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Management of Adult Patients With Isocitrate Dehydrogenase-Mutant Gliomas in Australia: An Expert Position Statement From the Cooperative Trials Group for Neuro-Oncology

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ABSTRACT

Isocitrate dehydrogenase (IDH)-mutant low-grade and high-grade gliomas are primary brain cancers with slower growth rates and longer survival than IDH-wildtype counterparts. However, these tumors are fatal and because of the younger age of patients, result in significant morbidity and loss of productivity. Several management options are available at initial diagnosis for IDH-mutant gliomas (including close surveillance, surgery, radiation therapy, chemotherapy and/or targeted therapies either alone or in combination), however, there is limited data about optimal timing and sequencing. When considering treatment, the risks associated with uncontrolled disease should be weighed against potential treatment-associated toxicities given the expected long overall survival times for many patients. Preservation of cognition, neurological function and quality of life remain a priority. Treatment decisions should therefore be made in the context of a neuro-oncology multidisciplinary team, and incorporating the patient's wishes and expectations. The management of recurrent IDH-mutant glioma is not well defined. This expert position statement aims to provide an Australian perspective on the evidence base and available treatments for contemporaneous management of IDH-mutant glioma in adults.

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1 | Introduction

Gliomas are the most common primary malignant tumor of the central nervous system (CNS). Diagnostic and prognostic classification according to the World Health Organization (WHO) Classification of Tumors of the CNS System (most recently the WHO CNS5, 2021) is based on combined histopathological and molecular features [1]. Isocitrate dehydrogenase (IDH) mutation screening is a standard component of glioma diagnostic profiling. Diffusely infiltrative gliomas harboring IDH 1 (*IDH1*) codon 132 and IDH 2 (*IDH2*) codon 172 mutations are termed "IDH-mutant gliomas" and are the second largest group of adult gliomas (IDH-wildtype glioblastoma make up the largest group) [2]. They are graded CNS WHO Grade 2–4 [1]. Importantly, they are distinct from pediatric-type diffuse gliomas and circumscribed gliomas (which lack IDH mutations) and these will not be discussed further [1]. IDH-mutant gliomas usually affect young-to-middle-aged adults, and typically present at a younger age than IDH-wildtype glioblastomas [2]. Although incurable, IDH-mutant gliomas are generally slower growing and associated with longer survival.

Accepted management options for IDH-mutant glioma after initial diagnosis include continued surveillance, surgical resection, radiotherapy (RT), chemotherapy, and targeted therapies [3, 4]. Treatment decisions are complex and require individualization. Substantial practice variation exist in Australia and internationally as robust data comparing different primary treatment approaches, sequencing, and optimal timing are lacking. No Australian guidelines or consensus statements currently exist for the management of patients with IDH-mutant glioma. International guidelines may have limited applicability in the Australian context due to differences in cultural perspectives, health funding, and drug access. This review aims to provide evidence-based recommendations on the management of IDH-mutant gliomas in Australian adults. Where evidence is limited, guidance reflects expert opinion of a group of experienced Australian neuro-oncology practitioners. Specific guidance on the management of IDH-mutant gliomas in children and adolescents has recently been published and so is not covered in this review [5, 6].

2 | Methods

A call for Expressions of Interest was circulated to the Cooperative Trials Group for Neuro-Oncology (COGNO) network, with applicants assessed on clinical and/or research expertise, experience in multidisciplinary collaboration or guideline development, and leadership of their respective disciplines. In May 2025, the COGNO Management Committee selected the working group members, comprising two medical oncologists, a neurosurgeon, two radiation oncologists, a radiologist, a neuropathologist, and a neuro-oncology care coordinator from different locations across Australia. Through an iterative review and discussion process, the group collaboratively developed the recommendations.

3 | Tumor Testing

3.1 | Molecular Diagnostics

In WHO CNS5 [1], IDH-mutant gliomas are further subcategorized based on the presence or absence of a combined deletion in the short arm of chromosome 1 (1p) and long arm of chromosome 19 (19q) (1p/19q codeletion) into astrocytoma, IDH-mutant (where 1p/19q codeletion is absent) and oligodendroglioma (where 1p/19q codeletion is present). Importantly, these tumors are further divided into different histological grades based on tumor morphology and key molecular features (Figure 1) [1]. Immunohistochemistry (IHC) only detects the most common IDH mutation, *IDH1* p.R132H [7]. Noncanonical mutations (*IDH1* non-p.R132H and *IDH2* mutations) can occur in up to 10% of IDH-mutant gliomas but prevalence is only 0.9% in patients aged ≥ 55 years [8]. Therefore, in the setting of negative *IDH1* R132H IHC, *IDH1/2* sequencing is recommended to detect noncanonical IDH mutations in patients under 55 years, irrespective of tumor grade [8, 9].

A new entity of astrocytoma, IDH-mutant, Grade 4 was recognized in the latest WHO CNS5 where there are well-defined morphological (microvascular proliferation and necrosis) and molecular (*CDKN2A/B* homozygous deletion) grading criteria [1, 10]. With next-generation sequencing (NGS) panel testing now readily available in Australia for suspected gliomas, assessment of 1p/19q codeletion and *CDKN2A/B* homozygous deletion can also be performed concurrently [11].

Where it may impact decision-making, clinicians should be mindful that grading of tumors into Grade 2 and 3 based purely on morphology (notably, mitotic count) can be affected by inter-rater variability [12, 13]. Molecular parameters to distinguish between Grade 2 and 3 IDH-mutant astrocytoma are lacking, although parameters such as heterozygous *CDKN2A/B* deletion have been proposed [14, 15]. Expert guidance from the Consortium to Inform Molecular and Practical Approaches to CNS Tumor Taxonomy (cIMPACT) is anticipated in the future [16]. Also, while *MGMT* promoter methylation is an established predictive biomarker in IDH-wildtype glioblastoma, where it may inform temozolomide (TMZ) use [17], its predictive value in IDH-mutant gliomas is unclear. Therefore, routine testing is not required, nor is it currently recommended to guide treatment decisions [18, 19].

3.2 | Imaging Diagnostics

Magnetic resonance imaging (MRI) is considered the standard-of-care modality and every patient with IDH-mutant glioma should undergo MRI before any treatment intervention [3]. The recommended minimum requirements for MRI acquisition include axial T2-weighted imaging (T2WI), axial (or volumetric) fluid-attenuated inversion recovery (FLAIR), axial diffusion-weighted imaging (DWI), and pre- and postcontrast volumetric T1-weighted imaging (T1WI) [20, 21]. Other helpful adjuncts include MRI perfusion and a

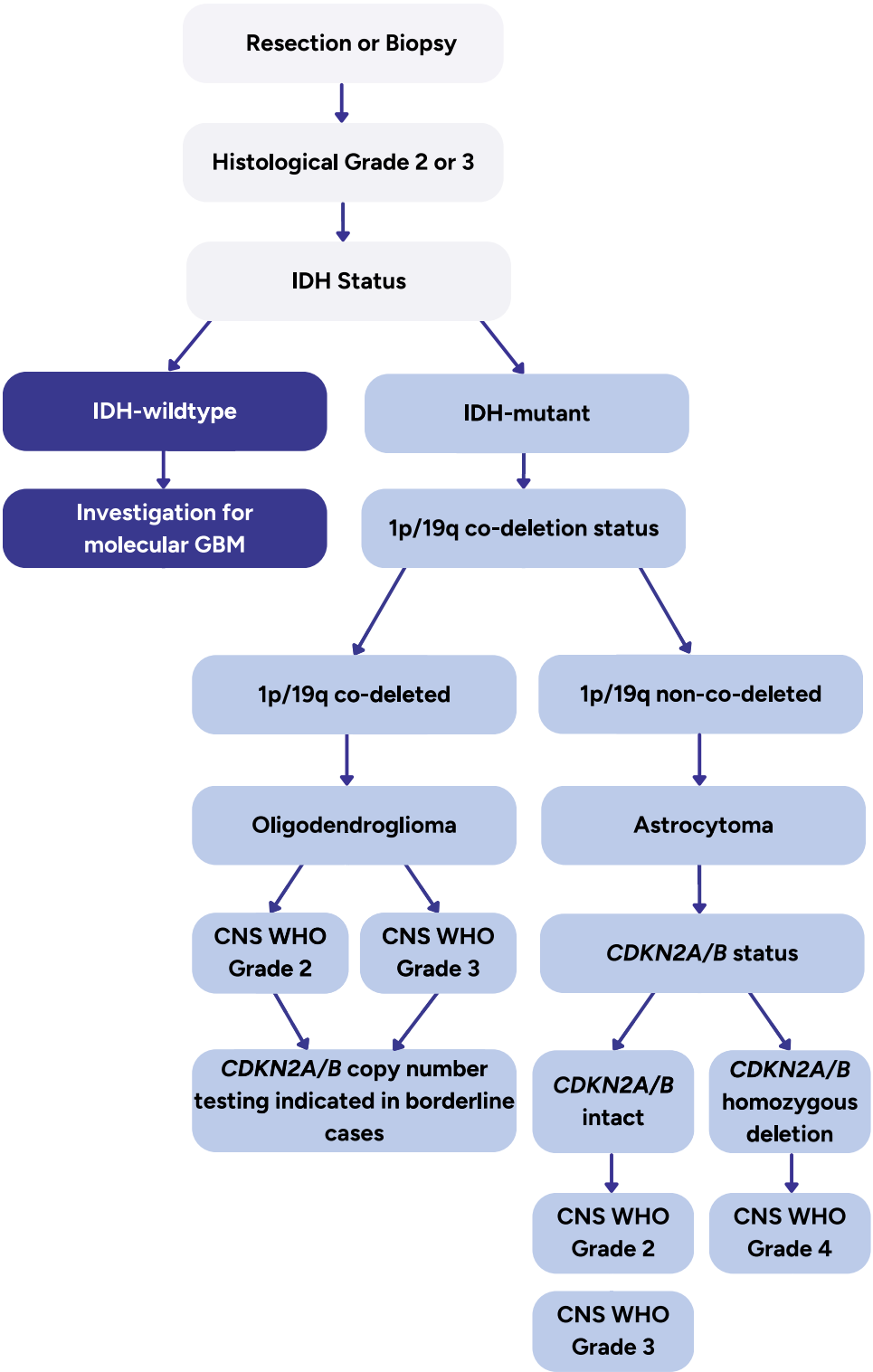

FIGURE 1 | Classification of histological Grade 2 and 3 adult-type IDH-mutant gliomas.

susceptibility-sensitive sequence such as susceptibility-weighted imaging (SWI) [20].

MRI findings that indicate a likely IDH-mutant glioma include the presence of T2-FLAIR mismatch (i.e., T2 hyperintensity with relatively suppressed FLAIR signal except for a hyperintense rim), which is the single most useful MRI feature of an IDH-mutant astrocytoma [22]. Intratumoral calcification is often associated with oligodendrogliomas [23]. Apparent diffusion coefficient (ADC) values are generally highest in IDH-mutant astrocytoma, intermediate in IDH-mutant oligodendroglioma and lowest in IDH-wildtype glioma [22]. Although not definitive, the presence of peripheral enhancement with central necrosis is suggestive of higher grade [24]. IDH-mutant gliomas typically demonstrate less enhancement than IDH-wildtype [22]. However, histological confirmation is always required. It is important

1 Recommendations for Testing

- IDH-mutant glioma diagnosis and grading follow the most recent edition of the WHO Classification of Tumors of the CNS, to arrive at the final integrated diagnosis based on both traditional morphology and newer molecular characteristics (Figure 1).
- IHC for the most common IDH mutation (*IDH1* p.R132H) should be performed in all patients. If negative, sequencing for noncanonical IDH mutations should be performed in patients under 55 years. Consider NGS panel testing, as it allows for concurrent *IDH1/2*, 1p/19q and *CDKN2A/B* testing to inform diagnostic classification and grading.
- *MGMT* promoter methylation status is not routinely required.

to distinguish between nonenhancing tumor and peritumoral edema for optimal treatment planning [25]. One caveat is that where imaging and biopsy results are discordant, the possibility of sampling error and need for additional tissue should be considered.

4 | Management

Standard-of-care treatments for IDH-mutant glioma include continued surveillance, maximal safe surgery, RT, and/or chemotherapy. Based on results from the international INDIGO trial, treatment with an IDH inhibitor (e.g., vorasidenib) is also an option, where available [26]. Selection of initial treatment after diagnosis is complex and must balance the competing risks of uncontrolled disease versus treatment-associated toxicities with respect to survival, cognition, neurologic function and quality of life (QoL) [27]. Enrollment in clinical trials should also be considered and discussed with patients and carers. All patients should be discussed in a dedicated neuro-oncology multidisciplinary team (MDT) to obtain consensus on the preferred therapeutic approach given these complexities and the relative rarity of these tumors [28]. A key consideration is the benefit–risk ratio of the various treatment options available. In addition, as IDH-mutant glioma typically affects younger individuals and survival often extends for many years, fertility should be addressed prior to treatment to support informed decision-making, family planning and fertility preservation [29]. A suggested treatment approach to IDH-mutant glioma in Australia is shown in Figure 2.

4.1 | Surgery

The goal of surgery is to obtain tissue for diagnosis and grading, to alleviate symptoms and to safely remove as much tumor as possible without compromising neurological function [4]. The area of tumor with the most concerning MRI appearances (including enhancement, diffusion restriction, and elevation of cerebral blood volume) should be targeted, if possible. There is considerable retrospective evidence that early maximal safe resection is associated with longer progression-free survival (PFS), overall survival (OS), and potentially slowed transformation to higher grade tumors [30, 31]. However, these studies are confounded by selection bias and the evolving WHO classifications. Smaller tumors and tumors in less eloquent locations are more likely to be completely resectable. In addition, patient characteristics such as age, performance status, comorbidities, and overall prognosis may influence the extent of resection (EOR). Smaller surgical specimens may be subject to undersampling of areas of higher histological grade [32]. Despite this, the evidence suggests that, on balance, maximal safe resection is recommended when possible. The more conservative strategy of biopsy followed by surveillance may be associated with inferior outcomes and should be reserved for cases where tumor resection may lead to significant neurological deficit due to involvement of eloquent brain [30]. There is debate as to whether the benefit of maximal safe resection is limited to certain molecular subgroups. Patients with oligodendroglioma may have a relatively more favorable prognosis and response to other treatments, so complete surgical resection may not provide an additional survival advantage [33]. However, other data support that OS is improved in all subgroups with early or more extensive resection [33, 34].

Historically, preoperative tumor size and residual disease following resection have been considered adverse prognostic factors in low-grade glioma [35, 36]. Whether these associations remain valid in the context of IDH-mutant disease specifically is uncertain [37]. Recently published data suggest residual postoperative T2/FLAIR of less than 5 cm^3 is associated with improved survival, compared with 5–25 cm^3 [38]. However, in addition to the residual volume, management decisions should consider anatomical location with respect to feasibility of further surgical intervention and the balance between the risks of disease progression and surgery-related morbidity.

Preservation of function is an important outcome alongside PFS and OS. There is a lack of direct comparative studies into the association between the EOR and functional outcomes, but one systematic review suggested that a greater EOR was associated with a higher chance of returning to work within 1 year in patients with diffuse low-grade glioma [39]. Surgical adjuncts have been developed to improve EOR and to minimize neurological deficits. These include preoperative functional MRI and/or diffusion tensor imaging fiber tracking to identify critical structures, intraoperative MRI to detect the presence and extent of residual tumor, and awake craniotomy with intraoperative neurophysiological monitoring to identify eloquent and noneloquent structures [40].

It has been suggested that supramaximal resection can lower the risk of malignant transformation by removing invading cells near the radiographic margin of the tumor, but the true impact is unclear [41]. One systematic review suggested that supramaximal resection may be noninferior to gross total resection, but it should not be achieved at the cost of undermining neurological function [42]. More recently, a study by the Response Assessment in Neuro-Oncology (RANO) resect group observed that resection of noninfiltrated structures beyond T2/FLAIR borders in patients with Grade 2 IDH-mutant glioma provided an OS benefit for both astrocytomas and oligodendrogliomas [38].

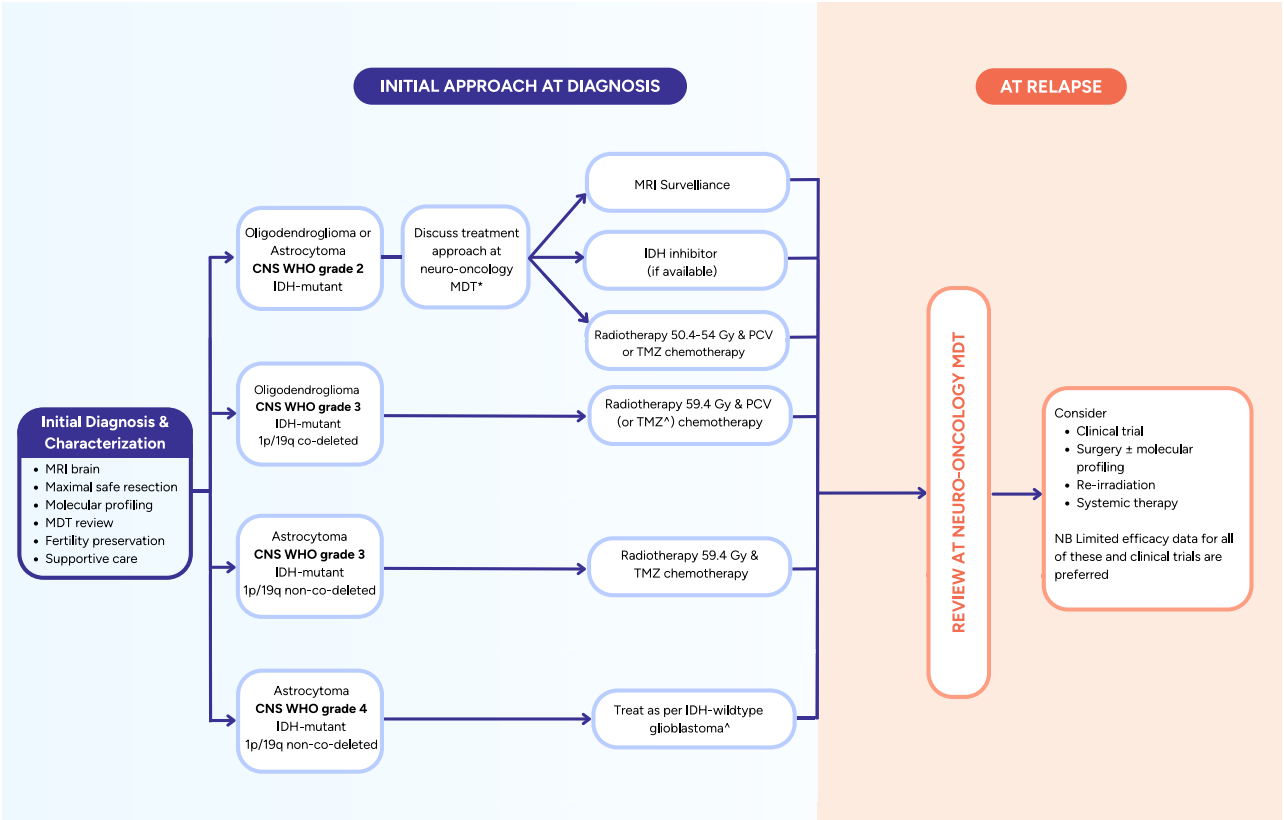

FIGURE 2 | A suggested treatment approach to IDH-mutant glioma in adults in Australia. *The treatment approach should consider risk factors including age, residual tumor, location of tumor, opportunity for surveillance imaging, opportunity for further surgery. ^Limited data but common practice.

2 Recommendations for Management

- Treatment decisions for IDH-mutant glioma are complex, and all patients should be discussed in a dedicated neuro-oncology MDT.
- Enrollment in clinical trials should be encouraged and discussed with patients.
- Fertility preservation should be discussed before commencing treatment.

3 Recommendations for Surgery

- Maximal safe resection is associated with longer PFS, OS, and potentially delayed progression to higher grade tumors; thus, early maximal safe resection should be considered in all patients.
- Biopsy alone may be associated with inferior outcomes and should be reserved for cases where resection risks significant neurological deficit.
- Surgical adjuncts may be used to maximize the extent of resection and minimize neurological deficits.
- Supramaximal resection may provide additional benefit. Surgeons should discuss this option with patients when appropriate if the neurological risks are low.

4.2 | Adjuvant Treatment

4.2.1 | IDH-Mutant WHO Grade 2 Oligodendroglioma or Astrocytoma

Currently, the optimal selection of postoperative treatment at diagnosis is complex, confounded by a lack of data about relative efficacy with different sequencing of the various available modalities. Long-term follow-up of multiple Phase 3 randomized studies demonstrates OS benefits with the addition of chemotherapy to RT for both Grade 2 and 3 gliomas [43–46]. However, the optimal timing of when to offer adjuvant therapy (early to maximize tumor control vs. late to delay potential toxicity) is uncertain. A randomized trial assessing this question in IDH-mutant glioma failed to accrue and was closed prematurely (EORTC-1635). Thus, this decision should be individualized based on multidisciplinary consensus and in consultation with the patient.

In general, observation may be considered in patients with a small residual or completely resected tumor (maximal T2/FLAIR resection) [38], where reliable surveillance with MRI scans and future surgical salvage is feasible, and for those particularly concerned about treatment or treatment-related toxicity. Upfront treatment may be preferred in patients with large residual, progressive or unresectable tumors, and those who opt for active treatment. Scoring systems to identify those at greatest risk of early death have been developed based on various demographic and clinicopathological factors including age, symptom burden,

histology, preoperative tumor size, volume of residual disease and tumor location [35, 43]. For example, the RTOG 9802 study (in patients with Grade 2 gliomas notwithstanding IDH status) defined a high-risk population based on age > 40 years and less than gross total resection [43].

Typical RT dose prescriptions for Grade 2 IDH-mutant glioma are 50.4 Gy in 28 fractions [47] or 54 Gy in 30 fractions [43]. The gross tumor volume (GTV) is defined as the postsurgical tumor bed and any residual macroscopic disease identified on either volumetric postcontrast T1WI, T2, or FLAIR planning MRI sequences. The clinical target volume (CTV) accounts for microscopic extension of disease and is typically a 10 mm expansion on GTV, adjusted for natural barriers of spread [48, 49]. The planning target volume (PTV) margin accounts for daily set up variations and other uncertainties, based on institutional practice and technology. Photon-based RT is considered the current standard-of-care in Australia. Techniques such as Intensity-Modulated Radiation Therapy (IMRT) and Volumetric-Modulated Arc Therapy (VMAT) are preferred because they offer improved target conformity and better sparing of organs-at-risk [48]. Reducing dose to uninvolved healthy brain and anatomical substructures is important to minimize the risk of RT-related cognitive decline [50, 51]. Non–co-planar beam arrangements may be useful in this regard [48]. Despite potential dosimetric advantages, the clinical benefit of proton beam therapy (PBT) in adult IDH-mutant glioma is uncertain and currently under evaluation (e.g., PRO-GLIO [NCT05190172], NRG BN005, APPROACH [ISRCTN13390479]). PBT may be considered in highly selected patients, such as those with cancer predisposition syndromes or treatment plans that exceed dose tolerances of adjacent organs-at-risk.

The historical basis for adding chemotherapy to RT in patients with high-risk IDH-mutant Grade 2 glioma comes from RTOG 9802 which found PFS and OS were longer in those who received up to six cycles every 8 weeks of procarbazine, lomustine, and vincristine (PCV) in addition to RT, compared to RT alone [43, 52]. The median OS benefit was 13.3 versus 7.8 years (HR: 0.59; 95% CI, 0.42–0.83). This meaningful survival benefit was observed despite patients receiving a median of only three cycles of procarbazine, and four cycles each of lomustine and vincristine, reflecting the significant toxicity associated with this regimen. For these reasons, some clinicians prefer concurrent and/or adjuvant sequential TMZ (up to 12 cycles every 4 weeks) over PCV. While TMZ use was initially supported by nonrandomized studies such as RTOG 0424 [53], more robust evidence has recently emerged from the Phase 3 ECOG-ACRIN E3F05 trial, which assessed RT with or without TMZ in patients with Grade 2 gliomas. With a median follow-up of 9.8 years, there was significant OS benefit for RT with TMZ (HR: 0.54; 95% CI, 0.31–0.95; 5-year OS 78% vs. 70%; 10-year OS 70% vs. 47%) compared to RT alone [54]. A real-world study of pattern-of-care in Australia between 2016 and 2022 found that, while RT and chemotherapy use had increased over time, postoperative observation was the most common strategy and only a minority of patients who met the definition of high risk in the RTOG 9802 study received immediate adjuvant chemotherapy and RT [55].

Recently, the brain-penetrant IDH inhibitor vorasidenib has shown clinical efficacy in patients with IDH-mutant Grade 2 glioma, providing an additional treatment option for these patients after initial diagnosis. The Phase 3 INDIGO study investigated vorasidenib versus placebo in 331 patients diagnosed with Grade 2 IDH-mutant glioma who had undergone surgery as their only previous treatment and who were considered to be appropriate candidates for a watch-and-wait approach; patients with significant contrast enhancement, uncontrolled seizures, or brainstem location were excluded [26]. Vorasidenib significantly improved PFS (median 2.3 vs. 0.9 years, HR: 0.39; 95% CI, 0.27–0.56, $p < 0.001$) in patients with both oligodendroglioma ($n = 172$, HR: 0.32; 95% CI, 0.18–0.57) and astrocytoma ($n = 159$, HR: 0.47; 95% CI, 0.29–0.75), and also prolonged time to next intervention (median not reached vs. 1.5 years, HR: 0.26; 95% CI, 0.15–0.43, $p < 0.001$). There were 22.8% of patients in the vorasidenib group who experienced toxicity ≥ Grade 3 (most commonly deranged liver function) and 3.6% of patients permanently discontinued due to adverse events [26]. Limited available data suggest preservation of health-related QoL, neurocognitive function and seizure control during the study period on treatment [56]. Based on these results, several international guidelines have been updated to include recommendations that vorasidenib may be offered to patients with Grade 2 glioma, in situations where it is thought that adjuvant treatment with RT and chemotherapy can be safely deferred [3, 57]. It is important to note that the impact of vorasidenib on OS is currently unknown. The PFS of 2.3 years for vorasidenib is considerably shorter than PFS reported in studies evaluating RT and chemotherapy as first-line therapy after surgery. It is also unclear whether RT and chemotherapy offered after progression on vorasidenib will be as effective. Vorasidenib is not currently available in Australia on the Pharmaceutical Benefits Scheme (PBS) and hence the significant financial implications of this treatment must be discussed with the patient.

4 Recommendations for Adjuvant Treatment for WHO Grade 2 Glioma

- For patients with Grade 2 oligodendroglioma or astrocytoma, adjuvant RT and chemotherapy should be considered when high-risk features are present (e.g., subtotal resection, older age, or early progression).
- PCV or TMZ chemotherapy may be used, with selection guided by patient factors. Phase 3 evidence supports both regimens in Grade 2 oligodendroglioma or astrocytoma in addition to RT.
- For patients with Grade 2 oligodendroglioma or astrocytoma with favorable prognostic factors (e.g., complete resection and younger age) or concerns about toxicity, initial RT and chemotherapy may be deferred.
- An IDH inhibitor may be considered in patients not requiring immediate RT and chemotherapy. In Australia, vorasidenib is approved by the Therapeutic Goods Administration but is not currently funded through the PBS.

4.2.2 | IDH-Mutant WHO Grade 3 Oligodendroglioma

After surgery, patients with Grade 3 oligodendroglioma should be routinely offered RT followed by chemotherapy. The most

common RT doses used in Australia are 59.4 Gy in 33 fractions and 60 Gy in 30 fractions [58]. For very large tumors, giving 54 Gy to the entire area and a simultaneous integrated boost (SIB) up to 60 Gy to a radiologically defined area(s) of higher risk disease in 30 fractions may be considered. A GTV to CTV expansion of 10–15 mm is recommended [48, 59].

The standard-of-care chemotherapy after RT had previously been PCV, supported by two randomized Phase 3 trials [58]. EORTC 26951 used RT followed by six cycles of PCV, whereas RTOG 9402 used four cycles of dose-intensive PCV prior to RT. Both studies were compared to RT alone and a long-term survival analysis found a 40% reduction in the risk of death in both trials in patients with 1p/19q codeleted tumors (median OS 9.3 vs. 14.2 years [EORTC 26951] and 7.3 vs. 13.2 years [RTOG 9402]). In these patients there was an estimated PFS and OS at 20 years of 30% and 35%, respectively [58]. In both studies, toxicity was higher in the combination treatment arms and only 14% completed six cycles of PCV in EORTC 26951 and 54% completed four cycles of PCV in RTOG 9402. In RTOG 9402, there was a high rate of acute toxicities (mainly hematologic), including two early deaths attributed to PCV-induced neutropenia [44]. Given the similar efficacy results of the two studies, and the two deaths that occurred from the intensive PCV regimen in RTOG 9402, Australian practice generally utilizes the EORTC 26951 approach in both sequence (RT followed by PCV) and dosing (lower intensity of lomustine) [60]. However, it remains a difficult regimen to deliver, with completion of four cycles in only 54% of patients in RTOG 9402 and a median of four cycles administered in EORTC 26951.

As for Grade 2 glioma, some clinicians choose TMZ as an alternative to PCV in Grade 3 glioma because it is less toxic and easier to administer [61]. This is highlighted by findings from an Australian pattern-of-care survey, where 58% of responding clinicians recommended TMZ in this context [62]. CODEL is a Phase 3 trial directly comparing PCV versus TMZ in oligodendroglioma (both Grade 2 and Grade 3), which is not yet reported, though now has completed recruitment [63]. Until these results are known, the question about whether to use PCV or TMZ remains unresolved. The NOA-04 Phase 3 randomized trial evaluated the efficacy of either upfront RT, TMZ or PCV in patients with Grade 3 gliomas. Subgroup analysis showed that PFS was longer in the PCV group compared to the TMZ group in historic anaplastic oligodendrogliomas [64]. A recent retrospective analysis from the French POLA registry suggested better OS associated with PCV/RT compared to TMZ/RT, although likely selection biases limit the generalizability of this nonrandomized study [65].

Patients with Grade 3 IDH-mutant glioma were excluded in the Phase 3 INDIGO study of vorasidenib versus placebo, due to a lack of response reported in an earlier study [66]. Thus, the role of IDH inhibitors in this population and whether standard RT and chemotherapy can be safely deferred is unknown. The 2025 National Comprehensive Cancer Network (NCCN) guidelines state that vorasidenib may be considered in certain circumstances for Grade 3 IDH-mutant glioma (category 2B evidence), although this recommendation is based on minimal clinical data [3]. Vorasidenib is not currently approved or funded in Australia for the treatment of patients with Grade 3 IDH-mutant glioma. However, it is recognized that differentiating Grade 2 from Grade 3 IDH-mutant glioma can be prone to interobserver variability and sampling limitations [67, 68]. Further research is warranted to clarify whether patients with Grade 3 disease derive benefit from IDH inhibitors.

5 Recommendations for Adjuvant Treatment for WHO Grade 3 Oligodendroglioma

- For Grade 3 oligodendroglioma, adjuvant RT and chemotherapy is standard-of-care. PCV has the most robust evidence, however TMZ may be an appropriate alternative if tolerability and drug access are concerns. The comparative efficacy of these regimens remains under investigation.

6 Recommendations for Adjuvant Treatment for WHO Grade 3 or 4 Astrocytoma

- For Grade 3 astrocytoma, adjuvant RT followed by sequential TMZ is standard-of-care.
- For Grade 4 astrocytoma, adjuvant RT, with or without concurrent TMZ followed by sequential TMZ is standard-of-care.

4.3 | IDH-Mutant WHO Grade 3 or 4 Astrocytoma

In contrast to Grade 3 oligodendrogliomas, the situation is clearer in patients with Grade 3 astrocytomas. After surgery, patients with Grade 3 IDH-mutant astrocytoma should be offered RT followed by chemotherapy. Typical RT dose prescriptions are 59.4 Gy in 33 fractions or 60 Gy in 30 fractions for Grade 3 and 60 Gy in 30 fractions for Grade 4 IDH-mutant glioma. Again, a SIB technique of 54–60 Gy in 30 fractions may be considered in select cases with large tumors. A GTV to CTV expansion of 10–15 mm is recommended [48, 59]. The standard-of-care chemotherapy is sequential TMZ, as supported by the CATNON trial [45, 69]. This Phase 3 randomized open-label study employed a 2 × 2 factorial design to investigate the benefit of RT with concurrent and/or 12 cycles of adjuvant TMZ every 4 weeks. CATNON showed futility of concurrent TMZ but an OS benefit for adjuvant TMZ chemotherapy (median OS 6.7 vs. 3.8 years; HR: 0.69 [95% CI, 0.58–0.82]) [45, 69, 70].

Lastly, the optimal management of the newly defined IDH-mutant Grade 4 astrocytoma remains a subject of investigation. In the CATNON study, such patients did not benefit from concurrent TMZ. There is currently no available randomized clinical trial specifically in patients with Grade 4 IDH-mutant astrocytoma. Historically, these tumors were included with glioblastoma [71] and therefore included in landmark studies defining standard-of-care in this population, consisting of RT with concurrent and then adjuvant TMZ (six cycles every 4 weeks; Stupp regimen) [72, 73]. The 2025 NCCN guidelines [3] acknowledge that clinicians may treat according to either Grade 3 IDH-mutant astrocytoma (CATNON trial) [69] or glioblastoma (Stupp regimen) [72, 73], however, the latter is most common in Australian practice.

5 | Follow-Up and Management of Recurrent Disease

The long-term risk of recurrence (and transformation to a higher grade) following first-line therapy with maximal safe surgery and RT and chemotherapy remains high. The frequency of MRI monitoring after initial diagnosis and treatment is dependent on the glioma subtype and grade. Common practice is to undertake MRI scans of patients every 3–4 months initially, with subsequent scanning intervals individualized based on clinical status, patient preference, and/or the need for specific monitoring for indeterminate findings on prior imaging [74]. The same imaging acquisition should be used at baseline and at all subsequent imaging timepoints to ensure that subtleties are not masked or mimicked by variation in scan parameters such as slice thickness [75].

Importantly, the interpretation of surveillance MRIs for progression can be complex and where concerns exist, review in a neuro-oncology MDT is advised. First, it is common to see treatment-related changes in imaging within the first few months after completion of RT; new findings on MRI should be interpreted with caution during this period [75]. MRI scanning at shorter intervals may help in distinguishing true tumor progression from other changes [75]. Advanced MRI techniques (e.g., DWI and perfusion) or amino acid positron emission tomography (PET) may also be helpful [76]. Second, even after this immediate postradiotherapy period, MRI changes should be interpreted with care. Small changes in T2/FLAIR alone do not necessarily represent progression in a clinically stable patient. Radiological enhancement alone is also insufficient to predict malignant progression. In one study, 23% of patients with isolated increase in T2/FLAIR abnormality showed progression in tumor grade, while 18% of those with contrast enhancement showed no increase in tumor grade [77]. Radiation necrosis can also be a late complication. It can be challenging for clinicians to diagnose recurrence and determine the optimal time to initiate further treatment. As such, it is acceptable in a well patient with minimal changes, to observe with more frequent imaging, before commencing further treatment. In contrast, reinstituting treatment or additional investigation should be considered when MRI changes are associated with the onset of a progressive neurological deficit. Treatment should also be considered if there are continued or progressive MRI changes during sequential follow-up MRIs. The decision to treat a recurrence must be made in collaboration with the patient. Some patients may have a low tolerance for uncertainty and become anxious about radiological changes that are clinically less concerning. Review and discussion at a neuro-oncology MDT is advised.

At confirmed recurrence, the evidence base for treatment is limited, and consideration of clinical trial enrollment is encouraged. As with first-line therapy, molecular characterization should be considered at relapse as new therapeutic targets may have emerged due to tumor evolution. In Australia, the COGNO-led LUMOS-2 platform trial has been commenced for patients with recurrent IDH-mutant Grade 2 and 3 gliomas, offering molecularly guided therapy selection following repeat surgical resection where feasible [78, 79].

7 Recommendations for Follow-Up and Recurrence

- The frequency of MRI monitoring after diagnosis and initial treatment is dependent on the glioma subtype and grade. In general, patients should initially have imaging every 3–4 months. Once the disease trajectory is apparent the interval can be extended and tailored to individual circumstances.
- Contemporaneous tissue should be obtained to confirm tumor recurrence and to assess tumor grade evolution, if possible.
- Management of recurrent IDH-mutant glioma is not well defined and should be individualized. The efficacy of current second line treatment options for recurrent disease is poor and enrollment in clinical trials is encouraged.

6 | Supportive Care/Survivorship

Patients with IDH-mutant glioma often experience progressive decline in cognitive functioning and increasing symptom burden related to both disease progression and treatment side effects [80]. Cognitive decline and symptoms such as fatigue, seizures and mobility issues may impact the ability to return to work/education, driving, decision-making, social participation, and relationships, which all adversely impact physical and psychosocial health-related QoL [81].

Preserving functional independence, cognition, and QoL should be priorities [82]. Consequently, regular supportive care review is important to assist with and plan for changes. Care coordinators can provide a single point of contact and streamline the process of regular reviews of support needs, coordination of services, and patient and caregiver support. Access to these roles should ideally be provided, acknowledging disparities nationally and for certain populations such as people living outside metropolitan areas or those from culturally and/or linguistically diverse backgrounds [83]. In high-grade glioma, this has been shown to improve patient outcomes and healthcare utilization [84]. The impacts of caring for a person with IDH-mutant glioma are significant and likely comparable to those experienced by caregivers of patients with high-grade glioma, with effects that may persist for an extended period [85]. Providing caregivers and families access to targeted advice, information and support is an integral part of follow-up care [86].

Psychological support is important as part of survivorship care to address psychological distress and anxiety associated with perceived changes to cognitive function and QoL [87]. Health services provide varying access to different modes of psychological care, including supportive counseling, individual psychological or targeted group interventions [87, 88]. A recent Australian study demonstrated efficacy of a psychological telehealth intervention to reduce depressive symptoms compared with standard care [89].

Significant financial burden is related to poorer QoL, which may in part be related to greater anxiety symptoms [90]. Hence, regular screening and management of financial toxicity is

8 Recommendations for Supportive Care and Survivorship

- Regular supportive care reviews should be conducted for patients and their caregivers. Areas to address are psychological and emotional needs, physical and neurocognitive impacts, social and practical support, and information needs.
- Access to brain cancer care coordination is required to support navigation of survivorship and QoL issues.
- Referral to allied health services to manage psychological and functional impacts of IDH-mutant glioma should be considered.
- Early access to legal advice and financial counseling support is important.

recommended to maximize QoL in these patients [90]. In addition, all patients and families should be advised to proactively manage key legal and financial arrangements, particularly wills, medical power of attorney and financial power of attorney. Delaying this may result in financial and emotional hardship in the future if undertaken at a time where cognitive competency is uncertain or could be challenged.

7 | Conclusions

This position statement provides recommendations from a multidisciplinary group of experienced Australian neuro-oncology practitioners on the management of IDH-mutant glioma in adults. Despite recent advances, including molecular diagnostics and targeted therapies, key questions remain regarding optimal treatment strategies, sequencing and long-term outcomes. Clinical trials are essential to increase the evidence base and inform decision-making. For complex cases, clinicians are encouraged to engage with colleagues in the setting of a dedicated neuro-oncology MDT.

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Consent

The authors have nothing to report. No written consent has been obtained from patients as there is no patient identifiable data included in this expert position statement.

Conflicts of Interest

Mark B. Pinkham has been a member of a Servier Australia advisory board and is a shareholder for ICON Cancer Care. Hao-Wen Sim has received consultancy fees form Servier and has been a member of a Servier Australia advisory board. Rosalind L. Jeffree has been a member of a Servier Australia advisory board. Arian Lasocki declares no conflicts of interest. Dianne M. Legge declares no conflicts of interest. Frank Saran declares no conflicts of interest. Laveniya Satgunaseelan declares no conflicts of interest. Hui K. Gan has received consultancy fees from Servier in 2023 and 2025 and has been a member of a Servier Australia advisory board.

Data Availability Statement

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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