) and is associated with a less favorable prognosis [1]. Adult-type diffuse grade 2 gliomas mainly

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affect young adults, peaking at 30–34 years for astrocytomas and around 44 years for oligodendrogliomas [6]. Although slow-growing, they are infiltrative and typically progress to higher grades, leading to recurrence and mortality risk; median survival with current standards is ~5–8 years for astrocytomas and ~10–15 years for oligodendrogliomas [6]. Management remains complex and variable, with persistent uncertainty about the extent and timing of resection, the role and sequencing of adjuvant radiotherapy and chemotherapy, and optimal surveillance to detect progression/recurrence [2, 4]. Emerging targeted therapies and advanced imaging further increase decision-making complexity and highlight the need for multidisciplinary consensus [7, 8]. Notably, mutant IDH inhibition to reduce 2-HG has emerged as a promising strategy, culminating in U.S. Food and Drug Administration (FDA) (August 2024) [9] and European Medicines Agency (EMA) (September 2025) [10] approvals of the dual IDH1/2 inhibitor vorasidenib for IDH-mutant grade 2 gliomas. These authorizations represent a major advance in precision neuro-oncology and are expected to expand clinical use as real-world data and experience accumulate, reinforcing the importance of multidisciplinary care as molecular diagnostics and targeted therapies continue to refine treatment paradigms.

The primary objective of this study is to synthesize current knowledge and expert opinion to provide practical, evidence-based recommendations for the management of IDH-mutant grade 2 gliomas. To achieve this, we conducted a structured Delphi process involving leading experts in neuro-oncology, enabling the development of consensus guidelines intended to harmonize clinical practice and improve outcomes for patients with these complex tumors. This work is distinguished by its multidisciplinary, society-endorsed panel and its focus on resolving real-world clinical uncertainties in the care of adult IDH-mutant grade 2 gliomas.

## Methods

This study used a modified Delphi methodology based on the RAND/UCLA Appropriateness Method [11] to reach expert consensus on the management of adult IDH-mutant grade 2 glioma. The primary objective was to develop consensus-based, evidence-informed recommendations for the diagnosis, treatment, and follow-up of IDH-mutant grade 2 gliomas, integrating current evidence and clinical expertise. While the consensus focused on IDH-mutant grade 2 tumors, some recommendations addressed low-grade gliomas (LGGs) more broadly because key decisions (initial imaging, surgical strategy, and tissue acquisition) are often made before IDH status is confirmed; therefore, guidance was also formulated for adult-type diffuse LGGs when

molecular characterization is not yet available. Throughout the manuscript, we use ‘IDH-mutant grade 2 glioma’ when molecular status is established, and ‘LGG’ only to describe the pre-molecular diagnostic setting in which key management decisions may be required before IDH status is confirmed.

A multidisciplinary scientific committee (neuro-oncology, neurosurgery, neuropathology, radiation oncology, neuroradiology, and medical oncology) with extensive experience in diffuse gliomas conducted a structured narrative literature review to support statement generation and to identify areas of uncertainty, evidence gaps, and emerging topics in the diagnosis, treatment, and follow-up of adult IDH-mutant grade 2 gliomas (and, when relevant, adult-type diffuse LGGs in the pre-molecular setting). First, key guidelines and position documents were screened on the websites of major scientific societies and organizations, including the Spanish Society of Medical Oncology (SEOM), the Spanish Group for Neuro-Oncology (GEINO), the European Association of Neuro-Oncology (EANO), the Society for Neuro-Oncology (SNO), the European Society for Medical Oncology (ESMO), the National Comprehensive Cancer Network (NCCN), and the American Society of Clinical Oncology (ASCO), as well as the WHO CNS tumor classification resources. Second, a focused PubMed search was performed to support statement drafting. The PubMed strategy combined terms for IDH-mutant grade 2 glioma and related entities (including astrocytoma and oligodendroglioma) with management- and outcome-related terms, excluded glioblastoma, and applied filters for humans, English or Spanish, and publication types prioritizing reviews, meta-analyses, guidelines, consensus development, and phase III trials. The search covered publications from August 1, 2018, to September 2, 2024 (the date of the search). Statements were formulated to address clinically relevant decisions, particularly where practice varies or evidence is limited or evolving, and were subsequently evaluated through the Delphi process.

Panelists were nominated by six Spanish scientific societies involved in LGG care: the Neuro-Oncology Group (NEUROCOR) of the Spanish Society of Radiation Oncology (SEOR), the Neuropathology Group of the Spanish Society of Pathology (SEAP), the Spanish Society of Neurology (SEN), the Neuro-Oncology Group of the Spanish Society of Neurosurgery (SENEC), the Spanish Society of Neuroradiology (SENRA), and the Spanish Society of Medical Oncology (SEOM); each appointed three specialists (total  $n = 18$ ) to ensure balanced representation across disciplines. Panelists were selected by their respective societies based on expertise criteria, including clinical experience, academic contributions, and participation in national/international glioma working groups. They rated the statements independently using anonymized online questionnaires to minimize dominance and social influence in a structured,

iterative process. Consensus was pursued in two rounds of online questionnaires using a 9-point Likert scale (1 = complete disagreement; 9 = complete agreement), categorized as disagreement (1–3), uncertainty (4–6), and agreement (7–9). After round 1, panelists could comment and suggest revisions; the scientific committee reviewed feedback and revised statements as needed for round 2, and only aggregated, anonymized summaries of response distributions and synthesized comments were shared between rounds. Panelists who did not participate in round 1 were excluded from subsequent analyses. A statement was considered to have reached consensus if: (1) the median score was within the agreement (7–9) or disagreement (1–3) range, (2) fewer than one-third of panelists provided ratings outside these ranges, and (3) the interquartile range (IQR) was < 4. Statements that did not reach consensus in the first round were re-evaluated in the second round. Results are presented in tables showing the median and IQR of responses, as well as the degree of agreement, defined as the percentage of panelists whose ratings fell within the range containing the median (Tables 1, 2, 3, 4, 5). Post hoc, we developed an implementation-focused operationalization table (Table 6) that groups statements by clinical domain and classifies them as recommendations (consensus), exploratory consensus (e.g., evolving-therapy implementation/monitoring), or non-recommendations (no consensus), mapping each domain to relevant guideline reference frameworks to support daily practice use. This post hoc categorization was descriptive and did not modify the prespecified consensus definition.

## Results

Eighteen expert panelists (three from each of six Spanish scientific societies) were invited, and all completed both Delphi rounds. Across two rounds, 85 statements were evaluated. Consensus was reached for 74 statements (87.1%), while 11 (12.9%) did not reach consensus after two rounds. Of the 74 consensus statements, 66 (77.6%) were agreed upon in round 1 and 8 (9.4%) in round 2 (Tables 1, 2, 3, 4, 5).

For initial diagnosis and confirmation (Table 1), the panel did not reach consensus on using liquid biopsy to guide management when no tissue biopsy is available (item 12; 55.6% agreement). Molecular characterization (Table 2) showed a single non-consensus item: the relevance of neurotrophic tyrosine receptor kinase (NTRK) mutations as key markers in IDH-wildtype gliomas (item 31; 22.2% agreement). Within risk stratification and adjuvant treatment (Table 3), consensus was not achieved on whether age is no longer a decisive risk factor for stratifying IDH-mutant LGGs (item 49; 50.0% agreement). In treatment of IDH-mutant grade 2 gliomas (Table 4), consensus was reached for 3 of 9 statements on vorasidenib, whereas six scenario-specific

statements did not reach consensus; items 52 (subtotal/partial resection or biopsy with non-enhancing residual lesions; 66.6% agreement) and 57 (slow progression after surgery with intent to avoid/delay chemoradiotherapy toxicity; 66.6% agreement) narrowly missed the threshold. Finally, in postoperative follow-up (Table 5), the panel did not reach consensus on whether Brain Tumor Reporting and Data System (BT-RADS) is simpler and more applicable than Response Assessment in Neuro-Oncology (RANO) criteria after chemoradiotherapy (item 81; 50.0% agreement) or on the utility of molecular biomarkers in cerebrospinal fluid (CSF) or blood for follow-up (item 82; 61.1% agreement).

Clinical implementation of the Delphi outputs by domain and consensus status is summarized in Table 6.

## Discussion

This Delphi consensus provides an updated, multidisciplinary perspective on the management of adult IDH-mutant grade 2 gliomas. A nationwide Spanish multidisciplinary panel spanning neuro-oncology, neurosurgery, neuropathology, radiation oncology, neuroradiology, and medical oncology used an iterative, anonymous survey to systematically assess current practice and uncertainty across key diagnostic and therapeutic domains, and to identify areas of strong agreement alongside persistent controversies. The panel endorsed the central role of molecular diagnostics, especially IDH1 and IDH2 testing, and individualized risk stratification and treatment planning, emphasizing clinical and imaging factors such as residual tumor and early progression. Established standards of care, including combined radiotherapy and chemotherapy approaches in appropriate patients, were supported, while other topics, such as the optimal integration of advanced imaging modalities and emerging targeted agents, did not consistently reach consensus. In particular, the positioning of IDH inhibitors such as vorasidenib, and selected risk criteria, remained areas of uncertainty, underscoring the evolving evidence base and the need for continued research and multidisciplinary dialog. In interpreting these findings, we present consensus items as recommendations, whereas non-consensus items are discussed only to delineate uncertainty and practice heterogeneity; implementation implications and alignment with guideline frameworks are summarized in Table 6.

### Initial diagnosis and confirmation

The panel endorsed gadolinium-enhanced MRI as the preferred presurgical technique, emphasizing T2 and FLAIR sequences to assess infiltration. The T2/FLAIR mismatch sign was recognized as a specific marker of IDH-mutant astrocytoma without 1p/19q codeletion [12]. Advanced MRI

**Table 1** Initial diagnosis and confirmation

	Median (IQR)	Percentage of agreement <sup>a</sup>	Result
<i>Imaging diagnosis</i>			
1. MRI with gadolinium is the technique of choice in the presurgical diagnosis of gliomas. The basic imaging protocol should include 3D T1 sequences before and after contrast administration, 2D or preferably 3D FLAIR sequence, axial T2-weighted sequence, and diffusion sequence in the axial plane	9 (8–9)	88.9%	Agreement in the 1st round
2. In low-grade diffuse gliomas, T2 and FLAIR sequences are used to determine the extent and location of tumor infiltration	9 (8–9)	88.9%	Agreement in the 1st round
3. The T2/FLAIR mismatch (homogeneous hyperintensity on T2 and hypointensity with hyperintense peripheral ring on FLAIR) is a highly specific radiological sign in the diagnosis of IDH-mutated astrocytomas without 1p/19q codeletion	8 (7–9)	77.8%	Agreement in the 1st round
4. Advanced MRI techniques, such as perfusion, diffusion, and spectroscopy, are useful for identifying areas of greater aggressiveness within the tumor and for differentiating between tumoral and pseudotumoral lesions	8 (7–9)	88.9%	Agreement in the 1st round
5. PET-MRI with FDG is not always useful in the assessment of CNS tumor pathology. Although other radiotracers for radiological evaluation of brain tumors are being investigated, their use is very complex, and they are not available in all centers <sup>b</sup>	8 (7–8)	77.8%	Agreement in the 2nd round
<i>Tissue acquisition</i>			
6. Tumor tissue biopsy should be considered in cases where glioma resection is not feasible, either due to the tumor's location, the patient's clinical condition, or because, given the characteristics of the tumor or the patient, an adequate resection cannot be guaranteed <sup>b</sup>	9 (9–9)	88.9%	Agreement in the 2nd round
7. The use of 5-aminolevulinic acid (5-ALA)-induced fluorescence during biopsy or surgery should be standard practice in cases of suspected high-grade lesions to improve sampling accuracy and ensure the acquisition of adequate tumor tissue	8 (6–9)	72.2%	Agreement in the 1st round
8. Except in cases of low complexity, initial surgical resection should be performed at high-volume centers by neurosurgeons experienced in the management of gliomas, in order to ensure maximum diagnostic accuracy and minimize risks	9 (9–9)	83.3%	Agreement in the 1st round
9. The quantity and quality of tissue obtained during surgery must be sufficient to allow for a comprehensive molecular evaluation that includes all relevant markers for diagnosis, prognosis, and treatment	9 (9–9)	100.0%	Agreement in the 1st round
10. The management of gliomas without biopsy should be discussed by a multidisciplinary team to ensure optimal decision-making	9 (9–9)	94.4%	Agreement in the 1st round
11. Patients with suspected glioma who have not undergone biopsy and have not been treated with radiotherapy or chemotherapy should be followed with serial MRI every 3 months during the first year of follow-up	7.5 (7–9)	77.8%	Agreement in the 1st round
12. Liquid biopsy, including the detection of circulating tumor DNA (ctDNA) and microRNA analysis, could be considered in the future to help guide the management of gliomas without tissue biopsy	7 (5–8)	55.6%	No consensus
<i>Determination of grade at diagnosis</i>			
13. Molecular testing is as critical as morphological analysis for the accurate classification of diffuse gliomas and is mandatory	9 (9–9)	100.0%	Agreement in the 1st round
14. Traditional histopathological criteria (presence of mitoses, necrosis, and vascular proliferation) remain important for distinguishing between WHO grade 2, grade 3, and grade 4 gliomas. In addition, new molecular markers have been incorporated to determine the WHO tumor grade	9 (8–9)	100.0%	Agreement in the 1st round
15. To determine the histological grade of IDH-mutant astrocytomas lacking necrosis or vascular proliferation, CDKN2A/B deletion status must be assessed. If present, the tumor should be classified as WHO grade 4	9 (8–9)	88.9%	Agreement in the 1st round
16. The presence of necrosis is a reliable criterion for distinguishing between grade 3 and grade 4 astrocytomas	9 (8–9)	77.8%	Agreement in the 1st round
17. A refinement of the WHO classification system is warranted to address gliomas with histomolecular discordance between grade 2 and 3 criteria	7 (5–8)	72.2%	Agreement in the 1st round

**Table 1** (continued)

	Median (IQR)	Percent- age of agreement <sup>a</sup>	Result
18. Advanced imaging techniques can complement histopathology in cases where radiological features suggest high-grade tumors and biopsy sampling may not be representative of the tumor's biology	8 (7–9)	83.3%	Agreement in the 1st round
19. As the determination of the molecular profile (IDH mutation and 1p/19q codeletion) is already integrated into the management of grade 2 and 3 diffuse gliomas, clinical and radiological characteristics, such as symptomatology or the presence of symptomatic lesions requiring biopsy, should also be considered when determining the therapeutic strategy	9 (8–9)	94.4%	Agreement in the 1st round

*CDKN2A/B* cyclin-dependent kinase inhibitor 2A/B, *CNS* central nervous system, *FDG* fluorodeoxyglucose, *IDH* isocitrate dehydrogenase, *IQR* interquartile range, *MRI* magnetic resonance imaging, *PET* positron emission tomography, *WHO* World Health Organization

<sup>a</sup>Percentage of panelists who voted within the category that included the median of the answers (1–3, 4–6, or 7–9)

<sup>b</sup>Items whose wording has changed between the first and second rounds

techniques were supported as adjuncts for selected complex cases, although wider implementation is limited by access and standardization [13]. FDG PET-MRI was considered not always useful in CNS tumors [14].

For tissue acquisition, maximal safe resection was preferred when feasible to optimize outcomes and enable integrated histomolecular diagnosis, with biopsy reserved for cases where resection is not safely feasible [2, 14]. Intraoperative imaging and neurophysiological monitoring were supported to improve the safety and extent of resection, whereas 5-ALA fluorescence was acknowledged as primarily established in high-grade gliomas [2, 15, 16].

At diagnosis, the panel supported integrated molecular and histopathological classification and highlighted the prognostic role of *CDKN2A/B* homozygous deletion in IDH-mutant astrocytoma grading [1, 17], consistent with WHO CNS5 and major guidelines [1, 4]. In histomolecular discordance, advanced imaging may provide complementary information to support clinico-radiologic correlation [18, 19].

### Molecular characterization

The panel agreed that IDH1/2 mutation testing should be the first molecular step in diffuse LGGs, consistent with WHO CNS5 and major guidelines [1, 4]. In IDH-mutant gliomas, assessment of 1p/19q codeletion, *ATRX*, *TP53*, and *CDKN2A/B* status was emphasized for integrated diagnosis and prognostication [14, 20]. In IDH-wildtype diffuse gliomas, markers including *TERT* promoter mutations, *EGFR* amplification, +7/–10, and selected *H3* and *BRAF* alterations were highlighted to distinguish adult-type tumors from pediatric and molecular mimics [14, 21].

Given that IDH1 R132H immunohistochemistry detects the most frequent IDH1 variant and that IDH-mutant gliomas are less common in older adults [22], the panel supported an

age- and morphology-informed approach to sequencing: in patients > 55 years with negative IDH1 R132H immunohistochemistry, IDH1/2 sequencing may be optional depending on morphology, whereas in diffuse LGGs with negative immunohistochemistry, sequencing should be performed regardless of age to detect non-canonical variants. *ATRX* immunohistochemistry was recommended to support astrocytoma classification when compatible with histology, and 1p/19q testing was considered essential to confirm oligodendroglioma in IDH-mutant tumors without *ATRX* loss when histology is compatible [1, 4].

Advanced molecular techniques, including next-generation sequencing (NGS) and methylation arrays, were supported for diagnostically uncertain or complex cases and for research settings, whereas routine testing for *NTRK* fusions was not endorsed outside specific clinical indications [23].

### Risk stratification and adjuvant treatment

Our consensus panel agreed on the need to update traditional Radiation Therapy Oncology Group (RTOG) and European Organisation for Research and Treatment of Cancer (EORTC) risk stratification criteria (based on extent of surgery and age) by incorporating molecular and advanced imaging parameters. There was unanimous agreement that, due to the infiltrative nature of diffuse gliomas, tumor cells are likely to remain even after complete resection, and that “complete resection” should be defined as the absence of visible tumor on postoperative MRI, while recognizing the limitations of this definition. The prognostic significance of postoperative residual tumor volume was strongly endorsed, with consensus that any residual tumor should be evaluated for its impact on prognosis and adjuvant treatment decisions. The timing of tumor growth after surgery was also considered a critical determinant for initiating adjuvant therapy.

**Table 2** Molecular characterization

	Median (IQR)	Percentage of agreement <sup>a</sup>	Result
20. Identification of IDH1/IDH2 mutations should be the first step in the molecular characterization of all diffuse gliomas	9 (9–9)	100.0%	Agreement in the 1st round
In the molecular characterization of gliomas, the most relevant molecular markers are:			
<i>In IDH-mutant gliomas:</i>			
21. 1p/19q codeletion	9 (9–9)	100.0%	Agreement in the 1st round
22. ATRX expression	8 (7–9)	88.9%	Agreement in the 1st round
23. TP53 mutations	7 (5–7)	72.2%	Agreement in the 1st round
24. CDKN2A/B deletions	9 (8–9)	94.4%	Agreement in the 1st round
<i>In IDH-wildtype gliomas:</i>			
25. TERT promoter mutations	9 (9–9)	100.0%	Agreement in the 1st round
26. EGFR amplification	9 (8–9)	94.4%	Agreement in the 1st round
27. Combined chromosomal alteration +7/–10	9 (7–9)	88.9%	Agreement in the 1st round
28. H3 K27M mutations	8.5 (8–9)	94.4%	Agreement in the 1st round
29. H3 G34 mutations	8 (8–9)	94.4%	Agreement in the 1st round
30. BRAF mutations	8 (7–8)	77.8%	Agreement in the 1st round
31. In the molecular characterization of IDH-wildtype gliomas, the most relevant molecular markers (based on therapeutic options rather than prevalence) are NTRK mutations <sup>b</sup>	6 (3–7)	22.2%	No consensus
32. In patients over 55 years old with negative immunohistochemistry for IDH1 R132H, sequencing of IDH1 and IDH2 may be considered optional depending on the tumor morphology, since the likelihood of mutations in these genes is low, and most cases will be IDH-wildtype	8 (6–9)	72.2%	Agreement in the 1st round
33. In cases of negative immunohistochemistry for IDH1 R132H in patients with low-grade gliomas, IDH1 and IDH2 sequencing should always be performed, regardless of age, in order to identify less common mutations that are not detected by immunohistochemistry	9 (8–9)	88.9%	Agreement in the 1st round
34. In IDH-mutant gliomas, subsequent immunohistochemical testing for ATRX is recommended. If nuclear loss of ATRX (indicating mutation) is observed, the tumor is classified as an astrocytoma provided the histology is consistent	9 (8–9)	83.3%	Agreement in the 1st round
35. In IDH-mutant tumors without ATRX mutation, testing for 1p/19q codeletion should be performed. Tumors showing codeletion of both are classified as oligodendrogliomas if the histology is consistent with this diagnosis	9 (9–9)	88.9%	Agreement in the 1st round
36. The use of advanced technologies such as NGS in IDH-mutant gliomas may be performed to identify potential targeted therapies, address complex cases, or support research initiatives	9 (8–9)	88.9%	Agreement in the 1st round
37. Methylation arrays may be used in cases where there is morphomolecular discordance and a diagnosis cannot be established according to WHO 2021 criteria	8 (5–9)	72.2%	Agreement in the 1st round

*IDH1* isocitrate dehydrogenase 1, *IDH2* isocitrate dehydrogenase 2, *IQR* interquartile range, *ATRX* alpha thalassemia/mental retardation syndrome x-linked, *TP53* tumor protein p53, *CDKN2A/B* cyclin-dependent kinase inhibitor 2a/b, *TERT* telomerase reverse transcriptase, *EGFR* epidermal growth factor receptor, +7/–10 chromosome 7 gain/chromosome 10 loss, *H3 K27M* histone h3 lysine 27 to methionine mutation, *H3 G34* histone h3 glycine 34 mutation, *BRAF* b-raf proto-oncogene serine/threonine kinase, *NTRK* neurotrophic tyrosine receptor kinase, *NGS* next-generation sequencing, *WHO* World Health Organization

<sup>a</sup>Percentage of panelists who voted within the category that included the median of the answers (1–3, 4–6, or 7–9)

<sup>b</sup>Items whose wording has changed between the first and second rounds

The panel fully concurred that grade 2 oligodendrogliomas with IDH mutation and 1p/19q codeletion have a better prognosis than other grade 2 gliomas, and agreed that LGGs with IDH mutation, 1p/19q codeletion, low residual tumor burden, and no evidence of early progression should be considered low risk, supporting less aggressive management

strategies in this subgroup. High symptomatic burden (understood as the presence of symptoms that significantly affect the patient's well-being and require medical management or intervention) and the need for a clinical response were also recognized as decisive factors for guiding personalized treatment. No consensus was reached regarding

**Table 3** Risk stratification and adjuvant treatment in low-grade gliomas

	Median (IQR)	Percentage of agreement <sup>a</sup>	Result
38. Risk stratification in gliomas should be updated by incorporating new criteria beyond those currently used by the Radiation Therapy Oncology Group (RTOG) and Pignatti	9 (8–9)	83.3%	Agreement in the 2nd round
39. The volume of visible residual tumor on postoperative imaging should be considered for administering adjuvant treatment	9 (8–9)	88.9%	Agreement in the 1st round
40. Complete tumor resection should be defined as the absence of tumor on postoperative MRI <sup>b</sup>	8.5 (8–9)	88.9%	Agreement in the 2nd round
41. In diffuse gliomas, even after complete resection according to imaging criteria, tumor cells are likely to remain due to their infiltrative nature, increasing the risk of progression	9 (9–9)	100.0%	Agreement in the 1st round
42. The presence of any amount of residual tumor should be carefully assessed based on its prognostic impact	9 (7–9)	88.9%	Agreement in the 1st round
43. Grade 2 oligodendrogliomas that meet the molecular diagnostic requirements (presence of IDH mutation and 1p/19q codeletion) have a better prognosis than other grade 2 gliomas	9 (9–9)	100.0%	Agreement in the 1st round
44. The time until tumor growth after surgical resection should be a critical factor in determining the need for adjuvant therapy for low-grade gliomas	8 (5–9)	72.2%	Agreement in the 1st round
45. Factors indicating higher risk in low-grade gliomas include significant residual tumor, early post-resection tumor progression, and absence of 1p/19q codeletion, according to updated EANO criteria	9 (7–9)	83.3%	Agreement in the 1st round
46. Low-grade gliomas with IDH mutation and 1p/19q codeletion, low residual tumor burden, and no evidence of tumor growth during initial follow-up are considered as low risk, and more aggressive treatment strategies should be avoided	8 (6–9)	72.2%	Agreement in the 1st round
47. In the therapeutic strategy for low-grade gliomas, a high symptomatic burden should be considered a decisive factor for guiding personalized treatment	8 (7–9)	83.3%	Agreement in the 1st round
48. The need for a clinical response can also be a key factor in selecting the therapeutic strategy for low-grade gliomas, complementing the assessment based on molecular profile and residual tumor volume <sup>b</sup>	8 (7–9)	88.9%	Agreement in the 2nd round
49. Age is no longer considered a decisive risk factor in the stratification of IDH-mutant low-grade gliomas <sup>b</sup>	5 (5–8)	50.0%	No consensus
50. The 2021 WHO grade should also be taken into account when deciding the therapeutic strategy for IDH-mutant gliomas	9 (8–9)	88.9%	Agreement in the 1st round

EANO European Association of Neuro-Oncology, IDH isocitrate dehydrogenase, MRI magnetic resonance imaging, RTOG Radiation Therapy Oncology Group, WHO World Health Organization

<sup>a</sup>Percentage of panelists who voted within the category that included the median of the answers (1–3, 4–6, or 7–9)

<sup>b</sup>Items whose wording has changed between the first and second rounds

the role of age as a stand-alone decisive risk factor in IDH-mutant LGGs, with only 50% agreement, reflecting ongoing debate.

These consensus findings are fully aligned with the 2021 WHO classification and recent guidelines, which advocate for a molecularly driven, individualized approach to risk stratification and adjuvant treatment [1, 4, 24]. The literature further supports the prognostic relevance of residual tumor volume, the superior outcomes of IDH-mutant, 1p/19q-codeleted oligodendrogliomas, and the move toward less aggressive management in well-defined low-risk subgroups [1, 4, 24]. Recent studies also highlight the increasing importance of molecular-based prognostic models over traditional clinical variables such as age [25].

In summary, our Delphi consensus confirms a clear trend toward molecularly driven, individualized risk stratification and treatment in LGGs, supporting less aggressive strategies in well-defined low-risk subgroups and highlighting the need for ongoing refinement of prognostic models as new molecular and imaging biomarkers become integrated into clinical practice.

### Treatment of IDH-mutant gliomas

Our consensus panel reached consensus on key overarching principles regarding vorasidenib, a brain-penetrant dual inhibitor of mutant IDH1/2, including its consideration as an emerging option in selected patients with IDH-mutant grade

**Table 4** Treatment of IDH-mutant grade 2 gliomas

	Median (IQR)	Percentage of agreement <sup>a</sup>	Result
<i>Use of vorasidenib</i>			
51. Vorasidenib represents an emerging therapeutic option for patients with IDH-mutant grade 2 gliomas who do not require immediate chemoradiotherapy	8 (7–9)	83.3%	Agreement in the 1st round
The use of vorasidenib may be considered in patients with IDH-mutant grade 2 gliomas:			
52. Who have undergone subtotal resection, partial resection, or biopsy and present a lesion with no residual contrast enhancement <sup>b</sup>	9 (5–9)	66.6%	No consensus
53. Patients who have undergone an apparently complete resection <sup>b</sup>	5 (1–7)	33.3%	No consensus
54. Who have not received chemotherapy or radiotherapy and present clinical features indicating a more favorable disease course	8 (5–9)	61.1%	No consensus
55. Who have declined chemoradiotherapy due to concerns about long-term toxicity	5 (5–8)	44.4%	No consensus
56. Who are not good candidates for chemoradiotherapy due to significant comorbidities or advanced age	5.5 (2–8)	22.2%	No consensus
57. Who have experienced slow progression after surgery and wish to avoid or delay the toxicity associated with chemoradiotherapy	7.5 (5–9)	66.6%	No consensus
58. The decision to use vorasidenib should be discussed in a multidisciplinary setting, considering the risks and benefits compared to standard chemoradiotherapy	9 (9–9)	100.0%	Agreement in the 1st round
59. Vorasidenib therapy requires careful monitoring due to the lack of long-term data on its impact on overall survival and its potential side effects	8.5 (7–9)	83.3%	Agreement in the 1st round
<i>Criteria for the use of radiotherapy and chemotherapy. Monitoring of toxicities</i>			
60. The strongest evidence for the efficacy of chemotherapy in low-grade gliomas is when it is combined with radiotherapy	8 (7–9)	83.3%	Agreement in the 1st round
61. The combined use of radiotherapy and chemotherapy (temozolomide or PCV) should be considered in grade 3 and grade 4 gliomas, whereas in grade 2 gliomas, the therapeutic strategy should be individualized according to prognostic factors and personal preferences <sup>b</sup>	8 (7–9)	77.8%	Agreement in the 2nd round
62. The decision to initiate radiotherapy should be based on a multidisciplinary approach that takes into account the extent of surgical resection, residual tumor burden, and symptomatology	9 (9–9)	88.9%	Agreement in the 1st round
63. The long-term side effects of radiotherapy, such as neurotoxicity and the risk of radionecrosis, should be carefully monitored in patients with low-grade gliomas	9 (8–9)	88.9%	Agreement in the 1st round
64. Hypofractionated radiotherapy may be an option for patients with gliomas who are unable to tolerate longer treatment regimens, but it should be evaluated in the context of tumor burden, irradiation field extent, and tumor location	8 (7–9)	83.3%	Agreement in the 2nd round
65. The administration of chemotherapy as monotherapy after surgery may be considered in exceptional cases where radiotherapy is not feasible due to the extent of disease or specific contraindications. However, the available evidence supports greater benefit with the combination of radiotherapy and chemotherapy in low-grade gliomas	8.5 (7–9)	83.3%	Agreement in the 1st round
66. In cases of early recurrence or rapid postoperative progression in low-grade gliomas, chemotherapy may be considered as a therapeutic option, either as monotherapy in exceptional situations or in combination with radiotherapy, depending on the clinical context and patient characteristics	8 (6–9)	72.2%	Agreement in the 1st round
67. The decision to administer chemotherapy after surgery in low-grade gliomas should be based on a multidisciplinary approach that evaluates the clinical, radiological, and molecular characteristics of the tumor, the extent of resection, and patient preferences	9 (9–9)	88.9%	Agreement in the 1st round
68. The combination of radiotherapy and chemotherapy with PCV after surgery is a viable option in grade 2 gliomas, as it has been shown to improve survival	8 (5–9)	72.2%	Agreement in the 1st round
69. Chemotherapy with temozolomide may be considered in certain cases, especially in astrocytomas, if the patient, due to age and/or frailty, is not a candidate for a standard PCV regimen	8 (7–9)	77.8%	Agreement in the 1st round
70. The long-term toxicity of adjuvant chemotherapy, such as myelosuppression and the risk of neurological side effects, should be carefully monitored in patients with low-grade gliomas	9 (8–9)	77.8%	Agreement in the 1st round
71. The long-term toxicity of adjuvant radiotherapy, especially radionecrosis and neurological and neurocognitive side effects, should be taken into consideration when using this treatment	9 (8–9)	83.3%	Agreement in the 1st round

IDH Isocitrate dehydrogenase IQR Interquartile range, PCV Procarbazine, lomustine, vincristine

<sup>a</sup>Percentage of panelists who voted within the category that included the median of the answers (1–3, 4–6, or 7–9)

<sup>b</sup>Items whose wording has changed between the first and second rounds

**Table 5** Postoperative follow-up

	Median (IQR)	Percentage of agreement <sup>a</sup>	Result
72. The follow-up plan for gliomas should be individualized, based on the patient's age, tumor grade, IDH mutation status, and other relevant clinical factors	9 (8–9)	88.9%	Agreement in the 1st round
73. It is recommended to perform a postoperative MRI within the first 24–48 h	9 (8–9)	94.4%	Agreement in the 1st round
74. In diffuse gliomas without contrast enhancement, a follow-up MRI can be performed 2–3 months after surgery; areas of edema and/or postoperative changes will have improved, and residual areas of T2 and FLAIR hyperintensity will correspond to remaining tumor tissue	8 (6–9)	72.2%	Agreement in the 1st round
75. Patients with IDH-mutant gliomas or with residual disease after surgery should undergo imaging studies (MRI) every 3 to 6 months during the first 5 postoperative years, adjusting the frequency according to clinical and radiological stability to detect early signs of progression	8.5 (7–9)	77.8%	Agreement in the 1st round
76. Although originally designed for clinical trials, the use of RANO criteria has become widespread in daily clinical practice to assess the response of gliomas to chemoradiotherapy	9 (8–9)	88.9%	Agreement in the 1st round
77. In the follow-up of brain tumors, both the contrast-enhancing area and the non-enhancing hyperintense area with infiltrative morphology should be compared	9 (9–9)	88.9%	Agreement in the 1st round
78. To differentiate between tumor progression and post-treatment changes, advanced MRI sequences, especially perfusion MRI, are useful. Although they have limitations, they can provide valuable information when assessed together with other clinical or radiological data <sup>b</sup>	8.5 (8–9)	94.4%	Agreement in the 2nd round
79. PET-MRI with amino acids can be useful for distinguishing between tumor recurrence and post-treatment changes, but it is not commonly available	7.5 (6–8)	72.2%	Agreement in the 1st round
80. The availability and lower cost of perfusion MRI make it possible to integrate it into follow-up protocols for brain tumors	9 (8–9)	88.9%	Agreement in the 1st round
81. The BT-RADS criteria are simpler to use than the RANO criteria and are more applicable to clinical practice in the follow-up of gliomas treated with chemoradiotherapy <sup>b</sup>	6.5 (5–8)	50.0%	No consensus
82. The evaluation of molecular biomarkers in cerebrospinal fluid or blood could potentially be useful in the future for postoperative follow-up in patients with gliomas, to detect early signs of recurrence or to differentiate progression from radionecrosis <sup>b</sup>	7.5 (5–8)	61.1%	No consensus
83. The inclusion of a multidisciplinary team in postoperative follow-up is essential to coordinate comprehensive management that addresses both the oncological and functional needs of the patient	9 (9–9)	94.4%	Agreement in the 1st round
84. Follow-up should include periodic assessments of quality of life using standardized tools, in order to identify and address any negative impact of treatment on the patient's well-being	9 (8–9)	88.9%	Agreement in the 1st round
85. Regular monitoring of neurocognitive function is essential in postoperative follow-up to detect early cognitive decline and adjust therapeutic interventions accordingly	8 (7–9)	94.4%	Agreement in the 1st round

*BT-RADS* Brain Tumor Reporting and Data System, *IDH* isocitrate dehydrogenase, *MRI* magnetic resonance imaging, *PET* positron emission tomography, *RANO* Response Assessment in Neuro-Oncology

<sup>a</sup>Percentage of panelists who voted within the category that included the median of the answers (1–3, 4–6, or 7–9)

<sup>b</sup>Items whose wording has changed between the first and second rounds

2 gliomas who do not require immediate chemoradiotherapy and the need for multidisciplinary team (MDT)-based decision-making and careful monitoring. This is consistent with the INDIGO trial results, which demonstrated a significant improvement in progression-free survival and a delay in time to next intervention with vorasidenib compared to placebo in patients with residual or recurrent non-enhancing IDH-mutant grade 2 gliomas [26, 27]. However, the panel

did not reach consensus on specific clinical scenarios for vorasidenib use, such as after subtotal or complete resection, in patients declining chemoradiotherapy, or those with comorbidities or indolent disease progression. Notably, the use of vorasidenib in patients with comorbidities or slow progression after surgery (item 57) and in those who have not received or have declined chemoradiotherapy (item 54) did not meet the prespecified consensus criteria and should

**Table 6** Practical operationalization summary of Delphi items by clinical domain, consensus status, and guideline reference frameworks

Domain	Item ID(s)	Consensus status	How to use in practice <sup>a</sup>	Guideline reference frameworks
Diagnosis & confirmation	1–11, 13–19	Consensus	Implement in routine practice: follow the standard diagnostic pathway for suspected adult diffuse LGG/IDH-mutant grade 2 glioma (MRI assessment, tissue strategy, integrated diagnosis prerequisites) and, when tissue sampling is not performed, apply the agreed surveillance approach (serial MRI) when clinically appropriate	WHO CNS5; EANO (diagnostic pathway principles)
Molecular characterization	20–30, 32–37	Consensus	Implement in routine practice: perform core molecular work-up for integrated diagnosis; reserve advanced assays for complex or discordant cases	WHO CNS5; EANO (molecular work-up principles)
Risk stratification & adjuvant strategy	38–48, 50	Consensus	Implement in routine practice: inform adjuvant decisions using residual disease, symptom burden, molecular profile, and WHO grade	WHO CNS5; EANO (risk/adjuvant principles)
Treatment (RT/chemotherapy)	60–71	Consensus	Implement in routine practice: use MDT-based, risk-adapted decision-making (symptoms, tumor burden/residual disease, molecular profile, and patient factors). RT + chemotherapy is typically prioritized when an active, higher-risk approach is indicated; active surveillance/deferment may be appropriate for lower-risk/stable disease. Monitor acute/late toxicities as applicable	EANO; SEOM-GEINO (treatment principles)
Follow-up (imaging/response)	72–80	Consensus	Implement in routine practice: tailor surveillance to risk/stability, obtain early postoperative MRI, apply response assessment framework, and use advanced imaging selectively when clinically indicated and locally available	RANO (response assessment); EANO (follow-up principles)
Survivorship/supportive follow-up	83–85	Consensus	Implement in routine practice: provide survivorship-focused multidisciplinary follow-up, including QoL and neurocognitive monitoring	EANO (supportive care principles)

**Table 6** (continued)

Domain	Item ID(s)	Consensus status	How to use in practice <sup>a</sup>	Guideline reference frameworks
Voridasenib (implementation and monitoring)	51, 58–59	Consensus (exploratory)	Implement in routine practice (within the approved indication): consensus on overarching principles for use in eligible patients; voridasenib is an EMA-approved option (predominantly non-enhancing CNS WHO grade 2 IDH1/2-mutant diffuse glioma after surgery, not requiring immediate RT/chemotherapy). Positioning/sequencing scenarios did not reach Delphi consensus and should be individualized in MDT	EMA SmPC (Voramigo); evolving guideline updates
Non-consensus items	12, 31, 49, 52–57, 81–82	No consensus	Do not operationalize as guidance: treat these as uncertainty/research priorities only (no clinical recommendation)	Not applicable (no consensus)

*EANO* European Association of Neuro-Oncology, *EMA* European Medicines Agency, *GEINO* Spanish Group for Neuro-Oncology, *IDH* isocitrate dehydrogenase, *LGG* low-grade glioma, *MDT* multidisciplinary team, *MRI* magnetic resonance imaging, *QoL* quality of life, *RANO* Response Assessment in Neuro-Oncology, *RT* radiotherapy, *SEOM* Spanish Society of Medical Oncology, *SmPC* Summary of Product Characteristics, *WHO* World Health Organization, *WHO CNS5* World Health Organization Classification of Tumors of the Central Nervous System, 5th edition

<sup>a</sup>Only items meeting the prespecified consensus definition are intended as recommendations. Items without consensus are included only to highlight uncertainty and research priorities

therefore be interpreted as areas of uncertainty and practice heterogeneity rather than directional clinical guidance. These findings highlight the need for further real-world data to better define the optimal use of voridasenib in these clinical settings [26].

There was a strong consensus among our Delphi panel that the management of high-risk IDH-mutant LGGs should be individualized, with combined chemoradiotherapy considered the standard of care for patients presenting adverse prognostic features such as significant residual tumor or early progression after surgery. Both procarbazine, lomustine, and vincristine (PCV) and temozolomide were recognized as appropriate adjuvant options; the toxicity profile, comorbidities, and patient preferences should guide the therapeutic strategy. Selective use of chemotherapy monotherapy was also supported for patients in whom radiotherapy is contraindicated or deferred, and the importance of multidisciplinary decision-making in initiating adjuvant therapies was emphasized. These expert recommendations are consistent with the current international guidelines, which also emphasize the integration of molecular markers, such as 1p/19q codeletion status, into risk stratification and therapeutic decision-making for IDH-mutant gliomas. Recent literature further supports the use of advanced radiotherapy techniques and the development of targeted therapies to improve outcomes and minimize long-term toxicity [14, 26, 28, 29]. For topics with evolving evidence (e.g., targeted-therapy positioning), recommendations may require future updating as data mature.

Importantly, there was a clear consensus on the need for systematic and long-term monitoring of treatment-related toxicities. The panel highlighted the importance of regular clinical, neuropsychological, and imaging assessments to detect and manage complications such as neurocognitive decline, radionecrosis, and hematological adverse effects at an early stage. This vigilant toxicity surveillance enables timely adaptation of adjuvant therapies, further supporting individualized care [4, 14].

Together, these findings underscore the importance of tailoring adjuvant treatment strategies and toxicity monitoring to the clinical and molecular context of each patient with low-grade IDH-mutant glioma, integrating both expert consensus and the latest evidence from international guidelines.

### Postoperative follow-up

Postoperative follow-up should be individualized according to patient and tumor characteristics. The panel endorsed early postoperative MRI to establish a baseline and assess the extent of resection. For patients treated with radiotherapy, RANO 2.0 specifies that the reference baseline for postradiotherapy response assessment is the MRI obtained approximately 1 month after completing radiotherapy [30].

During surveillance, regular MRI was supported, with perfusion and diffusion sequences used as adjuncts in selected cases to help distinguish progression from treatment-related changes. The panel broadly endorsed RANO criteria for routine assessment of both enhancing and non-enhancing disease, consistent with current guidance [4]. Multidisciplinary follow-up integrating imaging with clinical, neurocognitive, and quality-of-life assessments was emphasized. The panel did not reach consensus on whether BT-RADS offers advantages over RANO, or on the routine use of molecular biomarkers in blood or CSF for postoperative monitoring.

The non-consensus domains identified by the Delphi process define a pragmatic translational research agenda. For liquid biopsy and molecular biomarkers (blood/CSF), priorities include analytical validation, standardization of pre-analytical variables, and prospective clinical validation against imaging and clinical endpoints to determine added value in surveillance and treatment-response assessment. For IDH inhibition, the lack of consensus on scenario-based patient selection and sequencing highlights the need for prospective studies and real-world registries that capture clinically meaningful outcomes beyond progression-free survival (e.g., time to next intervention, seizure control, neurocognition, and quality of life) and enable subgroup analyses by extent of resection, residual disease, and molecular profile. Finally, implementation science approaches, including standardized data capture aligned with the operational domains in Table 6, could support harmonized real-world evaluation and inform future guideline updates. These priorities complement the implementation-focused summary provided in Table 6.

This study has limitations inherent to the Delphi methodology. The resulting statements are primarily based on expert opinion rather than prospective trial evidence, which may limit generalizability. The panel was relatively small and restricted to Spain, although it included balanced representation across the key disciplines involved in low-grade IDH-mutant glioma care and nominations from major national scientific societies. In addition, patient or caregiver input was not included, and external validation outside Spain was not performed. Recent approvals and rapidly evolving evidence for new treatments may have influenced voting patterns for related statements. Panelists were nominated by scientific societies, which may introduce selection bias despite the intent to achieve balanced multidisciplinary representation. While anonymity reduces groupthink, it may constrain in-depth discussion of complex topics; however, iterative rounds with controlled feedback helped refine judgments. Consensus thresholds based on a 9-point Likert scale and IQR are necessarily pragmatic and may not capture nuanced disagreement, but predefined criteria enhance transparency and reproducibility. Although conflicts of interest were disclosed, industry relationships could still have influenced individual ratings, particularly for statements addressing

novel agents (e.g., vorasidenib), and this possibility should be considered when interpreting these statements. Finally, as molecular diagnostics and targeted therapies evolve, some recommendations may need updating. Despite these limitations, this consensus provides practical, multidisciplinary guidance to help standardize care where high-level evidence remains limited.

## Conclusion

In this nationwide Delphi study, multidisciplinary recommendations are provided to help standardize diagnosis, risk stratification, treatment, and follow-up for IDH-mutant grade 2 gliomas in Spain. The high level of agreement across specialties supports harmonizing care pathways while prioritizing individualized decision-making. Vorasidenib may expand therapeutic options in selected patients consistent with available trial evidence and regulatory labeling. At the same time, non-consensus areas, particularly around newer targeted agents and the prognostic role of age, highlight the need for education, real-world data, and continued multidisciplinary discussion. Overall, these statements provide practical guidance to support more standardized, patient-centered care while identifying priorities for future research and updates.

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**Data availability** De-identified data that support the findings of this study are available from the corresponding author upon reasonable request.

## Declarations

**Conflict of interest** Inés Esparragosa Vázquez: consulting services as a member of the Glioma Working Group, Salud Harmon-Servier. Inmaculada Fortes de la Torre: expenses for attending meetings sponsored by Servier. Amaya Hilarío: consulting services as a member of the Glioma Working Group, Salud Harmon-Servier. Estela Pineda: advisory and consulting for Servier and Novocure; advisory for GSK and AstraZeneca. Juan Manuel Sepúlveda Sánchez: consulting and presentation fees from Servier. María Ángeles Vaz-Salgado: advisory and speaker fees from Novocure and Servier. Irene Iglesias Lozano: none declared. Aurelio Hernández-Lain: none declared.

**Ethical approval** This study involved only expert panelists who volunteered for the Delphi process. No patient data were used. Participation implied informed consent, and formal ethical approval was not required.

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