Single Technology Appraisal

Vorasidenib for treating astrocytoma or oligodendroglioma with IDH1 or IDH2 mutations after surgery in people 12 years and over [ID6407]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

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Contents:

The following documents are made available to stakeholders:

Access the **final scope** and **final stakeholder list** on the NICE website.

1. **Company submission** from Servier
   a. New analysis
   b. Further analysis in relation to EAG issue 7
   c. Analysis of TTNI and tumour volume variation

2. **Company summary of information for patients (SIP)** from Servier

3. **Clarification questions and company responses**
   a. Glioma AB report

4. **Patient group, professional group and NHS organisation submissions** from:
   a. Astro Brain Tumour Fund
   b. International Brain Tumour Alliance
   c. The Brain Tumour Charity
   d. Association of British Neurologists
   e. The British Neuro Oncology Society
   f. The Royal College of Pathologists
   g. The Society of British Neurological Surgeons

5. **Expert personal perspectives** from:
   a. Professor Keyoumars Ashkan, Professor of Neurosurgery and Consultant Neurosurgeon - Clinical expert, nominated by Society of British Neurological Surgeons
   b. Dr Heng Jeng Ching, Consultant Clinical Oncologist - Clinical expert, nominated by Astro Brain Tumour Fund
   c. Dr Liam Welsh, Consultant Clinical Oncologist – Clinical expert, nominated by Servier Laboratories
   d. Hugh Adams - Patient expert, nominated by Brain Tumour Research
   e. Shay Emerton - Patient expert, nominated by Astro Brain Tumour Fund

6. **External Assessment Report** prepared by York Technology Assessment Group

7. External Assessment Report – additional documents

a. EAG report factual accuracy check
b. EAG response to FAC additional evidence
c. EAG response to additional evidence in relation to EAG key issue 7

8. Managed access feasibility assessment

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Vorasidenib for treating astrocytoma or oligodendroglioma with IDH1 or IDH2 mutations after surgery in people 12 years and over [ID6407]

Company evidence submission

February 2025

File name	Version	Contains confidential information	Date
ID6407_Vorasidenib_main submission_[redacted]	1-0	Yes	4 February 2025

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1 Decision problem, description of the technology and clinical care pathway

1.1 Decision problem

The submission covers the technology's full marketing authorisation for this indication.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People 12 years and over with astrocytoma or oligodendroglioma with IDH1 or IDH2 mutations, who have had surgery	[redacted]	To align with proposed marketing authorisation
Intervention	Vorasidenib	Vorasidenib	
Comparator(s)	Established clinical management without vorasidenib.	Servier considers the established clinical management without vorasidenib in the population studied to be “active observation”	To align with Indigo trial. Vorasidenib should only be used in those patients who would otherwise have had active observation. It is not a substitute for chemotherapy/radiotherapy but delays the need for this treatment. The license stipulating not in immediate need of chemotherapy will also mean in clinical practice the comparator would be watch and wait.
Outcomes	• Progression Free Survival • Time to Next Intervention • Overall Survival • Tumour growth rate • Response rates • Adverse effects of treatment • Health-related quality of life.	• Progression Free Survival • Time to Next Intervention • Overall Survival • Tumour growth rate • Response rates • Adverse effects of treatment • Health-related quality of life.	

1.2 Description of the technology being evaluated

Table 2: Technology being evaluated

UK approved name and brand name	Vorasidenib (Voranigo)
Mechanism of action	Vorasidenib is an inhibitor that targets the mutant IDH1 and IDH2 enzymes. In patients with astrocytoma or oligodendroglioma, IDH1 and IDH2 mutations lead to overproduction of the oncogenic metabolite 2-hydroxyglutarate (2-HG), resulting in impaired cellular differentiation contributing to oncogenesis. Inhibition of the IDH1- and IDH2-mutated proteins by vorasidenib inhibits the abnormal production of 2-HG leading to differentiation of malignant cells and a reduction in their proliferation.
Marketing authorisation/CE mark status	Date of submission to MHRA: [redacted] Expected date of approval from MHRA: [redacted] UK - IRP Route B following TGA (Therapeutic Goods Administration-Australia)
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	[redacted]
Method of administration and dosage	The recommended dose of Voranigo in adults and adolescents 12 years of age and older is 40 mg orally once daily for patients weighing at least 40 kg. A 20mg dose recommendation is made in patients weighing less than 40 kg
Additional tests or investigations	Before taking Voranigo, patients must have confirmation of an isocitrate dehydrogenase-1 (IDH1) R132 or isocitrate dehydrogenase-2 (IDH2) R172 mutation using an appropriate diagnostic test.
List price and average cost of a course of treatment	£[redacted] Continue until radiographic disease progression as per INDIGO study
Patient access scheme (if applicable)	PAS simple discount-submission at list price as awaiting response from HST

1.3 Health condition and position of the technology in the treatment pathway

Table 3: Overview of the condition and place in pathway

IDH-mutant grade 2 gliomas consist of IDH-mutant astrocytoma, and IDH-mutant and 1p/19q-codeleted oligodendroglioma, with IDH mutations being a disease defining characteristic. They are considered to have better prognosis and survival outcomes compared to higher-grade gliomas. However, more than 70% of IDH-mutant diffuse gliomas have the potential to undergo a transformation, progressing to a higher grade or becoming more aggressive within a decade. The median OS for patients with IDH-mutant glioma is ~10 years

As IDH mutations are early genetic drivers of the disease, there is an unmet need for a targeted approach to suppress the mutant enzyme. This then offers an opportunity to intervene early (before radiotherapy or chemotherapy) in the disease course, delaying progression and the need for more aggressive therapies, that can have a detrimental effect on a patient's quality of life.

The patient pathway usually starts with a seizure, imaging, and surgical intervention, followed by histological examination and genetic analyses of brain tumour tissue samples for accurate diagnosis and classification, subsequent treatment considerations, or active surveillance. There are several historical prognostic factors that aid in identifying patients at potentially higher risk of early progression who may benefit from early adjuvant RT/CT. These factors include neurologic deficits before surgery, tumour diameter greater than 6 cm, tumour crossing the midline of the brain, and tumours located within or adjacent to eloquent areas of the brain.

However, RT/CT treatment is associated with neurocognitive dysfunction and transformation to aggressive tumours, affecting both QoL and clinical outcomes, and therefore delaying the time to this treatment is currently an unmet need within this young population who have a median age of 40. Therefore, it is recommended that patients not at immediate risk of disease progression remain under active surveillance to avoid the high treatment burden associated with RT and CT.

The benefits of a targeted treatment to delay progression, and also to delay aggressive treatment, go beyond what is measured in a cost effectiveness model, such as increased productivity due to the ability to continue at work, improved domestic work and completion of everyday tasks, as well as maintaining ability to drive.

Vorasidenib has been designated as an orphan medicine for the treatment of IDH-mutant glioma in the European Union (EU) on January 13, 2023, and the Australian government on 31st October 2023. It was also awarded ILAP status as an innovative product by the MHRA in January 2024.

It fits within the treatment pathway for those patients with grade 2 IDH mutant astrocytoma or oligodendroglioma, following surgical intervention if they are not in immediate need of chemotherapy /radiotherapy, reducing the risk of progression and the need for another intervention whilst offering a manageable safety profile.

Given the unmet need in this population for whom the available therapies can lead neuro cognitive decline that can severely impact a patients QOL, these efficacy results reflect a substantial clinical benefit. Vorasidenib is the first innovation in this space for 25 years and has the potential to make a significant and substantial impact on health-related benefits beyond those accounted for in quality adjusted life year calculations, especially as children over the age of 12 are included in the proposed license. Oral administration compared with chemotherapies, also addresses the unmet need for a more convenient therapy for both adults and children with glioma, again improving QoL. The availability of oral treatments has a positive impact on NHS capacity, through a reduction in the number of patients requiring IV chemotherapy. Avoiding hospital visits also reduces the financial and administrative strain on NHS capacity and has a positive impact on patient and carer QoL, as both may experience decreased anxiety and stress

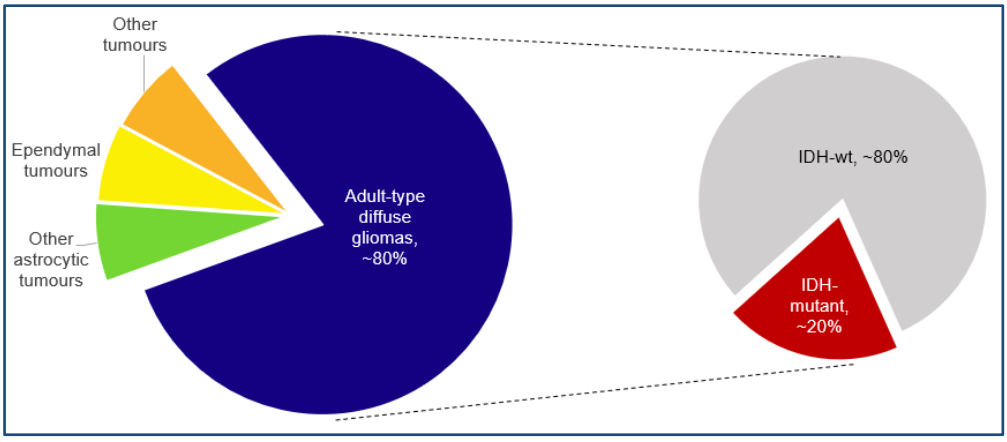
1.3.1 Overview of the disease

Gliomas are the most common primary malignant brain tumour in adults[1] They are neuroepithelial tumours that originate in the glial cells of the brain. Glial cells support and protect the brain and the spinal cord[2]. There are three common types of gliomas, which are classified based on the observable cell characteristics: astrocytomas, ependymomas, and oligodendrogliomas. These cell gliomas can be further classified to low-grade, atypical, and high-grade tumours based on cell morphology, mitotic activities, and molecular marker[3].

Diffuse gliomas have an estimated global prevalence rate of up to 42.8 per 100,000 people[4–6] and represent approximately 20% of the total brain and CNS tumour incidence[7]

IDH mutations are a disease defining characteristic with approximately ~20% of adult diffuse gliomas presenting with IDH mutation. This occurs early in tumorigenesis and is a disease defining characteristics of diffuse gliomas[4]

Figure 1: Distribution of IDH mutations in adult-type diffuse glioma



Source: (Ostrom 2022)[8]
Abbreviations: IDH: isocitrate dehydrogenase; WHO: World Health Organization; wt: wild type
Note: According to the WHO (2021) 5th edition classification, glioblastomas are considered IDH-wt

Even after surgical resection, IDH-mutant glioma remains incurable due to the diffuse and unpredictable nature of the disease**.** Adult IDH-mutant diffuse gliomas demonstrate infiltrative growth, with tumour cells characteristically percolating through normal CNS cellular components making these entities incredibly challenging to treat[1]. This diffuse and infiltrative nature of the tumour means that it cannot be fully resected or targeted with RT/CT[9]

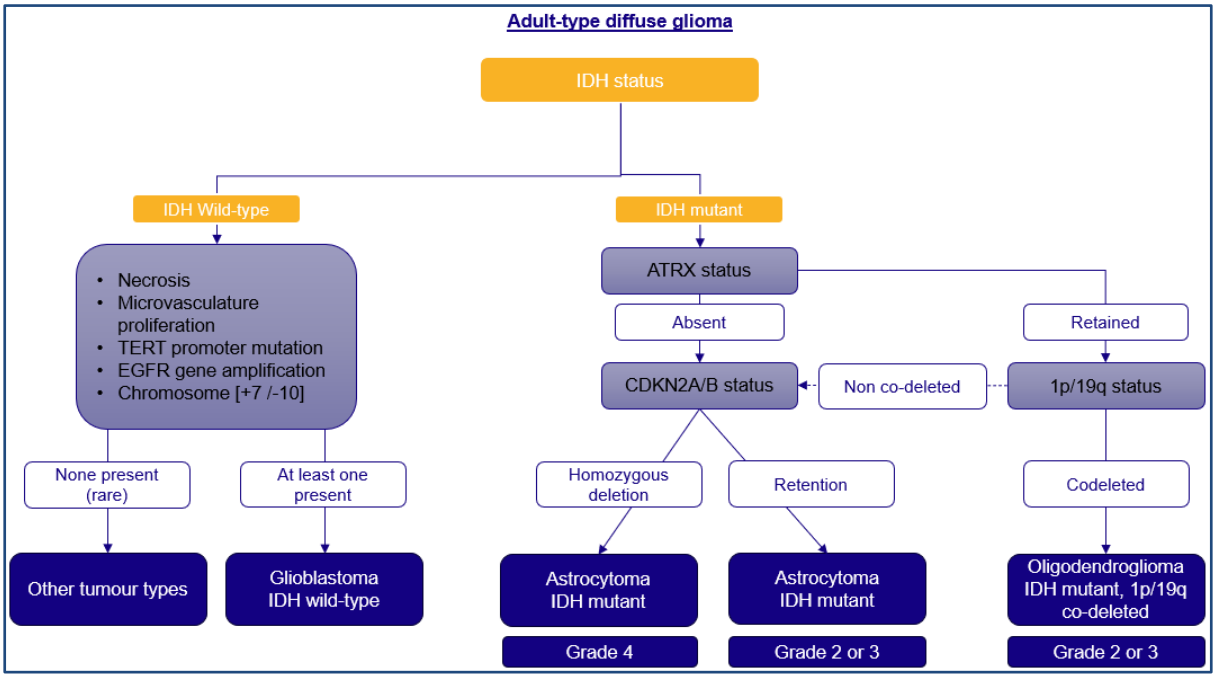
Compared to IDH wild-type (wt), IDH-mutant gliomas generally exhibit a slightly better survival due to their slower growth rate[10,11]. The tumour-growth dynamics are unpredictable, and rapid acceleration can occur suddenly, particularly in the absence of treatment[12,13]. Despite the slower growth, more than 70% IDH-mutant gliomas have the potential to undergo a transformation, progressing into a higher grade or becoming aggressive in behaviour within a decade[10,14]. A real-world study reported that around 65% of the patients with IDH-mutant glioma underwent malignant transformation, with 40% progressing from Grade 2 to 3 and 25% directly progressing from Grade 2 to 4[15]. Further, IDH-mutant gliomas are more likely to develop hypermutation characteristics which are associated with worse prognosis[11]

Therefore, the updated WHO (2021) 5th edition guidelines[16] have classified gliomas, using IDH mutation status as the primary diagnostic marker, along with additional molecular characterisation. It organises adult-type diffuse gliomas based on the presence or absence of IDH mutation, which divides them into

two key categories: the slower growing, IDH-mutant tumours and the more aggressive, IDH-wt tumours. IDH mutations occur in early tumorigenesis and are disease defining characteristics. This molecular characterisation is therefore the primary diagnostic marker and highlights IDH mutation status as a disease defining mutation.

Gliomas are divided into three main types: IDH-mutant astrocytoma, IDH-mutant and 1p/19q-codeleted oligodendroglioma, and IDH-wt glioblastoma. These are classified as Grade 1 to 4 based on histopathological characteristics[16].

Figure 2; Classification of Glioma[16]



Patients with IDH-mutant diffuse gliomas are considered to have better prognosis and survival outcomes compared to higher-grade gliomas. However, more than 70% of IDH-mutant diffuse gliomas have the potential to undergo a transformation, progressing to a higher grade or becoming more aggressive within a decade. The median OS for patients with IDH-mutant glioma is ~10 years[17,18]. However, this can range widely, given the varying tumour histopathology and the preferential response of oligodendrogliomas to RT and CT compared to astrocytomas with the median survival for IDH-mutant oligodendrogliomas ranging from 7.2 to 17 years[7,19] The median survival for IDH-mutant Grade 2 astrocytomas ranges between 5 to 8 years[20].

Symptoms of IDH-mutant glioma vary based on various tumour characteristics such as tumour size, location, and degree of infiltration. Symptoms can include headaches, nausea, vomiting, seizures, visual disturbance, speech and language problems, and changes in cognitive and/or functional ability[3]. However, patients may also be asymptomatic, without evident abnormalities on neurologic examination[21]. Epileptic seizures are the most common initial presentation, occurring in 20-50% of patients[22] and ranging from simple to complex seizures with or without secondary generalisation[10]. A significant portion of initial seizures tend to be unresponsive to medical treatment which negatively impacts patient QoL and cognitive function, potentially leading to additional complications[10]. Furthermore, patients then continue to experience seizures throughout the course of the disease.

In addition to seizures, patients with IDH-mutant glioma may also present with headaches (50-60%) and focal neurologic signs (10-40%)[22], as well as neurocognitive impairment. Cognitive deficits associated with brain tumours can be induced by compression of the brain, either directly or indirectly, by reactive oedema[23].

Patients with IDH-mutant glioma experience a detriment to QoL due to disease-related symptoms, which are exacerbated not only by disease progression but also the adverse effects associated with RT/CT. Studies have also demonstrated that both disease progression and treatment (i.e., surgery, RT, CT) have adverse implications for HRQoL, including worsening cognitive functioning, physical functioning and pain intensity of patients with IDH-mutant gliom[18,24]. These Cognitive deficits may be especially burdensome for patients with IDH-mutant glioma who are not at immediate risk of disease progression, as these patients are confronted with the deterioration in functioning whilst trying to resume their personal and professional life post-treatment[25]. This cognitive impairment can have many implications for the patients such an ability to lead the same life, continue in paid employment, and in some cases means a patient will need increased social care

In addition, to further look at productivity losses, a non-interventional observational retrospective longitudinal study using pseudonymized patient-level data was carried out by Servier to Generate real-world evidence on the burden of glioma – specifically regarding days absent from work – by use of Danish administrative registers. (Work Inactivity burden related to IDH-mutated gliomas: a Danish Non-interventional Observational retrospective study(Workido)). [redacted]

In addition, depression and anxiety are a serious problem in patients with glioma. In particular, patients on active surveillance experience depression and emotional distress[27]. The combined impact of the disease and tumour-related symptoms tied with the increased emotional distress of being on active surveillance could result in a detriment to HRQoL in this population. The Patient Pathway Study reported that patients have an ambivalent perception of this observation period as most patients acknowledged they could go back to work and daily life with adaptation, however, the recurrent anxiety experienced at every follow-up MRI while on active surveillance was a burden[28].All patients who experienced active surveillance found the period to be anxiety inducing, with one patient also reporting severe depression. Patients experience a peak of anxiety at follow-up MRI examinations, with repeating cycles of emotional extremes, due to feelings of dread at the thought of disease recurrence followed by intense relief sensation. A subset of patients did consider the positive aspects of being under active surveillance relating to the avoidance of the potential side effects associated with aggressive treatment[28]

IDH-mutant glioma also has a profound impact on caregiver QoL which is exacerbated as patient condition worsens due to disease progression or treatment-related side effects. Caregivers often experience disruptions in emotional, physical, and social well-being[29,30]. Care is primarily provided by relatives and friends and few patients with glioma rely solely on formal care[29]. As the condition of patients worsen, either through disease progression or the effects of treatments like RT/CT, it impacts them both physically and cognitively, affecting cognitive functions, personality, and behaviour. This deterioration has a direct negative impact on the QoL of caregivers, potentially hindering their ability to provide optimal care**.** This establishes a reciprocal relationship between the QoL of the patient and that of the caregiver[31]**.** Caregivers face difficulty in performing routine household tasks as well as substantial productivity loss which contributes to increased economic burden**.**

There is an urgent need for an active intervention for these patients to prevent progression and delay the use of RT/CT while maintaining their QoL, particularly when considering the younger age of the IDH-mutant glioma patient population. As IDH mutations are early genetic drivers of the disease, a

targeted approach suppressing the mutant enzyme offers an opportunity to intervene early in the disease course before the need for RT/CT, delaying progression and the need for more aggressive therapies.

1.3.2 Proposed place of Vorasidenib in the pathway

Vorasidenib has been designated as an orphan medicine for the treatment of IDH-mutant glioma in the European Union (EU) on January 13, 2023[32], and by the Australian government on 31st October 2023[33] It was also awarded ILAP status as an innovative product by the MHRA in January 2024[34]

It fits within the treatment pathway for those patients with grade 2 IDH mutant astrocytoma or oligodendroglioma, following surgical intervention and if they are not in immediate need of chemotherapy /radiotherapy, reducing the risk of progression and the need for another intervention whilst offering a manageable safety profile. Vorasidenib is the first and only brain penetrant targeted therapy in adult and paediatric diffuse glioma, allowing it to reach deeply infiltrated tumoral cells and complementing surgery benefits by delaying progression and the need for RT/CT. The high unmet need is driven by the fact this population only has the choice of active observation or wait until they are in immediate need of RT/Chemo which can lead to neuro cognitive decline that can severely impact a patients QOL. These efficacy results reflect a substantial clinical benefit.

Older guidelines established active observation & Rt/Ct with the notion of high/low risk. NICE Guideline (NG99)[35] states:
After surgery, offer radiotherapy followed by up to 6 cycles of PCV chemotherapy (procarbazine, CCNU [lomustine] and vincristine) for people who:

- have a 1p/19q codeleted, IDH-mutated low-grade glioma (oligodendroglioma) **and**
- are aged around 40 or over, or have residual tumour on postoperative MRI.

After surgery, consider radiotherapy followed by up to 6 cycles of PCV chemotherapy for people who:

- have a 1p/19q non-codeleted, IDH-mutated low-grade glioma (astrocytoma) **and**
- are aged around 40 or over, or have residual tumour on postoperative MRI.

Consider active monitoring for people who are aged around 40 or under with an IDH-mutated low-grade glioma and have no residual tumour on postoperative MRI.

Consider radiotherapy followed by up to 6 cycles of PCV chemotherapy for people with an IDH-mutated low-grade glioma who have not had radiotherapy before if they have:

- progressive disease on radiological follow-up **or**
- intractable seizures

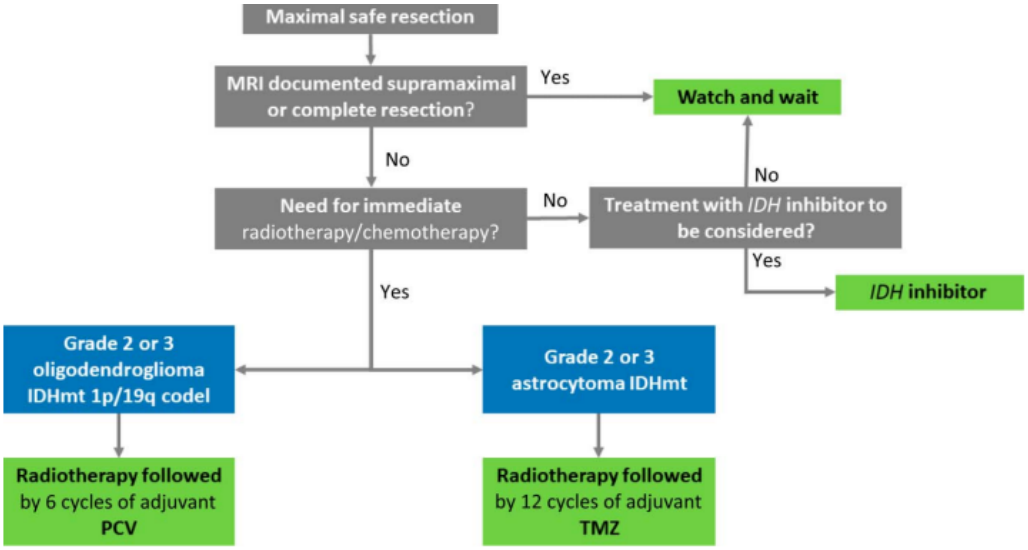
Patients not at immediate risk of progression may demonstrate a more favourable prognosis and are monitored with serial MRI scans instead of immediate post-surgery treatment. At an advisory board for Servier, it was reported that generally for active observation patients, scanning is performed every 6 months but if there any signs of concern at this point then would convert to every 3 months.[36]

IDH1/2 mutational testing is routine clinical practice for diagnosing non glioblastoma patients, in accordance with WHO 2021 guidance[37]. Although most patients progress to a more aggressive disease state, there are several historical prognostic factors that historically aided in identifying

patients at potentially higher risk of malignant transformation who may benefit from early adjuvant RT/CT.
As per NICE guidelines[35]these are often still based on information from historical series comprising both patients with IDH wild-type and IDH-mutant tumours. These recommendations are based on analyses from trials conducted prior to the discovery of the IDH mutation in 2008 and its introduction in the WHO classification of CNS tumours. They provide recommendations for radiotherapy and chemotherapy for so-called high-risk patients, usually based on age greater than 40 years, neurologic deficits before surgery, large residual disease volume after surgery , tumour crossing the midline of the brain, and tumours located within or adjacent to eloquent areas of the brain[38] More up-to-date studies give a better insight into clinical, radiological, and molecular factors associated with the outcome of patients with IDH-mutant glioma.[39]. More recently, several studies, including an ASCO 2024 publication, have demonstrated that age is not a prognostic factor when the IDH-mutation is taken into account and therefore age has not been included in recent guidelines[40–42]

The most recent NCCN and SEOM-GEINO guidelines, and ASCO publication, recommend either active surveillance or treatment with an IDH-inhibitor (i.e., vorasidenib) for patients with low-grade glioma who are neurologically asymptomatic or stable, reinforcing its target population[40,43,44]

Figure 3: Position of Vorasidenib in the patient pathway (adapted from Schaff et al, 2024)[40]



Variables favoring watch-and-wait

- Grade 2 histology
- Minimal postoperative tumor volume
- Documented low preoperative tumor growth rate
- Oligodendroglioma histology

Variables favoring radiotherapy/chemotherapy

- Grade 3 histology
- Substantial postoperative tumor volume (more critical in astrocytoma)
- Documented high preoperative tumor growth rate
- Contrast enhancement on brain MRI
- Poorly controlled seizures
- Neurologic deficits caused by the tumor
- Unfavorable genetic alterations: Astrocytoma: DNA methylation profile consistent with anaplastic astrocytoma, *CDK4* amplification, *PDGFRA* amplification, *PIK3CA* mutation; Oligodendroglioma: h

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Survival and treatment-related toxicities are prioritised in treatment decision-making given the relatively young age of the patient population (median age 36-42 years)[45]. The glioma patient pathway usually starts with a seizure, imaging, and surgical intervention, followed by histological examination and genetic analyses of brain tumour tissue samples for accurate diagnosis and classification, followed by subsequent treatment considerations, or active surveillance. Maximal safe surgical resection remains the initial treatment for IDH-mutant glioma irrespective of grade to enable an accurate diagnosis and improve clinical outcomes such as OS, PFS, and risk of malignant transformation.

It is recommended that patients not at immediate risk of disease progression as per the above prognostic criteria remain under active surveillance to avoid the high treatment burden associated with RT and CT,

As previously highlighted in section 1.3.1, Rt/Ct interventions are aggressive lines of treatment that can be safely postponed until patients' progression without compromising their long term survival

benefit, while preserving their quality of life considering the acute and long-term toxicity burden of Rt and Ct[46].

Evidence suggests that treatment with TMZ leads to a hypermutation phenotype associated with acquired defects in DNA mismatch repair genes. Such hypermutation is eventually found in approximately 60% and 30% of post-TMZ oligodendrogliomas and astrocytomas, respectively. Not only are hypermutant tumours resistant to further treatment with alkylating chemotherapies owing primarily to mismatch repair (MMR) pathway mutations, they seem inherently more aggressive.[18]

PCV (Procarbazine, Lomustine, Vincristine) is commonly used over 6 cycles for both oligodendroglioma and astrocytoma. PCV has shown potential for longer progression-free survival in high-risk patients but requires careful patient selection due to its higher toxicity, including bone marrow toxicity and vincristine-induced neuropathy. Although evidence and treatment guidelines all recommend using the full PCV regimen, some centres prefer to avoid using Vincristine[47]. PCV can be harder for patients to tolerate in terms of typically more fatigue, nausea, and bone marrow suppression, as well as being more time-consuming for neuro-oncologists to prescribe and monitor[18]

Considering the above, it can be considered a paradox to propose an intensive treatment to a population (IDH-mutated/codeleted tumour) with an a priori good prognosis (long-survival expected and lower tendency to progress to more aggressive tumours), while the risk of late toxicity due to RT, possibly increased by the association with CT is well known.[48]

Pseudo-progression, in which treatment causes a self-limited increase in contrast enhancement that mimics tumour progression, can also be observed in patients with IDH-mutant glioma, peaking between 3 and 78 months of radiation completion. Delayed toxicities, such as radiation necrosis, can develop within months of treatment completion, while others, like the stroke-like migraine attacks after radiation therapy (SMART) syndrome, can develop years later. In IDH-mutant gliomas, RT frequently results in homozygous deletion of the tumour suppressor CDKN2A which is linked to shorter survival time[18]

At an advisory board held by Servier, all advisors agreed that on the whole the population in the trial is reflective of those that would not be in need of radiotherapy/chemotherapy[36]. Hence, vorasidenib will play an important role in delaying the initiation of RT/CT and slowing down tumour growth while maintaining QoL by preserving cognitive function.

The benefits of a targeted treatment to delay progression, and delay the effects of aggressive RT/CT go beyond what is measured in a cost effectiveness model**.** IDH-mutant glioma is associated with high indirect costs, especially when treated with RT/CT, related to loss of productivity, inability to work, early retirement, and premature mortality[49]. Patients with IDH-mutant Grade 2 glioma not only face productivity losses at work but also are hindered by health issues in everyday tasks. More than half of the participants reported barriers in performing domestic work: around 45% reported issues completing and 25% reported difficulties in taking care of children[50]. The potential acute adverse effect of RT, such as elevated intracranial pressure, can manifest as headaches and vomiting[51]. These additional chronic side effects associated with RT for brain cancer include impaired wound healing, skin changes and skin cancer, lymphedema, secondary cancer, and damage to surrounding structures which potentially contribute to the detriment to daily function[52]. All advisors at an advisory board held by Servier expressed that the societal benefits of vorasidenib over RT/Chemo will be marked. Some of the benefits expressed were continuing to work due to a lack of neurological deficit, equating to reduced nursing home care that may be needed due to this. Four advisors expressed that it should not be underestimated the driving potential with Vorasidenib. In their opinion this is a large quality of life benefit as patients cannot drive on RT/Chemo. People lose their license for at least a year with RT/Chemo and similar after surgery.[36]

Vorasidenib is a ground-breaking, first-in-class, dual IDH1- and IDH2-mutant inhibitor and represents a new standard of care for the treatment for Grade 2 astrocytoma or oligodendroglioma with a susceptible IDH1 R132 mutation or IDH2 R172 mutations, in adults and paediatric patients 12 years and older who have only had surgical intervention and are not in immediate need of radiotherapy or chemotherapy. At an advisory board held by Servier, clinicians stated that the results are impressive results and first ground breaking results in this population for decades.[36]

1.4 Equality considerations

No equality considerations have been identified.

2 Clinical effectiveness

2.1 Identification and selection of relevant studies

See appendix B for full details of the process and methods used to identify and select the clinical evidence relevant to the technology being evaluated.

2.2 List of relevant clinical effectiveness evidence

A systematic literature review (SLR) was conducted to identify and summarize published clinical evidence from randomized controlled trials (RCTs) on the clinical efficacy, safety, and health-related quality of life (HRQoL) of treatments in patients with grade 2 or 3 diffuse glioma, with or without IDH mutations. Further, a targeted literature review (TLR) on the clinical burden of illness in patients with grade 2 or 3 diffuse glioma, including OS and PFS, as reported in non-randomized and observational/real-world studies was also conducted to complement the SLR.
Electronic databases (Embase, MEDLINE, Cochrane), conference proceedings and grey literature sources were searched initially on April 17th, 2023 (original SLR), followed by an updated search on May 20th, 2024 (2024 SLR update).
The research questions for both the SLR and TLR were addressed using the Population, Intervention, Comparator, Outcomes and Study Type (PICOS) framework, displayed in Table 4 and Table 5 respectively.
To provide a clear overview of available evidence for the target population of interest, the results section has been stratified into two categories, one focusing on studies involving post-resection patients under watch-and-wait regimens (like the INDIGO trial population) and the second presenting the remaining studies with broader mixed-type glioma populations (i.e. without specific watch-and-wait classification).
Titles and abstracts of the retrieved citations were screened against the inclusion/exclusion criteria defined in the tables below. Studies identified as potentially relevant based on their titles and abstracts were reviewed in full and included or excluded according to the same criteria. Articles at both title/abstract and full-text review stage were reviewed by two reviewers, independently and in parallel, based on the pre-specified study selection criteria. After completion of the full-text review, 20% of the screened articles were quality checked by a third independent reviewer. Any discrepancy was resolved by discussion. A third person was involved if a decision was not reached between the two reviewers.
Data extraction was carried out by one independent reviewer, and quality checked by a second reviewer. Study quality was assessed according to the criteria outlined in the NICE single technology appraisal (STA) template. The extracted evidence was then analysed, stratified, and presented in the form of narrative and tabular summaries in the full SLR report found in Appendix B. Further, a narrative summary of the efficacy outcomes from all study designs (RCTs, observational and non-randomized studies) has been developed to provide a consolidated view of the available clinical and is evidence in the dedicated report.

Table 4: Eligibility criteria for the clinical SLR

Category	Inclusion criteria	Exclusion criteria
Population	Patients aged 12 years or older with IDHmt grade 2 or 3 diffuse gliomas, who have undergone surgery (biopsy, sub-total resection, gross-total or supra-total resection) as their only treatment and are not in need for immediate radiation and chemotherapy. **Glioma also referred to as**: • Diffuse adult-type glioma • Diffuse astrocytoma, oligodendroglioma, oligoastrocytoma, or mixed type glioma • Anaplastic astrocytoma or oligodendroglioma • Grade 2 or 3 oligodendroglioma (*IDH*^{mt} and 1p/19q codeleted) • Grade 2 or 3 astrocytoma (*IDH*^{mt} without 1p/19q codeletion) **Surgery in first line referred to as:** • Gross-total or supra-total resection • Subtotal resection • Partial resection • Biopsy only	• Diffuse paediatric glioma • *IDH*^{wt} glioma • Glioblastoma • CNS neoplasms other than diffuse adult-type glioma Note: Animal/in vitro studies, cell lines and/or tissue sample analysis will be excluded
Intervention/ Comparator	No restriction	Not applicable
Study design	• Randomized controlled trials (phase II– III; single-blind, double blind, cross-over) • SLRs or meta-analysis§	• Non-interventional studies, observational studies, real-world studies • Non-randomized controlled trials • Case reports, case studies • Animal/in vitro studies, cell lines and/or tissue sample analysis
Publication type	• Peer-reviewed journal articles • Original research reports • Conference abstracts	• Non-peer-reviewed articles • Note/ News articles/ Editorials. • Letters / book chapters, if data are already published in peer-reviewed journal articles or original research reports
Language	No restriction	Not applicable
Publication year	• Full publication: No restriction (until May 20th, 2024) • Conference abstracts: 2020 to present (until June 3rd, 2024)	Conference abstracts prior to 2020
Geography	No restriction	Not applicable

*Watch-and-wait refers to monitoring patients with gliomas without administration of any treatment until disease progression changes. Definitions and criteria for watch-and-wait practices differ across studies.

†Systematic reviews and meta-analyses were reviewed only for cross-referencing purpose

Abbreviations: CNS: central nervous system; EORTC QLQ-C30: European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire; EQ-5D: EuroQoL 5-Dimentions; FACT-G: Functional Assessment of Cancer Therapy-General; IDH: isocitrate dehydrogenase; *IDH*^{mt}: IDH mutant; *IDH*^{wt}: IDH wildtype; HR: hazard ratio; HRQoL: health related quality of life; OR: odds ratio; RCTs: randomized clinical trials; RD: risk difference; RR: relative risk; SF-36: Short Form 36 items; SLR: systematic literature review

Table 5. Eligibility criteria for the TLR

Category	Inclusion criteria	Exclusion criteria
Population	Patients aged 12 and over with grade 2 or 3 diffuse glioma **Subgroups of interest**	• Diffuse paediatric glioma • IDH wildtype glioma • Glioblastoma

	• Diffuse astrocytoma or oligodendroglioma • Anaplastic astrocytoma or oligodendroglioma • Grade 2 or 3 oligodendroglioma (*IDH* mutant and 1p/19q codeleted) • Grade 2 or 3 astrocytoma (*IDH* mutant, without 1p/19q codeletion) • Patients who have previously undergone surgery (biopsy, sub-total resection, gross-total or supra-total resection) as their only treatment, and are not in need of immediate radiotherapy or chemotherapy • Patients with *IDH1* or *IDH2* mutation • Patients with non-enhancing glioma	• CNS neoplasm other than diffuse adult-type glioma Note: Animal/*in vitro* studies, cell lines and/or tissue sample analysis will be excluded
Intervention/ comparator	The following treatment options in the second line including, but not limited to: • Surgery followed by observation ("watch and wait") • Gross-total resection • Subtotal resection • Partial resection • Biopsy only • Radiotherapy or chemotherapy after a long observation period (then data on the observation period, if available, was of interest) • Targeted therapies • Combination of above modalities Note: Patients with progressive disease who underwent surgery were of interest for Servier	• Studies evaluating surgical procedures in the first line • Patients who received immediate radiotherapy or chemotherapy after the first surgery
Outcomes (including but not limited to)	• Progression-free survival • Overall survival • Event-free survival • Response rate • Time to progression • Time to response, time to next intervention, post-progressive survival • Changes in biomarkers • Intervention free survival • Seizure activity • Mortality • Treatment related complications • Tumour size, volume, growth rate	Studies reporting no outcomes of interest
Study design	• Non-randomized controlled trials • Controlled before- and after- (pre-post) studies • Cohort studies • Case control studies • Cross-sectional studies • Interrupted time-series studies • Interventional studies without concurrent controls (historical controls) • Interventional case-series • Observational/real world studies • Related systematic or targeted literature reviews (for cross-referencing only)	• Randomized controlled trials • Case reports/studies • Narrative reviews
Publication type	• Peer-reviewed journal articles	• Conference abstracts due to limited information • Non-peer reviewed articles • Notes/News articles/ Editorials/Letters
Language	English language only	Language other than English
Publication year	2013–present (until May 21st, 2024)	Publications prior to 2013

Geography	USA, EU4 (France, Germany, Italy, Spain), UK, Australia, Japan	Any other region

A total of seven publications comprising of three RCTs (INDIGO, EORTC 22845, NCT03343197) were included in the SLR.
In addition, 12 observational studies in patients with low-grade gliomas in the watch-and-wait regimen after initial surgery, and 29 observational studies including one near-randomized study) reporting on mixed cohorts (low-grade gliomas regardless of need of immediate postsurgical therapy) were identified from the TLR (Table 6)

Table 6. Characteristics of studies with post-resection patients in watch-and-wait regimens

Trial identifier Author (year)	Patient population	Region	Sample size	Study design	Intervention Comparator	Follow-up (median months)	Reported outcomes	
							For overall population	For IDHmt subgroups
Randomized controlled trials								
EORTC 22845 van den Bent (2005) Karim (2002)	Low-grade glioma (astrocytoma, oligoastrocytoma, or oligodendroglioma) (as per WHO 1979 classification)	Europe	311	Open-label RCT	• Early RT (total dose 54 Gy) • Deferred RT until time of progression (watch-and-wait)	60	OS, PFS, time to progression	NA
NCT03343197 Mellinghoff (2023a)	*IDH1*^{mt} non-enhancing recurrent grade 2 or 3 oligodendroglioma or astrocytoma (as per WHO 2016 classification)	US	49	Open-label phase I RCT*	• Vorasidenib (50 mg q.d. or 10 mg q.d.) • Ivosidenib (500 mg q.d. or 250 mg b.i.d.)	NR	Biomarker concentration, incidence of AEs	Biomarker concentration, response rate, PFS, incidence of AEs
INDIGO (NCT04164901) Mellinghoff (2023b) (2023), Wen (2023) Cloughesy (2023)	Residual or recurrent *IDH1/IDH2* grade 2 oligodendroglioma or astrocytoma (as per WHO 2016 classification) with at least one previous surgery and no immediate need of RT/CT	North America, western Europe, Israel	331	Double-blinded phase III RCT	• Vorasidenib • Placebo (watch-and-wait)	14.2	PFS, TTNI, response rates, safety, HRQoL, tumour growth rate	PFS, TTNI, response rates, safety, HRQoL, tumour growth rate
Observational studies								
Mandonnet (2003)	Grade 2 glioma (astrocytoma, oligodendroglioma, mixed glioma)	France	27	Retrospective cohort study	No treatment after biopsy	54.6	Tumour growth	NA
Rees (2009)	Supratentorial astrocytoma, oligodendroglioma, mixed oligoastrocytoma	Germany	126	Retrospective cohort study	No treatment after biopsy	58.8	Tumour growth rate	NA
Jansen (2019)	Grade 2 gliomas (WHO 2016 classification) put on watch-and-wait after initial surgery	Germany	110	Prospective cohort study	NA	120	OS, PFS rates, malignant transfor	OS

							mation rates, time to first progression	
Paľa (2019)	WHO grade 2 *IDH*^{mt} glioma receiving or not adjuvant therapy after surgery	Germany	144	Retrospective cohort study	Adjuvant RT or CT, no post-surgery therapy	72	OS, PFS	OS, PFS
Huang (2020)	*IDH*^{mt} grade 2 or 3 gliomas	US	230	Retrospective cohort study	RT, CT, no treatment after surgery (watch-and-wait)	NR	Tumour growth rate, TTNI	Tumour growth rate, TTNI
Weller (2022)	Astrocytoma, *IDH*^{mt}, grade 2 or 3	Germany	183	Retrospective cohort study	Wait-and-scan, radiotherapy, temozolomide	216	OS, PFS	OS, PFS
Allwohn (2023)	*IDH*^{mt} 1p/19q codeleted oligodendroglioma (WHO 2021 classification), either on watch-and-wait or RT/CT after initial surgery	Germany	114	Retrospective cohort study	Watch-and-wait, RT, CT	68.6-69.8	OS, PFS	OS, PFS
Kamson (2023)	RT and CT-naïve *IDH1*^{mt}, non-enhancing grade 2/3 glioma	US	12	Retrospective cohort study	Ivosidenib	13.2	PFS, tumour growth rate, time to response, safety	PFS, tumour growth rate, tumour volume, time to response, safety
Minniti (2023)	Grade 2 *IDH*^{mt} astrocytoma (WHO 2021 classification) with either early or delayed post-operative RT	Italy	103	Retrospective cohort study	RT	108	OS, PFS	OS, PFS
Tran (2023)	*IDH*^{mt} grade 2 or 3 astrocytoma	France	118	Retrospective cohort study	Adjuvant therapy, watch-and-wait	86.0	OS, TTNI	OS, TTNI
Bhatia (2024)	IDH^{mt} grade 2 astrocytoma or oligodendroglioma	US	128	Retrospective cohort study	Watch-and-wait	75.6	OS, TTNI, Tumour growth rate	OS, TTNI, Tumour growth rate
Bruno (2024)	*IDH*^{mt} low-grade glioma receiving or not adjuvant therapy after surgery	Italy	150	Retrospective cohort study	Adjuvant RT or CT, no post-surgery therapy	24	Seizure	Seizure

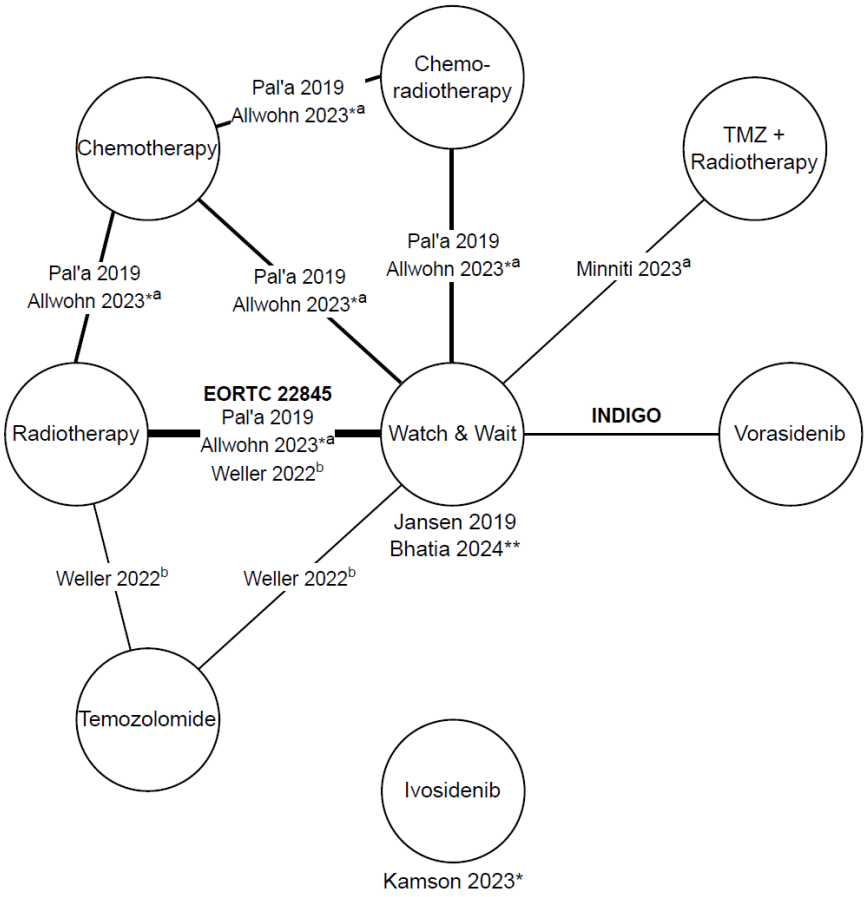
Abbreviations: AE: adverse event; b.i.d.: twice daily; IDH: isocitrate dehydrogenase; IDHmt: IDH mutant glioma; NA: not applicable; NR: not reported; OS: overall survival; PFS: progression-free survival; q.d.: once daily; RCT: randomized controlled trial; TTNI: time to next intervention; US: United States

Figure 4 below presents the evidence networks for OS and PFS of IDHmt glioma patients, not in immediate need of Rt/Ct. It comprises three RCTs (seven publications and 12 observational studies (12

publications) that included patients with IDHmt or low-grade glioma who were eligible to active observation regimens. It comprises eight interventions:

- Chemotherapy [either a mix of Procarbazine, lomustine, and vincristine (PCV) or Temozolomide (TMZ)], or unspecified regimen(s) – 2 studies.
- Chemoradiotherapy (comprising radiation therapy and a mix of PCV/TMZ or unspecified chemotherapy regimen) – 2 studies.
- Radiotherapy – 4 studies.
- Temozolomide (TMZ) – 1 study.
- TMZ + radiotherapy – 1 study.
- Active observation (defined as active surveillance, watchful waiting, or placebo) – 3 studies.
- Vorasidenib – 1 study.
- Ivosidenib – 1 study. Of note, ivosidenib is the only intervention not connected to the rest of the network as it is only present in one single arm study.

Figure 4: Evidence network for studies reporting OS and/or PFS in IDHmt grade 2 gliomas



Key: *Bold: Randomized controlled trials; *: PFS only; **: OS only; [a]: astrocytomas only; [b]: oligodendrogliomas only; Chemotherapy: includes a mix of PCV and TMZ or unspecified.*

The clinical relevance and completeness of the evidence network was assessed in the context of published treatment guidelines and clinical practices for the treatment of grade 2 IDH mutant gliomas. Nine treatment guidelines describing the management of IDHmt grade 2 gliomas were identified. All nine recommend maximal safe resection in newly diagnosed glioma patients for both diagnostic and therapeutic purposes. After resection, most guidelines recommend watch-and-wait for patients with more favourable prognostic factors (as discussed in section 1.3.2), or radiotherapy (RT) followed by chemotherapy (Ct) with a procarbazine, lomustine, and vincristine (PCV) or temozolomide (TMZ) regimen. Furthermore, the latest NCCN guidelines recommend IDH inhibitors as adjuvant therapy for grade 2 IDHmt gliomas and the SEOM-GEINO guidelines recommend vorasidenib for patients with grade 2 IDHmt not receiving post-surgical RT/CT.
Additionally, 20 studies reporting on the real-world management of grade 2 or grade 3 glioma, 11 of which reporting practices specific to IDHmt gliomas were analysed confirming that grade 2 IDHmt patients are most often treated following a watch-and-wait strategy or immediate adjuvant therapy with RT, CT (TMZ or PCV), or a combination of the two after surgery. Further, this analysis did not identify alternative chemotherapy regimens to PCV and TMZ in this setting.
Together, these findings confirm that the evidence network is representative of the existing treatment interventions recommended and used in practice to treat grade 2 IDHmt glioma.

Table 7: Clinical effectiveness evidence

Study	(NCT04164901) (Mellinghoff 2023b)[65]
Study design	The INDIGO trial is an international, double-blind, randomised, placebo-controlled trial, which assessed the efficacy and safety of vorasidenib therapy in patients with residual or recurrent Grade 2 IDH-mutant glioma
Population	The INDIGO study recruited patients with residual or recurrent predominantly non-enhancing Grade 2 oligodendroglioma or astrocytoma, with an IDH1 or IDH2 mutation, who have undergone surgical intervention as their only treatment. Patients were excluded if they had received any other prior treatment, including systemic CT or RT, or if they were in immediate need of CT or RT in the opinion of the Investigator
Intervention(s)	Vorasidenib 40mg od
Comparator(s)	Placebo
Indicate if study supports application for marketing authorisation	Yes
Indicate if study used in the economic model	Yes
Rationale if study not used in model	N/A
Reported outcomes specified in the decision problem	The primary end point of the trial was **progression-free survival**, which was defined as the time from randomization to the first documented progressive disease (as assessed on imaging by blinded independent review according to the modified Response Assessment for Neuro-oncology for Low-Grade Gliomas [RANO-LGG]30) or death from any cause, whichever occurred earlier. The key secondary end point was the **time to next intervention**, which was defined as the time from randomization to the initiation of the first subsequent anticancer therapy (including vorasidenib, for patients in the placebo group who subsequently crossed over to receive vorasidenib) or death from any cause. Secondary end points included objective response and safety, as well as tumour growth rate according to volume (determined on the basis of blinded independent review), health-related quality of life, and

Study	(NCT04164901) (Mellinghoff 2023b)[65]
	overall survival (not reported here). Objective response was determined on the basis of blinded independent review according to the modified RANO-LGG. • **Progression Free Survival** • **Time to Next Intervention** • **Overall Survival** • Tumour growth rate • Response rates • **adverse effects of treatment** • **health-related quality of life.**
All other reported outcomes	[Please mark in bold the outcomes that are incorporated into the model]

2.3 Summary of methodology of the relevant clinical effectiveness evidence

Study Design

The INDIGO trial is an international, double-blind, randomised, placebo-controlled trial, which assessed the efficacy and safety of vorasidenib therapy in patients with residual or recurrent Grade 2 IDH-mutant glioma after surgical intervention (NCT04164901)[65]. The summary of the study design has been presented in Figure 4. Patients received 40 mg of vorasidenib or matching placebo orally, once daily, in continuous 28-day cycles. An assessment (site visit) was conducted on the first day of each cycle for the first 36 cycles. On-site visits for the dispensation of vorasidenib or placebo and for safety and efficacy assessments were done according to the trial protocol.

Patients who had been randomly assigned to the placebo group were eligible to cross-over to vorasidenib treatment if they had imaging-based disease progression confirmed on blinded. Cross-over from placebo to vorasidenib upon centrally confirmed progressive disease (PD) was included in the study following feedback from clinicians and patients/advocates based on ethical considerations for subjects who were already on active surveillance being randomised to placebo.

If PD was confirmed by Blinded Independent Review Committee (BIRC), unblinding was performed and physicians thus had the option to offer the possibility for patients to cross-over to vorasidenib if their disease progressed on placebo. If unblinded patients were on vorasidenib treatment, continuation of vorasidenib was not permitted and patients were offered the next possible intervention such as surgery, RT and/or CT or as per investigator discretion. This process ensured that the investigator was not permitted to prematurely unblind patients to allow for cross-over and limited the bias in determining the need for another intervention.

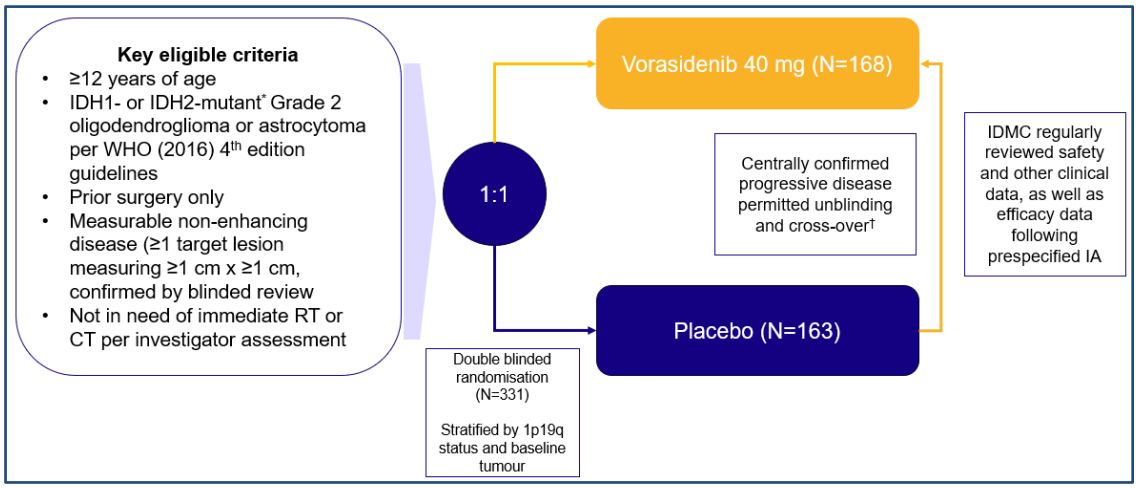
The trial followed a group sequential design with three prespecified analyses

- First interim analysis (IA1), for futility at approximately 55 events of progression or death
- Second interim analysis (IA2), for superiority or futility at approximately 123 events of progression or death
- Final analysis (FA) at approximately 164 events of progression or death
    - *Note:* Due to unblinding at IA2, there will be no FA data cut (see below)

As per protocol, the trial was unblinded after IA2 (data cutoff September 6, 2022) following recommendation of the data and safety monitoring committee based on early demonstration of efficacy by vorasidenib. After unblinding, patients on placebo were given the option of cross-over to vorasidenib.

IA2 is the final analysis due to early demonstration of efficacy and unblinding, therefore there will be no FA data cut.

Figure 5: INDIGO study design



Source: (Mellinghoff 2023b)[65]

Abbreviations: BIRC: blinded independent review committee; CT: chemotherapy; IDH: isocitrate dehydrogenase; IA: interim analysis; IDMC: independent data monitoring committee; RT: radiotherapy; WHO: World Health Organization

Note: *Centrally confirmed using an investigational clinical trial assay, based on the Oncomine Dx Target Test and developed in partnership with Thermo Fisher Scientific Inc. †Real-time single BIRC reader

Key Inclusion and Exclusion Criteria

The key inclusion and exclusion criteria have been described in Table 1. At the time of trial design, available guidelines recommended active surveillance for patients with IDH-mutant Grade 2 diffuse glioma with the aim of delaying the administration of RT/CT and associated toxicities. The INDIGO study recruited patients with residual or recurrent predominantly non-enhancing Grade 2 oligodendroglioma or astrocytoma, with an IDH1 or IDH2 mutation, who have undergone surgical intervention as their only treatment. Patients were excluded if they had received any other prior treatment, including systemic CT or RT, or if they were in immediate need of CT or RT in the opinion of the Investigator[65,66]

Table 8: Key inclusion and exclusion criteria

Key Inclusion Criteria	Key Exclusion Criteria
✓ ≥12 years of age ✓ Grade 2 oligodendroglioma or astrocytoma per WHO (2016) 4th edition criteria, not in need of immediate treatment and without high-risk features ✓ Centrally confirmed IHD1- or IDH2-mutant status ✓ ≥1 surgical intervention for glioma ≥1 year but ≤5 years from randomisation ✓ KPS ≥80% ✓ Centrally confirmed measurable non-enhancing disease evaluable by MRI	× Any prior anti-cancer therapy, other than surgery, for the treatment of glioma (e.g., systemic CT, RT, vaccines, glucocorticoids) × Presence of any features assessed by the investigator as indicating high risk (including uncontrolled seizures, brain-stem involvement, and clinically relevant functional or neurocognitive deficits caused by the tumour) and a heart-rate–corrected QT interval of at least 450 msec based on Fridericia's formula

✓ Tumours with minimal enhancement (i.e., non-nodular, non-measurable) ✓ Adequate hepatic and renal function	

Source: (Mellinghoff 2023b)[65]
Abbreviations: CT: chemotherapy; IHD: isocitrate dehydrogenase; KPS: Karnofsky performance scale; MRI: magnetic resonance imaging; RT: radiotherapy; WHO: World Health Organization

Study Endpoints

Based on recommendations from the FDA and CHMP, the key primary and secondary endpoints from the INDIGO trial were radiographic PFS and TTNI, respectively

Key Primary Endpoint

- **Radiographic PFS per BIRC:** defined as the time from randomisation to the first documented PD (as assessed on imaging by blinded independent review according to the modified RANO-LGG) or death from any cause, whichever occurred earlier

Key Secondary Endpoint

- **TTNI:** defined as the time from randomisation to the initiation of the first subsequent anticancer therapy (including vorasidenib, for patients in the placebo group who subsequently crossed over to receive vorasidenib) or death from any cause

Other secondary endpoints:

- **Tumour growth rate (TGR):** assessed by volume, defined as the percentage change in tumour volume every 6 months (determined on the basis of blinded independent review)
- **Objective response rate (ORR):** defined as a best overall response of complete response (CR), PR, or mR as determined on the basis of blinded independent review according to the modified RANO-LGG
- **Time to Response (TTR):** defined as the time from the date of randomisation to the date of first documented CR, PR, or mR per the modified RANO-LGG
- **Duration of response (DOR):** defined as the time from the date of first documented CR, PR, or mR to the earlier of the date of death due to any cause or first documented radiographic PD as assessed by the modified RANO-LGG
- **OS:** defined as the time from the date of randomisation to the date of death due to any cause
- **Safety and AE profiles:** Investigator assessed AEs, serious adverse events (SAEs), AEs leading to discontinuation or death, and severity of AEs as assessed by the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0. In addition, the Investigator assessed safety laboratory variables, vital signs, 12-lead electrocardiograms (ECGs), left ventricular ejection fraction (LVEF), Karnofsky Performance Scale (KPS), Lansky Play-Performance Scale (LPPS)
- **HRQoL Functional Assessment of Cancer Therapy-Brain (FACT-Br):** a 50-item measure comprising the following subscales: Physical Well-Being, Functional Well-Being, Emotional Well-Being, and Social Well-Being subscales from the FACT-General (FACT-G), with the addition of a 23- item brain tumour-specific subscale
- **PFS per the Investigator assessment:** as assessed by the Investigator using modified RANO-LGG

Exploratory endpoints:

- TGR before and after treatment with vorasidenib among subjects who cross-over from placebo to vorasidenib
- Neurocognitive function using a validated computerised battery of 5 neurocognitive performance outcome measures (EQ-5D-5L questionnaire)
- Data on seizure activity[66]

During study planning, Servier received divergent scientific advice from the FDA and CHMP regarding the primary endpoint and secondary endpoints. The FDA did not agree with the use of the novel endpoint TGR, as the primary endpoint and instead suggested radiographic PFS by BIRC using the modified RANO-LGG criteria. Based on the proposed 9-month median improvement in PFS by BIRC, and the ability to translate this to clinical benefit for the patient, the CHMP recommended use of TTNI (time to surgery, CT, or RT) as the primary endpoint and radiographic PFS by BIRC as the key secondary endpoint. The CHMP acknowledged the difficulty to define strict criteria to standardize the decision for intervention, which is a multifactorial decision, but considered that the subjectivity of TTNI as an endpoint is alleviated by the randomised, double-blind design of the study and this endpoint would be more relevant in terms of clinical relevance to patients.

The resolution of these divergent recommendations was as follows[66]:

- Proceed with radiographic PFS as the primary endpoint with revised statistical assumptions
- Elevate TTNI to a key secondary endpoint following a prespecified hierarchical testing strategy and the α-spending function
- Include TGR as a secondary endpoint

In the INDIGO study, radiographic progression was defined based on modified RANO-LGG; these modifications incorporated the following changes to the standard RANO-LGG criteria to minimise bias:

- BIRC reviewers had no access to clinical data (except date of surgery) or the Investigators assessments
- Clinical deterioration, a subjective measurement, was removed as an assessment criterion
- Steroid use for treatment of glioma (typically used to reduce the effect of symptomatic vasogenic oedema) was prohibited prior to enrolment and during the study[66]

<u>Tumour Growth Rate</u>

Following input from the FDA and CHMP, TGR was included as a secondary endpoint. Studies have demonstrated the correlation between TGR and survival in patients with glioma, thereby suggesting that TGR may be used as an early measure of clinical benefit, further shown in Appendix

A growing body of evidence supports a direct correlation between tumour volume and growth rate with OS and PFS, establishing these metrics as important predictive biomarkers

An array of studies on tumour size and growth in glioma have shown these measures are directly correlated with patient-relevant outcomes, including OS, establishing them as important predictive markers. While there is heterogeneity in the literature, consistency emerged regarding the prognostic significance of pre-surgical tumour size and growth as strong predictors of patient outcomes, particularly in IDH-mutant gliomas, influencing survival rates and symptom severity. Robust evidence indicates a

significant correlation between pre-surgical tumour volume and both OS and PFS, as well as mean time to progression.

Additionally, post-surgical tumour size or growth serves as a critical predictor of outcomes in IDH-mutant gliomas, significantly impacting survival, disease progression, and symptoms such as seizures. This is further supported by consistent correlations between residual tumour volume and OS/PFS. The timing of post-surgical measurements, particularly early assessments conducted within 48 hours, enhances prognostic accuracy. This underscores the critical role of residual tumour size as a prognostic tool.

TGR is a clinically significant predictor of OS and TTNI and may serve as an early indicator of clinical benefit

TVGR on MRI serves as an early indicator of clinical benefit during the active surveillance period. Increase in tumour volume corresponded to a more than 3-fold increase in the risk of death.[12] Additionally, in cases of Grade 2/3 gliomas, higher initial tumour volume and an increased annual tumour growth rate are associated with a higher likelihood of malignant transformation, emphasising the pivotal role of tumour volume in disease progression[67]. Another study determined that spontaneous velocity of diametric expansion was an independent prognostic factor for malignant PFS and OS (P<0.001) in patients with diffuse IDH-mutant glioma. The velocity of diametric expansion exhibited a linear relationship with OS[68].

Further studies providing supporting evidence of TGR as an early indicator of clinical benefit in glioma can be found in Table 6.

Table 9: Summary of studies providing supportive evidence of TGR as an early indicator of clinical benefit in glioma

Study	Author conclusions and key takeaways
(Bhatia 2024)	• Modelled TVGR per 6 months during active surveillance for patients with astrocytomas or oligodendrogliomas • Concluded that TVGR on MRI serves as an early indicator of clinical benefit during the active surveillance period. Increase in tumour volume corresponded to a more than 3-fold increase in the risk of death
(Rees 2009)	• All patients with IDH-mutant Grade 2/3 gliomas demonstrated progressive tumour growth • In cases of IDH-mutant Grade 2/3 gliomas, higher initial tumour volume and an increased annual tumour growth rate are associated with a higher likelihood of malignant transformation, emphasising the pivotal role of tumour volume in disease progression
(Pallud 2013)	• Spontaneous velocity of diametric expansion was an independent prognostic factor for malignant PFS and OS (P<0.001) in patients with diffuse IDH-mutant glioma. The velocity of diametric expansion exhibited a linear relationship with OS
(Leclerc 2024)	• In diffuse glioma without 1p19q codeletion, spontaneous radiographic TGR was higher in cases with a tumour volume ≥100 cm^3 (mean: 30.6; SD: 56.2 mm/year) than in cases with a tumour volume <100 cm^3 (mean: 14.4; SD: 32.2 mm/year; P=0.013) • The TGR of gliomas vary based on genetic mutations, malignancy grade, and microvascular proliferation. Faster tumour growth rates and higher mitotic counts were associated with worse patient outcomes, indicating the importance of these factors in assessing tumour aggressiveness and predicting survival in IDH-mutant diffuse gliomas
(Kros 2022)	• Mitotic count significantly influences PFS (P=0.0098) and marginally the OS (P=0.07) in IDH-mutant astrocytomas • The mitotic index is of prognostic significance in IDH-mutant astrocytomas without homozygous deletion CDKN2A/B. Therefore, the mitotic index may

	direct the therapeutic approach for patients with IDH-mutant astrocytomas with native CDKN2A/B status

Abbreviations: CDKN2A/B: Cyclin-Dependent Kinase Inhibitor 2A/B; CI: confidence interval; IDH: isocitrate dehydrogenase; MRI: magnetic resonance imaging; OS: overall survival; PFS: progression free survival; SD: standard deviation; TGR: tumour

Baseline Characteristics

The INDIGO study enrolled a total of 331 patients across 10 countries (with 58.3% of the patients from North America, 29.3% from Western Europe, and 12.4% from Israel) from February 2020 through February 2022, in a 1:1 randomisation, with 168 patients randomised to vorasidenib and 163 to placebo

The median age of the patients was 40.5 years in the vorasidenib group and 39 years in the placebo group. More than 50% of the patients in each group had a KPS score of 100. All patients had undergone brain tumour surgery previously, with 21.5% of patients having undergone two or more tumour surgeries before enrolment. The median interval between the last glioma surgery and randomisation was 2.4 years. The number of astrocytomas and oligodendrogliomas were similar in the two groups. Tumour size at baseline (determined on the basis of the longest diameter) was at least 2 cm in at least 80% of patients in each group. A summary of the demographics and baseline characteristics can be found in Table 2. At a median follow-up of 14.2 months, 226 patients (68.3%) were continuing to receive vorasidenib or placebo (Mellinghoff 2023b).

Table 10: Patient and tumour characteristics at baseline (Full Analysis Set)*

Characteristic	Vorasidenib (N=168)	Placebo (N=163)
Median age, years (range)	40.5 (21–71)	39 (16–65)
Age, n (%)		
16 or 17 years	0	1 (0.6)
18 to 39 years	76 (45.2)	87 (53.4)
40 to 64 years	90 (53.6)	74 (45.4)
≥65 years	2 (1.2)	1 (0.6)
Male sex, n (%)	101 (60.1)	86 (52.8)
Geographic region, n (%)		
North America	86 (51.2)	107 (65.6)
Western Europe	57 (33.9)	40 (24.5)
Israel	25 (14.9)	16 (9.8)
KPS, n (%)†		
100	90 (53.6)	87 (53.4)
90-80	77 (45.8)	76 (46.6)
Location of tumour at initial diagnosis, n (%)‡		
Frontal	107 (63.7)	115 (70.6)
Non-frontal	61 (36.3)	48 (29.4)
Time from initial diagnosis to randomisation, years		
Mean (SD)	3.3 (2.4)	3.1 (2.5)

Characteristic	Vorasidenib (N=168)	Placebo (N=163)
Median (range)	2.9 (1.0–19.5)	2.5 (0.9–19.2)
Number of previous surgeries for glioma, n (%)		
1	126 (75.0)	134 (82.2)
≥2	42 (25.0)	29 (17.8)
Time from last surgery for glioma to randomisation, years§		
Mean (SD)	2.7 (1.1)	2.6 (1.3)
Median (range)	2.5 (0.2–5.2)	2.2 (0.9–5.0)
Histologic subtype, n (%)		
Oligodendroglioma	88 (52.4)	84 (51.5)
Astrocytoma	80 (47.6)	79 (48.5)
IDH mutation status, n (%)		
IDH1-positive[4]	163 (97.0)	152 (93.3)
IDH2-positive	5 (3.0)	11 (6.7)
Chromosome 1p/19q codeletion status, n (%)‖		
Codeleted	88 (52.4)	84 (51.5)
Non-codeleted	80 (47.6)	79 (48.5)
Longest diameter of tumour, n (%)¶		
≥2 cm	139 (82.7)	137 (84.0)
<2 cm	29 (17.3)	26 (16.0)

Source: (Mellinghoff 2023b)[65]
Abbreviations: IHD: isocitrate dehydrogenase; KPS: Karnofsky performance-status score; no.: number; SD: standard deviation
Note: *The full analysis set included all the patients who had undergone randomisation. Percentages may not total 100 because of rounding; †KPS ranged from 0 to 100, with lower scores indicating greater disability. One patient (0.6%) in the vorasidenib group met the eligibility criteria (score of ≥80) during screening but had a score of 70 on day 1 of the first cycle; ‡Frontal tumour location included frontal, frontoparietal, and frontotemporal locations, and non-frontal tumour location included all other locations; §One patient in the vorasidenib group underwent biopsy during prescreening to obtain tumour tissue for testing of IDH mutation status, which was allowed by the protocol; ‖Two patients in the placebo group had CDKN2A homozygous deletion; ¶Data are reported on the basis of the electronic case-report forms, rather than from information in the interactive Web response system

Planned Analysis by Stratification Factors and Subgroups

Subgroup analyses were planned around two stratification factors and six demographic subgroups

Randomisation was stratified by local 1p19q status (co-deleted or not codeleted) and baseline tumour size per local assessment (longest diameter of ≥2 cm or <2 cm). The INDIGO trial also planned for several subgroup analyses (Table 6).

Table 11: Planned stratification factors and subgroup analyses in the INDIGO trial

Randomisation by stratification factors	• Chromosome 1p/19q codeletion status (codeleted or non-codeleted) • Longest tumour diameter at baseline ≥2 cm or <2 cm)
Pre-planned subgroups	• Age (<16, 16 or 17 years, 18 to 39, 40 to 64, ≥65) • Sex (male, female) • Geographic region (North America, West Europe, rest of the world) • Location of tumour at initial diagnosis (frontal, non-frontal) • Number of previous surgeries for glioma (1, ≥2) • Time from last surgery for glioma to randomization (<2 years, 2- <4 years, ≥4 years) • Chromosome 1p/19q codeletion status (codeleted or non-codeleted) • Longest tumour diameter at baseline ≥2 cm or <2 cm)

Source: (Servier 2023)[66]
Abbreviations: IDH: isocitrate dehydrogenase

2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

Approximately 340 subjects were to be randomized to the treatment arms using a 1:1 randomization, stratified by chromosome 1p19q co-deletion status (co-deleted or not codeleted) and baseline tumour size per local assessment (longest diameter of ≥2 cm or <2 cm).

For the primary endpoint, a total of 164 PFS events were required to have at least 90% power to detect a hazard ratio (HR) of 0.6 using a 1-sided log-rank test stratified by the randomization stratification factors at a significance level of 0.025, and a 3-look group sequential design with a Gamma family (-24) α-spending function to determine the efficacy boundaries and a Gamma family (-5) β-spending function to determine the nonbinding futility boundary.

For TTNI, a total of 152 TTNI events were required to have approximately 80% power to detect an HR of 0.636 using a 1-sided log-rank test stratified by the randomization stratification factors at a significance level of 0.025, and a 2-look group sequential design with a Gamma family (-22) α-spending function to determine the efficacy boundaries. To preserve the overall type I error in the study, the fixed sequence testing procedure (Westfall PH and Krishen A 2001) was followed; TTNI was to be tested only if PFS reached statistical significance (at the time of IA2 for PFS or FA for PFS).

The sample size for the study was determined based on the following assumptions.

• Based on a retrospective natural history study on which the Sponsor collaborated in patients with Grade 2 and Grade 3 predominantly non-enhancing IDH mutation positive glioma, the median time from surgery to next intervention was approximately 24 months (Huang R et al. 2017). Given the requirement of at least 1 year from the most recent surgery for eligibility, the median PFS for subjects

in the placebo arm was assumed to be 18 months and the median PFS for subjects in the vorasidenib arm was assumed to be 30 months; this corresponds to an HR of 0.6 under the exponential model assumption.

• Assuming TTNI to be equal to PFS plus an additional 3 months to accommodate any required washout periods for subsequent anticancer therapy and to prepare for subsequent anticancer therapy, the median TTNI for subjects in the placebo arm was estimated to be 21 (18+3) months, and the median TTNI for subjects in the vorasidenib arm was estimated to be 33 (30+3) months; this corresponds to an HR of 0.636 under the exponential model assumption.

• PFS and TTNI dropout rates of approximately 10% at 12 months

• Non-uniform recruitment period of approximately 42 months.

Two interim analyses and the FA for PFS based on the FAS were planned. The first interim analysis was for futility only at the time when approximately 55 PFS events (33.5% of the expected 164 events) had occurred; the second interim analysis (IA2) tested for superiority and futility when approximately 123 PFS events (75% of the expected 164 events) had occurred, and all subjects had been randomized in the study. The FA was planned at the time when 164 PFS events have occurred, and all subjects have been randomized in the study. The study will have met its primary objective if PFS is statistically significant at the time of the IA2 or FA at the corresponding α-level per the α-spending strategy. The data cutoff for the final PFS analysis occurred after all subjects had been randomized following protocol version 4.0 (20 July 2021) and the target number of PFS events had been reached.[66]

Table 12: Analysis Sets[66]

Analysis Set	Description	Endpoints
Full Analysis Set (FAS)	Included all subjects randomized. Subjects were classified according to the randomized treatment arm according to the ITT principle.	Demographic and other baseline characteristics, disposition, major protocol deviations, subsequent therapies, and efficacy.
Per Protocol Set (PPS)	A subset of FAS. Subjects who met any of the following criteria were excluded from the PPS: • Did not receive at least 1 dose of the randomized treatment • Did not have any measurable lesions at baseline as assessed by the BIRC per modified RANO-LGG • Did not have histopathologically diagnosed Grade 2 oligodendroglioma or astrocytoma per WHO 2016 criteria (ie, do not meet Inclusion Criterion #3). • Had had any prior anticancer therapy other than surgery (biopsy, subtotal resection, gross-total resection) for treatment of glioma including systemic chemotherapy, radiotherapy, vaccines, small-molecules, IDH inhibitors, investigational agents, etc. (ie, met Exclusion Criterion #1).	PFS and TTNI
Safety Analysis Set (SAS)	Include all subjects who received at least 1 dose of the study treatment. Subjects were classified according to the treatment received; subjects randomized to placebo who received at least one dose of vorasidenib prior to crossover, were classified to the vorasidenib arm.	Exposure and concomitant therapies, and safety

Critical appraisal of the relevant clinical effectiveness evidence

Table 13: Results of quality assessment by NICE STA template

Criteria	INDIGO (NCT04164901) Mellinghoff (2023b)[25]
Was randomization carried out appropriately?	Low risk
Was the concealment of treatment allocation adequate?	Low risk
Were the groups similar at the outset of the study in terms of prognostic factors?	Low risk
Were the care providers, participants and outcome assessors blind to treatment allocation?	Low risk
Were there any unexpected imbalances in dropouts between groups?	Low risk
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Low risk
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Low risk

Low risk Unclear

Clinical effectiveness results of the relevant studies

Key Primary Endpoint: Progression-Free Survival

The assessment of radiographic PFS in the INDIGO trial primarily relied on the modified RANO-LGG criteria. This standardised framework is based on the RANO-LGG criteria and enabled the evaluation of treatment response. In the INDIGO trial PFS was defined as the time from date of randomisation to

date of first documented radiographic PD (as assessed per the BIRC per modified RANO-LGG) or date of death due to any cause, whichever occurred earlier.

Imaging-based PFS (met at IA2 due to early demonstration of efficacy), assessed by blinded independent review occurred in 135 of 331 patients: in 47 of 168 patients (28.0%) in the vorasidenib group and in 88 of 163 patients (54.0%) in the placebo group. The median follow-up duration was 13.7 (95% CI: 11.2, 14.1) months and 14.1 (95% CI: 11.1, 15.2) months in the vorasidenib and placebo arms, respectively.

PFS per the BIRC was significantly improved in the vorasidenib arm compared with the placebo arm with an HR of 0.39 (95% CI: 0.27, 0.56; P=0.000000067) (Table 11). The mPFS was increased by 16.6 months with vorasidenib: with an mPFS of 27.7 (95% CI: 17.0, NE) months for the vorasidenib arm and 11.1 (95% CI, 11.0, 13.7) months for the placebo arm (Figure 5). All events were PD, and there were no death events in either arm.

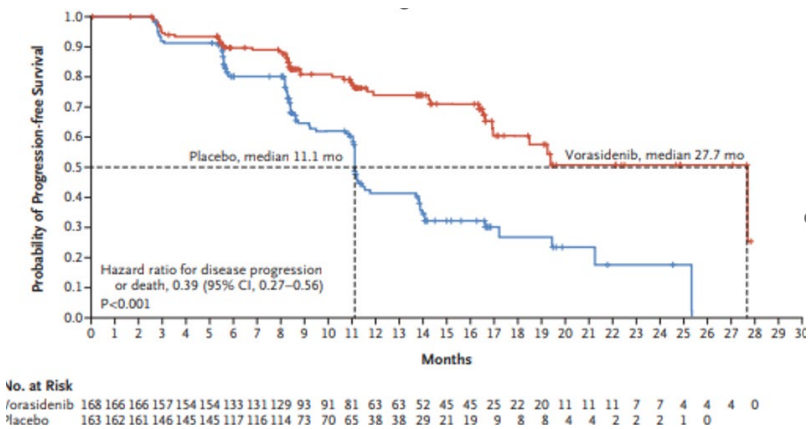
Investigator-assessed PFS by modified RANO-LGG which offers an objective method for assessing PD and treatment response was analysed as a secondary endpoint. This analysis yielded consistent results to those of primary analysis of PFS per BIRC, reporting improved PFS with vorasidenib compared to placebo.

Table 14: PFS per the BIRC (FAS), data cutoff date: 06 September 2022

PFS*	Vorasidenib (N=168)	Placebo (N=163)
Number of events, n (%)	47 (28.0)	88 (54.0)
PD	47 (28.0)	88 (54.0)
Death	0	0
HR (95% CI) †	0.39 (0.27, 0.56)	
P-value ‡	0.000000067	

Source: (Mellinghoff 2023b) (Table S1: supplementary material)[65]
Abbreviations: BIRC: Blinded Independent Review Committee; CI: confidence interval; FAS: Full Analysis Set; HR: hazard ratio; PD: progressive disease; PFS: progression free survival
Note: *PFS = (date of event or censoring – randomisation date + 1) / 30.4375; †HR was calculated from the Cox regression model stratified by the randomisation strata with placebo as the denominator, with two-sided 95% CIs; ‡P-value was calculated from the one-sided log-rank test stratified by the randomisation factors (chromosome 1p19q co-deletion status and tumour size at baseline per local assessment per interactive web response system)

Figure 6: Kaplan-Meier plot for PFS per the BIRC (FAS), data cutoff date: 06 September 2022



Source: (Mellinghoff 2023b)[65]
Abbreviations: BIRC: Blinded Independent Review Committee; CI: confidence interval; FAS: Full Analysis Set; PFS: progression free survival
Note: PFS based on the BIRC refers to death or documented radiographic PD as assessed by the BIRC per modified RANO-LGG. Tick marks indicate censored data

Ad-hoc Analysis (6 Months Follow-up) PFS Results

Vorasidenib continued to demonstrate a clinically meaningful improvement in imaging-based PFS reducing the risk of disease progression compared to placebo at follow up analysis

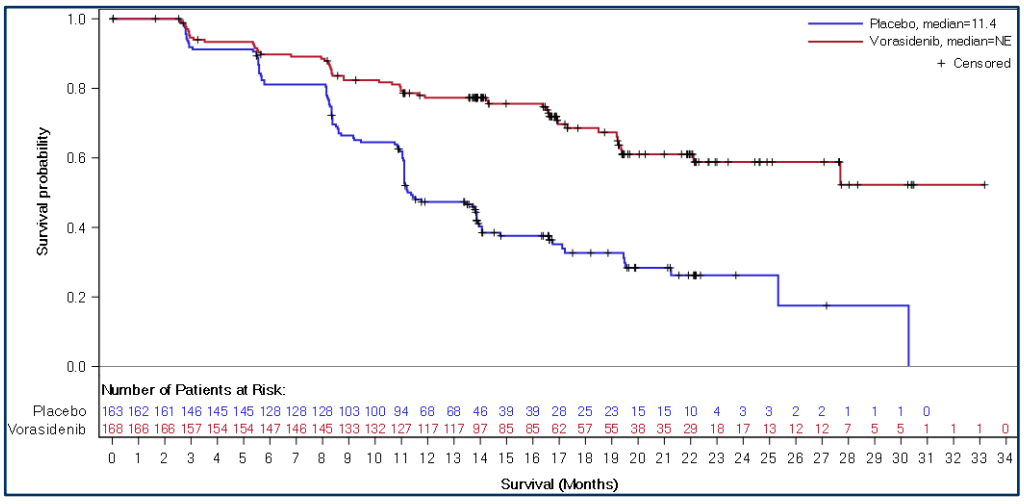
PFS per the BIRC was significantly improved in the vorasidenib arm compared with the placebo arm with an HR of 0.35 (95% CI: 0.25, 0.49; P=0.00000000013) (Table 12). The mPFS was not estimable (NE; 95% CI: 22.1, NE) with vorasidenib and 11.4 (95% CI: 11.1, 13.9) months for the placebo arm (Figure 6). All events were PD, and there were no death events in either arm[69] At 24 months, the PFS rate was 58.8% (95% CI: 48.4, 67.8) in the vorasidenib arm and 26.2% (17.9, 35.3) in the placebo arm.

Table 15: PFS per the BIRC (FAS), data cut-off date: 07 March 2023 (ad-hoc analysis)

PFS*	Vorasidenib (N=168)	Placebo (N=163)
Number of events, n (%)	54 (32.1)	104 (63.8)
PD	54 (32.0)	104 (54.0)
Death	0	0
HR (95% CI) †	0.34 (0.23, 0.50)	
P-value ‡	0.00000000013	

Source: (Servier 2024b) [69](supplementary material)
Abbreviations: BIRC: Blinded Independent Review Committee; CI: confidence interval; FAS: Full Analysis Set; HR: hazard ratio; PD: progressive disease; PFS: progression free survival
Note: *PFS = (date of event or censoring – randomisation date + 1) / 30.4375; †HR was calculated from the Cox regression model stratified by the randomisation strata with placebo as the denominator, with two-sided 95% CIs; ‡P-value was calculated from the one-sided log-rank test stratified by the randomisation factors (chromosome 1p19q co-deletion status and tumour size at baseline per local assessment per interactive web response system)

Figure 7: Kaplan-Meier plot for PFS per the BIRC (FAS), data cut-off date: 07 March 2023 (ad-hoc analysis)



Source: (Servier 2024b)[69]
Abbreviations: BIRC: Blinded Independent Review Committee; CI: confidence interval; FAS: Full Analysis Set; PFS: progression free survival

Note: PFS based on the BIRC refers to death or documented radiographic PD as assessed by the BIRC per modified RANO-LGG. Tick marks indicate censored data

Key Secondary Endpoint: Time to Next Intervention

Vorasidenib significantly delayed the initiation of subsequent anticancer therapy compared to placebo with around 80% patients not reaching the next intervention

The observed benefit of vorasidenib was further supported by a delay in the initiation of subsequent anticancer therapy, as demonstrated by the TTNI (met at IA2), which was statistically significantly improved in the vorasidenib arm compared with the placebo arm (HR=0.26, 95% CI: 0.15, 0.43; P=0.000000019) (Table 13). The likelihood of not receiving next intervention by 18 months was 85.6% (95% CI: 77.8-90.8) in the vorasidenib group, as compared with 47.4% (95% CI: 35.8, 58.2) in the placebo group; by 24 months, the likelihood of not receiving next intervention was 83.4% (95% CI: 74.0, 89.6) and 27.0% (95% CI: 7.9, 50.8), respectively (Figure 7)

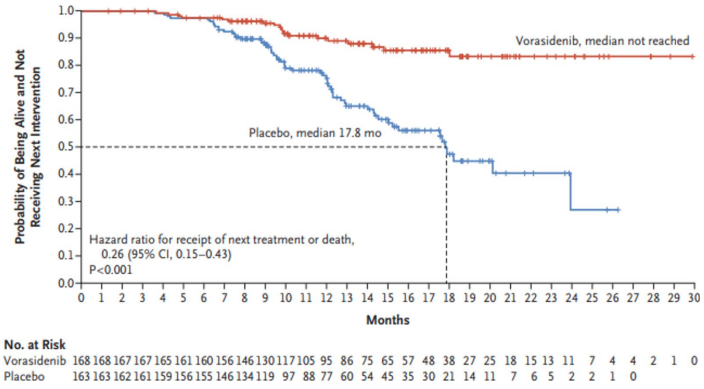
Out of the total cohort of 331 patients, 77 individuals received additional anticancer treatments after discontinuing their initial treatment. Specifically, within the placebo group comprising 163 patients, 58 individuals (35.6%) underwent further anticancer interventions, such as crossing over to vorasidenib (52 patients out of 58 who received another treatment, 90.7%), surgery, CT, or RT. Within the vorasidenib group consisting of 168 patients, 19 individuals (11.3%) received subsequent anticancer therapies, including surgery or chemotherapy/radiotherapy.

Table 16: Summary of TTNI (FAS), data cutoff date: 06 September 2022

TTNI*	Vorasidenib (N=168)	Placebo (N=163)
Number of events, n (%)	19 (11.3)	58 (35.6)
Received subsequent anticancer therapy (excluding cross-over)	19 (11.3)	6 (3.7)
Cross-over to vorasidenib	-	52 (31.9)
Death	0	0
HR (95% CI)†	0.26 (0.15, 0.43)	
P-value ‡	0.000000019	

Source: (Mellinghoff 2023b) (Table S2: supplementary material) [65]
Abbreviations: CI: confidence interval; FAS: full analysis set; HR hazard ratio; TTNI: time to next intervention
Note: *TTNI = (date of event or censoring – randomisation date + 1) / 30.4375; †HR was calculated from the Cox regression model stratified by the randomisation strata with placebo as the denominator, with two-sided 95% CIs; ‡P-value was calculated from the one-sided log-rank test stratified by the randomisation factors (chromosome 1p19q co-deletion status and tumour size at Baseline per local assessment per interactive web response system)

Figure 8: Kaplan-Meier plot for TTNI (FAS), data cutoff date: 06 September 2022



Source: (Mellinghoff 2023b)[65]
Abbreviations: CI: confidence interval; FAS: full analysis set; mo: months; P: probability; TTNI: time to next intervention
Note: Tick marks indicate censored data

Ad-hoc Analysis (6 Months Follow-up) TTNI Results

Vorasidenib continued to significantly delay the initiation of subsequent anticancer therapy compared to placebo at 24 months post-treatment initiation

With additional follow-up (March 2023), the number of TTNI events increased from 19 to 28 in the vorasidenib arm and from 58 to 78 in the placebo arm.[69]

TTNI was improved in the vorasidenib arm compared with that in the placebo arm, with an HR of 0.25 (95% CI: 0.16, 0.40; P=0.000000000048) (Figure 8)[69]. Median TTNI was NE (95% CI: NE, NE) in the vorasidenib arm and was 20.1 (95% CI: 17.5, 27.1) months in the placebo arm.

Out of the total cohort of 331 patients, 103 individuals received additional anticancer treatments after discontinuing their initial treatment. Specifically, within the placebo group comprising 163 patients, 78 individuals (47.9%) underwent further anticancer interventions, including crossing over to vorasidenib (70 patients out of 78 who received another treatment, 89.7%), surgery, CT, or RT. At 24 months, the likelihood of being alive and not receiving a next intervention was 80.3% (95% CI: 71.6, 86.6) in the vorasidenib arm and 41.4% (31.0, 51.5) in the placebo arm. This further demonstrates the delayed TTNI and efficacy of vorasidenib[69].

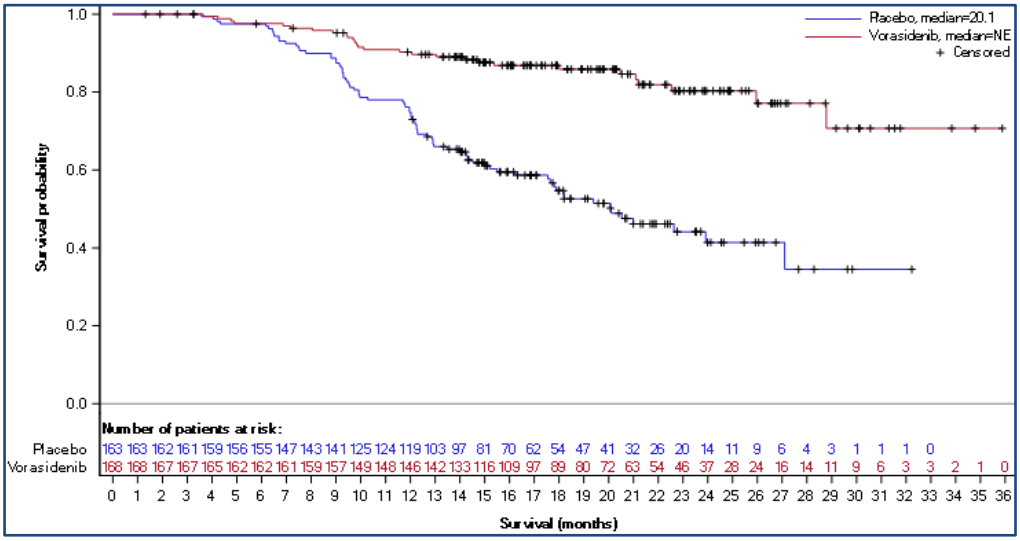
Table 17: Summary of TTNI (FAS), data cut-off date: 07 March 2023 (ad-hoc analysis)

TTNI*	Vorasidenib (N=168)	Placebo (N=163)
Number of events, n (%)	28 (16.7)	78 (47.9)
Received subsequent anticancer therapy (excluding cross-over)	28 (16.7)	8 (4.9)
Cross-over to vorasidenib	-	70 (42.9)
Death	0	0
HR (95% CI)†	0.25 (0.16, 0.40)	
P-value ‡	0.000000000048)	

Source: (Servier 2024b)[69] (supplementary material)
Abbreviations: CI: confidence interval; FAS: full analysis set; HR hazard ratio; TTNI: time to next intervention
Note: *TTNI = (date of event or censoring – randomisation date + 1) / 30.4375; †HR was calculated from the Cox regression model stratified by the randomisation strata with placebo as the denominator, with two-sided 95% CIs; ‡P-value was calculated

from the one-sided log-rank test stratified by the randomisation factors (chromosome 1p19q co-deletion status and tumour size at Baseline per local assessment per interactive web response system)

Figure 9: Kaplan-Meier plot for TTNI (FAS), data cut-off date: 07 March 2023 (ad-hoc analysis)



Source: (Servier 2024b) [69](supplementary material)
Abbreviations: CI: confidence interval; FAS: full analysis set; mo: months; P: probability; TTNI: time to next intervention
Note: Tick marks indicate censored data

Tumour Growth Rate

Patients who received vorasidenib demonstrated a reduction in tumour volume, as indicated through tumour shrinkage, compared to patients on placebo who showed continuous tumour growth.

In the primary analysis (IA2; data cut-off date: 06 September 2022) there was post-treatment reduction in tumour volume, as demonstrated though tumour shrinkage, in patients randomised to vorasidenib by a mean of 2.5% every 6 months (95% CI: -4.7%, -0.2%), while tumour volume increased, indicated by to tumour growth, by a mean of 13.9% every 6 months for the placebo arm (95% CI: 11.1%, 16.8%)[66] The mean percentage change in tumour volume over time suggests that vorasidenib induced tumour shrinkage, while aggregate data from subjects on placebo showed continuous tumour growth.

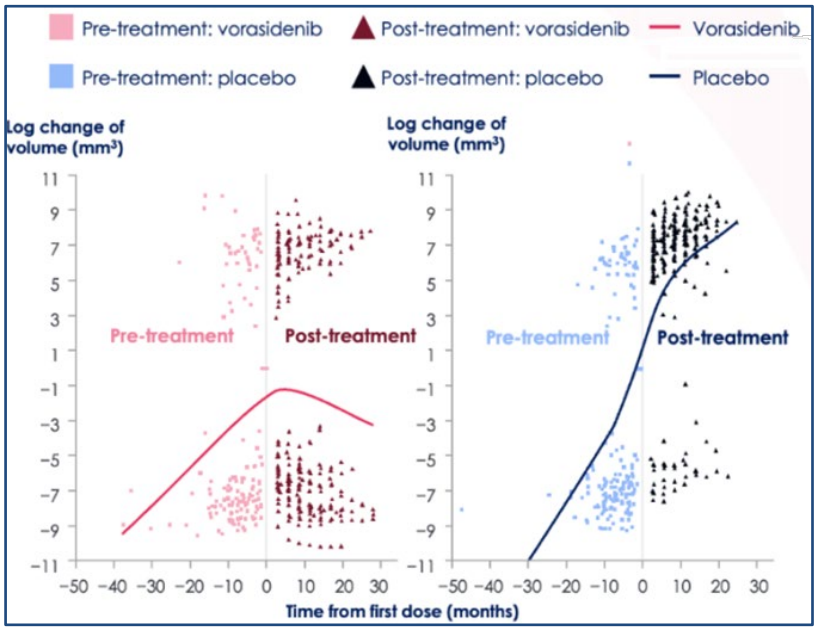
Patients who crossed over from placebo to vorasidenib following disease progression demonstrated a clinically meaningful decrease in TGR

As of September 6, 2022 (IA2), six subjects in the placebo arm initiated alternative therapy and did not crossover to vorasidenib, indicating that the treating physician selected alternative therapies rather than crossover when clinically indicated[66]

Given the limited treatment options for IDH-mutant glioma and based on feedback from experts, investigators, and patients, the option of cross-over to vorasidenib was included for patients on placebo following imaging-based disease progression as confirmed by BIRC. The cross-over process ensured that the investigator was not permitted to prematurely unblind their patients to allow for cross-over and limited the bias in determining the need for another intervention. Thus, the option to cross over did not prevent patients from accessing alternative therapies when needed, but rather presented a clinical trial option to patients for whom the benefit-risk assessment of alternative therapies was not yet favourable.

As an exploratory endpoint, TGR was measured before and after treatment with vorasidenib and placebo (IA2; data cut-off date: 06 September 2022). Patients were included in the pre- and post-treatment TGR analysis if they had at least one MRI record during the corresponding period. Patients were also included in the pre- and post-cross-over TGR analysis if they had at least one MRI record during the corresponding period[66]. The pre- and post-treatment TGR was 13.2% (95% CI: 10.3, 16.3) and -3.3% (95% CI: -5.2, -1.2), respectively, in patients randomised to vorasidenib and was 18.3% (95% CI: 15.0, 21.7) and 12.2% (95% CI: 9.5, 14.9), respectively, in patients randomised to placebo (Figure 10). Further, in patients who crossed over from placebo with available MRIs (n=38), TGR before and after cross-over was 22.4% (95% CI: 15.7, 29.4) and 5.2% (95% CI: -3.8, 15.0), respectively[66].

Figure 10: Change in tumour volume from pre-treatment to post-treatment for patients who received vorasidenib or placebo (exploratory analysis), data cut-off date: 06 September 2022 (primary analysis)



Source: Data on file
Abbreviations: TGR: tumour growth rate
Note: Includes subset of patients (n=56 for vorasidenib and n=67 for placebo) having available imaging data (up to three historical scans prior to inclusion in INDIGO study)

Objective Response (Best Overall Response)

ORR was higher for subjects receiving vorasidenib than those who received placebo

Objective response was defined as a best overall response (BOR) of CR, PR, or mR as assessed by the Investigator and by the BIRC per modified RANO-LGG criteria. The criteria assessed the sum of perpendicular diameters, excluding enhancement. CR indicates complete disappearance, PR is a reduction of 50% or more compared to baseline, while MR is a decrease ranging between 25% and 50% relative to baseline[70].

As per the primary analysis (IA2; data cut-off date: 06 September 2022) patients randomised to vorasidenib showed an ORR of 10.7% (95% CI: 6.5, 16.4) while those randomised to placebo showed an ORR of 2.5% (95% CI: 0.7, 6.2). Further, the odds ratio for ORR was 4.88 (95% CI:1.56, 15.25; P=0.003) (Table 13)[65,66]

Table 18: Best OR based on radiographic response per modified RANO-LGG by BIRC, data cut-off date: 06 September 2022 (primary analysis)

	Vorasidenib (N=168)	Placebo (N=163)
Best overall response, n (%)*		
Complete response	0	0
Partial response	2 (1.2)	0
Minor response	16 (9.5)	4 (2.5)
Stable disease	139 (82.7)	144 (88.3)
PD	10 (6.0)	14 (8.6)
Objective response rate, n (%)	18 (10.7)	4 (2.5)
Odds ratio (95% CI)	4.88 (1.56 to 15.25)	

Source: (Mellinghoff 2023b) (Table S4: supplementary material)
Abbreviations: BIRC: blinded independent review committee; CI: confidence interval; RANO-LGG: Response Assessment for Neuro-oncology for Low-Grade Gliomas; PD: progressive disease
Note: *One patient in the vorasidenib arm and one patient in the placebo arm were not evaluable as no post-baseline assessment was available

Ad-hoc Analysis Objective Response:

Objective response as assessed by the BIRC continued to favour the vorasidenib arm in the ad-hoc analysis (data cut-off date: 07 March 2023) with an ORR of 11.9% (95% CI, 7.4%, 17.8%), including 2 PRs and 18 mRs by the BIRC. An ORR of 2.5% (95% CI,0.7%, 6.2%) was reported in the placebo arm, with no reported PRs. The odds ratio for ORR was 5.45 (95% CI, 1.77, 16.78)[69]

Duration of Response

Subjects receiving vorasidenib showed durable response to treatment

DoR was defined as the time from the date of first documented CR, PR, or mR to the earlier of the date of death due to any cause or first documented radiographic PD as assessed by the Investigator and by the BIRC per modified RANO-LGG. The median duration of response by BIRC was 16.6 months (95% CI: 2.8, 16.6) in the vorasidenib group (duration of response was not evaluable in the placebo group)[66]

Time to Response

TTR was defined as the time from the date of randomisation to the date of first documented CR, PR, or mR for responders as assessed by the Investigator and by the BIRC per modified RANO-LGG. The median TTR per the BIRC was 11.0 (range: 3 to 17) months in the vorasidenib arm, and 6.9 (range: 3 to 11) months in the placebo arm. Results were consistent for TTR as assessed by the Investigator[69]

Investigator-Assessed PFS

As a secondary endpoint, a prespecified analysis of imaging-based PFS based on Investigator assessment was conducted before and after treatment with vorasidenib and placebo. PFS by the investigators yielded consistent results to those of primary analysis of PFS per BIRC with PFS improved with vorasidenib compared to placebo in the final (IA2) and the ad-hoc analysis.

Primary Analysis (IA2) Investigator-Assessed PFS results:

In the final analysis (06 September 2022), PFS by the investigators yielded consistent results to those of primary analysis of PFS per BIRC (section 0) with PFS improved with vorasidenib compared to placebo (HR=0.34, 95% CI: 0.23, 0.50, P=0.000000243) [65]. This improvement in PFS was consistent across all subgroups analysed[65] . The median PFS was NE (95% CI: 25.8, NE) for the vorasidenib arm and was 16.6 (95% CI: 13.9, 20.3) months for the placebo arm. At 24 months, the PFS rate was 71.8% (95% CI: 62.5, 79.3) in the vorasidenib arm and 29.8% (19.1, 41.3) in the placebo arm[66].

Ad-hoc Analysis Investigator-Assessed PFS:

In the ad-hoc analysis, PFS by the investigators yielded consistent results to those of primary analysis of PFS per BIRC with PFS improved with vorasidenib compared to placebo (HR=0.34, 95% CI: 0.23, 0.50;based on longer follow up (7 March 2023)[69]. The median PFS was NE (95% CI: 25.8, NE) for the vorasidenib arm and was 16.6 (95% CI: 13.9, 20.3) months for the placebo arm. At 24 months, the PFS rate was 71.8% (95% CI: 62.5, 79.3) in the vorasidenib arm and 29.8% (19.1, 41.3) in the placebo arm (Servier 2024b). Overall, the agreement between investigator-assessed and imaging-based mPFS was 84.0% (vorasidenib arm) vs. 77.3% (placebo arm)[69].

Health Related Quality of Life

In addition to the delayed disease progression and TTNI, vorasidenib was able to maintain patient HRQoL

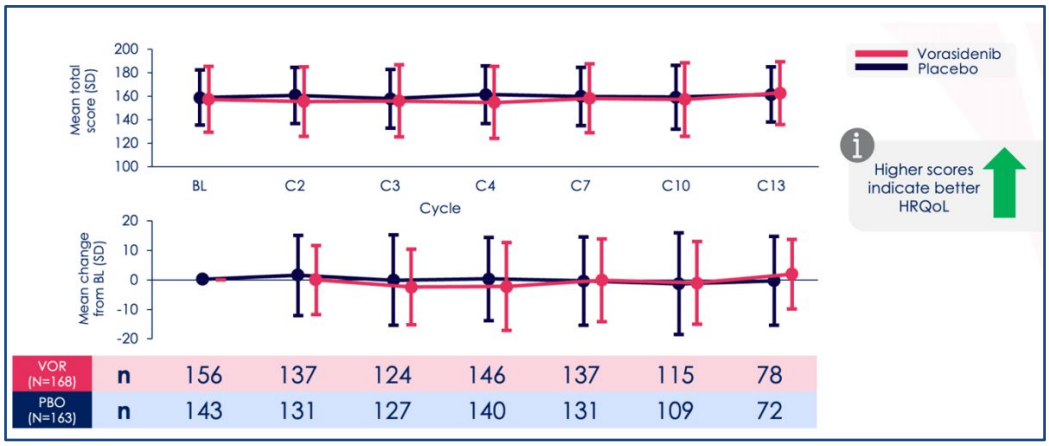
Analysis of the FACT-Br total score and subscale scores focused on time points up to and including Cycle 13, aligned with the median follow-up for the primary PFS endpoint and for which data were available for >40% of the FAS for each arm[66]

At baseline, there were no significant differences in FACT-Br scores between the two treatment arms. Until Cycle 13, there was no significant decline observed in FACT-Br total score or subscale scores in either the vorasidenib or placebo groups. Analysis using the Mixed-Effects Model Repeated Measures (MMRM) indicated no notable differences in FACT-Br scores between the two groups, including the total score, physical well-being, and brain cancer subscales. By Cycle 13, the FACT-Br total score for patients receiving vorasidenib was 163.3 (SD: 25.05), while for those on placebo, it was 161.4 (SD: 23.60). This indicates that patients maintained their HRQoL over the first 13 months despite active treatment with vorasidenib compared to placebo. Beyond Cycle 13, the percentage of participants contributing data decreased in both arms (max 23.3% placebo, 37.5% vorasidenib by Cycle 16), limiting the interpretability of results

The EQ-5D-5L descriptive analysis (exploratory endpoint) revealed similar findings with consistent EQ-5D-5L scores between both treatment arms (further detailed under exploratory endpoints below).

These results were consistent with longer follow up (7 March 2023) ad-hoc analysis, demonstrating the long term ability to control disease and maintain QoL in this population[69]

Figure 11: Patient HRQoL measured by the FACT-Br questionnaire



Source: Internal Servier document
Abbreviations: BL: baseline; C: cycle; FACT-BR: Functional Assessment of Cancer Therapy – Brain; HRQoL: Health related quality of life; PBO: placebo; SD: standard deviation; VOR: vorasidenib

Exploratory Endpoints

Seizure activity:

Seizures are a significant determinant of HRQoL for patients with IDH-mutant glioma and the rate of seizures were comparable across treatment arms

Exploratory analysis of seizure activity reported that 20 patients in each arm reported having had at least one seizure in the previous 30 days prior to the start of study treatment, with a median number of seizures of 2.5 in the placebo arm and 1.5 in the vorasidenib arm[66]. Up to and including Cycle 13, a reduction in the number of subjects reporting at least one seizure compared to baseline was observed at some cycles in each arm. A similar number of patients were reporting at least one seizure per cycle between treatment arms: 8-24 for vorasidenib vs. 10-24 for placebo. There was no clinically meaningful improvement or worsening of seizure activity in the vorasidenib arm relative to placebo. Given the relatively long median survival of patients with IDH-mutant diffuse gliomas seizures are a significant determinant of a patients' QoL and, overall, the rates of seizures were comparable across treatment arms.

As presented at SNO 2024, the frequency and rate of seizures per person-year on treatment was evaluated in the March 7, 2023 DCO[71] (Table 19). The seizure rate in the vorasidenib group was 64% lower compared to the placebo group suggesting vorasidenib was associated with better seizure control in patients who have seizure activity. The ratio of rates for vorasidenib versus placebo (95% CI) was equal to 0.36 (95% CI, 0.14 to 0.89; P= 0.0263).

Table 19: Seizure activity over treatment period using negative binomial model (FAS of subjects with at least 1 seizure; March 7, 2023, DCO)

	Vorasidenib (N=54)	Placebo (N=56)
Total number of seizure events on treatment	1541	5124
Rate of seizures per person-year on treatment (95% CI)	18.2 (8.4, 39.5)	51.2 (22.9, 114.8)
Ratio of rates vorasidenib vs placebo (95% CI	0.36 (0.14, 0.89)	
Two sided P-value	0.0263	

Abbreviations: CI = confidence interval; DCO = data cutoff; FAS = full analysis set

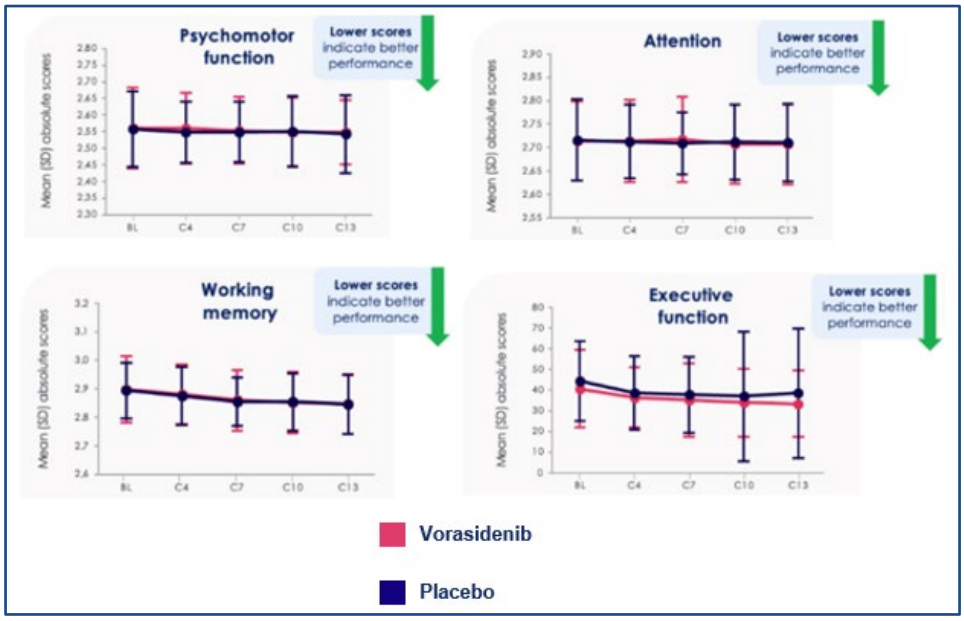
Source: Mellinghoff et al. (2024)[71]

Neurocognitive Function:

Treatment with vorasidenib was associated with preservation of neurocognition, including psychomotor function, attention, working memory, and executive function

Qualitative analysis of the exploratory endpoint showed minor improvements in executive function and verbal learning, inconsistent trends in psychomotor function and attention, and ongoing working memory enhancement up to Cycle 13 for patients receiving vorasidenib (Figure 12)[66].

Figure 12: Results for neurocognitive outcomes assessed in INDIGO trial (psychomotor function, attention, working memory, and executive function)



Source: (Servier 2023) and Data on file
Abbreviations: BL: baseline; C: cycle; SD: standard deviation

EQ-5D-5L:

At baseline, the proportions of patients reporting no problems across mobility, self-care, usual activity, pain/discomfort, and anxiety and depression were consistent between treatment arms. The proportion of patients reporting no problems, some problems, and extreme problems across the EQ-5D-5L questionnaire were consistent between arms on treatment. Although decreases in EQ-VAS scores occurred at individual time points for both arms, none reached the 7-point general response change threshold

2.5 Subsequent treatments used in the relevant studies

Considering vorasidenib's outcomes in terms of PFS and TTNI, for which very few events were observed during the INDIGO trial, it is expected that subsequent treatment lines and their associated costs will be delayed.

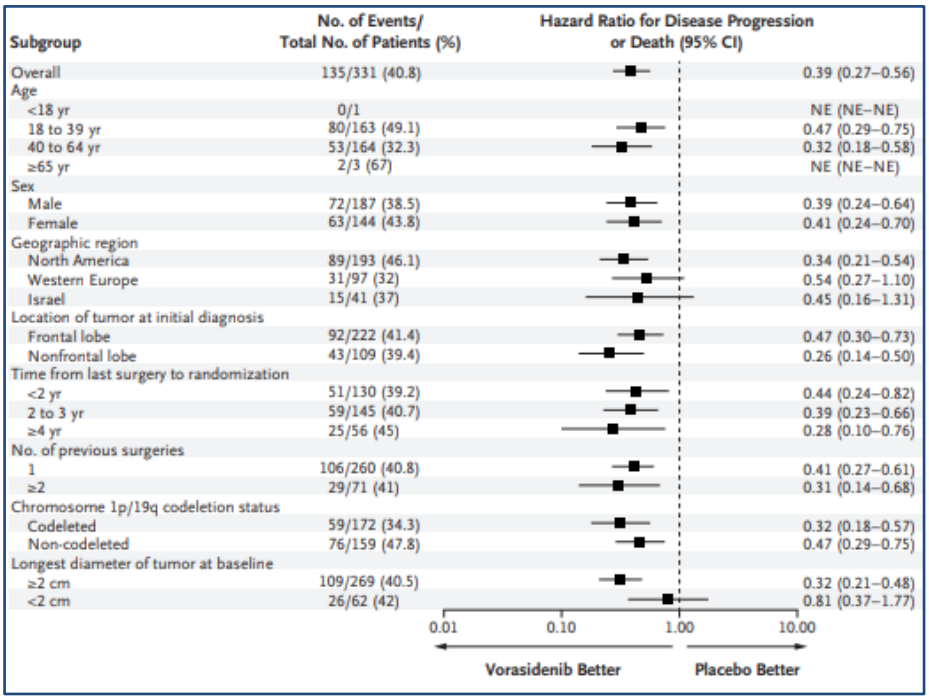
Subsequent antineoplastic therapies were defined as those therapies reported as a concomitant medication with the category of subsequent anticancer therapy; this does not include subjects who discontinued placebo and crossed over to vorasidenib, which is discussed separately. Following discontinuation of study treatment, 13 subjects (7.7%) in the vorasidenib arm and 3 subjects (1.8%) in the placebo arm had at least one subsequent antineoplastic therapy (not including subjects who crossed over from placebo to vorasidenib). The most common antineoplastic therapy was temozolomide, reported in 3 subjects (1.8%) and 10 subjects (6.0%) in the placebo and vorasidenib arms, respectively. Subsequent antineoplastic therapies are defined as therapies that are started after the last dose of study treatment (for subjects randomized and dosed) or after randomization (for subjects randomized and not dosed). Subsequent anticancer surgeries for glioma were reported in 3 subjects (1.8%) and 10 subjects (6.0%) in the placebo and vorasidenib arms, respectively Subsequent anticancer radiotherapy was reported in 5 subjects (3.1%) and 11 subjects (6.5%) in the placebo and vorasidenib arms, respectively [65]

2.6 Subgroup analysis

Vorasidenib demonstrated consistent improvement in PFS and TTNI across all prespecified subgroups compared to placebo

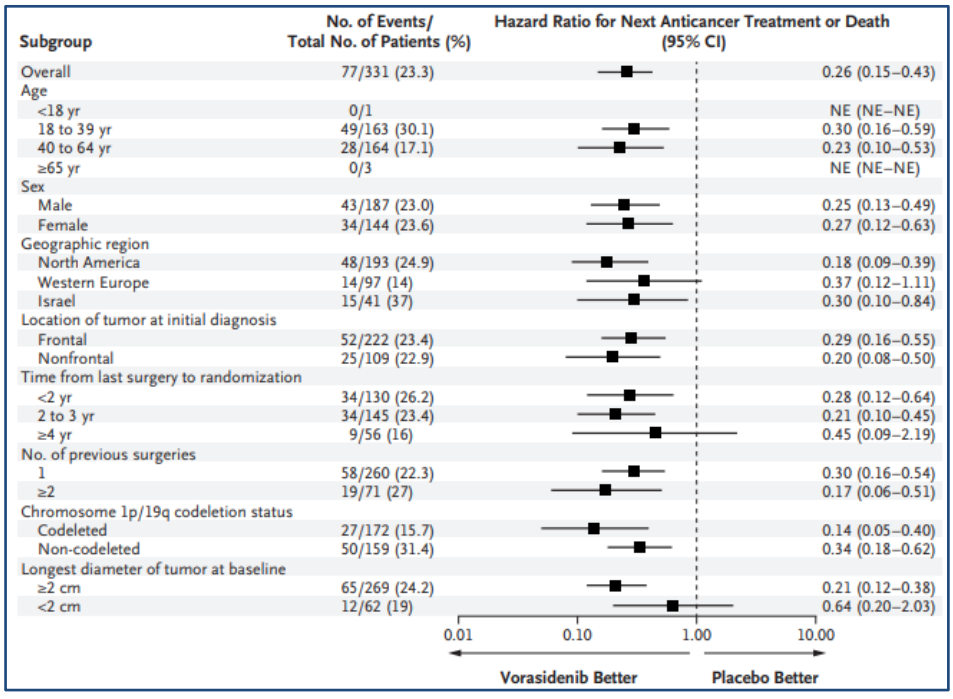
PFS and TTNI results were consistent (favouring vorasidenib) across all prespecified subgroups, including age (<40 years vs. ≥40 years), baseline tumour size (<2 cm vs. ≥2 cm), and histology (1p19q codeleted vs. not codeleted**)** (Figure 13 and 14)**.** This includes a statistically significant improvement in PFS (HR=0.47, 95% CI: 0.29, 0.75) and TTNI (HR=0.34, 95% CI: 0.18, 0.62) with vorasidenib in the 1p19q non-codeleted subgroup (astrocytoma), which typically have poorer prognosis.

Figure 13: Subgroup analyses of PFS



Source: (Mellinghoff 2023b)[65]
Abbreviations: CI: confidence interval; NE: not estimated; No: number; PFS: progression free survival
Note: Subgroup analyses were based on stratification-factor data as entered in the interactive Web-response system. Frontal tumour location included frontal, frontoparietal, and frontotemporal locations, and non-frontal tumour location included all other locations. In the analyses, the widths of the confidence intervals have not been adjusted for multiplicity. Thus, the confidence intervals should not be used to reject (or not reject) the effects of vorasidenib

Figure 14: Subgroup analyses of TTNI



Source: (Mellinghoff 2023b)[65]
Abbreviations: CI: confidence interval; NE: not estimated; No: number; TTNI: time to next intervention
Note: Subgroup analyses were based on stratification-factor data as entered in the interactive Web-response system. Frontal tumour location included frontal, frontoparietal, and frontotemporal locations, and non-frontal tumour location included all other locations. In the analyses, the widths of the confidence intervals have not been adjusted for multiplicity. Thus, the confidence intervals should not be used to reject (or not reject) the effects of vorasidenib

2.7 Meta-analysis

No meta-analysis

2.8 Indirect and mixed treatment comparisons

No Indirect comparisons

2.9 Adverse reactions

Overall, vorasidenib had a manageable safety profile in the INDIGO trial.

Treatment-Related Emergent Adverse Events

Vorasidenib demonstrated a consistent and manageable treatment-related AE profile and was associated with mainly low-grade toxicities, with most TEAE being Grade 1 or Grade 2. The proportion of patients reporting any TEAE was similar in the vorasidenib (94.6%, n=158) and placebo arms (93.3%, n=152). Overall, vorasidenib was associated with mainly low-grade toxic. An overall summary of TEAEs is presented in Table 15

Table 20: Overall summary of TEAEs (SAS), data cutoff date: 06 September 2022

	Vorasidenib (N=167)	Placebo (N=163)
Any TEAE, n (%)	158 (94.6)	152 (93.3)
Grade ≥3 TEAEs, n (%)	38 (22.8)	22 (13.5)
Treatment-related TEAEs, n (%)	109 (65.3)	95 (58.3)
Grade ≥3 treatment-related TEAEs, n (%)	22 (13.2)	6 (3.7)
Serious TEAEs, n (%)	11 (6.6)	8 (4.9)

Source: (Servier 2023)
Abbreviations: N: number of subjects in the SAS within each treatment arm; n: number of subjects in the SAS within each treatment arm in each category; SAS: safety analysis set; TEAE: treatment emergent adverse event

Grade ≥3 TEAEs

Vorasidenib has a low rate of Grade ≥3 TEAEs and a similar rate of serious TEAE compared to placebo

TEAEs of Grade 3 or higher were observed in 38 patients (22.8%) who received vorasidenib and in 22 patients (13.5%) who received placebo. Serious TEAE were reported in 11 (6.6%) patients randomised

to vorasidenib and 8 (4.9%) patients randomized to placebo (Table 15). The most common TEAE of Grade 3 or higher was an increased ALT (9.6% in the vorasidenib arm and none in the placebo arm)

Other TEAEs of Grade 3 or higher that were more common with vorasidenib than with placebo were an increased AST (4.2% in the vorasidenib arm and none in the placebo arm), increased GTT (3.0% and 1.2%, respectively), and seizures (4.2% in the vorasidenib arm and 2.5% in the placebo arm)[65]. The study protocol included specific guidelines for management of elevated liver transaminase AEs, which included dose modification guidelines and recommendations for increased laboratory monitoring[66]. A higher proportion of patients in the placebo arm experienced Grade 3 or higher headache and fatigue than in the vorasidenib arm

The proportion of patients experiencing serious TEAEs was similar in the placebo and vorasidenib arms, with eight patients (4.9%) and 11 patients (6.6%) reporting at least one SAE, respectively (Table 21). Serious TEAEs assessed by the Investigator as treatment-related, were all associated with liver abnormalities and occurred in the vorasidenib arm only (3 patients [1.8% of patients in the vorasidenib arm]). This included autoimmune hepatitis, hepatic failure, and increased ALT; each occurring in one patient (0.6% of patients in the vorasidenib arm).

Table 21: Most common TEAEs (any Grade in ≥10% of patients or Grade ≥3 in ≥5% of patients) (SAS), Data Cutoff Date: 06 September 2022

Event, n (%)	Vorasidenib (N=167)		Placebo (N=163)	
	Any Grade	**Grade ≥3**	**Any Grade**	**Grade ≥3**
Any adverse event	158 (94.6)	38 (22.8)	152 (93.3)	22 (13.5)
Increased ALT	65 (38.9)	16 (9.6)	24 (14.7)	0
Increased AST	48 (28.7)	7 (4.2)	13 (8.0)	0
Increased GTT	26 (15.6)	5 (3.0)	8 (4.9)	2 (1.2)
Coronavirus disease 2019	47 (28.8)	0	55 (32.9)	0
Fatigue	54 (32.3)	1 (0.6)	52 (31.9)	2 (1.2)
Headache	45 (26.9)	0	44 (27.0)	1 (0.6)
Diarrhoea	41 (24.6)	1 (0.6)	27 (16.6)	1 (0.6)
Nausea	36 (21.6)	0	37 (22.7)	0
Dizziness	25 (15.0)	0	26 (16.0)	0
Seizure	23 (13.8)	7 (4.2)	19 (11.7)	4 (2.5)
Constipation	21 (12.6)	0	20 (12.3)	0

Source: (Mellinghoff 2023b)[65]
Abbreviations: AE: adverse events; ALT: alanine aminotransferase; AST: aspartate aminotransferase; GTT: γ-glutamyltransferase; N=number of subjects in the SAS within each treatment arm; n=number of subjects in the SAS within each treatment arm in each; SAS: safety analysis set

TEAEs Leading to Death, Discontinuations, Interruption, or Reduction

There were no deaths and vorasidenib exhibited similar rates of treatment discontinuations, interruptions, and dose reductions due to TEAE when compared to the placebo arm

No deaths due to TEAEs or treatment-related TEAEs were reported in either the vorasidenib or placebo arm for (Table 22). The percentage of patients with at least one TEAE leading to treatment discontinuation was 3.6% in the vorasidenib arm (n=6) and 1.2% in the placebo arm (n=2), driven by

events of elevated liver transaminases [66]. An interruption of the regimen due to TEAEs was observed in 29.9% patients (n=50) in the vorasidenib group and in 22.7% (n=37) in the placebo group. These were driven by increased ALT, AST, and GTT, and COVID-19. TEAEs that led to dose reduction was reported in 10.8% patients (n=18) in the vorasidenib group and 3.1% patients in the placebo group (n=5). Increased ALT (13 patients [7.8%] in the vorasidenib arm and in 1 patient [0.6%] in the placebo arm), was the most reported reason for dose reduction.

Table 22: TEAEs leading to death, discontinuations, interruption, or reduction

	Vorasidenib (N=167)	Placebo (N=163)
TEAEs leading to discontinuation of study drug, n (%)	6 (3.6)	2 (1.2)
TEAEs leading to dose reduction of study drug, n (%)	18 (10.8)	5 (3.1)
TEAEs leading to interruption of study drug, n (%)	50 (29.9)	37 (22.7)
TEAEs leading to death, n (%)	0	0
Treatment-related TEAEs leading to death, n (%)	0	0

Source: (Servier 2023)[66]
Abbreviations: N: number of subjects in the SAS within each treatment arm; n: number of subjects in the SAS within each treatment arm in each category; SAS: safety analysis set; TEAE: treatment emergent adverse event

2.10 Ongoing studies

Data cut expected May 2025, May 2028

2.11 Interpretation of clinical effectiveness and safety evidence

The results of the prespecified second interim analysis of the INDIGO trial show that vorasidenib as a single agent has demonstrated clinical activity across multiple efficacy measures in participants with non-enhancing IDH-mutant gliomas who have had surgery as their only treatment, and are not in immediate need of RT/CT

Vorasidenib significantly improved PFS compared to placebo in both the primary analysis and the ad-hoc analysis, resulting in a 65% (HR=0.35; 95% CI: 0.25, 0.49; P=0.00000000013) [ad-hoc analysis]) reduction in the risk of progression or death. The median PFS was NE (95% CI: 22.1, NE) months for the vorasidenib arm and 11.4 (95% CI: 11.1, 13.9) months for the placebo arm[69] This demonstrates a clinically meaningful improvement in imaging-based PFS, reducing the risk of disease progression compared to placebo.

The key secondary endpoint of TTNI was statistically significantly improved in the vorasidenib arm compared with the placebo arm in both the primary and ad-hoc analysis (HR=0.25; 95% CI: 00.16, 0.40; P=0.000000000048 [ad-hoc analysis]) months in the placebo arm[69]. Results for PFS per the BIRC and TTNI favoured vorasidenib in all subgroup analyses and sensitivity analyses. This delay in progression translated into a delay in subsequent anticancer therapy

The confirmed trends between data cuts, clearly shows Vorasidenib delays the progression of disease and delays the time to the toxic effects of RT/CT, particularly of relevance considering the young working age of patients, and the additional societal benefits discussed in section 1.3.1.

A growing body of evidence supports a direct correlation between tumour volume and growth rate with OS and PFS, establishing these metrics as important predictive biomarkers. TGR is a clinically

significant predictor of OS and TTNI and may serve as an early indicator of clinical benefit. In addition, post-surgical tumour size or growth serves as a critical predictor of outcomes in IDH-mutant gliomas, significantly impacting survival, disease progression, and symptoms such as seizures. This is further supported by consistent correlations between residual tumour volume and OS/PFS[12,67,68]

Vorasidenib was associated with a decrease in tumour volume compared to continued growth on the placebo arm, with a decreased TGR of 2.5% every 6 months in the vorasidenib arm (primary analysis) (mean TGR=-2.5%; 95% CI: -4.7, -0.2), while an increase of 13.9% every 6 months for the placebo arm (mean TGR=13.9%; 95% CI: 11.1, 16.8). The reduction in volumetric TGR observed in patients treated with vorasidenib contrasts with the continued tumour growth seen in subjects receiving a placebo, highlighting the anti-tumour activity of vorasidenib

A higher ORR in the vorasidenib arm, and consistent clinical benefit across other endpoints including DOR, TTR, and PFS by Investigator (primary analysis).

The INDIGO Phase 3 trial also demonstrated that vorasidenib preserves QoL and has a manageable safety profile. INDIGO was shown to preserve patients QoL whilst on vorasidenib as they were relatively otherwise healthy patients and therefore it remains very relevant for these patients to not be impaired by their treatments.

At baseline (as per primary analysis), FACT-Br total scores were consistent with, or higher than, matched normative data, indicating patients in both arms had high HRQoL at study entry. There was no meaningful deterioration in HRQoL observed with vorasidenib within the first year of treatment as measured by the FACT-Br questionnaire, with no changes suggestive of a treatment effect on neurocognitive function in the areas of psychomotor function, attention, executive function, verbal learning, and working memory.

Safety data as per primary analysis in the study were consistent with Phase 1 data with no substantial worsening of severity or frequency of anticipated adverse events

TEAEs were generally low-grade and manageable as per the primary analysis. The most prevalent Grade 3 or higher TEAE with vorasidenib was an elevated ALT (9.6%), increased AST (4.2%) and GTT (3.0%). These were easily manageable with supportive care and dose adjustments and did not cause permanent liver damage

Overall, TEAEs leading to treatment discontinuation, interruption, and reduction occurred infrequently and were generally associated with events of elevated liver transaminases in the vorasidenib arm. At an advisory board held by Servier, all advisors expressed that the safety profile was ‘ very manageable’ and markedly improved compared to RT/Chemo[36].
They also explained that liver transaminases increases are easy to monitor with the stipulated blood tests required and would be performed. This would peak at 6 months and the bloods would not be taken in Oncology clinics, resulting in minimal resource impact.

Vorasidenib clearly demonstrates the solution to a high unmet medical need, safely postponing Rt/Ct. These are aggressive and harmful treatments that can potentially increase disease severity in the long term. Vorasidenib shows efficacious disease control with a safe and manageable safety profile, maintaining QoL. Therefore, when the need for RT/CT does arise later in the treatment pathway, it will be available and efficacious

Vorasidenib is a ground-breaking, first-in-class, dual IDH1- and IDH2-mutant inhibitor and represents a new standard of care for adult and paediatric patients 12 years and older with Grade 2 astrocytoma or oligodendroglioma with a susceptible IDH1 or IDH2 mutation following surgery, not in immediate need of RT/CT.

Expected Place in Treatment Guidelines

IDH mutations are a disease defining characteristic with ~20% of adult diffuse gliomas presenting with IDH mutations. IDH-mutant diffuse gliomas are incurable and are most commonly diagnosed in young patients who consequently suffer a range of debilitating symptoms. IDH-mutant diffuse gliomas grow continuously, infiltrate the normal brain, and mostly transform into an aggressive enhancing glioma. Lower-grade gliomas become progressively aggressive, with over half of patients experiencing recurrence within 5 years. Residual tumour cells after surgery drive further spread, and IDH mutations worsen tumour behaviour at cellular levels. Recurrences of IDH-mutant gliomas have poor outcomes, emphasising the need for effective targeted therapies early in disease management to improve outcomes and prevent further progression

Despite the high unmet need, there are currently no approved therapies for Grade 2 IDH-mutant diffuse gliomas and the majority of treatments used are adopted from the higher-grade setting. Current guidelines recommend maximal safe resection for newly diagnosed IDH-mutant glioma, followed by either active surveillance or RT/CT depending on individual risk of progression and patient preference. However, these guidelines still use age >40 years, >1-2 cm tumour after surgery, and Grade 3 diagnosis as criteria for high-risk glioma warranting further treatment after surgery, based on data not solely looking at IDH mutant glioma. Given the slow albeit continuous growth observed in most IDH-mutant Grade 2 glioma, it is considered more appropriate to consider prognostic factors as less favourable or more favourable. Adjuvant RT/CT is associated with improved PFS, however, there is a lack of evidence demonstrating a significant improvement in OS. Adjuvant RT/CT is associated with multiple short- and long-term toxicities which are a detriment to patient QoL. Without active treatment post-resection, IDH-mutant tumours continuously grow at an accelerating rate with increased risk of progression to a more aggressive disease state

Vorasidenib is an oral inhibitor of the IDH-mutant proteins and is specifically designed for brain penetrance, making it a targeted therapeutic candidate for the treatment of IDH-mutant gliomas. Vorasidenib is first-in-class and the first innovative treatment in decades for patients with IDH1- or IDH2-mutant gliomas. The ongoing Phase 3 INDIGO trial demonstrated that vorasidenib increases PFS and TTNI and reduces tumour volume. Vorasidenib improves overall disease control and delays subsequent treatment with aggressive RT/CT, allowing these working-age patients to maintain QoL.These benefits were further supported by the longer follow up data (ad-hoc analysis).

The latest NCCN CNS (v3.2024; September 30, 2024), SEOM-GEINO guidelines (2023), and ASCO consensus publication (2024) recommend IDH inhibitors as adjuvant treatment for patients with Grade 2 IDH-mutant gliomas not eligible for RT/CT.

- The NCCN CNS guidelines (v3.2024) recommend vorasidenib as adjuvant treatment after surgery/biopsy and treatment with RT and CT is not preferred for patients diagnosed with Grade 2 oligodendrogliomas and astrocytomas with KPS ≥60 (Category 1 recommendation)[43]
- The latest Spanish Society of Medical Oncology (SEOM) and the Spanish Group of Investigation in Neuro-Oncology (GEINO) guidelines (2023) recommend vorasidenib as the choice of treatment in patients who are not treated with RT/CT, have a tumour remnant after surgery, or have disease regrowth after surgery (Level I-A) [44]
- The ASCO consensus publication recommend IDH-inhibitors for patients with MRI documented supramaximal or complete resection or no need for immediate RT/CT[40]

The latest EANO diagnostic guidelines (October 2024) report that a key point with the approval of vorasidenib is the importance of IDH mutations and that assessment of IDH status now also has therapeutic implications. The guidelines recommend that all diffuse gliomas should be tested for IDH

mutations to meet standard diagnostic requirements. IDH mutations have been established as European Society for Medical Oncology Scale for Clinical Actionability of molecular Targets (ESCAT) I-A molecular treatment target in patients with Grade 2 IDH mutant gliomas treated with surgery but not with RT/CT and its use has been approved by the FDA.

The period of slow progressive growth early in the disease course represents a therapeutic window in which to target these tumours before clinical deterioration is imminent.

Patients with IDH-mutant diffuse gliomas are considered to have better prognosis and survival outcomes compared to higher-grade gliomas. However, more than 70% of IDH-mutant diffuse gliomas have the potential to undergo a transformation, progressing to a higher grade or becoming more aggressive within a decade. Despite treatments with surgery, RT, and/or CT, patients with IDH-mutant diffuse gliomas suffer from a decreased overall life expectancy due to the relentless nature of the disease. Since IDH-mutant gliomas grow continuously and infiltrate the normal tissue, the only two options available post-surgery (active surveillance or RT/CT) come with high compromise in QoL. Further, there is an urgent need to delay aggressive therapies in this young population group and extend the survival without impacting patient QoL. As IDH mutations are early genetic drivers of the disease, a targeted approach suppressing the mutant enzyme offers an opportunity to intervene early (before RT or CT) in the disease course, delaying progression and the need for more aggressive therapies. Additionally, recurrences of IDH-mutant gliomas have poor outcomes, further emphasising the need for effective targeted therapies early in disease management.

In this young, otherwise healthy, and active patient population, overall function and QoL are of particular importance when facing an incurable disease. The known burden of the short- and long-term toxicities of currently available therapies, including decreased neurocognition and QoL, is a challenge that patients and physicians face when determining the most appropriate intervention following surgery

Vorasidenib is a targeted therapeutic candidate for the treatment of patients with diffuse gliomas that harbour IDH1- or IDH2-mutations. By inhibiting IDH mutations, vorasidenib acts on the early driver of oncogenesis, making it most effective soon after first surgery. The INDIGO trial was not set up to compare RT and CT with vorasidenib, but rather aimed to investigate the activity of vorasidenib in patients in whom there was no need for immediate RT and CT. INDIGO establishes a role for IDH inhibitors in IDH-mutant glioma before RT and/or CT. Additionally, the trial suggests that inhibition of the mutant IDH enzyme during earlier stages of the disease might be more effective for tumour control than targeting mutant IDH at a later disease stage.

Vorasidenib can shift the treatment paradigm and make more options available to the patients who are suffering from this aggressive disease. Vorasidenib can be used to treat patients soon after surgery as an alternative to active surveillance, or in those who have been on active surveillance for a long period, or who have progressed while on active surveillance.

Vorasidenib reduces the risk of progression and the need for another intervention in patients with predominantly non-enhancing IDH-mutant gliomas and offers a manageable safety profile. Given the unmet need in this population for whom the available therapies can lead to long term toxicities, these efficacy results reflect a substantial clinical benefit. Hence, vorasidenib will play an important role in delaying the initiation of RT/CT and slowing down tumour growth while maintaining QoL by preserving cognitive function and maintaining seizure control.

3 Cost effectiveness

3.1 Published cost-effectiveness studies

An SLR was conducted in April 2023 and updated in May 2024 to identify published economic evidence reporting on the economic burden (costs, resource use and economic evaluations) for patients with grade 2 or 3 diffuse glioma. Full details of the methods and results are presented in Appendix E. In total, nine economic evaluations were identified for inclusion, of which one was conducted from a UK perspective[72] and used to inform NICE TA23[73] (Table 23). This study included limited methodological detail, concerned patients with malignant glioma and did not consider vorasidenib for the treatment of people aged 12 years and over with grade 2 astrocytoma or oligodendroglioma with IDH1 or IDH2 mutations, who have had surgical intervention and not in immediate need of radiation or chemotherapy (RT or CT).

Table 23: Summary list of published cost-effectiveness studies

Study	Year	Objective	Model summary	Incremental QALYs	Incremental costs	ICER (per QALY gained)
Dinnes et al 2001[72]	2001	To provide a rapid review of the effectiveness and cost-effectiveness of TMZ in the treatment of primary malignant brain tumours (AA)	Model structure: NR Time horizon: NR Perspective: NR (assumed NHS) Cycle length: 6 weeks Discounting: NA Efficacy: OS, PFS Utilities: QoL for recurrence measured using EORTC QLQ-C30; mapping NR Costs: drug costs (BNF), outpatient visits, MRI scans	Increase of 0.2 for TMZ vs best alternative care	PFS (13 weeks): £3,794 PFS (24 weeks): £7,607 PFS (35 weeks): £11,396	£40,534 (PFS of 11 weeks)

Abbreviations: AA, anaplastic astrocytoma; BNF, British National Formulary; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Core Quality of Life questionnaire; ICER, incremental cost-effectiveness ratio; NA, not applicable; NHS, National Health Service; NR, not reported; OS, overall survival; PFS, progression-free survival; QALYs, quality-adjusted life years; QoL, quality of life; TMZ, temozolomide.

3.2 Economic analysis

Based on the findings of the SLR reported, there are no previously published economic evaluations considering vorasidenib for the treatment of people aged 12 years and over with grade 2 astrocytoma or oligodendroglioma with IDH1 or IDH2 mutations, who have had surgical intervention and not in immediate need of RT or CT. Therefore, a *de novo* cost-effectiveness model was developed in Microsoft Excel® to assess the cost-effectiveness of vorasidenib against current care (active observation) from the perspective of the NHS and Personal Social Services.

The cost-effectiveness analysis adopts a lifetime horizon. It is assumed that 60 years is sufficient to constitute a lifetime horizon, given the average age of patients at baseline in the INDIGO trial (40 years). A 28-day cycle length is used, which is assumed to be short enough to adequately capture meaningful changes in health status for patients IDH1 or IDH2 positive LGG who have only undergone surgery as treatment, whilst respecting the time on treatment for vorasidenib. Due to the choice of cycle length, a half-cycle correction is applied.

In the base-case analysis, annual discount rates are applied at 1.5% per annum – lower than the standard NICE reference case of 3.5% per annum. The use of 1.5% discount rates has been considered in previous NICE appraisals, including TA538 of dinutuximab beta for treating neuroblastoma[74]. The NICE heath technology evaluation manual[75] states that a 1.5% discount rate for both costs and health outcomes may be applied based on the following criteria:

- The technology is for people who would otherwise die or have a very severely impaired life.
- It is likely to restore them to full or near-full health.
- The benefits are likely to be sustained over a very long period.

Firstly, overall, the methodology of using a 3.5% discount rate is flawed within this particular appraisal, as most of the benefits seen with vorasidenib are realised further downstream in the sense that it allows for a longer time period free of the harmful effects of RT/CT. In the 2019-2022 NICE Methods Review, NICE concluded that the best available evidence supported a change in the discount rate applied to both costs and health effects from 3.5% to 1.5%. Due to the downstream benefits here, a rate from 3.5% to 1.5% would support patient access, align to the NHS Prevention Programme, and ensure alignment with the Treasury Green Book.

The first criterion is met, based on established knowledge of outcomes for people living with LGG managed with current care (i.e., active observation). Without vorasidenib, and on current treatment (defined as active observation), patients experience the negative consequences of their disease at a much more rapid pace. As detailed in Section 1.3.2, these patients with IDH-mutant glioma suffer from a severely impaired life, especially when treated with RT/CT, related to loss of productivity, inability to work, early retirement, and premature mortality[49]. Patients with IDH-mutant Grade 2 glioma not only face productivity losses at work but also are hindered by health issues in everyday tasks. More than half of the participants reported barriers in performing domestic work: around 45% reported issues completing and 25% reported difficulties in taking care of children[50]. The potential acute adverse effects of RT, such as elevated intracranial pressure, can manifest as headaches and vomiting[51]. These additional chronic side effects associated with RT for brain cancer include impaired wound healing, skin changes and skin cancer, lymphedema, secondary cancer, and damage to surrounding structures which potentially contribute to the detriment to daily function[52]. All advisors at an advisory board held by Servier expressed that the societal benefits of vorasidenib over RT/CT (i.e., treatments

used later in the pathway for IDH-mutant glioma) will be marked, including continuing to work due to a lack of neurological deficit. This will equate to reduced nursing home care that may be later required. Four advisors expressed that the potential for people to continue to drive while treated with vorasidenib should not be underestimated. In their opinion this is a large quality of life benefit as patients cannot drive on RT/CT. People lose their license for at least a year with RT/CT and similar after surgery. The second criterion is evidenced through the observed effect of vorasidenib in the INDIGO study, wherein it is seen that vorasidenib prolongs the time people spend with relatively good health-related quality of life, prior to progression. Finally, the third criterion is met, by virtue of the benefits of treatment with vorasidenib applying over a lifetime horizon, including that median PFS was not reached in the INDIGO study for the vorasidenib arm (see Section 2.5). Alternative discount rates can be specified in the submitted economic model.

The model considers direct costs relating to drug acquisition and administration, healthcare resource use, adverse event (AE) management, subsequent treatment, and end-of-life (EoL) care. Direct health effects for patients are reported as life years (LYs) and quality-adjusted life years (QALYs), with health state utility values estimated using the EQ-5D-5L descriptive system (using a combination of data collected as part of the INDIGO trial) and the EQ-5D-3L mapping function (to convert EQ-5D-5L values to EQ-5D-3L values), supported by vignette study values for later health states. The model captures the main health effects on patients but does not capture any beneficial health effects to family members or caregivers due to limited data available to inform the model. The primary outcome of the model is the incremental cost-effectiveness ratio (ICER) for vorasidenib versus active observation (i.e., the cost per QALY gained).

3.2.1 Patient population

The population considered in the analysis is people aged 12 years and over with grade 2 astrocytoma or oligodendroglioma with IDH1 or IDH2 mutations, who have had surgical intervention and not in immediate need of RT or CT. This is in line with the anticipated marketing authorisation for vorasidenib (See Appendix A) and the population included in the INDIGO trial[66,71]. Baseline patient characteristics of the cohort entering the model were aligned with the population in the INDIGO study and are presented in Section 3.3.1, Table 25[66,71].

3.2.2 Model structure

A treatment status-based model structure was chosen for the *de novo* cost-effectiveness model as it is reflective of the management of LGG, which is a progressive disease where key treatment-related milestones signify important stages of disease progression. This in turn allows lifetime cost and health outcomes to be accurately estimated. This approach (i.e., developing a model around these treatment-related milestones) is consistent with a previous NICE appraisal in glioma (TA977[76] of

dabrafenib with trametinib for treating BRAF V600E mutation-positive glioma in children and young people aged 1 year and over)[1].

A state-transition model was used over a partitioned-survival model (PSM) model for several reasons, including critically, the absence of an overarching overall survival (OS) curve that could be robustly derived for both treatment arms due to the lack of mature data available from the INDIGO trial. Furthermore, a PSM would not be able to capture all relevant costs and outcomes over a lifetime horizon without making large simplifying assumptions for patients that have experience disease progression.

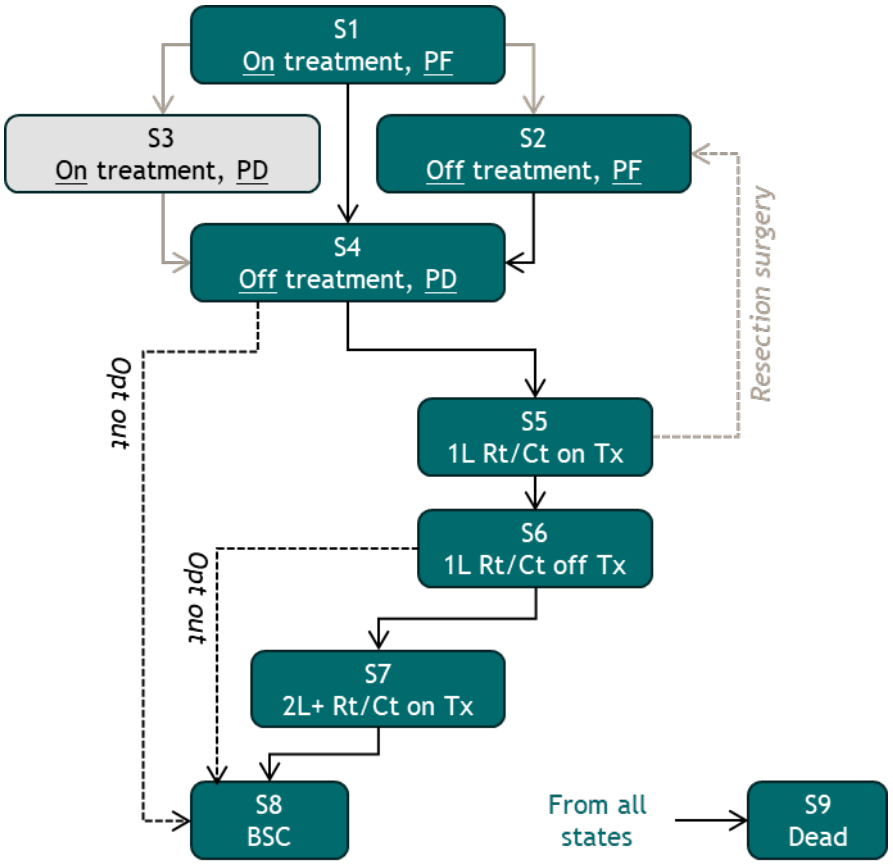
The model structure comprises up to 9 health states (labelled S1 to S9) which capture periods of time where patients are expected to be on treatment (Tx) with vorasidenib, off Tx (either following vorasidenib or otherwise), on the next intervention (NI), the following intervention (NI+), receiving best supportive care (BSC) or dead (Figure 15). By specifying these health states, the model allows the discrete breakdown of the pathway steps so that patients can transition between them. These states are also designed so they can be powered by different data sources such as the INDIGO study which provides time to progression, next intervention, and death (though very few death events were recorded).

The model schematic shows arrows which are formatted as follows:

- Solid black arrows denote transitions that can occur for each model cycle, and are applicable in the base-case analysis
- Solid grey arrows denote transitions that can occur for each model cycle, and are **not** applicable in the base-case analysis
- Dashed black arrows denote transitions that can occur for only the first model cycle upon entry to a given health state, and are applicable in the base-case analysis
- Dashed grey arrows denote transitions that can occur for only the first model cycle upon entry to a given health state, and are **not** applicable in the base-case analysis.

[1] **Note:** In TA977, movements between health states were described on the premise that patients would "cycle through a series of sub-health states representing different progression events/lines of treatment".

Figure 15: Economic model structure



Abbreviations: BSC, best supportive care; NI, next intervention; PD, progressed disease; PF, progression-free; Tx, treatment.

In the base-case analysis, discontinuation of vorasidenib is assumed to occur at the same time as disease progression, and so S3 (on treatment with progressed disease) is unoccupied. This is supported by clinical advisors at an advisory board held by Servier where the safety profile was explored[36] and also the SpC (Appendix A). Furthermore, S1 and S2 are only occupied for the vorasidenib and active observation arms, respectively; as vorasidenib patients are assumed to remain on treatment while progression-free, and active observation patients are not receiving any active treatment. Consequently, the base-case analysis may be viewed as a 7-state model, rather than a 9-state model (as S3 is omitted, and S1/S2 are essentially the same health state, but are separated for ease of model calculations for drug costs).

Patients managed with vorasidenib enter the model in the on-treatment state (S1), whilst patients managed with current care (active observation) enter in the off-treatment state (S2). Vorasidenib is associated with longer time to next intervention (TTNI) compared to active observation. Once patients initiate their next intervention (NI; i.e., enter S5), they are expected to be at a higher risk of death, experience higher morbidity and incur greater treatment and medical resource use costs, thus the use of vorasidenib is expected to have several downstream benefits, including continuing to work due to a lack of neurological deficit.

3.2.3 Health state occupancy

The distribution of patients across the health states in each model cycle, was determined using a microsimulation approach. Markov models are commonly utilised for economic evaluations as they provide a framework which is capable of transparently reflecting patient experience for those living with a disease which is progressive in nature. However, this transparency is paired with (relative) simplicity, as calculations are performed at the cohort-level. Microsimulation models consider calculations at the patient-level and are therefore better suited to evaluate more complex decision problems.

Visual Basic for Applications (VBA) code is used to project outcomes for a set of simulated individual patients per treatment cycle. This allows individual tracking of time within each health state and for the use of more complicated survival curve structures. The microsimulation approach allows a 'new baseline' to be specified for a particular endpoint when a patient enters a particular health state. In a typical oncology cost-effectiveness modelling setting, this is akin to building tunnel states for all possible entries into all possible states, but also tunnels within tunnels when additional nested dynamics are required. This is substantially less complex to implement in a microsimulation model compared to a cohort-level Markov model.

In brief, the key benefits of using the microsimulation model in preference to the Markov model for this decision problem are as follows:

- The microsimulation model allows selection of different survival models for later transitions. Constant transitions would need to be specified in a Markov model.

- The microsimulation model allows for considering patients taking different 'routes' through the model, such as the concept of patients 'opting out' of treatment in the NI and NI+ settings. This is not possible in a Markov model.

- The microsimulation model allows for more accurate capturing of downstream costs for later interventions. A simplified approach would be required for a Markov model.

Table 24: Features of the economic analysis

	Previous evaluations		Current evaluation	
Factor	**TA977[76]**	**TA23[73]**	**Chosen values**	**Justification**
Time horizon	Lifetime (100 years)	NR	Lifetime (60 years)	Given the early age at which the disease develops (40 years), 60 years was considered sufficient to capture all costs and benefits associated with each intervention
Cycle length	No cycle length. Individual-based approach. Time was sampled directly.	6 weeks	28 days with half cycle correction	Considered appropriate considering the treatment length of vorasidenib for patients with IDH1/IDH2 mutated LGG

	Previous evaluations		Current evaluation	
Factor	**TA977[76]**	**TA23[73]**	**Chosen values**	**Justification**
Perspective	NHS/PSS	Not reported but assumed NHS	NHS/PSS	In line with the NICE manual[75]
Discounting	3.5%	NA	1.5%	Lower discount rate considered per criteria outlined in the NICE manual[75]
Model structure	Individual-based state-transition model (STM)	NR	Microsimulation treatment status-based model	A patient-level simulation model was considered most appropriate for a complex disease pathway, and is consistent in approach with a previous NICE appraisal in glioma (TA977[76])
Source of utilities	Publishes EQ-5D sources	EORTC QLQ-C30 data for recurrent AA and GBM	EQ-5D data from the INDIGO trial + vignette study	EQ-5D data from INDIGO represent best available data, with vignette study values used to address gaps
Source of costs	BNF, NHS reference costs	BNF	BNF, eMIT, NHS reference costs, PSSRU	Standard UK sources for costs

Abbreviations: AA, anaplastic astrocytoma; BNF, British National Formulary; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Core Quality of Life questionnaire; GBM, glioblastoma; LGG, low grade glioma; NA, not applicable; NHS, National Health Service; NR, not reported.

3.2.4 Intervention technology and comparators

The intervention considered within this evaluation is vorasidenib. Vorasidenib is an oral, potent, targeted inhibitor of mutated IDH1 and IDH2, administered at a daily dose of 40mg in continuous 28-day cycles. Vorasidenib treatment should be continued until disease progression or until treatment is no longer tolerated by the patient (See Appendix A). The efficacy and safety of vorasidenib was investigated in the INDIGO trial.

There are currently no treatments [redacted]. Patients not in immediate need of RT/CT would benefit from delaying RT/CT, and thus not being in immediate need, implies it's best to postpone. This can be done safely (and even preferably considering the TMZ-driven hypermutations and RT-driven homozygous deletion of the tumour suppressor CDKN2A which is linked to shorter survival time[18]) in patients. This is discussed further in section 1.3.1. Clinical outcomes in the active observation arm of the cost-effectiveness model are informed by the placebo arm of the INDIGO trial.

3.3 Clinical parameters and variables

3.3.1 Baseline patient characteristics

Baseline characteristics of the patient cohort entering the model were aligned with the population entering the INDIGO study[66,71] and are presented in Table 25. Mean age was used in the model to calculate age-matched general population mortality rates and utility values. Height and weight were used to estimate body surface area (BSA) (using the Mosteller formula[77]), which was required to

calculate drug acquisition costs for any treatments with a weight-based dosing regimen (i.e., treatments that could be considered for later-stage disease).

As the model is a microsimulation, individual patient characteristics vary on a per-patient basis, sampled based on the INDIGO trial inclusion/exclusion criteria and summary statistics. For example, patient ages in the model ranged from a minimum sampled age of 12 years to a maximum sampled age of 76 years.

Table 25: Baseline patient characteristics

Characteristic	Mean	SE
Age	39.86	9.75
Female (%)	44%	N/A
Height (cm)	173.53	10.34
Weight (kg)	81.96	18.32
BSA (m^2)	1.98	0.26

Abbreviations: BSA, body surface area; SE, standard error.

3.3.2 Survival extrapolations

Overview

In the INDIGO study, the primary end point was progression-free survival (PFS), defined as the time from randomisation to first documented progressive disease or death by any cause, whichever occurred earlier as assessed by Blinded Independent Review Committee (BIRC). Progression was determined as per RANO-LGG which defines progression as a ≥25% increase in the T2/FLAIR signal area of the tumour[78]. The key secondary endpoint was the TTNI, as defined by the time from randomisation to the initiation of the first subsequent anticancer therapy (including vorasidenib for patients in the placebo arm).

In the base-case analysis, the two endpoints defined above were used from the INDIGO study to inform transitions. First, time to progression (TTP) was used to inform transitions from S1 (for vorasidenib: progression-free and on treatment) or S2 (for active observation: progression-free and off treatment) to S4 (progressed and off treatment). Only one death event was recorded in INDIGO, which occurred following progression (by either progression criteria) and therefore PFS in INDIGO can be interpreted as TTP. In addition to TTP (or PFS), the outcome of TTNI following progression was also used, to capture transitions from S4 (progressed and off treatment) to S5 (NI).

These transitions are briefly summarised in Table 26 and described in more detail in the subsequent sections.

Table 26: Selected sources for earlier transitions

Transition	Source selected	Rationale
S1->S4	PFS analysis of vorasidenib arm	Patients on vorasidenib enter the model in S1 and can either discontinue treatment or progress as their first event (no deaths recorded prior to either of these events in the INDIGO study). Given that most progression events are expected to occur around the same time as discontinuation events, the model assumes that PFS serves as the most suitable means of determining both progression and discontinuation events. Movement to S4 constitutes both a progression and a discontinuation event.
S2->S4	PFS analysis of placebo arm	Placebo arm assumed to serve as a proxy for active observation. Patients on active observation are not eligible for a discontinuation event, so enter the model in S2. Movement to S4 constitutes a progression event.
S4->S5	TTNI|P, separated by treatment arm	TTNI re-baselined at time of progression, owing to intercurrent event. TTNI differs by treatment arm, and so models were fitted separately.
S1->S9 S2->S9 S4->S9	General population life tables	No excess mortality assumed to apply, based on limited number of death events recorded in the INDIGO study for both treatment arms.

Abbreviations: PFS, progression-free survival; TTNI, time to next intervention.

In addition to the endpoints from the INDIGO study, published data sources were used to inform the remainder of the model transitions in the base-case analysis. These represent transitions after patients have progressed, discontinued treatment in the INDIGO study, and initiated their NI. These transitions are briefly summarised in Table 27 and discussed in detail in the following sections.

Table 27: Selected sources for later transitions

Transition	Source selected	Rationale
S5/6->S7	Baumert 2016[79] PFS, weighted, combined with HGG sPFS median from Juratli 2012[80]	Best available source of PFS for patients upon initiating first-line chemotherapy and/or radiotherapy. To account for people with HGG upon initiation of NI, median sPFS from study by Juratli *et al.*, (2012) is used to determine an average hazard.
S7->S8	Ma 2021[81] TTP	Salvage therapy time to progression is the best available proxy for time to BSC.
S5->S9 S6->S9 S7->S9	NA – general population	Assumption of no excess mortality
S8->S9	Ma 2021[81]	Only available source for salvage therapy or beyond, and no data at all for BSC.

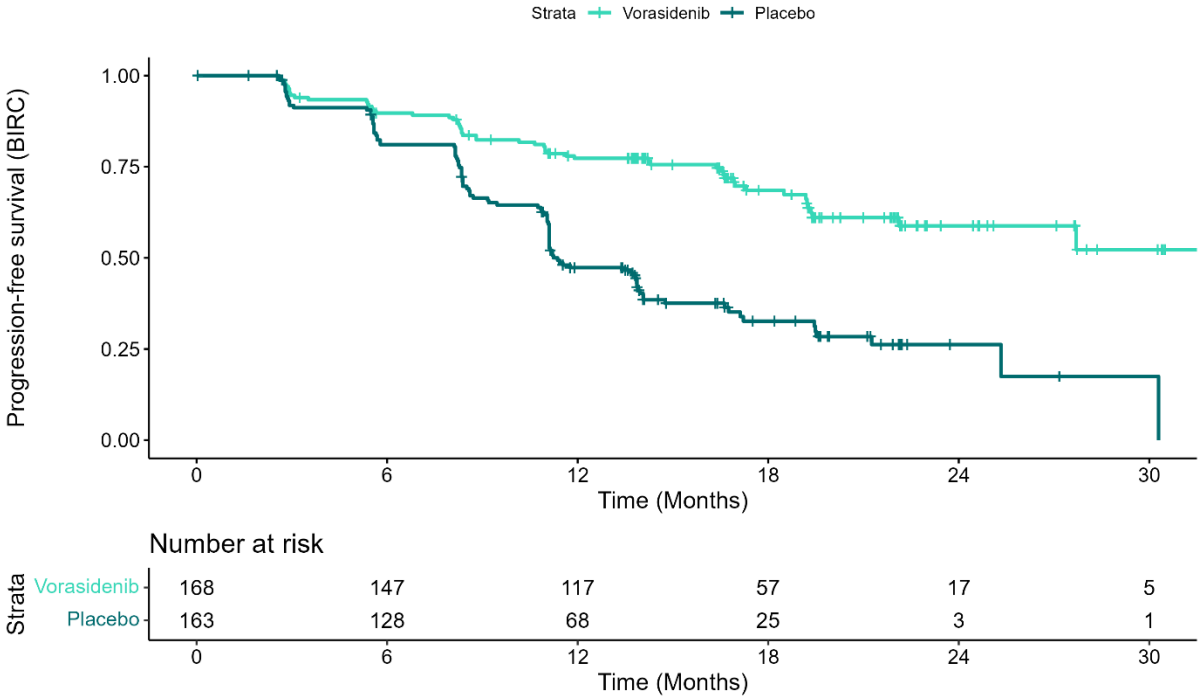
Abbreviations: BSC, best supportive care; HGG, high-grade glioma; NI, next intervention; OS, overall survival; PFS, progression-free survival; sPFS, secondary progression-free survival (i.e., the time between first diagnosis of a HGG and first tumour recurrence or tumour progression); TTP, time to progression.

Progression-free survival (INDIGO data)

The KM estimate showing data for PFS per BIRC ('PFS BIRC') is presented in Figure 16. The median PFS BIRC for the placebo arm was 11.4 months and was not reached in the vorasidenib arm. The proportions of patients who were progression-free at 6 months, 1 year and 2 years were 89.7%, 77.3%, and 58.8%, respectively in the vorasidenib arm and 81.1%, 47.3%, and 26.2%, respectively in

the placebo arm. A clinically meaningful benefit with vorasidenib versus placebo was observed for PFS BIRC, with a HR of 0.36 (95% CI: 0.26, 0.50).[2]

Figure 16: KM of PFS BIRC from INDIGO



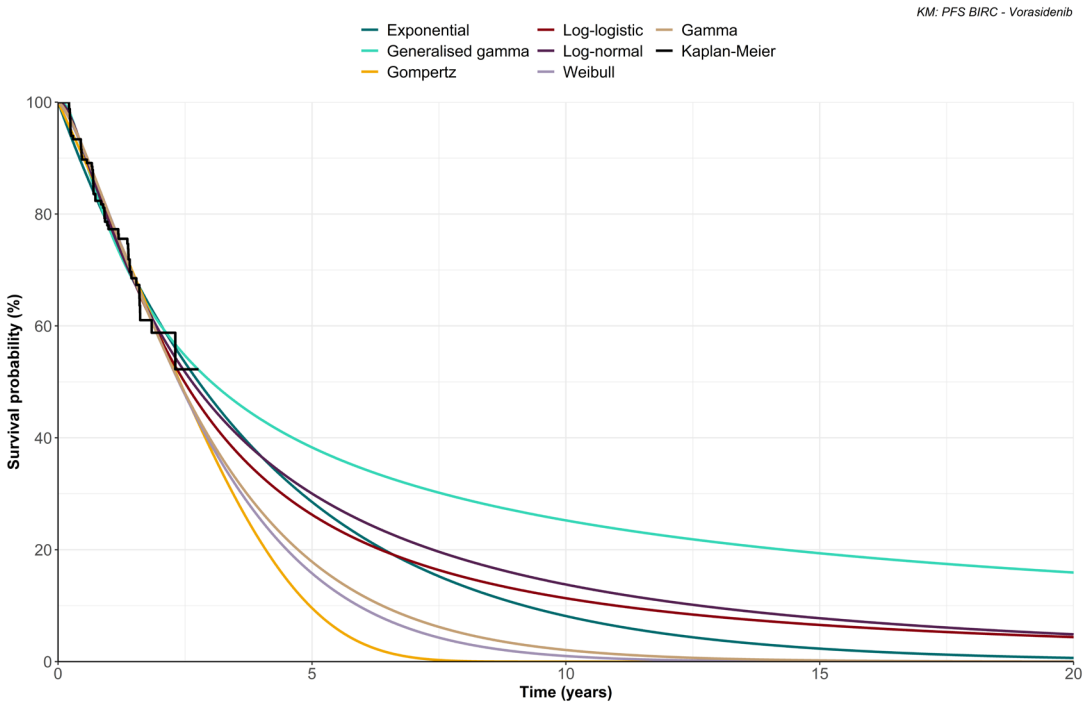
Abbreviations: BIRC, Blinded Independent Review Committee; KM, Kaplan-Meier; PFS, progression-free survival.

In line with NICE DSU TSD 14[82], parametric extrapolations of the PFS BIRC data from the INDIGO trial are presented in Figure 17 and Figure 18.

In the vorasidenib arm, all parametric distributions had a similar fit to the trial data, with estimates differing slightly in the long term. In the placebo arm, all models apart from the exponential model provided good fits to the trial data, with long-term estimates plateauing at close to 0 after around 10 years.

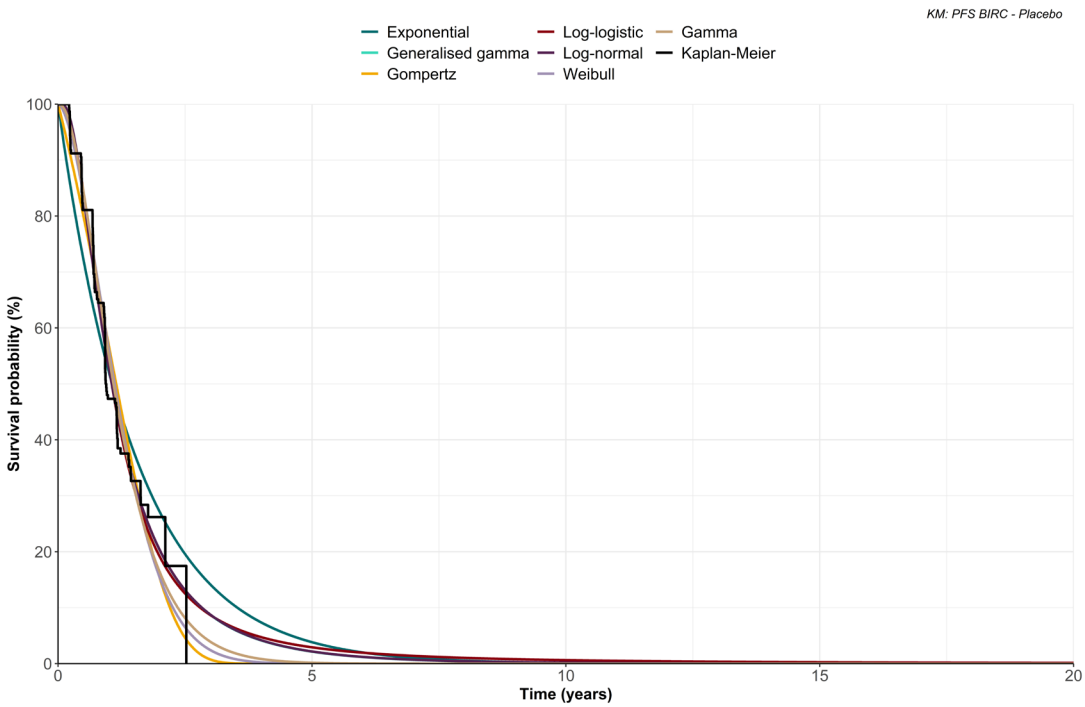
[2] **Note:** The HR and associated 95% CI presented in the company evidence submission does not match the published study by Mellinghoff *et al.*, (2023), which was 0.39 (95% CI: 0.27-0.56), as the data reported in this study come from the September 2022 data cut. The data presented in the company evidence submission come from the March 2023 data cut.

Figure 17: Extrapolations of PFS BIRC in vorasidenib arm



Abbreviations: BIRC, Blinded Independent Review Committee; KM, Kaplan-Meier; PFS, progression-free survival.

Figure 18: Extrapolations of PFS BIRC in placebo arm



Abbreviations: BIRC, Blinded Independent Review Committee; KM, Kaplan-Meier; PFS, progression-free survival.

Fit statistics for PFS BIRC in the INDIGO trial are presented in Table 28.

Table 28: Fit statistics for parametric extrapolations of PFS BIRC

Model	Vorasidenib		Placebo	
	AIC	BIC	AIC	BIC
Exponential	445.3	448.4	685.5	688.6
Generalised gamma	437.0	446.3	642.2	651.5
Gompertz	441.1	447.4	658.2	664.4
Log-logistic	436.6	442.9	**640.7**	**646.9**
Log-normal	**435.0**	**441.3**	641.1	647.3
Weibull	437.1	443.4	643.5	649.7
Gamma	436.4	442.6	**640.7**	**646.9**

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; BIRC, Blinded Independent Review Committee; PFS, progression-free survival.

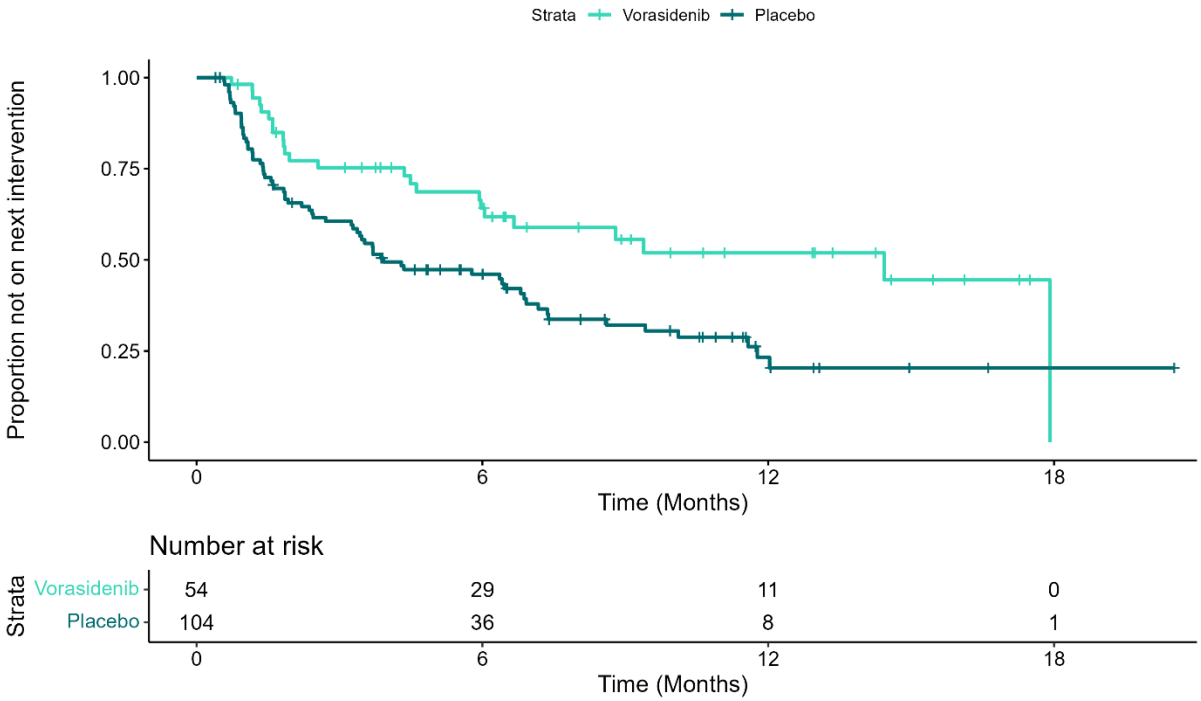
From the goodness-of fit statistics, the log-normal model was the statistically favoured model for extrapolating PFS BIRC in the vorasidenib arm. Based on clinical expert feedback provided to Servier, clinicians found this very difficult to choose. However, one did state that it would be reasonable to assume some pts would still be progression free and next intervention free at 15-20 years on vorasidenib, and another stated that we already know that on active observation, some don't need treatment for 10 years[47]. Therefore, the log normal, log-logistic and exponential distributions were considered to provide the most realistic estimates of PFS for patients treated with vorasidenib. Therefore, the log-normal model was selected in the base-case analysis. For the placebo arm, fit statistics suggested that the log-logistic and gamma models provided equally suitable estimates. However, the goodness-of fit statistics are similar to that of the log-normal model, and so for consistency with the vorasidenib arm, the log-normal model was also used to extrapolate PFS BIRC in the placebo arm.

Time to next intervention following disease progression (INDIGO data)

Time to next intervention (TTNI) was also assessed in the INDIGO trial[66,71], which measured the time until a patient continued onto their next anti-cancer therapy (i.e., NI). In some models (e.g., a partitioned-survival model) this endpoint could be used directly given the assumption of independence of outcomes. However, in the case of the model developed for vorasidenib, there is a need to 'break-down' TTNI into different components that contribute to the decision for a patient to move onto their next treatment, such as progression and discontinuation of prior treatment. Therefore, TTNI itself is not considered an endpoint in the cost-effectiveness model, but the derived TTNI following progression is used – that is, TTNI|P ('TTNI given progression').

The KM estimate for TTNI|P per BIRC ('TTNI|P BIRC') is presented in Figure 19 below. The median TTNI|P BIRC for the vorasidenib arm was 14.4 months and for the placebo arm was 3.9 months. The proportion of patients who were yet to receive their NI following BIRC progression at 6 months and 1 year were 64.2% and 51.9% in the vorasidenib arm, and 46.1% and 23.3% in the placebo arm.

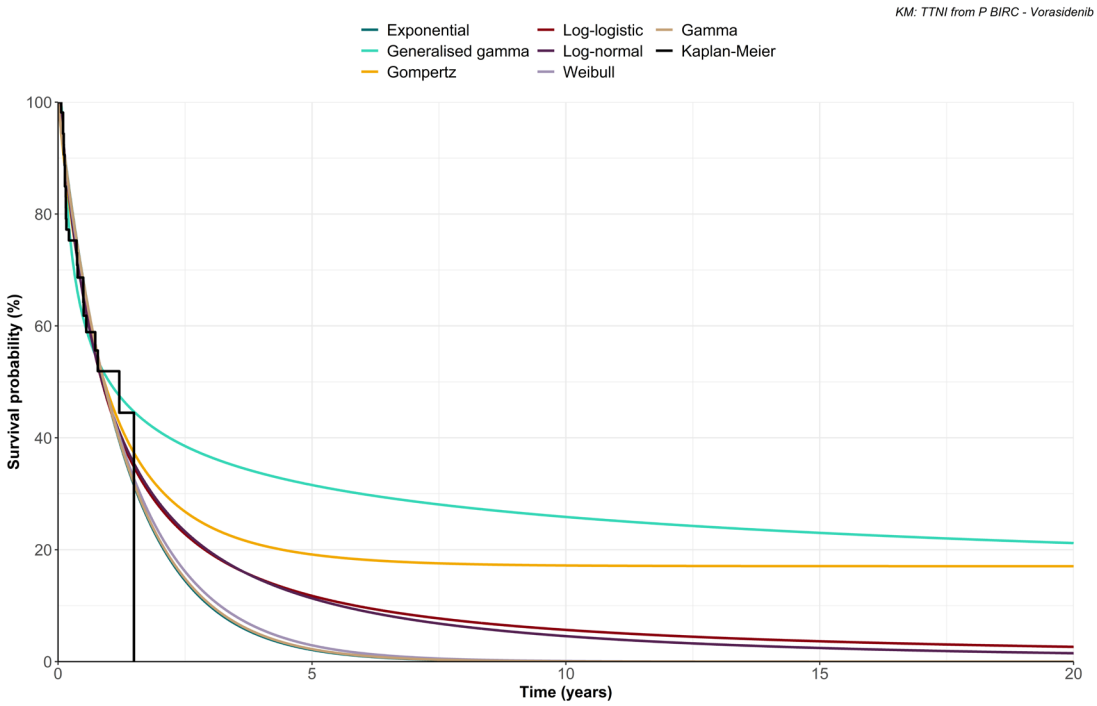
Figure 19: TTNI|P BIRC in the INDIGO trial



Abbreviations: BIRC, Blinded Independent Review Committee; TTNI|P, TTNI given progression.

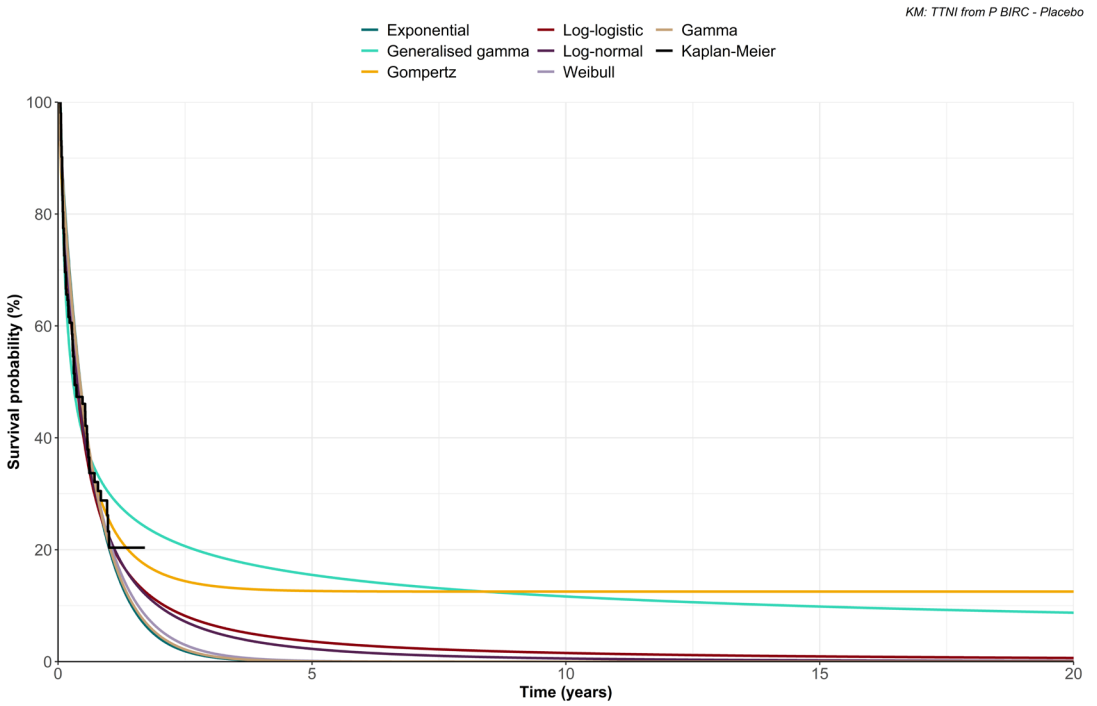
Parametric extrapolations of TTNI|P BIRC for the vorasidenib and placebo arms are presented in Figure 20 and Figure 21. The models in the vorasidenib arm provided different long-term extrapolations, with Gompertz and generalised gamma distributions providing the most optimistic estimates; compared to exponential, Weibull, and Gamma which provided the most pessimistic estimates. Similar patterns were seen in the extrapolations for the placebo arm.

Figure 20: Extrapolation of TTNI|P BIRC in the vorasidenib arm of the INDIGO trial



Abbreviations: BIRC, Blinded Independent Review Committee; TTNI, time to next intervention; TTNI|P, TTNI given progression.

Figure 21: Extrapolation of TTNI|P BIRC in the placebo arm of the INDIGO trial



Abbreviations: BIRC, Blinded Independent Review Committee; TTNI, time to next intervention; TTNI|P, TTNI given progression.

The fit statistics for parametric extrapolations of TTNI|P BIRC are presented in Table 29.

Table 29: Fit statistics for TTNI|P BIRC

Model	Vorasidenib		Placebo	
	AIC	BIC	AIC	BIC
Exponential	128.3	130.1	301.0	303.5
Generalised gamma	**123.1**	**128.6**	**290.5**	**297.9**
Gompertz	129.6	133.3	303.0	307.9
Log-logistic	128.3	132.0	299.2	304.1
Log-normal	126.4	130.1	294.9	299.8
Weibull	130.2	133.9	302.6	307.5
Gamma	130.1	133.8	301.9	306.9

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; BIRC, Blinded Independent Review Committee; TTNI|P, TTNI given progression.

The fit statistics indicated that the generalised gamma model was the best fitting model for both arms. Therefore, the generalised gamma model was chosen to extrapolate TTNI|P BIRC for both arms. It should be noted that clinical advice provided to Servier suggests that even under current management, some people managed with active observation remain NI-free after 10 years[47]. Appendix H: shows the modelled NI-free survival for both arms.

Exploratory analysis of time to next intervention for the placebo arm

In the INDIGO study, patients randomised to receive placebo could receive vorasidenib as their NI (i.e., placebo patients could crossover), which is not representative of the real-world use of vorasidenib (given that vorasidenib is not routinely available in current practice). The cost-effectiveness model requires analysis of TTNI to inform the transitions from S4 to S5 for both treatment arms, although it was noted that for the placebo arm this transition could potentially be influenced by the availability of vorasidenib after progression for patients randomised to placebo as part of the INDIGO study. To address this, an exploratory analysis was performed using multiple imputation (MI).

Two versions of TTNI were estimated for placebo:

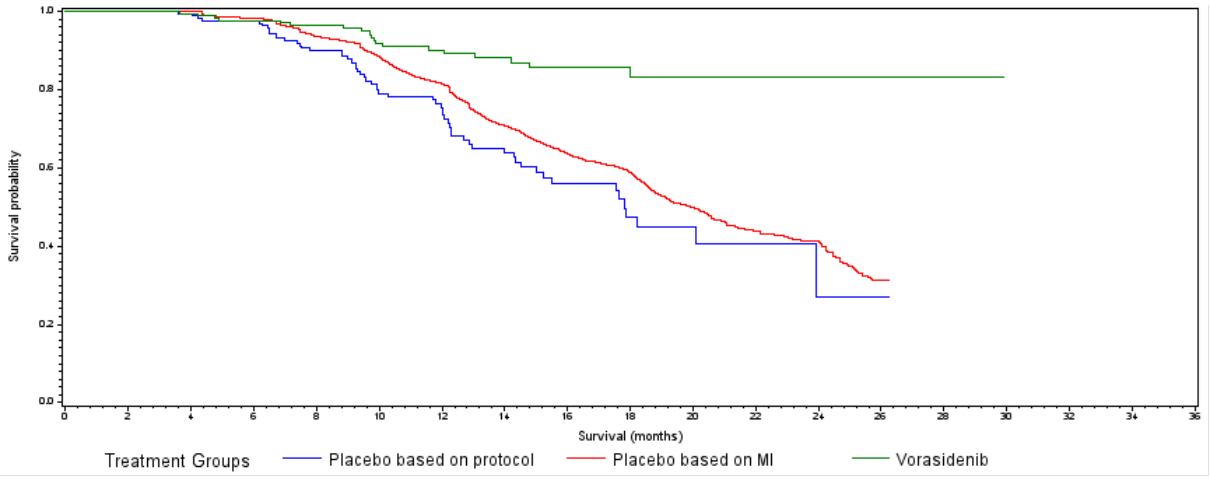
- Based on protocol definition, TTNI is the time from randomisation to the initiation of first subsequent anticancer therapy (including vorasidenib for subjects randomised to placebo who subsequently crossover to vorasidenib) or death due to any cause.

- Based on multiple imputation, TTNI is the time from randomisation to the initiation of first subsequent anticancer (imputed for crossover subjects) or death due to any cause, and TTNI event for crossover subjects refers to the imputed initiation of first subsequent anticancer before the data cut-off.

- The TTNI MI analysis was also performed e using the updated data cutoff date, and the results were consistent with the previously described analysis.

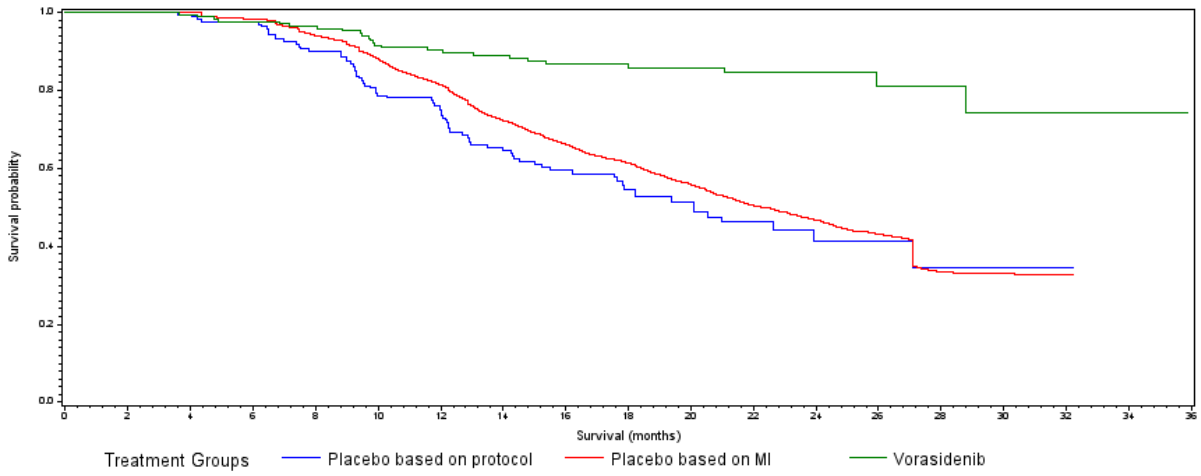
A visual overlay of the KM estimates from these alternative versions of TTNI is provided in Figure 22. Based on the MI analysis, the average TTNI is slightly longer than the unadjusted analysis. However, on the basis of this exploratory analysis, it was determined that any further adjustment of TTNI|P was likely to be reasonably similar to the unadjusted analysis used to inform the model.

Figure 22: Exploratory analysis of TTNI based on multiple imputation and protocol definition Sept 2022 DCO



Abbreviations: MI, multiple imputation; TTNI, time to next intervention.

Figure 23: Exploratory analysis of TTNI based on multiple imputation and protocol definition Mar 2023 DCO



Summary of base case curve fits (INDIGO data)

The base-case analysis uses the curve fits presented in Table 30.

Table 30: Base-case curve fits – INDIGO data

Transition	Arm (if applicable)	Model fit	Rationale

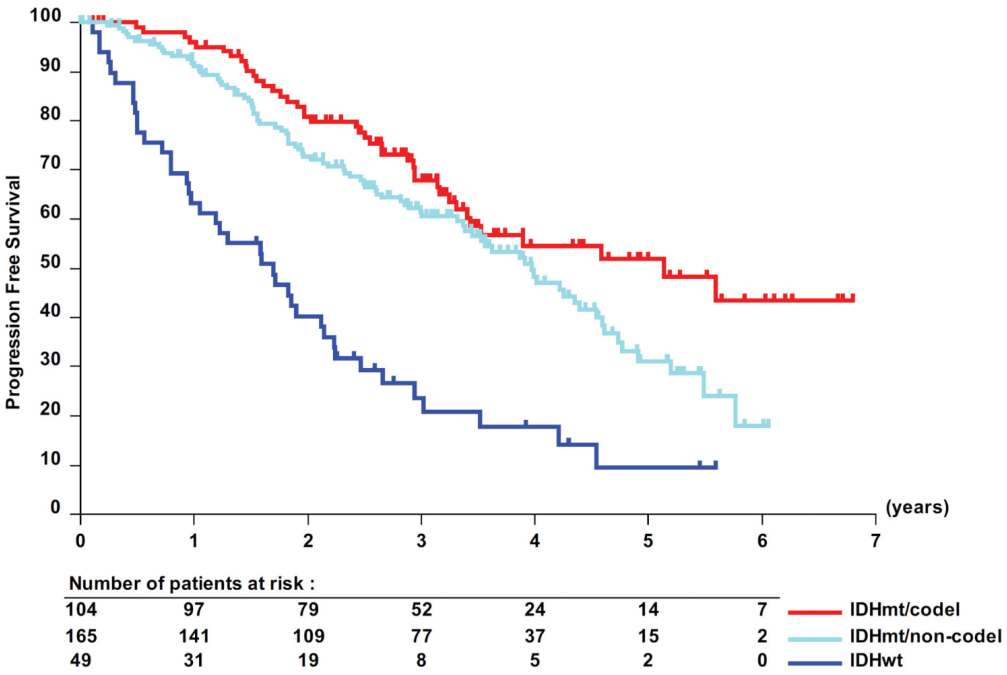
S1->S4	Vorasidenib	Log-normal	Best statistical fit for vorasidenib arm. For the placebo arm, fit statistics were similar across several models, but log-normal was chosen for consistency with the vorasidenib arm.
S2->S4	Active observation		
S4->S5	Vorasidenib	Generalised gamma	Best statistical goodness-of-fit across both arms.
	Active observation		

Time to discontinuation of next intervention (published literature)

A study by Baumert *et al.* (2016) provided survival outcomes for 477 patients with grade 2 glioma who were randomised to receive either conformal RT or dose-dense TMZ[79]. A KM estimate of PFS is presented in the paper which separates outcomes for IDHmt (both 1p/19q co-deleted and non-co-deleted) and IDH-wildtype gliomas. The KM estimates for PFS in the different glioma subtypes (IDHmt co-deleted, IDHmt non-co-deleted, and IDH-wildtype) from Baumert *et al.* (2016) are presented in Figure 24.

The KM estimates suggest differences in outcomes between the glioma subtypes. These are important to capture appropriately when implementing this data source in the cost-effectiveness model. Importantly, as the model is extrapolating long-term survival, the changing distribution of histology among the surviving cohort (prior to those patients initiating their next treatment line upon entering S7) should be taken into consideration.

Figure 24: KMs of PFS in different subtypes of grade 2 glioma, Baumert *et al.* (2016)



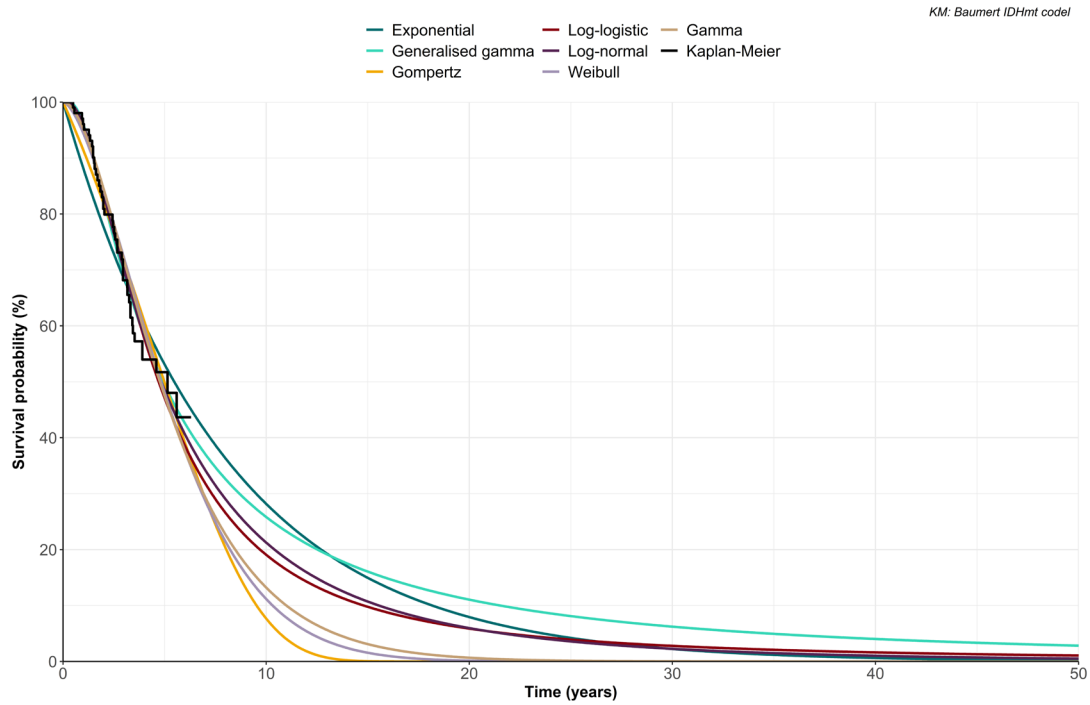
Abbreviations: codel, co-deleted; mt, mutant; wt, wild type.

One potential issue with the data from Baumert *et al.* (presented in Figure 24) is that the number of PFS events which were deaths is not reported. However, a study by Ma *et al.* (2021) reports both PFS

and TTP KM data. This allows a visual comparison of the KMs to determine the likely proportion of events in the PFS line which were deaths prior to progression. As the study population in Ma *et al.* (2021)[81] was for later treatment lines (salvage therapies, i.e., 2L+), and the TTP and PFS were almost identical, it was considered reasonable to assume that pre-progression deaths were rare in the context of an earlier treatment line, and therefore PFS and TTP were assumed to be similar.

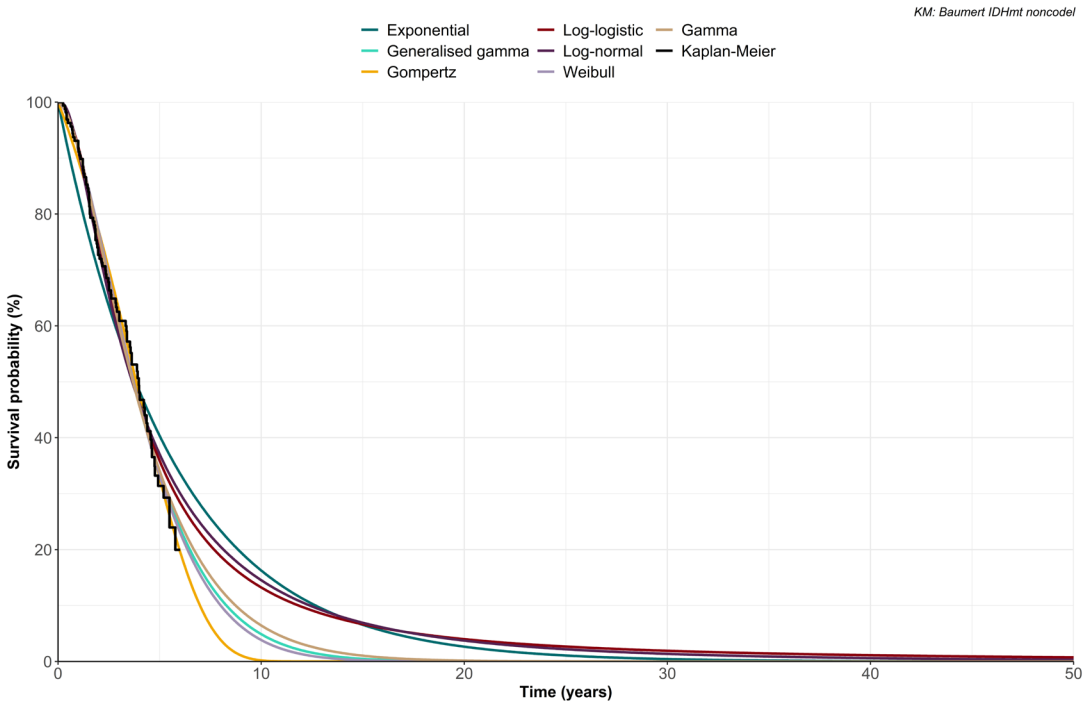
Parametric extrapolations of the PFS data for IDHmt/co-deleted glioma patients from the Baumert et al. study are presented in Figure 25 and Figure 26. Extrapolations of survival in patients with IDH-wildtype glioma were not included in the model given that these patients would not have been included in the INDIGO trial.

Figure 25: Extrapolations of PFS in IDHmt, 1p/19q co-deleted LGG, Baumert *et al.*, (2016)



Abbreviations: codel, co-deleted; KM, Kaplan-Meier; LGG, low-grade glioma; mt, mutant; PFS, progression-free survival.

Figure 26: Extrapolations of PFS in IDHmt, 1p/19q non-co-deleted LGG, Baumert *et al.,* (2016)



Abbreviations: codel, co-deleted; KM, Kaplan-Meier; LGG, low-grade glioma; mt, mutant; PFS, progression-free survival.

Given the relatively short follow-up in this study, there was substantial variation in the parametric extrapolations for IDHmt, 1p/19q co-deleted low-grade glioma. However, all survival models predicted reasonably poor survival outcomes after around 20 years. This was also seen in the patients who had IDHmt, 1p/19q non-co-deleted glioma. It is unclear from the visual fits for each of the cohorts which model was the best fitting and provided the most reasonable estimates of PFS, and therefore the statistical goodness-of-fit scores were assessed.

Fit statistics for parametric extrapolations of PFS for patients in the two relevant cohorts from Baumert *et al.* (2016) are presented in Table 31.

Table 31: Fit statistics for PFS in IDHmt, 1p/19q co-deleted glioma; IDHmt 1p/19q non-co-deleted glioma; and IDH-wild type glioma, Baumert *et al.,* (2016)

Model	PFS – IDHmt, 1p/19q co-deleted LGG		PFS – IDHmt, 1p/19q non-co-deleted LGG	
	AIC	BIC	AIC	BIC
Exponential	486.6	489.2	898.6	901.7
Weibull	478.4	483.7	**880.9**	**887.1**
Gompertz	484.6	489.9	884.4	890.6
Log-logistic	475.3	480.6	883.4	889.6
Log-normal	**473.6**	**478.9**	884.5	890.7
Generalised gamma	475.1	483.0	882.8	892.1
Gamma	476.6	481.9	**880.9**	**887.1**

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; LGG, low-grade glioma; mt, mutant; PFS, progression-free survival.

Fit statistics suggest that the best fitting model to PFS for the group with IDHmt, 1p/19q co-deleted glioma was the log-normal model. From the visual fits, this model provides middle-ground estimates in comparison to other models, and therefore seems realistic in the long term. This model was used for extrapolation of PFS in this group in the base case of the cost-effectiveness model. For patients with IDHmt 1p/19q non-co-deleted glioma, the Gamma and Weibull models provided the best statistical fit to PFS. Therefore, the Gamma model was selected to extrapolate PFS in this population in the base case of the cost-effectiveness model.

The histological mix of patients upon entering S5 in the cost-effectiveness model is unknown. Therefore, the model assumes no change from baseline in histological mix. In Figure 24, the number at risk at baseline of 104 IDH mutant co-deleted and 165 IDH mutated non-co-deleted was used, excluding patients with IDH-wildtype glioma. This resulted in an estimated histological mix for patients with LGG at baseline of 38.7% and 61.3% respectively. This histological mix was used along with the best-fitting extrapolations, applying the same technique as is often used in cost-effectiveness models to estimate the sex distribution of the general population becoming more female over time.

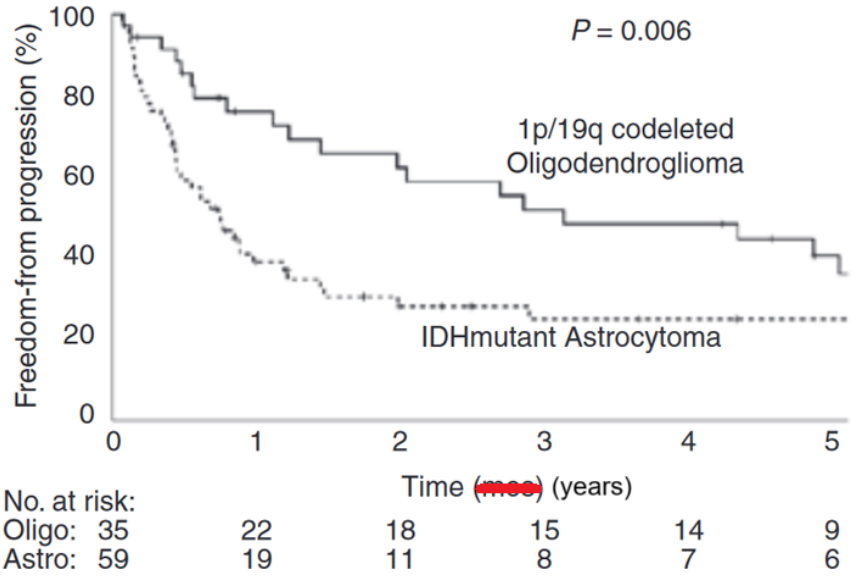
However, this histological mix of patients omits the possibility of some patients entering S5 with high-grade glioma (HGG); and data for this group of patients is not available from Baumert *et al.*, (2016)[79]. To account for this, 23.6% of patients were assumed to enter S5 with HGG (based on a study by Hervey Jumper *et al.*, [2023][83]), and a median survival estimate of 3.1 years (based on a study by Juratli *et al.*, [2012][80]) to further re-weight the hazard of a progression event after initiation of NI.

Time to discontinuation of next intervention plus (NI+) (published literature)

A study by Ma *et al.*, (2021) was identified which focused on salvage therapies which would likely be the various treatments that a patient receives before moving onto BSC[81]. However, no data specifically for an outcome defined as ‘time to BSC’ is available from any known data source. The closest proxy available for this is the PFS and TTP reported in Ma *et al.* Consequently, the assumption was made that PFS/TTP serves as a proxy for time to BSC. That is, that patients go into a planned palliative or supportive care setting upon exiting salvage therapies at 2L+, and that the reasons for stopping treatment align with disease progression at a salvage therapy baseline.

The KM estimate of TTP from Ma *et al.* (2021) is presented in Figure 27. A hazard ratio of 7.73 for astrocytoma vs oligodendroglioma published by Kavouridis *et al.* (2021)[84] was applied inversely to the best-fitting extrapolation to provide the estimated survival of oligodendroglioma patients on salvage therapy. Then, the baseline distribution of astrocytoma and oligodendroglioma was used to extrapolate the proportion of the remaining cohort with either histology. Finally, a pooled hazard estimate was produced, and this was used in the model as for the S7 to S8 transition probability.

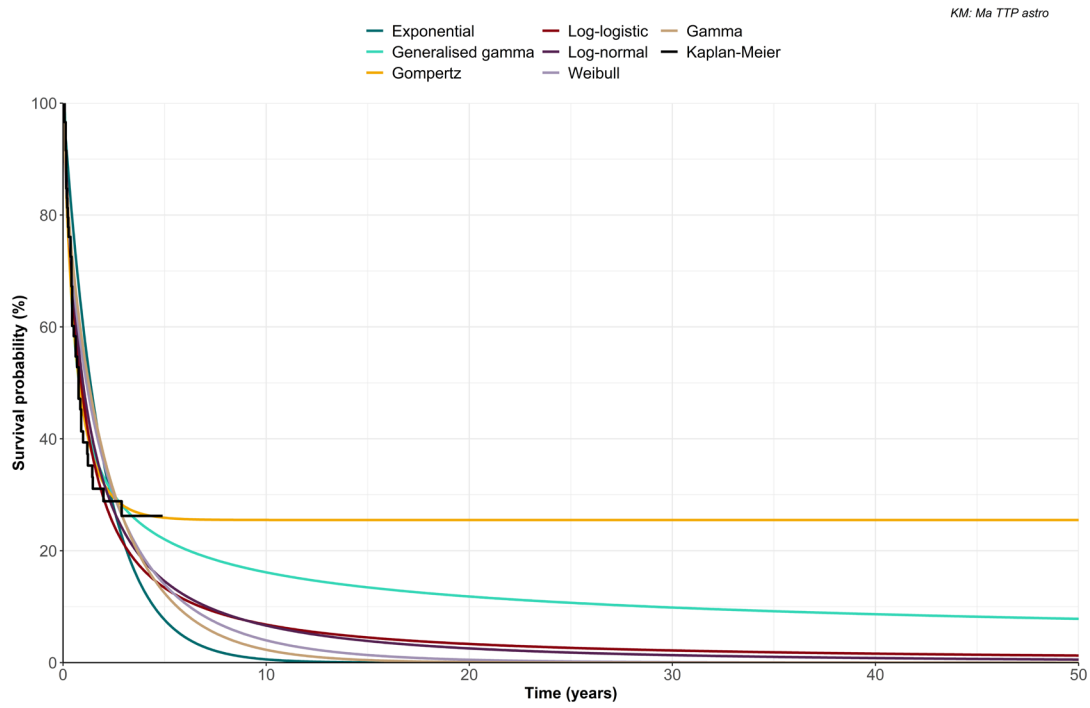
Figure 27: KM of TTP/FFP in IDHmt astrocytoma or 1p/19q co-deleted oligodendroglioma, Ma *et al.* (2021)



Abbreviations: astro, astrocytoma; KM, Kaplan-Meier; mos, months oligo, oligodendroglioma;.
Note: The time scale presented in the original publication was a typographical error, as this should be years instead of months – this was corrected in the diagram above.

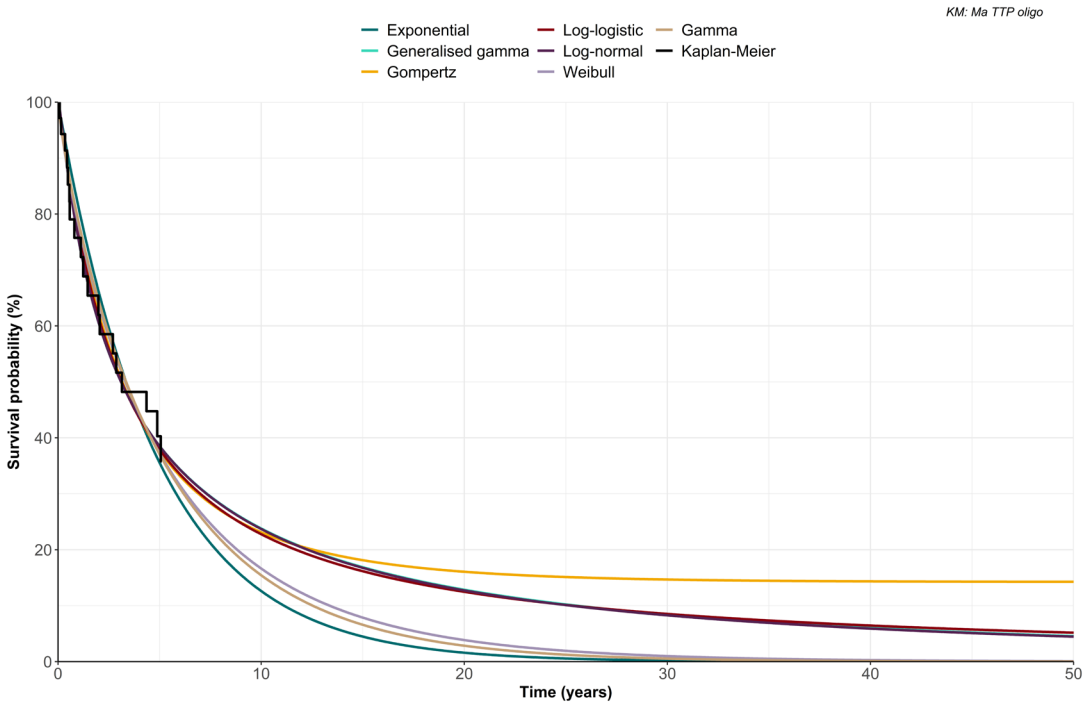
Parametric extrapolations are provided in Figure 28, fitted to the data for IDHmt astrocytoma patients, and in Figure 29, fitted to the data for 1p/19q co-deleted oligodendroglioma patients.

Figure 28: Extrapolations of TTP in IDHmt astrocytoma, Ma *et al.*, (2021)



Abbreviations: mt, mutant; TTP, time to progression.

Figure 29: Extrapolations of TTP in 1p/19q co-deleted oligodendroglioma, Ma *et al.,* (2021)



Abbreviations: mt, mutant; TTP, time to progression.

Fit statistics for extrapolations of TTP in IDHmt astrocytoma patients from Ma *et al.,* (2021) are presented in Table 32**.**

Table 32: Fit statistics for TTP extrapolations, Ma *et al.,* (2021)

Model	PFS – IDHmt astrocytoma		PFS – 1p/19q co-deleted oligodendroglioma	
	AIC	BIC	AIC	BIC
Exponential	340.6	342.7	**197.4**	**199.0**
Weibull	334.0	338.1	198.8	201.9
Gompertz	317.2	321.3	198.7	201.8
Log-logistic	323.3	327.5	198.5	201.6
Log-normal	321.7	325.9	197.9	201.0
Generalised gamma	**313.4**	**319.7**	199.9	204.6
Gamma	337.4	341.6	199.0	202.1

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; PFS, progression-free survival.

Fit statistics suggested that the best fitting model to TTP was the generalised gamma model, which was selected in the base-case analysis. The exponential model was the statistically favoured model to predict TTP in oligodendroglioma patients, however this model eventually crossed with the astrocytoma extrapolation. In reality, it would be expected that more astrocytoma patients would progress than oligodendroglioma patients over the full modelled time horizon, and therefore the extrapolation with consistently greater TTP in the astrocytoma arm was chosen which was a Gompertz model. This model provided much more optimistic estimates of TTP in the longer term than the exponential model.

Survival following progression and discontinuation of INDIGO treatment (published literature)

For mortality, three different curves were produced:

- Deaths from S5 or S6 were deemed deaths from NI.
- Deaths from S7 were deemed deaths from NI+.
- Deaths from S8 were deemed deaths from BSC.

Deaths from NI or NI+

The risk of death for people who initiate NI is expected to be comparable to the age- and sex-adjusted general population.

Deaths from BSC

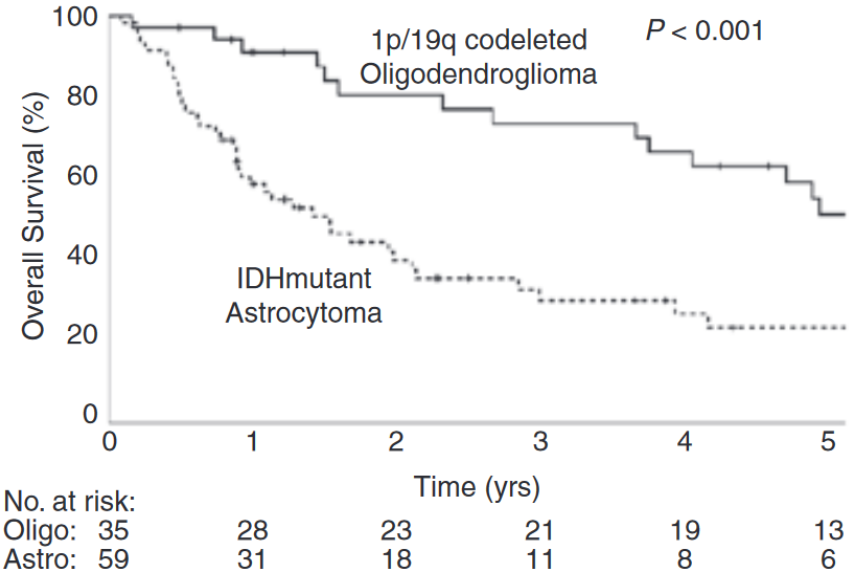
OS data were reported in Ma *et al.,* (2021)[81]. This endpoint was useful in providing a proxy for OS for patients who are on BSC. In the model, this translates to transitions from S8 (BSC) to S9 (Dead). This source was used in the base case of the cost-effectiveness model to inform this transition.

The proportions of patients at baseline with either an IDHmt astrocytoma or 1p/19q co-deleted oligodendroglioma in Ma *et al.* was the best available source on the relative frequency of these histologies upon initiating salvage therapy (35 oligodendroglioma versus 59 astrocytoma) and was used to inform a percentage at baseline (i.e., the new baseline upon entry to S8). As only the IDH mutant astrocytoma KM estimate in this article was directly relevant to the INDIGO population (i.e., the later-line population starting from that baseline, as INDIGO patients are IDH mutated at baseline), this KM estimate, and its best-fitting extrapolation (discussed later in this sub-section) were used as a reference curve. In conjunction with this, the hazard ratio of 7.76 [95% CI of 2.95-20.40] for astro vs oligo published by Kavouridis *et al.,* (2021)[84] was used to provide an estimate of the relative hazard of each histology. Combining the proportion of patients with astrocytoma at baseline (37.23% oligodendroglioma, 62.77% astrocytoma) with this hazard ratio then provides two different survival extrapolations, one for astrocytoma and one for oligodendroglioma.

From this starting point, the same method that was applied to estimating the changing sex distribution over time in general population mortality adjustment was used to compute a pooled hazard. For each cycle, the proportion of the remaining cohort that had either histology was re-calculated considering relative mortality to that point. As the balance of histology is then known for all cycles, the hazard of each extrapolation could be weighted in each cycle to provide an accurate pooled hazard which could be used as a time-varying transition probability in the cost-effectiveness model. This pooled hazard was used to inform the transition S8 to S9.

The KM estimate of OS in the Ma *et al.*, (2021) publication is presented in Figure 30. A hazard ratio of OS 0.34 (95% CI: 0.18, 0.64) was calculated for patients with 1p/19q co-deleted oligodendrogliomas indicating poorer OS in patients with IDHmt astrocytoma by comparison.

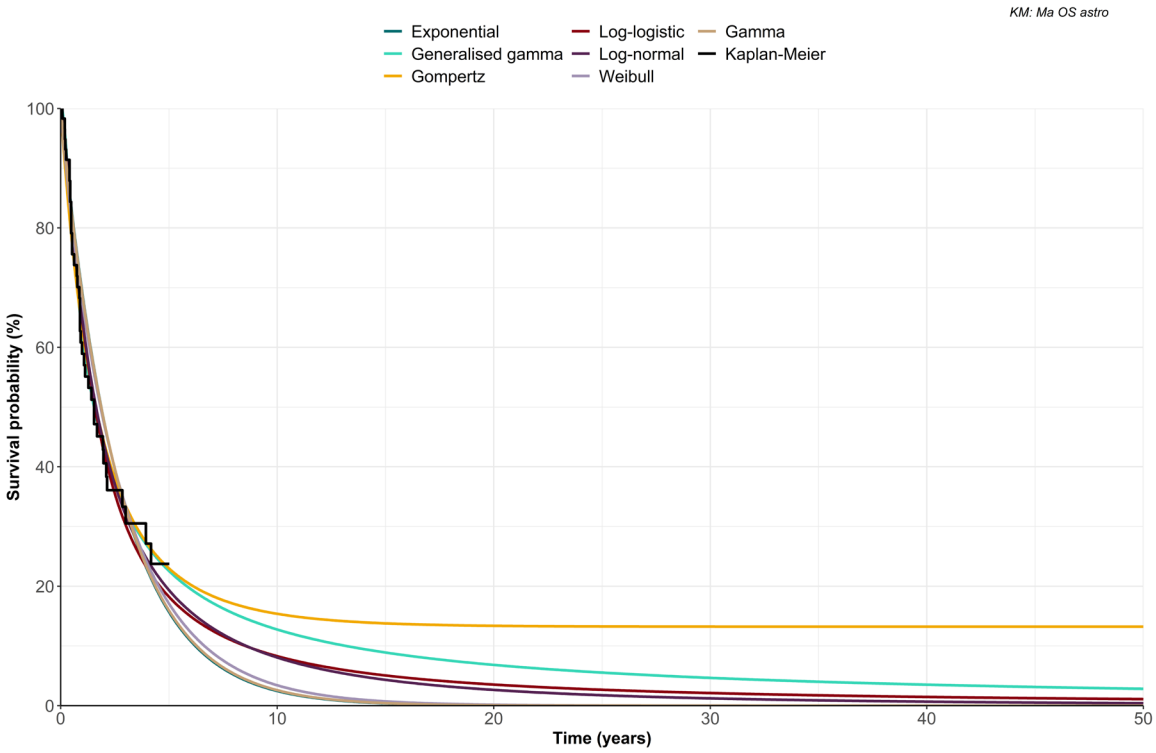
Figure 30: KMs of OS in IDHmt astrocytoma and 1p/19q co-deleted oligodendrogliomas, Ma *et al.*, (2021)



Abbreviations: astro, astrocytoma; KM, Kaplan-Meier; oligo, oligodendroglioma; OS, overall survival; yrs, years.

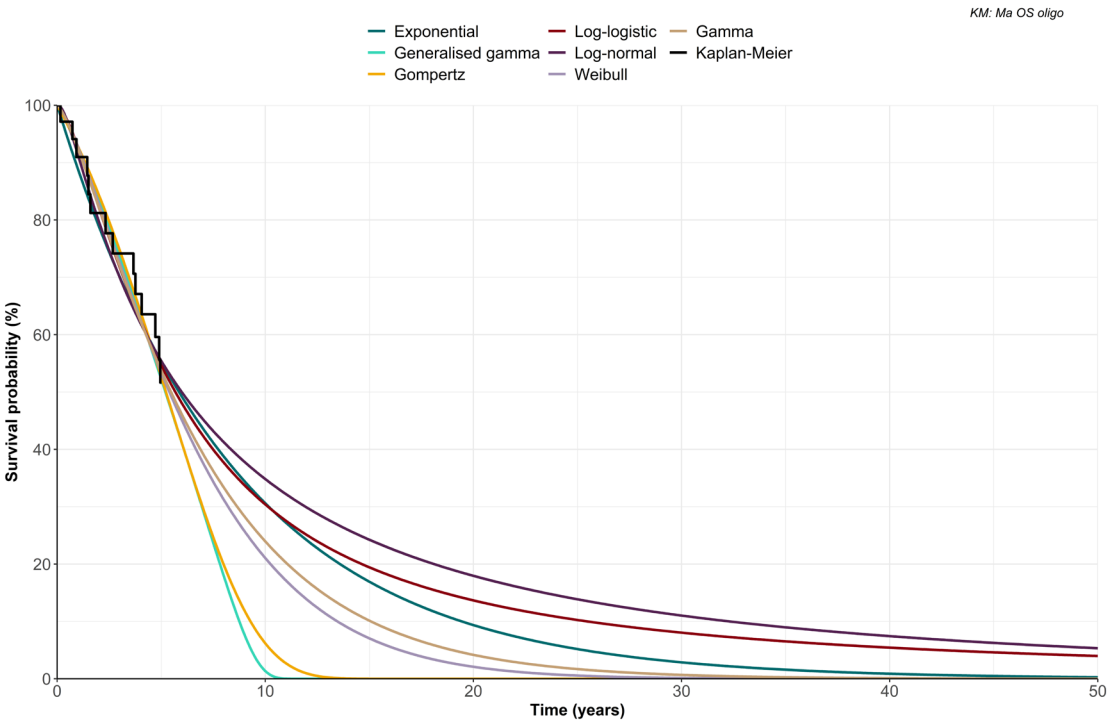
Parametric extrapolations of OS in patients with IDHmt astrocytoma or 1p/19q co-deleted oligodendroglioma are presented in Figure 31. For patients with IDHmt astrocytoma, long-term OS predictions were similar between the models, with the exception of the Gompertz model which predicted a plateau after around 15 years which seems unrealistic. The other models seem to plateau at close to 0 which would be expected after a long period of time.

Figure 31: Extrapolations of OS in IDHmt astrocytoma, Ma *et al.,* (2021)



Abbreviations: KM, Kaplan-Meier; mt, mutant; OS, overall survival.

Figure 32: Extrapolations of OS in 1p/19q co-deleted oligodendrogliomas, Ma *et al.,* (2021)



Abbreviations: KM, Kaplan-Meier; mt, mutant; OS, overall survival.

Fit statistics for extrapolations of OS in patients with IDHmt astrocytoma from Ma *et al.*, (2021) are presented Table 33.

Table 33: Fit statistics for OS in IDHmt astrocytoma and 1p/19q co-deleted oligodendrogliomas, Ma *et al.,* (2021)

Model	OS – IDHmt astrocytoma		OS – 1p/19q co-deleted oligodendroglioma	
	AIC	BIC	AIC	BIC
Exponential	348.7	350.8	**161.7**	**163.2**
Weibull	350.4	354.6	162.5	165.6
Gompertz	347.2	351.4	161.9	165.0
Log-logistic	345.0	349.1	163.1	166.3
Log-normal	**343.6**	**347.8**	164.1	167.3
Generalised gamma	344.2	350.4	163.9	168.6
Gamma	350.7	354.8	162.6	165.8

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; OS, overall survival.

Fit statistics suggested that the log-normal model provided the best statistical fit to OS in patients with IDHmt astrocytoma. This model provided middle-ground estimates of long-term OS in comparison to other models, with the surviving proportion of patients close to 0 at the tail which would be expected. Therefore, there was no evidence to suggest that this model would not be appropriate to extrapolate OS in this population and therefore this curve was selected. For the oligodendroglioma group, statistical fits suggested that the exponential model was the best fitting to the data. However, use of this model indicated that the survival curves for astrocytoma and oligodendroglioma patients would be expected to cross, which would not be realistic in practice given the much poorer prognosis of astrocytoma. Therefore, the log-normal model was also assumed to be an appropriate fit, given that AIC and BIC scores did not vary much between models.

Opting out of receiving further treatment

In real-world practice, it is expected that some people may 'opt out' of receiving treatment at two key stages: following completion of the initial treatment period (i.e., vorasidenib or active observation) or following completion of their NI. For those patients that opt for no further treatment, there is no data available to inform the model. Therefore, upon opting out of future treatment, patients are assumed to transition to S8 (i.e., BSC) are assigned OS estimates derived from Ma *et al.*, (2021)[81]. The possible transitions reflecting opting out of treatment are represented in the model schematic (Figure 15) as dashed lines from either S4 or S5, to S8. In the base-case analysis, assumed 'opt out' proportions of 5% are applied prior to initiation of NI and NI+, based on clinical expert feedback to Servier that opting out was relatively uncommon[47].

Resection surgery following progression and discontinuation

In real-world practice, it is possible that some patients undergo resection surgery following progression, which may (theoretically) return these patients to a 'progression-free' health state. In the

base-case analysis, this transition (from S5 to S2) was not permitted, but can be investigated via sensitivity analysis if the distribution of interventions offered in the NI health state is changed to include a non-zero percentage of patients that receive 'surgery alone'.

Summary of base case curve fits (literature data)

The base-case analysis uses the curve fits presented in Table 34.

Table 34: Base-case curve fits – literature data

Transition	Model fit	Rationale
S5->S7 S6->S7	IDH codeleted: Log-normal IDH not codeleted: Gamma	Best statistical goodness-of-fit scores.
S7->S8	Astro: Generalized gamma Oligo: Gompertz	Best statistical goodness-of-fit scores.
S5->S9 S6->S9 S7->S9	NA – general population	Assumption of no excess mortality
S8->S9	Astro: Log-normal Oligo: Log-normal	Best statistical goodness-of-fit scores, paired with consistency across subtypes.

Abbreviations: Astro, astrocytoma; oligo, oligodendroglioma;

3.3.3 Adverse effects

In the cost-effectiveness model, AE management costs are set to zero. The only AE which is expected to be associated with a substantial utility loss or cost is seizure, the management of which is captured separately within the model via the medical resource use (MRU) component. Consequently, AEs for people treated with vorasidenib or managed via active observation have no additional impact on model results, beyond those impacts implicitly captures via MRU and health state utility values.

Safety at later lines is unlikely to have a large effect on the cost-effectiveness of vorasidenib, as the choice of subsequent treatment is not affected by whether patients had vorasidenib previously or not. In addition, it is expected that average utility values for people residing in later health states will implicitly capture the impact of AEs, particularly longer-term effects. For these reasons, and due to the lack of robust safety information for later-line use by drug, AEs for all subsequent treatments also have no additional impact on model results but are expected to be implicitly captures via other aspects of the model (i.e., MRU and health state utility values).

3.4 Measurement and valuation of health effects

3.4.1 Health-related quality-of-life data from clinical trials

In the INDIGO trial, HRQoL outcomes were assessed using multiple disease specific and generic instruments, including the EQ-5D-5L[66,71]. Patients' EQ-5D-5L questionnaires were taken every 3 months following baseline, with many patients having an additional follow-up date on the day of discontinuation of either vorasidenib or placebo.

In the INDIGO trial, there were 1,518 total observations for EQ-5D across the 331 patients; 797 from the 168 patients assigned to vorasidenib and 719 from the 163 patients who were assigned to placebo (Table 35).

Table 35: Summary of utility values before and after clinical endpoints in the INDIGO trial

Endpoint		Number of patients	Number of observations	Mean (95% CI)	Median (LQ, UQ)
Prog status	PF	325	1,256	0.744 (0.735, 0.754)	0.777 (0.681, 0.905)
	PD	115	251	0.713 (0.689, 0.737)	0.747 (0.660, 0.809)
Tx status	On tx	326	1,443	0.742 (0.733, 0.751)	0.776 (0.680, 0.905)
	Off tx	71	73	0.683 (0.637, 0.729)	0.705 (0.621, 0.786)

Abbreviations: CI, confidence interval; LQ, lower quartile; PD, progressed disease; PF, progression-free; prog, progression; tx, treatment; UQ, upper quartile.
Note: Progression measured according to blinded independent review committee.

3.4.2 Mapping

The EQ-5D-5L responses from the INDIGO trial were 'cross-walked' to EQ-5D-3L responses using the mapping approach developed by Hernández-Alava *et al.*, (2018)[85]. Baseline was the EQ-5D assessment collected at Cycle 1, Day 1. The progression variable was defined by comparing a patient's 'date of progression' and their EQ-5D assessment date – thus where an EQ-5D assessment date occurred after the progression date, the patient's assessment was a 'post-progression' assessment. Otherwise, the progression status variable took the value "pre-progression". Furthermore, the pre-progression value was stratified according to whether the assessment occurred at baseline or not. For records where the date of progression was missing, the treatment discontinuation date or death/censoring (whichever came first) was considered a proxy for date of progression.

The treatment status variable was defined by comparing a patient's 'treatment end-date' and their EQ-5D assessment date – thus where an EQ-5D assessment date occurred after the treatment end-date the patient was "off treatment" (otherwise they were considered to be "on treatment"). For records where the treatment end-date was missing, it was assumed that patients remained on treatment until they experienced disease progression or death/censoring.

Mixed-effects models were used for regression analyses, with random-effects at the patient level to account for any apparent heterogeneity. This is an important aspect of analyses involving repeated measure data as there is expected to be a degree of autocorrelation between subsequent responses recorded by each patient. The regression model coefficients were used to calculate the utility values corresponding to each of the health states in the cost-effectiveness model.

Two regression models were fitted to the data and applied in the model:

- **Base-case analysis:** Progression flag and baseline utility.
- **Sensitivity analysis:** Progression flag only.

The health state utility values predicted by the regression models are presented in Table 36.

Table 36: Resultant utility values from regression models

Health state	HSUV for each model	
	Base case	Sensitivity analysis
S1 – PF and on tx	0.737	0.747
S2 – PF and off tx	0.737	0.747
S3 – PD and on tx	0.728	0.729
S4 – PD and off tx	0.728	0.729

Abbreviations: HSUV, health state utility value; PD, progressed disease; PF, progression-free; tx, treatment.

3.4.3 Health-related quality-of-life studies

An SLR was conducted in April 2023 and updated in May 2024 to identify and summarise published evidence on the humanistic burden (HRQoL and utilities) of grade 2 or 3 diffuse glioma. Full details of the methodology and results of the HRQoL SLR are provided in Appendix F. The original SLR identified 25 publications reporting on 20 studies and the SLR update identified a further 10 publications reporting on 10 studies that were considered relevant for inclusion.

Multiple sources were screened for available HRQoL data including Bhanja (2024)[86] and NICE TA23[73], which was not identified in the HRQoL SLR due to the date restriction of 2013-present which was applied to QoL outcome/PRO studies. Bhanja (2024) provided utility scores based on visual analogue scores (VAS) and time trade-off (TTO) which therefore could provide different estimates of utility values. However, given the lack of sources to approximate the quality of life in S5 and S6, values from this source were not applied in the model. In NICE TA23, TMZ was assessed for the treatment of recurrent malignant glioma. Within the clinical trial, HRQoL data were collected in the form of a global health score which is provided as part of the EORTC QLQ-C30 questionnaire. However, only one utility value of potential relevance was identified – a value for glioma recurrence (utility value = 0.60). None of the other studies identified in the HRQoL SLR provided suitable utility data for use in the economic model.

To address the evidence gap for utility values required in the later health states, a vignette study was conducted. This was a non-interventional study conducted in two phases: 1) development of descriptions of health states (vignettes) to describe symptoms, functioning and HRQoL impact of IDHmt glioma, which were reviewed and approved by HCPs, patients and patient-advocacy representatives, 2) elicitation of utility weights for each health state by the general public using EQ-5D and time trade-off valuation methods. Full details of the methods and results of the vignette study are provided in a separate report[87]. The raw outputs from the EQ-5D analysis were considered for use within the model. However, it was deemed implausible for utility to increase from S5 to S6 and then decrease for S7 and increase again for S8. More specifically, HRQL would be expected to typically worsen during and after RT/CT due to associated toxicities, and that for most people, HRQL would not recover to a persons' baseline after completion of treatment. Instead, HRQL tends to continuously decline over time, with spikes at each progression, especially driven by neurologic toxicity. Therefore,

in the base-case analysis, the utility values for S5 and S6 were averaged, and applied for both S5 and S6; and the utility values for S7 and S8 were averaged, and applied for both S7 and S8. Alternative applications of the vignette utility values were also considered, as presented in Table 37.

Table 37: Resultant utility values from vignette study

Health state	Utility value for each health state				
	Base case	Raw values	Lowest	Highest	Flat average
S5 – On NI	0.480	0.400	0.260	0.560	0.410
S6 – Off NI		0.560			
S7 – On NI+	0.340	0.260			
S8 – Off NI+ (BSC)		0.420			

Abbreviations: BSC, best supportive care; NI, next intervention.

3.4.4 Sensitivity analysis: QALY losses

In the base-case analysis, no additional QALYs losses were included in the model. However, in sensitivity analyses, QALY losses were assigned to the following events:

- A QALY loss for any patients who undergo debulking surgery when entering S5, S6, S7, or S8 (proportions presented in Section 0).
- A QALY loss for patients receiving end-of-life care.

Due to a paucity of data to inform these inputs, assumed values of 0.10 were applied (but not enabled in the base-case analysis).

3.4.5 Health-related quality-of-life data used in the cost-effectiveness analysis

Age-related utility decrements have also been included in the model base case to account for the natural decline in quality of life associated with age. Utility values from the general population at each age were calculated using the algorithm by Ara & Brazier (2011)[88]. The utility multiplier was the calculated per increase in age and applied in each cycle throughout the model time horizon.

$$General\ population\ utility\ value = 0.9508566 + 0.0212126 \times male - 0.0002587 \times age - 0.0000332 \times age^2$$

A summary of utility values used in the economic analysis is presented in Table 38.

Table 38: Summary of utility values for cost-effectiveness analysis

State	Utility value	Reference in submission	Justification
S1 – PF and on tx	0.737	§ 3.4.2	Regression model fitted to INDIGO data
S2 – PF and off tx	0.737		
S3 – PD and on tx	0.728		
S4 – PD and off tx	0.728		
S5 – On NI	0.480	§ 3.4.3	Outputs from vignette study[87]
S6 – Off NI	0.480		
S7 – On NI+	0.340		
S8 – Off NI+ (BSC)	0.340		
S9 - Dead	0	NA	No QALYs gained after death

Abbreviations: BSC, best supportive care; NA, not applicable; NI, next intervention; PD, progressed disease; PF, progression-free; tx, treatment; QALY, quality-adjusted life years.

In the cost-effectiveness model, adverse event (AE) management costs and HRQoL decrements were set to zero. The only AE which is expected to be associated with a substantial utility loss is seizure. The impact of seizures on HRQoL is implicit in the utility values specified for each of the model health states. Consequently, AEs for people treated with vorasidenib or managed via active observation have no additional impact on model results, beyond those impacts implicitly captured via health state utility values.

Safety at later lines is unlikely to have a large effect on the cost-effectiveness of vorasidenib, as the choice of subsequent treatment is not affected by whether patients had vorasidenib previously or not. In addition, it is expected that average utility values for people residing in later health states will implicitly capture the impact of AEs, particularly longer-term effects. For these reasons, and due to the lack of robust safety information for later-line use by drug, AEs for all subsequent treatments also have no additional impact on model results but are expected to be implicitly captures via other aspects of the model (i.e., resource use and health state utility values).

3.5 Cost and healthcare resource use identification, measurement and valuation

A systematic review of the literature was conducted in April 2023 and updated in May 2024 to identify relevant published cost and resource use data for patients with IDH1 and IDH2 positive LGG at least 1 year after surgical resection who are not candidates for either RT or CT (or both) but do have recurrent or residual disease. Searches were performed alongside the economic evaluation SLR. In line with the systematic review of cost-effectiveness studies, limited cost and resource use data were identified for the patient population relevant to this appraisal.

Due to the lack of relevant evidence identified as part of the SLR, the prior NICE appraisal in England for LGG (TA23[73] [temozolomide]) and NG99[35] were considered the most relevant sources for informing healthcare resource use estimates. Cost inputs, which are described in further detail throughout this section, were obtained from sources deemed typical for informing UK-based economic evaluations. The following sources were used to identify costs:

- The British National Formulary (BNF) and NHS electronic Market Information Tool (eMIT) for treatment acquisition costs.
- The NHS National Cost Collection (also known as NHS reference costs) for administration, resource use costs, and adverse event management costs.
- Published literature for end-of-life care costs.

3.5.1 Intervention and comparators' costs and resource use

Treatment acquisition costs

[redacted]

Patients are expected to take one 40 mg tablet per day unless there is a dose modification. Based on the use of vorasidenib in the INDIGO study[66,71], the model assumes a [redacted]% relative dose intensity.

Treatment administration costs

As vorasidenib is administered orally, it is assumed that no administration costs are incurred. In line with acquisition costs, patients in the active observation arm also do not incur administration costs.

Subsequent treatment costs

The cost of subsequent treatment commonly used in UK practice are included in the model base case. Taking into consideration the availability of treatments in UK practice, published guidelines, and based on the company's understanding of clinical practice, it is assumed that the cost of CCNU (also known as lomustine), procarbazine, CCNU and vincristine (PCV) or temozolomide (TMZ) is representative of a 'typical' chemotherapy regimen that may be offered to patients at this line of therapy in NHS England practice, for all patients who receive subsequent therapy, and echoed in clinical feedback provided to Servier[47]. In addition, a small number of patients may receive off-label bevacizumab (in combination with CCNU). The cost of subsequent treatment includes both treatment acquisition and administration costs. The microsimulation combines inputs for costs and market shares with inputs related to expected treatment durations and grace periods, in order to estimate the costs of subsequent therapies. This approach ensures the model accurately reflects treatment costs and regimens used in NHS England.

CCNU is a CT which can be given as a monotherapy or as part of two different combination therapies: PCV and bevacizumab (each described later in more detail). The pack cost for CCNU was taken from the BNF[89]. Only one pack size for one brand is listed, at £780.82 for a pack of 20, 40 mg capsules. The dosing of CCNU is 110mg per m^2, split over 3 days, after which patients will go on to receive 80–120 mg per dose round, which is 7 weeks long. The total dose expected for a patient with a BSA of 2 m^2 is 360 mg, whilst at a BSA of 1–2 m^2 it is 240 mg.

PCV is a regimen of three different drugs over a 7-week treatment cycle – procarbazine, CCNU and vincristine. According to NICE TA121[90], this regimen is "lomustine 110 mg/m^2 on Day 1, procarbazine 60 mg/m^2 on Days 8-21, and vincristine 1.4 mg/m^2 on Days 8 and 29 every 42 days." Almost all

patients receive the same dose with the same schedule, though within the tails of the BSA distribution the expected cost per cycle is different.

TMZ is a widely used CT with many different unit and pack sizes available. Costing TMZ appropriately is complex because there are six different unit sizes, and the drug is dosed based on BSA. Fortunately, at every possible TMZ dose exact numbers of packs are used per 28 days (five doses and pack sizes of five units for all doses). This means that in the microsimulation only the residency within on-TMZ states needs to be tracked, and the costing of the drug is handled within the model outside of the VBA code. To cost TMZ, a table was made detailing every possible dose between 0 and 4,000 mg per 28-day cycle (4 weeks, 5 doses), covering all possible BSA categories). The result of the calculation using the cumulative distribution function of BSA to establish all possible dose bands results in an expected cost of £118.92 per 28 days on treatment.

Bevacizumab has been reported in the literature to be used in recurrent LGG, and the treatment was included in a recent meta-analysis of recurrent LGG[91]. A monograph is available from Roche (manufacturer of bevacizumab) on the use of bevacizumab in conjunction with CCNU for malignant glioma[92]. NICE NG99 highlights the use of bevacizumab and suggests that it should be given in conjunction with CCNU[35]. According to the monograph, there is no limit on treatment duration. However, treatment discontinuation is implemented within the model via the transition probabilities and an assumed upper bound treatment duration of 4 years of consecutive treatment is applied to avoid overestimating bevacizumab cost in the cost-effectiveness model. The cost used for bevacizumab 400mg/16 ml concentrate for solution for infusion vials (pack size of 1 vial) of £810.00, which is taken from the BNF. Doses are administered every two weeks, meaning two administration visits to the hospital every model cycle. CCNU is administered in 6-week cycles at 110 mg/m^2 in line with use as a monotherapy.

Data from a Periodic synthesis report for Tibsovo® (ivosidenib AAC n°3, October 2023) in IDH1mut LGG patients that are ineligible for surgery and progressing after and/or ineligible to radiotherapy and chemotherapy in France is used in the cost-effectiveness model to inform the probability that a patient receives a given treatment, based on their current treatment line.[93] At each treatment line, the probability of receiving a given treatment is assigned according to the values presented in Table 39. For simplicity, the model costs the regimen 'Other' as if it were CCNU. Please note that clinical insights provided to Servier are that bevacizumab use is expected to be low, owing to the lack of established, routine funding mechanisms through which this treatment option is available to patients in UK clinical practice[47].

Table 39: Market shares at subsequent treatment lines

Line and treatment	Raw data	Values for model	
1L	**n (%)**	**Cohort %**	**Within-line %**
PCV	21 (25.6%)	25.60%	34.97%
TMZ	35 (42.7%)	42.70%	58.33%
Other	4 (4.9%)	4.90%	6.69%

Line and treatment	Raw data	Values for model	
		73.20%	**100%**
2L	**n (%)**	**Cohort %**	**Within-line %**
PCV	23 (28.0%)	28.00%	47.86%
TMZ	19 (23.2%)	23.20%	39.66%
Bevacizumab	1 (1.2%)	1.20%	2.05%
Other	5 (6.1%)	6.10%	10.43%
		58.50%	**100%**
3L	**n (%)**	**Cohort %**	**Within-line %**
Bevacizumab	8 (9.8%)	9.80%	34.88%
PCV	6 (7.3%)	7.30%	25.98%
TMZ	3 (3.7%)	3.70%	13.17%
Other	6 (7.3%)	7.30%	25.98%
		28.10%	**100%**
4L	**n (%)**	**Cohort %**	**Within-line %**
Other	4 (4.9%)	4.90%	57.65%
PCV	1 (1.2%)	1.20%	14.12%
TMZ	2 (2.4%)	2.40%	28.24%
		8.50%	**100%**
5L	**n (%)**	**Cohort %**	**Within-line %**
Bevacizumab	1 (1.2%)	1.20%	33.33%
Other	1 (1.2%)	1.20%	33.33%
PCV	1 (1.2%)	1.20%	33.33%
		3.60%	**100%**

Abbreviations: L, line; NI, next intervention; PCV, procarbazine, lomustine and vincristine; TMZ, temozolomide.

The expected treatment durations and grace periods (i.e., the time between completing one treatment line and initiating the next) for each of these treatment options are presented in Table 40. The average duration of treatment was derived from the following sources for each regimen:

- CCNU: Assumed per maximum duration (9 cycles = approximately 6 x 6 = 36 weeks).
- PCV: Assumed per maximum duration (9 cycles = approximately 6 x 6 = 36 weeks).
- TMZ: EAG report TA121 page 206 adjuvant TMZ median cycles per patient (Swiss patients). See also Table 16 (all <=6 cycles).
- Bevacizumab: Assumed one year (13 x 28 = 364 days).

Grace periods were all assumed to be one model cycle, owing to an absence of data available to populate the model.

Table 40: Market shares at subsequent treatment lines

Regimen	Average duration of treatment (cycles)	Grace period (cycles)			
		2L	**3L**	**4L**	**5L**
CCNU	9	1	1	1	1
PCV	9	1	1	1	1
TMZ	6	1	1	1	1
Bevacizumab	13	1	1	1	1

Abbreviations: CCNU, lomustine; L, line; NI, next intervention; PCV, procarbazine, CCNU and vincristine; TMZ, temozolomide.
Note: Cycles refer to model cycle length of 28 days.

The unit costs of subsequent therapies are summarised in Table 41.

Table 41: Unit costs for subsequent therapies

Regimen	Cost	Pack size/dose	Source
CCNU	£780.82	20 x 40mg capsules	Lomustine medac UK, BNF
PCV	P: £528.79 C: £780.82 V: £9.12 £25.38 £17.82 £33.89	P: 50 x 50mg capsules C: 20 x 40mg capsules V: 1 x 1mg vial 5 x 1mg vials 1 x 2mg vial 5 x 2mg vials	P: Alliance Healthcare (Distribution) Ltd, BNF C: Lomustine medac UK, BNF V: eMIT
TMZ	£3.54 £10.67 £38.53 £46.30 £80.47 £81.01	5 x 5 mg capsules 5 x 20 mg capsules 5 x 100 mg capsules 5 x 140 mg capsules 5 x 180 mg capsules 5 x 250 mg capsules	eMIT
Bevacizumab	£810.00	1 x 400mg vial	Celltrion Healthcare UK Ltd, BNF

Abbreviations: CCNU, lomustine; LPCV, procarbazine, CCNU and vincristine; TMZ, temozolomide.

In summary, the base case model includes the cost of subsequent treatments following vorasidenib, based on treatments commonly used in UK practice, published guidelines, and clinical understanding. These include the chemotherapy regimens CCNU (lomustine), PCV (procarbazine, CCNU, and vincristine), TMZ) as well as some use of off-label bevacizumab, with costs covering both acquisition and administration. The microsimulation combines inputs for costs and market shares with inputs related to expected treatment durations and grace periods, in order to estimate the costs of subsequent therapies. This approach ensures the model accurately reflects treatment costs and regimens used in English clinical practice. Whilst the use of vorasidenib does not necessarily prevent the use of these therapies, it delays the requirement for their action. This therefore delays the subsequent costing to NHS England in this setting.

3.5.2 Health-state unit costs and resource use

Resource use costs are sourced from a combination of previous NICE appraisals, literature, the PSSRU and standard NHS reference costs. MRU costs are important to capture as part of the treatment pathway for glioma, owing to the increased management costs required as disease progresses. The current base-case analysis adopts a simplified approach for the UK setting.

Frequencies for MRU were estimated for the following categories:

- **CT scan:** CT scans expected every three months prior to initiation of NI (i.e., for states S1, S2, S3, and S4). After initiation of NI, CT scans expected to be more frequent, approximately twice as often. CT scans assumed to no longer be required once patients enter S8.

- **MRI scan:** MRI scans expected every six months prior to initiation of NI (i.e., for states S1, S2, S3, and S4). After initiation of NI, MRI scans expected to be more frequent, approximately twice as often. MRI scans assumed to no longer be required once patients enter S8.

- **Hospital visit (unscheduled):** Boele *et al.*, (2020)[94], frequency of inpatient specialist care 1.1% per 4 weeks, assumed to apply for states S1, S2, S3, and S4. For S5 and S7 (NI and NI+, respectively), unscheduled hospital visits assumed to be twice per model cycle, broadly in keeping with increased hospitalisation for patients receiving active treatment per NICE TA23 (PCV) and TA121 (TMZ). For S6, same frequency assumed as per S1-S4. For S8, assumed same frequency as per S5 and S7.

- **Consultant doctor:** Boele *et al.*, (2020)[94], Table 2 – 'outpatient specialist care'. Assumed to be the same frequency across all model health states after progression but assumed 50% of frequency for progression-free health states (i.e., S1 and S2).

- **GP appointment:** Boele *et al.*, (2020)[94], Table 2 – 'GP'. Assumed to be the same frequency across all model health states after progression but assumed 50% of frequency for progression-free health states (i.e., S1 and S2).

- **Home visitor:** Boele *et al.*, (2020)[94], Table 2 – 'home care'. Assumed to be the same frequency across all model health states.

For costs, standard sources are used. Computed tomography scan cost uses code RD20A from the NHS cost schedule 2022-2023[95]. MRI scan uses RD01A Magnetic Resonance Imaging Scan of One Area, without Contrast, 19 years and over from the same source. Unscheduled hospital visits used a weighted average of NHS cost schedule (2022-2023) codes AA24C-H. Consultant doctor appointments used WF01A: Non-admitted face to face attendance, follow-up neurosurgery.

GP and home visitor costs were taken from the PSSRU (Tables 9.4.2 and Section 7.1.1). Rates of these and for a consultant doctor were taken from a Dutch costing study by Boele *et al.*, (2020)[94] due to lack of any UK-based information. This study was also used for unscheduled hospital visit rates in the states other than S5 and S7.

Seizure management

Seizure management for glioma is complex and so focus was placed on the need for secondary engagement rather than many successive and recursive lines of anti-seizure medication. No data for adults was available for the distribution of different intensities of health service engagement, and so proportions are assumed. The costs used in the model are presented in Table 42.

Table 42: Cost components for expected seizure management cost per event

Cost type	Unit cost	Proportion	Source(s)
Hospitalisation	£2,030.90	10%	Cost from Dickson *et al.*, (2018)[96], inflated to 2022/23.
No secondary engagement	£0.00	90%	Remainder assumed to incur zero cost.
Weighted average	£203.09		Calculation

Seizure management costs are applied on a health-state basis rather than being linked to treatment received. Rates were derived from the INDIGO pre-progression state for the placebo arm, and assumed to apply for S2 (18.7 seizure events per person-year during seizure assessment period within progression-free state). Based on a ratio of risks for on-treatment seizure events of 0.36 (95% CI: 0.14, 0.89)[97], there is a modelled difference in the requirement for seizure management between health states S1 and S2.

For later health states (i.e., S3 and beyond), it is expected that seizure management costs would increase over time as seizures are expected to worsen as disease progresses. This is supported by clinical opinion given to Servier[47] However, there is limited data available to inform the model. In the base-case analysis, it was assumed that seizure management resource use would increase by 25% at the following key milestones:

- Following initiation of NI and movement to S5.
- Following initiation of NI+ and movement to S7.
- Following cessation of all active treatment and movement to S8.

Debulking surgery

Additional debulking surgery with a palliative/symptom relief aim is an important part of the treatment array patients can receive when they reach the end of the treatment pathway. An article by Brown *et al.*, (2022) on glioblastomas suggested that 60% of patients had a debulking surgery[98]. This is the only potential proxy source found and was also assumed to apply to patients that enter NI (S5) and NI+ (S7). This was based on clinical expert feedback to Servier that debulking surgery would be used when a chemotherapy treatment would be considered afterwards[47]. While debulking surgery is an important and expensive facet of the treatment pathway, information on its frequency given an initial IDH1/2 LGG diagnosis is lacking. Clinical insights given to Servier suggest that 2-3 surgeries would be performed overall in each patient[47]. The average of codes AA51A-G in the NHS cost schedule under Complex Intracranial Procedures, 19 years and over weighted was used to capture the cost of a debulking surgery.

The model includes the capacity to enter a percentage to receive a one-off resource use upon entry to all 9 states, for as many categories as desired. This means that in the model, it is possible to also have a one-off cost (e.g., a palliative surgery, training, specialist appointment, counselling and so on) associated with initiating the next health state. Debulking surgery is included using this functionality, as described above. Palliative radiotherapy was not included in the model as no data were identified to inform resource use by health state. Table 43 highlights the rates of resource use per model cycle,

Table 44 highlights rates upon model health state entry, and Table 45 presents the cost associated with each use.

Table 43: Rates of resource use per 28 days per model health state per category

Resource	Model Health state								
	1	2	3	4	5	6	7	8	9
Computed tomography scan	0.13	0.13	0.13	0.13	0.25	0.50	0.25	-	-
MRI scan	0.17	0.17	0.17	0.17	0.33	0.33	0.33	-	-
Hospital visit (unscheduled)	0.01	0.01	0.01	0.01	2.00	0.01	2.00	2.00	-
Consultant doctor	0.17	0.17	0.33	0.33	0.33	0.33	0.33	0.33	-
Seizure management	0.52	1.43	1.43	1.43	1.79	1.79	2.24	2.80	-
GP appointment	0.16	0.16	0.31	0.31	0.31	0.31	0.31	0.31	-
Home visitor	0.08	0.08	0.08	0.08	0.08	0.08	0.08	0.08	-
Debulking surgery*	-	-	-	-	-	-	-	-	-

Abbreviations: GP, general practitioner; MRI, magnetic resonance imaging.
Note: *This item was captured upon entry to model health states.

Table 44: Rates of resources use upon health state entry

Resource	Model Health state								
	1	2	3	4	5	6	7	8	9
Computed tomography scan	-	-	-	-	-	-	-	-	-
MRI scan	-	-	-	-	-	-	-	-	-
Hospital visit (unscheduled)	-	-	-	-	-	-	-	-	-
Consultant doctor	-	-	-	-	-	-	-	-	-
Seizure management	-	-	-	-	-	-	-	-	-
GP appointment	-	-	-	-	-	-	-	-	-
Home visitor	-	-	-	-	-	-	-	-	-
Debulking surgery*	-	-	-	-	0.30	-	0.30	-	-

Abbreviations: GP, general practitioner; MRI, magnetic resonance imaging.
Note: *Total of 60% assumed to be spread over initiation of NI (S5) and NI+ (S7).

Table 45: Unit costs associated with resource items

Resource	Unit cost	Source
Computed tomography scan	£117.50	RD20A Computerised Tomography Scan of One Area, without Contrast, 19 years and over
MRI scan	£197.34	NHS ref costs: RD01A Magnetic Resonance Imaging Scan of One Area, without Contrast, 19 years and over
Hospital visit (unscheduled)	£873.26	Weighted average of NHS cost schedule (2022-2023) codes AA24C-H
Consultant doctor	£231.24	NHS ref costs: WF01A Non-admitted face to face attendance, follow-up neurosurgery
Seizure management	£167.15	See Table 42
GP appointment	£49.00	PSSRU unit costs of health and social care 2023, Table 9.4.2
Home visitor	£28.00	PSSRU unit costs of health and social care 2023, Table 7.1.1
Debulking surgery	£15,876.81	NHS ref costs: Complex Intracranial Procedures, 19 years and over weighted average of codes AA51A-G

Abbreviations: GP, general practitioner; MRI, magnetic resonance imaging.

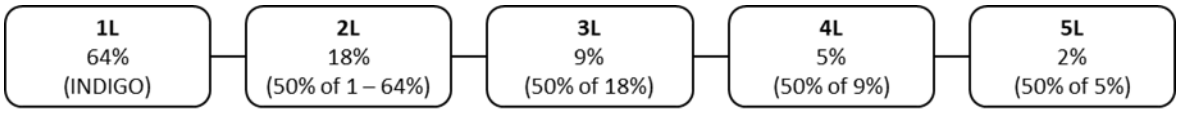
Radiotherapy

An important part of treatment for glioma at later stages is RT[35]. No data is available on the proportion of treatment initiations by treatment line which are in conjunction with RT. In the absence of any information on the frequency with which patients are and are not given RT in conjunction with CT at the five lines following vorasidenib built into the cost-effectiveness model, it was assumed that 50% of

patients would be treated with RT at each of the five successive treatment lines captured by the model. This is broadly aligned with clinical feedback to Servier[47].

The model is then based on the proportion of patients who have received RT as part of their first subsequent anticancer therapy from INDIGO (64%), alongside the 50% assumption in successive lines, as demonstrated via Figure 33.

Figure 33: Proportion of patients receiving radiotherapy at each subsequent line



The estimated cost of a course of RT consisting of a range of fractions is provided in Table 46. This is based on codes SC24Z, SC56Z, SC31Z, and SC29Z from NHS cost schedule 22-23 for the cost of preparation (if required) and delivery of the fraction[95]. The derived cost of 5 fractions is approximately £1,258.13, without factoring in any additional secondary care engagement (such as day-case, overnight stays, consultations, failed/blurry scans that need to be repeated and so on). Overall, this provides a marginally conservative estimate which ignores any issues during delivery for the cost of providing 10-15 fractions using NHS standard sources. The specification of 15 fractions of TMZ is based on NG99, which states “the use of concurrent and adjuvant temozolomide with 15 fractions of [RT] is a change of practice that will probably result in more people being treated”[35]. Older chemotherapies appear to be associated with more fractions, and the sources used within the evidence reviews of NG99 suggest up to 30 fractions are associated with PCV and CCNU monotherapy[35]. Due to a lack of data for bevacizumab, the same number of fractions was assumed to apply as per TMZ (given that bevacizumab is a more modern treatment compared to CCNU and PCV).

Table 46: Cost per course of radiotherapy, assuming a 2-3 week course (10-15 fractions)

Drug	Fractions†	Cost‡	Source(s) on fractions
CCNU	30	£5,269.17	Buckner 2016[99] 30 fractions over 6 weeks (5/week). Must come before CCNU. RT duration set to 2 cycles and cost multiplied by 2/3
PCV	30	£5,269.17	
TMZ	15	£3,951.88	NG99: "concurrent and adjuvant temozolomide with 15 fractions of RT" page 68[35]. 5/week is 3 weeks so contained within one 28-day model cycle
Bevacizumab	15	£3,951.88	Assumed same as TMZ

Abbreviations: CCNU, lomustine; PCV, procarbazine, CCNU and vincristine; RT, radiotherapy; TMZ, temozolomide.
Note: † Number of fractions per course; ‡ Cost per four weeks on RT.

End-of-life care costs

Standard sources for the UK were used to populate end of life (EoL) costs. A study by Round *et al.*, (2015) was used to inform a lump sum cost for terminal care which is applied upon death[100]. Round *et*

al. considered four types of cancer: lung cancer, breast cancer, prostate cancer, and colorectal cancer. Of these cancer types, lung cancer is expected to serve as the best proxy for glioma owing to its aggressive progression and overlapping symptom burden. The total cost of health and social care from this study was £4,515, which was then inflated to current values, and so a total cost of £5,554 is applied in the model.

Adverse reaction unit costs and resource use

Not applicable – adverse reaction costs are not included (see Section 3.3.3 for details).

Miscellaneous unit costs and resource use

No other costs were included in the model. Details of subsequent therapy and medical resource use are provided in Sections 3.5.1 and 3.5.2, respectively.

3.6 Severity

LGG is a severe form of cancer, associated with a poor patient prognosis and severe decrements in HRQoL. There has currently been no development in this disease area for the past two decades with the most relevant NICE appraisal dating back to 2001 (TA23)[73]. Therefore, for patients suffering with LGG, the only course of treatment is active observation where once patients initiate their NI, they are expected to be at a higher risk of death, experience higher morbidity and incur greater treatment and medical resource use costs. Within the context of the patient population considered in this appraisal – people aged 12 years and over with grade 2 astrocytoma or oligodendroglioma with IDH1 or IDH2 mutations, who have had surgical intervention and not in immediate need of RT or CT – there is an absence of overarching overall survival curve that could be robustly derived due to the lack of mature data available from the INDIGO trial. There is a clear unmet need for safe and efficacious targeted treatments for patients within this clinical setting.

QALY shortfall was calculated using the R-Shiny tool by Schneider *et al.*, (2021)[101]. Summary features used to estimate lifetime QALYs without the disease were sourced from INDIGO and are presented in Table 47.

Table 47: Summary features of QALY shortfall analysis

Factor	Value (reference to appropriate table or figure in submission)	Reference to section in submission
Proportion female*	44%	Table 25 (§ 3.3.1)
Starting age*	40 years	

Notes: * Sex distribution and starting age are rounded to 0 decimal places per the requirements of the published QALY shortfall tool.

The published QALY shortfall tool provides a reference case for estimating population quality-adjusted life expectancy, which is described below:

- **Scoring algorithm:** EQ-5D-3L value set from the 1993 MVH study.
- **Health state profiles:** EQ-5D-3L from the Health Survey for England 2014.
- **Model:** ALDVMM by Hernandez Alava, *et al.* (2022).

Results of the QALY shortfall calculator are presented in Table 48.

Table 48: Summary of QALY shortfall analysis

Input	Value
A: Expected total QALYs for the general population	7.76
B: Total QALYs that people living with a condition would be expected to have with current treatment	25.93
B – A: QALY shortfall	18.17

Key: QALY, quality-adjusted life years

Within the context of this appraisal, the absolute shortfall criterion for applying a 1.7x QALY weight is met, and is therefore applied in the base-case analysis.

3.7 Uncertainty

A key limitation of the cost-effectiveness analysis is the need to rely on literature sources for long-term outcomes due to the dearth of evidence for long-term outcomes for patients with LGG. For this reason, it is acknowledged that there is a high degree of uncertainty around the cost-effectiveness of vorasidenib. However, as described throughout this submission, the methods and data used to analyse the cost effectiveness of vorasidenib for IDH1-mutated or IDH2-mutated LGG have been carefully considered and are the most appropriate available to support decision making at present.

3.8 Managed access proposal

This submission proposes vorasidenib as a candidate for the Cancer Drugs Fund (CDF) under a managed access agreement until additional data from the INDIGO trial become available. Further OS data, as well as data for other endpoints such as PFS and TTNI, are expected in 2028 and are anticipated to address current uncertainties in the cost-effectiveness estimates. In addition, there are many registries in development with Servier support.

It is not anticipated that data collection from the Systemic Anti-Cancer Therapy (SACT) database would help address these uncertainties, owing to the need for longer-term follow-up data to address the key limitations of the cost-effectiveness analysis presented in this submission.

Table 49: List of uncertainties and the data that could be collected to resolve them

Clinical uncertainty	Outcome data	Data source
OS benefit of vorasidenib	Analysis of 2028 data cut from INDIGO	INDIGO trial
PFS benefit of vorasidenib		
TTNI benefit of vorasidenib		
Duration of treatment with vorasidenib		

Table 50: Overview of data source

Study	[Clinical trial name or primary author surname (year published)]
Study design	International, double-blind, randomised, placebo-controlled trial
Population	People with residual or recurrent Grade 2 IDH-mutant glioma after surgical intervention
Intervention(s)	Vorasidenib
Comparator(s)	Placebo
Outcomes	**PFS, TTNI, SAFETY, QOL**
Indicate if study used in the NICE economic model	Yes
Trial start date	Jan 2020
Data cut submitted to NICE	Sept 2022, March 2023
Anticipated data cut after a period of managed access	May 2028

3.9 Summary of base-case analysis inputs and assumptions

3.9.1 Summary of base-case analysis inputs

Table 51: Summary of variables applied in the economic model

Variable	Value	Measurement of uncertainty	Reference in submission
Model parameters			
Time horizon	60 years (lifetime)	-	§ 3.2.2
Cycle length	28 days	-	§ 3.2
Discount rate	1.5% for costs and outcomes	-	§ 3.2
Baseline patient characteristics			
Starting age	39.68	SE: 9.75	§ 3.3.1
Height, cm	173.53	SE: 10.34	§ 3.3.1
Weight, kg	81.96	SE: 18.32	§ 3.3.1
BSA, m^2	1.98	SE: 0.26	§ 3.3.1
Survival extrapolations			
PFS vorasidenib	Log-normal	-	§ 3.3.2
PFS placebo	Log-normal	-	§ 3.3.2
TTNI vorasidenib	Generalised gamma	-	§ 3.3.2
TTNI placebo	Generalised gamma	-	§ 3.3.2
TTD NI	IDH codeleted: Log-normal; IDH not codeleted: Gamma	-	§ 3.3.2
TTD NI+	Astro: Generalised gamma; Oligo: Gompertz	-	§ 3.3.2
Death from BSC	Astro: Log-normal; Oligo: Log-normal	-	§ 3.3.2
Death from all other states	Life tables	-	§ 3.3.2
Utility values			
S1 – PF and on tx	0.737	Varied via variance-covariance matrix	§ 3.4.5
S2 – PF and off tx	0.737		§ 3.4.5
S3 – PD and on tx	0.728		§ 3.4.5
S4 – PD and off tx	0.728		§ 3.4.5
S5 – On NI	0.480	Varied via variance-covariance matrix applicable to raw inputs	§ 3.4.5
S6 – Off NI	0.480		§ 3.4.5
S7 – On NI+	0.340		§ 3.4.5
S8 – Off NI+ (BSC)	0.340		§ 3.4.5
S9 – Dead	0		§ 3.4.5
Acquisition costs			

Variable	Value	Measurement of uncertainty	Reference in submission
Vorasidenib (proposed list)	30 x 40mg capsules: £[redacted] 30 x 10mg capsules: £[redacted]	-	§ 3.5.1
Subsequent treatment costs			
CCNU	20 x 40mg capsules: £780.82	Fixed	§ 3.5.1
PCV	P, 50 x 50mg capsules: £528.79 C, 20 x 40mg capsules: £780.82 V, 1 x 1mg vial: £9.12 V, 5 x 1mg vials: £25.38 V, 1 x 2mg vial: £17.82 V, 5 x 2mg vials: £33.89	P and C fixed V varied based on uncertainty information reported in eMIT	§ 3.5.1
TMZ	5 x 5 mg capsules: £3.54 5 x 20 mg capsules: £10.67 5 x 100 mg capsules: £38.53 5 x 140 mg capsules: £46.30 5 x 180 mg capsules: £80.47 5 x 250 mg capsules: £81.01	Varied based on uncertainty information reported in eMIT	§ 3.5.1
Bevacizumab	1 x 400mg vial: £810.00	-	§ 3.5.1
Please refer to Section 0 for details of other inputs related to subsequent therapy.			
Medical resource use costs			
CT scan	£117.50	Standard error assumed 10% of base-case value	§ 3.5.2
MRI scan	£197.34		§ 3.5.2
Hospital visit (unscheduled)	£873.26		§ 3.5.2
Consultant doctor	£231.24		§ 3.5.2
Seizure management	£167.15		§ 3.5.2
GP appointment	£49.00		§ 3.5.2
Home visitor	£28.00		§ 3.5.2
Debulking surgery	£15,876.81		§ 3.5.2
End-of-life care	£5,553.91		§ 3.5.2
Please refer to Section 3.5.2 for details of other inputs related to medical resource use.			

3.9.2 Assumptions

The key modelling assumptions are summarised in Table 52.

Table 52: Summary of key modelling assumptions

Assumption	Description	Justification
Time horizon	60 years constitutes a time horizon	Given the early age at which the disease develops (40 years), they could reach the conserved 100 years until death
Cycle length	28 days cycle length with a half-cycle correction	This cycle length is considered appropriate considering the treatment length of vorasidenib for patients with IDH1/IDH2 mutated LGG. Due to the cycle length, a half-cycle correction has also been applied.
No treatment beyond disease progression	In the base case, patients are assumed to discontinue treatment upon progression.	The SmPC notes that treatment with vorasidenib should be continued until disease progression or until treatment is no longer tolerated by the patient. Expert advice indicated that treatment beyond progression would not occur in real-world practice.
S1->S4 S2->S4	Log-normal (PFS, BIRC) curve selected in the base case. Alternative parametric models tested in scenario analysis.	Best statistical fit for vorasidenib arm. For the placebo arm, fit statistics were similar across several models, but log-normal was chosen for consistency with the vorasidenib arm.
S4->S5 (both arms)	Generalised gamma (TTNI|P, BIRC) curve selected in the base case.	Best statistical goodness-of-fit across both arms.

	Alternative parametric models tested in scenario analysis.	
S5->S7 S6->S7	IDH codeleted: log-normal, IDH not codeleted: gamma curves selected in the base case. Alternative parametric models tested in scenario analysis.	Best statistical goodness-of-fit scores.
S7->S8	Astro: generalized gamma, oligo: Gompertz curves selected in the base case. Alternative parametric models tested in scenario analysis.	Best statistical goodness-of-fit scores.
S5->S9 S6->S9 S7->S9	No curve fit – probability of death assumed to be same as general population.	Assumption of no excess mortality
S8->S9	Astro: log-normal, oligo: log-normal curves selected in the base case. Alternative parametric models tested in scenario analysis.	Best statistical goodness-of-fit scores, paired with consistency across subtypes.

Abbreviations: LGG, low grade glioma; OS, overall survival; PFS, progression free survival; ToT, time on treatment; SmPC, summary of product characteristics.

3.10 Base-case results

The base-case results of the cost-effectiveness analysis are presented in Table 53. The associated net health benefit results are presented in Table 54. Clinical outcomes and disaggregated results from the model are provided in Appendix H. In the base-case analysis, the ICER is £[redacted] per QALY gained. This ICER is comprised of incremental costs of £[redacted], and a 1.7-weighted QALY gain of 5.80.

Table 53: Base-case results (deterministic)

Technologies	Total costs	Total LYG	Total QALYs	Δ costs	Δ LYG	Δ QALYs*	ICER incremental (£/QALY)
Active observation	£397,496	20.76	7.76				
Vorasidenib	[redacted]	26.49	11.18	[redacted]	5.73	5.80	[redacted]

Abbreviations: Δ, incremental; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years;
Note: * 1.7 severity modifier applied to incremental QALYs.

Table 54: Net health benefit

Technologies	Total costs	Total QALYs	Δ costs	Δ QALYs*	NHB at £20,000	NHB at £30,000
Active observation	£397,496	7.76				
Vorasidenib	[redacted]	11.18	[redacted]	5.80	[redacted]	[redacted]

Abbreviations: Δ, incremental; QALYs, quality-adjusted life years; NHB, net health benefit.
Note: * 1.7 severity modifier applied to incremental QALYs.

3.11 Exploring uncertainty

A range of sensitivity analyses were undertaken to assess the structural and parameter uncertainty inherent within the cost-effectiveness model. These are described in the sub-sections that follow. Please note that for all sensitivity analyses, the severity modifier was not changed from the base-case analysis setting for consistency in interpretation.

3.11.1 Probabilistic sensitivity analysis

In probabilistic sensitivity analysis (PSA), inputs were randomly sampled from their assigned probability distribution (and model results recorded) across 500 probabilistic iterations, by which point costs and outcomes had stabilised and were considered reliable for capturing parameter uncertainty, as shown in Figure 34 and Figure 35.

Figure 34: PSA convergence (costs)

Abbreviations: PSA, probabilistic sensitivity analysis; SoC, standard of care; Vora, vorasidenib.

Figure 35: PSA convergence (QALYs)

Abbreviations: PSA, probabilistic sensitivity analysis; SoC, standard of care; QALY, quality-adjusted life years; Vora, vorasidenib.

The mean results of the PSA are presented in Table 55, showing similar results to the deterministic base-case analysis (presented in Table 53).

Table 55: Base-case results (probabilistic)

Technologies	Total costs	Total QALYs	Δ costs	Δ QALYs*	ICER incremental (£/QALY)
Active observation	£406,081	7.52			
Vorasidenib	[redacted]	10.94	[redacted]	5.81	[redacted]

Abbreviations: Δ, incremental; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.
Note: * 1.7 severity modifier applied to incremental QALYs.

The corresponding PSA scatterplot is presented in Figure 36, and a cost-effectiveness acceptability curve (CEAC) presented in Figure 37. At a WTP threshold of £30,000 per QALY gained, there is a [redacted]% probability that vorasidenib may be considered a cost-effective treatment option, compared to active observation.

Figure 36: PSA scatterplot

Abbreviations: PSA, probabilistic sensitivity analysis; QALYs, quality-adjusted life years.

Figure 37: Cost-effectiveness acceptability curve

Abbreviations: k, thousand(s); QALY, quality-adjusted life year

3.11.2 Deterministic one-way sensitivity analysis

In the deterministic one-way sensitivity analyses (OWSA), inputs were set in turn to their respective lower and upper limits, while all other parameters were maintained at their base case setting. Correlated inputs with joint uncertainty, such as parametric survival model coefficients and utility regression model coefficients, which are varied in PSA using a multivariate normal distribution, were not included in the OWSA. The results of this analysis are presented with the outcome of incremental net monetary benefit (INMB), at a willingness-to-pay threshold of £30,000 per QALY gained. The results of the OWSA are presented as a tornado diagram in Figure 38.

Figure 38: Tornado diagram

Abbreviations: ICER, incremental cost-effectiveness ratio; k, thousand(s); LB, lower bound; UB, upper bound.

The results of the OWSA suggest that the most influential parameters were those related to the risk of death, parameters that impact movements between health states based on opting out of further treatment, costs related to hospital visits based on health state occupancy, and the duration of treatment with TMZ. Of note, the OWSA omits parameters that are associated with joint uncertainty (e.g., parametric survival model coefficients), and so this type of analysis may not truly reflect the overall uncertainty in the model results.

3.11.3 Deterministic scenario analysis

Deterministic scenario analyses were performed to test key structural and methodological assumptions within the model. A list of the scenarios explored, and results of the analysis are presented in Table 56. The scenarios with the largest impact on cost-effectiveness results occurred

when changing the parametric extrapolations using data from the INDIGO study, annual discount rates, and reducing the model time horizon.

Table 56: Scenario analysis results

Scenario details				Vorasidenib		Active observation		ICER
#	Scenario name	Base-case	Scenario	Costs	QALYs	Costs	QALYs	
Base case				[redacted]	**11.18**	**£397,496**	**7.76**	[redacted]
1	INDIGO extrapolations: PFS	Log-normal	Log-logistic	[redacted]	11.01	£399,990	7.79	[redacted]
2			Gamma	[redacted]	10.44	£402,516	7.71	[redacted]
3	INDIGO extrapolations: TTNI | P	Generalised gamma	Log-logistic	[redacted]	9.11	£422,996	6.49	[redacted]
4			Gompertz	[redacted]	10.49	£396,571	7.89	[redacted]
5	Annual discount rates for cost and outcomes	1.5%	6.0%	[redacted]	6.84	£219,562	5.10	[redacted]
6			0.0%	[redacted]	14.04	£513,920	9.44	[redacted]
7			3.5%	[redacted]	8.73	£298,192	6.28	[redacted]
8	INDIGO utility regression	Progression and baseline	Progression only	[redacted]	11.23	£397,496	7.78	[redacted]
9	Time horizon	60 years	30 years	[redacted]	9.77	£338,943	7.02	[redacted]
10			40 years	[redacted]	10.63	£375,155	7.49	[redacted]
11			50 years	[redacted]	11.04	£392,177	7.70	[redacted]
12	SMR applied to background mortality rates	1.0	1.2	[redacted]	11.02	£391,789	7.69	[redacted]
13	% opt out of treatment at S4 and S6	5%	10%	[redacted]	10.97	£381,751	7.51	[redacted]
14			0%	[redacted]	11.40	£418,222	8.07	[redacted]
15	Increase in seizures at subsequent treatment lines	25%	50%	[redacted]	11.18	£431,726	7.76	[redacted]
16	S5/6 to S7 PFS non-co deleted from Baumert	Gamma	Weibull	[redacted]	11.18	£397,742	7.75	[redacted]
17	S7 to S8 TTP oligo from Ma et al	Gompertz	Exponential	[redacted]	11.08	£369,531	7.63	[redacted]
18	S7 to S9 OS astro and oligo from Ma et al	Log-normal	Exponential	[redacted]	10.65	£331,034	7.11	[redacted]

Abbreviations: MRU, medical resource use; AE, adverse events; QALYs, quality-adjusted life years; ICER, incremental cost-effectiveness ratio; SoC, standard of care; TTP, time to progression; OS, overall survival; PFS, progression free survival; TTNI | P, time to next intervention given progression.

3.12 Subgroup analysis

No subgroup analyses were conducted.

3.13 Benefits not captured in the QALY calculation

The model captures the main health effects on patients but does not capture any beneficial health effects to family members or caregivers due to limited data available to inform the model. IDH-mutant glioma is associated with high indirect costs, especially when treated with RT/CT, related to loss of productivity, inability to work, early retirement, and premature mortality[49].. All advisors at an advisory board held by Servier expressed that the societal benefits of vorasidenib over RT/Chemo will be marked. Some of the benefits expressed were continuing to work due to a lack of neurological deficit, equating to reduced nursing home care that may be needed due to this. Four advisors expressed that it should not be underestimated the driving potential with Vorasidenib. In their opinion this is a large quality of life benefit as patients cannot drive on RT/Chemo[36]. People lose their license for at least a year with RT/Chemo and similar after surgery. In addition, to further look at productivity losses, a non-interventional observational retrospective longitudinal study using pseudonymized patient-level data was carried out by Servier to Generate real-world evidence on the burden of glioma – specifically regarding days absent from work – by use of Danish administrative registers.(Work Inactivity burden related to IDH-mutated gliomas: a Danish Non-interventional Observational retrospective study (Workido)). [redacted]

IDH-mutant glioma also has a profound impact on caregiver QoL which is exacerbated as patient condition worsens due to disease progression or treatment-related side effects. Caregivers often experience disruptions in emotional, physical, and social well-being[29,30]. Care is primarily provided by relatives and friends and few patients with glioma rely solely on formal care[29]. As the condition of patients worsen, either through disease progression or the effects of treatments like RT/CT, it impacts them both physically and cognitively, affecting cognitive functions, personality, and behaviour. This deterioration has a direct negative impact on the QoL of caregivers, potentially hindering their ability to provide optimal care. This establishes a reciprocal relationship between the QoL of the patient and that of the caregiver[31]. Caregivers face difficulty in performing routine household tasks as well as substantial productivity loss which contributes to increased economic burden.

3.14 Validation

Internal validation of the cost-effectiveness analysis demonstrated that modelled clinical outcomes closely reflected outcomes from INDIGO (see Appendix H). In addition, prior to submission, the model was quality assured as part of the internal processes of the external analysts who built the model. As part of this quality-control process, the model was reviewed for potential coding errors, inconsistencies, and the plausibility of inputs by an economist who was not involved in the model development process.

3.15 Interpretation and conclusions of economic evidence

The current prognosis for people aged 12 years and over with grade 2 astrocytoma or oligodendroglioma with IDH1 or IDH2 mutations, who have had surgical intervention and not in immediate need of RT or CT is poor; there is a clear unmet need for safe and effective treatment options in the second- and third-line settings. Vorasidenib is an innovative treatment with a first-in-class mode of action, which specifically targets penetrating the blood brain barrier. Vorasidenib has been designated as an orphan medicine for the treatment of IDH-mutant glioma in the European Union (EU) on January 13, 2023, and the Australian government on 31st October 2023. It was also awarded ILAP status as an innovative product by the MHRA in January 2024.

To determine the cost-effectiveness of vorasidenib versus active observation, a *de novo* cost-effectiveness analysis was undertaken, from the perspective of the NHS and PSS. The cost-effectiveness analysis was informed by data collected in the INDIGO study, which provides evidence of a clinically meaningful benefit of vorasidenib in people aged 12 years and over with grade 2 astrocytoma or oligodendroglioma with IDH1 or IDH2 mutations, who have had surgical intervention and not in immediate need of RT or CT.

Longer-term costs and outcomes are informed by published literature. The model used to inform the cost-effectiveness analysis adopts a flexible structure such that alternative parametric models, settings, and assumptions can be explored in order to understand parameters of greatest importance, and to address uncertainty in results. Due to data limitations, expected broader expected benefits, such as increased productivity associated with delayed progression and spillover effects for families, which while important additional benefits of treatment, are not captured by the cost-effectiveness model.

In the base-case analysis, the ICER is £[redacted] per QALY gained. This ICER is comprised of incremental costs of £[redacted], and a 1.7-weighted QALY gain of 5.80. As demonstrated via sensitivity analyses, the main drivers of model results were assumptions related to survival and health-related quality of life.

As with any cost-effectiveness analysis, the model is not without limitations. A key limitation of the cost-effectiveness analysis is the need to rely on literature sources for long-term outcomes due to the dearth of evidence for long-term outcomes for patients with LGG. For this reason, it is acknowledged that there is a high degree of uncertainty around the cost-effectiveness of vorasidenib. However, as described throughout this submission, the methods and data used to analyse the cost effectiveness of vorasidenib for IDH1-mutated or IDH2-mutated LGG have been carefully considered and are the most appropriate available to support decision making at present.

In conclusion, the cost-effectiveness analysis demonstrates that, subject to pricing agreements, vorasidenib provides a plausibly cost-effective treatment option for patients with IDH1-mutated or IDH2-mutated LGG in NHS practice, in order to address a clear unmet need in this young population.

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5 Appendices

[See section 5 of the user guide for a list of the appendices that should be used to support the submission. Appendices A to I should be provided. Any additional appendices should start at appendix J.]

Appendix A: Summary of product characteristics (SmPC) and UK public assessment report

SmPC

UK public assessment report

Appendix B: Identification, selection and synthesis of clinical evidence

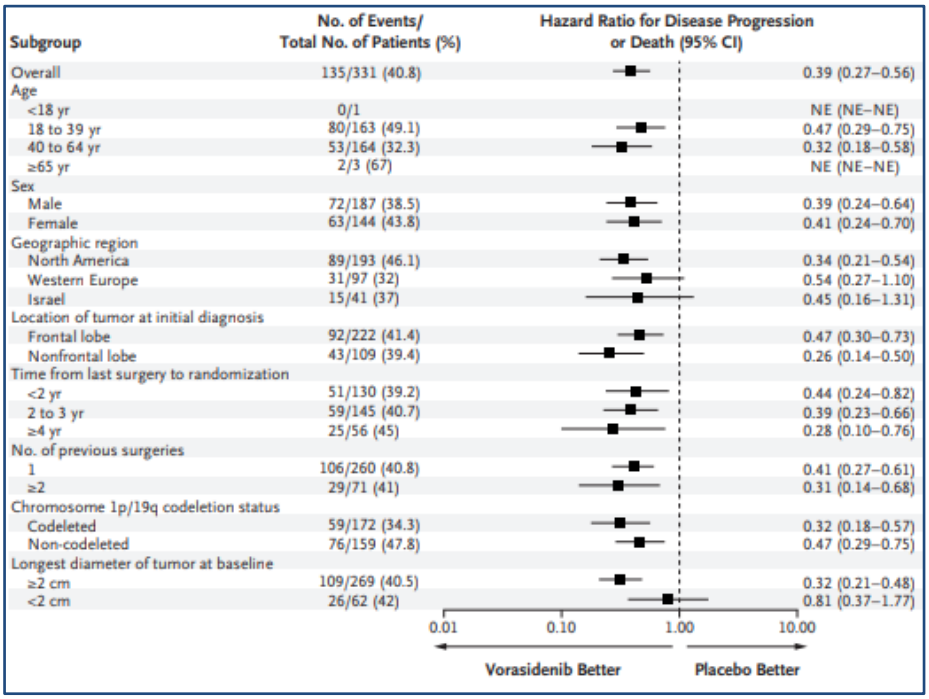
See additional attachment

Appendix C: Subgroup analysis

Vorasidenib demonstrated consistent improvement in PFS and TTNI across all prespecified subgroups compared to placebo

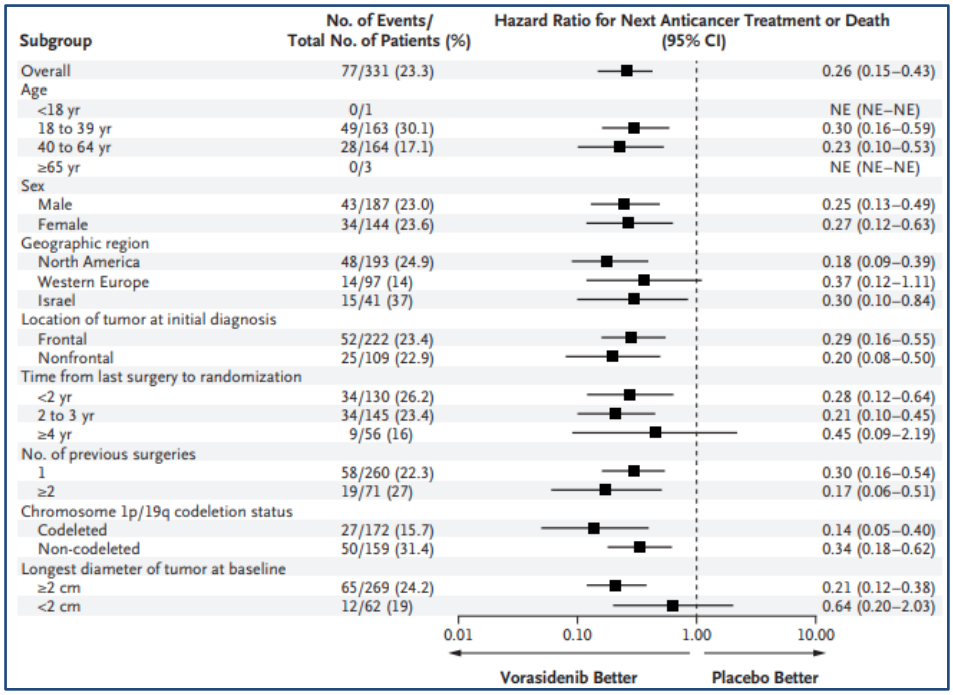
PFS and TTNI results were consistent (favouring vorasidenib) across all prespecified subgroups, including age (<40 years vs. ≥40 years), baseline tumour size (<2 cm vs. ≥2 cm), and histology (1p19q codeleted vs. not codeleted**)** (Figure 13 and 14)**.** This includes a statistically significant improvement in PFS (HR=0.47, 95% CI: 0.29, 0.75) and TTNI (HR=0.34, 95% CI: 0.18, 0.62) with vorasidenib in the 1p19q non-codeleted subgroup (astrocytoma), which typically have poorer prognosis.

Figure 39: Subgroup analyses of PFS



Source: (Mellinghoff 2023b)[65]
Abbreviations: CI: confidence interval; NE: not estimated; No: number; PFS: progression free survival
Note: Subgroup analyses were based on stratification-factor data as entered in the interactive Web-response system. Frontal tumour location included frontal, frontoparietal, and frontotemporal locations, and non-frontal tumour location included all other locations. In the analyses, the widths of the confidence intervals have not been adjusted for multiplicity. Thus, the confidence intervals should not be used to reject (or not reject) the effects of vorasidenib

Figure 40: Subgroup analyses of TTNI



Source: (Mellinghoff 2023b)[65]
Abbreviations: CI: confidence interval; NE: not estimated; No: number; TTNI: time to next intervention
Note: Subgroup analyses were based on stratification-factor data as entered in the interactive Web-response system. Frontal tumour location included frontal, frontoparietal, and frontotemporal locations, and non-frontal tumour location included all other locations. In the analyses, the widths of the confidence intervals have not been adjusted for multiplicity. Thus, the confidence intervals should not be used to reject (or not reject) the effects of vorasidenib

Appendix D: Adverse reactions

	Vorasidenib (N=167)	Placebo (N=163)
Any TEAE, n (%)	158 (94.6)	152 (93.3)
Grade ≥3 TEAEs, n (%)	38 (22.8)	22 (13.5)
Treatment-related TEAEs, n (%)	109 (65.3)	95 (58.3)
Grade ≥3 treatment-related TEAEs, n (%)	22 (13.2)	6 (3.7)
Serious TEAEs, n (%)	11 (6.6)	8 (4.9)

Source: (Servier 2023)
Abbreviations: N: number of subjects in the SAS within each treatment arm; n: number of subjects in the SAS within each treatment arm in each category; SAS: safety analysis set; TEAE: treatment emergent adverse event

Event, n (%)	Vorasidenib (N=167)		Placebo (N=163)	
	Any Grade	**Grade ≥3**	**Any Grade**	**Grade ≥3**
Any adverse event	158 (94.6)	38 (22.8)	152 (93.3)	22 (13.5)
Increased ALT	65 (38.9)	16 (9.6)	24 (14.7)	0
Increased AST	48 (28.7)	7 (4.2)	13 (8.0)	0
Increased GTT	26 (15.6)	5 (3.0)	8 (4.9)	2 (1.2)
Coronavirus disease 2019	47 (28.8)	0	55 (32.9)	0
Fatigue	54 (32.3)	1 (0.6)	52 (31.9)	2 (1.2)
Headache	45 (26.9)	0	44 (27.0)	1 (0.6)
Diarrhoea	41 (24.6)	1 (0.6)	27 (16.6)	1 (0.6)
Nausea	36 (21.6)	0	37 (22.7)	0
Dizziness	25 (15.0)	0	26 (16.0)	0
Seizure	23 (13.8)	7 (4.2)	19 (11.7)	4 (2.5)
Constipation	21 (12.6)	0	20 (12.3)	0

Source: (Mellinghoff 2023b)[65]
Abbreviations: AE: adverse events; ALT: alanine aminotransferase; AST: aspartate aminotransferase; GTT: γ-glutamyltransferase; N=number of subjects in the SAS within each treatment arm; n=number of subjects in the SAS within each treatment arm in each; SAS: safety analysis set

	Vorasidenib (N=167)	Placebo (N=163)
TEAEs leading to discontinuation of study drug, n (%)	6 (3.6)	2 (1.2)
TEAEs leading to dose reduction of study drug, n (%)	18 (10.8)	5 (3.1)
TEAEs leading to interruption of study drug, n (%)	50 (29.9)	37 (22.7)
TEAEs leading to death, n (%)	0	0
Treatment-related TEAEs leading to death, n (%)	0	0

Source: (Servier 2023)[66]
Abbreviations: N: number of subjects in the SAS within each treatment arm; n: number of subjects in the SAS within each treatment arm in each category; SAS: safety analysis set; TEAE: treatment emergent adverse event

Appendix E: Published cost-effectiveness studies

Objective

An SLR was conducted to identify published economic evidence reporting on the economic burden (costs, resource use and economic evaluations) for patients with grade 2 or 3 diffuse glioma.

Search strategy

Electronic databases

Literature was searched electronically on 24th April 2023 for the original SLR and 20th May 2024 for the SLR update, in a structured way through the following databases:

- EMBASE and MEDLINE (via www.embase.com).
- MEDLINE and MEDLINE In-Process (via https://pubmed.ncbi.nlm.nih.gov/).

The search terms were developed in line with the PICOS framework using subject headings (Emtree and MeSH) and free text terms to address each aspect of the research question. An HTA-compliant search strategy (Embase) is detailed below. The published search filter by SIGN/ISSG (Scottish Intercollegiate Guidelines Network/ InterTASC Information Specialists' Sub-Group Search Filter Resource) was used to identify economic evaluations as well as cost and resource use studies for this review[102].

Each database was searched individually, with the results of individual searches reported separately in the PRISMA flowchart. The results of all searches were combined into a single reference library, with duplicate records removed prior to commencing title and abstract screening.

Grey literature

In addition to the electronic databases, the following supplementary sources of evidence were hand searched.

Conference proceedings

Proceedings (abstracts, and posters if available) from the following congresses were hand searched from 2020 to June 2024 inclusive on 19th April 2023 for the original SLR and 3rd June 2024 for the SLR update:

- American Society of Clinical Oncology (ASCO) (via www.meetings.asco.org/abstracts-presentations/).
- European Society for Medical Oncology (ESMO) (via www.annalsofoncology.org/content/supplements?hit=OncologyPRO).
- European Association of Neuro-oncology (EANO) (via www.eano.eu).
- Society for Neuro-Oncology (SNO) (via www.soc-neuro-onc.org/).
- International Society for Pharmacoeconomics and Outcomes Research (ISPOR) (via www.ispor.org/heor-resources/presentations-database/search).

- Congress of Neurological Surgeons (via www.cns.org/Default.aspx).
- American Society for Radiation Oncology (via www.astro.org/).
- International Conference on Advances in Radiation Oncology (ASTRO) (via www.iaea.org/events/icaro-3/programme).
- European Society for Radiotherapy and Oncology (ESTRO) (via www.estro.org/Library).

HTA submissions

The following major HTA bodies were searched on 21st April 2023 for the original SLR and 4th June 2024 for the SLR update:

- National Institute for Health and Care Excellence (NICE)
- Scottish Medicines Consortium (SMC)
- Canadian Agency for Drugs and Technologies in Health (CADTH)
- Pharmaceutical Benefits Advisory Committee (PBAC)
- Federal Joint Committee (G-BA)
- Institute for Clinical & Economic Review (ICER)
- French National Health Authority (HAS)

Reference lists and other sources

The following were searched on 20th April 2023 for the original SLR and 5th June 2024 for the SLR update:

- Reference lists of included publications and related SLRs and meta-analyses were reviewed.
- Cost-Effectiveness Analysis registry (via https://cevr.tuftsmedicalcenter.org/databases/cea-registry).
- EconLit
- EconPapers
- Google Scholar.

Search strategies

Search terms for EMBASE and MEDLINE via www.embase.com using the SIGN economic search filter[102]. (Date of the search: Original SLR April 24th 2023; SLR update: May 20th 2024)

No.	Query	Original Results	Update Results
#01	'glioma'/de OR 'glioma*':ti,ab	115,035	124,403
#02	(('isocitrate dehydrogenase 1' OR 'isocitrate dehydrogenase 2' OR 'idh' OR 'isocitrate dehydrogenase' OR 'idh-' OR 'idh1' OR 'idh2') NEXT/3 ('mutant' OR 'mutated' OR 'mutation*' OR 'gene')) AND 'glioma'/exp	6,479	7,434
#03	'astrocytoma':ti,ab OR 'oligodendroglioma':ti,ab OR 'oligoastrocytoma':ti,ab OR (('astrocyt*' OR 'oligodendrogli*' OR 'idh' OR 'isocitrate dehydrogenase') NEXT/5 ('tumor' OR 'tumour' OR 'glioma*'))	24,796	26,212
#04	#1 OR #2 OR #3	128,769	138,691
#05	'socioeconomics'/exp	1,296,201	1,568,989

No.	Query	Original Results	Update Results
#06	'cost benefit analysis'/exp	93,182	96,626
#07	'cost effectiveness analysis'/exp	177,139	190,392
#08	'cost of illness'/exp	20,986	21,502
#09	'cost control'/exp	75,281	78,120
#10	'economic aspect'/exp	2,436,845	2,774,209
#11	'financial management'/exp	535,610	571,645
#12	'health care cost'/exp	335,161	353,657
#13	'health care financing'/exp	13,854	14,092
#14	'health economics'/exp	1,026,683	1,091,668
#15	'hospital cost'/exp	44,910	47,577
#16	fiscal:ti OR financial:ti OR finance:ti OR funding:ti	29,813	32,294
#17	'cost minimization analysis'/exp	3,920	4,107
#18	(cost NEAR/1 estimate$):ti,ab	8,764	9,284
#19	(cost NEAR/1 variable$):ti,ab	723	768
#20	(unit NEAR/1 cost$):ti,ab	5,498	5,793
#21	'cost'/exp	401,359	422,478
#22	'budget'/exp	32,895	34,597
#23	budget*:ti,ab,kw	47,215	50,421
#24	economic*:ti,kw OR cost:ti,kw OR costs:ti,kw OR costly:ti,kw OR costing:ti,kw OR price:ti,kw OR prices:ti,kw OR pricing:ti,kw OR pharmacoeconomic*:ti,kw OR 'pharmaco economic*':ti,kw OR expenditure:ti,kw OR expenditures:ti,kw OR expense:ti,kw OR expenses:ti,kw OR financial:ti,kw OR finance:ti,kw OR finances:ti,kw OR financed:ti,ab,kw	348,582	372,170
#25	(cost* NEAR/2 (effective* OR utilit* OR benefit* OR minimi* OR analy* OR outcome OR outcomes)):ti,ab,kw	300,999	327,324
#26	(value NEAR/2 (money OR monetary)):ti,ab,kw	4,017	4,302
#27	'statistical model'/exp	678,656	729,934
#28	'economic model':ab,kw	3,439	3,698
#29	'probability'/exp	143,229	157,889
#30	markov:ti,ab,kw	37,156	40,277
#31	'monte carlo method'/exp	50,766	55,360
#32	'monte carlo':ti,ab,kw	61,938	66,660
#33	'decision theory'/exp	1,832	1,872
#34	'decision tree'/de	20,228	24,328
#35	(decision* NEAR/2 (tree* OR analy* OR model*)):ti,ab,kw	49,414	57,163
#36	#5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35	3,410,155	3,819,159
#37	#4 AND #36	5,023	6,201
#38	'case study'/exp OR 'case study' OR 'case report':ti,ab OR 'letter'/exp OR 'letter' OR 'editorial':it OR 'letter':it OR 'note':it	3,734,641	3,949,877
#39	'animal experiment'/de NOT ('human experiment'/de OR 'human'/de)	2,520,620	2,640,605
#40	#37 NOT (#38 OR #39)	4,700	5,786

No.	Query	Original Results	Update Results
#41	#40 AND ([article]/lim OR [article in press]/lim)	2,642	3,386
#42	#40 AND ([article]/lim OR [article in press]/lim) AND [01-04-2023]/sd NOT [02-08-2024]/sd	N/A	689

Search terms for MEDLINE and MEDLINE-IN-PROCESS via https://pubmed.ncbi.nlm.nih.gov/ using the SIGN economic search filter[102] (Date of the search: Original SLR: April 24th 2023; SLR update: May 20th 2024)

No.	Query	Original Results	Update Results
#01	glioma[MeSH Major Topic]	82,102	86,766
#02	"glioma*"[Title/Abstract]	70,679	75,431
#03	(isocitrate dehydrogenase[MeSH Terms]) AND (("glioma*"[Title/Abstract]) OR (glioma[MeSH Terms]))	2,451	2,744
#04	"IDH mutant glioma"[Title/Abstract:~10] OR "IDH-mutant glioma"[Title/Abstract:~10] OR "IDH mutated glioma"[Title/Abstract:~10] OR "IDH mutation glioma"[Title/Abstract:~10] OR "IDH gene glioma"[Title/Abstract:~10] OR "IDH-mutated glioma"[Title/Abstract:~10] OR "IDH-mutation glioma"[Title/Abstract:~10] OR "IDH-gene glioma"[Title/Abstract:~10] OR "IDH1 mutant glioma"[Title/Abstract:~10] OR "IDH2 mutant glioma"[Title/Abstract:~10] OR "IDH1 mutated glioma"[Title/Abstract:~10] OR "IDH2 mutated glioma"[Title/Abstract:~10] OR "IDH1 mutation glioma"[Title/Abstract:~10] OR "IDH2 mutation glioma"[Title/Abstract:~10] OR "IDH1 gene glioma"[Title/Abstract:~10] OR "IDH2 gene glioma"[Title/Abstract:~10] OR "isocitrate dehydrogenase mutant glioma"[Title/Abstract:~10] OR "isocitrate dehydrogenase mutated glioma"[Title/Abstract:~10] OR "isocitrate dehydrogenase mutation glioma"[Title/Abstract:~10] OR "isocitrate dehydrogenase gene glioma"[Title/Abstract:~10]	864	1,022
#05	"astrocytoma"[Title/Abstract] OR "oligodendroglioma"[Title/Abstract] OR "oligoastrocytoma"[Title/Abstract]	15,437	16,052
#06	"astrocytic tumor"[Title/Abstract:~5] OR "astrocytic tumour"[Title/Abstract:~5] OR "astrocytic glioma"[Title/Abstract:~10] OR "IDH astrocytoma"[Title/Abstract:~5] OR "IDH astrocytic"[Title/Abstract:~5] OR "oligodendroglial tumor"[Title/Abstract:~5] OR "oligodendroglial tumour"[Title/Abstract:~5] OR "oligodendroglial glioma"[Title/Abstract:~10] OR "IDH oligodendroglioma"[Title/Abstract:~10] OR "IDH oligodendroglial"[Title/Abstract:~10] OR "idh tumor glioma"[Title/Abstract:~10] OR "idh tumour glioma"[Title/Abstract:~10] OR "IDH glioma"[Title/Abstract:~10] OR "isocitrate dehydrogenase tumor glioma"[Title/Abstract:~10] OR "isocitrate dehydrogenase tumour glioma"[Title/Abstract:~10] OR "isocitrate dehydrogenase glioma"[Title/Abstract:~10] OR "IDH oligoastrocytoma"[Title/Abstract:~10]	2,296	2,597
#07	#1 OR #2 OR #3 OR #4 OR #5 OR #6	112,837	119,720
#08	"Economics"[mesh:noexp]	27,498	27,534
#09	"costs and cost analysis"[mesh:noexp]	51,258	51,960
#10	"Cost allocation"[mesh:noexp]	2,018	2,019
#11	"Cost-benefit analysis"[mesh:noexp]	92,144	94,644
#12	"Cost control"[mesh:noexp]	21,662	21,685
#13	"Cost savings"[mesh:noexp]	12,696	12,818
#14	"Cost of illness"[mesh:noexp]	31,409	32,322

No.	Query	Original Results	Update Results
#15	"Cost sharing"[mesh:noexp]	2,730	2,785
#16	"deductibles and coinsurance"[mesh:noexp]	1,850	1,877
#17	"Medical savings accounts"[mesh:noexp]	547	549
#18	"Health care costs"[mesh:noexp]	44,006	44,956
#19	"Direct service costs"[mesh:noexp]	1,217	1,217
#20	"Drug costs"[mesh:noexp]	17,356	17,605
#21	"Employer health costs"[mesh:noexp]	1,097	1,098
#22	"Hospital costs"[mesh:noexp]	11,931	12,057
#23	"Health expenditures"[mesh:noexp]	23,842	24,723
#24	"Capital expenditures"[mesh:noexp]	2,001	2,003
#25	"Value of life"[mesh:noexp]	5,803	5,826
#26	"economics, hospital"[mesh]	25,696	25,847
#27	"economics, medical"[mesh]	14,386	14,433
#28	"Economics, nursing"[mesh:noexp]	4,013	4,013
#29	"Economics, pharmaceutical"[mesh:noexp]	3,098	3,134
#30	"fees and charges"[mesh]	31,324	31,450
#31	"budgets"[mesh]	14,096	14,208
#32	(("low"[tiab] OR "low"[nm] OR "low"[mh] OR "low"[tt] OR "low"[pmid]) AND ("cost"[tiab] OR "cost"[nm] OR "cost"[mh] OR "cost"[tt] OR "cost"[pmid]))	151,989	168,926
#33	(("high"[tiab] OR "high"[nm] OR "high"[mh] OR "high"[tt] OR "high"[pmid]) AND ("cost"[tiab] OR "cost"[nm] OR "cost"[mh] OR "cost"[tt] OR "cost"[pmid]))	162,964	181,265
#34	((health?care[tiab] OR health?care[nm] OR health?care[mh] OR health?care[tt] OR health?care[pmid]) AND (cost*[tiab] OR cost*[nm] OR cost*[mh] OR cost*[tt] OR cost*[pmid]))	216,716	169,947
#35	("fiscal"[tiab] OR "funding"[tiab] OR "financial"[tiab] OR "finance"[tiab])	197,596	218,225
#36	(("cost"[tiab] OR "cost"[nm] OR "cost"[mh] OR "cost"[tt] OR "cost"[pmid]) AND (estimate*[tiab] OR estimate*[nm] OR estimate*[mh] OR estimate*[tt] OR estimate*[pmid]))	67,544	72,538
#37	(("cost"[tiab] OR "cost"[nm] OR "cost"[mh] OR "cost"[tt] OR "cost"[pmid]) AND ("variable"[tiab] OR "variable"[nm] OR "variable"[mh] OR "variable"[tt] OR "variable"[pmid]))	10,405	11,334
#38	(("unit"[tiab] OR "unit"[nm] OR "unit"[mh] OR "unit"[tt] OR "unit"[pmid]) AND (cost*[tiab] OR cost*[nm] OR cost*[mh] OR cost*[tt] OR cost*[pmid]))	28,816	29,103
#39	(economic*[tiab] OR pharmacoeconomic*[tiab] OR price*[tiab] OR "pricing"[tiab])	424,555	463,382
#40	#8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39	1,084,757	1,171,199
#41	"case reports"[Publication Type] OR "editorial"[Publication Type] OR "letter"[Publication Type] OR "news"[Publication Type] OR "comment"[Publication Type]	4,453,742	4,624,901
#42	#7 AND #40	817	911
#43	(#7 AND #40) NOT #41	772	865
#44	(#7 AND #40) NOT #41	617	705
#45	#44 and 2023/04/01:2024/08/01[edat]	N/A	63

Study selection

Titles and abstracts of the retrieved citations were screened against the inclusion/exclusion criteria defined in Table 57. Studies identified as potentially relevant based on their titles/abstracts were reviewed in full and selected for inclusion/exclusion, according to the same criteria. Citations that do not meet the criteria were excluded. Articles at both title/abstract and full-text review stage were reviewed by two reviewers, independently and in parallel, based on the pre-specified study selection criteria. After completion of the full-text review, 20% of the screened articles were quality checked by a third independent reviewer. Any discrepancy was resolved by discussion. A third person was involved if a decision was not reached between the two reviewers.

Table 57: Eligibility criteria for the economic SLR

Category	Inclusion criteria	Exclusion criteria
Population	Patients aged 12 years or older with grade 2 or 3 glioma, referred to as: Diffuse adult-type glioma Diffuse astrocytoma or oligodendroglioma Anaplastic astrocytoma or oligodendroglioma Grade 2 or 3 oligodendroglioma (IDH-mutant with 1p19q codeletion) Grade 2 or 3 astrocytoma (IDH-mutant with intact 1p19q or ATRX loss) Subgroups of interest: Patients with IDH-mutant grade 2 diffuse glioma Patients who have undergone surgery (biopsy, sub-total resection, gross-total resection) as their only treatment Watch and wait, radiotherapy, chemotherapy, radiotherapy + chemotherapy	Pediatric diffuse glioma CNS neoplasm other than diffuse adult-type glioma Glioblastoma IDH wild-type glioma, if reported as the main focus of the study
Intervention/comparator	No restriction Note: Post-surgery and surgeries after the first one were of particular interest	Not applicable
Outcomes	Economic modelling studies: Incremental cost-effectiveness ratio (ICER) /cost-effectiveness ratio (CER) Incremental cost-utility ratio (ICUR) /cost-utility ratio (CUR) Model structure, inputs, drivers Direct/ indirect costs (per health state, mean cost per patient, etc.) Quality-adjusted life years (QALYs) /life years (LYs) Sensitivity analysis Subgroups Geographic setting (country/territory) and perspective Cost and resource use studies: Cost (per health state, mean cost per patient, etc.) Direct costs (e.g., drug acquisition, seizure related cost) Indirect costs (e.g., work productivity loss, absenteeism, presenteeism, sick leaves) Total costs Resource use related to disease and the associated intervention, e.g., hospital admissions, length of stay, physician visits, emergency department/accident and emergency visits and pharmacy costs	No outcomes of interest were reported in the study
Study design	Economic evaluations: Cost-consequence models Cost-minimisation models	Randomised controlled trials Case reports/studies/series

Category	Inclusion criteria	Exclusion criteria
	Cost-effectiveness models Cost-utility models Cost-benefit models Budget impact models Cost and resource use studies: Observational/real world studies (non-interventional) reporting original costs and resource use data Cost of illness studies	
Publication type	Peer-reviewed journal articles Original research reports Conference abstracts	Non-peer-reviewed articles Note/News articles/Editorials Letters/ book chapters, if data are already published in peer-reviewed journal articles or original research reports
Language	English language	Language other than English
Publication year†	Full publications: No restriction (up to 20th May 2024) Conference abstracts: 2020 to 3rd June 2024	Conference abstracts published prior to 2020
Geography	No restriction	Not applicable

†Typically, HTA-compliant SLRs for economic evidence are designed for the last 10 years, to cover the most recent evidence aligned to recent clinical practice. However, limited evidence was anticipated, and so the SLR timeframe was not restricted to ensure that all available publications are identified.
Abbreviations: CER: cost-effectiveness ratio; CNS: central nervous system; CUR: cost-utility ratio; ICER: incremental cost-effectiveness ratio; ICUR: incremental cost-utility ratio; IDH: isocitrate dehydrogenase; LY: life-year; QALY: quality-adjusted life-year; SLR: systematic literature review.

Results

A total of 3,179 records were identified through the electronic database searches run from database inception until 24th April 2023. After removal of duplicates, 3,005 citations were eligible for title and abstract screening. Of these, 2,937 citations were excluded, and 69 publications were reviewed at the full text review stage. Following the screening, 50 publications were excluded, and 19 publications were deemed eligible for inclusion in the SLR. In addition, two relevant publications were identified from the grey literature searches. As a result, a total of 21 publications were included in the original SLR (Figure 41).

In the 2024 SLR update conducted on 20th May 2024, a total of 752 records were identified through electronic database searches. After removal of duplicates, 732 citations were screened based on title and abstract, and 32 publications were retrieved for full text review. Following screening, 4 of the 32 publications were included from database searches. In addition, one relevant publication was identified from grey literature searches. As a result, a total of five publications were finally included for the SLR update (Figure 42).

Overall, 26 publications reporting on nine economic evaluations and 17 studies with costs and resource use outcomes, were included in the SLR.

Figure 41: PRISMA flow diagram – original economic SLR

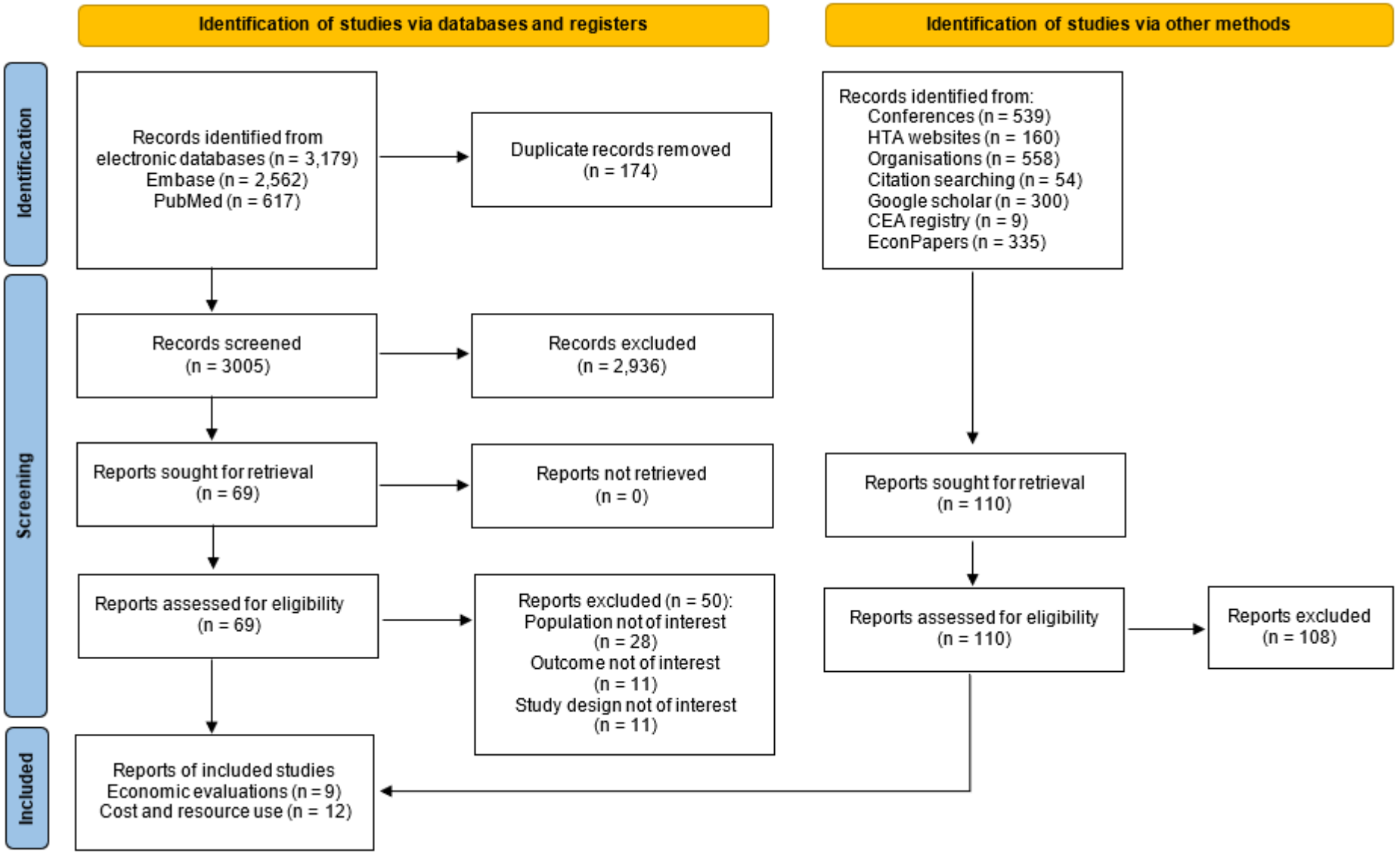
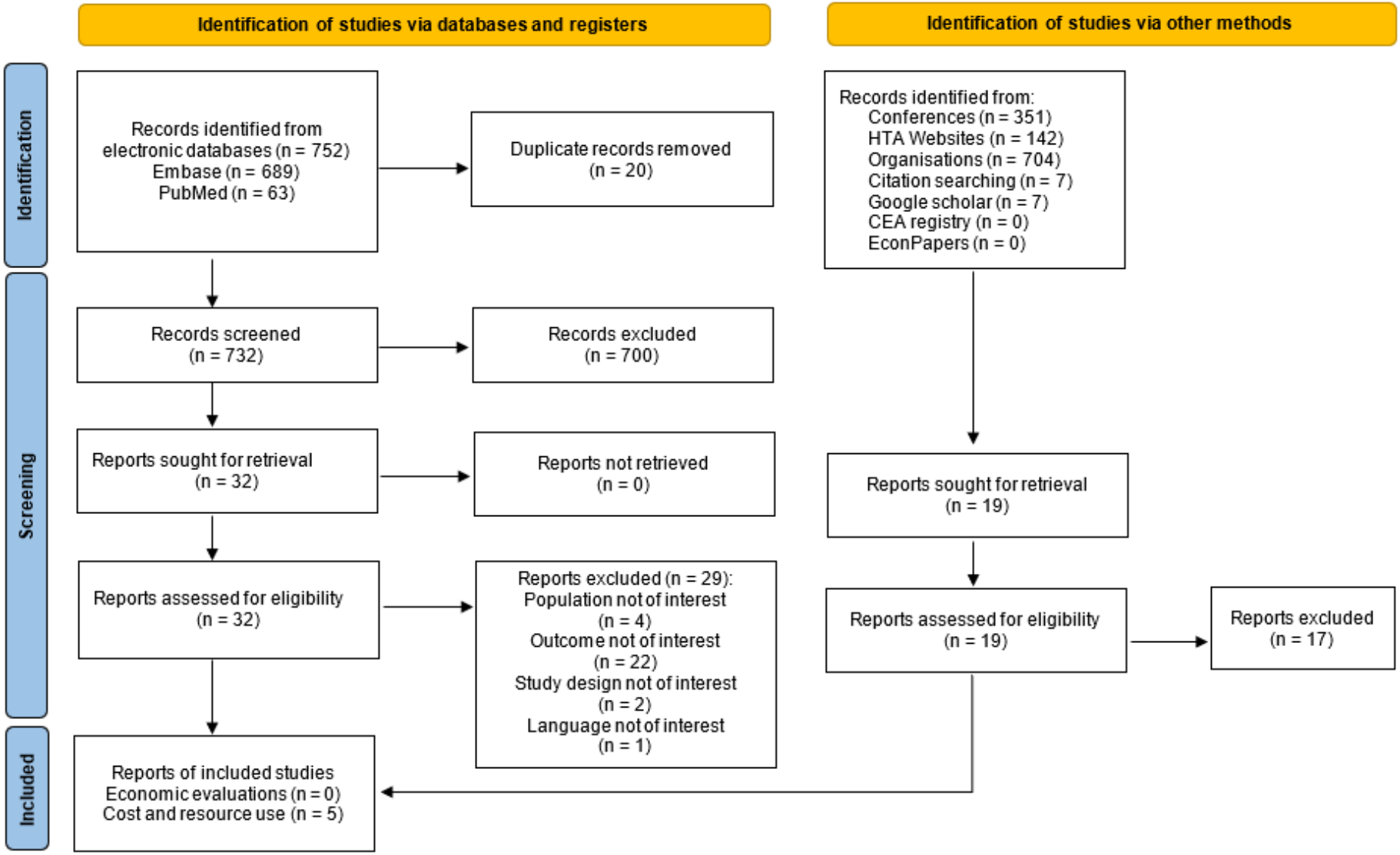


Figure 42: PRISMA flow diagram – economic SLR update



Of the nine included health economic evaluations, one was conducted from a UK perspective; this study is described in the Company Evidence Submission, Section 3.1.

List of included and excluded studies

A list of studies included in the original SLR and the SLR update is provided in Table 58.

Table 58: List of included studies – economic

Author, year	Title	Citation
Original SLR		
Haider, 2020	The economic impact of glioma survivorship: The cost of care from a patient perspective	Neurology. 2020 Sep 15;95(11):e1575-e1581
Qian, 2017	Cost-effectiveness of radiation and chemotherapy for high-risk low-grade glioma	Neuro Oncol. 2017 Nov 29;19(12):1651-1660
Reese, 2019	Analysis of Treatment Cost Variation Among Multiple Neurosurgical Procedures Using the Value-Driven Outcomes Database	World Neurosurg. 2019 Jun:126:e914-e920
Nassiri, 2019	Hospital costs associated with inpatient versus outpatient awake craniotomy for resection of brain tumors	J Clin Neurosci. 2019 Jan:59:162-166
Boele, 2020	Healthcare utilization and productivity loss in glioma patients and family caregivers: the impact of treatable psychological symptoms	J Neurooncol. 2020 Apr;147(2):485-494
Le Rhun, 2019	Complementary and alternative medicine use in glioma patients in France	J Neurooncol. 2019 Dec;145(3):487-499
Wasserfallen, 2005	Cost of temozolomide therapy and global care for recurrent malignant gliomas followed until death	Neuro Oncol. 2005 Apr;7(2):189–195
Osorio, 2018	Cost-effectiveness development for the postoperative care of craniotomy patients: a safe transitions pathway in neurological surgery	Neurosurg Focus. 2018 May;44(5):E19
Mabasa, 2006	Re-evaluation of the cost effectiveness of temozolomide for malignant gliomas in British Columbia	J Oncol Pharm Pract. 2006 Jun;12(2):105-11
Butenschön, 2018	Cost-effectiveness of preoperative motor mapping with navigated transcranial magnetic brain stimulation in patients with high-grade glioma	Neurosurg Focus. 2018 Jun;44(6):E18
Eseonu, 2017	The Cost of Brain Surgery: Awake vs Asleep Craniotomy for Perirolandic Region Tumor	Neurosurgery. 2017 Aug 1;81(2):307-314
Martino, 2013	Cost-utility of maximal safe resection of WHO grade II gliomas within eloquent areas	Acta Neurochir (Wien). 2013 Jan;155(1):41-50
Dinnes, 2001	The effectiveness and cost-effectiveness of temozolomide for the treatment of recurrent malignant glioma: a rapid and systematic review	Health Technol Assess. 2001;5(13):1-73
Konski, 1997	Cost-utility analysis of a malignant glioma protocol	Int J Radiat Oncol Biol Phys. 1997 Oct 1;39(3):575-8
Missios, 2017	Regional disparities in hospitalization charges for patients undergoing craniotomy for tumor resection in New York State: correlation with outcomes	J Neurooncol. 2016 Jun;128(2):365-71
Mosteiro, 2022	Is intraoperative ultrasound more efficient than magnetic resonance in neurosurgical oncology? An exploratory cost-effectiveness analysis	Front Oncol. 2022 Oct 28:12:1016264
Zhou, 2021	Analysis of the spectrum and characteristics of pediatric cancer based on hospital information systems in china	Cancer Manag Res. 2021 Feb 11:13:1205-1214
Pendharkar, 2020	Functional Mapping for Glioma Surgery: A Propensity-Matched Analysis of Outcomes and Cost	World Neurosurg. 2020 May:137:e328-e335

Author, year	Title	Citation
Greanya, 2004	Temozolomide for malignant gliomas in British Columbia: A population-based cost-effectiveness analysis	Journal of Oncology Pharmacy Practice. 2004;10(4):201-209
Tuohy, 2023	Early costs and complications of first-line low-grade glioma treatment using a large national database: Limitations and future perspectives	Front Surg. 2023 Feb 3:10:1001741
Ashour, 2018	Maximizing Resection of Diffused Low-Grade Glioma Functional Outcome	The Egyptian Journal of Hospital Medicine (April 2018) Vol. 71 (7), Page 3465-3472
SLR update		
Walker, 2023	Experiences of work for people living with a grade 2/3 oligodendroglioma: A qualitative analysis within the Ways Ahead study	BMJ Open. 2023 Sep 28;13(9):e074151
Barberis, 2024	Verbal fluency predicts work resumption after awake surgery in low-grade glioma patients	Acta Neurochir (Wien). 2024 Feb 19;166(1):88
Albuquerque, 2023	Awake Craniotomy for Diffuse Low Grade Gliomas in a Resource Limited Setting: Lessons Learned with a Consecutive Series of 51 Surgeries	World Neurosurg. 2023 Jun 28:S1878-8750(23)00879-3
Senft, 2020	The ability to return to work: a patient-centered outcome parameter following glioma surgery	J Neurooncol. 2020 Sep;149(3):403-411
Koo, 2020	Multi-institutional study of treatment patterns in Korean patients with WHO grade II gliomas: KNOG 15-02 and KROG 16-04 intergroup study	Neurooncol 2018. 138, 667–677

A list of studies excluded at the full text stage with reasons for exclusion can be found in the reference pack[103]

Appendix F: Health-related quality-of-life studies

Objective

An SLR was conducted to identify and summarise published evidence on the humanistic burden (HRQoL and utilities) of grade 2 or 3 diffuse glioma. Evidence associated with patients who have undergone surgery (biopsy, sub-total resection, gross-total resection) as their only treatment and are not in need of immediate RT and/or CT (as defined in the INDIGO study), was of particular interest.

Search strategy

Electronic databases

Literature was searched electronically in a structured way through the following databases searched on 18th April 2023 for the original SLR, followed by an updated search run on 20th May 2024.

- EMBASE and MEDLINE (via www.embase.com)
- MEDLINE and MEDLINE In-Process (via https://pubmed.ncbi.nlm.nih.gov/)

The search terms were developed in line with the PICOS framework using subject headings (Emtree and MeSH) and free text terms, to address each aspect of the research question. The HTA-compliant search strategy for all databases is detailed below. Search terms were modified for specific databases, to account for differences in syntax and thesaurus headings. The SIGN/ISSG published filter was used to identify quality of life as well as utility studies for this review[102].

Each database was searched individually, with the results of individual searches reported separately in the PRISMA flowchart. The results of all searches were combined into a single reference library, with duplicate records removed prior to commencing title and abstract screening.

Grey literature

In addition to the electronic database searches, the following supplementary sources of evidence were hand searched.

Conference proceedings

Conference proceedings were searched on 19th April 2023 and 3rd June 2024. Proceedings (abstracts, and posters if available) from the following congresses were hand searched from 2020 to 2024 inclusive:

- American Society of Clinical Oncology (ASCO) (via www.meetings.asco.org/abstracts-presentations/).
- European Society for Medical Oncology (ESMO) (via www.annalsofoncology.org/content/supplements?hit=OncologyPRO).
- European Association of Neuro-oncology (EANO) (via www.eano.eu).
- Society for Neuro-Oncology (SNO) (via www.soc-neuro-onc.org/).

- International Society for Pharmacoeconomics and Outcomes Research (ISPOR) (via www.ispor.org/heor-resources/presentations-database/search).
- Congress of Neurological Surgeons (via www.cns.org/Default.aspx).
- American Society for Radiation Oncology (via www.astro.org/).
- International Conference on Advances in Radiation Oncology (ASTRO) (via www.iaea.org/events/icaro-3/programme).
- European Society for Radiotherapy and Oncology (ESTRO) (via www.estro.org/Library).

HTA submissions

The following HTA bodies were searched on 21st April 2023 and 4th–5th June 2024:

- National Institute for Health and Care Excellence (NICE)
- Scottish Medicines Consortium (SMC)
- Canadian Agency for Drugs and Technologies in Health (CADTH)
- Pharmaceutical Benefits Advisory Committee (PBAC)
- Federal Joint Committee (G-BA)
- Institute for Clinical & Economic Review (ICER)
- French National Health Authority (HAS)

Glioma organisations

The following key organisations for glioma were searched on 21st April 2023 and 4th–5th June 2024:

- World Federation of Neuro-Oncology Societies (WFNOS) (via www.wfnos.org/).
- American Brain Tumor Association (via www.abta.org/).
- European Academy of Neurology (EAN) (via www.ean.org/).
- European Federation of Neurological Associations (EFNA) (via www.efna.net/).
- Brain Tumor Network (via www.braintumornetwork.org/).
- International Brain Tumor Society (via www.braintumor.org/).

Reference lists and other sources

The following other sources were searched on 20th April 2023 and 4th–7th June 2024.

- Reference lists of included publications and related SLRs and meta-analyses were reviewed.
- Google Scholar

Search strategies

Search terms for EMBASE and MEDLINE via www.embase.com using the SIGN QoL and utilities search filter[102]. Date of the search: Original SLR:18th April 2023; SLR update: 20th May 2024

No.	Query	Original Results	Update Results
#1	'glioma'/de OR 'glioma*':ti,ab	115,035	124,403
#2	(('isocitrate dehydrogenase 1' OR 'isocitrate dehydrogenase 2' OR '*IDH*' OR 'isocitrate dehydrogenase' OR '*IDH*-' OR '*IDH*1' OR '*IDH*2') NEXT/3 ('mutant' OR 'mutated' OR 'mutation*' OR 'gene')) AND 'glioma'/exp	6,479	7,434
#3	'astrocytoma':ti,ab OR 'oligodendroglioma':ti,ab OR 'oligoastrocytoma':ti,ab OR (('astrocyt*' OR 'oligodendrogli*' OR '*IDH*' OR 'isocitrate dehydrogenase') NEXT/5 ('tumor' OR 'tumour ' OR 'glioma*'))	24,796	26,212
#4	#1 OR #2 OR #3	128,769	138,691
#5	'quality adjusted life year'/exp OR 'quality of life'/exp	628,257	694,003
#6	'quality of life index'/exp	3,153	3,303
#7	'short form 12'/exp OR 'short form 20'/exp OR 'short form 36'/exp OR 'short form 8'/exp	47,364	52,431
#8	'sickness impact profile'/exp	2,327	2,345
#9	(quality NEAR/2 (wellbeing OR 'well being')):ti,ab	3,649	4,160
#10	'sickness impact profile':ti,ab	1,235	1,246
#11	'disability adjusted life':ti,ab	6,002	7,210
#12	qal*:ti,ab OR qtime*:ti,ab OR qwb*:ti,ab OR daly*:ti,ab	32,353	36,021
#13	euroqol*:ti,ab OR eq5d*:ti,ab OR 'eq 5d*':ti,ab OR '15d':ti,ab	32,060	35,619
#14	qol*:ti,ab OR hql*:ti,ab OR hqol*:ti,ab OR hrqol*:ti,ab	127,736	140,066
#15	'health utilit*':ti,ab OR 'utility score*':ti,ab OR 'utility value*':ti,ab OR disutilit*:ti,ab	10,706	11,706
#16	hui:ti,ab OR hui1:ti,ab OR hui2:ti,ab OR hui3:ti,ab	3,103	3,423
#17	'health* year* equivalent*':ti,ab	41	41
#18	hye:ti,ab OR hyes:ti,ab	168	196
#19	rosser:ti,ab	145	151
#20	'willingness to pay':ti,ab OR 'time tradeoff':ti,ab OR 'time trade off':ti,ab OR tto:ti,ab OR 'standard gamble*':ti,ab	16,150	17,896
#21	sf20:ti,ab OR 'sf 20':ti,ab OR 'short form 20':ti,ab OR 'shortform 20':ti,ab OR shortform20:ti,ab	494	522
#22	sf36:ti,ab OR 'sf 36':ti,ab OR 'short form 36':ti,ab OR 'shortform 36':ti,ab OR shortform36:ti,ab	48,476	51,187
#23	sf12:ti,ab OR 'sf 12':ti,ab OR 'short form 12':ti,ab OR 'shortform 12':ti,ab OR shortform12:ti,ab	11,795	12,667
#24	sf8:ti,ab OR 'sf 8':ti,ab OR 'short form 8':ti,ab OR 'shortform 8':ti,ab OR shortform8:ti,ab	1,190	1,266
#25	sf6:ti,ab OR 'sf 6':ti,ab OR 'short form 6':ti,ab OR 'shortform 6':ti,ab OR shortform6:ti,ab	2,823	3,023
#26	'european organization for research and treatment of cancer quality of life questionnaire core 30' OR 'eortc qlq-c30'	10,462	12,093
#27	'functional assessment of cancer therapy general' OR 'fact-g'	2,312	2,571
#28	'bn-20' OR 'bn20' OR 'fact-br' OR 'functional assessment of cancer therapy brain' OR 'functional assessment of cancer therapy cognitive function' OR 'fact-cog'	1,252	1,372
#29	#5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28	703,699	775,961
#30	#4 AND #29	2,756	3,067
#31	'animal experiment'/de NOT ('human experiment'/de OR 'human'/de)	2,520,620	2,640,605

No.	Query	Original Results	Update Results
#32	'case study'/exp OR 'case study' OR 'case report':ti,ab OR 'letter'/exp OR 'letter' OR 'editorial':it OR 'letter':it OR 'note':it	3,734,641	3,949,877
#33	#30 NOT (#31 OR #32)	2,485	2,740
#34	#33 AND ([article]/lim OR [article in press]/lim)	1,004	1,115
#35	#33 AND ([article]/lim OR [article in press]/lim) AND [01-04-2023]/sd NOT [02-08-2024]/sd	N/A	151

Search terms for MEDLINE and MEDLINE In-Process via https://pubmed.ncbi.nlm.nih.gov/ using the SIGN QoL and utilities search filter[102]. Date of the search: Original SLR:18th April 2023; SLR update: 20th May 2024

No.	Query	Original Results	Update Results
#1	glioma[MeSH Major Topic]	82,073	86,769
#2	"glioma*"[Title/Abstract]	70,634	75,434
#3	(isocitrate dehydrogenase[MeSH Terms]) AND (("glioma*"[Title/Abstract]) OR (glioma[MeSH Terms]))	2,449	2,744
#4	"*IDH* mutant glioma"[Title/Abstract:~10] OR "*IDH*-mutant glioma"[Title/Abstract:~10] OR "*IDH* mutated glioma"[Title/Abstract:~10] OR "*IDH* mutation glioma"[Title/Abstract:~10] OR "*IDH* gene glioma"[Title/Abstract:~10] OR "*IDH*-mutated glioma"[Title/Abstract:~10] OR "*IDH*-mutation glioma"[Title/Abstract:~10] OR "*IDH*-gene glioma"[Title/Abstract:~10] OR "*IDH*1 mutant glioma"[Title/Abstract:~10] OR "*IDH*2 mutant glioma"[Title/Abstract:~10] OR "*IDH*1 mutated glioma"[Title/Abstract:~10] OR "*IDH*2 mutated glioma"[Title/Abstract:~10] OR "*IDH*1 mutation glioma"[Title/Abstract:~10] OR "*IDH*2 mutation glioma"[Title/Abstract:~10] OR "*IDH*1 gene glioma"[Title/Abstract:~10] OR "*IDH*2 gene glioma"[Title/Abstract:~10] OR "isocitrate dehydrogenase mutant glioma"[Title/Abstract:~10] OR "isocitrate dehydrogenase mutated glioma"[Title/Abstract:~10] OR "isocitrate dehydrogenase mutation glioma"[Title/Abstract:~10] OR "isocitrate dehydrogenase gene glioma"[Title/Abstract:~10]	863	1,022
#5	"astrocytoma"[Title/Abstract] OR "oligodendroglioma"[Title/Abstract] OR "oligoastrocytoma"[Title/Abstract]	15,436	16,052
#6	astrocytic tumor[Title/Abstract:~5] OR "astrocytic tumour"[Title/Abstract:~5] OR "astrocytic glioma"[Title/Abstract:~10] OR "*IDH* astrocytoma"[Title/Abstract:~5] OR "*IDH* astrocytic"[Title/Abstract:~5] OR "oligodendroglial tumor"[Title/Abstract:~5] OR "oligodendroglial tumour"[Title/Abstract:~5] OR "oligodendroglial glioma"[Title/Abstract:~10] OR "*IDH* oligodendroglioma"[Title/Abstract:~10] OR "*IDH* oligodendroglial"[Title/Abstract:~10] OR "*IDH* tumor glioma"[Title/Abstract:~10] OR "*IDH* tumour glioma"[Title/Abstract:~10] OR "*IDH* glioma"[Title/Abstract:~10] OR "isocitrate dehydrogenase tumor glioma"[Title/Abstract:~10] OR "isocitrate dehydrogenase tumour glioma"[Title/Abstract:~10] OR "isocitrate dehydrogenase glioma"[Title/Abstract:~10] OR "*IDH* oligoastrocytoma"[Title/Abstract:~10]	2,295	8,935

No.	Query	Original Results	Update Results
#7	#1 OR #2 OR #3 OR #4 OR #5 OR #6	112,784	123,156
#8	"Quality of Life"[MeSH Terms]	263,677	288,405
#9	"Quality of Life"[Title/Abstract]	358,432	396,402
#10	"Quality-Adjusted Life Years"[MeSH Terms]	15,548	16,393
#11	"quality adjusted life"[Title/Abstract] OR "disability adjusted life"[Title/Abstract]	22,072	24,589
#12	"qaly*"[Title/Abstract] OR "qald*"[Title/Abstract] OR "qale*"[Title/Abstract] OR "qtime*"[Title/Abstract] OR "life year"[Title/Abstract] OR "life years"[Title/Abstract] OR "daly*"[Title/Abstract]	28,344	31,324
#13	"qol*"[Title/Abstract] OR "hql*"[Title/Abstract] OR "hqol*"[Title/Abstract] OR "hrqol*"[Title/Abstract]	71,941	79,343
#14	"sf36"[Title/Abstract] OR "sf 36"[Title/Abstract] OR "short form 36"[Title/Abstract] OR "shortform 36"[Title/Abstract] OR "short form36"[Title/Abstract] OR "shortform36"[Title/Abstract]	30,326	31,971
#15	"sf6"[Title/Abstract] OR "sf 6"[Title/Abstract] OR "short form 6"[Title/Abstract] OR "shortform6"[Title/Abstract] OR "sf6d"[Title/Abstract] OR "sf 6d"[Title/Abstract] OR "short form 6d"[Title/Abstract] OR "shortform 6d"[Title/Abstract] OR "sf six"[Title/Abstract] OR "sfsix"[Title/Abstract] OR "short form six"[Title/Abstract]	3,489	3,701
#16	"sf8"[Title/Abstract] OR "sf 8"[Title/Abstract] OR "short form 8"[Title/Abstract] OR "shortform8"[Title/Abstract]	754	804
#17	"sf12"[Title/Abstract] OR "sf 12"[Title/Abstract] OR "short form 12"[Title/Abstract] OR "shortform 12"[Title/Abstract] OR "short form12"[Title/Abstract] OR "shortform12"[Title/Abstract]	7,556	8,154
#18	"sf16"[Title/Abstract] OR "sf 16"[Title/Abstract]	42	46
#19	"sf20"[Title/Abstract] OR "sf 20"[Title/Abstract] OR "short form 20"[Title/Abstract]	438	454
#20	"sickness impact profile"[Title/Abstract]	1,095	1,101
#21	"quality of wellbeing"[Title/Abstract] OR "quality of well being"[Title/Abstract] OR "index of wellbeing"[Title/Abstract] OR "index of well being"[Title/Abstract] OR "qwb"[Title/Abstract]	413	419
#22	"hye"[Title/Abstract] OR "hyes"[Title/Abstract] OR "healthy year equivalent*"[Title/Abstract] OR "healthy years equivalent*"[Title/Abstract]	89	92
#23	"eq"[Title/Abstract] OR "euroqol"[Title/Abstract] OR "euro qol"[Title/Abstract] OR "eq5d"[Title/Abstract] OR "eq 5d"[Title/Abstract] OR "euroqual"[Title/Abstract] OR "euro qual"[Title/Abstract]	23,013	25,672
#24	"hui"[Title/Abstract] OR "hui1"[Title/Abstract] OR "hui2"[Title/Abstract] OR "hui3"[Title/Abstract]	1,958	2,120
#25	"health status indicators"[MeSH Terms] OR "health status"[Title/Abstract]	407,515	418,196
#26	"health utilit*"[Title/Abstract] OR "disutilit*"[Title/Abstract] OR "rosser"[Title/Abstract]	3,412	3,727
#27	"utility score"[Title/Abstract:~3] OR "utility scores"[Title/Abstract:~3] OR "utility value"[Title/Abstract:~3] OR "utility values"[Title/Abstract:~5] OR "utility measure"[Title/Abstract:~3] OR "utility measures"[Title/Abstract:~3] OR "utility health"[Title/Abstract:~3] OR "utlity life"[Title/Abstract:~3] OR "utlity estimate"[Title/Abstract:~3] OR "utility estimates"[Title/Abstract:~3] OR "utility estimation"[Title/Abstract:~3] OR "utlity elicit"[Title/Abstract:~3] OR "utility disease"[Title/Abstract:~3] OR "utility weight"[Title/Abstract:~3] OR "utility index"[Title/Abstract:~3]	14,839	16,214

No.	Query	Original Results	Update Results
#28	"willingness to pay"[Title/Abstract] OR "standard gamble*"[Title/Abstract] OR "time trade off"[Title/Abstract] OR "time tradeoff"[Title/Abstract] OR "tto"[Title/Abstract]	11,096	12,327
#29	"nottingham health profile*"[Title/Abstract] OR "duke health profile"[Title/Abstract] OR "functional status questionnaire"[Title/Abstract] OR "dartmouth coop functional health assessment*"[Title/Abstract]	1,460	1,497
#30	"EORTC"[Title/Abstract] or "EORTC-QLQ-C30"[Title/Abstract] or "EORTC QLQ C30"[Title/Abstract] or "EORTC QLQC30"[Title/Abstract] or "EORTCQLQC30"[Title/Abstract] or "european organisation for research and treatment of cancer quality of life questionnaire core 30"[Title/Abstract] or "european organization for research and treatment of cancer quality of life questionnaire core 30"[Title/Abstract]	10,149	10,883
#31	"bn-20"[Title/Abstract] OR "bn20"[Title/Abstract] OR "Functional Assessment of Cancer Therapy"[Title/Abstract] or "FACT"[Title/Abstract] or "FACT-G"[Title/Abstract] or "fact-br"[Title/Abstract] OR "functional assessment of cancer therapy brain"[Title/Abstract] OR "functional assessment of cancer therapy cognitive function"[Title/Abstract] OR "fact-cog"[Title/Abstract]	263,290	273,228
#32	#8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31	1,096,920	1,160,466
#33	"case reports"[Publication Type] OR "editorial"[Publication Type] OR "letter"[Publication Type] OR "news"[Publication Type] OR "comment"[Publication Type]	4,452,233	4,625,117
#34	#7 AND #32	3,985	4,315
#35	(#7 AND #32) NOT #33	3,634	3,946
#36	(#7 AND #32) NOT #33 Filters: Humans, English	2,962	3,352
#37	#37 AND 2023/04/01:2024/08/01[edat]	N/A	173

Study selection

Titles and abstracts of the retrieved citations were screened against the inclusion/exclusion criteria defined in Table 59. Studies identified as potentially relevant based on their titles and abstracts were reviewed in full and included or excluded according to the same criteria. Articles at both title/abstract and full-text review stage were reviewed by two reviewers, independently and in parallel, based on the pre-specified study selection criteria. After completion of the full-text review, 20% of the screened articles were quality checked by a third independent reviewer. Any discrepancy was resolved by discussion. A third person was involved if a decision was not reached between the two reviewers.

Table 59: Eligibility criteria for the quality of life SLR

Category	Inclusion criteria	Exclusion criteria
Population	Patients aged 12 years or older grade 2 or 3 diffuse glioma, referred to as: Diffuse adult-type glioma Diffuse astrocytoma or oligodendroglioma Anaplastic astrocytoma or oligodendroglioma Grade 2 or 3 oligodendroglioma (*IDH mutant* with 1p19q codeletion) Grade 2 or 3 astrocytoma (*IDH mutant* with intact 1p19q or ATRX loss) Subgroups of interest: Patients who have undergone surgery (biopsy, sub-total resection, gross-total resection) as their only treatment Watch and wait 12 months before radiotherapy, chemotherapy, radiotherapy + chemotherapy	Pediatric diffuse glioma IDH wildtype glioma Glioblastoma CNS neoplasm other than diffuse adult-type glioma
Intervention/ comparator	No restriction	Not applicable
Outcomes	Disease-specific or generic non-preference-based QoL and PRO instruments, as reported in literature Utilities derived using generic preference-based instruments (health states and adverse events utility data only), including but not restricted to EQ-5D (3 and/or 5-level), SF-6D, SG, TTO Mapping algorithms Treatment satisfaction Caregiver burden	Studies reporting no outcomes of interest
Study design	Observational/real-world studies (non-interventional) Utility studies Related SLRs for cross-referencing purposes only	Randomised controlled trials† Case reports/case studies/case series
Publication type	Peer-reviewed journal articles Original research reports Conference abstracts	Non-peer-reviewed articles Notes/ News articles/ Editorials Letters/ book chapters, if data are already published in peer-reviewed journal articles or original research reports
Language	English language	NA
Geographic scope	US, EU4 (France, Germany, Italy, Spain), UK, Australia, Japan Note: Given the limited evidence identified, the SLR was not restricted by geography.	NA
Publication year	QoL outcome/PRO studies: 2013–present (until to 20th May 2024) Utility studies: no restriction (until 20th May 2024)	QoL outcome/PRO studies: prior to 2013

†Utility evidence from randomised controlled trials was part of the clinical SLR scope. This SLR focuses on utility evidence available from observational/real world and utility studies.
Abbreviations: CNS: central nervous system; *IDH*: isocitrate dehydrogenase; HRQoL: health related quality of life; NA: not applicable; PRO: patient-reported outcome; QoL: quality of life; RCTs: randomised clinical trials; SF-6D: Short-Form Six-dimensional health state; SG: standard gamble; SLR: systematic literature review; TTO: time trade-off.

Results

In the original SLR, a total of 3,910 records were identified through electronic database searches run on 18th April 2023. After removal of duplicates, 3,418 citations were eligible for title and abstract screening. Of these, 3,194 citations were excluded, and 190 publications were reviewed at the full text review stage. Following screening, 170 publications were excluded, and 20 publications reporting 17 studies were deemed eligible for inclusion in the SLR. Further, an additional five publications reporting three relevant studies were identified from the grey literature searches. In total, 20 studies (25 publications) were included in the original SLR (Figure 43).

In the SLR update conducted on 20th May 2024, a total of 324 records were identified through electronic database searches. After removal of duplicates, 286 citations were eligible for title and abstract screening. Of these, 238 citations were excluded, and 48 publications were reviewed at the full text review stage. Following screening, 43 publications were excluded, and 5 studies (5 publications) were deemed eligible for inclusion in the SLR. An additional 5 relevant studies (5 publications) were identified from the grey literature searches. In all, a total of 10 studies (10 publications) were included in the SLR update (Figure 44).

Figure 43: PRISMA flow diagram – original HRQoL SLR

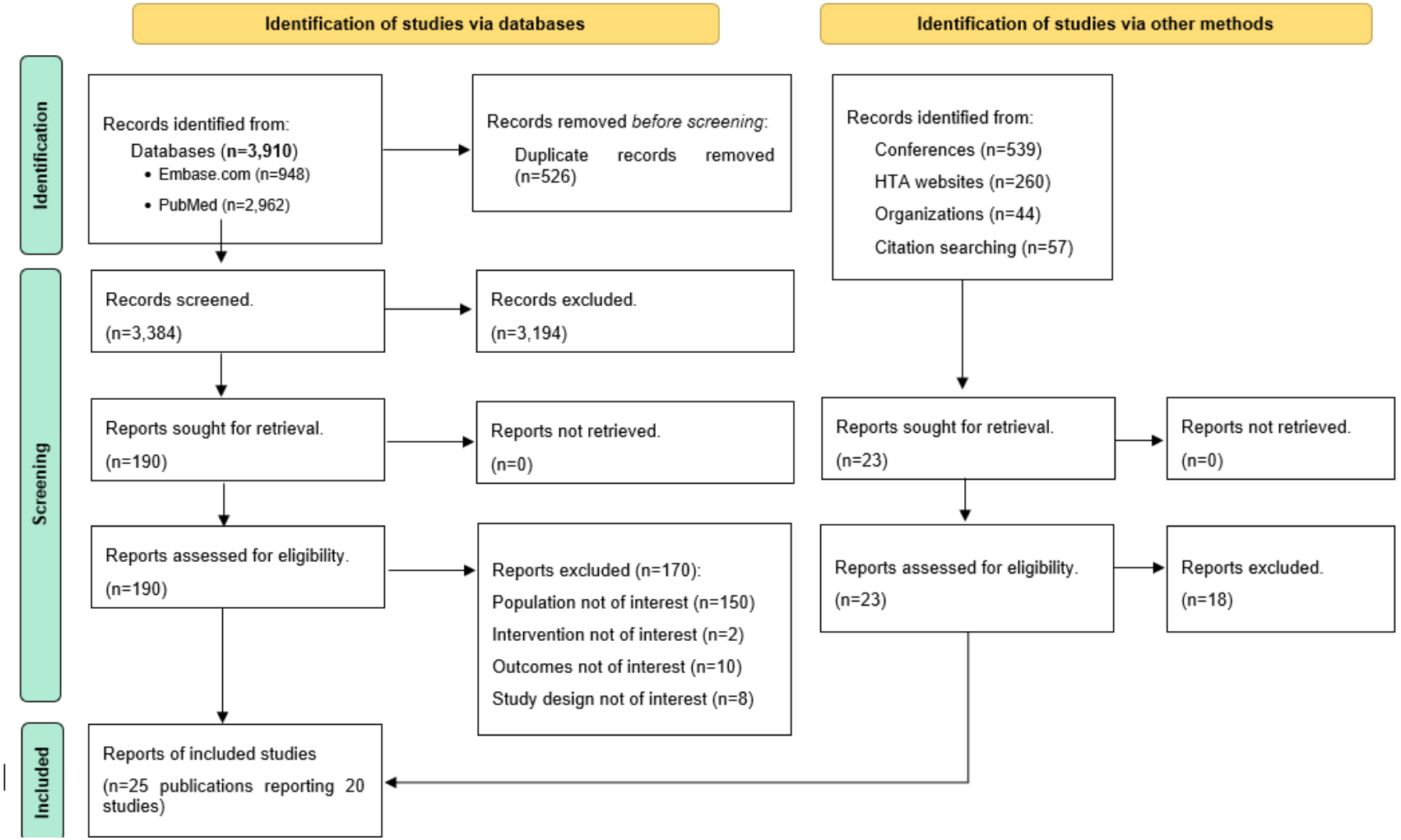
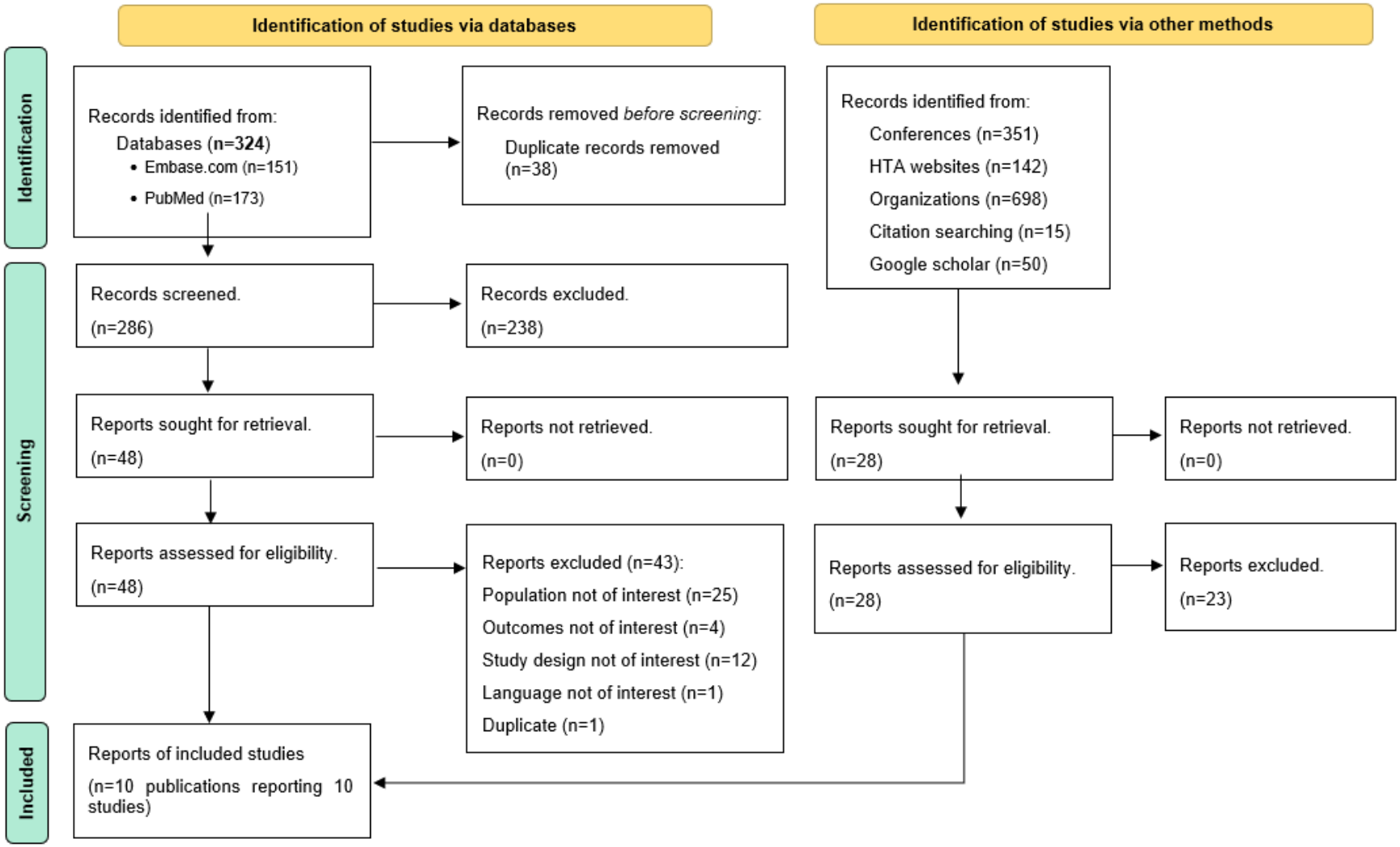


Figure 44: PRISMA flow diagram – HRQoL SLR update



Lists of included and excluded studies

A list of studies included in the original HRQoL SLR and SLR update is provided in Table 60.

Table 60: List of included studies – HRQoL SLR

Author, year	Title	Citation
Original SLR (N=25)		
Van Dyk, 2022	Daily functioning in glioma survivors: Associations with cognitive function, psychological factors and quality of life	CNS Oncol. 2022 Jun 1;11(2):CNS84
Jakola, 2022	The impact of resection in IDH-mutant WHO grade 2 gliomas: a retrospective population-based parallel cohort study	J Neurosurg. 2022 Mar 4;137(5):1321-1328.
Boele, 2023	Long-term wellbeing and neurocognitive functioning of diffuse low-grade glioma patients and their caregivers: A longitudinal study spanning two decades	Neuro-Oncology, Volume 25, Issue 2, February 2023, Pages 351–364
Leonetti, 2021	Factors Influencing Mood Disorders and Health Related Quality of Life in Adults With Glioma: A Longitudinal Study	Front Oncol. 2021 May 20:11:662039
Teng, 2021	Life after surgical resection of a low-grade glioma: A prospective cross-sectional study evaluating health-related quality of life	J Clin Neurosci. 2021 Jun:88:259-267
Chen, 2022	The Effect on Quality of Life after Three-Dimensional Intensity-Modulated Radiation Therapy in Patients with Low-Grade Glioma	Comput Math Methods Med. 2022 Aug 13:2022:5854013
Park, 2022	Quality of life following concurrent temozolomide-based chemoradiation therapy or observation in low-grade glioma	J Neurooncol. 2022 Feb;156(3):499-50
Svedung Wettervik, 2022	Patient-reported quality of life in grade 2 and 3 gliomas after surgery, can we do more?	Clin Neurol Neurosurg. 2022 Mar:214:107175
Umezaki, 2022	Factors associated with health-related quality of life in patients with glioma: impact of symptoms and implications for rehabilitation	Japanese Journal of Clinical Oncology, Volume 50, Issue 9 990–998
Drewes, 2018	Perioperative and Postoperative Quality of Life in Patients with Glioma - A Longitudinal Cohort Study	World Neurosurg. 2018 Sep:117:e465-e474
Gabel, 2019	Health Related Quality of Life in Adult Low and High-Grade Glioma Patients Using the National Institutes of Health Patient Reported Outcomes Measurement Information System (PROMIS) and Neuro-QOL Assessments	Front Neurol. 2019 Mar 15:10:212
Hickmann, 2017	Evaluating patients for psychosocial distress and supportive care needs based on health-related quality of life in primary brain tumors: a prospective multicenter analysis of patients with gliomas in an outpatient setting	J Neurooncol. 2017 Jan;131(1):135-151
Wang, 2018	Health-Related Quality of Life and Posttraumatic Growth in Low-Grade Gliomas in China: A Prospective Study	World Neurosurg. 2018 Mar:111:e24-e31
Habets 2014	Health-related quality of life and cognitive functioning in long-term anaplastic oligodendroglioma and oligoastrocytoma survivors	J Neurooncol. 2014 Jan;116(1):161-8
Boele, 2014	The association between cognitive functioning and health-related quality of life in low-grade glioma patients	Neurooncol Pract. 2014 Jun;1(2):40-46.
Boele, 2015	Health-related quality of life in stable, long-term survivors of low-grade glioma	J Clin Oncol. 2015 Mar 20;33(9):1023-9
Okita, 2015	Health-related quality of life in long-term survivors with Grade II gliomas: The contribution of disease recurrence and Karnofsky Performance Status	Jpn J Clin Oncol. 2015 Oct;45(10):906-13
Boele, 2013	Health-related quality of life of significant others of patients with malignant CNS versus non-CNS tumors: A comparative study	J Neurooncol. 2013 Oct;115(1):87-94

Author, year	Title	Citation
Mahalakshmi, 2015	Quality of life measures in glioma patients with different grades: A preliminary study	Indian J Cancer. 2015 Oct-Dec;52(4):580-5
van der Meer, 2021	Effect of antiepileptic drugs in glioma patients on self-reported depression, anxiety, and cognitive complaints	J Neurooncol. 2021 May;153(1):89-98
Jiang, 2019	Post-traumatic stress disorders in patients with low-grade glioma and its association with survival	J Neurooncol. 2019 Apr;142(2):385-392
Kim,2020	Relationship among symptoms, resilience, post-traumatic growth, and quality of life in patients with glioma 10.1016/j.ejon.2020.101830	Eur J Oncol Nurs. 2020 Oct:48:101830
Li 2019	The moderating role of depression on the association between posttraumatic growth and health-related quality of life in low-grade glioma patients in China	Psychol Health Med. 2019 Jul;24(6):643-653
Li, 2019	Are Posttraumatic stress symptoms and avoidant coping inhibitory factors? The association between posttraumatic growth and quality of life among low-grade gliomas patients in China	Front Psychol . 2019 Feb 19:10:330
Campanella, 2017	Long-Term Cognitive Functioning and Psychological Well-Being in Surgically Treated Patients with Low-Grade Glioma	World Neurosurg. 2017 Jul:103:799-808.e9
SLR update (N=10)		
Heffernan, 2023	Quality of life after surgery for lower grade gliomas	Cancer. 2023 Dec 1;129(23):3761-3771
Di Perri, 2023	Health-related quality of life and cognitive failures in patients with lower-grade gliomas treated with radiotherapy	Cancer Radiother. 2023 May;27(3):219-224
Pertz, 2023	Long-term neurocognitive function and quality of life after multimodal therapy in adult glioma patients: a prospective long-term follow-up	J Neurooncol. 2023 Sep;164(2):353-366
Willmann, 2023	Oncological Outcomes, Long-Term Toxicities, Quality of Life and Sexual Health after Pencil-Beam Scanning Proton Therapy in Patients with Low-Grade Glioma	Cancers (Basel). 2023 Nov 4;15(21):528
Rauschenbach, 2024	Longitudinal impact of intracerebral low-grade glioma disease on health-related quality of life	J Neurosurg Sci. 2024 Mar 14
Debarati Bhanja, 2024	Health state utility assessment for low-grade glioma.	J Clin Oncol Volume 42, Number 16_suppl
Gómez Vecchio, 2021	Classification of adverse events following surgery in patients with diffuse lower-grade gliomas	Front Oncol. 2021 Dec 21:11:792878
Gómez Vecchio, 2024	Global health status and fatigue score in isocitrate dehydrogenase-mutant diffuse glioma grades 2 and 3: A longitudinal population-based study from surgery to 12-month follow-up	Neurooncol Pract. 2024 Mar 1;11(3):347-357
Rimmer, 2024	“It changes everything”: Understanding how people experience the impact of living with a lower-grade glioma	Neurooncol Pract . 2024 Jan 29;11(3):255-265
Rydén, 2021	Psychotropic and anti-epileptic drug use, before and after surgery, among patients with low-grade glioma: a nationwide matched cohort study	BMC Cancer. 2021 Mar 8;21(1):248

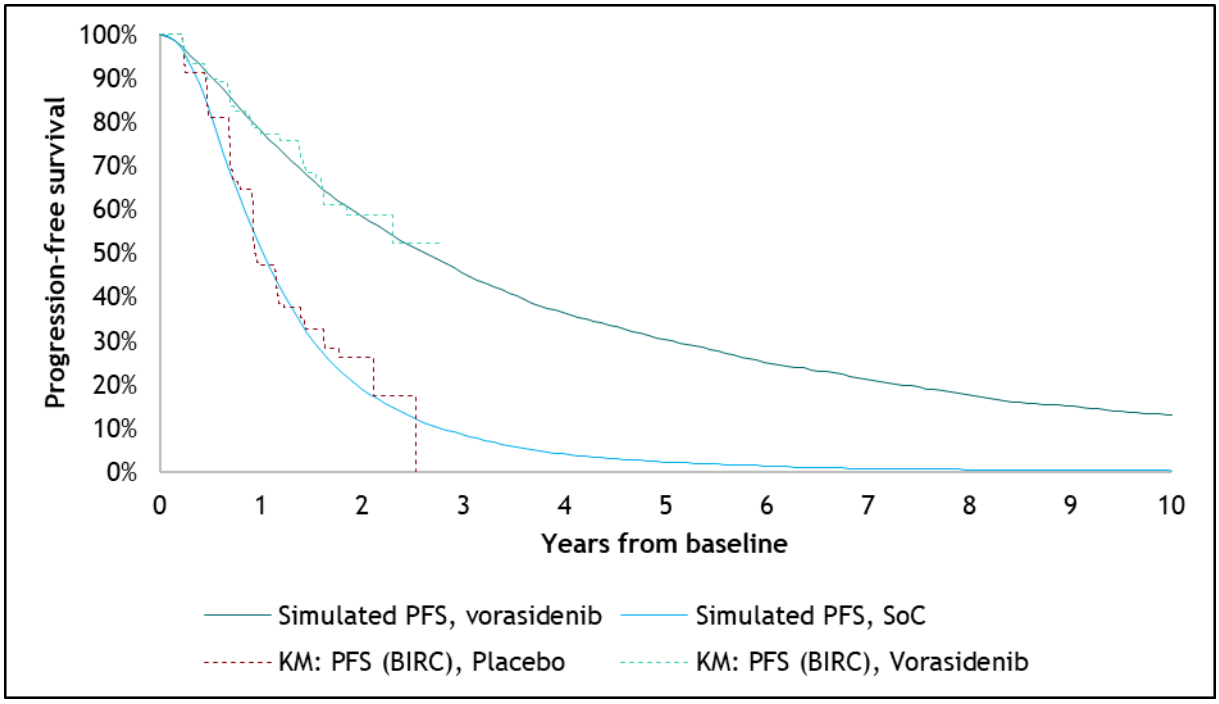
Appendix G: Cost and healthcare resource identification, measurement and valuation

Data relating to costs and resource use were systematically identified according to the methodology described in Appendix E:.

Appendix H: Clinical outcomes and disaggregated results from the model

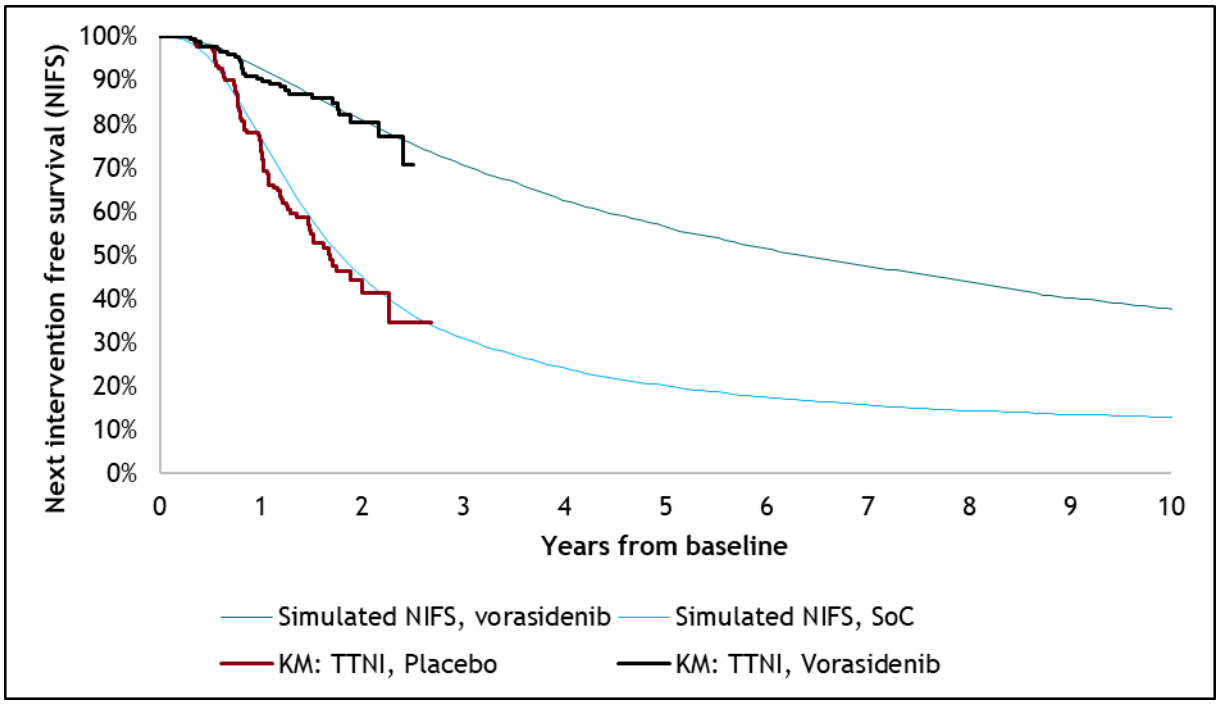
Clinical outcomes from the model

Figure 45: Progression-free survival in model versus INDIGO study



Abbreviations: KM, Kaplan-Meier; BIRC, blinded independent review committee; PFS, progression-free survival; SoC, standard of care ("watch and wait").

Figure 46: Next intervention-free survival in model versus INDIGO study



Abbreviations: KM, Kaplan-Meier; NIFS, next intervention-free survival; SoC, standard of care ("watch and wait"); TTNI, time to next intervention.

Disaggregated results of the base-case incremental cost-effectiveness analysis

Table 61: Summary of QALY gain by health state

Health state	QALY vorasidenib	QALY active observation	Increment	Absolute increment	% absolute increment
S1	3.37	0.00	3.37	3.37	47%
S2	0.00	1.02	-1.02	1.02	14%
S3	0.00	0.00	0.00	0.00	0%
S4	4.32	2.39	1.93	1.93	27%
S5	0.17	0.21	-0.04	0.04	1%
S6	1.48	1.74	-0.26	0.26	4%
S7	0.91	1.21	-0.30	0.30	4%
S8	0.94	1.19	-0.25	0.25	4%
AE	0.00	0.00	0.00	0.00	0%
Total	11.18	7.76	3.41	-	100%

Abbreviations: QALY, quality-adjusted life year. Table adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee

Table 62: Summary of costs by cost category

Health state	Cost vorasidenib	Cost active observation	Increment	Absolute increment	% absolute increment
Drug cost: vorasidenib	[redacted]	£0	[redacted]	[redacted]	[redacted]
Drug cost: NI	£1,252	£1,525	-£274	£274	[redacted]
Drug cost: NI+	£40,765	£55,254	-£14,490	£14,490	[redacted]
AE costs (total)	£0	£0	£0	£0	[redacted]
RT costs: NI	£2,894	£3,544	-£650	£650	[redacted]
RT costs: NI+	£641	£799	-£158	£158	[redacted]
Admin costs: NI	£0	£0	£0	£0	[redacted]
Admin costs: NI+	£9,382	£12,687	-£3,305	£3,305	[redacted]
EoL costs	£3,774	£4,138	-£365	£365	[redacted]
Other MRU costs	£282,907	£319,548	-£36,641	£36,641	[redacted]
Societal costs	£0	£0	£0	£0	[redacted]
Total	[redacted]	£397,496	[redacted]	-	100%

Table. Table adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee

Appendix I: Price details of treatments included in the submission

Price of intervention, comparators and subsequent treatments

Table 63: Details of all costs, including intervention, concomitant, comparator and subsequent medicines, for each formulation used in the model

Name	Form	Dose per unit	Pack size	List price	Source	PAS price (if known)	eMIT price/date searched for (if available)
Vorasidenib	Tablet	40mg	30	[redacted]	Servier	-	-
		10mg	30			-	
Vincristine	Solution for injection vials	1mg/1mL	1	£9.12	eMIT	-	See footnote
		1mg/1mL	5	£25.38		-	
		2mg/2mL	1	£17.82		-	
		2mg/2mL	5	£33.89		-	
Temozolomide	Capsules	100mg	5	£38.53	eMIT	-	See footnote
		140mg	5	£46.30		-	
		180mg	5	£80.47		-	
		20mg	5	£10.67		-	
		250mg	5	£81.01		-	
		5mg	5	£3.54		-	
Lomustine	Capsules	40mg	20	£780.82	BNF	-	-
Procarbazine	Capsules	50mg	50	£528.79	BNF	-	-
Carmustine	Implant	7.7mg	1	£5,203.00	BNF	-	-
Bevacizumab	Solution for infusion vials	10mg/kg	1	£810.00	BNF	-	-

Abbreviations: eMIT, drugs and pharmaceutical electronic market information tool; PAS, patient access scheme
eMIT source: Pharmex data for the period 1 July 2022 to 30 June 2023, for Pharmex products shown as Generic in the period 1 January 2023 to 30 June 2023.

The company are submitting the new analysis in response to the below from the EAG report:

- The TTNI | P curve affects the duration of time spent off-treatment with PD before moving to 1L RT/CT.
- The EAG suggests **using a common TTNI | P curve for both vorasidenib and active observation**, based on pooled data instead of separate curves by treatment arm.
  - **No evidence supports managing patients differently post-progression based on initial intervention**.
  - The **follow-up for some vorasidenib patients may have ended before the next intervention could be given**, indicating data immaturity and biasing TTNI|P.
  - The company suggests that progression in LGG might not immediately necessitate the next intervention due to its slow progression and the challenging decision to move to RT/CT. They also claim that vorasidenib treatment in the INDIGO study leads to tumour shrinkage, potentially resulting in smaller tumours at progression than at baseline. However, **the EAG views these claims as unproven hypotheses, noting that no evidence from the INDIGO trial supports these assertions**, and it remains unclear how the disease behaves after progression. **The company has not demonstrated that tumour size is smaller at progression for vorasidenib.**

New analysis submitted 8th May 2025

Several post-hoc analyses of INDIGO indicate that patients who progress while receiving vorasidenib do so with more favorable features that allow for longer TTNI|P period, potentially allowing these patients to remain on active observation before unequivocal progression identified through higher tumor growth or volume warrants initiation of a subsequent treatment.

Figure 1: Box Plot of On-Treatment Tumor Growth by PD vs non-PD per BIRC Until Study Unblinding (FAS)

FAS including all subjects who are randomized before IA2 data cutoff date: 06SEP2022. Individual on-treatment tumor growth is defined as the tumor volume (mL) change in every 6 months. Screening volume records were included. P-value is calculated from Wilcoxon test at 2-sided alpha level of 0.05.

Table 1: Summary of Log Tumor Volume vs Baseline at PD per BIRC (Full Analysis Set)

	Vorasidenib	Placebo
N		
Mean Log Tumor Volume (Baseline)		
Mean Log Tumor Volume (PD)		
Mean Change (PD - BL) (95% CI)		
Difference in Mean Change (95% CI)		
P-Value (vs Placebo)		

Note: Mean change (PD – Baseline) is calculated at the individual subject level. Difference in Mean Change represents the difference in average change between Vorasidenib and Placebo. P-value is calculated from Wilcoxon test at 2-sided alpha level of 0.05.

- Further, Figure 2 highlights that almost half of patients who received vorasidenib have a smaller tumor volume at progression than baseline.

Figure 2: Box Plot of Change in Log Tumor Volume (PD per BIRC - Baseline) (Full Analysis Set)

Further plots and KM curves are provided as attachments.

This document provides evidence to support a significantly longer TTNI | P period for vorasidenib compared to active observation. This relates specifically to the EAG Issue 7 which states that it is unclear why the outcome of TTNI | P should be separated by treatment arm, i.e., evidence has not been presented to show that patients should be managed differently post-progression (where progression has been defined using the same criteria in both arms of INDIGO) depending on initial intervention, especially when there are no differences assumed for treatments at subsequent lines.

Please see below and attached the evidence to support the important ongoing effects of vorasidenib post-progression

Perioperative study

Vorasidenib via 2HG suppression has an impact on tumour biology[1]:

- 2-HG reduction was associated with reduced tumour cell proliferation, increased DNA5hmC content(mediated by TET 5mC hydroxylase activity) and a reversal of gene expression programs typically associated with *IDH* mutations in LGGs
- 2-HG reduction was associated with the induction of genes associated with antitumor immunity and a modest increase in tumour infiltration with CD8+ T cell
- Reversal of the 'proneural' gene expression signature, a molecular hallmark of m*IDH* gliomas and downregulation of genes linked to stem cell properties in a variety of cancers

Conversely, when IDH mutated gliomas progress (not having received an IDH inhibitor), there is a difference in tumour biology[2]:

- Gliomas acquired a median of 21 protein-altering mutations as they progress, while exhibiting nonlinear clonal evolution through the loss of 27% of the mutations and 30% of the CNAs present in the initial tumors. However, the recurrent IDH1 mutation affecting Arg132 was never lost during glioma progression and remained clonal in all progressed tumors.
- The genomic alterations seen in the study reflect the genomic changes seen in glioma progression

In conclusion patients who have received Vorasidenib are at a different place molecularly when they progress than those who have not had IDH mutation inhibition. Those without IDH mutation inhibition will have progression of further acquiring mutations and epigenetic changes as a result of not having the IDH mutation inhibited– molecularly priming that tumour to be more aggressive.

Growth trajectory

Cohort-level mathematical modelling of TGRs also confirm the notion that vorasidenib fundamentally altered the growth trajectory of mIDH1/2 gliomas, leading to gradual tumour shrinkage, contrasting with the continuous tumour growth on placebo [3]. In the primary analysis (Sep-22) there was post-treatment reduction in tumour volume, as demonstrated though tumour shrinkage, in patients randomised to vorasidenib by a mean of 2.5% every 6 months (95% CI: -4.7%, -0.2%), while tumour volume increased, indicated by TGR, by a mean of 13.9% every 6 months for the placebo arm (95% CI: 11.1%, 16.8%). At longer follow-up (Mar-23), tumour volume continued to reduce with vorasidenib by 1.3% (95 CI: -3.2%, 0.7%) and increased with placebo by 14.4% (95% CI: 12%, 16.8%).

Furthermore, Volume change from baseline calculated from (tumour volume − baseline tumour volume) / baseline tumour volume in individual patients at 6, 12, and 24 months were examined

[redacted]

[redacted]

These results clearly hint at a sustained activity of voranigo over time, leading to improved outcomes in tumor growth and tumor biology over longer follow-up.

Subsequent results from the INDIGO trial and supporting data from mouse models further reinforce the sustained activity of voranigo.

Experimental analysis

Furthermore, to experimentally determine whether vorasidenib treatment impacts salvage chemoradiotherapy, a genetically engineered mouse model (GEMM) of IDH-mutant astrocytoma (harboring Idh1, Atrx, Trp53, and Pik3ca mutations) was developed and utilized[4]. Initially, the response of this GEMM to vorasidenib monotherapy was assessed. Subsequently, it was tested whether progression on vorasidenib affects the efficacy of salvage chemoradiotherapy. Mice were treated with vorasidenib or a vehicle until tumor progression was observed on MRI. Following this, treatments were stopped, and mice were randomized to receive either concurrent radiotherapy (RT) and temozolomide (TMZ) or sham salvage treatments, with survival being the primary endpoint. Additionally, single-cell RNA sequencing, spatial transcriptomics, metabolomics, and whole exome sequencing were performed on treated tumor samples.

[redacted]

In conclusion, while the longer-term impact of vorasidenib on IDH-mutant astrocytoma and oligodendroglioma tumor biology and growth rate remains to be fully elucidated, preclinical

models suggest that vorasidenib does not impair but rather enhances efficacy of salvage chemoradiation in IDH-mutant gliomas, and early clinical data provides encouraging evidence that salvage chemoradiation may therefore be effective in IDH-mutant glioma patients who have progressed on vorasidenib.

Although further long-term data and analyses are needed to fully understand the sustained impact of vorasidenib, there is a plausible suggestion that there are ongoing effects of Vorasidenib post progression.

References

1. Mellinghoff et al, Vorasidenib and ivosidenib in IDH1-mutant low-grade glioma: a randomized, perioperative phase 1 trial. Nature Med; 2023. https://doi.org/10.1038/s41591-022-02141-2

2. Bai et al, Integrated genomic characterization of *IDH1*-mutant glioma malignant progression. *Nat Genet* **48**, 59–66 (2016). https://doi.org/10.1038/ng.3457

3. Cloughesy et al Vorasidenib in IDH1- or IDH2-mutant low-grade glioma: tumour growth rate, seizure frequency, quality of life, and neurocognitive outcomes from the randomised, double-blind, placebo-controlled, phase 3 INDIGO trial. Draft manuscript Lancet oncology 2025

4. Shi et al. A genetic mouse model of IDH-mutant glioma responds to mutant IDH inhibition and reveals enhanced efficacy of salvage chemoradiation after vorasidenib. EANO abstract 2025

TTNI|P and tumour volume variation

The company also provides outputs of TTNI|P (progression per BIRC) segmented by tumor volume variation vs. baseline.

Different cutoffs were applied in this analysis and shared within attachments:

- One with: decreased volume=25% decrease; stable=-25 to +25% variation; increased volume=+25% increase
- One with a cutoff of 10%
- Another one with only 2 groups: increase vs. decrease volume.

These results confirm our assumption that TTNI|P is linked with tumor volume variation with growing tumors having shorter TTNI|P than stable and shrinking tumors. This can be assessed in line with the tumour volume shrinkge data with Vorasidenib already provided to the EAG

The information contained in the attachments is confidential

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Vorasidenib for treating astrocytoma or oligodendroglioma with IDH1 or IDH2 mutations after surgery in people 12 years and over [ID6407]

Summary of Information for Patients (SIP)

February 2025

Template version	Date amended	Changes since previous version
2.0	Dec 2023	Clarifications made to guidance notes in section 3i regarding inclusion of statements on cost effectiveness.

File name	Version	Contains confidential information	Date
ID6407_Vorasidenib_SIP_[nocon]	**1.0**	**Yes**	**4th Feb 2025**

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The **Summary of Information for Patients** template has been adapted for use at NICE from the Health Technology Assessment International – Patient & Citizens Involvement Group (HTAi PCIG). Information about the development is available in an open-access IJTAHC journal article

SECTION 1: Submission summary

1a) Name of the medicine (generic and brand name):

Vorasidenib (Voranigo)

1b) Population this treatment will be used by. Please outline the main patient population that is being appraised by NICE:

Vorasidenib is used to treat adults and adolescents from 12 years of age and older with grade 2 cancers of the brain called astrocytoma or oligodendroglioma who have had surgical intervention as their only treatment and who do not immediately need other cancer treatments such as radiation or chemotherapy. This medicine is only used in patients whose brain cancer is related to a change (mutation) in the IDH1 or IDH2 protein.

1c) Authorisation: Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

Expected date of approval from MHRA: pending (referenced in company submission section 1.2)

1d) Disclosures. Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

Please see below a list of collaborations Servier Global and affiliate have undertaken:

International Brain Tumour Alliance:

Low grade glioma Patient pathway mapping project = £5,050.00
International Patient working committee master service agreement = £9,520.00
Sponsorship of IBTA international patient organisation activities= £22,000
Lay summary=£1960.00
International Dialogue with a patient = £2,100.00

Brain tumour Charity:

Low grade glioma patient pathway mapping project = £5,050.00
International patient working committee = identify and develop meaningful projects to:
• Contribute to the improvement of low-grade glioma care management, contribute to the development of communication/education materials for patients with low-grade glioma= £3780.00

Astro fund=

Low grade glioma patient pathway mapping project = £5050
Patient pathway manuscript = £1,400.00

Brains Trust=

Low grade Glioma Patient and Carer experience video = £3,400

SECTION 2: Current landscape

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England.

Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.

Around 200 people are currently living with this condition in England.

Symptoms can include headaches, nausea, vomiting, seizures, visual disturbance, speech and language problems, and changes in cognitive and/or functional ability However, patients may also be asymptomatic. Epileptic seizures are the most common initial presentation, occurring in 20-50% of patients. A significant portion of initial seizures tend to be unresponsive to medical treatment which negatively impacts patient QoL and cognitive function, potentially leading to additional complications.

In addition to seizures, patients with IDH-mutant glioma may also present with headaches (50-60%) and focal neurologic signs (10-40%), as well as neurocognitive impairment.

Rimmer at al[1] showed the impact seizures have on people living with low grade glioma, The anxiety about having a seizure influenced their approach to daily life. Some avoided certain physical activities that they had enjoyed pre-diagnosis due to the anticipated negative repercussions of having a seizure; whilst patients will refuse to travel far from home due to the worry of having a seizure in an unfamiliar environment.

There is a cognitive decline experienced by patients and worsened by RT/Chemo. This decline

frequently impacted numerous aspects of daily life, with potentially substantial consequences. They described possible security and safety repercussions of forgetting how to cook or leaving the front door open, and ability to work[1]

Obara et al[2] showed from 63 low grade patients interviewed 63% of the patients had a clinically significant cognitive deficit strongly associated with worsened role and social functioning; therefore highlighting the profound impact on patient's daily lives and the need to consider preventing these impairments from the early stages of the disease. The study reported that over one-third of patients experienced anxiety, while over one-quarter experienced depression.

Those patient on active surveillance also have expressed an impact on their emotional wellbeing with anxiety sometimes referred to as scanxiety, Some feared they were *'a ticking time bomb'* or "*waiting to be even more disabled*." Several expressed how anxiety worsened around scan appointments[1] Participants described having to *"learn to live*" with how this uncertainty negatively impacted their ability to make decisions, both about smaller(e.g., booking a holiday) and larger (e.g., having children) aspects of life.

IDH-mutant glioma is associated with high costs, related to loss of productivity, inability to work, early retirement, and premature death. From a study where 28 oligodendroglioma patients were interviewed[3] the number of patients with oligodendroglioma after diagnosis still in employment dropped by 61% and of those working full time 77% dropped to part time work.

Patients have described that being unable to work post-diagnosis(e.g., due to fatigue and cognitive impairments) talked about how that "*kicks your confidence*," with several feeling "*stripped*" of their identity, direction, purpose, and control over their life[1]
Quote from patient "*The financial side puts an awful lot of pressure. I mean my husband's been working two jobs and we try and run a tight ship but the work, the hobbies, the driving, your interests, your social life, when you're stripped of everything it's very grounding."*

Patients not only face productivity losses at work but also are hindered by health issues in everyday tasks. More than half of the participants reported barriers in performing domestic work: around 45% reported issues completing and 25% reported difficulties in taking care of children. In addition, people lose their driving license for at least a year following a seizure.
Losing their driving license following diagnosis and treatment and how long their license was revoked for was also influenced by the presence of seizures. In those no longer able to drive, reactions were centred around the substantial impact this had on their independence, with some participants expressing that it was their "biggest loss." This loss of independence had implications for participants' work and hobbies[1].

There is also a profound impact on caregiver QoL which is exacerbated as patient condition worsens due to disease progression or treatment-related side effects. Caregivers often experience disruptions in emotional, physical, and social well-being. Care is primarily provided by relatives and friends and few patients with glioma rely solely on formal care. As the condition of patients worsen, either through disease progression or the effects of treatments like RT/CT, it impacts them both physically and cognitively, affecting cognitive functions, personality, and behaviour. This deterioration has a direct negative impact on the QoL of caregivers, potentially hindering their ability to provide optimal care. This establishes a reciprocal relationship between the QoL of the patient and that of the caregiver. Caregivers face difficulty in performing routine household tasks as well as substantial productivity loss which contributes to increased economic burden[4]**.**

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?
Following initial symptoms, a patient would undergo imaging, and surgical intervention, histological tissue assessment and molecular testing followed by subsequent treatment considerations, or active surveillance. Surgery remains the initial treatment and IDH1/2 mutational testing is routine clinical practice for diagnosis.

2c) Current treatment options:

The purpose of this section is to set the scene on how the condition is currently managed: • What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP. • Please also consider: o if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data. o are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.
Surgery remains the initial treatment for IDH-mutant glioma to enable an accurate diagnosis and improve clinical outcomes. This surgery may involve a patient undergoing a gross total resection, subtotal resection or just a biopsy if surgery is not deemed possible. Patients will undergo molecular testing where IDH1/2 mutational testing is routine clinical practice for diagnosing patients that are mIDH glioma compared to wildtype IDH gliomas, historically known as glioblastomas . The two treatment options for patients diagnosed with a mIDH glioma, post-surgical intervention are active surveillance or RT/Chemo. Although most patients progress to a more aggressive disease state, there are several historical prognostic factors that aid in identifying patients at potentially higher risk of malignant transformation who may be in immediate need of early adjuvant RT/CT. These factors include neurologic deficits before surgery, residual tumour volume, tumour crossing the midline of the brain, and tumours located within or adjacent to eloquent areas of the brain. There are potential acute adverse effect of RT and CT, such as elevated intracranial pressure, can manifest as headaches and vomiting. These additional chronic side effects associated with RT for brain cancer include impaired wound healing, skin changes and skin cancer, lymphedema, secondary cancer, and damage to surrounding structures which potentially contribute to the detriment to daily function. The cognitive deficits may be especially burdensome for patients, as these patients are confronted with the deterioration in functioning whilst trying to resume their personal and professional life post-treatment, Therefore, in England, those patients not at immediate risk of disease progression as per the above prognostic criteria remain under active surveillance to avoid the high treatment burden associated with RT and CT until the patient is either in immediate need of RT/Chemo or undergoes further surgery. Vorasidenib is expected to be used for those patients not in immediate need of RT/Chemo as an alternative to Active surveillance, to delay progression of the glioma and delay the need for RT/Chemo.

2d) Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

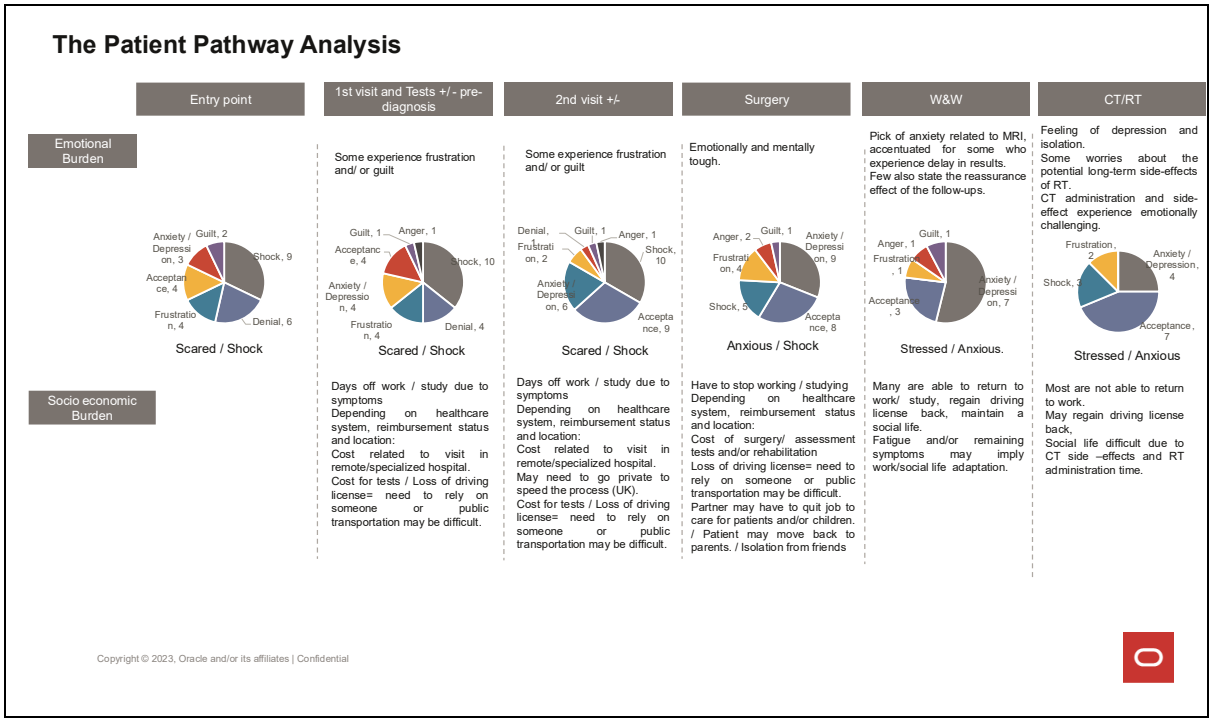
Servier have undertaken a multi- national patient pathway qualitative research project which included in depth qualitative interviews and SF-12/ SF6D scale based questionnaire.
This Servier-sponsored qualitative study was undertaken to better understand the mIDH1/2 diffuse glioma clinical pathway, and experiences of the disease and perceptions of treatment from the patient perspective. Patients, caregivers, and patient association group (PAG) representatives undertook individual interviews.
Materials were developed in collaboration with the International Brain Tumour Alliance, a global brain tumour patient organization.
Patients were aged 12 years and over and had mIDH1/2 glioma, with last resection occurring at least 6 months before enrolment. Patients were undergoing active observation or receiving radiotherapy (RT) and/or chemotherapy (CT).
The study was conducted from November 2023 to April 2024, during which 53 patients (from China: n=13; Australia/New Zealand: n=13; France: n=9; Canada: n=7; UK: n=6; Japan: n=5), 23 caregivers (from China, n=6; Australia/New Zealand: n=5; France: n=4; UK: n=3; Japan: n=3; Canada: n=2) and eight PAG representatives (from Australia/New Zealand: n=2; UK: n=2; France: n=1; Canada: n=1; Japan: n=1; Spain, n=1) participated.

Main results:
There were 84 interviewees in total, of whom 53 were patients, 23 were caregiver participants, and 8 were PAG representatives.
The median age of patients was 41.0 years (range 29–59), 33 (62.3%) were female, and 20 (37.7%) were male.
In total, 29 (54.7%) patients had been diagnosed with mIDH1/2 astrocytoma and 24 (45.2%) patients with mIDH1/2 oligodendroglioma. Twenty-three patients were undergoing active observation, while 30 were receiving RT/CT.

Patients experienced a heterogeneous range of symptoms prior to obtaining a diagnosis. In the weeks and months before diagnosis, patients reported initial symptoms such as headaches (n=21), seizures (n=18), weakness and fatigue (n=12), and dizziness or fainting (n=11). Some patients (n=4) reported having no symptoms at all. The main initial symptoms that led to patients consulting an HCP and being diagnosed with mIDH1/2 diffuse glioma were disease specific, such as seizures (n=25), and non-disease specific, such as headaches (n=23)
Of the 53 patients, 23 were undergoing active observation. Patients were aware that active observation would continue until tumour reoccurrence and believed that this was the most appropriate treatment management option in their situation. The active observation period was perceived with ambivalence by patients, and was seen as a time when their physical wellbeing was counterbalanced with the emotional burden of living with mIDH1/2 diffuse glioma.

However, in practice, the active observation period was a difficult time for many. Key challenges regarding the active observation period were underlined by the lack of certainty or unpredictability felt during the time between scans due to the risk of tumour recurrence. Patients outlined how it was difficult to plan ahead and find purpose in life while waiting for results, knowing that these plans could change every few months depending on the results of their next scan. Making plans around study or work, or even planning for holidays and obtaining travel insurance, was challenging.
RT/CT was also perceived as a difficult period for patients, but one that was instilled with a sense of action and control over their disease. Of the 53 patients interviewed, 30 were receiving RT/CT,

There was general awareness of the side effects associated with CT; one patient refused CT because of the potential physical impact. Some patients were very worried about the long-term consequences of RT, but, generally, patients were less aware of the consequences of RT than they were of those associated with CT. PAG representatives highlighted how RT can impact physical and cognitive function in later life, which was especially relevant because many patients with mIDH1/2 diffuse gliomas live for long enough to experience some of the longer-term effects.
Receiving RT/CT was burdensome for patients and their caregivers, and key challenges included experiencing side effects, having difficulty accommodating RT/CT within normal daily living, and the associated financial burden. Most patients experienced side effects from RT/CT, such as fatigue, alopecia, nausea, headaches, constipation, loss of appetite, rash, peripheral neuropathy, and brain fog.
RT/CT often required inconvenient daily trips to hospitals, and this came with logistical difficulties: patients who experienced uncontrolled seizures were unable to drive themselves to appointments, and public transport was unpleasant when also experiencing the symptoms associated with RT/CT, such as fatigue and nausea. Financial impacts arose from the travel expenses required to attend appoints and, in some countries, out-of-pocket costs for medical bills.
In the study population (n=53), the mean (SD) SF-12 physical score encompassing physical pain, physical functioning, health limitations, and general health was 49.1 (±9.3) (median 49.9 [range 26.1–63.9]). The mean (SD) SF-12 mental score, which encompassed mental health limitations, social functioning, mental health, and vitality, was 39.8 (±10.8) (median 40.1 [11.5–64.8]).
For patients with ongoing seizures, the burden of lifelong antiseizure medication impacted them negatively.
Patients receiving active observation experienced strong and ongoing anxiety, as the uncertainty of tumour recurrence took a toll on their emotional wellbeing in the long term. The uncertainty of progression caused feelings of anxiety to peak when close to MRI follow-up appointments and, coupled with delays between scans and results, this period of time was marked with significant emotional turmoil.
Dealing with the side effects of RT/CT was emotionally tiring and there were also fears about the long-term side effects of RT. Caregivers were worried about the next steps after RT/CT and hoped that new drugs would be developed. CT was viewed as the most difficult part of treatment, more difficult than RT, by seven patients.



SECTION 3: The treatment

3a) How does the new treatment work?

What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

Voranigo is a cancer medicine that contains the active substance vorasidenib. It is used to treat specific cancers of the brain, referred to as atrocytomas or oligodendrogliomas with changed (mutated) genes that make proteins known as IDH1 or IDH2, which play an important role in making energy for cells. When the IDH1 gene or IDH2 gene is mutated, the IDH1 or IDH2 protein is changed and does not function properly. This results in changes in the cells that can lead to the development of cancer. Voranigo blocks the mutated form of the IDH1 or IDH2 protein and helps to slow or stop the cancer from growing.
Vorasidenib is an oral treatment that can be taken at home that has been shown to delay progression for those patients who have a grade 2 astrocytoma or oligo dendroglioma
In addition, it reduces overall seizure rate and does not have a detrimental effect on quality of life.
This will be the first targeted treatment that could be made available to patients with low grade glioma.

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

- Yes / No

If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together.

If yes, please also provide information on the availability of the other medicine(s) as well as the

main side effects.

If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.

N/A

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for.

How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?

Vorasidenib is an oral tablet to be taken once a day whole with a glass of water. This will enable the treatment to be taken at home.
The recommended dose in adults and adolescents 12 years of age and older is 40 mg taken orally once daily for patients weighing at least 40 kg and 20 mg taken orally once daily for patients weighing less than 40 kg Treatment should be continued until disease progression or unacceptable toxicity.
Do not eat food at least 2 hours before and 1 hour after you take the tablet.

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.

The INDIGO trial is an international, double-blind, randomised, placebo-controlled trial, which assessed the efficacy and safety of vorasidenib therapy in patients with Grade 2 IDH-mutant glioma after surgical intervention compared to those who were on active surveillance[6]

NCT06478212 – Phase 1b/II Vorasidenib in combination with Temozolomide in IDH mutant high grade Gliomas

Not yet recruiting

NCT05484622 - Recruiting

Phase 1 Study of Vorasidenib and Pembrolizumab Combination in Recurrent or Progressive IDH-1 Mutant Glioma

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

Vorasidenib improved the time to progression, reduced tumour growth and reduced seizure rate compared to active surveillance. In addition, it delayed the time until a patient was given RT/CT, and maintained quality of life.

Given the unmet need in this population for whom the available therapies can lead to long term toxicities, efficacy results reflect a substantial clinical benefit. Hence, vorasidenib will play a significant role in delaying the initiation of RT/CT and slowing down tumour growth while maintaining QoL by preserving cognitive function.

Vorasidenib can shift the treatment paradigm and make more options available to the patients who are suffering from this aggressive disease. Vorasidenib can be used to treat patients soon after surgery as an alternative to active surveillance, or in those who have been on active surveillance for a prolonged period, or who have progressed while on active surveillance.

3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as **patient reported outcomes (PROs).**

Please include any **patient preference information (PPI)** relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

Vorasidenib was able to maintain patient quality of life compared to active surveillance[6].

In addition, vorasidenib is delaying the time to radiotherapy and chemotherapy and so therefore has a positive impact on the quality of life in this regard due to the known toxicities of these treatments.

Patients with IDH-mutant glioma not only face productivity losses at work but also are hindered by health issues in everyday tasks. More than half of the participants reported barriers in performing domestic work: around 45% reported issues completing and 25% reported difficulties in taking care of children. The potential acute adverse effect of RT, such as elevated intracranial pressure, can manifest as headaches and vomiting. These additional chronic side effects associated with RT for brain cancer include impaired wound healing, skin changes and skin cancer, lymphedema, secondary cancer, and damage to surrounding structures which potentially contribute to the detriment to daily function.

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

Very common (may affect more than 1 in 10 people):

- Increased amount of liver enzymes in blood (Monitoring of liver function)

Other side effects

Very common (may affect more than 1 in 10 people):
- Diarrhoea
- Decreased count of blood platelets that can cause bleeding and bruising.

Common (may affect up to 1 in 10 people):
- Increased blood sugar levels (hyperglycaemia)
- Decreased appetite.
- Low blood phosphate levels that can cause confusion or muscle weakness (hypophosphatemia)

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:
- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration
-

First targeted therapy for IDH mutated gliomas showing a delay in progression compared to active surveillance whilst delaying the need for RT/Chemo. This in turn reduces the need for RT/Chemo and associated detrimental impact on QOL and cognitive functioning from these treatments.
It will also reduce the financial and societal impact on patients who have to undergo extensive surgery and RT/Chemo such as the ability to return to work and keep their driving license.
It is oral treatment so can be administrated at home.

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:
- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments

Response:
The most common adverse reactions, including laboratory abnormalities, were increased liver enzymes, fatigue, and diarrhoea.
Patients should not eat food at least 2 hours before and 1 hour after taking Voranigo.

3i) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)
- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

There are no existing economic models which assessed the costs and effects of vorasidenib for the treatment of people with IDH-mutant gliomas, and therefore a new cost-effectiveness model was developed for this submission to NICE. The model was designed to reflect key stages of management for people with IDH-mutant glioma, centred around progression of disease as well as starting and stopping treatments. In total, the model captures nine different 'health states', which aim to capture both the costs to the NHS and the impact on both quantity and quality of life, for the average patient with IDH-mutant glioma.

The costs captured by model include treatment costs, the costs of monitoring patients, the costs associated with subsequent treatments, and the costs of care at the end of life. The health effects captured within the analysis are a combination of quantity and quality of life (known in economic modelling as quality-adjusted life years [QALYs]). A QALY of 1 is equivalent to a person living for 1 year while feeling in 'perfect health'.

Outcomes from the INDIGO clinical trial are used to inform part of the model – namely, the time to progression, and the time to the start of a next intervention. However, data from other sources are used to inform other aspects of the model, such as the duration of treatment with subsequent treatments. Extrapolated outcomes are used to project beyond the follow-up period of the INDIGO trial, as well as other short-term data sources, as is often necessary when estimating the lifetime costs and effects of a new treatment.

Based on the model developed for this submission, vorasidenib is expected to increase the amount of time people spend free of disease progression, and therefore in a better quality of life. In turn, this means that vorasidenib is modelled to extend the duration of life. From a cost perspective, vorasidenib is associated with increased costs related to the cost of treatment, but cost savings associated with reduced medical resource use (e.g., fewer seizures and therefore lower costs associated with the management of seizures).

The INDIGO trial is relatively immature, which means that the model relies on long-term projections where data are currently not available. In addition, because vorasidenib is used early in the treatment pathway for people with IDH-mutant glioma, the model needs to include data from a range of supporting sources. While this is necessary in order to build a model for decision-making, this means that the results of the model are subject to additional uncertainty.

The base-case results demonstrate that vorasidenib is associated with more QALYs and more costs, compared to a conventional 'watch-and-wait' treatment strategy. The price of vorasidenib is not yet finalised, and therefore the cost per QALY gained (the main measure used to assess cost effectiveness) cannot be presented here. Servier intends to work collaboratively with NICE to make vorasidenib available in NHS practice.

3j) Innovation

NICE considers how innovative a new treatment is when making its recommendations. If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)
Vorasidenib is a ground-breaking, first-in-class, inhibitor of IDH, representing a new standard of care for the treatment for Grade 2 astrocytoma or oligodendroglioma.

3k) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here
N/A

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc. Where possible, please provide open access materials or provide copies that patients can access.
Response: Further information on NICE and the role of patients**:** • Public Involvement at NICE Public involvement | NICE and the public | NICE Communities | About | NICE • NICE's guides and templates for patient involvement in HTAs Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector (VCS) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE • EUPATI guidance on patient involvement in NICE: https://www.eupati.eu/guidance-patient-involvement/ • EFPIA – Working together with patient groups: https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf

- National Health Council Value Initiative. https://nationalhealthcouncil.org/issue/value/
- INAHTA: http://www.inahta.org/
- European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe: http://www.inahta.org/wp-content/themes/inahta/img/AboutHTA_Policy_brief_on_HTA_Introduction_to_Objectives_Role_of_Evidence_Structure_in_Europe.pdf

4b) Glossary of terms

CT-chemotherapy
HCP-healthcare professional
IDH-isocitrate dehydrogenase
MHRA-Medicines and Healthcare products Regulatory Agency
NHS-National Health Service
NICE-National Institute for Health and Care Excellence
PAG-Patient advisory group
QALY-Quality adjusted life year
QOL-Quality of life
RT-radiotherapy

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:

1. Rimmer et al. “It changes everything”: Understanding how people experience the impact of living with a lower-grade glioma. Neuro-Oncology Practice. 2024;11, ,((3)):255–65.

2. Obara et al. Health-related quality of life in 62 patients with diffuse low-grade glioma during a non-therapeutic and progression-free phase: a cross sectional study. Journal of Neuro-Oncology [Internet]. 2024; Available from: https://doi.org/10.1007/s11060-024-04888-9

3. Walker et al. Experiences of work for people living with a grade 2/3 oligodendroglioma: a qualitative analysis within the Ways Ahead study. BMJ Open. 2023;

4. Minaya Flores, P., Berbis, J., Chinot, O. and Auquier, P. Assessing the quality of life among caregivers of patients with gliomas. Neurooncol Pract. 2014;1(4):191–7.

5. Brook, I. Late side effects of radiation treatment for head and neck cancer. Radiat Oncol J. 2020;38(2):84–92.

6. Mellinghoff IK, van den Bent MJ, Touat M, et al. A global, randomized, double-blinded, Phase 3 study of vorasidenib versus placebo in patients with adult-type diffuse glioma with an IDH1/2 mutation (INDIGO): UPDATED RESULTS. Presented at SNO 2024.Houston, TX. 2024. 2024.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Vorasidenib for treating astrocytoma or oligodendroglioma with IDH1 or IDH2 mutations after surgery in people 12 years and over [ID6407]

Clarification questions

February, 2025

File name	Version	Contains confidential information	Date
ID6407 Vorasidenib Clarification questions [CON]	1	Yes	19/02/2025

Section A: Clarification on effectiveness data

INDIGO methods

A1. PRIORITY: Please provide all trial protocol and protocol amendment documentation and all statistical analysis plan documentation.

Trial protocol attached with amendments. Statistical analysis plan attached.

Selection effect in the INDIGO trial

A2. Please explain the rationale for the trial inclusion criterion of surgery being ≥1 year but ≤5 years from randomisation. Please comment on how representative the trial population of INDIGO is to NHS practice considering this selection effect where participants with less stable disease (i.e., more likely to progress before randomisation) were excluded. Do you anticipate the license will cover patients whose surgery was less than a year (from commencing vorasidenib)? If yes, how applicable do you think the INDIGO results data are to this excluded subgroup?

The 1–5-year post-surgery window is not used in routine clinical practice to determine treatment eligibility and, therefore, should not be considered a criterion for reimbursement. The 1 to 5 year requirement was implemented in the trial to homogenize the enrolled patient population and to allow adequate and robust assessment of radiographic disease progression. This window was used to identify patients who had been in a watch-and-wait period for at least 1 year and who would be appropriate candidates for a placebo-controlled study. The upper range of 5 years post surgery was implemented to exclude very indolent tumors that exhibited a very slow growth rate, which could impact the readout of radiographic PFS, and to ensure the testing of an IDH mutation was recent enough. The upper range of 5-years post-surgery window was implemented as it is the median time patients spend on active surveillance and, therefore, was used to ensure patients would not progress whilst the disease was untreated and continuously growing. This time from surgery may not match clinical practice nor was it meant to be prescriptive regarding how patients would benefit from vorasidenib in the intended patient population. Rather, this

window was intended to ensure that the study population would be sufficiently homogenous to enable robust evaluation for the study primary endpoint.

Servier anticipate the license to state “following surgical intervention.”

In an advisory board held by Servier, it was highlighted by all advisors that the clinicians would have to manage and to take into account the patient influence on this clinical decision. It was recognised that for the patient to wait for 1 year will be difficult to manage, so this will also need to be a factor into the clinical decision on when to initiate after surgery.
Three advisors felt waiting 1 year post surgery is biologically artificial and 6-9 months probably is more realistic. They stated 6-9 months is a reasonable time to wait before initiating and ensure rapid progression does not occur.

IDH1/2 mutations are early drivers mutations in gliomagenesis and are disease defining characteristics of diffuse gliomas, used along with histological grading to classify gliomas according to the WHO 2016 and 2021 guidelines. As IDH mutations are early genetic drivers of the disease, a targeted approach suppressing the mutant enzyme offers an opportunity to intervene early in the disease course, delaying progression and the need for more aggressive and toxic therapies. Ruda et al state that based on the mechanisms of gliomagenesis IDH inhibitors such as Vorasidneib are likely to be effective earlier in the disease course[1].

Hence, there is an urgent unmet need for alternative therapies that target IDH-mutant gliomas early in their development.

A3. Please describe the rules used to classify patients as being censored (in the K-M plots) and state how many patients in each treatment group were censored within 6 months of randomisation and, for those participants, the reasons for censoring.

The censoring rules can be found in the CSR Table 6: Censoring Reasons and Hierarchy for Primary Analysis of PFS. This table is re-produced below for completeness:

Hierarchy	Condition	Censoring Reason
1	No adequate baseline assessment	No adequate baseline assessment
2	Start of subsequent anticancer therapy before event	Start of subsequent anticancer therapy

3	Event after 2 or more missing or inadequate postbaseline tumor assessments/date of randomization	Event after 2 or more missing or inadequate postbaseline assessments
4	No event and (EOS date ≥date of randomization when reason for EOS=Withdrawal by Subject)	Withdrawal of consent
5	No event and lost to follow-up in any disposition page or survival follow-up page	Lost to follow-up
6	No event and EOS date not missing and no adequate postbaseline tumor assessment	No adequate postbaseline tumor assessment
7	No event and none of the conditions in the prior hierarchy are met	Ongoing without event

Table 14.2.1.1
Summary of Reason of Censoring for Progression-Free Survival (PFS) per BIRC - 6 months
(Full Analysis Set)

	Placebo N=163	Vorasidenib N=168
Progression-free survival (months)		
Number of events, n (%)	30 (18.4)	17 (10.1)
Progressive disease	30 (18.4)	17 (10.1)
Number censored, n (%)	5 (3.1)	4 (2.4)
No adequate baseline assessment	0	1 (0.6)
Start of subsequent anticancer therapy	1 (0.6)	0
Withdrawal of consent	4 (2.5)	3 (1.8)

The values in the table are presented as the number of events (n) and their percentage (%) within each treatment group. Censoring reasons refer to patients who had not experienced disease progression or an event within the first 6 months of analysis.

A4. PRIORITY. Please state when the decision was made to amend the protocol to allow cross-over from placebo to vorasidenib upon centrally confirmed progressive disease - had the trial already begun? If so, how many patients had already been randomised?

The option to cross over from placebo to vorasidenib upon centrally confirmed progressive disease was incorporated into the trial design from the outset. This was not an amendment made after trial initiation; rather, it was an integral part of the study protocol as initially approved. As such, no patients were randomised before the crossover mechanism was in place.

The decision to include crossover in the design of the INDIGO study reflects a patient-centric and ethically responsible approach to trial design, particularly in the context of a disease with no approved treatment options and a high unmet need. Allowing patients randomised to placebo to access vorasidenib following confirmed progression ensures that all participants were granted the opportunity to benefit from the investigational treatment.

While the inclusion of crossover can introduce complexity and uncertainty into the interpretation of survival outcomes, these challenges should be considered in light of ethical consideration regarding access to potentially beneficial treatment.

During the design of the study, the Applicant sought advice on the study elements from both external clinical experts in the field involved in the clinical development program and patient advocacy groups. Crossover from placebo to vorasidenib upon centrally confirmed PD was included in the study based on the feedback from clinicians and patients/advocates based on ethical considerations for subjects who were already in active observation being randomized to placebo and undergoing a multitude of trial assessments including serial blood draws without the option to receive vorasidenib upon progression.

Importantly, as described previously, decision making for next interventions can be highly subjective and multifactorial and as such crossover to vorasidenib was not mandatory. For subjects randomized to placebo to be permitted to crossover, they had to be clinically stable and meet protocol-defined eligibility criteria. The protocol required radiographic PD documented by the Investigator to be centrally confirmed by the BIRC before unblinding and assessment of eligibility for crossover. Only if BIRC confirmed radiographic PD, was the Investigator informed of the treatment assignment. The Investigator then assessed the best possible next intervention, including crossover, in subjects on placebo. Subjects randomized to vorasidenib were not permitted to continue vorasidenib beyond centrally confirmed radiographic PD.

INDIGO outcome measures

A5. Please explain why 13 secondary outcome measures were deleted from the trial's clinicaltrials.gov record in Summer 2023 and why only two outcome measures are currently listed.

The information registered into CT.gov are submitted to a CT.gov reviewer before publication on the public website. It is common that the reviewer asks questions to clarify some information. The delay between posting the results and the final publication may take several weeks/months as the final publication on the website is done only when all the questions have been solved. On the 7th July 2023, the results

were not yet registered. All the outcomes were listed in the section “Study details” (published on 10th July 23)
On the 5th Sept 2023, preliminary results were recorded (following IDMC decision to unblind the study for early demonstration of efficacy) with : Progression Free survival (PFS) and Time to Next Intervention (TTNI); after several exchanges with the reviewer, these results were publicly released on 22 November 2023. At this step, since results are recorded, the (entire) list of outcomes measures switch from the “Study details” section to the “Study results” section. However, as only 2 outcomes were recorded at this date, only PFS and TTNI appeared.
The last published record was on the 4th December 2023 (still with only the 2 outcomes)
On the 23rd July 2024, all the study outcomes were recorded on CT.gov . After this step, there were many questions from the reviewer.
Servier submitted on the 6th March 2025, the response to the final pending question. Therefore, the publication of the full list of outcomes should be done in the next days.

A6. Please describe whether the definition of TTNI has changed over time – e.g. did it initially align with the CHMPs suggestion of “time to surgery, CT, or RT” as described on p28 of the CS?

TTNI is defined as the time from randomisation to the initiation of the first subsequent anticancer therapy (including vorasidenib, for patients in the placebo group who subsequently crossed over to receive vorasidenib; antineoplastic drug, anticancer surgery, anticancer RT) or death from any cause. Amendment 2 of the protocol (version 3.0) modified the definition of TTNI to include death as an event.No death event happened before NI as of Mar-23 DCO, thus having no impact on the results

During study planning the applicant received divergent scientific advice from the FDA and CHMP about the primary endpoint and secondary endpoints. The FDA did not agree with using the novel endpoint of tumor growth rate (TGR) as the primary endpoint and suggested radiographic PFS by BIRC using the modified Response Assessment in Neuro-Oncology Criteria-Low Grade Glioma (RANO-LGG) criteria instead. Based on the proposed 9-month median improvement in PFS by BIRC, and the ability to translate this to clinical benefit for the patient, the CHMP recommended

use of TTNI (time to surgery, chemotherapy, or RT) as the primary endpoint and radiological PFS by BIRC as the key secondary endpoint. The CHMP acknowledged the difficulty to define strict criteria to standardize the decision for intervention, which is a multifactorial decision, but considered that the subjectivity of the TTNI as an endpoint is alleviated by the randomized double-blind design of the study and this endpoint would be more relevant in terms of clinical relevance to patients. The resolution of these divergent recommendations was to proceed with radiographic PFS as the primary endpoint with revised statistical assumptions, elevate TTNI to a key secondary endpoint following a prespecified hierarchical testing strategy and the α-spending function, and move TGR to a secondary endpoint.

INDIGO results

A7. Please present a table listing all subsequent anti-cancer therapies (including radiotherapy, with or without chemotherapy) received by patients, for each treatment arm, and the number of patients who received each therapy.

Please see requested tables below.

Table 14.1.13
Summary of Subsequent Antineoplastic Therapies
(Full Analysis Set)

Anatomical Therapeutic Chemical (ATC3) Preferred Name	Placebo N=163 n (%)		Vorasidenib N=168 n (%)		Overall N=331 n (%)	
Subjects with at least one antineoplastic therapy	3	(1.8)	13	(7.7)	16	(4.8)
ALKYLATING AGENTS	3	(1.8)	13	(7.7)	16	(4.8)
LOMUSTINE	0		3	(1.8)	3	(0.9)
TEMOZOLOMIDE	3	(1.8)	10	(6.0)	13	(3.9)
MONOCLONAL ANTIBODIES AND ANTIBODY DRUG CONJUGATES	0		1	(0.6)	1	(0.3)
BEVACIZUMAB	0		1	(0.6)	1	(0.3)
OTHER ANTINEOPLASTIC AGENTS	0		3	(1.8)	3	(0.9)
LOMUSTINE;PROCARBAZINE;VINCRISTINE	0		1	(0.6)	1	(0.3)
PROCARBAZINE	0		1	(0.6)	1	(0.3)
PROCARBAZINE HYDROCHLORIDE	0		1	(0.6)	1	(0.3)
PLANT ALKALOIDS AND OTHER NATURAL PRODUCTS	0		1	(0.6)	1	(0.3)
VINCRISTINE	0		1	(0.6)	1	(0.3)

Table 14.1.15
Summary of Subsequent Anti-Cancer Radiation Therapies
(Full Analysis Set)

Indication Preferred Name	Placebo N=163 n (%)		Vorasidenib N=168 n (%)		Overall N=331 n (%)	
Subjects with at least one anti-cancer radiation therapy	5	(3.1)	11	(6.5)	16	(4.8)
Subsequent anti-cancer therapy	5	(3.1)	11	(6.5)	16	(4.8)
PROTON RADIATION THERAPY	1	(0.6)	3	(1.8)	4	(1.2)
RADIOTHERAPY	3	(1.8)	8	(4.8)	11	(3.3)
RADIOTHERAPY TO BRAIN	1	(0.6)	0		1	(0.3)

Table 14.1.14
Summary of Subsequent Anti-Cancer Surgery Therapies
(Full Analysis Set)

Indication Preferred Name	Placebo N=163 n (%)		Vorasidenib N=168 n (%)		Overall N=331 n (%)	
Subjects with at least one subsequent anti-cancer surgery	3	(1.8)	10	(6.0)	13	(3.9)
Subsequent anti-cancer therapy	3	(1.8)	10	(6.0)	13	(3.9)
ASTROCYTOMA SURGERY	0		1	(0.6)	1	(0.3)
BIOPSY	0		1	(0.6)	1	(0.3)
BRAIN LOBECTOMY	1	(0.6)	0		1	(0.3)
BRAIN TUMOUR OPERATION	1	(0.6)	5	(3.0)	6	(1.8)
CRANIOTOMY	1	(0.6)	2	(1.2)	3	(0.9)
TUMOUR EXCISION	0		2	(1.2)	2	(0.6)

A8. Given that the trial was unblinded after IA2 (data cutoff September 6, 2022) please comment on the risk of bias of results reported after this date (e.g. data cutoff 7 March 2023) as compared to the IA2 results.

As described in the AG881-C-004 Primary CSR the primary endpoint (progression-free survival [PFS]) and key secondary endpoint (time to next intervention [TTNI]) were met at the second preplanned interim analysis (IA2; data cutoff date 06 September 2022). On 24 February 2023, the Independent Data Monitoring Committee (IDMC) recommended unblinding the study due to early demonstration of efficacy.

The study was unblinded on 07 March 2023, at which time subjects receiving placebo were given the opportunity to cross over to vorasidenib provided certain eligibility criteria were met. The IA2 results were considered final and are reported in the AG881-C-004 Primary CSR.

This clinical study report (CSR) addendum provides additional results from randomization through study unblinding (data cutoff 07 March 2023), representing an additional 6 months of study follow-up from the planned IA2 (data cutoff: 06 September 2022) where patients and investigators were blinded of the study drug.

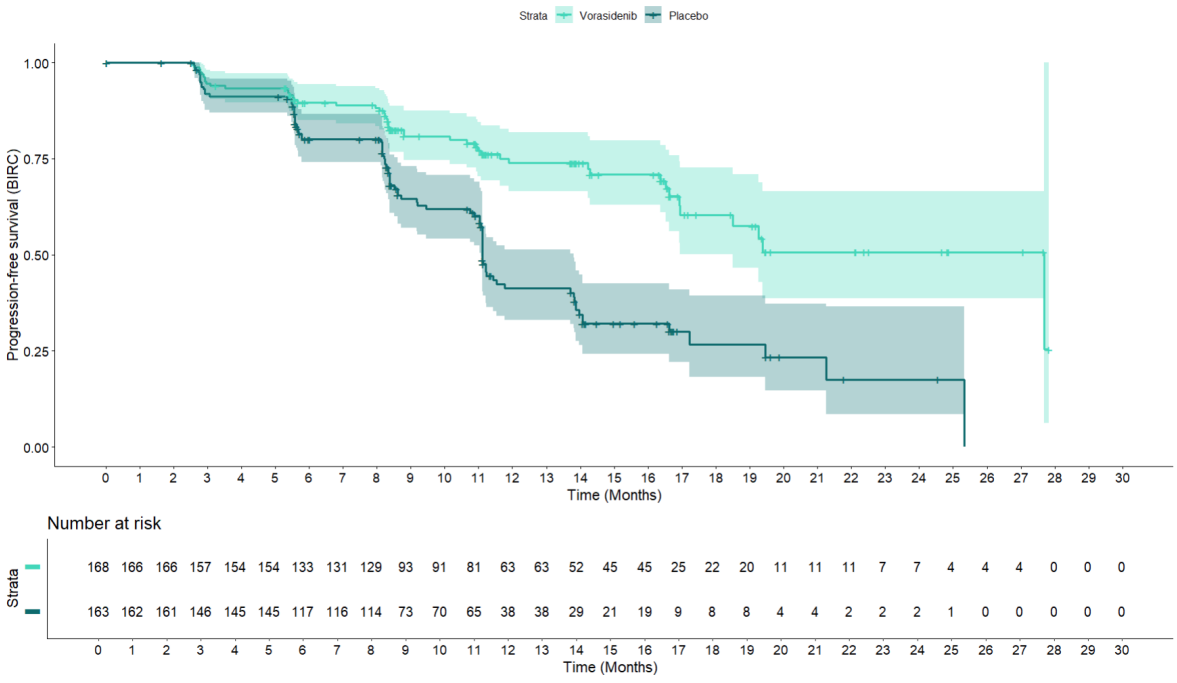
Therefore, there is no additional risk of bias. The additional data cutoff of 07 March 2023 reported data were blinded data prior to the unblinding period.

A9. Section 2.6 of the CS presents subgroup analyses for two outcomes. Please report the number of events by treatment group for the 'longest diameter of tumour at baseline' analyses. Please also report the test for interaction results for the two analyses of 'longest diameter of tumour at baseline'.

Documents attached

A10. For Figure 6 please present 95% confidence intervals for each line (as shaded bands).

The Kaplan Meier estimate for PFS per the BIRC (data cutoff date 06/09/22) with 95% confidence intervals as shaded band is presented below.



A11. Please justify the statement that vorasidenib "delays subsequent treatment with aggressive RT/CT" (CS, p51) when subsequent treatment with RT/CT was not analysed as an outcome.

Post-operative active observation is a standard of care option for patients with Grade 2 IDH mutant gliomas who are not in immediate need of chemoradiotherapy. The goal of this approach is to defer the need for more toxic regimens (eg, RT and chemotherapy) until there is evidence of progression and/or evidence of clinical deterioration. Although subsequent treatment with RT/CT was not analysed as an outcome in the trial, time to next intervention (TTNI) defined as the time from randomisation to the initiation of the first subsequent anticancer therapy (including vorasidenib, for patients in the placebo group who subsequently crossed over to receive vorasidenib) or death from any cause was a key secondary outcome. TTNI in this disease area is RT/Chemo due to the lack of other treatments. Therefore, by delaying disease progression by using vorasidenib, you are delaying TTNI and therefore prevent the use of RT/Chemo which includes the debilitating effects that follow this. Many guidelines and literature present watch & wait/active observation as a way to postpone Rt/Ct due to the neurotoxicity and burden of these treatments. In many patients with IDH-mutant grades 2 and 3 glioma, if carefully monitored postponing radiotherapy and chemotherapy is safe, and will not jeopardize the overall outcome of patients[2]

In light of the relatively young patient population of low grade glioma patients, when assessing the need for RT/Chemo, the benefit associated with the treatments has to be considered against the cost of therapy-related side effects and toxicities.

Mair et al 2021, summarises literature which look at effects of administrating Rt/Chemo on neurocognitive decline, non-phonemic verbal fluency, mood and quality of life, as well as the effect on fertility for low grade glioma patients[3]. Effects such as neurocognitive decline and losing the ability to drive also have a knock on effect on the patient's ability to work and lead an active lifestyle.

Hence active observation, ' watch and wait', has been become an established modality for patients not at immediate risk of progression to delay the side effects and toxicities of RT/chemo.

The goal of delaying RT/Chemo, due to the detrimental effects seen, though an active observation approach are further pronounced in a scenario where vorasidenib substitutes active observation due to the prolongation of PFS and TTNI seen in the INDIGO study.

Although immature , TTNI in the INDIGO study, in the whole, will represent a delay for patients receiving RT/Chemo compared to active observation. Any patient receiving, secondary surgery in the INDIGO study would eventually receive RT/chemo upon recurrence and the presence of ‘ high risk factors’ , however again this will be delayed via the early administration of vorasidenib in the clinical pathway.

A12. Seizure activity

a. Please clarify the seizure activity results reported on p43. The submission states both that “There was no clinically meaningful improvement or worsening of seizure activity in the vorasidenib arm relative to placebo” and that “The seizure rate in the vorasidenib group was 64% lower compared to the placebo group suggesting vorasidenib was associated with better seizure control in patients who have seizure activity”.

Seizure activity was an exploratory endpoint in the INDIGO trial and this refers to the analysis of seizure activity (including the patient-reported monthly frequency andseverity of seizures, type of seizures as assessed by the investigator, seizure AEs, and changes in anti-seizure medications (including dose and frequency)) based on descriptive statistics and changes from baseline by treatment arm and visit; acknowledging that the number of subjects reporting seizures at each cycle, while reduced at some cycles compared to baseline, was similar in both arms.

However, by analyzing data by looking at difference vs. baseline at each visit and by arm, the seizure activity is diluted by the fact that 2/3 patients had no seizure at all during the trial, and among patients with seizures, many had 0 event at some visits. Therefore this approach did not allow to characterize a difference between arms, but highlighted that mIDH inhibition with VORA did not lead to increase seizure activity.

Therefore, the initial results refer to the no clinically meaningful improvement or worsening of seizure activity in the vorasidenib arm relative to placebo. However, as presented at SNO 2024, the frequency and rate of seizures per person-year on

treatment was evaluated in the March 7, 2023 data cut associated with better seizure control.This is based on exploratory analyses for the number of on-treatment seizures in patients with >=1 seizure in the baseline or on-treatment periods using a negative binomial regression model.

In this analysis, performed on the March 23 DCO, patients treated with vorasidenib had lower on-treatment rates of seizures than those treated with placebo. Thus, treatment with vorasidenib was associated with lower seizure activity than with placebo in patients with mIDH1/2 glioma

b. Please comment on how the seizure activity results reported on p43 relate to the adverse reactions for seizures reported in Table 21, p48 of CS (and Appendix D, p118 of CS), where seizure adverse event rates are higher for vorasidenib compared to placebo.

The results in the table 19 on page 43 relate to the seizure data at the March 2023 data cut off. The adverse reactions for seizures reported in Table 21, p 48 and appendix D relate to the data cutoff date: 06 September 2022

Overall survival data

A13. PRIORITY: If OS data after the 7th of March 2023 data cut-off is available, please provide the Kaplan-Meier OS data for INDIGO with numbers of patients at risk for the most recent data cut or report the numerical numbers of deaths in each arm of INDIGO (if numbers are small).

No other data cut off is available at this point in time.

Malignant transformation

A14. PRIORITY:

a. Please provide data on the rates of malignant transformation (MT) and time to MT for the vorasidenib and placebo arms of INDIGO from the most recent data cut.

Malignant transformation is part of the natural progression of Grade 2 gliomas. The INDIGO study used a conservative definition of malignant transformation that included changes from Grade 2 to either Grade 3 or Grade 4.

An additional analysis of time to malignant transformation as of the 07 March 2023 study unblinding date was performed and has calculated time to malignant transformation from initial diagnosis and from randomization. In the vorasidenib arm (N=168 subjects), 6 subjects had malignant transformation (5 subjects with astrocytoma and 1 subject with oligodendroglioma). At time of progression, 4 subjects showed Grade 3 tumour and 2 subjects showed Grade 4 tumour. In these 6 subjects, the median treatment duration on vorasidenib was 15.13 months (interquartile range [8.94, 19.98])and the median time from initial diagnosis to malignant transformation was 44.19 months (interquartile range [43.17, 61.21]). In the placebo arm (N=163 subjects), 2 subjects, both with astrocytoma, had malignant transformation. At time of progression, 1 subject showed a Grade 4 tumour and 1 subject showed a Grade 3 tumour. The subject with a Grade 4 tumour had a treatment duration on placebo of 8.8 months and time from initial diagnosis to malignant transformation of 26.1 months. The subject with a Grade 3 tumour had a treatment duration on placebo of 5.7 months and time from initial diagnosis to malignant transformation of 25.4 months.

In patients who crossed over from placebo to vorasidenib, 2 subjects had a malignant transformation after discontinuation of vorasidenib (1 subject with astrocytoma and 1 subject with oligodendroglioma). The subject with a Grade 4 tumor had a treatment duration of 2.7 months on placebo and 1.3 months on vorasidenib after crossover before discontinuing for progression. The time from initial diagnosis to malignant transformation was 37.2 months. The subject with a Grade 3 tumor had a treatment duration of 6.4 months on placebo and 2.8 months on vorasidenib after crossover before discontinuing for progression. The time from initial diagnosis to malignant transformation was 25.9 months

Overall, across the 10 subjects who had a malignant transformation as of 07 March 2023, the time from initial diagnosis to malignant transformation ranged from 25.4 to 62.9 months, occurring more frequently in subjects with astrocytoma, both of which are consistent with the literature. However, the rate of malignant transformation in Study AG881-C-004 is remarkably lower than that reported in the literature as these patients represent an homogeneous population of patients not in immediate need of Rt/Ct. In addition, the 2 subjects who had malignant transformation after crossover to

vorasidenib had an extremely short treatment duration on vorasidenib, suggesting that the transformation likely occurred prior to initiation of vorasidenib therapy.

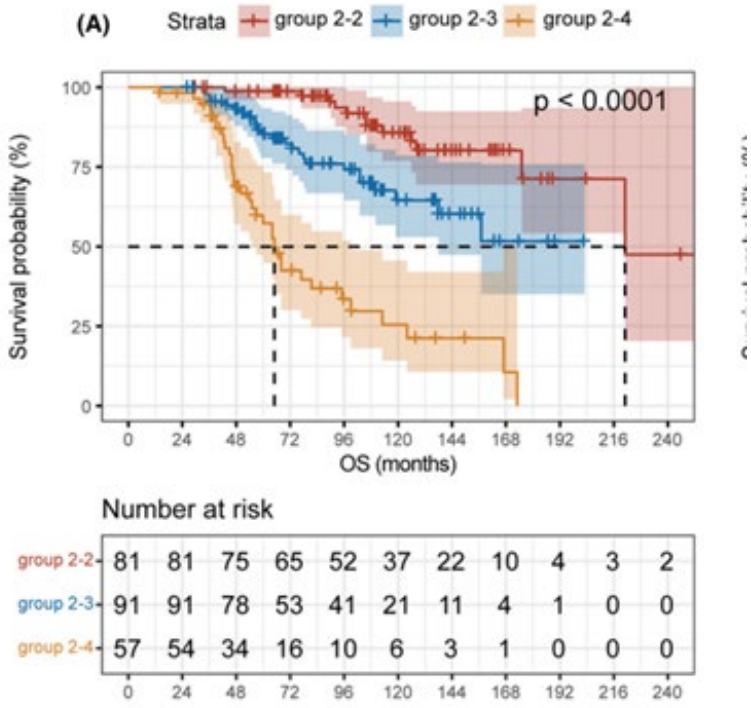
b. Please comment on the differences in MT between treatment arms.

As of 07 March 2023, 2 of 167 subjects had observed cases of histologically proven Grade 2 to Grade 4 transformation in the vorasidenib arm compared to 1 of 163 subjects in the placebo arm; the rate of Grade 2 to Grade 3 transformation was 4 of 167 subjects in the vorasidenib arm and 1 of 163 subjects in the placebo arm. Overall, the number of subjects with malignant transformation in the AG881-C-004 study was 10 of 331 subjects. This analysis should be interpreted with caution given the limited number of observed events in both arms. Indeed, assessment of MT requires biopsy or surgery to be assessed which causes a lot of bias, especially in the Pbo arm, where many patients crossed over to VORANIGO: at the Sep-22 DCO, only 3 patients from the placebo arm had received a surgery vs. 10 in the Vora arm (Those figures are 9 and 14 respectively at the Mar 23 DCO).

c. Please provide any evidence to support a link between the rates of MT and/or time to MT and mortality risk in the target population.

Malignant transformation is part of the natural progression of Grade 2 gliomas. Grade 2 gliomas inevitably transform to malignant, although lower rates may be seen in the whole cohort because of the natural course of the patient. Variance in rates of MT is seen within the literature due to data sets with immature read outs or censoring. Malignant transformation is associated with an adverse prognosis**.**

A retrospective cohort study based on 229 adults with recurrent LGG looked at the characteristics of different MT patterns and to build predictive models for patients with LGG.Based on pathology findings of recurred lesions, 148 (64.6%) of these patients underwent MT, including 91 (39.7%) patients with tumour progressed to grade 3 (group 2–3) and 57 (24.9%) patients with direct progression to grade 4 (group 2–4); whereas the remaining 81 (35.4%) patients were exempt from MT (group 2–2). Patients in group 2–2 had the longest OS (median OS [mOS]: 221.0 months), followed by group 2–3 (mOS: not reached), and lastly group 2–4 (mOS: 65.0 months)[4].



Tom et al (2019) performed a single institute analysis, from 1980 to 2018, in 489 low grade glioma patients to analyse the time to transformation and prognosis. With a median follow up of 5.3 years, malignant transformation occurred in 17% of patients. The median overall survival after MT was 2.4 years (95% CI, 1.5-3.3)

Median OS for those with MT and IDHm ranged from 2.6 – 4.0 years. Median OS after MT to grade 3.0 was 3 years (95% CI 1.0 – 4.9) and 0.8 years for those with MT to grade 4. (P<.001)[5].

Hence malignant transformation, over the disease course of low grade gliomas, is associated with increased mortality risk over a extended time horizon.

PFS-2

A15. If available, please provide data on progression-free survival 2 (PFS-2), defined as the time from randomisation to progression on first subsequent therapy, for vorasidenib and placebo arms of INDIGO. Please explain why this data was not used in the model, but instead the conditional time to next

intervention following progression (TTNI|P) had to be derived from the trial outcomes of TTP and TTNI.

PFS2 is not a INDIGO endpoint. It is not collected in the study. PFS after cross over will be available for patients who crossed over from placebo.

INDIGO follow-up includes Extent of disease, response and progression until six cycle post end of treatment («PFS Follow-up»). After six cycles, patients enter «OS follow-up» where only survival and subsequent therapies are followed every 6 months

TTNI|P does not substitute to PFS2. It is used to track time between progression event and next intervention, as both events are sequential and there can be some differences between patients with regards to the time it takes from progression to NI, especially because RANO progressed tumors may be smaller than at baseline (since progression is 25% increase in tumor size vs nadir).

Thus, it was important to distinguish between time to progression, initiation of NI and progression on or after NI, none of which would correspond to INDIGO PFS2 (rather it would be duration between NI and second progression).

In the CEM, the transition closest to «PFS2» is the transition between S5/S6 and S7 which is informed by EORTC 22033-26033 - Baumert et al. 2016)

Section B: Clarification on cost-effectiveness data

Model structure

B1. Please justify why the model structure was based on lines of therapy (i.e., time to next intervention) rather than progression events, such as transition from low-grade gliomas (LGG) to high-grade gliomas (HGG) or transformation to malignant gliomas (secondary HGG).

While some people with IDH mutant glioma will experience malignant transformation around the time of documented disease progression, leading to increased risks of subsequent progression, death, deterioration, etc.; others may not experience malignant transformation for a long time. Established clinical practice for these patients is to control the tumour to prevent/delay the occurrence/worsening of

symptoms caused by the tumour (tumour volume and biology) and improve survival. Furthermore, it should be noted that treatment is independent of the grade of tumour at progression: all patients receive similar treatments and these treatments bear significant toxicity leading to quality of life impairments.

Thus, the main determinant of costs and quality of life are initiation of RT/Chemo. Data shows that most patients will proceed to receive 1 or 2 lines of RT/Chemo with appropriate tumour control, leading to multiple years progression free before experiencing a sudden increase in disease specific mortality risk as more and more patients eventually progress to high grade disease.

Due to the currently limited follow-up data from the INDIGO trial and lack of evidence in the literature in the disease area, progression-event proportions are unknown and so there would be an increased number of assumptions in the model based on limited literature available. To address the uncertainty in and around progression, the model structure allows each state in the model to be powered by different data sources, using progression and time to next intervention (TTNI) data from INDIGO. For later lines, line-based health states aim to use what little literature is available to capture main milestones in disease management.

In NICE TA977[6] (dabrafenib with trametinib for treating BRAF V600E mutation-positive glioma in children and young people aged 1 year and over), subsequent lines were captured using progression events rather than line-based health states. However, one single data source was used for these transitions (Kandels *et al.*, 2020)[7]. To the best of our knowledge, no equivalent source of data exists for an adult population with IDH-mutant glioma. Consequently, the model developed for this appraisal adopts a simplified approach based around treatment duration, though time to progression is used for patients moving from S5 or S6 to S7, as well as S7 to S8. On- versus off-treatment is also relevant because treatments have an acute impact on quality of life and costs, and because RT/Chemo are typically administered for a limited period, followed by long monitoring phases (e.g., 6 to 12 months of treatment followed by several years without treatment).

Additionally, there is a lack of consensus with regards to the definition of malignant transformation and a lack of data regarding its association with other outcomes. This

is especially complicated by the fact that this disease is an early stage cancer with slow progression that has documented modifications to how it is classified in 2007, 2016 and 2021, especially with the identification of IDH mutation as a key prognostic and classification factor, which therefore means that longitudinal data linking such outcomes over a long term horizon is limited and often not appropriate for IDHmutant patients (especially since these patients have better prognosis and are likely under-represented in the older longitudinal series).

For these reasons, lines of therapy were considered as the most appropriate way to characterise the progression of the disease and increasing impacts of oncologic treatments in terms of both quality of life and costs and were reflected in the model structure instead of disease grade. This structure was validated by experts, who considered it appropriately conveyed the disease and treatment pathway in a relevant way.

Surrogacy relationship for overall survival

B2. PRIORITY: The approach to modelling used in the CS relies on the relative effect of vorasidenib on time to progression (TTP) and time to next intervention following progression (TTNI|P) being predictive of its relative effect on overall survival (OS).

a. Please present evidence to support the validity and biological plausibility of a surrogacy relationship between delaying TTP (or PFS gain) and OS benefit for vorasidenib in the target population. If no evidence exists in the target population, please present the evidence for a surrogacy relationship from studies in closely related populations (e.g., HGGs) and treatments (e.g., RT/CT).

There is no conclusive evidence for this surrogacy relationship between TTP (or PFS gain) and OS benefit in IDHmutant glioma. However, a study by Han *et al* [8]presented an analysis of 91 clinical trials of populations with HGG to investigate the relationship between PFS and OS, and the authors found that hazard ratios for PFS and OS were strongly correlated (R^2 = 0.92).

Additionally, a growing body of evidence supports a direct correlation between tumour volume and growth rate with other outcomes, including OS and quality of life, establishing these metrics as important predictive biomarkers.

A targetted literature review was conducted by Servier alongside 3 experts in the field, to better characterize current practices regarding the evaluation of tumour size, including volume and growth rate, and to evaluate the correlation between tumour size and/or growth with OS, PFS, quality of life (QoL), and other clinical outcomes, such as symptoms, malignant transformation (MT), or time to next intervention (TTNI). This report is provided as an attachment. The review of 56 studies showed consistent prognostic significance of tumour size and growth as strong predictors of patient outcomes, particularly in IDH-mut diffuse gliomas, influencing survival rates and symptom severity, with robust evidence indicating an inverse correlation between pre-surgical tumour volume and both OS and PFS, as well as symptoms or MT, suggesting the prognostic value of pre-surgical assessments. Additionally, consistent inverse correlations between residual tumour volume and OS/PFS further support the notion that tumour size and growth are key predictors of patient outcomes.

Specifically, Bhatia et al, 2024[9] analysed a cohort of IDHmt gliomas that were in active observation after surgical resection. The continuous % TvGR / 6 months growth rate for mIDH gliomas was 9.54%. When looking at the longitudinal course of TvGR and overall survival it was found by the investigators that one natural logarithm tumour volume increase resulted in more than a 3-fold increase in risk of death.

In the INDIGO trial, vorasidenib was associated with a decrease in tumour volume compared to continued growth on the placebo arm, with a decreased TGR of 2.5% every 6 months in the vorasidenib arm (primary analysis) (mean TGR=-2.5%; 95% CI: -4.7, -0.2), while an increase of 13.9% every 6 months for the placebo arm (mean TGR=13.9%; 95% CI: 11.1, 16.8). The reduction in volumetric TGR observed in patients treated with vorasidenib contrasts with the continued tumour growth seen in subjects receiving a placebo, highlighting the anti-tumour activity of vorasidenib.

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Altogether, the significant effect of vorasidenib on PFS and its established correlation with tumour volume and growth in the INDIGO trial demonstrate that PFS improvements are expected to translate into improvements in terms of OS, PFS, TTNI, and symptom severity for patients with IDHm gliomas, suggesting the validity and biological plausibility of a surrogacy relationship between delaying TTP (or PFS gain) and OS benefit for vorasidenib by assuming that outcomes for patients following progression and initiation of NI would be similar, regardless of prior treatment history.

b. Please explain why a surrogacy relationship was not estimated directly from the trial outcomes (e.g., using the hazard ratio (HR) of treatment on PFS from INDIGO to predict the corresponding HR on OS), but instead inferred indirectly through progression on multiple lines of subsequent treatments. If alternative approaches were explored but not reported in the CS, please provide estimates of the predicted OS hazard ratio, with details of the approaches used.

The model was developed in keeping with the available evidence to inform clinically-relevant health states and associated transition probabilities. The model captures two endpoints from the INDIGO study: progression-free survival (PFS, or time to progression [TTP], given that no deaths were recorded prior to documented disease progression), and time to next intervention (TTNI). OS was not estimated directly,

because the model structure aims to capture sequential lines of therapy based on estimated treatment durations. Estimating a formal surrogacy relationship between PFS and OS was not considered appropriate, owing to a combination of few death events having been recorded in the INDIGO study.

Survival predictions

B3. PRIORITY: Please comment on whether the predictions from the extrapolated survival curves for both the initial interventions (vorasidenib and active observation) and subsequent treatment lines were subject to external validation. If so, please provide a detailed report of the findings from the external validation.

Servier did not conduct a formal validation exercise for the survival curves, as our engagement with clinical experts was limited to informal one-to-one discussions. As part of these discussions, clinicians found it challenging to provide feedback on estimated survival outcomes. Clinicians also highlighted that both outcomes and treatment decisions varied according to tumour histology (i.e., astrocytoma versus oligodendroglioma).

As part of these discussions (details of which were provided as a reference in the CS), clinicians were asked about long term estimates of progression-free survival and next intervention free survival, for both vorasidenib and active observation after 10 years. Feedback suggested that for those managed with active observation, treatment may not be needed for 10 years – particularly for people with oligodendrogliomas.

One advisor noted that literature states astrocytoma survival to be around 7 years and oligodendroglioma beyond 10 years, so they would expect survival for people treated with vorasidenib to be around 15-20 years. In addition, another advisor explained that those with an oligodendroglioma are expected to live around 14 years median OS although this could be as much as 20+ years. When asked about the likelihood of a small proportion of people still being alive after 50 years, one advisor explained that in their practice they had a 40-year survivor, with the majority expecting 1% to be alive at 50 years.

To address this further, Servier has scheduled an advisory board, as discussed during the clarification call, and we will share the outputs in due course.

B4. PRIORITY:

a. Please provide a detailed summary of the modelled predictions of survival time in each health state for both vorasidenib and active observation.

From the goodness-of fit statistics, the log-normal model was the statistically favoured model for extrapolating PFS BIRC in the vorasidenib arm. Based on clinical expert feedback provided to Servier, clinicians found this very difficult to choose. However, one did state that it would be reasonable to assume some patients would still be progression free and next intervention free at 15-20 years on vorasidenib, and another stated that we already know that on active observation, some don't need treatment for 10 years. The log normal, log-logistic and exponential distributions were hence considered to provide the most realistic estimates of PFS for patients treated with vorasidenib. Therefore, the log-normal model was selected in the base-case analysis. For the placebo arm, fit statistics suggested that the log-logistic and gamma models provided equally suitable estimates. However, the goodness-of fit statistics are similar to that of the log-normal model, and so for consistency with the vorasidenib arm, the log-normal model was also used to extrapolate PFS BIRC in the placebo arm.

The fit statistics indicated that the generalised gamma model was the best fitting model for TTNI in both arms. Therefore, the generalised gamma model was chosen to extrapolate TTNI|P BIRC for both arms. It should be noted that clinical advice provided to Servier suggests that even under current management, some people managed with active observation remain NI-free after 10 years.

A study by Baumert et al. (2016) provided survival outcomes for 477 patients with grade 2 glioma who were randomised to receive either conformal RT or dose-dense TMZ. A KM estimate of PFS is presented in the paper which separates outcomes for IDHmt (both 1p/19q co-deleted and non-co-deleted) and IDH-wildtype gliomas. Fit statistics suggest that the best fitting model to PFS for the group with IDHmt, 1p/19q co-deleted glioma was the log-normal model. From the visual fits, this model provides middle-ground estimates in comparison to other models, and therefore

seems realistic in the long term. This model was used for extrapolation of PFS in this group in the base case of the cost-effectiveness model. For patients with IDHmt 1p/19q non-co-deleted glioma, the Gamma and Weibull models provided the best statistical fit to PFS. Therefore, the Gamma model was selected to extrapolate PFS in this population in the base case of the cost-effectiveness model.

The histological mix of patients upon entering S5 in the cost-effectiveness model is unknown. Therefore, the model assumes no change from baseline in histological mix. However, this histological mix of patients omits the possibility of some patients entering S5 with high-grade glioma (HGG); and data for this group of patients is not available from Baumert et al., (2016). To account for this, 23.6% of patients were assumed to enter S5 with HGG (based on a study by Hervey Jumper et al., [2023]), and a median survival estimate of 3.1 years (based on a study by Juratli et al., [2012]) to further re-weight the hazard of a progression event after initiation of NI.

A study by Ma et al., (2021) was identified which focused on salvage therapies which would likely be the various treatments that a patient receives before moving onto BSC. However, no data specifically for an outcome defined as ‘time to BSC’ is available from any known data source. The closest proxy available for this is the PFS and TTP reported in Ma et al. Consequently, the assumption was made that PFS/TTP serves as a proxy for time to BSC. That is, that patients go into a planned palliative or supportive care setting upon exiting salvage therapies at 2L+, and that the reasons for stopping treatment align with disease progression at a salvage therapy baseline. A hazard ratio of 7.73 for astrocytoma vs oligodendroglioma published by Kavouridis et al. (2021) was applied inversely to the best-fitting extrapolation to provide the estimated survival of oligodendroglioma patients on salvage therapy. Then, the baseline distribution of astrocytoma and oligodendroglioma was used to extrapolate the proportion of the remaining cohort with either histology. Finally, a pooled hazard estimate was produced, and this was used in the model as for the S7 to S8 transition probability.

Fit statistics suggested that the best fitting model to TTP was the generalised gamma model, which was selected in the base-case analysis. The exponential model was the statistically favoured model to predict TTP in oligodendroglioma patients, however this model eventually crossed with the astrocytoma extrapolation.

In reality, it would be expected that more astrocytoma patients would progress than oligodendroglioma patients over the full modelled time horizon, and therefore the extrapolation with consistently greater TTP in the astrocytoma arm was chosen which was a Gompertz model. This model provided much more optimistic estimates of TTP in the longer term than the exponential model.

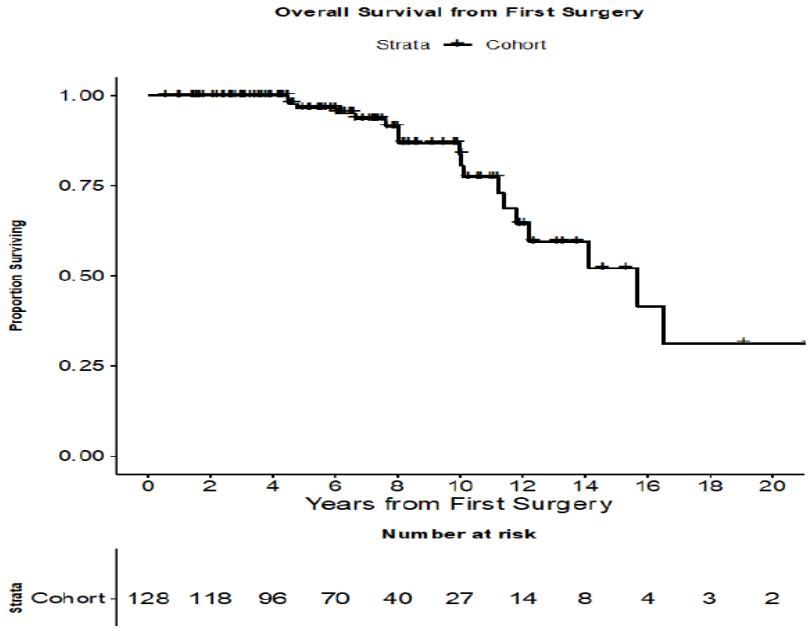
b. Please comment on the clinical plausibility of the modelled predictions for both vorasidenib and active observation and contextualise the predictions in terms of evidence on median OS for IDH-mutant grade 2 gliomas (for example, page 9 of the CS states that the median OS for patients with IDH-mutant glioma is ~10 years, but average OS (undiscounted) in the base case analysis is 26.53 years for vorasidenib and 20.80 years for active observation).

As noted by the EAG, the CS states: *"The median OS for patients with IDH-mutant glioma is ~10 years"* (CS, Section 1.3.1, p.11). To support this statement, two studies are cited. One of these (Hertler *et al.*, 2023)[10] considers a population with IDH wildtype *glioblastoma*, not *glioma*. This is an important distinction, and Servier apologises for the error in presenting this finding as an estimate of median survival for a *glioma* population. For people with glioblastoma, prognosis is notably poorer.

- The second study states the following: *"The main rationale for delaying radiation in patients with grade 2, IDH-mutant gliomas is to preserve cognitive function in younger patients with an expected median overall survival in excess of 10 years, as there is increasing evidence that radiation can lead to worse neurocognitive function in multiple domains, predominantly in attention and processing speed"* (Miller *et al.*, 2023, p.13).[11] Again, Servier apologises for the error in presenting this finding in the CS as a median survival estimate of 10 years, rather than maintaining the original wording as median survival being *in excess of* 10 years. Taken together, both of these studies suggest that median survival for people with IDH-mutant glioma could be greater than 10 years.

- In addition, a further paper looking at IDHmutant not in immediate need of RT/CT population has a 15yr median OS with an astro/oligo split similar to INDIGO[9].

Supplementary Figure S3.



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Outside this specific statement, the CS also highlights how variable survival can be, with a median survival range between 5 to 17 years, depending on the data source, treatments given, and tumour histopathology. The base-case analysis produces estimates of median survival that are towards the upper end of this range; however,

this is not surprising given the small number of death events observed in the INDIGO study. In the latest data cut from INDIGO, only one death event was recorded (07 March 2023 data cut, median follow-up of approximately 20 months), and this death event occurred after disease progression and initiation of NI.

Another important consideration when comparing the model to historical data is how to define 'time zero'. Establishing time zero is inherently challenging, as historical studies do not necessarily define this in the same way as the INDIGO clinical trial, leading to potential discrepancies in survival estimates. Unfortunately, to the best of our knowledge, this is no external evidence source that perfectly aligns with both the inclusion/exclusion criteria of the INDIGO clinical trial and therefore anticipated positioning of vorasidenib in NHS practice (displacing active observation for eligible patients). As a result, any external comparison is subject to limitations, which may further contribute to differences in estimated median survival.

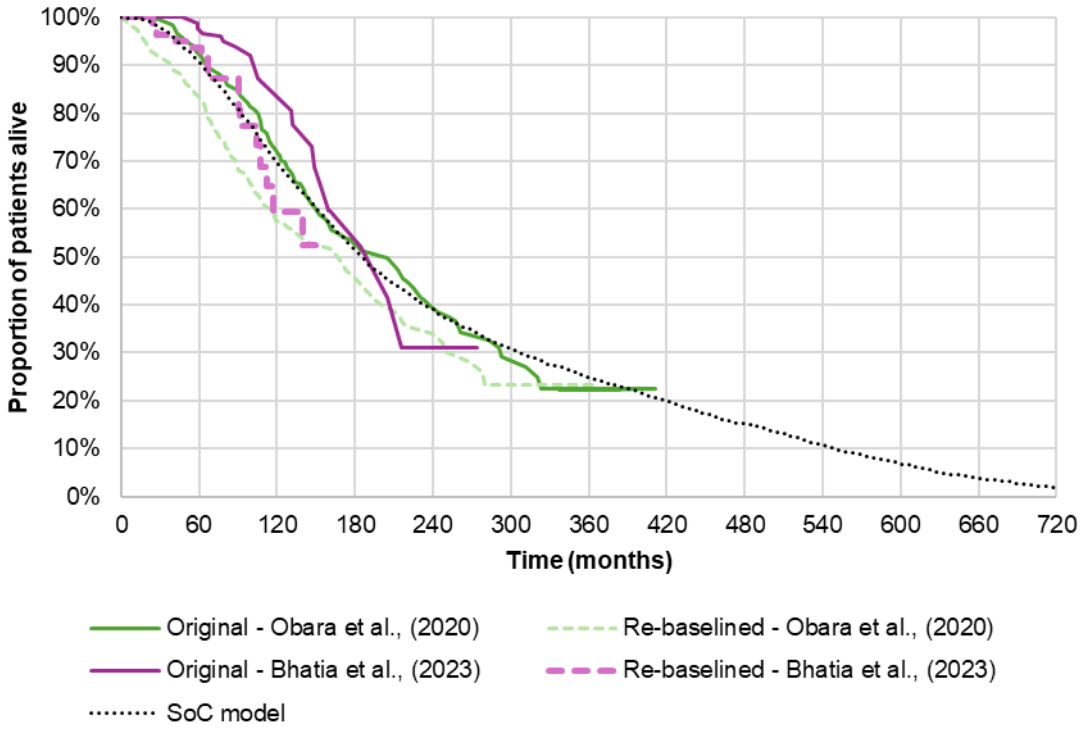
Servier also notes that median and mean survival estimates can vary markedly, particularly in cases where there is heterogeneity in prognosis.

In terms of validation, of projections, the model includes estimates of survival from a study by Obara *et al.*, (2020)[12]. This study reports survival data from a single centre in France of 339 patients diagnosed with a new diffuse low-grade glioma between 1982 and 2017, using date of radiological diagnosis as 'time zero'. An alternative study was also identified by Bhatia *et al.*, (2023)[9]. This study reports survival data from a retrospective cohort study, with 'time zero' being the data of first surgery.

A plot comparing the estimated OS curve for the comparator arm in the model is presented alongside two estimates of survival from Obara *et al.* and two estimates of survival from Bhatia *et al.*:

- **Original Obara:** This is a digitised version of the OS estimate from Obara *et al.*, (2020), reported in Figure 2 of the study publication.
- **Re-baselined Obara:** This is the same KM as above, but re-baselined using median PFS from Fukuya 2019 OS. In other words, 3.3 years was subtracted from the digitised survival estimates, negative survival times were removed, and the KM was re-estimated using pseudo individual patient data.

- **Original Bhatia:** This is a digitised version of the OS estimate from Bhatia *et al.*, (2023), reported in Supplementary Figure 3 of the study publication.
- **Re-baselined Bhatia:** This is the same KM as above, but re-baselined using an estimated 2.5 years time since surgery, based on the population in INDIGO.



From this plot, the following observations can be taken:

- Despite the base-case analysis not using data from Obara *et al.*, (2020), the estimated survival curve is broadly aligned with this data source, as well as the re-baselined Bhatia *et al.*, (2023) estimate.
- It could be argued that the model over-estimates survival slightly for the standard of care arm, versus the Obara *et al.*, (2020) study, given the difference in 'time zero'. However, RT/chemo eligibility was not a specific consideration in the Obara study; patients eligible for active treatment would be expected to have more rapidly progressing disease, and hence lower survival, which may also contribute to the difference. IN addition, not all

patients in Obara *et al.* were IDHmutant – around 10% were IDH wild type, which has a poorer prognosis.

- The data from Obara *et al.* consider a cohort of people diagnosed as early as 1987. It would be expected that survival outcomes have improved over time, owing to advances in identifying and understanding glioma diagnoses, improvements in imaging and diagnostic techniques, and the development of more effective treatments for people with glioblastoma. As such, survival estimates from this earlier cohort are likely to be lower than those observed in more recent studies.

- The re-baselined estimate from Bhatia *et al.* covers a shorter time period, but is also aligned with the base-case estimate of OS in the model.

Overall, Servier considers the base-case survival estimates for the active observation arm to be broadly reasonable, in light of the historical evidence which suggests median survival would be expected to be greater than 10 years. However, Servier recognises the inherent uncertainty introduced when producing estimates of survival for people currently managed with active observation.

Finally, as an additional clarification, the submitted base-case analysis estimates median survival for active observation of 15.33 years, and 22.69 years for vorasidenib. Base-case estimates of mean survival were 20.76 years for active observation, and 26.49 years for vorasidenib. Linked to the questions raised in Section C of this document, this may account for the discrepancy between the values stated in this question versus the submitted model (cell ranges E23:F24 on the 'Results' sheet), but this is highlighted here for completeness.

c. Please provide an estimate of the OS hazard ratio for vorasidenib relative to active observation that is implied by the modelled OS predictions, and interpret the OS HR in relation to:

(i) the outcomes of the INDIGO trial (including PFS HR);

The submitted base-case analysis estimates total undiscounted life-years of 26.49 for vorasidenib, and 20.76 for active observation. To address this question, the implied survival curve for the active observation group was extracted as x- and y-

coordinates from the submitted model, and the built-in 'goal seek' functionality in Excel was used to determine the HR required to obtain a survival estimate of 26.49 years. The outcome of this analysis was that the model is approximately equivalent to an HR of 0.69 for OS.

(ii) the evidence from other studies in this population for both PFS and OS; and

In the latest interim analysis of INDIGO, the HR for the primary endpoint of PFS per BIRC was 0.34 (95% CI: 0.23, 0.50, CS Table 15). This suggests that the 66% reduction in the hazard of progression or death estimated from INDIGO is slightly more than double the 31% reduction in the hazard of death implied across the entire model.

(iii) the clinical plausibility of achieving similar outcomes in NHS practice, if vorasidenib were to be recommended for use in this target population.

There are unfortunately, to the best of our knowledge, no other studies available to compare these HRs to in this patient population. Servier considers the modelled relationship in its base-case analysis between OS and PFS to be reasonable.

Time to next intervention

B5. PRIORITY: Patients enter the modelled health state S4 upon disease progression and remain in this health state off-treatment until time to next intervention given progression (TTNI|P).

a. **Please provide clinical evidence to support the assumption that patients in NHS practice would not move directly to a subsequent treatment upon evidence of radiographic progression of their disease.**

Progression may not immediately trigger NI, especially when we consider that low grade gliomas can be a slow progressing disease. It can be a difficult choice to move to the NI, such as RT/Chemo. The NI, especially in the case of RT/Chemo, could still pose a risk of neurocognitive decline, that could impact a person's ability to work and perform normal daily tasks. The decision may also be complicated by other factors such as the choice to start a family which may outweigh the benefit of starting RT/Chemo straight away. Here the patient may choose to delay initiating RT/Chemo

on progression of first intervention. The tumour could also be in an area of the brain where RT and surgery are deemed unsafe and here the patient may again wait to delay RT/Chemo or opt out in later lines.

In an Australian registry of grade 2 gliomas (Gately et al, 2024)[13], 104 patients (46%) had radiologically progressed at a median follow-up of 35.8 months (range 0.1–98 months). Of these, 69 patients (66%) had been observed post-surgery, and 35 (44%) had received post-surgery anticancer treatment. Of the patients who were observed post-surgery, almost half received chemoradiotherapy, however 29% underwent re-resection and 7% did not receive an immediate NI at the data analysis cut off point. The term 'best supportive care' was used for any patient that had not received an intervention at progression. These patients may reflect the patients that have decided to delay the NI as outlined above.

Treatment with vorasidenib in the INDIGO study leads to tumour shrinkage, therefore it is likely that patients have a smaller tumour at time of progression than at baseline. In such cases, it is expected the decision for use of RT/Chemo may be further postponed in some circumstances . Also risk factors that inform the immediate need for RT /chemo may have been diminished after vorasidenib use, and therefore in a small patient cohort the decision may again be to delay RT/Chemo at progression on vorasidenib.

b. Please explain why a large percentage of participants in the INDIGO trial in the vorasidenib arm (83.3% at the 07 March 2023 data cut) did not receive a subsequent treatment despite having documented progressive disease (as assessed on imaging by blinded independent review according to the modified Response Assessment for Neuro-oncology for Low-Grade Gliomas [RANO-LGG]), i.e., time to progression (TTP) is significantly lower than time to next intervention (TTNI) for vorasidenib.

This response is provided for parts a. and b. above.

The choice to go onto the next intervention for patients in clinical practice is a difficult choice for patients to make. Next interventions including RT/CT are debilitating and lead to loss of daily functions that most patient wouldn't want to give up such as the ability to drive and other issues such as loss of appetite, depression etc. It also

causes a catastrophic drop in quality of life because of the inability to complete normal daily tasks. Therefore, patients could choose to delay this next intervention and even in later lines opt out of treatment entirely. Opting out is hence incorporated in the model.

Servier considers it important to recognise that in the context of a population with grade 2 mIDH glioma patients not in immediate need of RT/Chemo, progression does not immediately lead to next intervention. The disease is slow growing – a clinical expert has previously commented that in their practice, they have seen a patient who was diagnosed 40 years ago. The type of clinical progression seen in the trial may not necessarily immediately trigger the decision to initiate a next intervention. In many cases, patients will experience a radiographic progression with constant/slow growth, indicative that the cancer needs to be controlled but not warranting an urgent treatment decision. In such cases, it is well recognised that RT/Chemo is not suitable for some patients at certain points in their life and they want to delay it because of neurocognitive decline, fertility, remaining in work, ability to drive.

Management of low-grade gliomas is an area of ongoing debate. Blonski *et al.*, (2022) describe a paradox with respect to treatment decisions for this population: *"… concerns the paradox of proposing an intensive treatment to a population (IDH-mutated/codeleted tumor) with an a priori good prognosis (long-survival expected and lower tendency to progress to more aggressive tumors), while we know the risk of late toxicity due to RT possibly increased by the association with CT…"* (Blonski *et al.*, 2022, p.9)[14].

In the vorasidenib arm of the INDIGO study, progression events were fewer and occurred later compared to the placebo arm. Consequently, TTNI events were more often censored, as many patients' follow-up ended shortly after progression, providing less time to capture the TTNI event. Servier acknowledges this as a key uncertainty in the data and have therefore suggested that vorasidenib is a key candidate for the CDF.

As treatment with vorasidenib leads to tumour shrinkage, it is likely that patients have a smaller tumour at time of progression than at baseline. In such cases, it is

expected the decision for use of RT/Chemo can be further postponed and more options become available to patients (e.g., inoperable tumours becoming operable or total resection becoming possible when they previously were not). In such cases, it is expected for the treatment decision following progression to take even more time.

c. Please explain the reasons (and at what time points) participants in the placebo arm of INDIGO received subsequent treatments (42.9% crossed over to vorasidenib and 4.9% received subsequent anticancer therapy at the 07 March 2023 data cut), i.e., a break-down of the reasons for switching to a subsequent treatment at specific time points, e.g., percentage switching at the time point of documented progressive disease, evidence of malignant transformation, and other reasons for moving to next intervention.

Reasons for initiation of subsequent anticancer therapy in the INDIGO trial is not available. An analysis performed to assess whether patients initiated their NI before progression found a single patient who developed PD after NI. Further context for this patient can be provided on request, but details are not presented here to protect the identity of the patient.

d. Please justify how the outcome of TTNI from the placebo arm of INDIGO can be used to represent TTNI for patients in NHS clinical practice, considering that 42.9% of participants in the placebo arm of INDIGO crossed over to vorasidenib, which is not currently available in the NHS. In particular, please explain how comparative efficacy can be inferred from the data on TTNI given the post-randomised nature of the data, with cross-over permitted in the placebo arm.

In the INDIGO study, TTNI was a key secondary endpoint and was defined as the time from randomisation to the initiation of the first subsequent anticancer therapy (including vorasidenib, for patients in the placebo group who subsequently crossed over to receive vorasidenib) or death from any cause.

As of the September 6, 2022 data cut-off, out of the total cohort of 331 patients, 77 individuals received additional anticancer treatments after discontinuing their initial treatment. Specifically, within the placebo group comprising 163 patients, 58 individuals (35.6%) underwent further anticancer interventions, including crossing over to vorasidenib (52 patients out of 58 who received another treatment, 89.7%),

surgery, CT, or RT. Within the vorasidenib group consisting of 168 patients, 19 individuals (11.3%) received subsequent anticancer therapy, including surgery or RT/CT. With additional follow-up (March 2023), 103/331 individuals received additional anticancer treatments after discontinuing their initial treatment. Specifically, within the placebo group comprising 163 patients, 78 individuals (47.9%) underwent further anticancer interventions, including crossing over to vorasidenib (70 patients out of 78 who received another treatment, 89.7%), surgery, CT, or RT.

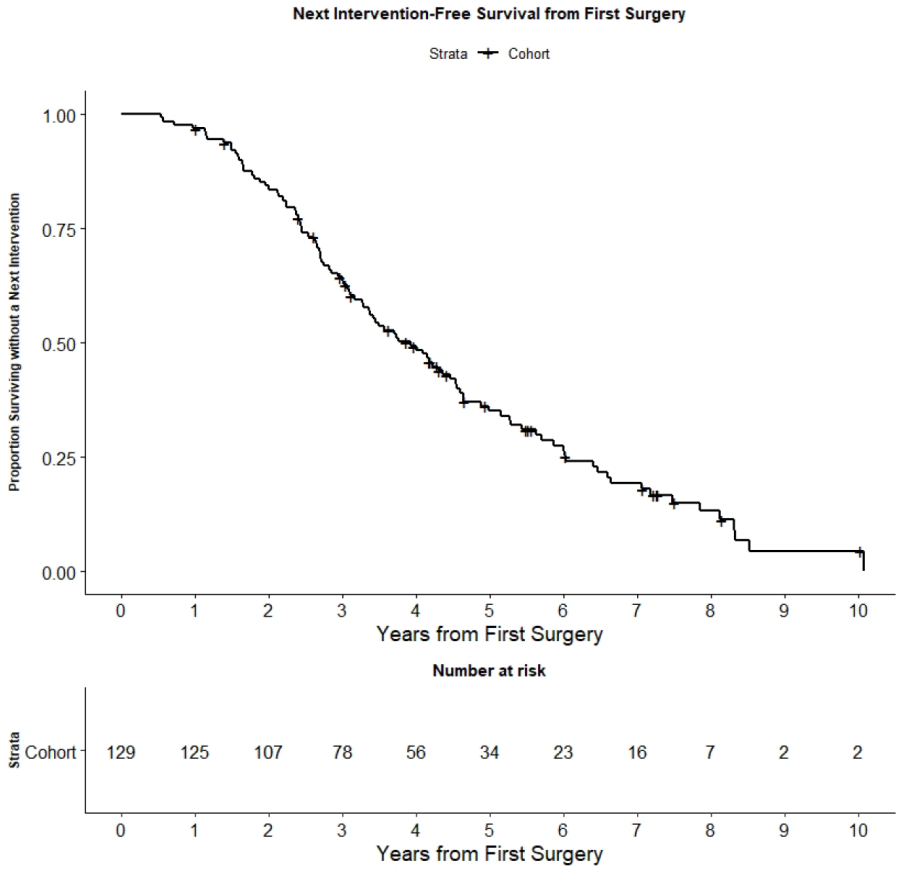
To evaluate if the option to cross over from placebo to vorasidenib impacted the conclusion of TTNI benefit observed in INDIGO trial a conservative multiple imputation (MI) method assuming the option to cross over had not been available at both the Sep-22 and March-23 DCO. In this analysis, the TTNI for the 52 subjects (and 70 in the case of the March-23 DCO) who crossed over to vorasidenib from placebo was considered as missing data and was imputed based on the time to next anti-cancer therapy for the patients who discontinued treatment for any reason in the vorasidenib arm. A summary of the MI results was generated using the second interim analysis data cutoff date (Sep-22) and showed a hazard ratio (HR) of 0.33 (95% CI: 0.19, 0.57), consistent with the TTNI results described in the AG881-C-004 CSR (0.26, 95% CI:0.15, 0.43). At the Mar-23 data cutoff date, the results (HR, 0.26; 95% CI: 0.16, 0.42) were consistent with the previously described analysis and the TTNI results described in the AG881-C-004 CSR Addendum 2 (0.25, 95% CI: 0.16, 0.40). This demonstrated that the TTNI results of patients in the placebo arm of INDIGO would have been similar, had the option to cross over not been available to patients.

In order to assess the external validity of INDIGO TTNI outcomes in NHS clinical practice, a comparison of the TTNI for the placebo arm of INDIGO with observational data relevant to NHS practice was sought after. This validation exercise presents several challenges:

- Grade 2 IDH mutant glioma represents an early stage cancer with slow progression that has documented modifications to how it is classified in 2007, 2016 and 2021, especially with the identification of IDH mutation as a key prognostic and classification factor. This means that longitudinal data linking

TTNI over a long term horizon is limited and often not appropriate for IDHmutant patients (especially since these patients have better prognosis and are likely under-represented in the older longitudinal series).

- Few studies report TTNI, Time To Treatment (TTT) or Next Intervention Free Survival (NIFS). In a systematic literature review (SLR) conducted to identify and summarize published clinical evidence from randomized controlled trials (RCTs) on the clinical efficacy, safety, and health-related quality of life (HRQoL) of treatments in patients with grade 2 or 3 diffuse glioma, with or without IDH mutations, only 3 observational studies reported TTNI after active observation:
    - Tran *et al.* 2023 [15]is a French retrospective study following 118 adult IDHmt grade 2 or 3 astrocytoma patients treated with either adjuvant therapy or a watch-and-wait approach after a first neurological resection and no prior CT or RT over a median duration of 86 months; Median time to treatment (95% CI) were respectively 4.2 (0.42–14.8) and 4.4 (0.50–18.6) years in the active observation and adjuvant therapy groups.
    - Huang *et al.* 2020[16] is a retrospective study on 230 US patients with IDHmt grade 2 or 3 gliomas (190 grade 2) who received treatment (surgery, RT and/or CT) for progressive non-enhancing glioma. Authors report that the median time between surgery and the next intervention was 36.8 months (3.06 years).
    - Bhatia *et al.* 2024[9], reported NIFS curves for a cohort of 128 adult IDHmt grade 2 astrocytoma or oligodendroglioma patients followed over a median 75.6 months in the US. Although no data was reported, a median NIFS of 3.9 years can be estimated from the curve (bottom part of figure S3 below).



Importantly, these studies reported TTNI/NIFS from the time of surgery, whereas INDIGO included patients not in immediate need of Rt/Ct one to five years after their last surgery. This implies a selection of patients who have not had a progression requiring oncologic (i.e. radiotherapy and/or chemotherapy) treatment during at least 1 year following surgery and that the follow-up of these studies begins at an earlier point in time than randomization in INDIGO, which needs to be accounted for when attempting to externally validate time to event outcomes from the trial. In the placebo arm, the mean (SD) time from last surgery for glioma to randomization was 2.60 (1.285) years.

In the INDIGO trial, at the March-23 DCO, the median TTNI in the placebo arm was 20.1 (95% CI, 17.5, 27.1) months. The table below provides a comparison of this median TTNI with the three studies reporting TTNI described before.

Source	Median TTNI (years)	Rebaselined* TTNI (years)
Tran 2023	4.4	1.8
Huang 2020	3.06	0.46
Bhatia 2024	3.9	1.3
INDIGO	1.675	NA
*Rebaselined median TTNI was obtained by subtracting the mean time from last surgery for glioma to randomization in the placebo arm of the INDIGO trial to the reported median TTNI from last surgery of the studies.		

Adjusting on the differences in studies' baseline, median TTNI from the INDIGO appears to be in line with published evidence, especially with results from Tran *et al.* and Bhatia *et al.* that report on IDHmutant glioma patients managed with active observation after surgery; whereas it appears considerably longer that the median TTNI reported by Huang *et al.*

However, it is important to note that TTNI was not an outcome of this study but rather a baseline characteristic for which limited information is available (notably percentage of missing data is not reported) and that only 101 patients out of the 230 only received surgical intervention prior to the pretreatment growth rate measurement, indicating a population with a more severe prognosis than INDIGO where patients had to have been on active observation for at least 1 year before inclusion. Furthermore, this study only included patients with a progressing disease, whereas INDIGO also included patients with residual post-operative disease.

Thus, in light of the adjusted comparison between the INDIGO TTNI outcomes versus those reported in patients with IDHmutant glioma initially managed with active observation after glioma surgery by Tran *et al.* and Bhatia *et al.*, it can be considered that the TTNI from the placebo arm of INDIGO appropriately represents TTNI for patients in NHS clinical practice.

e. Please provide details on how the outcome of time to next intervention following disease progression (TTNI|P) is derived for both the vorasidenib and placebo arms of INDIGO based on the trial outcomes of TTP and TTNI.

The data were first filtered for only those who had a TTP event in treatment period 1 – the period starting from the initiation of either vorasidenib or placebo in the first instance and ending upon initiation of next treatment (i.e., TTP events that occurred following initiation of next intervention were excluded). Progression data for these patients were then combined with their TTNI information, including both events and censors for TTNI. TTNI information differed in interpretation for patients on vorasidenib and those on placebo. For placebo patients, TTNI events included initiation of vorasidenib or a subsequent anti-cancer therapy. For vorasidenib patients, TTNI events included only initiation of next anti-cancer therapy. Therefore, the TTNI|P endpoint was derived as time between TTP event and TTNI event or

censor (TTNI event or censor date minus TTP event date). The interpretation of censoring for this endpoint was therefore the same as the TTNI endpoint.

f. Please comment on the clinical plausibility of the assumption that the average time to next intervention following disease progression (TTNI|P) is greater than the average time to progression (TTP) from initial intervention, i.e., patients remain longer in the progressive disease health state of S4 (PD and off-treatment) than in the progression-free health states of S1 (PF and on-vorasidenib) and S2 (PF and off-treatment).

g. Please clarify why patients with documented progressive disease would be treated differently in health state S4 depending on their initial intervention (median TTNI|P of ~1 year for vorasidenib and ~4 months for active observation), and present clinical evidence to support the validity of treatment effects post-progression for vorasidenib.

This response is provided for parts f. and g. above.

As vorasidenib leads to tumour shrinkage, it is likely that people will have a smaller tumour at the time of progression than they did at baseline. When this occurs, it is reasonable to expect that subsequent treatment decisions could be delayed, as the reduced tumour size may allow people to remain clinically stable for longer.

Please see responses to earlier parts of this question for further context regarding TTNI and TTP in an IDHmutant glioma population.

h. Please provide clinical evidence to justify the assumption that after 20 years, ~21% of patients with documented progressive disease remain untreated (i.e., remain in health state S4 post-progression without treatment) following vorasidenib, while ~9% remain in S4 for active observation.

The assumption that approximately 21% of patients treated with vorasidenib and 9% of patients on active observation remain in health state S4 (post-progression without treatment) after 20 years is grounded in the natural history of slow-growing gliomas and clinical patterns observed in practice.

Firstly, it is well recognised that a proportion of patients with progressive but indolent disease may not require immediate further intervention. Some tumours progress

slowly and may remain asymptomatic or stable in size for prolonged periods, particularly when located in areas where surgery is high risk or not feasible. Additionally, patient preferences play a role; some individuals may choose to defer treatment due to the risks associated with further intervention or potential impact on quality of life.

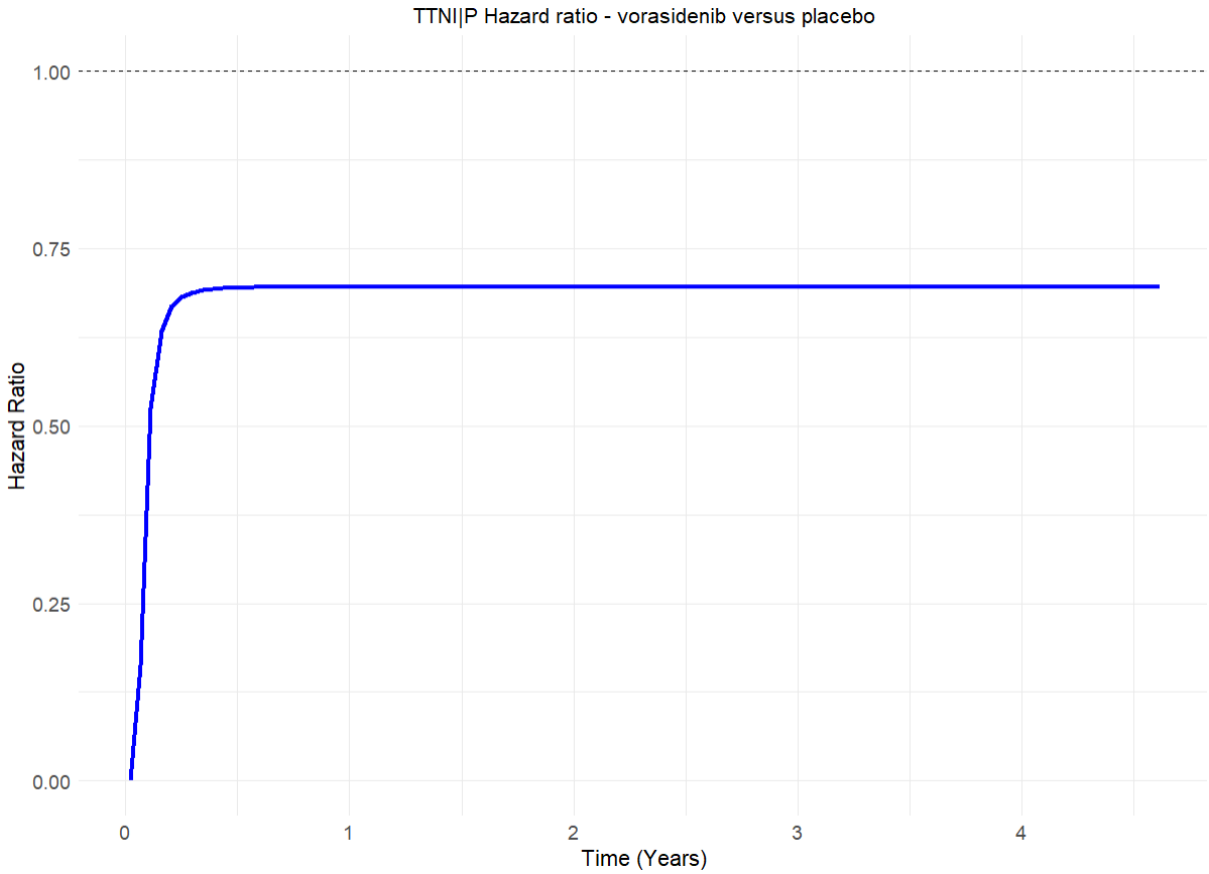
Secondly, vorasidenib is expected to achieve tumour shrinkage, which effectively 'resets' the tumour trajectory to an earlier stage of disease. As a result, when progression eventually occurs, the tumour burden may remain relatively low, and progression may be sufficiently slow that it does not immediately trigger the need for NI. For example, in cases where only a small residual tumour remains following vorasidenib, subsequent progression may not reach a threshold for active treatment for an extended period.

This rationale is supported by Bhatia *et al.*, (2023), who demonstrated a clear relationship between tumour growth and risk of next intervention or death: for each 10% increase in MRI-based tumour volume, there was only a 5% increase in the risk of initiation of NI or death (95% CI: 3%–7%)[9]. This indicates that relatively modest increases in tumour size do not always prompt immediate further treatment, especially in the context of a previously reduced tumour burden.

Taken together, these considerations support the assumption that a higher proportion of patients treated with vorasidenib would remain untreated post-progression (i.e., reside in S4) compared to those under active observation, reflecting both the impact of tumour shrinkage and the natural variability in clinical management of slowly progressing disease.

i. Please provide the implied TTNI|P hazard ratio for vorasidenib relative to active observation in the modelled extrapolations.

Given that the survival extrapolations were carried out separately for each treatment arm, proportional hazards were not assumed which limits the ability to provide a constant hazard ratio from the models directly. Presented below is a visualisation of how the hazard ratio changes over time from the generalised gamma model predictions for each treatment arm.



Based on the above, the *implied* HR for vorasidenib versus placebo predicted by the generalised gamma model for TTNI|P stabilises after around 1 year. After around 1 year, the *implied* HR stabilises at around 0.70.

j. Please provide a revised version of the model that allows a scenario analysis to be conducted that does not include differential TTNI|P curves for health state S4 by initial intervention received (i.e., same TTNI|P curve for vorasidenib and active observation), and with sufficient flexibility to switch between alternative data sources used to inform the TTNI|P curve. Please signpost the changes made to the model and present the cost-effectiveness results for a scenario analysis using the same TTNI|P curve for vorasidenib and active observation in S4 using an appropriate data source to inform the TTNI|P curve.

A scenario has been implemented in the model to consider the use of the same TTNI|P curve for both treatment arms. For this scenario, the model considers a pooled estimate of TTNI|P across both arms to inform each arm. Owing to the differences in TTNI|P across both arms, this leads to the model under-estimating TTNI for vorasidenib, and over-estimating TTNI for active observation. Servier

considers this scenario to be exploratory only – it is expected that use of vorasidenib would lead to longer TTNI versus active observation, for the reasons outlined in responses to earlier parts of this question.

To do this, additional parameters have been added onto the 'Surv_param' sheet, which can be found in cell range B248:J281. These are enabled when cell range EAG_pooled_TTNI_P on the 'Inputs' sheet is set to 'Yes'.

Adjustment for crossover

B6. PRIORITY: An exploratory analysis of TTNI with adjustment for crossover to vorasidenib in the placebo arm of INDIGO is presented on page 67 of CS.

a. Please provide a clear and detailed explanation of how multiple imputation (MI) was used for crossover subjects in this analysis, and the assumptions underlying the type of MI used.

MI was used to estimate TTNI for patients in the placebo arm who crossed over to vorasidenib, under the assumption that crossover had not occurred (i.e., to estimate what would have happened if these patients had remained on placebo). In the placebo arm, 58 patients experienced radiological disease progression, and 52 of these crossed over to vorasidenib. For these 52 patients, the time to subsequent anticancer therapy (e.g., chemotherapy, radiotherapy, surgery) was considered missing, as they switched to vorasidenib before receiving other treatments.

To impute these missing TTNI values, we used an exponential distribution fitted to data from vorasidenib patients who required subsequent therapy — specifically:

- 19 vorasidenib patients who had started additional therapy (observed events), and
- 17 vorasidenib patients censored without starting further therapy at data cut-off.

Imputation approach:

- An exponential model was fitted to estimate time from end of treatment (EOT) to next therapy, including:

- Observed and censored data from vorasidenib patients.
- Randomisation time to placebo as a covariate, to ensure balance between treatment groups.
- Using this model, missing TTNI values for 52 crossover patients were imputed, assuming a truncated exponential distribution (bounded by observed EOT-to-therapy times).
- This imputation process was repeated 50 times, generating 50 complete datasets.
- For each imputed dataset, stratified Cox regression was used to estimate the HR and CIs. KM estimates were also produced for visualisation.
- Results across imputations were combined using Rubin's rule, and estimates were transformed back from the log scale for interpretation.

Key assumptions:

- Exponential distribution for TTNI is appropriate.
- Patients who crossed over would have experienced similar TTNI as vorasidenib patients, had they not switched.
- Randomization time helps to control for differences in follow-up time and other potential confounders.

b. Please explain why MI was used rather than the inverse probability of censoring weights (IPCW) method.

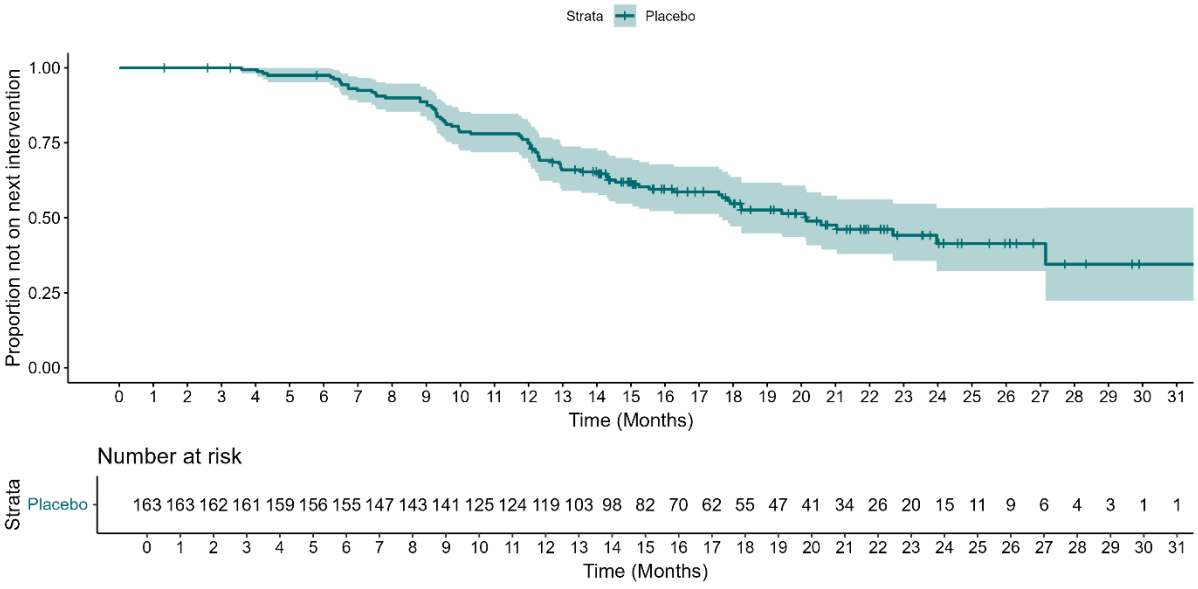
MI was used instead of IPCW because the nature of the missing data required estimation, not just reweighting. For patients who crossed over from placebo to vorasidenib, TTNI was entirely unobserved, as these patients switched before receiving any further treatment. Unlike IPCW, which adjusts for informative censoring by reweighting observed cases, MI allows us to generate plausible estimates for missing data points based on observed patterns.

In this analysis, we assumed crossover was not available, so we needed to estimate what would have happened if patients had stayed on placebo. MI, using an exponential model fitted to relevant observed data, provided a structured and consistent way to generate these estimates, reflecting real-world treatment patterns.

Additionally, IPCW would require a well-specified censoring model, which was challenging given the variability in when and why patients crossed over. MI offered a more stable and efficient approach, helping to reduce bias and improve precision in HR estimates. Nevertheless, MI remains an exploratory analysis only and should be interpreted accordingly.

c. Please provide the adjusted Kaplan-Meier TTNI curve (with numbers of patients at risk) for the placebo arm of INDIGO with crossover subjects censored from the curve, with parametric goodness of fit measures and corresponding extrapolation curves applied to the adjusted Kaplan-Meier TTNI curve (censored for crossover subjects).

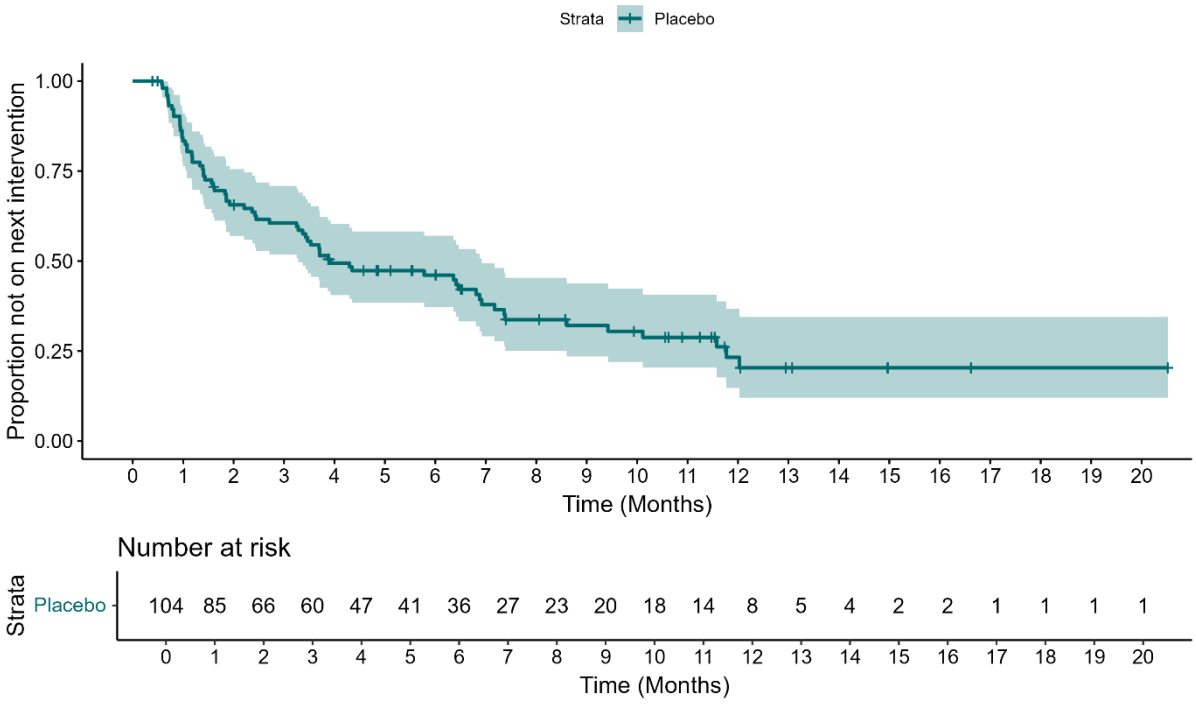
The adjusted KM curve for TTNI which censors patients for crossover is presented below.



The parametric curve parameters for this KM, along with goodness-of-fit statistics are provided in the revised model.

d. Please provide the adjusted Kaplan-Meier TTNI|P curve (i.e., time to next intervention given progression, with numbers of patients at risk) for the placebo arm of INDIGO with crossover subjects censored from the curve, with parametric goodness of fit measures and corresponding extrapolation curves applied to the adjusted Kaplan-Meier TTNI|P curve (censored for crossover subjects).

The adjusted KM curve for TTNI|P which censors patients for crossover is presented below.



The parametric curve parameters for this KM, along with goodness-of-fit statistics are provided in the revised model.

Mortality risk

B7. On p57 of CS, it states that "Once patients initiate their next intervention (NI; i.e., enter S5), they are expected to be at a higher risk of death…". It also states this in worksheet 'Introduction' of the model workbook and on p92 of CS. However, no excess mortality risk (relative to general population mortality risk) is applied in health states S5, S6 and S7. Please clarify that the only

excess mortality risk is applied to health state S8 (best supportive care) and justify this assumption.

Thank you for highlighting this – the EAG is correct, and the text on p57 of the CS is an error. The text should read as follows: *"Once patients **exhaust all lines of subsequent treatment** (i.e., enter S**8**), they are expected to be at a higher risk of death…"*

Subsequent treatment lines

B8. PRIORITY: Please explain how the post-progression studies to model outcomes associated with subsequent treatment lines were identified and selected (e.g., Baumert et al., 2016, Ma et al., 2021, Juratli et al., 2012, Kavouridis et al., 2021, Hervey Jumper et al., 2023, Bhatia 2024). Please indicate the inclusion/exclusion criteria used and provide the justification for the choice of studies selected.

Studies used to inform post-progression outcomes and model subsequent treatment lines were identified through targeted, pragmatic searches, drawing on both institutional knowledge and recommendations from clinical advisers. No formal SLR was undertaken specifically for these transitions, as such an approach was outside the scope of the original SLR performed in line with NICE guidance. Servier acknowledges the limitations of this approach but considers it an appropriate and proportionate response to the constraints of the appraisal, particularly with respect to timelines.

The targeted searches were designed to identify the most suitable sources for each transition within the post-progression pathway. This presented several challenges, as data needed to be drawn from studies that:

- Provide time-to-event data with 'time zero' at the point of therapy initiation, rather than at diagnosis or surgery, to appropriately reflect the modelled transitions.
- Include populations with disease histories comparable to the INDIGO study participants.

- Offer sufficient follow-up to estimate outcomes over a relevant time horizon, which is particularly challenging given evolving glioma classification criteria and limited long-term datasets.

B9. PRIORITY: Please comment on the comparability of the populations (e.g., in terms of age, setting, radiological characteristics, tumour size, extent of symptoms, risk of malignant transformation, time since surgery or prior treatments) used in the post-progression studies to model outcomes associated with subsequent treatment lines and their relevance to the population of INDIGO and NHS clinical practice.

[Company: please enter your answer to this question here]

The mean age between these studies was 47.8. This is comparable to both real world practice in which the mean age for glioma appears to be ~40 years old and further mimicked within the INIDGO which had a mean age of 39.8. All the tumours reported were Grade 2+ found primarily in the frontal lobe. Characteristics such as size, symptom extent, risk of malignant transformation and time since last surgery were not reported.

The clinical relevance to the NHS is difficult to quantify. There are several papers cited within the CS (such as Baumert et al., 2016, Ma et al., 2021, Juratli et al., 2012, Kavouridis et al., 2021, Hervey Jumper et al., 2023, Bhatia 2024), but none of these directly concern IDHmutant gliomas for adults not in immediate need or RT/Chemo in a UK setting. Therefore, it was felt that these papers would be more appropriate for use informing later line therapy. These papers were the only comparable published literature available due to the lack of research into the disease area with the best relevant study from a UK setting being TA23, appraised over twenty years ago. Furthermore, the fact that these studies report survival estimates baselined at beginning of therapy and not surgery, aligns with their use in the model which aims to capture key treatment-related milestones in the disease sequence.

Of note, the population demographics in INDIGO are not necessarily directly comparable to the population demographics of studies used to inform later health state transitions in the model. This is expected, owing to the relatively long periods of

time that may have elapsed since a comparable baseline could be assessed. Baseline characteristics for published studies should ideally be interpreted in the context of patients who have progressed in INDIGO, and not versus INDIGO baseline.

B10. PRIORITY: Please clarify why the histological mix of patients (both LGG and HGG) upon moving to next intervention from INDIGO is unknown. If this data is available, please provide a summary of the data and justify why it is not used in the cost-effectiveness model.

In this indication, there are two dimensions of histology which are independent at the point of initiating next intervention (1L Rt/Ct). These are i) grade of glioma, and ii) astrocytoma, 1p/19q-codeleted oligodendroglioma. Combined, this makes four groups that someone could be categorised within. All patients in INDIGO were specifically grade 2 IDHmutant glioma at baseline (i.e., a specific type of low-grade glioma), but whether patients were high-grade upon progression is difficult to establish due to the design of the trial not including grading upon initiation of next intervention, and re-grading requiring further biopsy.

It is therefore not possible to perform a statistical analysis to determine what the histological mix is likely to look like when patients arrive in S5. This means that the source by Hervey Jumper et al of 23.60% high grade at first-line treatment remains the most recent and useful source available and is used in the model (NI_surv colum CQ and its downstream calculations). However, whether patients were astrocytoma or oligodendroglioma at baseline was a randomization factor, so can potentially be used. For instance, we could:

- Take the NI events from INDIGO in the vorasidenib and SoC arms (for period 1 for SoC, such that crossover to vorasidenib would be an NI event) and produce summary statistics on histology on the date of NI event. We could then apply these counts in cells C108:D108 in NI_surv.
- Apply the histological mix at baseline in INDIGO into C108:D108 in NI_surv, though this would bias the model as they are expected to progress and subsequently initiate subsequent treatments at different rates

Both of these approaches are likely inferior to utilising the published literature data on histological mix at first-line therapy, as the sample is smaller and the study was not designed to capture histological mix upon initiating subsequent therapy. However, these values are provided below in case they are useful to the EAG.

	Vorasidenib		Placebo	
	Astrocytoma	Oligodendroglioma	Astrocytoma	Oligodendroglioma
Baseline	88 (52.4%)	80 (47.6%)	84 (51.5%)	79 (48.5%)
BIRC progression event	34 (63.0%)	20 (37.0%)	57 (54.8%)	47 (45.2%)
TTNI event	23 (82.1%)	5 (17.8%)	47 (60.3%)	31 (39.7%)

B11. PRIORITY: Please provide a clear and detailed intuitive explanation of how the pooled hazard estimates were produced for the transition probabilities from health state S7 to S8 (corresponding to the last paragraph of page 72 of CS) and from health state S8 to S9 (corresponding to the last two paragraphs of page 75 of CS) when undertaking the back transformations for histology mix.

It is not possible to back calculate histological mix upon entry to S7 given full patient history with the current model structure. Doing this would require a substantial restructuring of the model, with considerable increases in model complication. For instance, the TTE sheet would have to be expanded to include Kaplan-Meier for each histology at each line, some of which is not likely to be available (for instance, 1L Rt/Ct OS given HGG is not available, 1L Rt/Ct time to HGG given LGG at the time of initiating 1L Rt/Ct is not available, the probability of patients entering later lines and still technically being low-grade is not available, 2L+ Rt/Ct OS, PFS, TOT or TTP given LGG are all not available, subsequent treatment mixes by histology are not available). Then, the VBA would have to be substantially extended to track baseline histology and histology at each subsequent line in order to extend the column selector function for the TTE sheet. Then, the VBA would need extending to modify the selection of rows in the TTE table according to the patient's current baseline time $t(L)$ for each of those columns (for instance, to incorporate something like OS from the point of initiating 3L therapy rather than salvage therapy as a proxy for 2L+ Rt/Ct as we currently use). This would require a significant amount of effort and time, and would diminish the effort to minimize the microsimulation element of the model in the interest of transparency, useability, flexibility and potentially reliability.

Per C76:D78 of the NI_surv sheet, the histological mix used for S7 and S8 corresponds to the literature source, which is to our knowledge the only literature source available giving any indication of mix upon entering 2L+ Rt/Ct in a similar group of patients following the INDIGO baseline to later treatment lines. The use of the percentage values for astrocytoma can be seen in columns FX:FZ in NI_surv.

The method applied to derive a weighted hazard is identical to that which is used "as standard" in cohort-level models incorporating general population mortality to adjust for the changing sex distribution over time. Similarly to the differential rates of mortality in males and females given age in the general population, the PFS, TTP and OS transition rates in Ma *et al.* differ by histology. PFS, TTP and OS transition rates also differ from each other, so the proportion of each histology remaining in each event-free population differs by endpoint over time. The method in column FX, for instance, simply takes the baseline proportion of astrocytoma and uses the corresponding asctrocytoma and oligodendroglioma OS extrapolations to derive the proportion alive with each histology as time passes. This proportion astrocytoma/oligodendroglioma can them be sued to weight the conditional probability derived from the extrapolations for either histology to produce a pooled hazard reflecting the hazard of the changing population over time. As stated earlier, this is the same method which is commonly used in partitioned survival models to adjust for changing sex distribution in cohort-level general population mortality extrapolations. To summarise the method as clearly as possible:

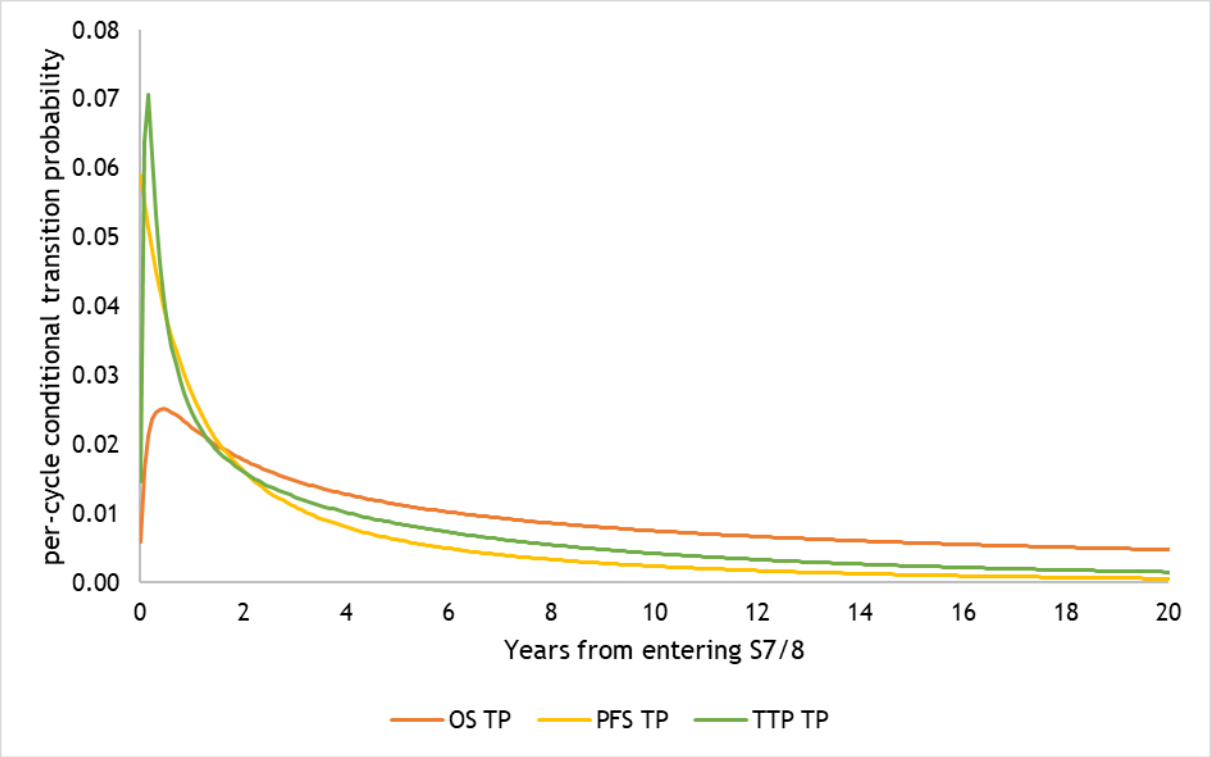
- Data used
    - FR:FT astrocytoma OS, PFS and TTP extrapolations
    - FU:FW oligodendroglioma OS, PFS and TTP extrapolations
    - D78 % of patients entering S7/8 with astrocytoma
- Calculation steps
    - FX:FZ: proportion of event-free with astrocytoma calculated

        - $pr(a)_t = \frac{(pr(a)_0 * OS(a)_t)}{(pr(a)_0 * OS(a)_t) + \left((1 - pr(a)_0) * OS(o)_t\right)}$, where a is astrocytoma, o is oligodendroglioma, 0 is baseline time, t is current time, pr is proportion, OS is overall survival. PFS and TTP utilise the same approach.
        - Plainly, OS for astrocytoma divided by the sum of OS for astrocytoma and OS for oligodendroglioma, weighted by "baseline" (i.e., entering S7/8) proportion with astrocytoma
    - GA:GC: pooled hazard (transition probability) estimate
        - $TP_t = \frac{s(t+1)}{s(t)}$ used to calculate TP_{at} and TP_{ot}, where $s(.)$ Is survival at a time point (see clarification C8 for explanation of why TP_t is calculated "looking forward" for this model's non-baseline states)
        - $TP_{pt} = (pr(a)_t * TP_{at}) + \left((1 - pr(a)_t) * TP_{ot}\right)$, where p is for pooled
        - I.e., OS lines used to estimate TP at each cycle for each histology, then weighted by estimated % in each histology for that endpoint
- Result
    - Pooled hazard for astrocytoma and oligodendroglioma for OS, PFS and TTP, which takes different transition rates and subsequent effect on histological mix over time into account

In case it assists the EAG, visualising the different absolute extrapolations and of the conditional transition probabilities over time is helpful for both the method applied to Ma et al 2021 and Baumert et al plus Juratli et al for S5 in this case. The interpretation of columns CC to CV in NI_surv is simplified through visualization. Incorporating low- and high-grade glioma to the histological mix using the proportion reported in Hervey Jumper et al. as a weighting and the median provided by Juratli et al in the base case adds another step, but the process is the same. By doing this,

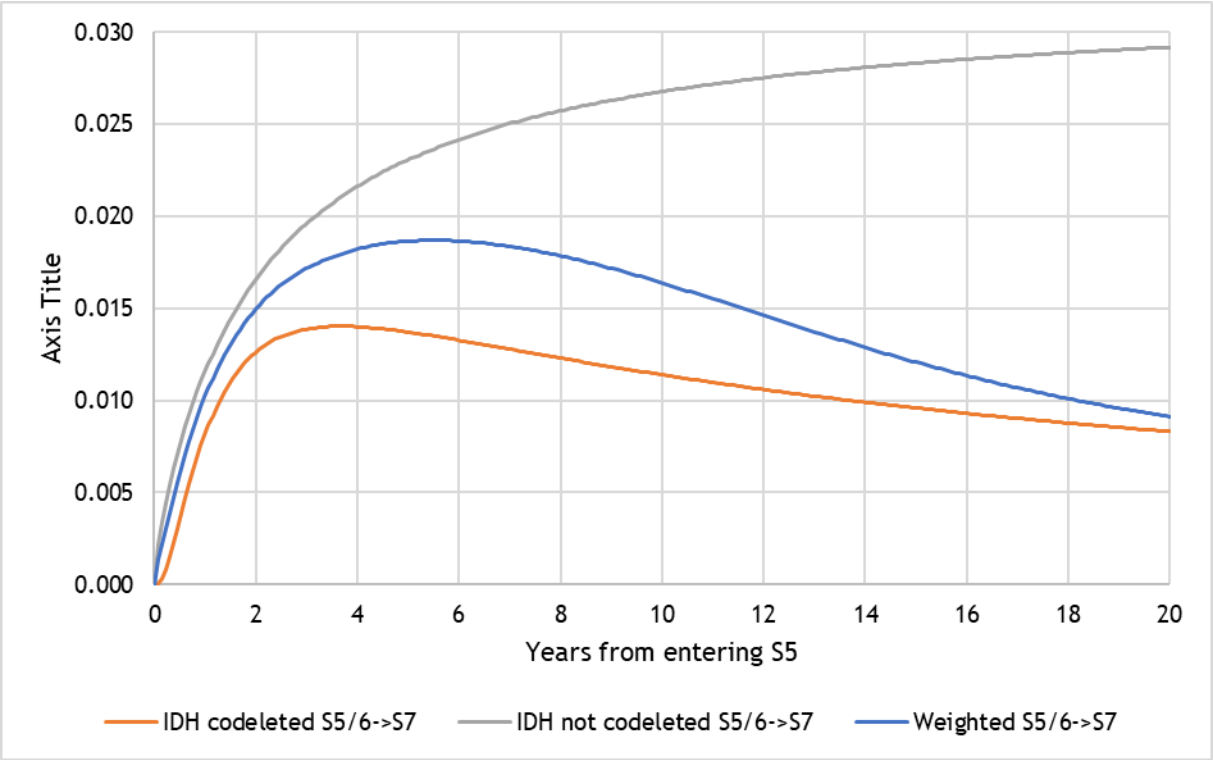
one can see the final conditional probability lies between the corresponding probabilities for different histology and tends towards the probability of the population which becomes most prevalent over time (i.e., oligodendrogliomas and/or LGG). We hope that the above helps to elucidate what is being done in this component of the model, and how that subsequently populates the corresponding TTE sheet columns.

As an example, the below shows the final transition probabilities for OS, PFS and TTE for Ma et al after weighting and accounting for changing histological mix among event free populations:

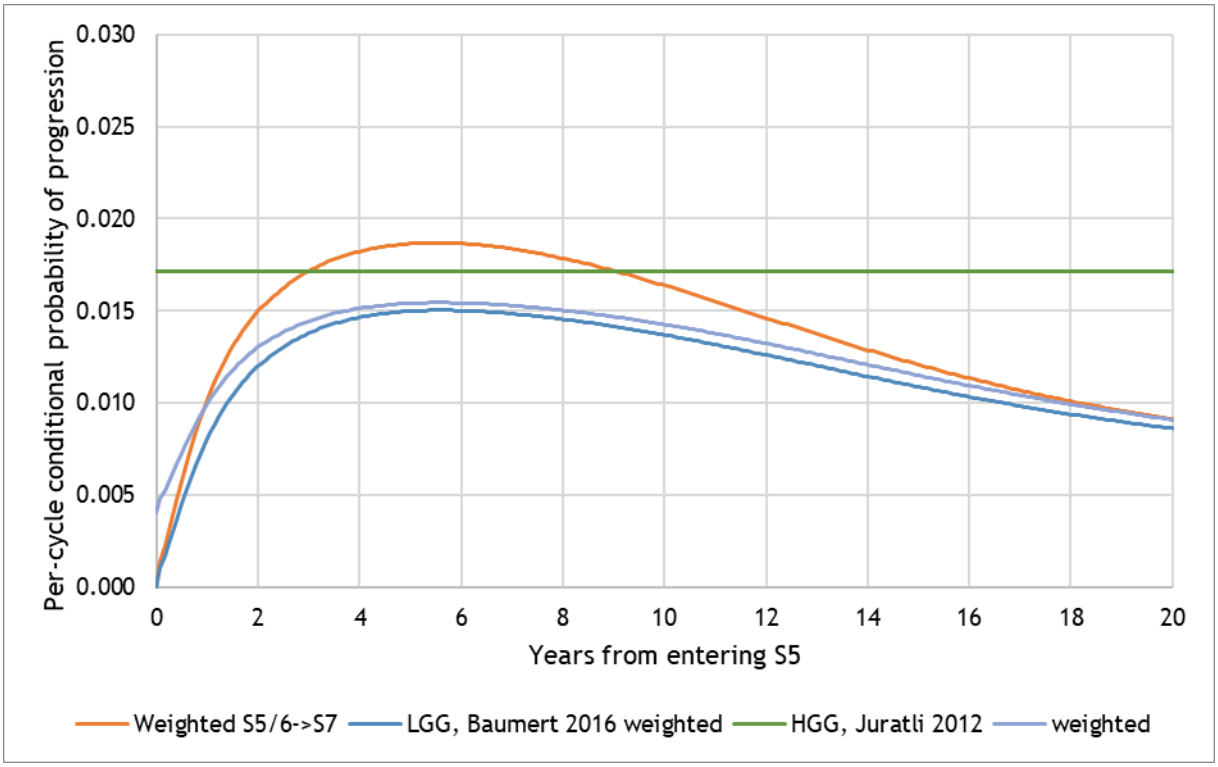


For the lengthier process of TTP in S5, the graphs are as follows:

Step 1: weighting by co-deletion status (which corresponds to astrocytoma/oligodendroglioma), does not yet account for split of LGG vs HGG upon entering S5



Step 2: re-weighting and repeating the process using high-grade vs low grade glioma (blue line in the above is the orange line in the below)



The graphical representation in our view makes the process clear. For the Baumert PFS pooled hazard, the proportion of remaining survivors tends towards 100% oligodendroglioma due to the higher progression rate in astrocytoma HGG. Consequently, the influence of HGG hazard and astrocytoma LGG hazard reduces over time and the hazard tends towards the LGG oligodendroglioma hazard.

We hope this helps to clarify the process of deriving pooled hazard estimates using the various sources incorporated to power this model.

B12. PRIORITY: Please justify the use of OS data reported in Ma et al., (2021) to inform the transition from health state S8 (best supportive care, BSC) to health state S9 (dead) given that the study by Ma et al., (2021) is based on patients who received salvage systemic therapy (defined as either alkylating chemotherapy, including temozolomide, PCV [Procarbazine, Lomustine, Vincristine] or lomustine, and non- alkylating chemotherapy, including bevacizumab, immunotherapy, biological agents or tumour-treating field), whereas BSC is defined in the model as patients who move to planned

palliative or supportive care setting upon exiting salvage therapies at 2L+. Moreover, the study by Ma et al., (2021) is used in the model to inform the transition from health state S7 (NI+) to S8 (BSC) based on salvage therapy time to progression; therefore, the transition from S8 to S9 requires post-progression OS, whereas the OS curve from Ma et al., (2021) includes pre-progression deaths.

In the Ma *et al.* paper, the TTP is similar to PFS. This can be seen by overlaying the TTP and PFS Kaplan-Meier estimates. This means that there were very few pre-progression deaths, and most death events occurred post-progression. This supposition was further supported in all clinical validation attempts. Clinical experts felt that very few patients died during active treatment lines, and most of the time deaths occur at the end of the pathway.

Secondly, the endpoint being used from Ma *et al.* for the progression transition is TTP, which censors for death events. Therefore, we do not double count deaths in S7. The Ma *et al.* study is used in the model as a proxy for BSC in the absence of any other evidence on the expected survival of patients once they cease all treatment.

The model is flexible, in that if any such evidence did become available, one would simply need to update column P in the TTE sheet (or introduce some additional downstream calculations which feed to that position) with applicable transition probabilities. For instance, if a median OS for patients following discontinuation of salvage therapy from an initial baseline of INDIGO following at least 2 subsequent therapies were available, this could be leveraged. However, we do not have access to any such information and therefore the OS from Ma et al is the only hazard we have access to.

Furthermore, it is worth noting that in line with the labelling in Cell P33 in the TTE sheet, the hazard applied uses a baseline of *either* (i.e., the first of) entering S7 or S8. This is to account for the changing shape of the hazard in Ma et al over time with respect to the underlying progression rate. It would be incorrect to “clock-reset” the OS extrapolation upon entry to S8, because at that point in the OS line all patients are progression free. Thus, to appropriately simulate the results of the study in the context of the microsimulation, the counter for the row in the TTE sheet used starts

when patients enter the first of S7 or S8. This can be seen in the following lines of code in the VB module sim05_Microsim in “case 8” i.e., when the patient is in S8:

```
' Track arrival, TiS, TP, TfE, LS


If (status <> status_lag) Then
t0(status) = cycle
c_death = tp_col(tp_lu, "BSC", 8, 9)
If (status_lag = 4) Or (status_lag = 5) Or (status_lag = 6) Then
' Patient has opted out of further treatment and come to BSC so go from start of extrap
s8_tadj_history = 0
Else
' Patient is continuing from the same salvage therapy baseline so continue time
s8_tadj_history = t_L_NIplus
End If
End If

patient_tis(t_L_bsc + 1, status) = patient_tis(t_L_bsc + 1, status) + 1

status = tr_8( _
rands(cycle, 1), _
MaxOfTwoNumbers(TP(t_L_bsc + 1 + s8_tadj_history, c_death), gpop_mort) _
)
```

In plain English, If the patient has not opted out of further treatment at an earlier line (related to status_lag), then s8_tadj_history is set equal to the time the patient spent in S7 (i.e., t_L_NIplus), and this value is added to the row selector for the death probability column (i.e., column P in TTE) with the code:

```
MaxOfTwoNumbers(TP(t_L_bsc + 1 + s8_tadj_history, c_death)
```

This means that the probability of death used each cycle for that patient continues to move down in rows from the amount of time they spent in S7. That is, the overall survival hazard applied reflects time since their baseline of entering S7.

Therefore, given that there is:

- No alternative long-term evidence on patient outcomes in later lines available to our knowledge
- Evidence from Ma *et al.* suggesting that pre-progression events are rare, even at the salvage therapy stage
- A model accounting for time since “baseline” for each individual patient, and attempting to account for histological mix using the best available evidence

We consider the modelling of excess mortality beginning at entry to S8 to be reasonable, as it reflects the best available relevant evidence for IDHmt patients, though it is plausible that this provides an optimistic estimate of OS at later stages.

By changing the values in the TTE sheet, different hazards (e.g., based on a median OS expectation from clinical experts) can easily be incorporated and tested. However, this may result in the overall survival no longer resembling the rebaselined OS KM estimate from Obara *et al.*

Health-related quality of life

B13. Please provide the baseline EQ-5D utility value by treatment arm from INDIGO.

The mean (SD) utility values at baseline using the EQ-5D-3L cross-walked algorithm as described in the submission were 0.837 (0.179) and 0.850 (0.134) for the vorasidenib and placebo arms in INDIGO respectively.

B14. Please clarify whether crossover subjects to vorasidenib in the placebo arm of INDIGO were censored from the EQ-5D utility analysis.

The EQ-5D analysis only included utility values reported in treatment period 1 of the INDIGO trial which was defined as the period between initiation of vorasidenib or placebo in the first instance and subsequent anti-cancer therapy (which included crossover for patients on placebo). This approach inherently censored EQ-5D observations once they had moved onto vorasidenib from placebo, in addition to observations for those who had moved directly onto CT/RT.

B15. Please provide a summary of EQ-5D utility values for progression status by treatment arm of INDIGO (i.e., Table 35 with PF and PD utility values reported separately for vorasidenib and placebo)

The mean (SD) of EQ-5D utility values by progression status and treatment arm from the INDIGO trial are presented in the table below. Please note that all of the observations for which utilities are presented below occurred before initiation of next treatment (following vorasidenib or placebo), at which point subsequent observations were censored.

	Vorasidenib, progression-free	Vorasidenib, progressed disease	Placebo, progression-free	Placebo, progressed disease
Number of observations	716	81	549	170
Mean utility (95% CI)	0.744 (0.731, 0.621)	0.678 (0.621, 0.735)	0.745 (0.732, 0.758)	0.730 (0.707, 0.753)
SD	0.179	0.258	0.152	0.151
Median	0.777	0.742	0.777	0.774

Abbreviations: CI, confidence interval; SD, standard deviation.

B16. Please clarify whether the EQ-5D utility values for treatment status of 'off treatment' in Table 35 refers to participants post-progression and off-treatment, i.e., patients in health state S4 of the model, or whether it also includes patients in health state S2 pre-progression and off-treatment.

The EQ-5D analysis was conducted only on observations between a patient's first initiation of vorasidenib or placebo and initiation of their next therapy (which could have been crossover to vorasidenib for the placebo arm). Any visit following initiation of subsequent therapy was then censored from the analysis.

Table 35 firstly presents the mean and median for all observations whilst patients were either progression-free or progressed, which were calculated independent of treatment status. Then, the table presents the mean and median utility value for all observations where patients were either still on treatment ('on tx') or had discontinued treatment ('off tx'), independent of progression status.

B17. PRIORITY: Please comment on the small decrement in EQ-5D utility for progressive disease compared to progression-free from INDIGO in Table 36 and contextualise this in relation to (i) the first of the NICE criteria used to support a 1.5% discount rate, i.e., "The technology is for people who would otherwise die or have a very severely impaired life", and (ii) the utility decrement for PD relative to PF from other cost-effectiveness studies in related populations.

Measuring disease progression in glioma is inherently challenging. Unlike many other cancers, where progression is clearly defined by measurable tumour growth or metastasis, gliomas often exhibit subtle and heterogeneous patterns of progression. In clinical practice, the most significant determinant of health-related quality of life (or utility) is not necessarily tumour growth itself but the decision to initiate radiotherapy and/or chemotherapy (RT/Chemo). These treatments, while essential for disease management, are toxic and have a profound impact on a person's physical and cognitive function.

Under current care in NHS practice, all patients with glioma will eventually require RT/Chemo (though they may choose to 'opt out', given the aforementioned issues with these treatments). Therefore, the key question is not whether RT/Chemo will be given, but when. Importantly, the initiation of these therapies marks a turning point in

disease trajectory. Utility declines sharply due to side effects such as fatigue, nausea, neurocognitive impairment, and functional decline. Moreover, once all treatment options have been exhausted, prognosis is extremely poor.

Given this reality, our view is that vorasidenib is indicated for people who would otherwise face death or a severely impaired life (i.e., meets criterion 1 as described in this question). By delaying the need for toxic treatment, there is a meaningful opportunity to extend the period during which patients remain relatively asymptomatic and maintain better health-related quality of life.

B18. PRIORITY: Please provide a copy of the final health state vignettes used to value the post-progression health states in the model.

Please see final health state vignettes used to value the post-progression health states in the model in the table below:

	NI	Post-NI	NI+	Post-NI+
Description of health state	You have a life-altering condition. You are currently receiving treatment because your condition has progressed (i.e., has become worse).	You have a life-altering condition. You previously received treatment because your condition had progressed (i.e., had become worse) but you are now stable.	You have a life-altering condition. You are currently receiving further treatment because your condition has progressed (i.e., has become worse).	You have a life-altering condition. You previously received treatment because your condition had progressed (i.e., had become worse) but you are now stable.
Physical functioning/Mobility	You have some difficulty with physical activity such as walking, going up or down the stairs and doing moderate exercise.	You have a little difficulty with physical activity such as walking, going up or down the stairs and doing moderate exercise.	You have quite a bit of difficulty with physical activity such as walking, going up or down the stairs and doing moderate exercise.	You have some difficulty with physical activity such as walking, going up or down the stairs and doing moderate exercise.
Pain	You get headaches some of the time.	You get headaches some of the time.	You get headaches some of the time.	You get headaches some of the time.
Seizures	You sometimes have seizures. During a seizure, you experience changes in your movements, visions, smell or hearing or you may lose awareness of your surroundings. You take medications to manage your seizures.	You sometimes have seizures. During a seizure, you experience changes in your movements, visions, smell or hearing or you may lose awareness of your surroundings. You take medications to manage your seizures.	You often have seizures. During a seizure, you experience changes in your movements, visions, smell or hearing or you may lose awareness of your surroundings. You take medications to manage your seizures.	You often have seizures. During a seizure, you experience changes in your movements, visions, smell or hearing or you may lose awareness of your surroundings. You take medications to manage your seizures.
Fatigue	You often experience fatigue and lack of energy.	You sometimes experience fatigue and lack of energy.	You often experience fatigue and lack of energy.	You sometimes experience fatigue and lack of energy.
Personality or behaviour changes	You may experience personality changes, mood changes, or reduced interest in your daily life.	You may experience personality changes, mood changes, or reduced interest in your daily life.	You may experience personality changes, mood changes, or reduced interest in your daily life.	You may experience significant personality changes, mood changes, or reduced interest in your daily life.
Cognitive impairment	You have some difficulty concentrating, making	You have some difficulty concentrating, making	You have a lot of difficulty concentrating, making	You have quite a bit of difficulty concentrating, making

	decisions, remembering information, or finding the right words in conversation.	decisions, remembering information, or finding the right words in conversation.	decisions, remembering information, or finding the right words in conversation.	decisions, remembering information, or finding the right words in conversation.
Daily activities (inc. work)	Your ability to perform daily activities (e.g., work, household chores, self-care activities, driving) is limited quite a bit of the time.	Your ability to perform daily activities (e.g., work, household chores, self-care activities, driving) is limited some of the time.	Your ability to perform daily activities (e.g., work, household chores, self-care activities, driving) is limited most of the time.	Your ability to perform daily activities (e.g., work, household chores, self-care activities, driving) is limited quite a bit of the time.
Emotional Wellbeing	You feel anxious or low in mood. You worry about your condition getting worse.	You feel anxious or low in mood. You worry about your condition getting worse.	You feel anxious or low in mood. You worry about your condition getting worse.	You feel anxious or low in mood. You worry about your condition getting worse.
Social functioning	Your condition interferes with your social activities (e.g. going out for a meal with friends and family) most of the time. This may affect your relationships with your friends, family or partner.	Your condition interferes with your social activities (e.g. going out for a meal with friends and family) some of the time. This may affect your relationships with your friends, family or partner.	Your condition interferes with your social activities (e.g. going out for a meal with friends and family) most of the time. This may affect your relationships with your friends, family or partner.	Your condition interferes with your social activities (e.g. going out for a meal with friends and family) quite a bit of the time. This may affect your relationships with your friends, family or partner.
Treatment adverse event	You may experience side effects of treatment such as itchy or red skin, hair loss vomiting/nausea, constipation, or diarrhoea.		You may experience side effects of treatment such as itchy or red skin, hair loss vomiting/nausea, constipation, or diarrhoea.	

B19. PRIORITY: Please explain how the health state vignette descriptions separated symptoms by grade of IDH mutant gliomas and type (astrocytoma, 1p/19q-codeleted oligodendroglioma).

Vignettes were designed to describe symptoms and impact associated with IDH mutant glioma and were not intended to distinguish between IDH mutant grades but rather between stages in the treatment pathway. We included published literature covering astrocytoma and oligodendroglioma tumour types to inform vignette development. In addition, we also included patients with astrocytoma or oligodendroglioma type tumours to validate the vignettes.

B20. Please explain why the health state utility values derived from the time trade-off (TTO) valuation were substantially higher than the utility values derived from the EQ-5D valuation of the vignette study.

The differences between methods may be attributed to methodological variations in the two elicitation approaches. The EQ-5D-5L required participants to evaluate health states against five specific dimensions, while the TTO method asked

participants to trade years of life against quality of life. Individual attitudes toward quantity versus quality of life can be influenced by personal beliefs and experiences. For example, previous research has shown that individuals with significant others may be less willing to trade years of life, potentially leading to higher TTO utilities[17]. Previous vignette utility studies employing both valuation methods also found TTO-derived utilities were higher than EQ-5D-derived utilities[18–20].

B21. PRIORITY: Please provide a clear and detailed explanation of how the utility values derived from the EQ-5D valuation of the vignette study (reported in Tables 3 and 4 of reference 87 of CS) were used to derive the base case utility values reported in Table 37 of CS.

In Table 3 of reference 87 of the CS, EQ-5D values are presented as follows:

- NI: 0.40 (0.18)
- Post NI: 0.56 (0.13)
- NI+: 0.26 (0.21)
- Post NI+: 0.42 (0.15)

These utility values were applied for states S5, S6, S7, and S8; in the order detailed above. However, it was considered implausible for utility to increase, decrease, then increase again as patients transitioned from S5 through to S8 via both S6 and S7. Therefore, in the base-case analysis, a simple average of the utility values for NI and NI+ was applied:

- Utility value for S5 and S6: $\frac{0.40+0.56}{2} = 0.48$
- Utility value for S7 and S8: $\frac{0.26+0.42}{2} = 0.34$

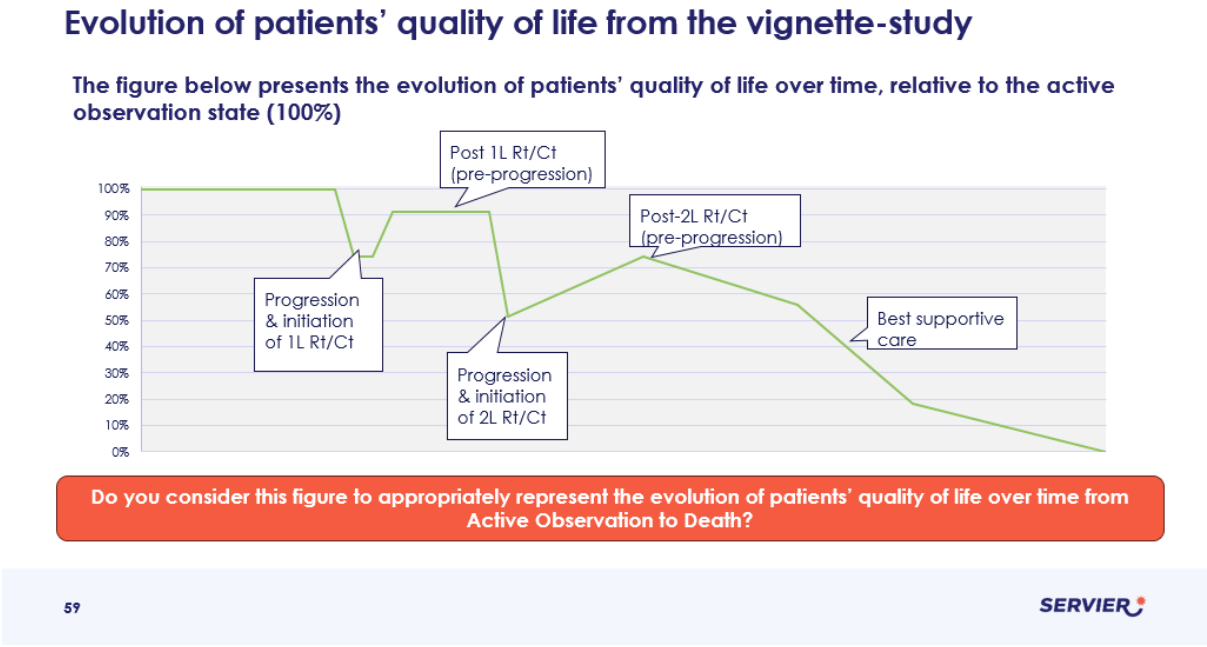
These values are then presented in Table 37 of the CS.

B22. PRIORITY: Please justify the assumption that the utility values for next intervention (NI) and post next intervention (NI+) in Table 37 of CS are the same for on- and off-treatment, i.e., please justify the use of the same utility

values in health states S5 and S6, and the same utility values in health states S7 and S8.

Health state utility values at later lines of treatment are expected to be low, but there is very limited data available, hence why a vignette study was conducted. The outputs of the vignette study were applied in the model in a simple and transparent manner, while also acknowledging face validity concerns raised by clinicians consulted by Servier. Clinician feedback on the relative utility values across these health states highlighted issues with the raw vignette outputs, which led to the decision to apply the same utility values for S5 and S6, as well as S7 and S8. Alternative approaches can be explored in the model as sensitivity analyses, though Servier considered the base-case approach to be the most appropriate way of applying the vignette study utility values in the model.

With respect to the clinical expert input sought, the Servier global team discussed the visual below to understand their views of how health-related quality of life changes over time:



The experts highlighted that patients' quality of life typically worsen during and after treatment due to their toxicities and that most don't recover their baseline quality of life after treatment. Instead, the quality of life tends to continuously declines over time, with spikes at each progression, especially driven by neurologic toxicity.

Experts considered that the quality-of-life trajectory presented was too optimistic and does not fully align with patients' quality of life over the course of the disease. Importantly, they noted that treatments rarely lead to significant improvements in quality of life as they are accompanied by neurological toxicities, fatigue, and nausea. After treatment, patients often experience sequelae that can impair their quality of life.

Thus, experts recommended to account for a constant drop in quality of life after progression, with patients never fully recovering and continuing to deteriorate over time to appropriately depict the enduring and progressive nature of the decline in quality of life after progression. In particular, the full recovery in quality of life translated into utilities from the vignette study after the 1st line of Rt/Ct was considered as unrealistic.

Patients with large tumours may constitute an exception with treatments potentially improving patients' quality of life due to tumour shrinkage.

B23. PRIORITY: Please comment on the plausibility of the very low utility values derived for health states S5 to S7 considering there is no excess mortality from these health states and compare the utility values to those from other studies in related populations.

Low utility values do not necessarily equate to poor survival while people receive active treatment. This reflects the key trade-off patients face when choosing RT/chemo versus 'opting out' of any further treatment – i.e., people may accept a lower quality of life during treatment in exchange for potential survival benefits. The base-case approach recognises this distinction while ensuring the utility values align with clinical expectations.

The utilities used in the CEM are based on INDIGO and a a vignette study that was the first study to elicit health state utilities for IDHmt glioma across the full clinical pathway starting from an active observation phase describing patient populations following initial tumour resection through to palliative care. In a longitudinal study by Drewes *et al*,[21] individuals with LGG had a median EQ-5D-3L utility of 0.78 at 6-months post-surgery, which is similar to the utility value of patients at baseline in the

placebo arm in the INDIGO trial (0.85) representing the active observation health state following initial surgical resection.

Recently, Bhanja *et al*[22]. conducted a vignette-based valuation study using TTO to elicit utilities associated with LGG. Vignettes of health states corresponding to patients with stable LGG and progressive LGG were developed, and utilities were valued by healthy, adult participants surveyed through an online form. Utilities were obtained using both VAS and TTO approaches.

Compared to progressive LGG, stable LGG was associated with significantly higher utility values in both VAS and TTO ($p<0.0001$). Stable LGG associated with different conditions, such as motor and language deficits led to significantly lower utility values compared to the overall stable LGG state, whereas the differences were not significant for progressive LGG [progressive LGG vs progressive LGG and motor ($p=0.73$), language ($p=0.6$) or visual deficits ($p=0.6$)]. Similarly, the VAS-based utility values for stable LGG with RT/CT therapy were reportedly significantly lower than for stable LGG with CT alone despite having the same reported mean value ($p=0.018$; 0.43 [0.23] for both; possible reporting error).

Their reported utility value for stable LGG with chemoradiation (0.32) was lower compared to the value for treatment with first-time RT/CT (0.63) estimated in our study. These differences may arise due to variations in the definitions of the population, health states and the content of the vignettes, and derivation of the utilities, which may mean the results are not directly comparable. However, they did not assess the utilities for health states beyond progressive LGG.

Health State	VAS score, mean (SD)	p-value	TTO score, mean (SD)	p-value
Patients with stable LGG	0.64 (0.21)	<0.0001	0.54 (0.42)	<0.0001
Patients with progressive LGG	0.44 (0.26)	NA	0.36 (0.37)	NA
Patients with stable LGG who received RT/CT	0.43 (0.23)	<0.0001	0.32 (0.34)	<0.0001
Patients with stable LGG with motor deficit	0.45 (0.23)	<0.0001	0.23 (0.32)	<0.0001
Patients with stable LGG with language deficit	0.52 (0.22)	<0.0001	0.43 (0.4)	0.04
Patients with progressive LGG with motor deficit	0.43 (0.23)	0.69	0.32 (0.34)	0.73

Patients with progressive LGG with language deficit	0.43 (0.23)	0.62	0.32 (0.34)	0.6
Patients with progressive LGG with visual deficit	0.43 (0.23)	0.78	0.32 (0.34)	0.6
Patients with stable LGG who received CT alone	0.43 (0.23)	0.018	0.32 (0.34)	0.28

In order to assess how utility values at later stages of the disease compare with related indications, a targeted search of utilities available for patients with glioblastoma was performed. Few utility values are available in the indication. A comprehensive review of the published literature regarding health utility values in GBM patients performed by Proescholdt *et al.* in 2018,[23] only retrieved 3 relevant publications. All three publications used utilities for GBM derived from the same source that published health economic evaluations for GBM by Garside et al. through the standard gamble method in 36 healthy panel members of the UK National Health System, while no published utilities for GBM were based on a general population sample.

In the aforementioned study, Garside *et al*[24]*.* Reported utility values ranging from 0.887 to 0.731 for stable disease and progressive disease, respectively. Because the scope of these utility values was limited to the peri-surgical setting, cost-effectiveness analyses by Waschke *et al*[25]*.* and Kovic *et al*[26]*.* that both used the values from Garside, applied a utility decrease of 0.02 QALYs per consecutive month of progression (-0.24 per year) to the 0.731 utility of progressive disease, implying that patients with a progressive disease were associated with utility values as low as 0.491 and 0.251 after 1- and 2-years post-progression.

In a study conducted in Norway and published in 2011 including 67 patients with glioblastoma, Jakola et al.[27] evaluated HRQOL deterioration after surgery using EQ-5D valued from a UK population perspective. Authors reported that the mean preoperative EQ-5D index was 0.67 compared to 0.62 postoperatively. The mean

decline of -0.05 (95% CI -0.15–0.05) was non-significant (p= 0.285) although there was a wide range in the difference (-0.96 to +0.87) after surgery.

Resource use and costs

B24. Please justify how data on market share at subsequent treatment lines from France is relevant to NHS clinical practice (noting that reference 93 of CS is a report in the French language, which has not been translated).

Although the data on market share at subsequent treatment lines are derived from a French source, we consider these data to be relevant and applicable to NHS clinical practice for several reasons.

Firstly, the treatment landscape for glioma is extremely limited in both France and the UK. There are only three main treatment options available: radiotherapy (which is typically used once, but can occasionally be re-used), and chemotherapy, where only two regimens are recommended in guidelines: (i) PCV, and (ii) temozolomide (TMZ). These constraints mean that clinical practice patterns are somewhat determined by the same limited set of options in both countries.

Secondly, bevacizumab, although not formally approved for glioma/glioblastoma in France, is often used at later stages in high-grade disease for symptom control, based on evidence from glioblastoma studies. This practice is also observed in the UK. Thus, the way clinicians in both countries approach later-line treatments, particularly for symptom management, is expected to be similar.

Given these similarities in available treatments and clinical management approaches, Servier considers the French data to be a reasonable proxy for UK clinical practice in this context, especially in the absence of detailed UK-specific data on treatment patterns at later lines.

B25. Please comment on whether the resource use assumptions were subject to external clinical validation. If so, please provide a detailed report of the findings from the expert clinical validation.

Resource use assumptions were subject to clinical validation at the global level, including 1 UK expert. Findings were as follows:

Distinction must be made between partial and generalized seizures with regards to resource utilization related to these events. Furthermore, these events have significant secondary impacts on daily life activities due to loss of driving licenses and impaired ability to work.

- Partial seizures are easily managed by patients, while tonic-clonic seizures can require hospitalization.
- The seizure rates from INDIGO reflect all types of seizures noticed and reported by patients. Therefore, although, all were noticeable event, affecting the patients, it was considered only a minority would lead to actual resource use.
- Radiotherapy can also induce seizures independently from tumor activity.
- Considered that 1 out of ten of all seizures would lead to a NHS resource use (GP consultation, ER visit or hospitalization) and 1 out of 20 would lead to a hospitalization.
- Seizures also have consequences to patients' activities of daily living such as loss of driving licenses and impaired ability to work. Patients may need to stop working, work less or face difficulties commuting to work, which should be considered when evaluating the consequences of seizures.

Seizure management

	Vorasidenib/Active Observation				Progressed Disease				1L Rt/Ct			
	(S1 & S2)				(S3 & S4)				(S5)			
	AA (PT)	MVV (SP)	BH (DK)	CMB (UK)	AA (PT)	MVV (SP)	BH (DK)	CMB (UK)	AA (PT)	MVV (SP)	BH (DK)	CMB (UK)
For 10 seizures, how many are **generalized** seizures ?	3	2.5	0.5	1	4	3.5	1.5	2	3	3.5	1.5	1
Comments	AA: Correct term for "generalized seizure" is "bilateral tonic-clonic seizure". CMB: Generalized seizures are uncommon in LGG patients, who typically experience.											

	partial seizures if on proper medication; self-management is encouraged to reduce hospital visits.											
For 10 **generalized** seizures, how many are leading to emergency room visit / outpatient consultation (GM, specialist)?	10	8	9	5	10	8	9	6	10	8	9	6
For 10 **generalized** seizures, how many are leading to emergency hospitalization	3	4	5	2	4	4	5	3	4	4	7	3
Comments	AA: Hospitalization probability after "generalized" seizures depends on multiple factors, not just the therapeutic line. However, it is true that patients with longer illness often have greater disability and harder-to-control epilepsy, leading to more frequent hospitalizations. BH: If the patient has come to the ER they mostly have at least one night/day of hospit.											
Other resources used when seizures occur?	AA: Laboratory and other diagnostic tests (EEG, Brain CT / MRI); Increase in the number of anti-epileptic drugs, and other medications (ex: steroids); Sick leave from work and other indirect costs; Restriction of driving. MVV: medication will increase and often a second drug is added; patients might become not able to work, because they cannot drive. BH: Often work and driving license issues. If they lose their driving license it often affects their work and social life. CMB: Telephone calls to clinical nurse specialists.											
For **non-generalized** seizures, are there any medical resource use to consider? If so, can you estimate their frequency?	AA: "Focal" seizures are more frequent than "generalized" ones and increase with progression, improving with oncological treatment. Prolonged "focal" seizures (status epilepticus) significantly impact quality of life and may require hospitalization, especially during disease progression. Same medical resources as above, but much less likely to lead to emergency room visits or hospitalization, or sick leave. Only 20-30% will lead to the patients to the emergency room, and less than 10% patients need hospitalization. MVV: Patients still use emergency resources in 20-30% of partial seizures. Not usually hospitalization. BH: Outpatient consultations due to measuring of effect of medical treatment. For example, one-twice a months CMB: Telephone calls to clinical nurse specialists and additional clinic appointments if seizures are not controlled. For every 10 non-generalised seizures, say 3 additional clinic visits.											
Clinic Visits (CMB) / Consultations (BH)	-	-	2	3	-	-	2	3	-	-	2	3
ER (MVVV & AA)	2.5	2.5	-	-	2.5	2.5	-	-	2.5	2.5	-	-
Hospitalization (AA)	0.5	-	-	-	1	-	-	-	1	-	-	-

	Post-1L Rt/Ct				2LRt/Ct				Post-2L Rt/Ct			
	(S6)				(S7)				(S8)			
	AA (PT)	MV V (SP)	BH (DK)	CM B (UK)	AA (PT)	MV V (SP)	BH (DK)	CM B (UK)	AA (PT)	MV V (SP)	BH (DK)	CM B (UK)
For 10 seizures, how many are **generalized** seizures ?	4	4.5	0.5	1	4	4.5	1.5	2	4	4.5	1.5	2

For 10 **generalized** seizures, how many are leading to emergency room visit / outpatient consultation (GM, specialist)?	10	8	9	4	10	8	9	5	10	8	9	6
For 10 **generalized** seizures, how many are leading to emergency hospitalization	5	4	7	2	5	4	7	2	5	4	7	3
Other resources used when seizures occur?	See above											
For **non-generalized** seizures, are there any medical resource use to consider? If so, can you estimate their frequency?	See Above											
Clinic Visits (CMB) / Consultations (BH)	-	-	2	3	-	-	2	3	-	-	2	3
ER (MVV & AA)	2.5	2.5	-	-	2.5	2.5	-	-	2.5	2.5	-	-
Hospitalization (AA)	1	-	-	-	1	-	-	-	1	-	-	-

Additional comments:

- Highlighting the total number of seizures relative to disease progression is more useful than comparing "generalized" to "focal" seizures.
- Seizure frequency is influenced by factors beyond tumour behaviour, including management of anti-seizure meds, adherence, and external factors like stress and lack of sleep.

Debulking surgeries

	Vorasidenib/Active Observation				Progressed Disease				1L Rt/Ct			
	(S1 & S2)				(S3 & S4)				(S5)			
	AA (PT)	MVV (SP)	BH (DK)	CMB (UK)	AA (PT)	MVV (SP)	BH (DK)	CMB (UK)	AA (PT)	MVV (SP)	BH (DK)	CMB (UK)
For 10 patients how many will receive a debulking surgery while in this state?									7	7	8	0*

Comments (S5):	AA: Occurred immediately before RT or after a surveillance period, after evidence of progression estimating how many patients had at least one debulking surgery before treatment versus just a biopsy. BH: None, since they are in chemotherapy. A more relevant question would be have many received debulking surgery before 1L Rt/Ct and that would be around 7-9/10 CMB: We would exhaust the surgical options first, before looking to vora. If they have progressed following RT and chemo, re-operating is not common because one is then in a very palliative situation. *Figures from AA, MVV and BH should be interpreted similarly as "how many patients receive (a) re-surgery(ies) before initiating 1st line of Rt/Ct, whereas CMB reported on the number of patients who would receive (a) re-surgery(ies) during the course of 1st line Rt/Ct, in line with BH comment that no patient would receive surgery during Rt/Ct.											
For those patients who received surgery, how many surgeries would they receive while in this state on average?									1	1	1	N/A

	Post-1L Rt/Ct				2LRt/Ct				Post-2L Rt/Ct			
	(S6)				(S7)				(S8)			
	AA (PT)	MVV (SP)	BH (DK)	CMB (UK)	AA (PT)	MVV (SP)	BH (DK)	CMB (UK)	AA (PT)	MVV (SP)	BH (DK)	CMB (UK)
For 10 patients how many will receive a debulking surgery while in this state?	0	2	0	3	3	2	5	0	1	0	2	3
For those patients who received surgery, how many surgeries would they receive while in this state on average?	0	1	0	2	1	1	1.5	N/A	0	0	2	2

Additional comments:

- CMB: The answers to all of the columns are so individualised and patient-specific. In most cases, Vora & Rt/Ct positioning is after two lines of surgeries typically, when a third would often be incomplete.

B26. Please comment on the relevance of the Dutch study by Boele et al., (2020), which is used to inform medical resource use, to NHS clinical practice.

The Dutch study by Boele et al is used to inform MRUs in an NHS setting due to the lack of other available published literature. The next appropriate literature in a UK setting would be from the start of the century in TA23 which the company thought would be too outdated for use now and so unapplicable. Whilst the Boele study is not

in an English setting, it has more recent/contains updated guidance on the use of medical resources when treating adult patients with glioma. The Boele study is also going to be asked to be validated at the advisory board with clinicians on the 24th of March with a detailed report able to send to the EAG following completion of this exercise. It should be noted that the final report from this advisory board may be finalised after the EAR response window.

Section C: Textual clarification and additional points

Literature Searching

C1. Please provide all search strategies used to identify non-randomized clinical trials and real-world/observational studies for the targeted literature review referred to on page 22, Section 3.1.1.4 of Appendix B.

Provided as attachment.

C2. Please provide the search strategies/list of keywords/browsing techniques used to search Conference Proceedings and HTA submissions reported on pages 119-120, Section 3.1.2.2, Appendix E.

All listed conference proceedings and HTA agency websites were searched using the keyword “glioma” or “IDH”. The search results from all sources were reviewed based on the pre-specified eligibility criteria. For conference proceedings, abstracts or posters published from 2020 to June 2024 were assessed for inclusion. HTA submissions retrieved in the search were reviewed for relevant publications reporting studies of interest. The full report is provided as an attachment.

C3. Please provide the search strategies for the Cost-Effectiveness Analysis Registry, EconLit and EconPapers referred to on page 120 of Appendix E.

The full report is provided as an attachment. The keywords used to search the databases were “glioma”, “brain tumor”, “brain tumour”, “glioblastoma”, or “brain cancer”. No date restriction was used across the databases. None of the articles identified from these databases met the eligibility criteria (see table below).

Database	Keywords	Number of hits	Relevant articles
EconLit	“glioma”, “brain tumor”, “brain tumour”,	22 hits	None

	"glioblastoma", or "brain cancer"		
Cost-Effectiveness Analysis Registry	Glioma	9 hits	None
EconPapers	Glioma	382 hits	None

C4. Please explain what publication types are removed by the following:

a. line 38, on page 109, Appendix B (Search strategy for clinical-effectiveness studies, Embase and MEDLINE via Embase.com).

This line excludes conference abstracts, reviews, letters, note, editorial, surveys, chapters, books. The line restricts the citations to ones indexed as peer-reviewed articles.

b. line 41, on page 122, Appendix E (Search strategy for cost-effectiveness studies, Embase and MEDLINE via Embase.com).

This line excludes conference abstracts, reviews, letters, note, editorial, surveys, chapters, books. The line restricts the citations to ones indexed as peer-reviewed articles.

c. line 34, on page 133, Appendix F (Search strategy for HRQoL studies, Embase and MEDLINE via Embase.com).

This line excludes conference abstracts, reviews, letters, note, editorial, surveys, chapters, books. The line restricts the citations to ones indexed as peer-reviewed articles.

C5. Please provide details of how google scholar was searched, providing any search strings used as referred to in the following appendices:

a. page 25, Section 3.1.2.2, Appendix B, clinical effectiveness searches.

Different keywords were used to identify citations in Google Scholar. The keywords used for the clinical SLR were "glioma AND (rct OR trial OR study)", "IDH-mutant AND (rct OR trial OR study)", "'isocitrate dehydrogenase 1' OR 'isocitrate dehydrogenase 2' OR 'idh' OR 'isocitrate dehydrogenase' OR 'idh-' OR 'idh1' OR 'idh2' AND glioma", "idh2 AND glioma", "glioma AND chemotherapy", "glioma AND radiotherapy", "glioma OR id mutation OR quality of life AND trial". For each search, the articles were filtered by year and up to 50 citations were screened.

b. page 120, Appendix E, cost-effectiveness searches.

Different keywords were used to identify citations in Google Scholar. The keywords used for the economic SLR were "'low grade glioma' AND cost", "economic evaluation of low-grade glioma", "'low grade glioma' AND hospitalization". For each search, the articles were filtered by year and up to 50 citations were screened.

c. page 131, Appendix F, HRQoL searches.

Different keywords were used to identify citations in Google Scholar. The keywords used for the HRQoL SLR were "glioma AND quality of life", "glioma AND utility". For the search, the articles were filtered by year and up to 50 citations were screened.

C6. Please provide the search strategies/list of keywords/browsing techniques used to search Conference Proceedings, HTA submissions, Clinical trial registries and Key organizations for glioma reported on:

a. pages 23-25, Section 3.1.2.2, Appendix B, clinical effectiveness searches.

All conference proceedings, HTA submissions, clinical trial registries, and key organizations were searched using the keywords "glioma" or "IDH". The search results from all sources were reviewed based on the pre-specified eligibility criteria. For conference proceedings, abstracts or posters published from 2020 to June 2024 were assessed for inclusion. Key organisation websites were searched to identify any documents which included any references for relevant studies of interest. HTA submissions retrieved in the search were reviewed for relevant publications reporting studies of interest. Clinical trial registries were reviewed for any ongoing or completed trials that matched the population, intervention, comparators, and outcomes of interest.

b. pages 130-131, Appendix F, HRQoL searches.

All conference proceedings, HTA submissions, and key organizations were searched using the keywords "glioma" or "IDH". The search results from all sources were reviewed based on the pre-specified eligibility criteria. For conference proceedings, abstracts or posters published in from 2020 to June 2024 were assessed for inclusion. Key organisation websites were searched to identify any documents which included any references for relevant studies of interest. HTA submissions retrieved in the search were reviewed for relevant publications reporting studies of interest.

Additional points

C7. PRIORITY. The tables and figure links (listed on p127-140) in the CS do not link to any tables or figures – please provide the tables and figures.

The page numbers referenced in the question above refer to Appendices E and F. Servier has reviewed these again, and no missing tables or figures have been identified. Starting on page 127, figures and tables are as follows:

- Page 127: Figure 42: PRISMA flow diagram – economic SLR update
- Page 128: Table 58: List of included studies – economic + reference to this table
- Page 135: reference to Table 59
- Page 136: Table 59: Eligibility criteria for the quality of life SLR
- Page 137: references to Figures 43 and 44
- Page 138: Figure 43: PRISMA flow diagram – original HRQoL SLR
- Page 139: Figure 44: PRISMA flow diagram – HRQoL SLR update
- Page 140: Table 60: List of included studies – HRQoL SLR + reference to Table 60.

We hope this response clarifies, but if there are any other missing tables and figures, please advise and we will address accordingly.

Model workbook

C8. PRIORITY. Please clarify why the time period/ model cycle referencing for the calculation of transition probabilities is different in columns GA7:GD789 in the "NI_surv" worksheet compared to CI7:CK789 in the same worksheet and also in the calculations for transition probabilities in columns V14:AF795 in the "Surv" worksheet. For example, in the "NI_surv" worksheet, cell GA8 calculates the transition probability for cycle 1 as: 1-(OS in Cycle 1 / OS in Cycle 0), whereas in cell CI8, the calculation for the transition probability for

cycle 1 is calculated as: 1-(PFS in Cycle 2 / PFS in Cycle 1) and in the "Surv" worksheet, cell AA8 calculates the transition probability for cycle 1 as: 1-(TTNIP in Cycle 2 / TTNIP in Cycle 1).

The EAG has correctly highlighted a small error, the correction of which reduces the ICER slightly.

The use of $TP_t = \frac{s(t)}{s(t-1)}$ or $TP_t = \frac{s(t+1)}{s(t)}$ should be consistent to avoid confusion, though it has no practical implications. Usually, $TP_t = \frac{s(t)}{s(t-1)}$ is used, and this is what was initially implemented throughout the model. However, the issue with this approach is that in cycle 0, the resulting TP_t is 0 as $s(t-1)$ does not exist and a 0 is typically produced in Excel models to avoid error/NA in the first row of tables of transition probabilities. In models which do not track time from entry to subsequent lines and only track time from initial baseline for all states, this is not an issue as the transition probability associated with cycle 0 is never applied.

In the microsimulation, this is not the case. This is because patients entering a "new baseline" should then immediately be exposed to the transition probabilities at that baseline (i.e. in cycle 0 for that $t(state)$). The EAG is therefore correct to point out an inconsistency in the TTE sheet with respect to using $TP_t = \frac{s(t)}{s(t-1)}$ or $TP_t = \frac{s(t+1)}{s(t)}$. The mortality in column P (mortality in BSC), and TTP transition from Ma et al in column X use $TP_t = \frac{s(t)}{s(t-1)}$ and therefore have a 0 in the first row. The result is that in the first cycle that patients are present in state 7, their progression probability is 0% for 4 weeks, in line with column X. Similarly, when patients enter state 8, their death probability is 0% for the first 4 weeks of presence.

To demonstrate in the VBA code as simply as possible, case 8 (simulation of S8) in the microsimulation is provided in full below (the equivalent for S7 is substantially longer so the S8 case is used to demonstrate here for brevity):

```
Case 8

'~'~'~'~'~'~'~'~'~'~'~'~'~'~'~'~'~'~'~'~'~'~'~'~'~'~'~'~'~'~'~'~'~'~'~'~'~'~'~'~'~'~'~'~'~'~'~'~'~'~'~'~'~'~'~'~'~'~'~'~'~'~
    ' ~~~ STATE 8: BSC

'~'~'~'~'~'~'~'~'~'~'~'~'~'~'~'~'~'~'~'~'~'~'~'~'~'~'~'~'~'~'~'~'~'~'~'~'~'~'~'~'~'~'~'~'~'~'~'~'~'~'~'~'~'~'~'~'~'~'~'~'~'~

    Dim s8_tadj_history&
    s8_tadj_history = 0

    ' Track arrival, TiS, TP, TfE, LS
    If (status <> status_lag) Then
        t0(status) = cycle
        c_death = tp_col(tp_lu, "BSC", 8, 9)
        If (status_lag = 4) Or (status_lag = 5) Or (status_lag = 6) Then
            ' Patient has opted out of further treatment and come to BSC so go from start of extrap
            s8_tadj_history = 0
        Else
            ' Patient is continuing from the same salvage therapy baseline so continue time
            s8_tadj_history = t_L_NIplus
        End If
    End If

    patient_tis(t_L_bsc + 1, status) = patient_tis(t_L_bsc + 1, status) + 1

    status = tr_8( _
        rands(cycle, 1), _
        MaxOfTwoNumbers(TP(t_L_bsc + 1 + s8_tadj_history, c_death), gpop_mort) _
    )

    t_L_disc = t_L_disc + 1
    t_L_prog = t_L_prog + 1
    t_L_NI = t_L_NI + 1
    t_L_NIplus = t_L_NIplus + 1
    t_L_bsc = t_L_bsc + 1

    status_lag = 8
    t8 = t8 + 1
```

Note that array TP() is the entire table in the TTE sheet (named range pf_vb_TP in Excel), and the time point used in the transition function tr_8() adds 1 to the row index of TP(). t_L_bsc initially is 0, meaning that (as VBA is set to “Base 1”) the first row in the TTE sheet is used for that individual patient’s first cycle in S8.

Therefore, this is an error which can be corrected either by:

1. Shifting the values in columns P and X in the TTE sheet up by 1 row
2. Adding 2 instead of 1 in the VBA code

In the interest of consistency, we have opted for option 1. This was done by taking the formula text in e.g., NI_surv!GC8 and pasting it into NI_surv!GC7, then pasting formulas to the rest. We have added a switch in the model to turn this correction on and off to be able to reproduce the original company base case.

Making this fix reduces the ICER by between £30 and £40 compared to the original base-case, so makes little difference. The reduction in ICER is due to post-NI OS falling slightly, so the consequences of earlier progression are worsened marginally.

C9. PRIORITY. Please amend the formula in column AU of the "Surv" worksheet where in rows 14 to 795 there appears to be too many options for the CHOOSE formula (i.e., extra "0,"), which results in the microsimulation having an error if you select the option "Apply HR to…." in cell C82 of the "Inputs" worksheet.

The EAG is correct, we have tidied up this dropdown menu and corresponding CHOOSE functions.

C10. PRIORITY. Please clarify if the formula in cells AV14:AV795 (SoC: TTNIP) of the "Surv" worksheet are correct: (i) in the cell AV14 formula "…,IF($AI14=0,1,AU13*(1-(Surv!Z14*p_surv_TTNI_SoCHR" should this be referring to column AU (SoC: TTNI) or should it be referring to AV13 (SoC: TTNIP), and (ii) in cell AV14 formula "…,IF($AI14=0,1,AU13*(1-(Surv!Z14*p_surv_TTNI_SoCHR" should this be referring to "Surv!AA14" (transition probability for TTNIP from the vorasidenib arm) or "Surv!AA14" (transition probability for TTNI from the Vorasidenib arm).

Firstly, option 3 in the CHOOSE() formula is "Apply HR to INDIGO vorasidenib arm", which is not used in the base case or any model scenarios. However, the EAG is correct that the cell reference should be the cell above as the extrapolation of TTNIP should be a probability applied to $s(t-1)$. Furthermore, the EAG is correct in pointing out that the TTNIP to apply a hazard ratio to is referring to the TTNT in column Z.

To simplify, we have used the typical $s(t)^{HR}$ approach, so the HR is now applied directly to the absolute TTNI | P for the vorasidenib arm for the hazard ratio applied to vorasidenib TTNI | P scenario.

After correction, this does not affect any ICERs in the base case or any scenarios within the original set of 18 scenarios submitted. This is because such a hazard ratio was not available to us, so there was no value to apply in the model, yet in the interest of flexibility and potential future availability it is incorporated into the model. We thank the EAG for pointing out the cell reference error.

C11. PRIORITY. In the "Surv" worksheet, please clarify if AU14:AV795 are referring to the appropriate transition probabilities. When using transition

probabilities calculated in Z14:Z795, the transition probability calculated in cycle zero (Z14) is not utilised.

Fixed along with C9 and C10. Z14 now has dependents AU14 and TTE sheet T41, so are used in the line containing TP(t_L_progdist + 1, c_NI) in the VBA code sim_cohort function.

C12. PRIORITY. Please clarify whether cells T41:T822 in worksheet "TTE" should be referring to column Z (transition probability for vorasidenib arm TTNI) or column AA (transition probability for vorasidenib arm TTNIP) in worksheet "Surv". In the "TTE" worksheet cell T41, the formula reads "…Surv!AA14),MIN(Surv!$Z14*p_surv_TTNIPProg_HR,1))". Cells T34 and T40 are labelled as "TTNI|P", however, the formula option which utilises the TTNIP HR applies the TTNIP HR to the transition probability for TTNI (i.e., column Z in worksheet "Surv"). Similarly, in the same cell T41, when selecting the curve for SoC, in the HR option, the formula applies the HR to the SoC TTNI curve (column AE in the "Surv" worksheet").

There appear to be two points and/or questions embedded in this question. To ensure that we understand the EAG's question, we list these below:

1. Is it correct that column T in the TTE sheet is referring to column Z in the Surv sheet when option 3 is active?

2. Is column T in the TTE sheet labelled correctly in rows 32-40?

In summary, the answers are yes the formula is correct and yes the labelling is correct, though the labelling has to be carefully considered when reading.

To clarify – the base-case in the CHOOSE function is option 2, which does not refer to the code in question. The highlighted code is for option 3 from the named range lists_surv_TTNIProg_sources within the code CHOOSE(MATCH(surv_TTNIPProg_source,lists_surv_TTNIProg_sources,0)). In the base-case, this matches the TTNI post-progression source using the list of TTNI post-progression sources, and this returns the number 2. Option 3 is not used in the base-case or any scenarios but is present for sense checks and additional scenarios

should appropriate hazard ratios or potentially other methods become available from clinical evidence in the future.

The value of the third element in lists_surv_TTNIProg_sources is "HR applied to overall TTNI line for post-progression" (cell J19 in the Lists sheet). In other words, to apply a hazard ratio to overall INDIGO TTNI (i.e., from baseline rather than TTNI | P or TTNI | PD and a clock-reset assumption) associated with being post-progression and use that to simulate TTNI | P or TTNI | PD when running the model. As such, the application to column Z in Surv (labelled Vorasidenib TTNT, rather than TTNI, which could be amended for clarity) is correct for the vorasidenib arm and correct for column AE for the SoC arm. Named range surv_TTNIPProg_source (cell C95 in the inputs sheet) is a different assumption from the assumption associated with named range surv_TTNI_SoCSource (cell C82 in the Inputs sheet) and has different implications for the model. The two interact so should be considered together when running scenarios.

The workings of the two settings are listed below, in case this helps to further clarify:

- surv_TTNIPProg_source: global post-progression TTNI source. Options:
    - Apply a simple median (constant transition via exponential)
    - Use extrapolated TTNI (default is TTNI | P for both arms, can be TTNI | PD for vorasidenib if splitting initial event transitions)
    - Use extrapolated TTNI (i.e., without the clock-reset assumption and separate independent extrapolation like a partitioned survival model) and apply a hazard ratio associated with progression to it
- surv_TTNI_SoCSource: SoC arm specific TTNI source. Options (after updating the dropdown and formula per clarification question C9):
    - Extrapolate the TTNI or TTNI|P from the INDIGO placebo arm
    - Apply a hazard ratio to the TTNI or TTNI | P from the INDIGO vorasidenib arm to simulate INDIGO placebo arm TTNI | P

For the labelling, the EAG is correct to point out that in the scenario whereby a hazard ratio is being applied across arms for post-progression TTNI, the endpoint being used to power the model is ultimately TTNI. However, the endpoint being *simulated* remains TTNI | P or TTNI | PD (depending on whether first event is progression/death or progression/discontinuation/death per setting surv_S1exitSource). This is because when a patient is in S4, the probability of moving to S5 required is TTNI from their current baseline, which depending on surv_S1exitSource is either progression of disease or the last of progression and discontinuation. Therefore, the labelling in cell T34 remains correct in all settings, though is complicated and understandably requires some careful thought upon reading. Potentially, this could be made clearer if cell G34 in the TTE sheet were to be replaced with something along the lines of “Endpoint simulated by the model”.

Company base-case analysis

For transparency, Servier considers its revised base-case analysis to include the corrections addressed as part of Section C of this document. However, for ease of reporting (given the small impact of these edits on the ICER), Servier would be happy for the EAG to consider the original base-case ICER as the starting point for any EAG edits, including the corrections included in the model submitted alongside this response.

Following the clarification call, a simple Patient Access Scheme (PAS) discount has been proposed, of [redacted]%. In addition, as requested at clarification stage, results are presented below with the following options:

- 1.5% discounting, x1.7 severity modifier.
- 1.5% discounting, x1.2 severity modifier.

These include a PAS discount for vorasidenib of [redacted]%.

1.5% discounting, x1.7 modifier

Arm	Costs	QALYs	d(cost)	d(QALYs)	ICER
Vorasidenib	[redacted]	11.18			
Active observation	£397,496	7.76	£119,265	5.80	[redacted]

1.5% discounting, x1.2 modifier

Arm	Costs	QALYs	d(cost)	d(QALYs)	ICER
Vorasidenib	[redacted]	11.18			
Active observation	£397,496	7.76	£740,241	4.10	[redacted]

During the clarification teleconference, NICE asked the company to clarify its approach to estimating the severity modifier. To confirm, Servier used the QALY Shortfall Calculator (https://shiny.york.ac.uk/shortfall/), with the following settings:

- Age: 40 years
- Female: 44%
- Remaining QALYs of untreated (discounted): 7.76
- Discount rate: 1.5%

As noted during the call, the potential discrepancy between estimates produced by Servier and NICE is likely due to the choice of a 1.5% discount rate for calculating expected QALYs and modelled QALYs. Servier's approach was undertaken purely to align the discount rate in the model and the estimation of population QALYs. When using the settings above (i.e., 1.5% in both the model and the calculator), the criteria for a x1.7 modifier are met. However, if using a 1.5% discount rate in the model and 3.5% discount rate in the QALY Shortfall Calculator, the criteria for a x1.2 modifier are met.

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UK Cost Effectiveness Model Advisory Board Report

Virtual: MS TEAMS 24/03/2025

This is a report of the discussions from the 'UK Cost Effectiveness Model Advisory Board meeting held virtually via TEAMS, on the 25/03/2025.

The objectives of this meeting were :

1. To gain clinical expert validation on the feasibility of assumptions used to calculate outcomes of Vorasidenib in grade 2 glioma in the clinical and cost effectiveness model
   This will include parametric curve validation for long term PFS and TTNI (time to next intervention) based on modelling from the INDIGO study.

2. To assess and validate projected healthcare utilisation that would be necessary for vorasidenib, watch and wait patients, RT/Chemo that is proposed within the cost-effective model.

   - This includes:
     - Factors that affect the cost effectiveness of Vorasidenib (eg. resources required for administration of treatments, adverse event management, supportive co medication/measures that may be required, assumptions on long term treatment durations, surrogates for overall survival.)

3. To gain clinical opinion on the clinical parameters incorporated by Servier in the cost effectiveness model.

   This will include inventions used across the modelled pathway and the current treatment pathway; the median time on interventions, and the median time on best supportive care

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<u>Introduction</u>

The goal of the adboard was to discuss the appropriate modeling structures and assumptions for the cost-effectiveness model of vorasidenib in grade 2 IDH mutant glioma.

Four clinical experts for the management of grade 2 IDH mutant glioma participated to an e-meeting on Mar 25, 2025.

The adboard consisted in an e-meeting held over Microsoft Teams on Mar 24 2025. Four UK clinical experts in the management of grade 2 IDH mutant glioma patients participated.

ATTENDEES	
Servier:	Kelly Gomes (Chair and Facilitator), Leanne Hamerton (Facilitator),

Presenter:	Leanne Hamerton
Advisors:	[redacted]

Parametric extrapolations from INDIGO

PFS

- Experts noted that whilst there are differences in astros and oligos, as both were included in the INDIGO population, it was considered appropriate to model a combined population.
- It was commented by one advisor that we have modelled long term from short term gradients and we really need to consider if there is any reason why the disease trajectory would change. For example with chemotherapy treatments, there can be a sudden fall off but we have no evidence to suggest this would apply to vorasidenib. The only reason may be if this treatment promoted a subpopulation of cells that were going to grow more aggressively after but we have no real data to show that yet
- Experts focused on PFS projections in the standard of care arm and felt that at 5 years, there would be between 5-10% PFS. It is difficult to say as oligos and astros are grouped together and it would be the oligos pushing it up but generally the overall figure would be 5-10%
- The experts highlighted that the difficulty is that in real life there is only half as many oligos as astros and so the proportions may be out here as the split was equal in INDIGO. This may distort the data
- One expert then focused on the potential long tail in the untreated group which he felt exists but may not have been picked up in INDIGO. There is definitely a cohort of pts who would have a very surgically well located tumour that would give them this survival advantage.
- At 10 years the figure for PFS is going to be pretty low. Advisors suggested 2-3% as reasonable if there was a well resected oligo subset in the population, and at 20-40 years it will be closer to zero
- All advisors stated they did not feel comfortable commenting on the vorasidenib curves as there is no data currently to understand how it works at these time points

Parametric extrapolations from INDIGO

TTNI

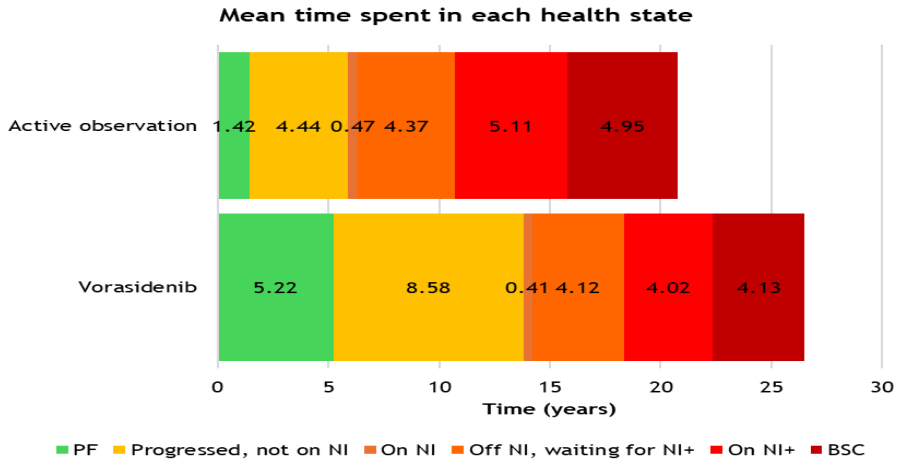
- All advisors agreed that progression on imaging wouldn't necessarily lead to the next intervention. If there has been tumour shrinkage previously or if the tumour has

been classed as slow growing, even though its progressing, this wouldn't automatically trigger the next intervention.

- These patients are more likely to enter a period of active surveillance, especially if they have been on vorasidenib previously and the tumour has shrunk from the original.
- One advisor stated that we are yet to understand if there is such a thing as pseudo progression with vorasidenib
- It was highlighted that radiotherapy is a big step in this patients journey, and there is rarely an imperative to rush. All advisors agreed that if enhancement is appearing or you have worries about transformation this would be different but not if we are talking small degrees of change
- Advisors stated that if a patient were to progress on vorasidenib, if there was no enhancement, then effectively that patient goes back to the S2 state of active surveillance
- However, there are exceptions to this if the tumour is in an eloquent area or if there is uncontrolled epilepsy, you would be more likely to move on to the next intervention
- Advisors commented that may be more likely to do surgery after progression but less likely to commence RT/CT
- Would estimate less than 1 in 10 not moving on to CT/RT at 10 years in active observation arm. In addition, there may be the odd oligo at 20 years not moved on to next intervention but not likely at 40 years. However, one advisor stated that he does have a couple but these are fairly unique patients with small frontal tumours with big resections. Overall view was they do exist
- Again, advisors felt unable to comment on this for vorasidenib as there is no data here. They commented on other targeted treatments where they stop responding and then theres "bounce back" but this is an unknown with Vorasidenib. In this situation, the pattern of natural behaviour has changed and advisors therefore felt uncomfortable projecting forward with Vorasidenib
- More data is really needed to understand what happens with growth once Vorasidenib is discontinued.

<u>Next Intervention and beyond</u>

- Experts agreed that patients on vorasidenib would spend relatively less time in later states but more time alive overall as they spend more time prior to the initiation of RT/CT. This was seen to be clinically plausible although exact numbers remain unclear. These patients are likely to be older as they come on to the later health states



- ON NI seems too short. RT would be 6 weeks, followed by 6-7 months of CT so they will actually be on treatment for 8-9 months. Even with discontinuation, the 0.41/0.47 seems too short. Average number cycles is 3-4 cycles of 6 weeks
- Off NI waiting for NI+, advisors agreed this figure was reasonable
- On NI+, 4 years is not reasonable. When they have the second line CT, it is not as effective as first line. Maybe 2-3 years if NI+ is combining on and off NI+?
- Experts confirmed that the 2021 study from Ma et al. study is an appropriate source to model the transition from S7 to S8 and mortality from S8. The study reflects typical practice at this stage of the disease and treatment and its outcomes are representative of the experts' experience with the second and subsequent lines of Rt/Ct. Experts were not aware of any other data that could be used here. However, it was suggested that some centres may have real world evidence that could be utilized but this was not available in any of the centres the advisors were working in
- 4 years very long for BSC. Expect 6-18 months or if astros maybe even lower at 3-6 months
- In terms of the figures being fairly similar in both arms from NI+ onwards, theres no obvious reason to believe why they would behave differently, although again advisors stated more data is needed to understand what happens when patients come off vorasidenib

<u>Medical Resource Use</u>

- CTs would not be done routinely. Only if patients present at A&E with a seizure generally
- Advisors reported variability in MRI's. Some would do every 3-4 months, another 3 monthly for first few months, then 6 monthly if on Vora. Another 6 monthly from the start. Another stated 4 months in the active observation arm.
- Advisors all agreed that seizure management would increase as patients move through health states and progression occurs although the resource needed for this may just be a telephone call in some instances to tweak anti seizure medication. Advisors agreed on a rate of 1-2 resource management use for seizures per month at the end of the pathway

Quality of Life

- Advisors highlighted that patients' quality of life typically worsen during and after treatment due to their toxicities and that most don't recover their baseline quality of life after treatment. Instead, the quality of life tends to continuously declines over time, with drops at each progression, especially driven by neurologic toxicity.
- Advisors noted that treatments rarely lead to significant improvements in quality of life as they are accompanied by neurological toxicities, fatigue, and nausea, and as you move through the pathway, more seizures will impact quality of life.
- However one advisor also noted that there is a cohort of patients where RT/CT reduces seizure rate and therefore improves QOL, although generally patients without seizure burden will follow a smooth declining trajectory

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Vorasidenib for treating astrocytoma or oligodendroglioma with IDH1 or IDH2 mutations after surgery in people 12 years and over [ID6407]

Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1.Your name	[redacted]
2. Name of organisation	Astro Brain Tumour Fund
3. Job title or position	Treasurer/Trustee
4a. Brief description of the organisation (including who funds it). How many members does it have?	Astro Brain Tumour Fund is a charity which raises funds for research into Low Grade Glioma (LGG) brain tumours and offers support to LGG patients and their families. We are the only charity in the UK to concentrate purely on research into LGG. We are funded entirely by supporters who carry out fundraising events and also make donations, plus we receive occasional grants from charitable trusts and also legacies. The charity has seven trustees – all volunteers – plus supporters who help with fundraising events and also organise their own. We run a closed Facebook support page for patients and their carers/families which has over 600 members worldwide and also a general Facebook page which has over 1,400 followers.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	In July 2024, Astro Brain Tumour Fund received a payment of £3,644 from Servier in respect of the charity's assistance in a project which Servier undertook titled "Diffuse Glioma Patients Experience and Pathway". Our role was helping recruit patients and their carers, plus a patient representative, for the study. The study had no relevance to this Appraisal of Vorasidenib.

4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	The charity runs a closed Facebook Support page for LGG patients and their families. Information was mainly obtained through this group plus some patients/carers who had direct contact with the charity, mainly via email**.**

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Following surgery, those patients who are placed on active monitoring receive no treatments leading to the possibility that their tumour will continue to grow with the risk of impacting eloquent areas such as speech and movement. There is also a risk that it will transform to a higher grade. Living with what some describe as a "ticking time bomb" and being aware that they are receiving no treatment to halt/delay growth or transformation in the tumour, can result in a tremendous toll on the mental well being of the patient, their carers and family. Following is one LGG patient's experience of living with the condition, for whom Vorasidenib was not available after surgery: *"I have a diffuse grade 2 astrocytoma and had aggressive surgery in May 2023. They were only able to remove 20-40% (still to be determined) and my only remaining options were radiotherapy and chemotherapy. I had hoped to be able to access Vorasidenib, but sadly this wasn't possible. I began an intense 6 week daily course of radiotherapy followed by 12 months of chemotherapy. I've been left with memory loss, reduced ability to focus and retain information, poor attention span, increased seizures, increase in infections, nausea, anxiety and low mood".* For those patients where radiotherapy and/or chemotherapy may be suggested, these harsh treatments need to be avoided if at all possible due to possible devastating side effects which are of particular significance to LGG patients as they are often young and desperate to lead 'normal' lives. Furthermore, radiotherapy can cause long term cognitive effects and necessitates daily hospital visits for a number of weeks and this, with the follow up of chemotherapy, can greatly impact on the patients' ability to fully participate in their daily life of education/work and family life, causing a great negative effect on their mental health and well-being, including feelings of isolation and desperation. It should also be noted that these treatments are not a cure - in the majority of cases, the tumour returns and then the patient really has very few if any other options. Following are the experiences of two LGG patients who are taking part in the Vorasidenib "named patient scheme" *"Living with the condition is a constant state of anxiety as you are forced to live for each day, knowing that one day, someone will most likely tell you that your time could now be limited. I have had to question several life choices since being diagnosed with the condition, such as whether to have children or not.* *Since receiving Vorasidenib, I have experienced no seizures and near to no symptoms (mild diarrhoea in the first initial weeks but that subsided) and have had a brain scan since then that came back as no change from my initial scan last year. My consultant was so happy with it that he would have been happy to go to a six monthly scan. Taking this drug has definitely helped to ease my anxiety around an incurable condition as I feel that this potentially will be able to give me the chance at a longer life".*

	"*I have a grade 2 astrocytoma. In July 2021 I underwent a craniotomy and was then placed on 'watch and wait '. It was so hard to cope knowing that the tumour would likely grow/return. I was absolutely petrified every time I felt a slight odd pain or headache. I also was so fearful when my scan was due. My anxiety levels were sky high - my mental health suffered badly. In March 2024 I was told my scan showed some growth in the tumour, resulting in my mental health plummeting further and I stopped work.* *In May 2024 I was lucky enough to be accepted on a named patient programme for Vorasidenib. Life is still very hard, but knowing I am actually receiving some treatment I have felt much more hopeful. My anxiety has improved as have my seizures. Given my age, 28 years, I feel I have a lot to give and a lot of living to do. I wish to try to avoid radio/chemo for as long as I possibly can - I have read a lot about the effects on the brain and utter disruption to day-to-day life. Life will never be the same for me but since my diagnosis this is the most 'normal' I have felt, I feel less isolated and have returned to work".* Caring for someone with the condition can be a rollercoaster of emotions. Many carers do their best to hide their emotions on a day to day basis, trying to protect the patients' wellbeing but the concern and worry is there for them at all times, affecting their ability to lead normal, fulfilling and happy lives. Following is a statement from an LGG patient regarding their caregivers' experience: *"My family, particularly my mother and my husband, experience anxiety almost all the time, sometimes quite crippling, but has absolutely left a lasting impact on both of them".* From a patient who has had surgery/chemo/radiotherapy: *"It is hard to know what to say to my children, because I don't want them to worry and I also don't want to give them false hope in terms of prognosis. So I'm honest with them, but veer more towards the positive. They help with the chores more now, as they understand how much I struggle with fatigue. They are used to seeing me sleeping during the day, and not having the energy to do a great deal more. I hate this for them! I have never been this way before! During my final cycle of chemotherapy, I fainted in the bathroom and my eldest two found me lying on the floor. They put me in the recovery position, and stayed by my side the rest of the evening. I mention this to highlight the impact the cancer and the treatments have had and continue to have on my children. It is hard as a single parent to live with this condition, but the impact it has on my children is so much worse. They don't really talk about the cancer. I suspect this stems from a combination of fear, not wanting to face or acknowledge what's happening, and maybe even trying to be 'brave' for their mum. This is devastating! They deserve better than this".*

	The wife of an LGG patient who is trying to access Vorasidenib: *"It takes a constant emotional and mental toll. We're fortunate that my husband doesn't have symptoms currently, so we're able to focus on living the best life we can while he's well, but the anxiety surrounding the 6 monthly scans is particularly stressful, as is the unknown element of the tumour, celebrating the time since his craniotomy in 2020, but aware that every year probably means less time of him being alive.* *We are incredibly keen to get hold of Vorasodenib and so far we've been unable to due to delays in the setup of the access scheme. Because my husband's tumour is in an operable location, it feels like we are treated as though we're a low priority.* *Ultimately the main aim for us is to ensure my husband's ongoing stability and prevent the tumour progressing, which is why we're looking to access Vorasidenib and ensure we're doing everything possible to impact his condition"*

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	Patients are of the opinion that current treatments available on the NHS (chemotherapy/radiotherapy) can be harsh and disrupt their lives extensively, often leaving them unable to work when many have young families to support. This is turn affects their carers/families, putting an extra burden on them, often causing financial problems. Patients on watch and wait, and their carers, suffer high levels of anxiety, resulting in their quality of life being very adversely affected. Waiting for the inevitable return or growth of the tumour whilst being aware that they are receiving no treatment to try to delay or stop this, places an enormous toll on the patient and the whole family. The ability to continue with study or work is frequently affected.
8. Is there an unmet need for patients with this condition?	There is an unmet need for some patients as there is no treatment given other than to watch and wait for the tumour to grow. The only treatment option thereafter is radio and chemotherapy with all the associated risks. These treatments are in any event not a cure. Chronic fatigue and frequent hospital attendances, often with complications from treatment has significant effect on their quality of life. There is a great unmet need for a kinder, less disruptive form of treatment which would enable patients to carry on their day-to-day activities and lead as normal a life as possible.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	Patients and/or Carers are of the opinion that the technology will offer a new pharmacological option which will result in more successful immediate outcomes without the need for the life changing negative impacts of more invasive treatments. These young patients need to access a drug that can delay, for as long as possible, radio and chemotherapy and the resultant side effects of those treatments including radiation necrosis, hypermutation , cognitive deficits , emotional toll, fatigue and insomnia . A kinder treatment is of the utmost importance to them. They consider that Vorasidenib is a drug which has the ability to deliver this kinder treatment - living with the condition but knowing they are actually receiving a treatment that will help stop or slow the progression of the disease will positively affect their quality of life. Patients need access to a drug that reduces the physical symptoms of tumour progression so they can continue to work. In addition, living with the condition knowing they are actually receiving a treatment that will help stop or slow the progression of the disease will positively affect their mental wellbeing. Seizures affect many patients with LGGs. Seizures, and the anxiety and fear associated with seizures, have an enormous negative effect on patients quality of life. It appears patients on Vorasidenib may suffer less seizures.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	They believe that the only disadvantages of the technology would be the inconvenience of regular visits required to the dispensing neuro centres for ongoing monitoring purposes (believed to be twice monthly initially and then monthly). However, in comparison to the standard treatments of radio/chemotherapy, this is a minor disadvantage.

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	The groups of patients who are likely to be accepted for the technology, we believe, are defined by those patients who took part in the Indigo trial i.e. LGG patients with IDH1/2 mutations who have undergone surgery only so it would appear that these patients will benefit more. However, we hope very much that other groups of patients with IDH1/2 mutations – those who have already undergone chemo/radiotherapy plus those whose tumours are inoperable, will be in a position to take advantage of the technology in the not too distant future.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	Age is a protected characteristic in the Equality Act 2010. As gliomas disproportionately impact a younger age group more profoundly, we are of the opinion that age is a relevant consideration which should be taken into account when considering this technology.

Other issues

13. Are there any other issues that you would like the committee to consider?	Health effects, physical and mental, of living with the condition for patients, family and carers. Loss of quality of life in the present and future for patients living with the condition. Toxicity of present standard treatments after surgery i.e. chemotherapy/radiotherapy – affecting all aspects of young peoples' lives especially family, social, finance, education and workplace

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	· This is a clear, unmet need - many patients are, following surgery, placed on 'monitoring', receiving no further treatments, again, negatively impacting on quality of life, including mental wellbeing ·Current treatments for LGGs are limited and harsh - patients who go on to receive chemo/radiotherapy following surgery can suffer devastating side effects, both physical and mental. ·Vorasidenib, according to reports from the trials, is a treatment which is kinder and less risky for patients with very few side effects, leading to a much improved quality of life ·There would be a financial benefit to the NHS in delaying radio/chemo therapy and also further surgery often deemed necessary on incidents of regrowth of tumours · Vorasidenib is the first new treatment for LGGs for decades, it is is an innovative drug that is aimed at preventing or at least slowing progression of these tumours (in some cases shrinking the tumour) with very few side effects .

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Single Technology Appraisal

Vorasidenib for treating astrocytoma or oligodendroglioma with IDH1 or IDH2 mutations after surgery in people 12 years and over [ID6407]

Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1.Your name	[redacted] (for and on behalf of the International Brain Tumour Alliance)
2. Name of organisation	International Brain Tumour Alliance (IBTA)
3. Job title or position	Chair and Co-Director
4a. Brief description of the organisation (including who funds it). How many members does it have?	The International Brain Tumour Alliance (IBTA), a UK-registered organisation, is a global network founded in 2005 as a dynamic worldwide community for brain tumour patient organisations in various countries and others involved in the field of neuro-oncology. The IBTA brings together experience and expertise from all over the world with the aim of enhancing the well-being and quality of life of brain tumour patients and their families. We encourage the establishment of brain tumour patient organisations in countries where they don't yet exist; we promote collaboration on programmes and projects to benefit the brain tumour community, we raise awareness of the challenges of brain tumours; we disseminate knowledge, information and best practice; we help shape health and research policies at national and international levels. Our vision is a world free from the fear of brain tumours and our mission is to advocate for the best treatments, information, support and quality of life for brain tumour patients offering them, their families and caregivers hope – wherever they live in the world. The IBTA is funded from a range of sources: individuals, other patient organisations, industry and the occasional bequest. We are primarily a volunteer-based organisation. We don't have a formal membership. Organisations can be considered "supporters" of the IBTA if they agree to our Statement of Principles (https://theibta.org/governance/). In this manner, we work with over 40 brain tumour patient organisations around the world as well as collaborating with various medical societies, researchers and patient organisations from other cancer-site-specific disease areas (ie patient organisations representing primary tumour sites which can give rise to brain metastases). The IBTA uses a range of methods to disseminate information about brain tumours and raise awareness of them. We interact with brain tumour patients and their families through our monthly IBTA e-News (https://theibta.org/news/) and our magazine (https://issuu.com/ibta-org). We provide support to patients who live in countries which don't yet have their own patient organisations. We also organise and run the biennial World Summit of Brain Tumour Patient Advocates. At the Summit we offer masterclasses, workshops and clinical lectures to the leaders (some of whom are patients/caregivers/former caregivers) of brain tumour patient organisations around the world. For further information, please see our website at www.theibta.org

4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	Yes, we have received grant funding from Servier (the company bringing the new technology to NICE for evaluation) for some of our 2024 projects including a survey on which we are working, our awareness raising work and our publications (£22,000). The IBTA has also acted in an advisory committee capacity for Servier for which the IBTA has received honoraria/payments (£8420). Kathy Oliver, as an individual, has received no direct payments from Servier. There are no comparator treatment companies involved with this evaluation.
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	We confirm that we have no direct or indirect links with, or funding from, the tobacco industry.
5. How did you gather information about the experiences of patients and carers to include in your submission?	The IBTA has gathered its information from twenty years of supporting patients with different types of brain tumours, including those with low grade glioma (ie astrocytoma and oligodendroglioma). Additionally, many of the IBTA's team of advisors have had direct experience of a loved one with a low grade glioma or have worked professionally in treating and supporting patients with low grade glioma.

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Brain tumours intersect three extremely challenging disease areas: they are a cancer, they are a neurological disease and they are a rare disease. Patients with low grade glioma brain tumours (astrocytoma and oligodendroglioma) can face significant physical/mobility issues, and neuro-cognitive and psychosocial problems such as anxiety, personality changes and depression. Patients with low grade glioma also suffer from fatigue, and, in the later part of their disease journey (when progression takes place and beyond), many will experience reduction in the ability to care for themselves, to communicate, to be mobile, etc. Other areas of a person's life may also be impaired such as their ability to work and maintain a social life. Family dynamics can be significantly altered as well. Low grade gliomas are not yet curable, although they usually have a better prognosis to start with than other types of brain tumours (for example, glioblastoma). Tragically, low grade gliomas almost invariably progress to a higher, more malignant grade which ultimately is fatal. Over time, more than 70% of low grade gliomas can transform into a higher grade or become aggressive in behaviour within a decade (https://www.ncbi.nlm.nih.gov/books/NBK560668/). People with low grade glioma and their families often describe their experience of living with the condition as "like having the sword of Damocles hanging over our heads all the time" as they very much fear progression or "a devastating roller coaster ride where one lives with glioma knowing that every single aspect of your life will be affected including your independence, your ability to do physical activities, your neurocognitive state, your relationships with people…". Considering how glioma can affect so many aspects of one's existence, quality of life is a major issue for this group of patients. The side effects of treatments (ie surgery, chemotherapy and radiation therapy) can take an enormous toll. Patients with low grade glioma also suffer from seizures which can lead to the loss of one's driving license, seriously affecting a patient's independence and quality of life. Patients have told us that of all the issues they face, seizures often pose the most devastating reduction in quality of life. The psychological and physical aspects of someone living with a low grade glioma are made all the worse by the knowledge that these tumours progress to a more malignant variety with fatal consequences. This is why an increase in progression-free survival is so important for people with low grade glioma. With all of these challenges as a daily part of living with a loved one who has a low grade glioma, caregivers are under tremendous stress and strain as well. Research (see Appendix) has shown that quality of life for caregivers of people with glioma is substantially negatively affected as well, and caregivers can experience a range of physical and mental health problems as a result of the burden they bear. Studies also reveal that caregivers of low grade glioma brain tumour patients can experience profound distress, hopelessness and anticipatory grief. Additionally, when their loved one is diagnosed with a glioma, caregivers must quickly learn how to navigate their healthcare system, monitor symptoms and oversee medication regimens without any advance formal training.

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	Current treatments for low grade glioma on the NHS comprise surgery (if possible and safe), radiation therapy and chemotherapy. These treatments can result in a range of debilitating side effects and significant reduction in quality of life for a patient, in addition to the side effects from the tumour itself, as described above. Therefore, there is a desperate – currently unmet – need for more treatment options which spare significant side effects for this population of low grade brain tumour patients. Equitable, timely access to new, evidence-based, efficacious therapies is one of the biggest challenges that patients in the UK with a brain tumour face. It is absolutely crucial that people with glioma in the UK can access a range of effective therapies on the NHS. A dearth of clinical trials for brain tumours in the UK also makes it extremely challenging for patients to access innovative, cutting-edge therapies. Therefore, current treatments and care on the NHS for people with low grade glioma are simply not enough to offer to people with this devastating disease. We also believe that there is a real danger that the UK may slip further behind its European neighbours and other countries such as the United States if emerging new technologies with proven efficacy are not accessible to UK glioma patients.
8. Is there an unmet need for patients with this condition?	Absolutely! On a personal level, I've seen first-hand the devastation wrought when my young adult son was diagnosed with a low grade glioma. He passed away in 2011 after his low grade glioma progressed to a glioblastoma. Patients with this diagnosis in the UK are still facing huge unmet need for better treatments. The responses already highlighted in this submission demonstrate a range of unmet needs in this patient population as evidenced by our work as an advocacy organisation.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	There are a number of important advantages of this first-in-class, targeted technology, vorasidenib. The double-blind, phase 3 international trial (INDIGO) of the technology showed that "In patients with grade 2 IDH-mutant glioma [astrocytoma and oligodendroglioma], vorasidenib significantly improved progression-free survival [PFS] and delayed the time to the next intervention". Imaging-based PFS was the primary endpoint of the INDIGO trial (https://www.nejm.org/doi/full/10.1056/NEJMoa2304194) and results from the study indicate that median progression-free survival was more than doubled (27.7 months in the vorasidenib arm of the trial versus 11.1 months in the placebo arm). The key secondary endpoint was the "time to the next anticancer intervention" According to the INDIGO trial, vorasidenib also demonstrated a good safety profile. All of these aspects – increased progression free survival, lengthening the time to next anticancer intervention and a good safety profile – are very important to people with IDH-mutant low grade glioma. Additionally, vorasidenib is taken as an oral treatment via a tablet which further enhances its advantages for patients and caregivers because time-consuming trips to hospital for treatment (ie in-clinic infusions) are not necessary and the therapy can be taken easily and conveniently at home. We understand that quality of life data analysis from the INDIGO trial is ongoing (as is follow-up for overall survival). But in the meantime, the study shows very promising results which are much welcomed by patients with low grade glioma and their caregivers.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	As with all treatments, there are associated side effects. So patients and their caregivers must always weigh up the benefits and risks of a potential therapy and determine how much in the way of side effects will be tolerable for them. Patients and caregivers should always discuss potential side effects of treatment with their healthcare team, and through the process of shared decision-making determine what is best for them. The safety profile for vorasidenib, as mentioned above, is apparently "good" according to the INDIGO trial. Most side effects have apparently been mild with vorasidenib. Vorasidenib tends to be better tolerated than traditional chemotherapy because it specifically targets (inhibits) mutant IDH1 and IDH2 enzymes in IDH-mutant glioma. Long term studies for this technology have not yet been done so there remain unanswered questions about its long-term use.

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	As a targeted therapy for IDH1- or IDH2-mutant low grade glioma, patients within this specific group of glioma brain tumours will benefit the most. People of any age can be diagnosed with a low grade glioma but many adults with this type of brain tumour are diagnosed relatively young, ie in their 20s, 30s or 40s (https://www.ncbi.nlm.nih.gov/books/NBK560668/). This is a population of people who are making their mark on society at the beginning or mid-stage of their professional lives. This population also generally has young families and are in the prime of their lives when they are active contributors to society. This age group of people represents the "promise of tomorrow". The productivity lost to society when both the patient (and their caregivers in some circumstances) may not be able to work because of a glioma diagnosis is significant. Therefore, a therapy which increases progression free survival and time to next intervention in this population should be accessible to all who need it and can benefit from it.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	Equitable access to the best evidence-based therapies for all is a crucial aspect of high-quality healthcare. Approving a therapy for use on the NHS such as the one being considered in this submission (vorasidenib) is a vital step in ensuring equitable access so that low grade glioma patients have a chance at extended progression-free survival and increased time to next intervention. It is not envisioned that any groups of people with low grade glioma and for whom this therapy is intended will have difficulty actually using the therapy as it is in tablet form and easily administered. Neuro-cognitive issues around low grade glioma may come into play in terms of a patient not remembering to take the tablet when he/she should, but this can be overcome by the use of medication apps, support from a caregiver, digital reminder devices, etc. Side effects of the tumour in terms of mobility, manual dexterity, etc should not pose any equality issues in using this treatment.

Other issues

13. Are there any other issues that you would like the committee to consider?	In summary, we would like to emphasise that vorasidenib is an innovative, first-in-class IDH1/IDH2-mutant inhibitor with blood-brain-barrier penetration and a good safety profile. Vorasidenib is a tablet which can be taken at home, thus patients can avoid often-costly and time-consuming trips to hospital for therapy provision. Importantly, treatments such as vorasidenib give patients and their families hope that their tumour may not progress as quickly as it would have done without a targeted intervention such as this IDH1/2-mutant inhibitor. In our opinion, it is crucial that people with low grade glioma have access to vorasidenib. Low grade brain tumour patients need to have the opportunity to increase the time to their next treatment intervention. Many patients who could benefit from vorasidenib are relatively young people with their lives in front of them. They must have the chance to live their lives to the fullest despite their brain tumour diagnosis and the marathon of challenges that this diagnosis brings.

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• There are significant unmet needs regarding treatments, survivorship and quality of life for people diagnosed with an IDH1- or IDH2-mutant low grade glioma. • Access to innovative and efficacious treatments which can lessen the burden on both the low grade glioma patient and their caregiver/s is desperately needed. • Vorasidenib is a first-in-class, innovative, evidence-based therapy which has been hailed as a “game changer” by the neuro-oncology community. • Results from a major international, phase 3, double blinded trial (INDIGO) have shown that vorasidenib increases progression-free survival significantly in this patient population and delays time to next anticancer intervention • The safety profile of vorasidenib has been shown in a major clinical trial (INDIGO) to have side effects which are “mainly low-grade”.

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Vorasidenib for treating astrocytoma or oligodendroglioma with IDH1 or IDH2 mutations after surgery in people 12 years and over [ID6407]

Patient Organisation Submission

About you

1.Your name	[redacted]
2. Name of organisation	The Brain Tumour Charity
3. Job title or position	Director of External Affairs & Strategy
4a. Brief description of the organisation (including who funds it). How many members does it have?	The Brain Tumour Charity is the world's leading brain tumour charity that is solely funded by voluntary donations. Our vision is for people diagnosed with a brain tumour to lead live longer and better lives. The Charity's goals are to double survival and to halve the harm that brain tumours have on quality of life by 2030. These goals are driven by our community and 119 employees. We are committed to funding research that will increase survival whilst improving the quality of life for brain tumour patients. A key value for The Charity is being community-first, ensuring we involve the community in internal work and external research projects.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	The Brain Tumour Charity has a current agreement with Servier, the manufacturer for the Glioma Patient Committee. The aims of this project is to identify, and develop collaboratively with Patients, projects to improve low grade glioma care and low grade glioma patient's lives. The total value of this project is £4,672.50. The Brain Tumour Charity We have additionally had a zero-value contract to provide Servier, via an consultancy for: Providing feedback as requested by the Company on the health state descriptions and/or study materials (possibly the study screener, background questionnaire and/or the interview questions)

	drafted by the Company. Feedback included the applicability and appropriateness of the language and content of the documents. Supporting the Company in recruiting Participants for the Study. Including up to 8 adult patients and 5 caregivers of adult or paediatric patients to participate in a 1-hour long teleconference interview. The Brain Tumour Charity also hold a consultancy agreement with Novartis for providing consultancy to understand the needs and perspectives of patients with Brain Cancer and will provide insight to Novartis on clinical/education/awareness activities in Solid Tumours. The maximum value of this activity is £2,360. The Brain Tumour Charity is currently exploring a consultancy agreement with DayOne Biopharma for: A member of The Brain Tumour Charity staff team serving as Co-Chair of the International pLGG Advocacy Discovery Workshop. Collaborating and providing advice, materials and assistance to the company as mutually agreed by the Parties. Participating in planning meetings remotely with the company and participating in a one-day, in-person workshop in a European city. The maximum proposed value of this contract would be £2,640. The Brain Tumour Charity has published a blog news piece for our community discussing vorasidenib, which you can see here: https://www.thebraintumourcharity.org/news/research-news/recent-clinical-trial-suggests-the-drug-vorasidenib-could-offer-a-new-treatment-option-for-low-grade-glioma/
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	The Brain Tumour Charity has no direct or indirect links, or funding, from the tobacco industry.
5. How did you gather information about the experiences of patients and carers to include in your submission?	**1. Methods** We used two methods to gather insights from patients and carers:

	• **Online Survey:** A structured survey was developed to collect a wide range of experiences and perspectives. • **Community Insight Workshop:** We organised an online workshop designed to explore participants' views in greater depth and capture qualitative insights. **2. Recruitment** Both opportunities were shared via our involvement programmes, including our Involvement Network, Young Ambassador Programme, and Involvement Champions Programme. Additionally, we shared the opportunities via a closed Facebook support group and The Brain Tumour Charity public social media channels. Eligibility criteria: Please see the eligibility criteria for both the survey and insight workshop below: “To ensure the survey responses are as relevant and useful as possible, participants met meet the following criteria: A confirmed diagnosis of one of the following brain tumour types: · Diffuse or Low-Grade Astrocytoma (Grade 2) · Anaplastic Astrocytoma (Grade 3) · Oligodendroglioma (Grade 2 or 3) Exclusions - Pilocytic Astrocytoma (Grade 1) - Glioblastoma - Grade 4 Astrocytoma Or The feedback was also gathered from carers, family members, or close friends of those diagnosed with those in the eligibility criteria. Please note: They were all aged 18 or over. They all lived in the UK and had experience receiving NHS care for this condition

	Timing • The **online survey** was open between 19th December 2024 to 17th January 2025 • The **Community Insight Workshop** took place on 16th January 2024 between 6pm-8pm. **3. Participation** • **Survey Participation:** 276 individuals completed the survey, providing valuable quantitative and qualitative insights. • **Workshop Attendance:** 9 individuals attended the community insight workshop.

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Our insights show that living with an astrocytoma or oligodendroglioma profoundly impacts every aspect of life—physical, emotional, and social. Patients face physical and cognitive challenges, including fatigue, seizures, and memory issues, often struggling with mobility, speech, and sensory impairments that disrupt daily life and erode their sense of normalcy and identity. Some key themes from our Community Insight Workshop and Questionnaire are outlined below. **Emotional and Psychological Struggles:** • **Uncertainty and Anxiety:** The condition creates fear and worry for many. Many participants express living "scan-to-scan" or feeling like they have a "bomb in their head" that could go off at any moment. *"The watch and waiting is the hardest part. Like I've got a bomb in my head that could go off at any time."* • **Isolation:** Living with the diagnosis is often isolating, with challenges in maintaining social connections. *"It was an isolating time, having had my brain tumour when I was very young. I felt very alone."* • **Mental Health:** Many express profound mental health struggles, including the impact on their identity and purpose. *"The uncertainty of when it will come back… brought me close to taking my own life."* **Physical Limitations and Fatigue:** • **Fatigue and Energy Loss:** Overwhelming fatigue is a recurring issue, exacerbated by treatments such as radiotherapy and chemotherapy. *"Brain fatigue… [is] …not normal tiredness; your brain is tired and forgetful.."* • **Seizures and Epilepsy:** Seizures, often medication-managed, affect daily life. *Epilepsy is my most impactful side effect."* • **Treatment and Side Effects:** Ongoing side effects of surgeries, radiotherapy, and chemotherapy include memory issues, balance problems, and cognitive impairments. *"Having a brain tumour is literally always on my mind… the worry is always there."* **Impact on Independence and Daily Life:** • **Driving and Mobility:** Losing the ability to drive and challenges with mobility are setbacks. *"The forced surrender of my driving licence to DVLA has made a bad situation even worse."* • **Career and Financial Stability:** Many have had to leave jobs or shift roles, creating financial strain. *"I've had to give up working in a job I loved as my executive functions are impaired."* **Impact on Family and Relationships:** • **Fear of Burdening Loved Ones:** Participants frequently express guilt or concern for their families, particularly children. *"It is a profound mental challenge… the prospect of an early death weighs heavily on me, raising fears of leaving my young family behind."* Carers supporting someone with an astrocytoma or oligodendroglioma often face profound emotional and practical challenges. They share the emotional burden of uncertainty and fear, navigating anxiety about the future alongside their loved ones. Many adjust their personal and

	professional lives, sacrificing goals and taking on new responsibilities to provide care. The overlap between caregiving and personal relationships can blur boundaries, creating emotional complexity and strain. While many carers experience exhaustion and feel overwhelmed by the demands of their role, some find a sense of purpose and resilience in supporting their loved ones through such a difficult journey. **Survey Statistics:**. While 61% of patients experience moderate to severe impacts, this rises to 78% for carers, with 41% of carers reporting severe effects compared to 17% of patients. A minority in both groups report mild or no impact, perhaps highlighting the pervasive challenges faced by those living with or supporting someone with the condition.

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	Patients and carers often express a mix of gratitude and frustration regarding the medical treatments available to them through the NHS. While there is acknowledgment of the free access to essential medications and the dedication of healthcare staff, the overarching sentiment is that treatment options are often outdated, insufficiently innovative, or fail to address the specific needs of individuals. The challenges patients and carers face regarding NHS-provided medical treatments are outlined below: **Limited Range of Treatment Options** • Patients frequently voice concerns about the lack of access to innovative therapies. • One patient remarked, *"The treatment I was offered was the same as what was available a decade ago—there's no sense of progress."* Patients voiced concerns about lengthy waiting times for certain drugs, especially those requiring specialised funding or approval, were another area of dissatisfaction. **Side Effects and Burden of Treatment** Many patients struggle with the physical and emotional toll of existing treatments, particularly chemotherapy and radiation therapy. A patient shared, *"Chemotherapy was brutal—it felt like the cure was worse than the condition at times. But I didn't have any other option."* The long-term effects of radiation, including side effects like fatigue, skin damage, and secondary conditions were also highlighted as areas where patients felt that side effects were difficult and hard to manage. **Fertility Concerns** For younger patients, the effects of treatment on fertility remain a significant worry, often exacerbated by inadequate counselling or proactive fertility preservation measures. One carer noted, *"It felt like fertility wasn't even a consideration until I brought it up, and by then, it was too late for some interventions."* Our survey data underlines these sentiments: • Only 37% of respondents rated the quality of current treatments as 'Good' or 'Excellent'. • A portion (30%) rated it as 'Poor,' reflecting dissatisfaction with the adequacy of treatment options.

	While patients and carers value the accessibility of NHS-provided medical treatments, many feel underserved by the limited range, outdated protocols, and lack of personalisation. Addressing these gaps—especially through faster, but equally robust, adoption of innovative therapies and enhanced support for treatment side effects—could greatly improve patient satisfaction and outcomes.
8. Is there an unmet need for patients with this condition?	The survey data reveals there are unmet needs for patients with this condition, with **82% of respondents** agreeing there are gaps in treatment or support. Only **2%** felt current provisions were sufficient, while **16%** were unsure. These figures reflect dissatisfaction, particularly regarding the availability of innovative treatments and the harshness of existing options. **Access to Innovative Treatments: "We need treatments that give people some hope."** A pressing concern for patients and carers is the limited access to modern therapies that could improve survival and quality of life. Many respondents emphasised the importance of newer drugs, which have shown promise in delaying tumour growth. Despite being approved in other countries, these treatments remain currently out of reach for most NHS patients. Other advanced therapies, including immunotherapy and targeted treatments, are also not widely offered for this condition, leaving patients with few options beyond traditional methods. This lack of innovation has contributed to feelings of hopelessness among patients. **A Kinder, Less Invasive Approach** Existing treatments, such as chemotherapy and radiotherapy, are often described as harsh and debilitating, with severe side effects that diminish quality of life. Patients and carers consistently expressed a desire for therapies that are less invasive and better tolerated. Many suggested that new drugs capable of crossing the blood-brain barrier, while minimising side effects, would be a significant breakthrough. A carer shared their perspective: "My nephew is a young man with a small child, and this worry is hanging over the family. There's a new drug that will slow the regrowth, and it's desperately needed." In summary, the overwhelming consensus is that current treatment options are insufficient to meet the needs of patients with this condition. Innovative drugs, less invasive therapies, and access to cutting-edge treatments must be prioritised to offer patients genuine hope for the future.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	Our survey reveals that 96% of participants believe the development of a new treatment is extremely important and 94% of the community are open to advances in treatment or technology. ***"The side effects of Vorasidenib seem less damaging than radiotherapy or chemo. When you're in it, you'll do anything to try and survive."*** ***"This new drug is giving me a bit of hope, and a glimmer of hope is what we need"*** In the survey, 96% of participants expressed a desire for increased survival rates. Patients and carers yearn to overcome a brain tumour diagnosis, and any treatment that can increase survival rates is a tremendous step in doing so. Many feel they have limited options, or the current options are too "invasive and damaging." Therefore, new technology provides the community with 'hope and confidence' that survival rates may increase if the technology proves to be differing from current treatment. ***"If this drug means that young people can have some normality, then please give it. My son has had lots of chemotherapy, and his quality of life is not good. Some people think you have chemotherapy and you're better the next day, but that's not the reality. It can take days and sometimes even weeks to recover. You are worn out by it. Anything that's not that toxic is good in my opinion"*** The survey revealed that 75% of respondents expressed a need for improved quality of life and 58% echoed a need for fewer side effects. Patients and carers highlight how side effects of current treatment options leave patients feeling extremely fragile and fatigued resulting in them being unable to return to a social or work environment. In discussion a carer described a chemotherapy treatment as 'barbaric' due to its harsh impact on their child's quality of life. If the new treatment can reduce side effects, day to day quality of life could be improved for both carers and patients. ***"The last 10 years have not been easy and it has been a battle on various fronts"*** A reduction in treatment duration would be desirable for 41% of respondents. We found that carers are heavily affected by the length of time treatment can take and how this causes implications on their daily life. Secondary implications expressed by the community include the reliance on carers for transportation and financial strain. Overall consensus reveals that patients are hopeful for the new technology to prevent or delay them having to turn to chemotherapy and radiotherapy.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	**"*When a new drug is on the market, you're not sure how you'll respond to it*."** Patients and carers generally view the availability of new treatment options positively, but concerns remain. Many express uncertainties about how they might respond to new drugs, with worries about side effects, effectiveness, and the potential to worsen their condition or rule out future treatment options. Long-term impacts on cognition, fertility, and overall quality of life are also concerns. **"*When you go in to hospital, you get the support that you didn't think you needed. Either seeing other patients or getting face to face time with professionals. Being at home for treatment might stop that*."** Additionally, some feel that shifting treatment from hospitals to home settings might reduce access to valuable support from peers and healthcare professionals, which many didn't realise they needed until it was offered. While these concerns are important, most patients remain open to trying new treatments, especially when supported by clear information and the hope of improving their prognosis.

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Our survey results show that younger patients may benefit from this technology due to concerns around fertility, as treatments like chemotherapy can affect reproductive health. Patients who need to continue working may also find this technology advantageous, as it could offer less disruptive treatment options. Those in rural or remote areas could benefit from easier access to treatments, reducing the need for long-distance travel. However, patients who are unable to have surgery due to the location of their tumour report feeling "left behind," with limited treatment options and little hope.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	Our community has highlighted several potential equality issues that could arise when considering this condition and the proposed technology. Socioeconomic factors have also been raised as a potential issue. Treatment costs, whether related to the technology itself or the associated expenses like travel or time away from work, could disproportionately affect those from lower-income backgrounds. Younger patients in our community have also expressed concerns about how treatments may impact fertility, suggesting the need for careful consideration and clear communication around these issues. Finally, some patients who cannot undergo surgery or current standard treatments have shared feelings of being left behind, highlighting the importance of ensuring that new options address the needs of as many people as possible. These insights from our community suggest a need for equitable implementation that ensures everyone has access to meaningful treatment opportunities.

Other issues

13. Are there any other issues that you would like the committee to consider?	N/A

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• Living with astrocytoma or oligodendroglioma deeply affects patients and carers, disrupting physical, emotional, and social well-being. Patients face symptoms such as seizures, fatigue, and cognitive impairments, while carers often experience emotional strain and practical challenges in providing support. • Patients and carers express dissatisfaction with current NHS treatments, describing them as outdated and harsh. A key concern is the profound impact of these treatments on quality of life, with many struggling to cope with debilitating side effects that diminish day-to-day functioning and overall well-being. Access to innovative therapies is urgently needed to address these gaps. • There is a clear unmet need for less invasive, more effective therapies that not only improve survival rates but also prioritise enhancing patients' quality of life, which is a critical aspect of care. • The proposed technology is seen as a potential breakthrough, offering hope for better outcomes, fewer side effects, and a lighter treatment burden, which could improve the lives of patients and their families. • Equality issues, including barriers faced by lower-income, and non-surgical patients, must be addressed to ensure this technology is accessible to all who need it, fostering equitable opportunities for improved care and outcomes.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Vorasidenib for treating astrocytoma or oligodendroglioma with IDH1 or IDH2 mutations after surgery in people 12 years and over [ID6407]

Professional organisation submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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- Your response should not be longer than 13 pages.

About you

NICE National Institute for Health and Care Excellence

1. Your name	[redacted]
2. Name of organisation	ABN SIG Neuro-oncology
3. Job title or position	Consultant Neurologist
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? **Yes** or No A specialist in the treatment of people with this condition? **Yes** or No A specialist in the clinical evidence base for this condition or technology? Yes or **No** Other (please specify):
5a. Brief description of the organisation (including who funds it).	The Association of British Neurologists' is a professional membership organisation and its mission is to improve the health and well-being of people with neurological disorders by advancing the knowledge and practice of neurology in the British Isles. The ABN receives funding mainly from its member subscriptions and annual conference income. Additional funding from external charity organisations is received to solely fund fellowships. Additionally, the ABN receives sponsorship from pharmaceutical companies. Sponsoring companies have no input, control nor opportunity to influence the ABN.

5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] **If so, please state the name of manufacturer, amount, and purpose of funding.**	In the past 12 months, the ABN has received sponsorship from the following companies to support the ABN Annual Conference. Sponsorship companies have no editorial input, control over the agenda, speaker selection, content development nor opportunity to influence the conference. Sponsorship is £18,020 per company. • Abbvie • Alnylam • Angelini • argenx • Biogen • Eisai • Eli Lilly • Janssen • Pfizer • Roche • Sanofi • Teva • UCB
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	NO

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To stop disease progression
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Progression free survival
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes, IDH mutated glioma has an unpredictable disease course with inevitable progression to a high grade glioma over time. Progression often occurs despite existing treatments – surgery +/- adjuvant radiochemotherapy. These treatments are often associated with debilitating neurological side effects such as cognitive impairment. There is a need for an alternative targeted treatment which addresses the underlying disease mechanism, can be maintained over time and potentially delays disease progression.

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	Debulking surgery where feasible, plus the option of adjuvant radio chemotherapy.
9a. Are any clinical guidelines used in the	European Association of Neuro-oncology (EANO) Guidelines for treatment of adult astrocytic and oligodendroglial gliomas 2017 – Guidelines cover both IDH1/2 mutated and astrocytic tumours.

treatment of the condition, and if so, which?	Brain tumours (primary) and brain metastases in over 16s. NICE guideline [NG99] Published July 2018 Last updated: January 2021
9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Pathway of care is well defined for grade 3 and 4 brain tumours but to a lesser extent for grade 2 brain tumours. The pathway is likely to vary across the country.
9c. What impact would the technology have on the current pathway of care?	The technology would increase the treatment options available to patients with grade 2 astrocytoma or oligodendroglioma and could potentially delay the need for oncological intervention - radiotherapy and chemotherapy in a subgroup of low-grade gliomas. It would potentially enable non-oncologists to be involved in treatment.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes
10a. How does healthcare resource use differ between the technology and current care?	Current care – utilises separate teams to deliver both radiotherapy and chemotherapy. This resource can be administered by a range of clinicians without the requirement for radiotherapy.
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Specialist secondary care neuro-oncology clinics
10c. What investment is needed to introduce the technology? (For example,	Training and funding of both neuro-oncologists and neurologists.

for facilities, equipment, or training.)	
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes
11a. Do you expect the technology to increase length of life more than current care?	Yes, there is potentially for progression free survival beyond that achieved with existing therapies.
11b. Do you expect the technology to increase health-related quality of life more than current care?	Yes- the current therapies, radiotherapy in particular, are associated with debilitating long-term effects.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	The technology would be more effective for those with confirmed IDH1/2 mutation status on histology.

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant	The technology will be easier to administer as an oral agent than existing radiotherapy and chemotherapy which requires specialist pathways for administration and monitoring. Liver function test monitoring may be required

treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Tumour progression in spite of treatment would be considered as a potential indication to stop therapy.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Productivity, eg through ability to return to work in those who maintain progression-free survival is an additional benefit which may not be included in the QALY calculation. Potential favourable impact on long-term seizure control.
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes, the treatment is innovative in that it can be administered by a number of clinicians within the team, leading to greater efficiency of administration.
16a. Is the technology a 'step-change' in the	Yes – as above. It is the first targeted treatment directed at the IDH mutation.

management of the condition?	
16b. Does the use of the technology address any particular unmet need of the patient population?	Targeted treatment. The current therapies are non-specific in that they do not directly address mechanism of action.
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Unable to comment at this stage.

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	Unable to comment as neurology is not involved in delivery of existing surgical/ radio chemotherapy pathways.
18a. If not, how could the results be extrapolated to the UK setting?	
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	Progression-free survival is the most important outcome – it was measured against placebo in the INDIGO trial.
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	

18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Surrogate radiological outcomes, eg change in tumour on MRI imaging or surrogate neurological outcomes – change in seizure control may adequately predict long term clinical outcomes.
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	Unable to comment
20. How do data on real-world experience compare with the trial data?	Unable to comment

Equality

21a. Are there any potential equality issues that should be taken into account when considering this treatment?	Nil
21b. Consider whether these issues are different from issues with current care and why.	

Key messages

22. In up to 5 bullet points, please summarise the key messages of your submission.	• Vorasidenib is a novel targeted oral treatment for IDH mutated glioma • Clinical trials suggest that Vorasidenib delays progression free survival • Vorasidenib has the potential to offer patients an oral alternative to radio+chemotherapy post surgery for glioma and thus prevent the need for oncological intervention • Vorasidenib has the potential to improve efficiency and access to treatment for this patient group, as the medication could be administered by neurologists/ neurosurgeons in addition to neuro-oncologists. • •

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- Your response should not be longer than 13 pages.

About you

1. Your name	[redacted]
2. Name of organisation	The British Neuro Oncology Society (BNOS)
3. Job title or position	Associate Clinical Professor and Honorary Consultant in Medical Oncology, University of Birmingham. Member of the BNOS clinical advisory committee
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? Yes A specialist in the treatment of people with this condition? Yes A specialist in the clinical evidence base for this condition or technology? Yes Other (please specify):
5a. Brief description of the organisation (including who funds it).	A registered charity of clinicians who treat patients with brain tumours. Funded by subscription from its members, and the proceeds of the annual general scientific meeting.
5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] **If so, please state the name of manufacturer, amount, and purpose of funding.**	
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To delay progression of low grade IDH mutant gliomas (classified WHO grade 2 or 3) following surgical intervention To delay the time before additional therapy is required
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	• Prolonged time before tumour growth by more than two years • Prolonged time before further intervention with either surgery, radiotherapy and/or chemotherapy
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Vorasidenib offers a new therapeutic option for patients with grade 2 gliomas who are not in immediate need of radiotherapy or chemotherapy; although future progression to these treatments is likely to be inevitable. Vorasidenib has a low toxicity that may delay the need for radiotherapy and chemotherapy, allowing maintenance of a good quality of life over a longer period of time. Therefore, vorasidenib fills an existing treatment gap where observation or earlier treatment with greater side effects was previously the only option.

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	At present, the recommended standard of care for patients with low grade glioma is maximal safe surgery to remove the tumour. Recurrence is usually inevitable and ultimately leads to reduced quality of life, through symptoms such as seizures or cognitive decline. Adjuvant treatments that may be used to delay recurrence include radiotherapy and chemotherapy (temozolomide or PCV for astrocytoma and oligodendroglioma, respectively). Such treatments carry significant risk of side effects, including cerebral oedema, neutropenic infections, low platelets and thrombosis. Long term side effects include fatigue, cognitive decline, and long term

	bone marrow suppression. In the case of radiotherapy, the risk of long-term toxicity (including stroke, secondary tumours, radionecrosis) often precludes it's use in more than one line of therapy. These treatments can lead to the affected individual being unable to work. Therefore, in patients with gliomas holding more indolent features (e.g. slow tumour growth rate, lack of contrast enhancement) there is a growing tendency to spare these patients from the toxic effects of chemoradiotherapy. Patients undergoing watchful waiting will have regular surveillance imaging.
9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	EANO guidelines on the diagnosis and treatment of diffuse gliomas of adulthood (2023) - https://doi.org/10.1038/s41571-020-00447-z NICE guideline (NG99) Brain tumours (primary) and brain metastases in over 16s (updated 2021) Therapy for Diffuse Astrocytic and Oligodendroglial Tumors in Adults: ASCO-SNO Guideline (2021) - https://doi.org/10.1200/JCO.21.02036
9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	In most cases, the treatment pathway is well defined, however there are areas of uncertainty: • The choice of chemotherapy for low grade gliomas can vary, particularly in WHO grade 2 astrocytomas • The definition of patients who would benefit from immediate adjuvant therapy versus watchful waiting is not universally accepted • The interval for imaging surveillance of patients on watchful waiting is not uniform between NHS centres
9c. What impact would the technology have on the current pathway of care?	The landmark double-blind, phase 3 INDIGO study (DOI: 10.1056/NEJMoa2304194) found that in patients with grade 2 IDH-mutant glioma, vorasidenib significantly improved progression-free survival (mPFS 27.7 months vs 11.1 months; Hazard ratio for progression or death 0.39 [95% CI 0.27 to 0.56]) and delayed the time to the next intervention (HR 0/26 [95% CI 0.15 to 0.43]). Thus, vorasidenib opens up a new therapeutic avenue for patients with grade 2 IDH-mutant glioma, who are not in immediate need of adjuvant chemotherapy or radiotherapy following surgery, to delay the need for more toxic treatment and to maintain quality of life (DOI: https://doi.org/10.1093/neuonc/noad179.0978).
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Vorasidenib is not currently available in routine NHS clinical practice for any indication. It is available in some UK centres on an early access scheme for this indication.
10a. How does healthcare resource use differ	Current care for patients with low grade glioma following maximal safe debulking, who do not immediately require adjuvant chemoradiotherapy involves watchful waiting with magnetic resonance imaging (MRI) and

between the technology and current care?	symptom surveillance. Intervals between clinical review/imaging surveillance can vary, with a minimum interval of three months, though in the majority of cases imaging intervals will be much longer. On vorasidenib, patients will be expected to have closer monitoring, with regular blood tests, clinical reviews and MRI. In the INDIGO clinical trial, patients were required to undergo clinical review on 28-day cycles for a minimum of three years, with associated haematological and serum biochemical laboratory assessments. MRI scans were conducted 12-weekly for the first 3 years, then 6 monthly for a further 2 years and annually thereafter.
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Vorasidenib should be administered in secondary care via specialist clinics, where monitoring with regular blood tests and MRIs can be arranged. Non-surgical oncologists with experience in managing brain tumour patients are best equipped to manage care for patients on vorasidenib due to expertise in delivery of systemic anti-cancer treatment and in the management of complications arising from these therapies. Moreover, there are existing pathways for patients experiencing toxicity from anti-cancer treatment via acute oncology services. Finally, non-surgical oncologists are core members of the brain tumour multidisciplinary team and would be in a position to rapidly escalate care in the event of treatment failure.
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Delivery of vorasidenib is expected to utilise existing services available to patients with low grade glioma. However, it will also increase resource use, therefore investment into improving capacity in non-surgical oncology and associated support services will be necessary.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes, vorasidenib provides a new treatment option for patients with low grade glioma following surgical intervention, where there is no immediate need for chemoradiotherapy. Vorasidenib may spare these patients for a period of time from the short- and long-term harmful effects of chemotherapy and radiotherapy. By lengthening time to progression, patients are expected to experience a longer period without deterioration in symptoms. Based on the clinical trial, patients on vorasidenib were found to live for more than 16 months longer than the control arm before progression was detected compared to patients on watchful waiting.
11a. Do you expect the technology to increase length of life more than current care?	It is not known whether vorasidenib will increase survival in patients. Due to the design of the INDIGO trial permitting crossover of patients in the placebo arm to the vorasidenib arm, it will not be possible to determine the potential effect on overall survival. Additional research will be required to answer whether vorasidenib improves survival in treated patients compared to current standard of care.
11b. Do you expect the technology to increase health-related quality of life more than current care?	The INDIGO study included a health-related quality of life measures, using the Functional Assessment of Cancer Therapy – Brain (FACT-Br) questionnaire (secondary endpoint), the EQ-5D-5L and the PGI-C questionnaires (exploratory endpoints). The results of this measures have not been published, however presented evidence suggests that quality of life was preserved on vorasidenib treatment compared to watchful waiting. Longer term data is required to understand the impact of avoiding adverse effects on cognitive function, employment status

	and functional independence that are associated with surgery, radiotherapy and chemotherapy. It is anticipated that vorasidenib will result in a net increase in health-related quality of life.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Based on the INDIGO trial, vorasidenib was found to be effective in patients with grade 2 glioma with predominantly non-enhancing residual or relapsed disease following surgical intervention. Early evidence suggests that patients with grade 3 or 4 glioma and with significant contrast-enhancing disease have a lower chance of response (doi: 10.1158/1078-0432.CCR-21-0611), although further clinical trials are ongoing/anticipated in these patient populations. The trial only included one patient (in the placebo arm) younger than 18yrs and only 3 greater than 65 yrs. It is not clear how the extent of resection, size of tumour, timing of treatment, if recurrent disease, and site of tumour (2/3rds of tumours were frontal) affect the effectiveness of treatment.

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	Additional blood tests and monitoring will be required for patients taking vorasidenib, which will impact on existing cancer services.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these	Given the multidimensional aspects that must be considered for eligibility to receive vorasidenib, including histopathology (grade 2 IDH mutant glioma), radiology (predominantly non-contrast enhancing residual/relapsed disease), maximal safe debulking when possible, and non-surgical oncology (timing of next intervention), the decision should be discussed in the neuro-oncology multidisciplinary team

include any additional testing?	meeting before start of treatment. Stopping treatment should be based on lack of evidence of benefit, defined as confirmed radiographic evidence of progressive disease, or poor tolerability.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	The side effects of standard treatments with radio / chemotherapy and their impact on the ability of the patient to work, may be unlikely to be included (unless thought about) in a standard QALY calculation.
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes, vorasidenib is a brain penetrant small molecule inhibitor of isocitrate dehydrogenase1/2. It is the first drug of its kind to have shown benefit in patients with brain tumours. Vorasidenib has the potential to make a substantial impact on patients with IDH mutant low grade gliomas, significantly improving their time to progression, maintaining their quality of life for longer, and hopefully significantly improving their life expectancy.
16a. Is the technology a 'step-change' in the management of the condition?	Yes, vorasidenib represents a significant advance that opens a new therapeutic avenue for patients with low grade glioma.
16b. Does the use of the technology address any particular unmet need of the patient population?	Yes, vorasidenib will fill a gap in the management pathway for patients with low grade glioma, who were previously watched until progression. Low grade gliomas are usually incurable and often relapse and progress to a higher grade.
17. How do any side effects or adverse effects of the technology affect the management of the	According to the results of the INDIGO trial, vorasidenib was well tolerated with mainly low grade toxic side effects. The most common significant (grade 3 or higher) adverse event was a raised liver enzyme (alanine aminotransferase, ALT), which occurred in less than 10% of the treated population. Adverse events leading to discontinuation of vorasidenib occurred in less than 5% of trial patients on vorasidenib. The trial identified three serious adverse events: raised ALT, hepatic failure and hepatitis, which all

condition and the patient's quality of life?	resolved before the end of the trial. Presentation with a significant adverse event would require treatment interruption and potentially subsequent dose reduction or treatment discontinuation.

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes. Moreover, the INDIGO study included 5 centres in the UK (The Christie Hospital, University College London Hospital, The Royal Marsden Hospital, Western General Hospital Edinburgh, Freeman Hospital). There does remain some variablity in practice across the UK.
18a. If not, how could the results be extrapolated to the UK setting?	N/A
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	The most important outcomes are overall survival, progression-free survival, objective response rate and quality of life. All four outcomes were measured. However, as crossover was permitted the INDIGO trial, it will not be possible to use overall survival as an efficacy measure.
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	No surrogate outcome measures were used
18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	None that we are aware of
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No

20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TAXXX]? [delete if there is no NICE guidance for the comparator(s) and renumber subsequent sections]	N/A
21. How do data on real-world experience compare with the trial data?	At present, there is no mature real-world data suitable for comparison with the trial data.

Equality

22a. Are there any potential equality issues that should be taken into account when considering this treatment?	No data is available regarding ethnicity and socioeconomic status of participants recruited to the INDIGO trial. Therefore, it is not possible to comment on vorasidenib's effectiveness across diverse populations.
22b. Consider whether these issues are different from issues with current care and why.	Existing health inequalities, such as differential healthcare access, will be relevant to vorasidenib use, particularly since this treatment will require greater patient engagement with secondary care.

Topic-specific questions

23 [To be added by technical team at scope sign off. Note that topic-specific questions will be added only if the treatment pathway or likely use of the technology remains uncertain after scoping consultation, for example if there were differences in opinion; this is not expected to be required for every appraisal.] **if there are none delete highlighted rows and renumber below**	

Key messages

24. In up to 5 bullet points, please summarise the key messages of your submission.	• Significant increase in progression free survival in a group of patients iwht IDH mutant low grade gliomas • Treatment helps delay more toxic treatments • The treatment should be given by clinical neurooncologists after neurooncology MDT discussion • Fits easily into current treatment pathways with apropriate checks and balences • Significant economic benefit may not be incorporated into QALY calculation.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

Your privacy

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Please select YES if you would like to receive information about other NICE topics - **YES** ~~or NO~~

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Vorasidenib for treating astrocytoma or oligodendroglioma with IDH1 or IDH2 mutations after surgery in people 12 years and over [ID6407]

Professional organisation submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
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- Your response should not be longer than 13 pages.

About you

1. Your name	[redacted]
2. Name of organisation	The Royal College of pathologists
3. Job title or position	Professor of neuropathology at University College London Consultant neuropathologist at University College London hospitals NHS foundation trust Chair of the specialty advisory committee in diagnostic neuropathology at RCPath
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? Yes (if diagnostic histopathologists/neuropathologists are considered as "clinicians"). A specialist in the treatment of people with this condition? No/ as a pathologist, I provide the diagnosis, but do not treat the patients directly. A specialist in the clinical evidence base for this condition or technology? To some extent. Other (please specify):
5a. Brief description of the organisation (including who funds it).	The Royal College of Pathologists is a professional membership organisation with charitable status concerned with all matters relating to the science and practice of pathology. It is a body of its Fellows, Diplomates, Affiliates and trainees, supported by the staff who are based at the College's London offices. It is funded through membership payments.
5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] **If so, please state the name of manufacturer, amount, and purpose of funding.**	Not to our knowledge

5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No links (direct or indirect) to tobacco industry

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	vorasidenib can delay the progression of some low-grade gliomas with *IDH1* or *IDH2* mutations and postpone the need for additional therapies
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	1) delay of recurrence, extension of time to progression 2) delay of progression and extension of lifespan
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	Depending on patient specific parameters, surgery, adjuvant radiotherapy, chemotherapy.
9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	Nice guidelines brain tumours
9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The pathway is established.
9c. What impact would the technology have on the current pathway of care?	Treatment with this drug can be implemented into existing pathways.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	It is mostly used for low-grade IDH-mutant tumours, prior to radiotherapy and chemotherapy, with the aim of delaying the need for these adjuvant therapies, and delaying the need for redo surgery
10a. How does healthcare resource use differ between the technology and current care?	
10b. In what clinical setting should the technology be used? (For example,	Specialist clinics

primary or secondary care, specialist clinics.)	
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	According to the evidence, it is expected that there are significant, clinically meaningful benefits.
11a. Do you expect the technology to increase length of life more than current care?	According to existing data, there is a doubling of the progression free survival.
11b. Do you expect the technology to increase health-related quality of life more than current care?	Following on from section 11a, there will be a concomitant improvement of quality of life
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Patients with these two tumour types are found across all ethnicities. These neoplasms are found in people in their 20s-50s, but can also occur earlier and later.

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	It is expected that the administration of the drug can be integrated into the current care pathway. It is expected that it may be easier than chemotherapy/radiotherapy. For details, please refer to the opinion of clinical oncologists.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Testing for the presence of IDH mutations is already standard of care. It is performed by the neuropathology departments, supported by molecular tests delivered through the genomic laboratory hubs.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	According to existing data (clinical trial outcome), there are substantial health-related benefits expected. (Chances of not needing another cancer therapy after 2 years were much higher in the vorasidenib group than in the placebo group (83% versus 27%)).

16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	The clinical trial outcomes suggest a significant positive impact on health-related benefits.
16a. Is the technology a 'step-change' in the management of the condition?	Yes, the treatment with the new drug can be considered a step change.
16b. Does the use of the technology address any particular unmet need of the patient population?	The clinical trial findings established a new standard of care for these patients.
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	According to the clinical trial outcome, the treatment is generally very well tolerated by patients. Common side-effects include fatigue, headache, and diarrhoea.

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes, according to the study documentation.

18a. If not, how could the results be extrapolated to the UK setting?	Not applicable
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	Improvement of progression free survival lengthening the time until the next cancer treatment.
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Cannot comment
18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Too early to comment
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	Too early to comment, not able to comment
20. How do data on real-world experience compare with the trial data?	Too early to comment.

Equality

21a. Are there any potential equality issues that should be taken into account when considering this treatment?	Access to adequate diagnostics is available to all ethnic groups. No difference in diagnostics between different patients, no difference in accessing the drug if available at any NHS trust.
21b. Consider whether these issues are different from issues with current care and why.	Cannot comment, please refer to opinions of clinical oncologists.

Key messages

22. In up to 5 bullet points, please summarise the key messages of your submission.	• Diagnosis of the condition (astrocytoma, oligodendroglioma) can be performed equally at all clinical neurosciences centres in the UK. • The drug improves progression free survival, and delays the need of subsequent cancer therapy • The drug is expected to be well-tolerated • •

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Vorasidenib for treating astrocytoma or oligodendroglioma with IDH1 or IDH2 mutations after surgery in people 12 years and over [ID6407]

Professional organisation submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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- Your response should not be longer than 13 pages.

About you

1. Your name	[redacted]
2. Name of organisation	The Society of British Neurological Surgeons (SBNS)
3. Job title or position	Consultant Neurosurgeon and Honorary Associate Clinical Professor, The Walton Centre NHS Foundation Trust, and The University of Liverpool.
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? Yes A specialist in the treatment of people with this condition? Yes A specialist in the clinical evidence base for this condition or technology? Yes Other (please specify):
5a. Brief description of the organisation (including who funds it).	A registered charity of British Neurosurgeons. Funded by subscription from its members, and the proceeds of the bi-annual scientific conference.
5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] **If so, please state the name of manufacturer, amount, and purpose of funding.**	No
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To delay progression of low grade IDH mutant gliomas following surgical intervention To delay the time before additional more toxic treatments To increase lifetime quality of life To increase time in paid employment To increase life expectancy (evidence not yet available)
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	• Improved progression free survival of more than 1 year. • Delay in further surgery, chemo, and / or radiotherapy of more than 1 year. • Significantly improved median and overall survival
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes. Vorasidenib is a potential new therapeutic option for patients with IDH mutant grade 2 gliomas who do not need radiotherapy or chemotherapy immediately. Vorasidenib has a low toxicity. It's use may delay the need for the more toxic radiotherapy and chemotherapy, allowing maintenance of a good quality of life over a longer period of time. Therefore, vorasidenib fills a current treatment gap.

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	At present, the recommended standard of care for patients with low grade glioma is maximal safe surgical resection, which can be followed by further surgery, radiotherapy, and or chemotherapy to delay recurrence. Patients usually die of the disease. Treatments carry significant risk of side effects, both cognitively and physically, and can lead to the affected patient being unable to work. Therefore, there is a growing tendency,

	when thought possible, to delay these patients from the toxic effects of chemoradiotherapy. Patients undergoing active surveillance will have regular imaging and clinical review.
9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	NICE guideline (NG99) Brain tumours (primary) and brain metastases in over 16s (updated 2021) EANO guidelines on the diagnosis and treatment of diffuse gliomas of adulthood (2023) - https://doi.org/10.1038/s41571-020-00447-z Therapy for Diffuse Astrocytic and Oligodendroglial Tumors in Adults: ASCO-SNO Guideline (2021) - https://doi.org/10.1200/JCO.21.02036
9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Yes, although: • Surgical intervention timing and extent is not agreed (or who should do the surgery and with what adjuncts) • Surveillance imaging protocols are not standardised (timing and imaging sequences) • Chemotherapy choice can vary
9c. What impact would the technology have on the current pathway of care?	The INDIGO trial found that in patients with grade 2 IDH-mutant glioma, vorasidenib significantly improved progression-free survival (mPFS 27.7 months vs 11.1 months) and delayed the time to the next intervention. Vorasidenib use may allow more toxic treatment delay to maintain quality of life.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes. Vorasidenib is available in some UK centres on an early access scheme for IDH mutant LGG.
10a. How does healthcare resource use differ between the technology and current care?	Use of Varasidenib will require regular blood monitoring, clinical review, and imaging. Compared to patients who where being reviewed with active surveillance, there will be more blood tests, and clinical reviews, and it is likely to require slightly more imaging (at least early on in the treatment).
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Vorasidenib should be in secondary care via specialist clinics by clinical or medical oncologists who routinely treat patients with brain tumours and regularly attend a neurooncolgoy MDT.

10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Improve capacity in medical neuro-oncology and associated support services
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes, vorasidenib provides a new treatment option for these patients following surgical intervention. Vorasidenib would be expected to delay the more toxic effects of chemo- and radiotherapy, allowing the patient to extent their quality of life and ability to work. It would also delay the need for further surgical procedures, and therefore delaying the associated potential complications.
11a. Do you expect the technology to increase length of life more than current care?	Yes, but this is not proven. The INDIGO trial design permitted crossover of patients in the placebo arm to the treatment arm, so potential effect on overall survival is not known. Additional research is required
11b. Do you expect the technology to increase health-related quality of life more than current care?	The INDIGO study suggested that quality of life was preserved on vorasidenib treatment compared to watchful waiting. It is likely therefore that there will be a significant positive impact for patients by avoiding or delaying adverse effects on cognition, employment, and function related to surgery, radiotherapy and chemotherapy. Overall, it is likely that vorasidenib will improve the patient's lifetime quality of life.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Less effective in contrast enhancing disease in higher grade tumours. The impact on <18 and > 65 years not clear (limited participation from these age groups in the trial) The relationship and importance of the extent and timing of surgery is not clear

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are	Patients will require regular blood tests and clinical and radiological monitoring, which will impact on existing cancer services.

there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	Treatment is life long or until progression, which also impacts on ability to have children, unless the treatment is stopped.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	MDT discussion and agreement. Histological verification of IDH mutant low grade glioma Lack of contrast enhancement on imaging. Progression that does not require other treatments (surgery, chemo or radiotherapy) To stop, evidence of progression, significant toxic side effects, or lack of patient tolerance.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Extending time in employment leading to Improved quality of life, economic security, and increased tax revenues by delaying the more toxic side effects of repeated surgery and radio / chemotherapy.
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and	Yes, Vorasidenib could significantly improving their time to progression, maintaining their quality of life for longer, and hopefully significantly improving their life expectancy. By delaying the need for second surgery, chemo and radiotherapy and their associated toxic effects.

how might it improve the way that current need is met?	
16a. Is the technology a 'step-change' in the management of the condition?	Yes, vorasidenib is a significant advance.
16b. Does the use of the technology address any particular unmet need of the patient population?	Yes, vorasidenib will fill a gap in the treatment pathway for patients with low grade glioma.
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Presentation with a significant side event would require treatment interruption and potentially subsequent dose reduction or treatment discontinuation. It may effect the patients quality of life during that time. The INDIGO trial suggested vorasidenib was well tolerated with mainly low grade toxic side effects. 10% had a raised alanine aminotransferase (ALT). Less than 5% had to discontinue vorasidenib. There were 3 serious side events, raised ALT, hepatic failure and hepatitis, which resolved before the end of the trial.. Treatment is life long, or until progression, toxicity, or patient non tolerance.

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes, but see 9b above. INDIGO included 5 UK centres.
18a. If not, how could the results be extrapolated to the UK setting?	N/A
18b. What, in your view, are the most important	Overall survival - no

outcomes, and were they measured in the trials?	progression-free survival - yes quality of life - yes need for ongoing treatment - yes
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	n/a
18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	no
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TAXXX]? [delete if there is no NICE guidance for the comparator(s) and	N/A

renumber subsequent sections]	
21. How do data on real-world experience compare with the trial data?	Not available

Equality

22a. Are there any potential equality issues that should be taken into account when considering this treatment?	No data is available regarding ethnicity and socioeconomic status of participants recruited to the INDIGO trial, so it is not possible to comment.
22b. Consider whether these issues are different from issues with current care and why.	Existing health inequalities, such as differential healthcare access, will be relevant to vorasidenib use, particularly since this treatment will require greater patient engagement with secondary care.

Topic-specific questions

23 [To be added by technical team at scope sign off. Note that topic-specific questions will be added only if the treatment pathway or likely use of the technology remains uncertain after scoping consultation, for example if there were differences in opinion; this is not expected to be required for every appraisal.] **if there are none delete highlighted rows and renumber below**	

Key messages

24. In up to 5 bullet points, please summarise the key messages of your submission.	• Significant increase in progression free survival in a group of patients wiht IDH mutant low grade gliomas • Treatment helps delay more toxic treatments, and increase the time between surgical interventions • The treatment should be given by clinical neurooncologists after neurooncology MDT discussion • Fits easily into current treatment pathways • Significant economic benefit may not be incorporated into QALY calculation.

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Vorasidenib for treating astrocytoma or oligodendroglioma with IDH1 or IDH2 mutations after surgery in people 12 years and over [ID6407]

Clinical expert statement

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

NICE National Institute for Health and Care Excellence

Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals (section 3.2) for more information.

The deadline for your response is **5pm** on **Monday 16 June 2025.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

NICE National Institute for Health and Care Excellence

Part 1: Treating astrocytoma or oligodendroglioma with IDH1 or IDH2 mutations after surgery and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Prof Keyoumars Ashkan
2. Name of organisation	The Society of British Neurological Surgeons (SBNS)
3. Job title or position	Professor of Neurosurgery and Consultant Neurosurgeon, King's College Hospital, London.
4. Are you (please tick all that apply)	☒ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with astrocytoma or oligodendroglioma with IDH1 or IDH2 mutations after surgery? ☒ A specialist in the clinical evidence base for astrocytoma or oligodendroglioma with IDH1 or IDH2 mutations after surgery or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	In part 1, the only additional point I would like to make relates to question 21. I have therefore completed the corresponding box; otherwise nothing further to add to the remaining boxes over and above my organisation submission. I have also completed part 2.

7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	
8. What is the main aim of treatment for astrocytoma or oligodendroglioma with IDH1 or IDH2 mutations after surgery? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	
10. In your view, is there an unmet need for patients and healthcare professionals in astrocytoma or oligodendroglioma with IDH1 or IDH2 mutations after surgery?	
11. How is astrocytoma or oligodendroglioma with IDH1 or IDH2 mutations after surgery currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	

• How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	

16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials?	

• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	Yes, The British Neuro-Oncology Society published an appraisal of the technology in May 2025. The appraisal summarised the study for the members. Of note, it provided a section under the heading: "Results of INDIGO trial need to be interpreted cautiously because:" where it listed the following points: • PFS and Time to next intervention improved but no evidence of overall survival benefit yet • This study did not reveal the details of extent of surgery – i.e. percentage of patients who had gross total resection or subtotal resection or biopsy only. 21.5% patients have undergone 2 or more surgeries before enrolment • Study did report that 16.6% patients had tumour <2 cm and rest 83.4% had ≥ 2cm tumour, but it did not report the maximum size of tumours deemed eligible for the study • Patients included in trial were those who had surgery between 1-5 years ago to understand the trajectory of disease with median interval of 2.4 years between last glioma surgery and randomisation. No evidence of use immediately after first surgery, if there is residual disease. • This study did not show how many patients were recurrent or had residual disease, and did not therefore show if there was any difference in PFS in these subgroups • Although the inclusion criteria were patient 12 years or over, there was only 1 patient (in placebo arm) who was less than 18 years. At the other end of the age spectrum, there were only 3 patients who were ≥65 yr (2 in Vora arm and 1 in placebo group) • About 2/3rd (67%) patients had a frontal tumour

	• Neurocognitive side effects are not known
23. How do data on real-world experience compare with the trial data?	
24. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme.	

Find more general information about the Equality Act and equalities issues here.	

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Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

1, Significant increase in progression free survival in a group of patients with IDH mutant low grade gliomas, although no data on impact on overall survival as yet.
2, Treatment helps delay more toxic chemotherapy/ radiotherapy treatments.
3, Fits easily into current treatment pathways.
4, In the trial, patients were not stratified based on the extent of surgical resection (biopsy vs partial resection vs radical resection); it is therefore hard to know if there were any differential benefits for each patient cohort.
5, Duration of treatment (and therefore the costs) will need further clarification since in the trial the treatment was continued until disease progression (in practice could be decades) or unacceptable toxicity.

Thank you for your time.

Your privacy

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Vorasidenib for treating astrocytoma or oligodendroglioma with IDH1 or IDH2 mutations after surgery in people 12 years and over [ID6407]

Clinical expert statement

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals (section 3.2) for more information.

The deadline for your response is **5pm** on **Monday 16 June 2025.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

NICE National Institute for Health and Care Excellence

Part 1: Treating astrocytoma or oligodendroglioma with IDH1 or IDH2 mutations after surgery and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Heng Jeng Ching
2. Name of organisation	University Hospital Southampton NHS Foundation Trust
3. Job title or position	Consultant Clinical Oncologist
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with astrocytoma or oligodendroglioma with IDH1 or IDH2 mutations after surgery? ☐ A specialist in the clinical evidence base for astrocytoma or oligodendroglioma with IDH1 or IDH2 mutations after surgery or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	No direct or indirect links to tobacco industry, past or current.

8. What is the main aim of treatment for astrocytoma or oligodendroglioma with IDH1 or IDH2 mutations after surgery? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	The main treatment goal for IDH1 or IDH2 gliomas is to halt tumour growth or progression and, ideally, to delay the need for subsequent lines of therapy, as these treatments are non-curative.
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	In the context of glioma – stable disease is considered a clinically significant treatment response.
10. In your view, is there an unmet need for patients and healthcare professionals in astrocytoma or oligodendroglioma with IDH1 or IDH2 mutations after surgery?	The treatment outlook for patients with IDH-mutant glioma after surgery has remained largely unchanged for several decades, resulting in a significant unmet need. Our aim is to avoid offering radiation therapy—which does provide a survival benefit—too early, if it can be safely delayed for several years. Therefore, it is necessary to intervene with treatments that carry low morbidity and can delay the need for therapies associated with long-term, irreversible side effects.
11. How is astrocytoma or oligodendroglioma with IDH1 or IDH2 mutations after surgery currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	According to the pathway appraised by NICE, active surveillance remains the most appropriate approach for patients under the age of 40 when there is no definite residual disease post-operatively. At the other end of the spectrum, for patients over 40 with only a biopsy (and no resection), the standard of care is radiotherapy combined with chemotherapy, as per RTOG 9802. However, there is a wide spectrum of patients in between these scenarios, and clinical practice varies across the country. My perspective is based on my experience in clinical practice in England, UK. This technology has the potential to delay the need for primary treatment, particularly in patients who require intervention before the age of 40; however, it could also be applicable to selected patients over the age of 40.

12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	The current technology is not an approved treatment within NHS clinical practice. Patients who are currently accessing this technology or treatment are doing so via a compassionate access scheme. This technology should only be delivered in a specialist environment. Most centres are expected to have the resources for training and will deliver it as part of outpatient neuro-oncology systemic anti-cancer services.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	The INDIGO trial has not yet matured, and the rationale for offering this treatment is to delay the need for more definitive therapies, which are associated with irreversible neurocognitive side effects. We also know that the vast majority of patients receiving this drug remain clinically well and rarely require emergency inpatient services. We anticipate that this approach will result in measurable improvements in patients' quality of life
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	This treatment is only applicable in patients with non-enhancing IDH-mutant astrocytoma or oligodendroglioma, where there is no urgent need to start radiotherapy or chemotherapy.
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient	This treatment requires outpatient management, with frequent blood tests at the start of therapy, which can be reduced once the patient's condition is stable. Apart from these blood tests, there is very little need for hospital services.

acceptability or ease of use or additional tests or monitoring needed)	
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	There are two key factors in monitoring this treatment. First, ensuring that the patient is tolerating therapy, which is assessed through regular blood tests. Second, MRI scans are performed to evaluate whether the tumour is responding to treatment. If there is evidence of progression, this treatment must be discontinued, and the patient would need to consider more definitive therapies such as radiotherapy, chemotherapy, or, if clinically appropriate, surgery.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	Yes. While quality-adjusted life year (QALY) calculations capture overall survival and general health-related quality of life, there are additional benefits from this treatment that may not be fully reflected in such measures. These include the ability to maintain patients in a clinically well state with minimal hospital visits, reduced exposure to the irreversible neurocognitive side effects of more definitive therapies, and the psychological benefit of delaying the need for radiotherapy, and, or chemotherapy. Collectively, these factors contribute to a meaningful improvement in patients' day-to-day functioning and overall well-being, which may not be fully captured in standard QALY assessments.
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	Vorasidenib being the first targeted treatment specifically for low-grade gliomas with IDH mutations is indeed a major step-change in neuro-oncology. Low-grade gliomas have historically lagged behind other tumour types in terms of effective, targeted therapies. Most treatment options until now have been limited to surgery, radiation, and conventional chemotherapy—approaches that can have significant side effects and often don't specifically address the underlying biology of the tumour. As of now, vorasidenib is not widely available in the UK. Some patients have accessed the medication through compassionate use or named patient access programs, facilitated by the, Servier . However, these avenues are limited and not universally accessible.

19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Vorasidenib is generally well tolerated by patients. The most common side effects observed include: • Grade 1 diarrhea, typically occurring during the initiation phase, which is usually mild and manageable. • Asymptomatic liver dysfunction, which requires careful monitoring—typically with monthly liver function tests to detect and manage any abnormalities early. A key advantage of vorasidenib is that the majority of patients are able to maintain an active lifestyle while on treatment. Many continue working, studying, and contributing to society without significant disruptions. The primary goal of vorasidenib is to minimise interruptions to patients' day-to-day lives, supporting their ability to engage fully in education, employment, and other meaningful activities. This not only benefits patients individually but also has a positive impact on broader social and economic productivity.
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	The INDIGO trial, the pivotal study for vorasidenib, closely reflects current UK clinical practice. It enrolled patients with IDH1/2-mutant low-grade gliomas following surgery, mirroring the population eligible for this treatment in the UK. While the trial setting was more controlled and selective, with stricter eligibility criteria and monitoring compared to routine NHS practice, which can be more variable, the overall patient population and management approach align well with UK standards.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No

23. How do data on real-world experience compare with the trial data?	Real-world experience with vorasidenib appears to be very similar to the data observed in clinical trials. When patients selected for treatment reflect the trial's inclusion criteria, outcomes in terms of efficacy and safety closely mirror those reported in the INDIGO trial. This consistency supports the applicability of the trial results to routine clinical practice and reinforces the reliability of vorasidenib's benefits and tolerability outside of the controlled trial environment.
24. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why.	A significant clinical dilemma arises with patients who have already undergone radiation and chemotherapy and subsequently experience disease progression. While vorasidenib's mechanism suggests potential efficacy in this setting, such use has not been formally tested in clinical trials, including INDIGO, which focused on treatment-naïve or post-surgical patients without prior progression. Given this gap, it would be valuable to consider establishing a managed access scheme or dedicated clinical trial targeting patients outside the current inclusion criteria—specifically those with prior radiation and chemotherapy who might still benefit from vorasidenib. This approach would help generate real-world evidence on efficacy and safety in this subgroup and provide access to potentially beneficial treatment for patients with limited options.

More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Vorasidenib is a groundbreaking targeted treatment for low-grade gliomas with IDH mutations, addressing a significant unmet need in this patient population.
It offers a major step-change by specifically inhibiting mutant IDH enzymes, potentially slowing tumour progression with fewer side effects than traditional therapies.
The INDIGO trial, which reflects UK clinical practice, demonstrated promising efficacy and good tolerability, with mild diarrhea and manageable liver enzyme elevations as the main adverse effects.
Real-world experience aligns closely with trial data, supporting its use in appropriately selected patients.
However, there remains an important gap regarding its use in patients who have progressed after radiation and chemotherapy, highlighting the need for further studies or access schemes in this group.

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Single Technology Appraisal

Vorasidenib for treating astrocytoma or oligodendroglioma with IDH1 or IDH2 mutations after surgery in people 12 years and over [ID6407]

Clinical expert statement

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NICE National Institute for Health and Care Excellence

Part 1: Treating astrocytoma or oligodendroglioma with IDH1 or IDH2 mutations after surgery and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Dr Liam Welsh
2. Name of organisation	The Royal Marsden Foundation NHS Trust
3. Job title or position	
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with astrocytoma or oligodendroglioma with IDH1 or IDH2 mutations after surgery? ☒ A specialist in the clinical evidence base for astrocytoma or oligodendroglioma with IDH1 or IDH2 mutations after surgery or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None

8. What is the main aim of treatment for astrocytoma or oligodendroglioma with IDH1 or IDH2 mutations after surgery? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	To control the disease in the long-term; to improve seizure control; to prevent neurological deterioration; to allow for the deferral of further neurosurgery, and the need for brain radiotherapy and cytotoxic chemotherapy with their attendant long-term side-effects including neuro-cognitive deterioration.
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	Absence of tumour growth with neurological stability. Improvement in seizure control.
10. In your view, is there an unmet need for patients and healthcare professionals in astrocytoma or oligodendroglioma with IDH1 or IDH2 mutations after surgery?	Yes, there is a substantial unmet need in this population of mostly younger working age patients. Receiving brain radiotherapy and cytotoxic chemotherapy can have an irreversible impact on neuro-cognitive function which can limit quality of life and the ability to live and work independently. Moreover, these treatments are not curative, and will merely hold back the disease for a period of time before there is tumour recurrence and/or malignant transformation.
11. How is astrocytoma or oligodendroglioma with IDH1 or IDH2 mutations after surgery currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	There are specific NICE guidelines (NG99) regarding the management of patients with astrocytoma or oligodendroglioma with IDH1 or IDH2 mutations after surgery - "**Brain tumours (primary) and brain metastases in over 16s**". Sections 1.2.6 through to 1.2.10 of NG99 address the management of these patients. These guidelines make a distinction between patients who are over or under the age of 40 years, and those who have residual disease following surgery. However, the NG99 guidelines are not entirely in keeping with current clinical practice and are not wholly concordant with current EANO guidelines covering this area of practice (**EANO guidelines on the diagnosis and treatment of diffuse gliomas of adulthood – Nat Rev Clin Oncol 2020**). The current EANO guideline for patient with WHO grade 2 IDH-mutant oligodendroglioma states: "Following surgery, watch-and-wait strategies are justified in those with gross total resection and potentially also in younger patients (<40 years of age) with incomplete resection if the tumour has not yet

	caused neurological deficits beyond symptomatic epilepsy.". For patients with WHO grade 2 IDH-mutant astrocytoma the EANO guideline states: " Younger patients (pragmatic cut-off ~40–45 years of age) who are asymptomatic or with seizures only, can be managed through observation alone after gross total resection. Involved-field radiotherapy (50 Gy in 1.8 Gy fractions) should be considered for patients with incomplete resection and/or for patients aged >40 years.". The **IWOT (EORTC 1635-BTG)** clinical trial attempted to address the timing of brain RT and adjuvant chemotherapy following surgery for newly diagnosed patients with IDH-mutant astrocytoma. This trial was closed due to poor accrual as both patients and clinicians had strong views on the best management after surgery and were largely unwilling to submit to randomisation to surveillance or upfront brain RT and adjuvant chemotherapy. This episode illustrates the uncertainties and difficulties surrounding the management of this group of patients and the remaining uncertainty as to the optimal timing of brain RT and adjuvant chemotherapy following surgery for many patients with newly diagnosed low grade IDH-mutant gliomas. There are certainly differences across the NHS regarding the timing of treatment after surgery for this group of patients. Furthermore, many patients with low-grade gliomas are reluctant to submit to brain RT and adjuvant chemo due to the perceived toxicities (particularly neuro-cognitive function, and fertility). The new technology of IDH-inhibitor therapy enters this fraught area of practice as a significantly less toxic alternative to treatment with brain RT and chemotherapy, and as a treatment that has been shown to be superior to surveillance in terms of tumour control, and seizure control. The Indigo clinical trial demonstrated that the IDH-inhibitor vorasidenib can delay the need for brain RT and chemotherapy in patients with grade 2 IDH-mutant astrocytoma and oligodendroglioma who have had surgery. DH-inhibitor therapy therefore

	represents a new, low toxicity, low risk treatment pathway for patients with grade 2 IDH-mutant astrocytoma and oligodendroglioma who have had surgery.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	IDH-inhibitor therapy will be used instead of surveillance and potentially to some extent instead of brain RT and chemotherapy for patients with grade 2 IDH-mutant astrocytoma and oligodendroglioma who have had surgery. IDH-inhibitor therapy will be used in a hospital outpatient clinic setting in specialist neuro-oncology treatment centres. I do not perceive that the introduction of IDH-inhibitor therapy into clinical practice will require significant investment, but there will be additional clinical workload for neuro-oncologists due to the need to manage regular blood tests for liver function monitoring and for pharmacies managing the dispensing of the drug on a monthly basis.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	It is too early to have been able to demonstrate a survival benefit for IDH-inhibitor therapy for patients with grade 2 IDH-mutant astrocytoma and oligodendroglioma who have had surgery, but it is plausible that this will be the case. This drug is likely to change the natural history of these incurable brain tumours in a favourable direction. By delaying the need for brain RT and chemotherapy, which we know will achieve only a finite period of tumour control, it is very likely that IDH-inhibitor therapy will extend the lives of patients with grade 2 IDH-mutant astrocytoma and oligodendroglioma who have had surgery. By enabling patients with grade 2 IDH-mutant astrocytoma and oligodendroglioma who have had surgery to defer brain RT and chemotherapy and thereby avoid the attendant side-effects, IDH-inhibitor will permit effective treatment with improved quality of life. Vorasidenib has a very favourable side-effect profile compared to brain RT and chemotherapy.

14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	The technology is specifically relevant only to patients with WHO grade 2 IDH-mutant astrocytoma and oligodendroglioma who have had surgery.
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	The technology of IDH-inhibitor therapy is vastly easier to deliver and manage than brain RT and/or cytotoxic chemotherapy and is only marginally more difficult to manage than surveillance.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Clinical and radiological monitoring would be used to determine treatment start/stop – this would be no different from post-surgery surveillance
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	Potentially, yes – it will be difficult to capture the benefits in terms of maintained neurological wellbeing and ability to live and work relatively normally. Seizure control is likely to be improved with vorasidenib. It is an oral medication.
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Vorasidenib represents a breakthrough for patients with IDH-mutant low-grade gliomas. This treatment represents a major advance over surveillance followed by RT and cytotoxic chemotherapy at progression. It is likely that a subgroup of these patients will derive a long term benefit from receiving this treatment which

• Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	could substantially alter the natural history of these diseases for the better. This technology does represent a 'step-change' in my view – there is nothing else like it available for patients with IDH-mutant gliomas. There is a major unmet need for these patients in terms of achieving tumour control, seizure control and maintaining neurological well being with acceptable side-effects – this new technology addresses these needs.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The main (and typically the only) side-effect with vorasidenib is liver function disturbance. This does necessitate regular blood tests to monitor liver function. A very small number of patients will experience liver toxicity necessitating the discontinuation of this medicine. There is therefore a minor impact in terms of the need for more frequent hospital attendances for monitoring. Vorasidenib is also incompatible with pregnancy and fathering children, which will impact on younger patients.
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	The Indigo trial is the relevant clinical trial. This trial was conducted, in part, in the UK. The trial fitted into existing UK practice and recruitment to the trial was rapid. The trial outcomes are directly relevant to UK neuro-oncology practice. The most important outcomes are tumour control, seizure control, toxicity, and QoL. Impact on survival cannot be quantified and will take many years to establish. It is not reasonable to expect the Indigo trial to address survival. However, it can be anticipated that the improvement in tumour control, and the ability to defer the need for RT and chemo will likely lead to improved survival.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	There are unpublished data from the Indigo trial and from additional pre-clinical and clinical studies of vorasidenib that are relevant.
23. How do data on real-world experience compare with the trial data?	Real-world experience with vorasidenib in the UK comes from patients receiving this treatment via the Managed Access Programme (MAP) which opened in the UK in mid-2024. I have over 40 patients on treatment with vorasidenib in the MAP – my experience in treating these patients mirrors my experience in

	treating patients in the Indigo trial. I have not observed any unexpected or additional side-effects. The Indigo trial data therefore appear to be realistic and relevant in routine neuro-oncology practice.
24. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme.	I am not aware of any equalities issues specific to this technology.

Find more general information about the Equality Act and equalities issues here.	

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Patients with IDH-mutant low-grade gliomas are often managed with surveillance following surgery, regardless of guidelines; the standard of care for patients with progressive IDH-mutant low-grade gliomas after surgery is radiotherapy and adjuvant chemotherapy, treatments that are associated with significant short-term and longer-term side-effects, including neuro-cognitive impairment.

Vorasidenib has been shown to result in tumour control, seizure control, and delay in the need for brain RT and chemotherapy for IDH-mutant low-grade glioma patients following surgery.

Vorasidenib is well tolerated with a low impact on QoL; the main side-effect of liver toxicity is easily managed and does not usually impact on patient welling or QoL.

Vorasidenib represents a breakthrough in the care and treatment of patients with IDH-mutant low-grade gliomas, and is a new standard of care for such patients.

Thank you for your time.

Your privacy

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Single Technology Appraisal

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Patient expert statement

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources

Information on completing this form

In part 1 we are asking you about living with astrocytoma or oligodendroglioma with IDH1 or IDH2 mutations after surgery or caring for a patient with astrocytoma or oligodendroglioma with IDH1 or IDH2 mutations after surgery. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

NICE National Institute for Health and Care Excellence

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Your response should not be longer than 15 pages.

The deadline for your response is **5pm** on **Monday 16 June 2025.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Patient expert statement

Vorasidenib for treating astrocytoma or oligodendroglioma with IDH1 or IDH2 mutations after surgery in people 12 years and over

NICE National Institute for Health and Care Excellence

Part 1: Living with this condition or caring for a patient with astrocytoma or oligodendroglioma with IDH1 or IDH2 mutations after surgery

Table 1 About you, astrocytoma or oligodendroglioma with IDH1 or IDH2 mutations after surgery, current treatments and equality

1. Your name	Hugh Adams
2. Are you (please tick all that apply)	☐ A patient with astrocytoma or oligodendroglioma with IDH1 or IDH2 mutations after surgery? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with astrocytoma or oligodendroglioma with IDH1 or IDH2 mutations after surgery? ☒ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	Brain Tumour Research
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☒ No (please review all the questions and provide answers when possible) ☐ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☐ I agree with it and **will be** completing

5. How did you gather the information included in your statement? (please tick all that apply)	☐ I am drawing from personal experience ☒ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: ☐ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with astrocytoma or oligodendroglioma with IDH1 or IDH2 mutations after surgery? **If you are a carer (for someone with astrocytoma or oligodendroglioma with IDH1 or IDH2 mutations after surgery) please share your experience of caring for them**	My experience is as a patient advocate and my submission is from their viewpoint to give them a voice
7a. What do you think of the current treatments and care available for astrocytoma or oligodendroglioma with IDH1 or IDH2 mutations after surgery on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	We have shown little progress in this area and whether that is due to poor research funding, a lack of endeavour, issues with the regulatory system is of no matter for a patient diagnosed with a LGG
8. If there are disadvantages for patients of current NHS treatments for astrocytoma or oligodendroglioma with IDH1 or IDH2 mutations after surgery (for example, how they are given or taken, side effects of treatment, and any others) please describe these	Please see patient statements at the end of my submission for feedback on issues with current treatments namely chemotherapy and radiotherapy

9a. If there are advantages of vorasidenib over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** **9c. Does vorasidenib help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	9a. Please see patient statements at the end of my submission in advocating for NICE approval for Vorasidenib 9b. The delaying of need to administer harsher treatments 9c. Yes – see above
10. If there are disadvantages of vorasidenib over current treatments on the NHS please describe these. For example, are there any risks with vorasidenib? If you are concerned about any potential side effects you have heard about, please describe them and explain why	None noted in patient submissions below
11. Are there any groups of patients who might benefit more from vorasidenib or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	Younger patients
12. Are there any potential equality issues that should be taken into account when considering astrocytoma or oligodendroglioma with IDH1 or IDH2 mutations after surgery and vorasidenib? Please explain if you	

think any groups of people with this condition are particularly disadvantage Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	
13. Are there any other issues that you would like the committee to consider?	As a campaigning charity and as provider of the secretariat for the APPG on Brain Tumours Brain Tumour Research have engaged with Servier (manufacturer of Vorasidenib) and facilitated a meeting between Servier and several political stakeholders including Dame Siobhain McDonagh in December 2023 with the aim to understanding their ambitions and any barriers in the route to UK market access. They were very engaged and impressed as a company with a real drive to do all they could to improve outcomes for UK LGG patients. We have also worked with LGG patients and their families and helped give them a voice at Westminster (and at Holyrood) and what follows is the patient voice. We have been supported in gathering this content by a family affected who are also closely associated with a member charity of Brain Tumour Research namely Astro Brain Tumour Fund (ABTF).

	A summation of a patient family member overview: LGG's are clearly an area of 'unmet need 'so there is a desperate need for patients with LGGs , to have a treatment available to them . Currently patients are often guided to 'watch and wait' – wait for what and why? This has led to this course of action being now described as active surveillance. At this point they receive no treatment but there are side effects to receiving no treatment. The affect on mental wellbeing , depression impinging on work and day to day quality of life . Being told you have a very serious illness but knowing you are receiving no treatment , is devastating . Knowing the future is likely progression of the tumour and thereafter radio and chemo (which is not a cure) compounds the cruelty of such a diagnosis . LGGs generally affect young people in the prime of their life .Radiotherapy to the brain (unlike other parts of the body) risks long term cognitive problems . Attending hospital for 5 days for a continuous period , around 6 weeks , causes severe disruption to education or work . Chemotherapy has serious side effects , again causing real difficulties in maintaining studies , work and caring for children . Chemotherapy is not effective and real difficulties arise because of the blood brain barrier . These 'treatments ' , should be delayed for as long as possible . Vorasidenib , is a tablet taken each day at home . The patient has to be 'monitored' , initially every 2 weeks , thereafter each month . Compared to attendance for radiotherapy (continuous 6 weeks) and approx a year of chemo , with all the side effects , Vorasidenib results in an increased quality of life for these patients . This is a new , first in decades, drug , the big advantage being it crosses the blood brain barrier and has been demonstrated in a clinical trial to increase progression free survival by more than double the time for those on the placebo. Time to next intervention(ie radio / chemo) is also an important measure , as this was not reached at the time of the closing of the trial . Demonstrating , these harsh

	treatments are substantially delayed by Vorasidenib . For these patients being able to maintain a reasonable quality of life for as long as possible , is absolutely vital . **A patient quote in support of Vorasidenib as their clinical pathway;** *"Given the opportunity to take vorasidenib rather than rely on Radiotherapy and Chemotherapy has given me a fighting chance of survival without the disruption and long term side effects of the traditional therapies, allowing me to carry on in society and remain a key technical contributor in B2B trade show events, valued in the 10s of billions in the UK."* **Case Study 1 - Please give them hope for the future.** *“Vorasidenib has given our son hope”* Vorasidenib has given our son, and others living with Low Grade Gliomas (LGGs), hope for the future as these tumours almost always progress to become High Grade which are invariably fatal. Our lives changed forever when our 25-year-old son was diagnosed with an astrocytoma. We were all in shock. He underwent brain surgery in February 2020 and most of the tumour was successfully removed, however we were told that the chances of tumour regrowth were ‘one hundred per cent’. We felt powerless and desperate. Our son's diagnosis was obviously devastating to him, to his partner, to us and to his sister. He was very afraid and said "Mum, am I going to die?", no words a mother ever wants to hear. His fear filled me. As a parent it is like waking up in a

	nightmare with no way out. There is no relief from the anxiety and sadness. You wake up with it, struggle throughout the day, and go to bed with it. How our son must have felt is unimaginable. There was no hope as there had been no drug treatments in the preceding 20 years. We were in a very dark place and needed hope to exist. The impact on him and us was and is indescribable. In 2022 an MRI scan showed evidence of tumour regrowth and our son was referred to the Royal Marsden Hospital where there followed a period of 'watchful waiting', a state of uncertainty which was frustrating and stressful and made usfeel constantly anxious. In the meantime, we had become aware that Vorasidenib was undergoing what was known as the Indigo trial. However, we were told that although our son was clinically eligible to participate, the trial had closed. This was obviously hugely disappointing. Then, in 2023, the neuro-oncologist told us that tumour had grown further and that our son's condition had reached a stage at which there was a mandate for radiotherapy and chemotherapy. By early 2024 preparations were made for our son to commence 6 weeks of daily radiotherapy followed by 18 months of chemotherapy. The negative impact on him was immense. We were all devastated. He was and still is a highly active and competitive athlete; the prospect of the treatments had an immediate detrimental effect on his physical, psychological and emotional wellbeing. Just before his last neuro-oncology appointment prior to commencing radiotherapy, we learned that Vorasidenib had become available on a compassionate use basis. The neuro-oncologist contacted the manufacturer, Servier, and the next day our son received a phone call from the Royal Marsden offering him access to Vorasidenib. He was ecstatic! His quality of life would now not be affected by arduous radiotherapy and chemotherapy treatments, and instead of the onerous regime of

	daily travelling to the hospital, he could take oral medication at home. This was an immense relief. Our son has now been taking Vorasidenib every day for over a year. He has been having MRI scans at three monthly intervals and thankfully the tumour has remained stable with no further regrowth. Additionally, monthly blood tests show that he is tolerating the drug well with minimal side effects. Vorasidenib has given our son, his partner, and his family hope - something none of us had before. For the first time we can dare to be optimistic for the future. He is able to carry on with his work and leisure activities and lead a normal life. He sees his hopes and aspirations for the future as being entirely dependent upon continued access to Vorasidenib. Vorasidenib is a major breakthrough for a cancer that previously had no other oral drug treatment options. We are very concerned that if this treatment became unavailable, our son's wellbeing would suffer greatly due to the inevitable prospect of tumour regrowth and the impact of the radiotherapy and chemotherapy treatments on his quality of life. We know that he would be devastated. In short, we hope that Vorasidenib will prolong our son's life and may even halt the tumour growth completely. Please give him and other young patients like him a chance to continue with this drug therapy. Please give them hope for the future. **Case Study 2 - The whole family are constantly on alert.** *"There seems little point in seeking researchers, funding projects if at the end of the day excellent outcomes cannot be supported by the NHS"*

	Our son ****, then aged 37, suffered an unexpected seizure at work in July 2019 and a scan showed a large, right frontal brain tumour that was operated on and removed ten days later at RSCH, Brighton. Some tumour remains. Histology and further sequencing defined it as an Oligodendroglioma IDH mutant and 1p 19q co-deleted (WHO grade2). That was five years ago and he has been closely monitored since. Fortunately the remaining tumour has, as far as I know, shown little to no change. But his oncologist suggested in late 2023 that he then opt to receive radiotherapy but seemingly with no particular rationale for this. Coincidentally the success of Vorasidenib was, around the same time, reported on in the USA and we have been avidly following its progress. At the start of this journey **** declined the recommended radio/ chemotherapy after taking a second opinion from an expert on Oligodendrogliomas who suggested 'Watch and Wait.' This as **** was then only aged 37 and any therapy might have had detrimental side effects then and later on in life. **** is very determined still to avoid therapy that might affect his cognitive function and his ability to work. Of course, therapy and time off work would also be a huge cost to the state. He sees the patients that have had or are undergoing chemo/ radio while he is waiting at his Clinics and is upset by this and is adamant to leave making a decision on taking this route for as long as possible. He decided to return to the same consultant in July 2024 to discuss the suggested radiotherapy but when the consultant was told about the possibility of **** being offered Vorasidenib the consultant was very excited and recommended this as the most definite route he should take. His consultant in Brighton then applied to Servier and he has been on the drug since September 2024 with no problems. However he

	has been told that this will only be supplied by Servier for 18 months. If acceptance into the NHS is not forthcoming, the NHS Trust in Brighton cannot fund it. Of course this adds to the anxiety already felt awaiting scan and blood test results, clinic visits and the consequences of seizures that can happen anywhere at any time. **** is now 42 and almost immediately after his craniotomy returned to full time employment as a web developer for a trade events company and he still manages to travel abroad on holiday and business. Unfortunately, his favourite activities around water sports are out of bounds now and he is also reluctant to go snowboarding as he is concerned he might injure others if he has a seizure. He has a wide network of friends who all support each other and he is also much needed by them and their children. He lives alone without any help and has never needed benefits during these health issues. We, his parents, are in our mid seventies and came down from Suffolk to live in Brighton to be close at hand. But he is there for us too, enjoying taking us out for meals and theatre etc. His older brother, ****** is extremely supportive but is also permanently busy with work as a Professor in Computational Genomics at Queen Mary's. **** is very close to him and his niece ****, aged 13 who like all of us becomes very stressed with ****'s situation at times. When she visits Brighton they spend lots of time together chatting and board gaming. She is an only child and doesn't have many close relatives. To lose her Uncle early would be devastating. The whole family are constantly on alert. **** suffers the inevitable seizures related to low grade gliomas for which he takes medication but he is very philosophical about these. Nonetheless, the uncertainty that Vorasidenib might not be funded, and especially if it is successfully arresting further tumour growth, is causing further unnecessary anxiety for him, his family and

	friends. And no doubt worry to the other patients who might be benefiting from early access. I understand that, worldwide there has been some improvement in seizure frequency and indeed **** went from having monthly seizures to them being spaced 13 then 18 weeks apart shortly after starting on Vorasidenib. We have also noticed that he is more chatty, less worried and happier in himself. Access to this drug has given him more confidence than just 'Watching and Waiting.' So to conclude, a positive decision on provision of Vorasidenib through the NHS would be extremely welcome and as soon as possible. This drug is so far a much awaited, unique ground breaker so we must try to make use of it after all these years of lack of progress for brain tumour sufferers. It might not be a cure but it could act as a growth inhibitor while a permanent cure is found. There seems little point in seeking researchers, funding projects if at the end of the day excellent outcomes cannot be supported by the NHS. I remember ****'s surgeon who had just seen the tumour on a scan saying to me 'This will change the rest of your lives.' I thought he was being overly dramatic at the time but of course have since realised he was just warning us of the cruel reality.

	Case Study 3 - A patient treated with Radiotherapy and Chemotherapy *"Whilst it seems everyone else has been able to get on in life with girlfriends , independent living and travel, he has been stuck with battling a deadly tumour."* Our son was diagnosed with a low grade glioma in June 2020, following a seizure and subsequent referral to a first seizure clinic. The first seizure he had was unwitnessed and was misdiagnosed by a GP as a panic attack. There were six months between each seizure; therefore, six months of the potential to have treatment were missed. The effect this had on our whole family was utterly devastating. One minute we were planning a holiday, the next we were contemplating losing our oldest son to a tumour. His siblings were frozen, unable to see a future for themselves. Life had changed beyond all recognition—the thought of ever being happy again as a family was quashed in an instant. There was nothing but grief to look forward. This was in lockdown, so he had an MRI before seeing a neurologist. The MRI scan revealed that the tumour was in a position against the motor board in his brain, making removal of the tumour extremely dangerous with the potential for paralysis. One method of doing this would be by having him awake for an operation that could easily take 8 hours. He had a history of anxiety, and it was felt that this would not be an option for him. A surgeon did not see him to talk this through. We were advised that the only approach was to watch and wait. As the tumour was steadily growing, we felt very uneasy about this, and we sought a second opinion privately. We were advised that the operation could be done under the NHS by having an MRI scanner running the whole time he was being operated on. A discussion with the surgeon in Charing Cross would no doubt have informed us of this possibility. We decided that we should try this to slow the progress of the tumour. Our GP made a referral to Queens Square, and our son was put on Mr Thornes' list. The operation was done

	in January 2022. It was eight hours long. Unfortunately, he developed supplementary motor area syndrome (SMA). This meant he was paralysed down the right side with no use of his arm or leg. Full movement of all limbs was gradually regained after more than 2 months, with his fingers being the last to recover fully. His scar appeared to be healing well; however, swelling and leakage were evident. We were pushed from pillar to post trying to get the correct treatment for him. Queens Square refused to see him. If Mr Thorne had been working that week, this certainly would not have been the case. Five hours in Hillingdon A&E was a waste of time as the consultant there merely advised to get him seen at Queens Square asap. When Mr Thorne returned the following week, he diagnosed an infection and expressed concern that the bone flap was infected. Oral antibiotics were tried with no effect. He decided that the bone must be removed, and our son would have to have a section of his skull removed for several months to allow the infection to clear. He had a second operation opening the scar that had healed. He would have to be very cautious if he went out. He bought protective hats for himself. He had a PIC (peripherally inserted central catheter) inserted in the main vein in his arm and was put on IV antibiotics, given daily at home by his dad. After three months, Mr Thorne felt confident the infection had gone and he could have the third operation to fit a prosthesis to the hole in his skull. Three operations in one year with a change of appearance and loss of confidence. It was horrendous. Six months after the final operation, the tumour had regrown, and radiotherapy and chemotherapy were required. The disappointment was beyond belief. He had six weeks of daily radiotherapy. Followed by six months of chemotherapy tablets. This was another year written off, unable to progress with his life, including the humiliation of not being able to drive due to seizures. The one silver lining from all of this was that he has not had a seizure for 2 years, however due to having three years of treatment on and off he has not been able to find work and his confidence to be among his peers is lost . Whilst it seems everyone else has been able to get on in life with

	girlfriends , independent living and travel, he has been stuck with battling a deadly tumour. It is heartbreaking. **Case Study 4 – A mother's story** *"We dread Vorasidenib being withdrawn from patients. It feels like a death sentence being imposed again."* When my son **** unexpectedly came over with his sister to see me one evening last December, I was delighted. He then told me that he had been at Epsom Hospital all day and that they had found a large Brain Tumour. .I felt as if I had been struck by lightening. I have never been so upset in my life and I could see how scared **** was. I saw him as a child again and just needed to protect him. He had suffered a seizure whilst travelling in the USA where he DJ's. The days after went in a blur of mental pain and anxiety until he was taken on at St.Georges Hospital under Mr.Tim Jones. **** had a Craniotomy in January and came home. He had been told that his Astrocytoma was probably Grade 3 and that it could be on the point of changing to faster ,more aggressive growth. After an anxious wait, the results came back Grade 2 with IDH mutation. **** was given 3 options ; watch and wait, chemo and radiation and lastly Vorasidenib. The first two options were harsh. Waiting for your tumour to progress inevitably

	Or adjusting to the side effects of the old treatments. No change in treatment for over 50 years ! Vorasidenib shone out as a torch into the darkness of ****'s future. I felt calm for the first time since his diagnosis and **** could see a future once again. We are all, as a family so grateful for the Compassionate access to this innovative and life extending treatment. We dread Vorasidenib being withdrawn from patients. It feels like a death sentence being imposed again. **** is 49 years old, a father, he works hard and pays his taxes. He has paid towards his state pension which he has been told he may never live to take. I am literally begging for the continuation of Vorasidenib as a standard treatment for Astrocytoma patients. These patients are also providing valuable data for future care for the NHS. Life saving progress in treatments for Low Grade Gliomas is so greatly needed and research projects must be supported . **Case Study 5 - A story of hope** *"It breaks my heart to think I may have to tell my daughter, sister and Mother I may have to stop taking this life extending drug that I have been so lucky to have been given the opportunity to take, ever hopeful I will not have to."*

	When I found out I had a brain tumour last December after experiencing a seizure whilst away in the US in November I had the hardest few days of my life letting my sister, mother, daughter and friends know. To see how much pain they were in finding out was both heartbreaking and strangely heartwarming at the same time. The NHS were amazing and came to my rescue. Within a matter of weeks I was being operated on and there was a glimmer of hope that I may be around for some time to come. Leading up to the operation I mentally prepared myself for a period of rehabilitation once I awoke but when I did wake I needed very little, just rest and recuperation. Once again, down to the amazing skill of my surgeon and the wonderful NHS. Then I waited to find out what the biopsy had to say, trying to stay positive and awaiting my fate. When I was called to the Royal Marsden I was prepared for the worst but hoped for better. To my surprise I was offered options and was told my tumour was in fact Grade2, I walked in prepared to accept a death sentence but was once again given hope by the NHS. The consultant informed me that I may be able to qualify for a new treatment under a compassionate use agreement, whilst not licensed in the UK the drug had been approved in the US by the FDA. This could potentially extend my life substantially, hope once again given by the NHS.

	The NHS has given me nothing but help and hope since all this began and all I ask is that this continues as I continue to hope that NICE decide to make Voransidenib available on the NHS to continue to give me and others in my predicament the hope that we get to live a longer life with the people we care about and who care about us. It breaks my heart to think I may have to tell my daughter, sister and mother I may have to stop taking this life extending drug that I have been so lucky to have been given the opportunity to take, ever hopeful I will not have to. Thank you for considering us in your decision.

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Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

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Single Technology Appraisal

Vorasidenib for treating astrocytoma or oligodendroglioma with IDH1 or IDH2 mutations after surgery in people 12 years and over [ID6407]

Patient expert statement

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources

Information on completing this form

In part 1 we are asking you about living with astrocytoma or oligodendroglioma with IDH1 or IDH2 mutations after surgery or caring for a patient with astrocytoma or oligodendroglioma with IDH1 or IDH2 mutations after surgery. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

NICE National Institute for Health and Care Excellence

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Your response should not be longer than 15 pages.

The deadline for your response is **5pm** on **Monday 16 June 2025.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

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Patient expert statement

Vorasidenib for treating astrocytoma or oligodendroglioma with IDH1 or IDH2 mutations after surgery in people 12 years and over

NICE National Institute for Health and Care Excellence

Part 1: Living with this condition or caring for a patient with astrocytoma or oligodendroglioma with IDH1 or IDH2 mutations after surgery

Table 1 About you, astrocytoma or oligodendroglioma with IDH1 or IDH2 mutations after surgery, current treatments and equality

1. Your name	Shay Emerton
2. Are you (please tick all that apply)	☒ A patient with astrocytoma or oligodendroglioma with IDH1 or IDH2 mutations after surgery? ☒ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with astrocytoma or oligodendroglioma with IDH1 or IDH2 mutations after surgery? ☐ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	Astro Brain Tumour Fund
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☒ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☒ I agree with it and **will be** completing

5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience ☐ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: ☐ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with astrocytoma or oligodendroglioma with IDH1 or IDH2 mutations after surgery? **If you are a carer (for someone with astrocytoma or oligodendroglioma with IDH1 or IDH2 mutations after surgery) please share your experience of caring for them**	On the 9th April 2021 I was a young healthy regular 24 year old having graduated from Bath University achieving a degree in Biochemistry. Spending time with friends and family, competing in many different sports and working hard in his career to achieve his dreams. On the 10th April 2021 I was a brain tumour patient who was recovering in the intensive care ward after a tonic clonic seizure unable to see a future where I could ever get my life back. I was diagnosed with a grade 2 IDH mutant Astrocytoma. 12th July 2021 I underwent a 14 hour awake craniotomy, which left me paralysed down one side of my body and unable speak. Over the course of many months, hours of physio and speech therapy I learnt to become myself again. However, truth be told I'll never be back to myself. Yes physically I am near enough back to where I once was, but mentally I was million miles away. No young 24 year old should ever have to think about their own mortality, and yet here I was now faced with an incurable disease that will be with me for the rest of my life. I remember explaining to a family member, 'basically what they are saying is that you are fine now, but in the not too distant future you're going to be really ill.' How can one get their head around that? I'm meant to be in my early 20s, doing everything everyone else is doing and yet I can't even face leaving the house with

	the fear of what is going on side my head. The hardest part is pretending you are fine, when friends see you doing well and you mix in and go along with it, but inside you can't tell them how jealous you are of them for living a normal life? So what does my life look like going forward? I guess no one really knows what's to come but for most people that's exciting. A new career somewhere, a new house, moving to another country, start of a family. My reality is going from 6 month to 6 month scans, with the knowledge at some point I'll spend 6 weeks strapped to a radiotherapy machine and a year on chemotherapy, not being able to work, see friends as and when I want and have my life dictated by treatment.
7a. What do you think of the current treatments and care available for astrocytoma or oligodendroglioma with IDH1 or IDH2 mutations after surgery on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	a) Chemotherapy and radiotherapy. That's what the future holds for me. After battling through an awake brain surgery, months of rehabilitation, waking up everyday battling this disease in my own head, putting a smile on my face for those around me, just to have to go through another year of turmoil and appointments only to be left with potential long term cognitive issues and even further away from the 24 year old I know on the 9th April 2021. Watch and Wait – The watch and waiting is the hardest part. Like I've got bomb in my head that could go off at any time. Not a day goes by where I don't think about what might be happening inside my brain. • What was that funny feeling, • Why have I got pins and needles • Why can't I remember that word? It's the anxiety itself which is the most draining. Yes I feel weaker and more tired having undergone such a major surgery, but the anxiety and depression are the hardest to fight.

	b) I have met a number of other people in my position, mostly young people. My experiences described, above, accurately describe their feelings too.
8. If there are disadvantages for patients of current NHS treatments for astrocytoma or oligodendroglioma with IDH1 or IDH2 mutations after surgery (for example, how they are given or taken, side effects of treatment, and any others) please describe these	Yes. Watch and Wait – for patients on watch and wait that are not receiving any treatment (i.e those not on Vorasidenib) this is allowing the tumour to grow, even by a tiny bit, but also extremely debilitating mentally just waiting from scan to scan. You are expected to carry on with normal life like everyone else, and yet quite literally, the tumour is on your mind every single second of every single day. Not only this but allowing the tumour to grow even slowly can bring side effects, with the most serious one of being seizures. The chemicals produced by the tumour when growing can initiate seizures which you are already more susceptible to after surgery. The combination of the mental challenges of living with this constant fear alongside the mental and physical challenges of seizures can result in a serious detrimental effect of mental health and the ability to carry on with life like seeing friends and going to work. Chemotherapy – the main disadvantage is that chemotherapy is not particularly effective against low grade gliomas (many are unmethylated tumours). They are not specific and it is difficult to get across the blood brain barrier (**where as Vorasidenib does cross the blood brain barrier**). Many patients experience serious side effects, including fatigue, skin reactions but more significantly worsening of pre-existing neurological symptoms. When combined with radiotherapy, where a patient has to attend the hospital every day normally for 6-8 weeks (ultimately leading to not being able to work or socialise) the side effects are not only short term but also long term. Hair loss is a common

	side effect from radiotherapy and can effect many peoples mental health and confidence. Alongside hair loss more serious side effects like long term memory loss, long term cognitive impairment impacting thinking and problem solving and increases in seizures due to the scarring of the brain radiotherapy causes are all terrible side effects which ultimately reduces quality of life both short and long term. What people need to realise is that people can live with low grade gliomas for a comparatively long period of time when compared to other cancers, therefore the long term effects of radiotherapy to the brain must be put off for as long as possible. This is different to radiotherapy to other parts of the body where the long term side effects are not comparable to the effects it has on the brain.
9a. If there are advantages of vorasidenib over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** **9c. Does vorasidenib help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	**a)** Vorasidenib offers a world of advantages over current treatments. The first being it is a targeted therapy which has proven to work against these types of low grade gliomas. I feel extremely lucky to have accessed the early access scheme. It's the only thing that has allowed me to even begin to imagine and dream of what my life used to be like. I don't deny I still think about my brain tumour every day, but having accessed Vorasidenib I feel like those thoughts are lighter. Where now I think at least I'm fighting back which is one thing I didn't feel while on watch and wait. One tablet in the morning and the days don't seem so dark. I am able to smile properly for the first time since my surgery and do not have to 'put a face on', with the knowledge I'm taking something which allows me to live a nearer 'normal' life. My mental health has improved vastly, and I have been

	able to return to work and socialise with my friends and family which is something I was unable to properly do before accessing Vorasidenib. It does not have the major side effects that chemotherapy or radiotherapy has, actually on the contrary it has shown (unlike radiotherapy) that seizure control is improved in patients. This is such a huge part as patients are able to get their quality of life and independence back. **b)** One of the most important advantage for me is the improvement in mental health. As stated before, while on watch and wait I felt mentally paralysed and unable to work or socialise. Now finally being on something which is a treatment for my tumour, my quality of life has skyrocketed and I am able to finally get back to doing what most young people in their 20s should be doing. **c)** It overcomes pretty much all the disadvantages listed with current treatments. It has improved my seizure control, I do not feel anymore fatigued then before being on it. I have not suffered any hair loss or skin irritation and unlike radiotherapy and chemotherapy where you might not be able to return to work, I have been able to return to work and crack on with my day after taking my one tablet in the morning.
10. If there are disadvantages of vorasidenib over current treatments on the NHS please describe these. For example, are there any risks with vorasidenib? If you are concerned about any potential side effects you have heard about, please describe them and explain why	I have experienced no disadvantages.
11. Are there any groups of patients who might benefit more from vorasidenib or any who may benefit less? If so, please describe them and explain why	Young people who are in education, working in the early part of their careers and those with a young family to look after, would find the current treatments to be completely disruptive if they needed to attend for radiotherapy every day for around 6-8 weeks and follow up chemotherapy.

Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	If this can be delayed by taking a tablet at home each day and only attend the hospital once a month for monitoring (this might be reduced if approved) this would be a massive advantage to that group of people. In addition people with other disabilities or impact from recent surgery who may not be as mobile as they might, Vorasidenib would again be massively advantageous as would not require daily hospital visits.
12. Are there any potential equality issues that should be taken into account when considering astrocytoma or oligodendroglioma with IDH1 or IDH2 mutations after surgery and vorasidenib? Please explain if you think any groups of people with this condition are particularly disadvantage Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	Low grade gliomas mainly effect young people. The current treatments of chemotherapy and radiotherapy have long term side effects which can result in decreased quality of life especially within the younger population. I think young people need to be given the option of Vorasidenib to reduce the impact and side effects of long term damage to the brain resulting in long term cognitive issues.
13. Are there any other issues that you would like the committee to consider?	The ability to treat patients currently on watch and wait by offering them a treatment rather than offering them “nothing” until their tumour grows / transforms is absolutely vital for all the reasons I have stated above.

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- The physical and mental toll of living with this disease for children and young people is enormous.
- At last there is a treatment for this devastating disease which means this group of patients have a chance to live a near normal life for as long as possible.
- The alternative to offering these patients no treatments but to tell them to wait until the tumour progresses when they will then be offered chemotherapy and radiotherapy (not a cure) as the only option is a very scary world to be in.
- This group of patients need hope and to be able to function whether it be education, work, or looking after their young family for as long as possible.
- These tumours are very rare and so we are only talking about a very small group of patients and they deserve to be recognised and looked after by the NHS.

Thank you for your time.

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External Assessment Group Report

Vorasidenib for treating astrocytoma or oligodendroglioma with IDH1 or IDH2 mutations after surgery in people 12 years and over

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Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

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Contributions of authors

Mark Corbett wrote the critique of the clinical effectiveness evidence in sections 1 and 3 and contributed to the critique of the decision problem and safety evidence.

Rojé Layne contributed to drafting the summary and critique of the resource use and costs and Section 5, and produced the results for the EAG's economic analyses in the main report and confidential appendices.

Chinyereugo Umemneku-Chikere performed the critical review of the clinical effectiveness evidence, drafted Section 2 and contributed to drafting Section 3 of the report.

Melissa Harden reviewed the systematic review searches, wrote sections of the report pertaining to the searches and provided editorial support.

Natalia Kunst contributed to the critical review of the economic analyses and to drafting the summary and critique of health-related quality of life in Section 4 of the report.

Kerry Dwan provided methodological advice, commented on drafts of the report and reviewed the whole report, and takes joint responsibility for the report as a whole.

Claire Rothery performed the critical review of the economic analyses, contributed to drafting Sections 4, 5, 6 and 7 of the report, led the overall economic analyses and takes joint responsibility for the report as a whole.

Note on the text

All commercial-in-confidence (CON) data have been [redacted].

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List of abbreviations

Abbreviation	Definition
1L	First line
2L	Second line
2L+	Second line and subsequent
3L	Third line
4L	Fourth line
5L	Fifth line
AE	Adverse event
AEDC	Discontinuation due to adverse events
BIRC	Blinded independent Review Committee
BID	Twice daily
BSC	Best supportive care
CCNU	A chemotherapy drug also called lomustine
CDF	Cancer Drug Fund
CI	Confidence interval
CNS	Central nervous system
CNS-PD	Central nervous system progressed disease
CrI	Credible interval
CS	Company submission (Document B)
CT	Chemotherapy
DARE	Database of abstracts of reviews of effects
DoR	Duration of response
DSU	Document support unit
EAG	External Assessment group
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EMA	European Medicines Agency
EoL	End of life
EU	European Union
EQ-5D	standardised instrument for use as a measure of health outcome
FAD	Final appraisal document
EORTC QLQ-C30	European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire
FA	Final Analysis
FACT-Br	HRQoL Functional Assessment of Cancer Therapy-Brain
FAS	Full Analysis Set
FTA	Fast track appraisal
HCPs	Healthcare professionals
HCRU	Healthcare resources Utilisation
HGG	High grade glioma
HR	Hazard ratio
HRQoL	Health-related quality of life
HTA	Health technology assessment
IA	Investigator assessed
IA1	First interim analysis
IA2	Second interim analysis
ICER	Incremental cost effectiveness ratio
IDH	Isocitrate Dehydrogenase
IDH1	Isocitrate Dehydrogenase 1
IDH2	Isocitrate Dehydrogenase 2
IDHmt	IDH mutant

IDHwt	IDH wild type
IDMC	Independent data monitoring committee
ILAP	Innovative Licencing and Access Pathway
INAHTA	International Health Technology Assessment database
INHB	Incremental Net Health Benefit
INV	Investigator
IPCW	Inverse-probability-of-censoring weighting
IPD	Individual patient data
IQR	Inter-quartile range
KM	Kaplan–Meier
LY	Life years
LGG	Low grade glioma
MHRA	Medicines and Healthcare products Regulatory Agency
MRI	Magnetic resonance imaging
MT	Malignant transformation
NHB	Net health benefit
NHS	National Health Service
NI	Next Intervention
NI+	Following Intervention
NICE	National Institute for health and care Excellence
NMA	Network meta-analysis
ORR	Objective response rate
OS	Overall survival (Not spelt first time page 12)
PAS	Patient Access Scheme
PCV	A chemotherapy drug also called Vincristine
PD	Progressed disease
PF	Progression Free
PFS	Progression free survival
PH	Proportional hazard
PICOS	Population, Intervention, Comparator, Outcomes, Study-type
PPS	Post-progression survival
PSM	Partitioned survival model
PSSRU	Personal Social Services research Unit
QALY	Quality adjusted life year
QoL	Quality of Life
RANO-LGG	Response Assessment for Neuro-oncology for Low-Grade Gliomas
RCT	Randomised controlled trial
RECIST	Response Evaluation Criteria in Solid Tumour
RR	Relative risk
RT	Radiotherapy
SLR	Systematic Literature Review
SmPC	Summary of product characteristics
STA	Single Technology Assessment
STM	State transition model
TA	Technology Appraisal
TGR	Tumour growth rate
TLR	Targeted literature review
TMZ	Temozolomide
TTNI	Time to next intervention
TTNI|P	Time to next intervention given progression
TTO	Time Trade-Off

TTP	Time to progression
TTR	Time to response
ToT	Time on treatment
TRAE	Treatment related adverse event
QALY	Quality-adjusted life year
UK	United Kingdom
US	United States
WHO	World Health Organization

1 EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the external assessment group (EAG) as being potentially important for decision making. It also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Data presented in the company submission (CS) are primarily from the ongoing INDIGO study, using the 06 September 2022 and 07 March 2023 (ad-hoc analysis) data cut-off. In response to EAG clarifications (question A13), the company states that no other data cut-off is available at this point in time. A data cut is expected in May 2025 and May 2028 (page 49 of CS). The company's base case analysis is based on the March 2023 data cut.

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.3 to 1.6 explain the key issues in more detail. Background information on the condition, technology and evidence and information on non-key issues are in the main EAG report.

All issues identified represent the EAG's view, not the opinion of NICE.

1.1 Overview of the EAG's key issues

Table 1 Summary of key issues

ID6407	Summary of issue	Report sections
1	Restricted trial population compared to patients seen in the NHS	**3.2.1.2**
2	Limited applicability of the progressed disease and time to next intervention (TTNI) INDIGO data to the NHS setting	**3.2.1.2**
3	Immaturity of the data reported in the company's submission	**3.2.4, 3.2.1.2**
4	Non-reference case discount rate for costs and health effects	**4.2.5.2**
5	Surrogacy relationship for overall survival (OS) benefit	**4.2.6.2**
6	Interpretation of the conditional outcome of time to next intervention given progression (TTNI | P)	**4.2.6.2**
7	Duration of time spent off-treatment with progression before moving to first line radiotherapy or chemotherapy (1L RT/CT)	**4.2.6.2**
8	Evidence used to model outcomes for subsequent treatment lines	**4.2.6.2**
9	Off-label bevacizumab use at subsequent treatment lines	**4.2.9.3**
10	Percentages of RT/CT used at subsequent treatment lines	**4.2.9.3**
11	Health state utility values for subsequent treatment lines	**4.2.8.2**
12	Monitoring with CT scans	**4.2.9.4**

There are six key differences between the EAG's preferred assumptions and the company's preferred assumptions:

(i) NICE reference case discount rate of 3.5% per annum rather than the non-reference case discount rate of 1.5% per annum used in the company's base case.
(ii) Use of a common TTNI | P curve for both vorasidenib and active observation based on the pooled curve across arms of INDIGO, with a log-normal extrapolation, rather than separate TTNI | P curves by treatment arm (generalised gamma extrapolation) used in the company's base case.
(iii) Exclusion of off-label bevacizumab use at subsequent treatment lines.
(iv) Percentages of RT/CT used at subsequent treatment lines changed to proxy NHS practice rather than based on market share data from France in the company's base case.
(v) Exclusion of monitoring costs associated with CT scans.
(vi) Use of the unadjusted EQ-5D utility values from the vignette study for subsequent treatment lines rather than the adjusted values used in the company's base case that do not differentiate utility values for on- and off-treatment.

The EAG identified other key uncertainties, which the EAG is unable to resolve based on the data currently available. These are described further in the sections below.

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Vorasidenib is modelled to reduce the risk of progression (i.e., slow the tumour growth rate such that it delays the transformation into higher grade gliomas or a more aggressive disease state) and the time to next intervention (i.e., delays the initiation of RT/CT) in patients with predominantly non-enhancing IDH-mutant gliomas.

Overall, the technology is modelled to affect QALYs by:

- Increasing the time that patients are progression-free (PF) compared to active observation, where PF is associated with improved health-related quality of life (HRQoL) relative to progressive disease (PD).
- Delaying the time to RT/CT, which is given when the prognosis of the target population is worse and modelled with a significant drop in HRQoL.

Overall, the technology is modelled to affect costs by:

- Increasing the time that patients are PF and on-treatment, where treatment acquisition costs are incurred until discontinuation of treatment upon evidence of disease progression, whereas active observation is associated with no treatment costs.
- Upon progression, vorasidenib is modelled to delay the time to RT/CT (i.e. PD and off-treatment) compared to active observation, where RT/CT is associated with drug acquisition and administration costs, in addition to higher medical resource use costs (e.g., frequencies of CT and magnetic resonance imaging (MRI) scans, unscheduled hospital visits, doctor appointments).
- No differences in adverse event costs are assumed.

The most critical parameter in the model impacting the cost-effectiveness of vorasidenib relative to active observation is the time to next intervention given progression (TTNI | P).

The modelling assumptions that have the greatest effect on the ICER are:

- The TTNI | P curve used in the model and its extrapolation over time. The TTNI | P curve affects the duration of time spent off-treatment with PD before moving to 1L RT/CT. The company's base case uses a generalised gamma model to extrapolate Kaplan-Meier (KM) data for TTNI | P from INDIGO, separated by treatment arm. The use of alternative models of log-normal and exponential to extrapolate the KM data by treatment arm show that both incremental costs and QALYs are highly sensitive to the extrapolation model selected.
- The TTNI | P curve separated by treatment arm used in the company's base case analysis. In the absence of evidence to support ongoing effects of vorasidenib post-progression and the issues with the TTNI | P data from INDIGO (post-randomised, confounded by cross-over, high censoring and immature data), the use of a common TTNI | P curve independent of initial intervention received (i.e., vorasidenib delays time to RT/CT by delaying time to progression, without assuming an additional effect associated with TTNI data from INDIGO) shows that the company's base case ICER increases by a large amount.
- The health state utility values for subsequent treatment lines, where the total QALYs are highly sensitive to the utility values for RT/CT and best supportive care (BSC).
- The percentages of RT/CT and off-label bevacizumab used at subsequent treatment lines have a moderate effect on the ICER.

1.3 The decision problem: summary of the EAG's key issues

There are no key issues related to the decision problem.

1.4 The clinical effectiveness evidence: summary of the EAG's key issues

Issue 1 Restricted trial population compared to patients seen in the NHS

Report section	3.2.1.2
Description of issue and why the EAG has identified it as important	An inclusion criterion in the INDIGO trial was that patients' last surgery had to have been between 1 and 5 years prior to randomization. This approach to recruitment means that patients with less stable disease may have been filtered out of the trial population. The anticipated marketing authorization is not expected to place restrictions on how long ago surgery was (before patients can commence vorasidenib), yet the <1 year post-surgery patients may have worse outcomes than the population recruited in INDIGO. Patients with little or no visible residual disease were also excluded from INDIGO. These patients may have a better prognosis than the trial participants and, considering the baseline tumour diameter subgroup results for the progression free survival (PFS) analyses in INDIGO, vorasidenib may not be as effective. Given these important differences between the INDIGO population and both the marketing authorization scope and the expected National Health Service (NHS) population – which are both broader - the EAG considers that careful consideration should be given to the possible impacts on cost-effectiveness of both when patients should commence taking vorasidenib, and of treating patients with little or no visible residual disease post-surgery.
What alternative approach has the EAG suggested?	Not applicable as this is a trial design issue.
What is the expected effect on the cost-effectiveness estimates?	N/A
What additional evidence or analyses might help to resolve this key issue?	Not possible, given the available trial evidence.

Issue 2 Limited applicability of the progressed disease and time to next intervention (TTNI) INDIGO data to the NHS setting

Report section	3.2.1.2
Description of issue and why the EAG has identified it as important	*Progressed disease* - In INDIGO, only around half of patients in the vorasidenib arm whose disease had progressed (based on modified response assessment for neuro-oncology for low-grade-gliomas (RANO-LGG) criteria) received a subsequent treatment. This might be a consequence of using the modified RANO-LGG criteria - one of the modifications was the removal of 'clinical deterioration' as an assessment criterion; although not considered in the trial, this would be considered as part of NHS disease progression assessments. The absence of clinical deterioration may have led to hesitancy and uncertainty about the need for subsequent treatment in many vorasidenib arm patients, following modified RANO-LGG progression.

	The *TTNI* outcome was judged by the EAG to have a high risk of bias due to lack of blinding. TTNI conditional on progression (TTNI | P) was used in the cost-effectiveness modelling to represent time to receive RT/CT (which was not evaluated as a trial outcome). However, for the majority of patients in the placebo arm, the next intervention was vorasidenib. The EAG considers that this created a bias in the TTNI data between the trial arms for several reasons. The clinical decision to treat placebo patients with vorasidenib (thus generating a 'next intervention' event) in INDIGO, in which patients have already been unblinded, is easier than the decision to commence RT/CT in progressed, unblinded patients in the vorasidenib arm; this being based on the perceived risks of administering these treatments. This is exacerbated by the use of the modified RANO-LGG criteria to assess progression in INDIGO, where a decision to commence RT/CT following progression will be less likely than would be expected in clinical practice, given that clinical deterioration was not part of the modified RANO-LGG criteria, and given that some INDIGO progression events will not have had any associated clinical deterioration. Using TTNI to represent time to receive RT/CT is therefore not appropriate and the TTNI results should not be considered as being applicable to the NHS setting. Moreover, vorasidenib is not currently available in the NHS, so it is not a relevant next intervention to consider in the placebo arm, with respect to the TTNI outcome.
What alternative approach has the EAG suggested?	Although excluding vorasidenib as a type of 'next intervention' could be considered, this would have needed to have been done when the trial was designed in order to produce unbiased results.
What is the expected effect on the cost-effectiveness estimates?	See Issues 6 and 7 below.
What additional evidence or analyses might help to resolve this key issue?	It is unlikely that any additional analyses would resolve this issue.

Issue 3 Immaturity of the data reported in the company's submission

Report section	3.2.4, 3.2.1.2
Description of issue and why the EAG has identified it as important	The median follow-up of patients in INDIGO was only around 14 months (although a data cut was provided with a further 6 month analysis). Although the company proposes the use of the Cancer Drugs Fund to allow uncertainty to be resolved by further data collection, the EAG notes that some uncertainty could be resolved much sooner, in terms of progression-free survival and time to next intervention, if the company provided a more recent data cut than March 2023 i.e. a new data-cut could provide two years' more PFS and TTNI data. Also, since vorasidenib patients tended to progress at later timepoints than placebo patients, the follow-up for some vorasidenib patients may have ended

	(in terms of the data-cut) before the next intervention could be given. A more recent data-cut would help resolve this issue.
What alternative approach has the EAG suggested?	A more up-to-date data-cut for INDIGO PFS and TTNI analyses.
What is the expected effect on the cost-effectiveness estimates?	Unknown.
What additional evidence or analyses might help to resolve this key issue?	A more up-to-date data-cut for INDIGO PFS and TTNI analyses.

1.5 The cost-effectiveness evidence: summary of the EAG's key issues

Issue 4 Non-reference case discount rate for costs and health effects

Report section	4.2.5.2
Description of issue and why the EAG has identified it as important	The company's base case uses a non-reference case discount rate of 1.5% per annum for both costs and health effects. The EAG has significant concerns regarding the company's justification for the use of a non-reference case discount rate and believes it does not meet NICE methods guide criteria: • Vorasidenib is indicated for people with indolent, non-enhancing LGG, who have stable disease and not in immediate need of RT/CT, i.e., it is not indicated for people who would otherwise die; modelled median OS is 15.26 years for active observation and only one death recorded in INDIGO. • EQ-5D utility values from INDIGO suggests that HRQoL is associated with only a modest decrement compared to age- and sex-matched general population utility values. While HRQoL may be impaired at later stages of disease when receiving subsequent treatments of RT/CT the evidence is not available to support 'severely impaired quality of life'. • IDH-mutant glioma remains incurable; therefore, vorasidenib cannot be demonstrated to represent a cure to 'full or near-full health'. • Voraidenib is demonstrated to slow progression in INDIGO but the extent to which vorasidenib delays the time to RT/CT over and above active observation remains unknown. • No information on OS is yet available from INDIGO and no difference in the rates of malignant transformation have been shown for vorasidenib and placebo arms.
What alternative approach has the EAG suggested?	Use the NICE reference case discount rate of 3.5% per annum.

What is the expected effect on the cost-effectiveness estimates?	The company's base case ICER increases from [redacted] (with severity weighting of 1.7 based on 1.5% annual discount rate) to [redacted] (with severity weighting of 1.2 based on 3.5% annual discount rate).
What additional evidence or analyses might help to resolve this key issue?	None because additional follow-up evidence from INDIGO is unlikely to resolve uncertainty about the comparability of vorasidenib and active observation on time to RT/CT due to confounding with cross-over permitted on the placebo arm. The EAG considers this issue resolved.

Issue 5 Surrogacy relationship for OS benefit

Report section	4.2.6.2
Description of issue and why the EAG has identified it as important	In the absence of mature OS data from INDIGO, the approach to modelling relies on the relative effect of vorasidenib on PFS/TTP and time to next intervention given progression (TTNI | P) being predictive of its relative effect on OS. However, the company have not presented evidence to support the validity of a surrogacy relationship between delaying PFS/TTP and TTNI | P and OS benefit for vorasidenib relative to active observation in the target population. The EAG is particularly concerned about the use of TTNI | P as a surrogate for OS as this outcome is confounded by cross-over in the placebo arm, with the next intervention being any subsequent therapy rather than RT/CT as required for the model. Furthermore, the company have not provided evidence to show that vorasidenib reduces the likelihood or delays the transition from LGG to HGG, or transformation to malignant gliomas (secondary HGG). No difference in the rates of malignant transformation (MT) by treatment arm were observed in INDIGO. Therefore, it remains impossible to judge and interpret the appropriateness of the implied OS hazard ratio of 0.69 for vorasidenib vs. active observation in the company's base case analysis.
What alternative approach has the EAG suggested?	The mortality benefit for vorasidenib is modelled as a function of delaying time to RT/CT and subsequent lines of therapy, which has not yet been proven with data. In the absence of data, no alternative approach is suggested by the EAG. Two key structural assumptions must hold: (1) subsequent treatments are a good surrogacy for progression of disease in terms of transitions to HGG and MT in the target population; and (2) the relative effect of vorasidenib on TTP

	and TTNI | P from INDIGO is predictive of its relative effect on OS; neither of which have been demonstrated with data for vorasidenib vs. active observation.
What is the expected effect on the cost-effectiveness estimates?	N/A
What additional evidence or analyses might help to resolve this key issue?	Even with more mature OS data from INDIGO over a long follow-up period, the survival data will be difficult to interpret given the large percentage of participants in the placebo arm that crossed over to vorasidenib at progression. In addition, the extent to which a heterogeneous set of subsequent therapies impact on mortality will make interpretation of OS from INDIGO challenging.

Issue 6 Interpretation of the conditional outcome of time to next intervention given progression (TTNI | P)

Report section	4.2.6.2
Description of issue and why the EAG has identified it as important	The model uses data from INDIGO for the conditional outcome of TTNI | P, separated by treatment arm, to inform the duration of time spent off-treatment with progression before moving to 1L RT/CT. The EAG's primary concern with this outcome is the fact that it is confounded by cross-over in the placebo arm, where participants in the placebo arm are likely to have moved to the NI quicker because they had access to a treatment that would otherwise not be available outside of the trial setting. Vorasidenib is not currently available in the NHS; therefore, NI in the placebo arm of INDIGO is not informing time to RT/CT as required for the model. In addition, the timing of progression differs between the arms of INDIGO, with later progressors on the vorasidenib arm versus early progressors on the placebo arm resulting in TTNI events more often censored in the vorasidenib arm as many patients' follow-up ended shortly after progression.
What alternative approach has the EAG suggested?	Inverse-probability-of-censoring weighting (IPCW) is typically used to adjust for cross-over subjects that are censored; however, due to the very high cross-over in the placebo arm there is limited data for non-censored subjects in the placebo arm to undertake an IPCW. Therefore, in the absence of data, no alternative approach is suggested by the EAG, but the EAG highlights caution with interpretation of the outcome TTNI | P from INDIGO for modelling time to RT/CT, which remains an important uncertainty. [Note that the company undertook a cross-over adjustment with multiple imputation, but this was subject to several concerns (see Section 4.2.6.2) and not applied to the conditional outcome of TTNI | P required for the modelling].

What is the expected effect on the cost-effectiveness estimates?	N/A
What additional evidence or analyses might help to resolve this key issue?	It is unlikely that any additional analyses from INDIGO would resolve this issue as the data is not specifically informing time to RT/CT as required for the model.

Issue 7 Duration of time spent off-treatment with progression before moving to 1L RT/CT

Report section	4.2.6.2
Description of issue and why the EAG has identified it as important	The model uses the conditional outcome of TTNI | P to determine the duration of time spent off-treatment with progression (in health state S4) before moving to 1L RT/CT. The EAG has several critical issues with the approach used: • TTNI | P is based on post-randomised data and not informing time to 1L RT/CT as required for the model (issue 6). • It is unclear whether patients would be held in a progressed disease health state off-treatment rather than move directly to NI upon evidence of radiographic progression. The company have not shown data that tumour size is smaller at the point of progression than at baseline for vorasidenib, and it remains unknown which tumoral changes are potentially triggered by vorasidenib and how the disease will eventually behave after progression. • Clinical plausibility of the modelled predictions for average time to RT/CT given progression. The selected model predicts that ~21% of patients with PD remain untreated at 20 years for vorasidenib, while ~9% remain off-treatment at 20 years for active observation post-progression. The EAG does not consider the predictions reasonable relative to the time spent PF in model, where patients remain longer off-treatment with PD than PF (e.g., life years for active observation are over three times as much in the PD than PF health state). • It is unclear why the outcome of TTNI | P should be separated by treatment arm, i.e., evidence has not been presented to show that patients should be managed differently post-progression (where progression has been defined using the same criteria in both arms of INDIGO) depending on initial intervention, especially when there are no differences assumed for treatments at subsequent lines. Furthermore, the EAG notes that the HRQoL utility values by progression status and treatment arm of INDIGO indicates that patients with PD had better quality of life in the placebo arm than the vorasidenib arm.

What alternative approach has the EAG suggested?	The EAG considered in scenario analyses the implications of using alternative models to extrapolate the TTNI | P curves from INDIGO, which produce more reasonable predictions of life years off-treatment with PD, and highlights the sensitivity of the cost-effectiveness results to the model predictions for TTNI | P. However, the inherent uncertainty with cross-over and lack of robust data for TTNI | P remains a key issue. In the absence of evidence to support important ongoing effects of vorasidenib post-progression and the issues with the TTNI | P data (post-randomised, confounded by cross-over, high censoring and immature data), the EAG considers it more reasonable to assume a common TTNI | P curve post-progression, independent of initial intervention received (i.e., vorasidenib delays time to RT/CT by delaying time to progression, without assuming an additional effect associated with TTNI data from INDIGO).
What is the expected effect on the cost-effectiveness estimates?	In EAG scenarios for TTNI | P, separated by treatment arm (as per company base case), alternative extrapolation models increase the company's base case ICER (with a 3.5% annual discount rate and severity weighting of 1.2 - see Issue 4) from [redacted] (generalised gamma model) to [redacted] with log-normal model and [redacted] with exponential model. In EAG scenarios that use a common TTNI | P curve for vorasidenib and active observation, the ICER increases substantially, ranging from [redacted] to [redacted]
What additional evidence or analyses might help to resolve this key issue?	It is unlikely that any additional analyses from INDIGO would resolve this issue.

Issue 8 Evidence used to model outcomes for subsequent treatment lines

Report section	4.2.6.2
Description of issue and why the EAG has identified it as important	To capture outcomes at subsequent treatment lines, effectiveness evidence from a range of different sources, external to the INDIGO trial, is used. The EAG is concerned about the reliance on multiple sources from non-comparable populations and several assumptions required to inform long-term survival outcomes where there is a dearth of evidence for the target population of LGG. In particular, the EAG expresses concern about: • The limited justification for the choice of post-progression studies and relevance to NHS practice. None of the studies are directly concerned with isocitrate dehydrogenase (IDH) mutant gliomas for adults in a United Kingdom (UK) setting, or specific to progression

	for patients who were previously not in need of immediate systemic therapy and post-surgery. • The company makes several simplifying assumptions to include PFS from these studies, but the company is mixing and matching data from different populations and histological mix that is unlikely to be comparable. • The costs of subsequent treatments in the model reflect a range and distribution of treatments (including number of treatment lines) that is expected to be given in clinical practice, but the long-term survival outcomes informing the rate of subsequent progression are reflecting outcomes of specific treatments used in the selected studies rather than the different treatment modalities used in NHS clinical practice. • The excess mortality risk applied to the last line of BSC is based on OS data for salvage systemic therapy that does not represent BSC as defined in the model, in addition to concerns about the relevance of the study to UK practice (e.g., small United States (US) cohort, with therapies not licensed in UK, and include pre-progression deaths).
What alternative approach has the EAG suggested?	The EAG considers it appropriate to undertake a systematic literature review (SLR) to identify the most relevant source of data, with clear criteria specified for study selection. The survival estimates used to model long-term outcomes should be relevant to the target population and NHS clinical practice.
What is the expected effect on the cost-effectiveness estimates?	Unknown; although the EAG notes that delaying the time to subsequent treatment lines for vorasidenib relative to active observation is the key driver of cost-effectiveness as the outcomes at subsequent treatment lines do not differ by initial intervention.
What additional evidence or analyses might help to resolve this key issue?	Additional evidence for long-term survival outcomes in the target NHS population.

Issue 9 Off-label bevacizumab use at subsequent treatment lines

Report section	4.2.9.3
Description of issue and why the EAG has identified it as important	In the company's base case, a large proportion of subsequent therapies include off-label bevacizumab (34.88% at third line and 33.33% at fifth line), which is associated with a higher cost compared to the costs of RT/CT. The EAG does not consider it appropriate to include the use of bevacizumab at subsequent treatment lines because bevacizumab is not licensed in the UK for

	the treatment of gliomas. The EAG's clinical advisor confirmed that off-label bevacizumab is not routinely used in the treatment of gliomas.
What alternative approach has the EAG suggested?	Exclude the use of bevacizumab at subsequent treatment lines.
What is the expected effect on the cost-effectiveness estimates?	The company's base case ICER with a 3.5% annual discount rate and severity weighting of 1.2 (see Issue 4) increases from [redacted] to [redacted] when the use of bevacizumab is excluded at subsequent treatment lines (reweighting the proportion of RT/CT to 100% at subsequent lines).
What additional evidence or analyses might help to resolve this key issue?	None. The EAG considers this issue resolved.

Issue 10 Percentages of RT/CT used at subsequent treatment lines

Report section	4.2.9.3
Description of issue and why the EAG has identified it as important	In the company's base case, market share data from France was used to inform the proportion of patients receiving each CT regimen, while the proportion of patients receiving RT in conjunction with CT was based on assumptions. The EAG does not consider it appropriate to use market share data from France to reflect treatment patterns in NHS clinical practice. The EAG's clinical advisor indicated that there are important differences between the UK and other parts of Europe, e.g., in the use of procarbazine, CCNU (lomustine) and vincristine (PCV). The EAG's clinical advisor indicated that at first line, PCV is used most in the UK in line with NICE guideline NG99 recommendations, whereas the periodic synthesis report based on French data suggests only 25.6% use of PCV at 1L. The EAG's clinical advisor also indicated that a higher percentage of patients would receive RT combined with adjunctive CT at 1L than assumed in the company's base case analysis, but that this would diminish at subsequent treatment lines as RT is typically given twice only.
What alternative approach has the EAG suggested?	In the absence of UK data, an EAG scenario analysis aims to proxy NHS practice for subsequent treatment use based on NG99 recommendations and clinical advice to the EAG. In EAG scenario 5, the proportion of treatments used at subsequent lines are as follows: • 1L: 100% PCV in conjunction with RT. • 2L: 100% temozolomide (TMZ), in conjunction with % RT per company assumptions. • 3L to 5L: Equal percentages of PCV, TMZ, and CCNU, with no RT.

	[Note that the company's model did not appear to have sufficient flexibility to remove lines of treatment; therefore, equal percentages of PCV, TMZ, and CCNU were assumed at 3L+].
What is the expected effect on the cost-effectiveness estimates?	The company's base case ICER with a 3.5% annual discount rate and severity weighting of 1.2 (see Issue 4) increases from [redacted] to [redacted] when the percentage of subsequent treatment use is changed to proxy NHS practice.
What additional evidence or analyses might help to resolve this key issue?	Data on the percentages of RT/CT used to treat the target population in NHS practice.

Issue 11 Health state utility values for subsequent treatment lines

Report section	4.2.8.2
Description of issue and why the EAG has identified it as important	In the absence of utility values for subsequent treatment lines of RT/CT and BSC, the company undertook a vignette study to elicit utility values using both EQ-5D and time trade-off (TTO) methods, valued by the UK general public. The EAG notes that vignettes represent the lowest quality of evidence in the NICE hierarchy of preferred HRQoL methods. The EQ-5D and TTO responses resulted in substantially different estimates of utility values for subsequent treatment lines, with EQ-5D producing lower utility values. Furthermore, the EQ-5D utility values from the vignette study produced substantially lower HRQoL compared to the EQ-5D utility values from INDIGO (e.g., a utility value of 0.728 from INDIGO was used for health state S4, off-treatment with PD, while a utility value of 0.480 from the vignette study was used for health state S5 receiving RT/CT). The EAG considers the utility values for subsequent treatment lines to be highly uncertain and represent an unrealistic drop in utility when moving to RT/CT. The EAG also notes that the company adjusted the EQ-5D utility values from the vignette study by averaging the estimates for on- and off-treatment with RT/CT. However, the wording used in the health state descriptions of the vignettes clearly distinguish between on- and off-treatment, e.g., on-treatment includes "You may experience side effects such as itchy or red skin, hair loss vomiting/nausea, constipation, or diarrhoea", while off-treatment excludes treatment-related adverse events. Therefore, the EAG considers it inappropriate to use an average utility value across the on- and off-treatment health states at subsequent treatment lines given that the vignette health state descriptions differentiate outcomes for on- and off-treatment.

What alternative approach has the EAG suggested?	In the absence of alternative utility values for subsequent treatment lines, use the unadjusted EQ-5D health state utility values from the vignette study and explore the implications of the TTO utility values on the cost-effectiveness of vorasidenib.
What is the expected effect on the cost-effectiveness estimates?	The company's base case ICER with a 3.5% annual discount rate and severity weighting of 1.2 (see Issue 4) marginally increases from [redacted] to [redacted] with the unadjusted EQ-5D utility values from the vignette study. However, when the TTO utility values from the vignette study are used instead of the EQ-5D responses, the ICER increases to [redacted]
What additional evidence or analyses might help to resolve this key issue?	Additional evidence is required for utility values for subsequent treatment lines in the target population.

1.6 Other key issues: summary of the EAG's view

Issue 12 Monitoring with CT scans

Report section	4.2.9.4
Description of issue and why the EAG has identified it as important	The company's base case includes monitoring costs associated with CT scans, in addition to MRI scans. The EAG's clinical advisor indicated that CT scans are not used routinely for monitoring progression in NHS practice (only used in specific circumstances such as presenting with a seizure), with MRI scans being the standard used to monitor progression. This also aligns with NICE guidelines NG99 recommendations and feedback from the company's UK Cost Effectiveness Model Advisory Board Report, which indicates that CT scans would not be done routinely.
What alternative approach has the EAG suggested?	Exclude monitoring costs associated with CT scans.
What is the expected effect on the cost-effectiveness estimates?	The company's base case ICER with a 3.5% annual discount rate and severity weighting of 1.2 (see Issue 4) decreases from [redacted] to [redacted] when monitoring costs associated with CT scans are excluded.
What additional evidence or analyses might help to resolve this key issue?	None. The EAG considers this issue resolved.

1.7 Summary of EAG's preferred assumptions and resulting ICER

Table 2 summarises the EAG's preferred assumptions and resulting ICER for the comparison of vorasidenib with active observation in the target population.

Table 2 Cost-effectiveness results of EAG preferred assumptions

Scenario	Incremental cost	Incremental QALYs	ICER
Company's corrected base-case results (1.5% annual discount rate)	[redacted]	5.83**	[redacted]
EAG Scenario 1: Discount rate of 3.5% per annum	[redacted]	2.94*	[redacted]
EAG Scenario 3b: A common TTNI | P curve for both interventions based on the pooled curve across arms of INDIGO, with log-normal extrapolation	[redacted]	1.76*	[redacted]
EAG Scenario 4: Exclude the use of bevacizumab at subsequent treatment lines	[redacted]	2.94*	[redacted]
EAG Scenario 5: Proportion of treatments used at subsequent lines reflects a proxy for NHS clinical practice	[redacted]	2.92*	[redacted]
EAG Scenario 6: Exclude CT scans	[redacted]	2.94*	[redacted]
EAG Scenario 7: Unadjusted health state utility values for subsequent treatment lines	[redacted]	2.90*	[redacted]
EAG Scenarios 1+3b+4+5+6+7 (EAG base case – deterministic analysis)	[redacted]	1.73*	[redacted]
EAG base case – probabilistic analysis	[redacted]	1.81*	[redacted]

*Adjusted by applying a 1.2 severity weight
**Adjusted by applying a 1.7 severity weight

For further details of the exploratory and sensitivity analyses undertaken by the EAG, see Sections 6.1, 6.2 and 6.3.

Several important uncertainties remain, which cannot be adequately addressed with the available evidence:

- The absence of mature OS data from INDIGO and the assumption that the relative effect of vorasidenib on time to progression and time to next intervention given progression (TTNI | P) as predictive of its relative effect on OS remains unknown.
- The TTNI | P curve for both intervention arms of INDIGO are subject to concerns and not informing the time to 1L RT/CT required for the model; the placebo arm is confounded by a very high percentage of cross-over to vorasidenib (with limited data available from non-censored subjects to allow an adjustment for cross-over), and the vorasidenib arm has a significant amount of censoring due to progression events occurring later compared to the placebo arm and the numbers of patients at risk is extremely low at 12 months to extrapolate the curve over the long-term.
- The absence of survival outcomes for subsequent treatments relevant to the target population that reflect treatment modalities used in NHS clinical practice.

- The absence of health-related quality of life for subsequent treatment lines, with significant uncertainty in the estimates derived from the vignette study.

2 INTRODUCTION AND BACKGROUND

2.1 Introduction

This report reviews the clinical effectiveness and cost effectiveness submitted by the company to the National Institute for Health and Care Excellence (NICE) in support of vorasidenib as a monotherapy to delay the progression of Grade 2 astrocytoma or oligodendroglioma with a susceptible isocitrate dehydrogenase-1 (IDH1) mutation or isocitrate dehydrogenase-2 (IDH2) mutation in adults and paediatric patients 12 years and older, who are not in need of immediate chemotherapy (CT) or radiotherapy (RT) following surgical intervention.

Vorasidenib is an oral inhibitor of IDH-mutant proteins which is designed to penetrate the blood-brain barrier, making it a targeted therapeutic candidate for the treatment of IDH-mutant gliomas.

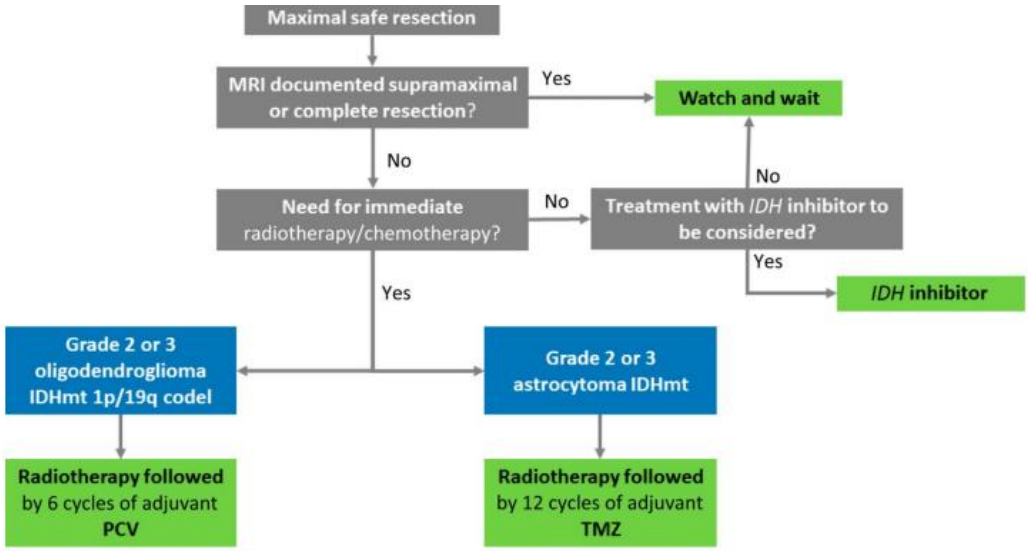
Vorasidenib was approved in United States by the Food and Drug Administration (FDA) on August 6, 2024[1, 2] for patients with grade 2 astrocytoma or oligodendroglioma with suspected IDH1 and IDH2 mutation. This population is wider than the population recruited in the INDIGO study and proposed for use in the UK; because, in the UK, the therapy is restricted to patients "***not in need of immediate radiotherapy or chemotherapy***". It is currently under review in the European Union (EU) by the European Medicines Agency (EMA) but was granted accelerated access assessment in February 2024[3]. It was designated as an orphan medicine for the treatment of IDH-mutant glioma in the EU on January 13, 2023[4], and by the Australian government on 31st October 2023[5]. In the UK, vorasidenib was awarded Innovative Licensing and Access Pathway (ILAP) status as an innovative product by the MHRA in January 2024[6]. However, the planned date of submission to the Medicine and Healthcare products Regulatory Agency (MHRA) is on the 9th of April 2025 and the anticipated approval from MHRA is in August 2025.

2.2 Treatment Pathway

The EAG considers the company's description of the health condition (Company submission [CS] Section B.1.3) to be appropriate and relevant to the decision problem. The description of the diagnosis, burden, the classification of glioma using IDH mutation status (depicted as Figure 2, CS, Doc B), and the management of glioma reflects current UK practice. The EAG considers the company's description of the unmet need to provide targeted therapy to delay progressive disease in patients with low grade IDH-mutant glioma following surgery to be appropriate.

The proposed position of vorasidenib in the National Health Service (NHS) clinical pathway, if approved by NICE, is presented in Figure 3 in CS and reproduced below in Figure 1. Vorasidenib is proposed to be administered to patients with the target condition and not in need of immediate RT or CT. The EAG noted that in Figure 1, patients with complete resection won't get vorasidenib but the wording of the proposed marketing authorisation does not exclude them, even though there is no trial evidence for them.

Figure 1: Company's positioning of vorasidenib in the treatment pathway (adapted from Schaff et al, 2024)[7]



Source: CS, Document B, Figure 3

The EAG's clinical advisor noted that in current NHS practice, RT / CT would be considered as a standard treatment for patients with low grade glioma who have residual disease following surgery[8, 9]. However, the multidisciplinary team may consider it safe to monitor patients with residual disease with active surveillance (also known as active monitoring, watch and wait or observation). This decision could depend on factors such as seizure rate (controlled or uncontrolled), size of the tumour and tumour location (if progression could lead to loss of function, then earlier RT/CT may be important).

Therefore, with the proposed position of vorasidenib, the EAG's clinical advisor noted that patients with low grade glioma not in need of immediate RT / CT have treatment options of either active surveillance, or IDH inhibitor (which is where vorasidenib comes in). Hence, the EAG consider the proposed position of vorasidenib in the treatment pathway to be appropriate.

2.3 Critique of company's definition of decision problem

Table 3 presents a description of the NICE final scope, the decision problem addressed within the CS and the EAG comments on the differences between the two.

Population

The EAG noted that the population addressed in the company decision problem is narrower than NICE's final scope. The population in the NICE scope included patients 12 years and over with astrocytoma or oligodendroglioma with IDH1 or IDH2 mutations who have had surgery. However, the population reflected in INDIGO is in line with the company's proposed marketing authorisation which recruited patients with "***grade 2"*** astrocytoma or oligodendroglioma "***who are not in need of immediate chemotherapy or radiotherapy***" following surgical intervention. Hence, the target population addressed by the company are patients (with low grade glioma having residual disease) that the multidisciplinary team (MDT) within UK clinical practice would consider for active surveillance following surgery.

Intervention

The intervention, vorasidenib (40mg for patients weighing 40kg and above and 20mg for patients weighing below 40kg), administered orally once daily is in line with the NICE scope.

Comparators

The comparator, watch and wait – active surveillance, is in line with the NICE final scope.

Active surveillance with most NHS centres follows the NICE 2018 guidelines. This involves patients undergoing magnetic resonance imaging (MRI) scans at 3 months, 6 months and then annually following surgery.

Outcomes

The company reported all outcomes as per the NICE final scope. The outcomes measured in INDIGO were progression free survival (PFS) per the blinded independent review committee (BIRC) according to the modified Response Assessment for Neuro-oncology for low-Grade Gliomas (RANO-LGG)[10], PFS by investigator assessed (IA), time to next intervention (TTNI), tumour growth rate (TGR), overall survival (OS), objective response (ORR) on the basis of BIRC according to RANO-LGG, time to response (TTR), duration of response (DoR), health related quality of life (HRQoL), EQ-5D-5L, seizure activity, neurocognitive function, and adverse events (AE). The company presented the results of all outcomes at the 6th September 2022 data cut-off. In addition, the company presented ad-hoc analyses of a further 6 months follow up in the 7th March 2023 data-cut for PFS by BIRC, PFS by IA, TTNI and ORR. Data from the 7th March 2023 data cut is used to inform the company's cost-

effectiveness analysis. The next expected data cut-off is in May 2025, but this is expected to be for safety data only.

The modified RANO-LGG assessment differs from the NHS assessments in that clinical deterioration has been removed from the RANO-LGG and this is left to the discretion of the treating clinician. [11]In addition, data from the most recent cut offs of 6th September 2022 and 7th March 2023 used by the company is quite old compared to the time of this appraisal (April 2025). Moreover, with the expected data cut in May 2025, the EAG considers it more appropriate to evaluate the clinical effectiveness of vorasidenib with more mature data.

Table 3 Summary of decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission
Population	People 12 years and over with astrocytoma or oligodendroglioma with IDH1 or IDH2 mutations, who have had surgery	[redacted]
Intervention	Vorasidenib	Vorasidenib

Comparator(s)	Established clinical management without vorasidenib.	Servier considers the established clinical management without vorasidenib in the population studied to be “active observation”
Outcomes	• Progression Free Survival • Time to Next Intervention • Overall Survival • Tumour growth rate • Response rates	• Progression Free Survival • Time to Next Intervention • Overall Survival • Tumour growth rate • Response rates • Adverse effects of treatment • Health-related quality of life.

	• Adverse effects of treatment • Health-related quality of life.	
Economic analysis	As per NICE reference case	As per NICE reference case with the exception of a non-reference case discount rate for costs and health effects.
Subgroups	If evidence allows, the following subgroups may be considered:	The company undertook subgroup analysis included in the NICE final scope.

	Astrocytoma Oligodendroglioma Type of surgery	

3 CLINICAL EFFECTIVENESS

3.1 Critique of the methods of review(s)

The company conducted a systematic literature review (SLR) to identify all relevant evidence regarding the clinical efficacy, safety and health related quality of life (HRQoL) of current treatment in patients with IDH mutant grade 2 or 3 diffuse glioma who were not in need for immediate RT/CT following initial surgery (biopsy, sub-total resection, gross-total or supralocal resection). The company also undertook a targeted literature review (TLR). Details of the reviews are reported in CS, Appendix B.

The SLR, which included RCTs only, was used to inform the clinical effectiveness of the treatment. The targeted literature review included non-RCTs of interventions given at subsequent lines (after first surgery and first RT/CT) and was used to inform the clinical burden of the disease.

This section presents a critique of the SLR methods for bibliographic searches, study selection, data extraction and quality assessment.

Searches

The company conducted an initial search on April 17th, 2023, followed by an updated search on May 20th, 2024. The CS stated that trial based clinical evidence associated with IDH mutant grade 2 or 3 diffuse glioma was very limited especially for patients who were not in need for immediate RT/CT intervention following surgery. The EAG appraisal of the literature searches can be found in Table 4.

The company searches to identify randomised controlled trials of treatments for astrocytoma or oligodendroglioma with IDH1 or IDH2 mutations were detailed in Appendix B of the CS.

The search strategies were clearly reported; however, some weaknesses and errors were noted by the EAG which may have caused relevant studies to be missed by the searches presented.

Table 4 EAG appraisal of evidence identification

Topic	EAG response	Note
Is the report of the search clear and comprehensive?	YES	Extra information on the searches was provided in the company response to the PFCs which was missing from the original CS.
Were appropriate sources searched?	PARTLY	No search of the International Health Technology Assessment database (INAHTA). No searches of databases containing non-Cochrane systematic reviews (e.g. Epistemonikos, KSR Evidence, DARE).
Was the timespan of the searches appropriate?	YES	Databases and grey literature sources were searched from inception to May 21st 2024.

		Conference proceedings were searched from 2020-2023
Were appropriate parts of the PICOS included in the search strategies?	YES	Population: astrocytoma or oligodendroglioma with IDH1 or IDH2 mutations AND Study design: RCTs
Were appropriate search terms used?	PARTLY	Search terms were appropriate. However, some search syntax was incorrect in the search of CENTRAL: Lines #7 and #10 of the search strategy were tested by the EAG and would not run as truncation was applied inside of quotation marks. In addition, Lines #7, #9 and #10 had missing truncation. Missing truncation in the Embase search strategy – at line #3, tumor and tumour should have been truncated to cover tumors or tumours.
Were any search restrictions applied appropriate?	NO	Inappropriate search restrictions applied: - Case studies, case reports, letters and editorials were removed from the search results in Embase, MEDLINE and MEDLINE in process. Study results or adverse effects data can sometimes be reported in these publication types. - Conference abstracts were removed from the search results in Embase and MEDLINE. - Systematic reviews were removed from the results in Embase and MEDLINE. - PubMed search results were incorrectly restricted to human studies – this results in the loss of records that are awaiting indexing – see https://pubmed.ncbi.nlm.nih.gov/help/#filters-species
Were any search filters used validated and referenced?	YES	1. The Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity- and precision-maximizing version was used to limit search results to RCTs. 2. The Cochrane Highly Sensitive Search Strategy used for identifying controlled trials in Embase for CENTRAL was used. However, the following lines from the filter were missing: 'intermethod comparison'/de (compare:ti,tt OR compared:ti,tt OR comparison:ti,tt) ((evaluated:ab OR evaluate:ab OR evaluating:ab OR assessed:ab OR assess:ab) AND (compare:ab OR compared:ab OR comparing:ab OR comparison:ab)) In addition, the Emtree heading randomized controlled trial was not exploded therefore the narrower headings (equivalence trial/, non-inferiority trial/, pragmatic trial/, superiority trial/) would not have been included in the search.

EAG response = YES/NO/PARTLY/UNCLEAR/NOT APPLICABLE

Further searches were carried out to identify non-randomized clinical trials and real-world/observational studies for a targeted literature review. The search strategies were missing from the submission but provided in the company response to the PFCs. The search strategies were pragmatic rather than comprehensive.

Inclusion criteria

The eligibility criteria were presented in CS Appendix B, Table 1. The review's intervention and comparators were unrestricted and wider than the NICE final scope. The studies included were RCTs alongside SLR and meta-analysis. Non-randomised studies, single-arm studies, prospective and retrospective cohort studies and long-term follow-up studies were excluded in the company's eligible criteria table (Table 1, CS Appendix B).

The CS did not report whether the study selection was performed in duplicate and how disagreements in the study selection process (if any) were resolved. The EAG clinical adviser believe that all relevant trials were identified, therefore it is unlikely that any relevant evidence was excluded.

Data extraction

The data extraction process was performed by one reviewer and independently checked for errors by a second reviewer, minimising the possibility of errors or bias.

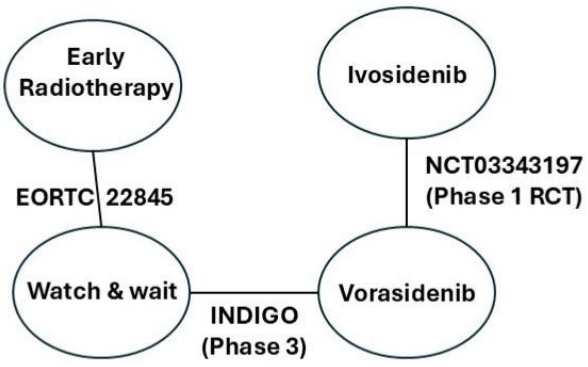
Quality assessment

The quality of the RCTs included in the SLR was assessed using NICE's quality assessment checklist (CS Appendix B, section 4.4, Table 39). The CS did not report whether the quality assessment was performed in duplicate and how disagreements (if any) in quality assessments were resolved.

Evidence synthesis

Three RCTs[12-16] (including the company's study) were identified that had the same population as the NICE final scope. A network plot of the three RCTs is presented in Figure 2 below. The company did not perform any indirect treatment comparison.

Figure 2: Network plot of randomised controlled trial



The network plot is a simplified version of CS Figure 4 to display network of RCTs only. INDIGO[13] and EORTC[12] are phase III but NCT03343197 [14]is a phase I.

OS data was reported only in EORTC 22845 [12] study and PFS data were reported in INDIGO[13], EORTC 22845[12] and NCT03343197[14].

The EAG noted that given the NICE final scope on the intervention and comparator(s), and the limited evidence available (Figure 2); there is a RCT that has direct evidence between vorasidenib and watch and wait (INDIGO). The other two RCTs (EORTC 22845 and NCT03343197) identified in the SLR evaluated comparators (ivosidenib and early radiotherapy) that were outside of NICE's final scope. Although ivosidenib is an IDH1 inhibitor, it is not approved for treatment of low-risk glioma. Therefore, ivosidenib is not a comparator in the NICE final scope.

Moreover, there is some heterogeneity in the definition/criteria of PFS in all three RCTs (CS, Appendix B, Table 9). The EAG agrees with the company's decision of not undertaking an indirect treatment comparison.

3.2 Critique of trials of the technology of interest, the company's analysis and interpretation (and any standard meta-analyses of these)

The CS included one eligible RCT. The INDIGO trial is a placebo-controlled RCT, which assessed the efficacy and safety of vorasidenib 40mg in patients with residual or recurrent Grade 2 IDH-mutant glioma.[17] Although another randomised trial of vorasidenib has been published, it is a phase I trial of unlicensed doses of vorasidenib (versus ivosidenib).[14]

3.2.1 Critical appraisal of INDIGO

3.2.1.1 Risk of bias

The company judged the INDIGO trial results to be at low risk of bias (CS, Table 13). The EAG agrees with this assessment, except for the TTNI outcome, which was mostly assessed after patients had progressed and had therefore been unblinded; knowledge of the randomised treatment would be likely to affect decisions about both next intervention choice, and timing, a bias which would be exacerbated by the decision to allow cross-over from placebo to vorasidenib. Further issues with the TTNI outcome are discussed below in Section 3.2.1.2.

The EAG notes that randomization was stratified according to locally determined chromosome 1p/19q status (codeleted or non-codeleted) and baseline tumour size (i.e. whether the longest diameter was ≥2 cm or <2 cm), so subgroup results for these populations may be particularly important.

3.2.1.2 Applicability of the INDIGO trial's methods to NHS practice

The INDIGO trial excluded patients with high-risk features, defined as including: uncontrolled seizures, (defined as persistent seizures interfering with activities of daily life and failed 3 lines of antiepileptic drug regimens including at least 1 combination regimen), brain-stem involvement, and

clinically relevant functional or neurocognitive deficits (caused by the tumour) and a heart-rate–corrected QT interval of at least 450 msec based on Fridericia's formula. The EAG's advisor thought that these exclusion criteria were reasonable. However, the EAG noted several aspects of the INDIGO trial which differ significantly from what would be expected to be seen in the NHS setting.

Population

An inclusion criterion in the INDIGO trial was that patients' last surgery had to have been between 1 and 5 years prior to randomization. The EAG asked the company to clarify the rationale for this criterion. In its response (to clarification question A2) the company stated that this requirement "*was implemented in the trial to homogenize the enrolled patient population and to allow adequate and robust assessment of radiographic disease progression*". This approach to recruitment means that patients with less stable disease may have been filtered out of the trial population. This issue is important because the anticipated marketing authorization does not place restrictions on how long ago surgery was. The lack of such restrictions means that patients with less stable disease may be treated with vorasidenib in the NHS setting; these patients may have worse outcomes than the population recruited in INDIGO.

Another inclusion criterion was that patients had to have measurable non-enhancing disease (defined as ≥1 target lesion measuring ≥1 cm by ≥1 cm in the two longest dimensions), yet in the NHS there will be patients (eligible for vorasidenib) who do not have measurable non-enhancing disease. INDIGO's Clinical Study Report indicates that 24 patients were ineligible for not having centrally confirmed MRI-evaluable, measurable, non-enhancing disease at screening (reason codes INCL06 and INCL06A). There is no trial evidence for this subgroup of patients, although they appear likely to be covered by the expected license. In light of the subgroup effect for the analyses of PFS (CS Figure 13), vorasidenib may not be as effective in patients with little or no visible residual disease. Consequently, vorasidenib may be less effective in the IDH1/IDH2 mutated LGG NHS population as a whole, when compared with the trial population.

Outcomes

In INDIGO, disease progression was assessed based on modified RANO-LGG criteria (CS p28). One of the modifications was clinical deterioration being removed as an assessment criterion. However, the EAG's advisor stated that clinical deterioration would be assessed in NHS patients and would be used (in addition to imaging) to inform the decision as to whether disease had progressed. In INDIGO, only around half of patients in the vorasidenib arm whose disease had progressed (based on the modified RANO-LGG criteria) received a subsequent treatment. In light of this, the clinical relevance and value of the progressed disease outcome in the INDIGO trial is questionable. Supportive evidence for the limitations of using only an imaging-based progressed disease outcome in INDIGO comes from the results of the neurocognitive function and health-related quality of life

outcomes; the highly significant difference between treatment groups in the number of progressed disease events did not correlate at all with the HRQoL, neurocognitive function and seizure outcomes, for which there were no significant differences between groups (see Sections 3.2.2.6, 3.2.2.7, and 3.2.2.8)

The EAG's adviser was surprised at how many patients (who progressed) did not receive a subsequent treatment; a possible suggested reason could be that this cohort of patients may have been counselled that RT/CT should be avoided for as long as possible e.g. patients may be particularly wary of neurocognitive outcomes following RT/CT. The absence of clinical deterioration may have led to hesitancy and uncertainty about the need for subsequent treatment in many vorasidenib arm patients following modified RANO-LGG image-based progression.

The time to next intervention (TTNI) outcome, conditional on progression (TTNI | P), was used in the cost-effectiveness modelling to represent time to receive RT/CT (time to receive RT/CT was not evaluated as an outcome in INDIGO). However, for the majority of patients in the placebo arm, the next intervention was vorasidenib (for 70 out of the 78 patients (90%) who received another intervention). The EAG considers that this created a bias in the TTNI data between the trial arms. This is because the clinical decision to treat placebo patients with vorasidenib (thus generating a 'next intervention' event) in INDIGO, in which patients have already been unblinded, seems likely to be easier than the decision to commence RT/CT in progressed, unblinded patients in the vorasidenib arm, based on the perceived risks of administering these interventions (it should be noted that patients in the vorasidenib arm cannot continue to receive it following progression).

This bias is exacerbated by the use of the modified RANO-LGG criteria to assess progression in INDIGO, where the decision to commence RT/CT following progression will be less likely than would be expected in clinical practice. This is because clinical deterioration was not part of the modified RANO-LGG criteria and some INDIGO progression events will not have had any associated clinical deterioration.

Moreover, vorasidenib is not currently available in the NHS, so it is not a relevant next intervention to consider in the placebo arm, with respect to the TTNI outcome. Also, considering that the median follow up of patients in INDIGO was only around 14 months (although a data cut was also provided with a further 6 month analysis), and because vorasidenib patients tended to progress at later timepoints than placebo patients, the follow-up for some vorasidenib patients may have ended before the next intervention could be given. The immaturity of the trial data is therefore an issue for the TTNI outcome. Given all these issues, the use of TTNI to represent time to receive RT/CT is not appropriate and the TTNI results should not be considered as being applicable to the NHS setting.

3.2.2 Clinical efficacy results of the INDIGO trial

3.2.2.1 Baseline characteristics

The baseline characteristics of the INDIGO trial cohort were reported in Table 10 of the CS. The median age was around 40 years and the mean time from initial diagnosis to randomisation was just over 3 years. Just over 20% of patients had had two or more surgeries prior to randomization.

Given that tumour diameter may be an effect modifier (see Section 3.2.2.2) the EAG asked their advisor to comment on the tumour diameter data: although 80% of patients having tumour diameters of >2cm seems a little high - it could be 60-70%, or even lower in the NHS - it was nevertheless difficult to comment on this. A smaller proportion of patients with tumour diameters >2cm in the NHS population may reduce the treatment effect size, which would reduce cost-effectiveness.

3.2.2.2 Progression free survival

Although vorasidenib demonstrated a statistically significant improvement compared to placebo at the March 2023 data-cut in imaging-based PFS (HR 0.34, 95% CI: 0.23 to 0.50, see CS Table 15), the EAG consider this result to have limited applicability to the NHS setting (see Section 3.2.1.2 for details).

Subgroup analysis

PFS subgroup analyses were presented in Figure 13 of the CS. These suggested that baseline tumour size may be an effect modifier, with minimal treatment effect in patients with a longest tumour diameter <2 cm. This result is important because randomization was stratified by baseline tumour size (i.e. whether the longest diameter was ≥2 cm or <2 cm) meaning it was considered by the company to be a known or potential prognostic factor or affect modifier. However, the subgroup of patients with tumour diameters <2 cm is quite small (n=62) compared to the subgroup with tumour diameters <2 cm (n=269). The EAG therefore asked the company to provide a test for interaction result, to quantify the significance of this result (clarification question A9), but this was not provided. Given that in the NHS, patients with non-measurable, non-enhancing disease (who were excluded from INDIGO) will be eligible for vorasidenib, the proportion of patients with smaller tumours in the eligible NHS population is likely to be larger than was seen in the INDIGO trial. This may mean that the INDIGO PFS estimates are larger than would be seen in the NHS.

3.2.2.3 Time to next intervention (TTNI)

Table 17 of the CS reported a highly statistically significant difference in TTNI favouring vorasidenib over placebo (HR 0.25, 95% CI: 0.16 to 0.40) at the March 2023 data-cut. However, as discussed in section 3.2.1.2, TTNI, conditional on progression, was used to represent time to RT/CT in the cost-effectiveness model, but one of the next interventions (included in the TTNI definition) was vorasidenib. The EAG therefore does not consider this to be a useful outcome measure; time to

RT/CT would have been a much more clinically-relevant outcome and would have fitted with the model structure (CS, Figure 15).

The EAG asked the company (clarification question A7) to report specific details of all subsequent anti-cancer therapies for each treatment arm. These are presented in Table 5 below. The date of the data-cut was not stated by the company, although only 11 vorasidenib patients had received subsequent radiation therapy. In most patients the antineoplastic therapy received was temozolomide.

Table 5 Summary of subsequent anti-cancer treatments (excluding vorasidenib) used in the INDIGO trial

Type of treatment	Placebo arm n (%)	Vorasidenib arm n (%)	Overall n (%)
Antineoplastic therapy	3 (1.8)	13 (7.7)	16 (4.8)
Radiation therapy	5 (3.1)	11 (6.5)	16 (4.8)
Surgery	3 (1.8)	10 (6.0)	13 (3.9)

3.2.2.4 Response rates

Best overall response (also called objective response) as assessed by the Blinded Independent Review Committee (BIRC) significantly favoured the vorasidenib arm (07 March 2023 data-cut) with an odds ratio for objective response rate of 5.45 (95% CI: 1.77 to 16.78). It is evident from Table 18 in the CS that most patients' best response (in both treatment arms) was stable disease; the EAG's adviser said this was not unusual in glioma trials. However, more patients had a best response of 'minor response' in the vorasidenib arm (9.5%) than was seen in the placebo arm (2.5%); these data were reported only for the September 2022 data-cut.

3.2.2.5 Tumour growth rate

Results were presented only for the September 2022 data-cut for tumour growth rate. There was reduction in tumour volume in vorasidenib patients by a mean of 2.5% every 6 months (95% CI: -4.7%, -0.2%), compared to tumour volume increase in the placebo arm, by a mean of 13.9% every 6 months (95% CI: 11.1%, 16.8%).

3.2.2.6 Health-related quality of life

There were no significant differences between treatment groups in either EQ5D or FACT-Br (Functional Assessment of Cancer Therapy – Brain). Result details were reported in the CS on p41 but these were limited (by the lack of confidence intervals or p-values, although Figure 11 of the CS provided graphical representation of the FACT-Br results).

3.2.2.7 Seizure activity

There was no clinically meaningful improvement or worsening of seizure activity in the vorasidenib arm relative to placebo (CS, p43). The company also presented a subgroup analysis of patients who reported ≥1 seizure while on treatment (n=110). The seizure rate in the vorasidenib group was 64% lower compared to the placebo group with the ratio of rates for vorasidenib versus placebo being 0.36 (95% CI, 0.14 to 0.89; P= 0.026). This appeared to be a post-hoc analysis, as the EAG could not find it specified in the company's statistical analysis plan documentation.

3.2.2.8 Neurocognitive Function

The CS reported (in Figure 12) that there were no changes suggestive of a treatment effect on neurocognitive function with respect to psychomotor function, attention, executive function, verbal learning, and working memory.

3.2.2.9 Malignant transformation

The EAG asked the company (in clarification question A14) to provide data on the rates of malignant transformation (MT) and time to MT for the vorasidenib and placebo arms of INDIGO from the most recent data cut. The company stated that INDIGO study used a conservative definition of malignant transformation that included changes from Grade 2 to either Grade 3 or Grade 4. In the vorasidenib arm, six patients had malignant transformation, with a median time from initial diagnosis to malignant transformation of 44.19 months. In the placebo arm, two patients had malignant transformation (both had a time from initial diagnosis to malignant transformation of around 25 months). In patients who crossed-over from placebo to vorasidenib two patients had a malignant transformation after discontinuing vorasidenib.

3.2.3 Safety outcomes of the INDIGO trial

A summary of the safety outcomes such as treatment related emergent adverse event (TREAEs), Grade ≥ 3 treatment emergent adverse events (TEAEs), and TEAEs leading to death, discontinuation, interruption or reduction of dose are presented in the CS Document B, Section 2.9 with a data cut-off of the September 2022. A new safety data cut-off is expected in May 2025. The comprehensive safety results are reported in the company's clinical study report, section 12.

Median time on treatment for the vorasidenib group was 14.0 months (IQR: 10.1 months to 17.9 months) and the median time on placebo for the control group was 14.3 months (IQR: 10.0 to 18.1 month). At the primary data cut-off (6th September 2022), no death was recorded in either group during the follow up period before disease progression. However, one death was recorded in the placebo arm post progression. The percentage of patients who discontinued treatments regardless of any reason as at 6th September 2022 were 21.6% (36 subjects) in the vorasidenib arm and 41.7% (68 patients) in the placebo arm. The percentage of patients who discontinued allocated treatments and

had centrally confirmed disease were 14.3% (24 patients) in the vorasidenib arm and 36.2% (59 patients) in the placebo arm.

All-cause any-Grade AEs occurred in 94.6% of vorasidenib patients and 93.3% of placebo patients. Patients who experienced TREAEs was 65.3% of patients in the vorasidenib arm compared to 58.3% in the placebo arm. All-cause Grade ≥ 3 AEs occurred in 22.8% of patients in the vorasidenib arm and 13.5% of patients in the placebo arm, driven by higher rates of increased alanine aminotransferase (9.6% versus 0%), and increased aspartate aminotransferase (4.2% versus 0%). All-cause serious AEs occurred more in the vorasidenib arm compared to the placebo arm (6.6% versus 4.9%).

Overall, the evidence from INDIGO suggests that vorasidenib is more toxic than placebo especially in terms of increased alanine aminotransferase (ALT), increased aspartate aminotransferase (AST) and Increased γ-glutamyl transferase (GTT). The EAG's clinical advisers consider the safety profile of vorasidenib to be acceptable and manageable.

3.2.4 Managed access proposal

The company proposes use of the Cancer Drugs Fund (CDF) to allow uncertainty to be resolved by further data collection (CS Section 3.8, page 93). However, the EAG notes that some uncertainty could be resolved much sooner, in terms of progression-free survival and time to next intervention, if the company provided a more recent data cut than March 2023 i.e. a new data-cut could provide two years' more PFS and TTNI data. The EAG also considers that the value of CDF data is likely to be limited, for the following reasons:

i) The time to next intervention comparative data produced from the CDF would likely be of limited value, given the extensive number of patients who have crossed-over from placebo to vorasidenib and given the limited clinical relevance of this outcome measure (see Section 3.2.1.2).
ii) Given that the maximum follow up allowed in the cancer drugs fund is five years, it is unlikely that a median overall survival for vorasidenib will be calculable.

3.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

The company did not conduct an indirect comparison.

3.4 Critique of the indirect comparison and/or multiple treatment comparison

The company did not conduct an indirect comparison.

3.5 Conclusions of the clinical effectiveness section

The company's evidence on the efficacy and safety of vorasidenib was based on the results of INDIGO, a randomised placebo-controlled trial. The EAG considers that the results for PFS and Time to Next Intervention should not be considered as reliable estimates of the effects expected to be seen in the NHS setting. This is because of the way both of these outcomes were defined in INDIGO. The Time to Next Intervention results, in particular, appear likely to be significantly biased in favour of vorasidenib. Furthermore, the NHS population will be broader and more heterogeneous than the population recruited to INDIGO; there are reasons to be concerned that vorasidenib may be less effective when used across the broader NHS population.

Therefore, the EAG concludes that the company's claim that vorasidenib "delays subsequent treatment with aggressive RT/CT" is not supported by the trial evidence. Although significant improvements in tumour growth rate, and in response rate, were reported in INDIGO, the clinical significance of the results remains unclear, given INDIGO's methodological limitations. Although the company proposes use of the Cancer Drugs Fund to allow uncertainty to be resolved by further data collection, the EAG notes that some uncertainty could be resolved much sooner, if a more recent data cut than March 2023 were provided.

Vorasidenib appears to have acceptable and manageable safety profile.

4 COST EFFECTIVENESS

4.1 EAG comment on company's review of cost-effectiveness evidence

4.1.1 Summary of company's submission

The company's systematic literature review did not identify any economic evaluations of vorasidenib for the treatment of people aged 12 years and over with grade 2 astrocytoma or oligodendroglioma with IDH1 or IDH2 mutations, who have had surgical intervention and not in immediate need of RT/CT (see Appendix E of the CS for a detailed description of the searches and results of the review). One study was identified comparing temozolomide (TMZ) with best alternative care from a UK perspective and used to inform NICE TA23 (guidance on the use of TMZ for the treatment of recurrent malignant glioma, first published in 2001 and updated in March 2016[18]). Table 23 of the CS provides a summary of the one included study, Dinnes et. al. (2001)[18].

4.1.2 Points for critique

The literature searching for the company's review of cost-effectiveness evidence appears to have been conducted to a high standard and is well reported – See Appendix 1 for details. The EAG considers that all relevant publications are likely to have been identified. The EAG considers the one identified study by Dinnes et. al. (2001)[18] to have limited applicability to the decision problem because TMZ is not considered a comparator in the CS. Furthermore, the study is outdated and involves a very simple cost-utility model with limited methodological detail reported.

4.2 Summary and critique of the company's submitted economic evaluation by the EAG

The company submitted a *de-novo* model to assess the cost-effectiveness of vorasidenib with active observation (also referred to as 'watch and wait' or 'no treatment') for people aged 12 years and over with grade 2 astrocytoma or oligodendroglioma with IDH1 or IDH2 mutations, who have had surgical intervention and not in immediate need of RT or CT from the perspective of the NHS and Personal Social Services.

The cost-effectiveness model uses a microsimulation approach where individual characteristics vary on a per-patient basis, which are sampled from the summary statistics for the baseline participant characteristics of INDIGO. The model adopts a time horizon of 60 years for an average patient age of 40 years old entering the model at baseline.

Vorasidenib is modelled to reduce the risk of progression (i.e., slow the tumour growth rate such that it delays the transformation into higher grade gliomas or a more aggressive disease state) and the time

to next intervention (i.e., delays the initiation of RT/CT) in patients with predominantly non-enhancing IDH-mutant gliomas.

In the absence of mature overall survival (OS) data from INDIGO (where only one participant died post-progression in the 07 March 2023 data cut off), the approach to modelling relies on the relative effect of vorasidenib vs. active observation on time to progression (TTP) and time to next intervention following progression (TTNI | P) being predictive of vorasidenib's relative effect on OS.

Vorasidenib is modelled to affect QALYs by increasing the time that patients are progression-free (PF) compared to active observation, where PF is associated with improved HRQoL relative to progressive disease (PD) and delaying the time to RT/CT, which is associated with a significant drop in HRQoL in the company's model.

Vorasidenib is modelled to affect costs by increasing the time that patients are PF and on-treatment, where treatment acquisition costs are incurred until discontinuation of treatment upon radiographic evidence of disease progression, whereas active observation is associated with no treatment costs. Upon progression, vorasidenib is modelled to delay the time to RT/CT (i.e. PD and off-treatment) compared to active observation, where RT/CT is associated with drug acquisition and administration costs, in addition to higher medical resource use costs. No differences in adverse event costs are assumed.

4.2.1 NICE reference case checklist

The model submitted by the company is assessed in relation to the NICE reference case in Table 6.

Table 6 NICE reference case checklist

Element of health technology assessment	Reference case	EAG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	The CS is appropriate.
Perspective on costs	NHS and PSS	The CS is appropriate.
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	The CS is appropriate.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	The economic model has a lifetime horizon of up to 60 years based on an average baseline age of 40 years. However, the baseline population characteristics vary by age, with some patients <40 years old in the model; therefore, after a time horizon of 60 years, some patients are expected to be alive beyond this period.

Synthesis of evidence on health effects	Based on systematic review	The CS is appropriate.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life (HRQoL) in adults.	The CS is appropriate but health state utility values for subsequent treatment lines are based on EQ-5D responses from a vignette study with members of the UK general public rather than elicited directly from patients.
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	Utility values applied to later health states in the model are elicited using vignettes describing each health state and not reported directly by patients and/or carers.
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	The CS is appropriate.
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	The CS is appropriate.
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	The CS is appropriate.
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Not appropriate. A discount rate of 1.5% per annum is applied to both costs and health effects. Scenario analysis considered a discount rate of 3.5% per annum.
CS: company submission; PSS: personal social services; QALYs: quality-adjusted life years; HRQoL, health-related quality of life; EQ-5D: standardised instrument for use as a measure of health outcome.		

4.2.2 Model structure

4.2.2.1 Summary of company's submission

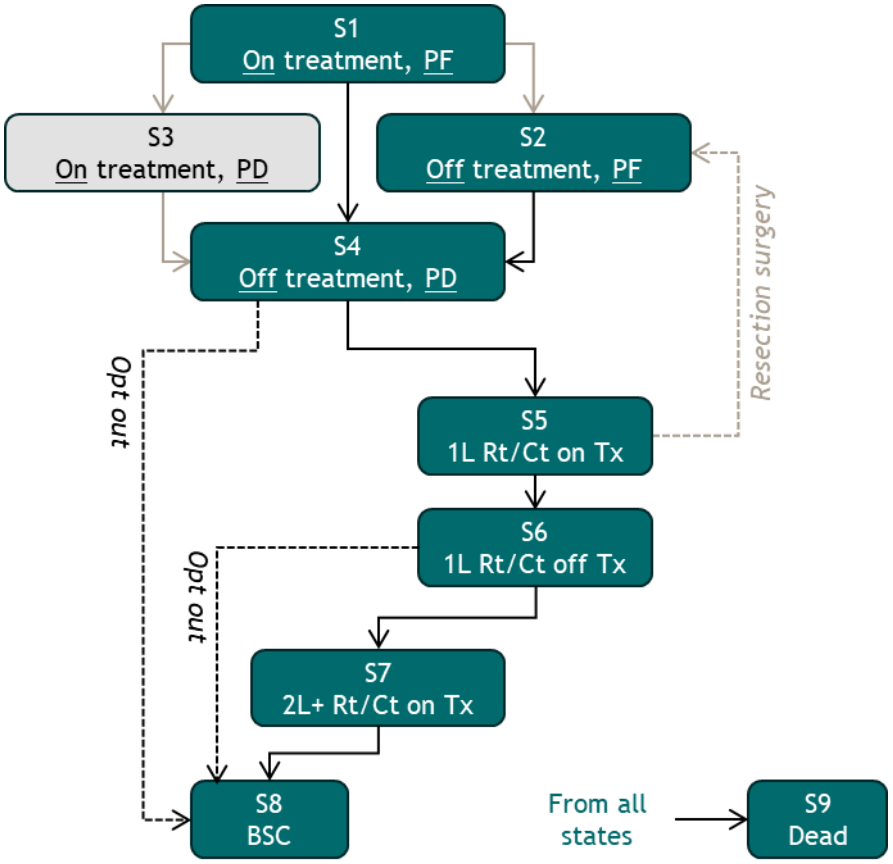
The model structure is based on health states relating to treatment status, where treatment-related milestones are used to signify stages of disease progression and the management of low-grade glioma (LGG). Figure 3 shows the model structure, which comprises up to 9 health states (labelled S1 to S9) that capture periods of time where patients are expected to be on-treatment with vorasidenib (health states S1 and S3), off-treatment (either following vorasidenib or under active observation), on the next intervention (NI), the following interventions (NI+), receiving best supportive care (BSC) or dead. By selecting a state-transition model by treatment lines instead of a partitioned-survival model, the model allows the discrete breakdown of the pathway steps so that patients can transition to subsequent treatment lines and the costs and outcomes associated with these treatment lines can be captured over a lifetime horizon.

In the company's base case analysis, patients start in either health state S1 (PF and on-treatment with vorasidenib) or S2 (PF and off-treatment under active observation). Upon progression of their disease, based on time to progression data from the INDIGO study by treatment arm, patients transition to health state S4 (PD and off-treatment), i.e., discontinuation of vorasidenib is assumed to occur at the same time as disease progression. Patients remain in health state S4 until receiving their next intervention (NI), where it is assumed that vorasidenib is associated with longer time to next intervention (TTNI) compared to active observation based on the INDIGO study by treatment arm. Once patients initiate their NI, they enter health state S5, where they receive first line (1L) RT/CT and remain in this health state whilst receiving treatment, informed by a maximum treatment duration (see Section 4.2.9.3) and time to progression to the next treatment line. If patients in S5 have completed treatment with 1L RT/CT and not progressed in their disease, they move to health state S6 (i.e., 1L RT/CT and off-treatment). Patients remain in health states S5/S6 until time to next subsequent line of RT/CT, which is informed by external sources to INDIGO (see Section 4.2.6.1). Once patients initiate their next intervention (NI+) they enter health state S7, where they receive second and subsequent treatment lines (2L+) of RT/CT and remain in this health state based on time to progression with salvage therapy. Upon progression with 2L+ RT/CT, patients transition to health state S8 of BSC, which is used to represent planned palliative or supportive care at end of life upon exiting salvage therapies at 2L+. All patients in the model are at a risk of death (health state S9) from any health state. However, general population mortality risk is applied in health states S1 to S7, with no excess mortality risk considered for these states, with the only excess risk of mortality applied to BSC (health state S8).

The company expects that some people may 'opt out' of receiving treatment at two key stages: following completion of the initial treatment period (i.e., vorasidenib or active observation) or following completion of their NI. Upon opting out of future treatment, patients are assumed to transition to S8 (i.e., BSC). The possible transitions reflecting opting out of treatment are represented in the model schematic (Figure 3) as dashed lines from either health states S4 or S6, to S8.

A model cycle length of 28 days (with half cycle correction) is implemented. A microsimulation approach is used to allow individual tracking of time within each health state for capturing downstream costs and effects of later interventions.

Figure 3: A schematic of the model structure (reproduced from Figure 15 of CS)



Abbreviations: BSC, best supportive care; NI, next intervention; PD, progressed disease; PF, progression-free; Tx, treatment.

4.2.2.2 Points for critique

The EAG considers the company's model structure to be broadly appropriate given that the goal of treatment with vorasidenib is to reduce the risk of disease progression and delay the time to next intervention. However, the EAG does not necessarily agree that this is best captured using a treatment status-based model structure, where treatment-related milestones based on lines of therapy are used to model the stages of disease progression. The EAG considers it more appropriate to model progression events and changes to these events over time, such as the transition from LGG to high-grade gliomas (HGG) or transformation to malignant gliomas (secondary HGG). The company notes that their approach to developing a model around treatment-related milestones is consistent with NICE technology appraisal 977 (TA977 of dabrafenib with trametinib for treating BRAF V600E mutation-positive glioma in children and young people aged 1 year and over[19]). In TA977, the progressive disease health state was divided into a series of sub-health states representing different progression events/lines of treatment to capture the impact of subsequent progressions on costs and HRQoL. However, the EAG notes that the model in TA977 also included a separate health state of transformation to malignant glioma, where the rate of malignant glioma and event-free survival

following malignant transformation was explicitly modelled. In addition, the model in TA977 included an upper limit on progression for LGG, where no progression was assumed once patients reached 25 years of age, and a separate model was developed for HGG.

The EAG is broadly in agreement with the company that assuming a single 'progressed disease' health state following initial intervention is not appropriate, as patients may experience several progression events and receive several lines of treatment over their lifetime. However, the EAG's primary concern is the granular level of information required to accurately model survival outcomes on subsequent lines of treatment, and the lack of explicit link between progression events and treatment received. Modelling the clinical pathway for LGG is extremely challenging and data intensive due to the different treatment modalities (surgical, RT/CT, watch and wait), administered individually or in combination. Furthermore, IDH-mutant glioma has a diffuse and unpredictable nature, where the tumour-growth dynamics are unpredictable, and rapid acceleration can occur suddenly. The company states that more than 70% of IDH-mutant gliomas have the potential to undergo a transformation, progressing into a higher grade or becoming aggressive in behaviour within a decade. The company's approach to model the complexity of this pathway via multiple lines of treatment is not only data intensive but also requires a clear link between treatments received and progression events such as the transition from LGG to HGG, transformation to malignant gliomas and type of glioma (astrocytoma, ependymoma, and oligodendroglioma). The EAG is concerned that the company's model does not explicitly model progression to health states based on high-grade disease and malignant transformation, which are key in the context of prognosis, HRQoL and survival. Instead, the model is relying on many simplifying assumptions from a host of external studies from different populations (e.g., age, setting, radiological characteristics, tumour size, extent of symptoms, risk of malignant transformation, time since surgery, prior treatments received) to model post-progression survival outcomes associated with subsequent treatment lines. The comparability of the populations used in the post-progression studies is unclear, as well as their relevance to the target population from INDIGO and NHS clinical practice (see Section 4.2.6.2).

The company states that it was unable to adopt a simpler model structure of a partitioned survival model due to the absence of mature overall survival (OS) data from INDIGO. The mortality benefit for vorasidenib is modelled as a function of delaying time to RT/CT and subsequent lines of therapy, i.e., delaying the time to BSC drives the mortality benefit achieved for vorasidenib relative to active observation. This effectively means that a surrogacy relationship for OS is inferred through delaying progression to subsequent treatment lines. However, the company have not presented evidence from the INDIGO trial that shows a relationship between delaying time to progression and OS benefit for vorasidenib relative to active observation in the target population (see Section 4.2.6.2).

In summary, the EAG considers the model structure to be broadly appropriate for capturing the downstream effects of initial intervention but it relies on two key structural assumptions to hold, which have not yet been proven with data: (1) subsequent treatments are a good surrogacy for progression of disease in terms of transitions to HGG (and type of gliomas) and malignant transformation; and (2) the relative effect of vorasidenib on time to progression and time to next intervention following progression from INDIGO is predictive of its relative effect on OS, inferred through delaying progression to subsequent treatment lines. Furthermore, the data and evidence informing the link between subsequent treatments received and progression events must come from comparable populations and settings, with relevance to the target population and NHS clinical practice (see Section 4.2.6.2).

4.2.3 Population

4.2.3.1 Summary of company's submission

The target population is people aged 12 years and over with grade 2 astrocytoma or oligodendroglioma with IDH1 or IDH2 mutations, who have had surgical intervention and not in immediate need of RT or CT, in line with the anticipated marketing authorisation for vorasidenib and the population included in the INDIGO trial.

The modelled population is based on the baseline characteristics of participants in INDIGO, with a mean age of 40 years, proportion of females 44%, and a mean weight of 82 kg (see Table 25 of CS). In the microsimulation model, baseline characteristics vary on a per-patient basis by sampling from the summary statistics for baseline characteristics included in INDIGO, with 5,000 patient profiles generated for the analysis.

No subgroups are considered.

4.2.3.2 Points for critique

The EAG is satisfied that the approach used in the model to generate a population similar to INDIGO and in line with the anticipated marketing authorisation for vorasidenib is appropriate. However, the EAG is concerned about the generalisability of the INDIGO trial population to NHS patients who could potentially benefit from treatment with vorasidenib. The EAG is primarily concerned that the population recruited in INDIGO may have been subject to a selection effect, where participants with less stable disease (i.e., more likely to progress before randomisation) were excluded from the trial due to the inclusion criterion of surgery ≥1 year but ≤5 years at randomisation. The EAG notes that the average time since surgery is approximately 2.5 years in the model; therefore, the population is a pre-selected slower tumour-growth, more stable population because patients who relapsed post-surgery or progressed within a year are omitted, while approximately 50% of patients are over 2.5 years since surgery and not requiring treatment.

4.2.4 Intervention and comparator

4.2.4.1 Summary of company's submission

The intervention considered is vorasidenib, which is an oral, potent, targeted inhibitor of mutated IDH1 and IDH2 and administered at a daily dose of 40mg, which is aligned with the regimen used in INDIGO. The company states that vorasidenib should be continued until disease progression or until treatment is no longer tolerated by the patient. Participants in the INDIGO trial discontinued treatment mainly due to disease progression or intolerability (see Section 3.2.1.2). The model does not incorporate a stopping rule for vorasidenib and patients are assumed to remain on treatment until progressed disease (health state S4).

The comparator included in the model is active observation, with clinical outcomes informed by the placebo arm of INDIGO. The company justified the choice of comparator because there are no treatments indicated for the target population who are *'*not in immediate need of RT or CT'.

Subsequent treatment use after discontinuation from initial intervention (vorasidenib or active observation) is explicitly modelled by accounting for both costs and outcomes associated with 1L RT/CT, followed by 2L+ RT/CT, followed by BSC until end of life.

4.2.4.2 Points for critique

The 40mg daily dose of vorasidenib used in the model is appropriate. A 20mg dose is recommended for patients weighing less than 40kg; however, the EAG notes that the minimum weight in the model is 40kg, therefore the 40mg dose is appropriate. The company assumes that patients remain on treatment until progressed disease, which implies that progression events occur at the same time as discontinuation events. The company have not presented separate time to progression and time to discontinuation curves from INDIGO for the EAG to assess the appropriateness of this assumption. However, the EAG considers it reasonable to make the simplifying assumption that time to progression represents both progression and discontinuation events (i.e., transitions from health state S1 to S4 constitute both a progression and a discontinuation event) in light of the safety profile for vorasidenib.

For the comparator, the final NICE scope states 'established clinical management without vorasidenib'. The EAG considers it reasonable to use active observation (no treatment) as the comparator provided that the MHRA marketing authorisation for vorasidenib specifically states for patients diagnosed with LGG who are *'*not in immediate need of RT or CT'. The EAG notes that vorasidenib has been approved by the US Food and Drug Administration (FDA) in August 2024 for the 'treatment of adult and pediatric patients 12 years and older with grade 2 astrocytoma or oligodendroglioma with a susceptible IDH1 or IDH2 mutation following surgery including biopsy, sub-total resection, or gross total resection', but without reference to *'*not in immediate need of RT or CT'. Given that the evidence from INDIGO is for a relatively stable population of predominantly non-

enhancing IDH-mutant LGG with slower tumour-growth, the EAG considers it reasonable to assume that active observation is the most relevant comparator in this stable population. The same subsequent treatment use is assumed after progression on initial intervention, i.e., only the timing of subsequent treatment lines differs by initial intervention, which is critiqued in Section 4.2.6.2.

4.2.5 Perspective, time horizon and discounting

4.2.5.1 Summary of company's submission

The analysis is conducted from the perspective of the NHS and Personal Social Services (PSS) in England and Wales over a 60-year time horizon to reflect a lifetime for an average baseline age of 40 years.

The economic model presented in the CS uses a non-reference case discount rate of 1.5% per annum for both costs and effects.

4.2.5.2 Points for critique

The economic model has a lifetime horizon of up to 60 years based on an average baseline age of 40 years. However, the EAG notes that the baseline distribution varies by age, with some patients <40 years old in the model; therefore, after a time horizon of 60 years, some patients are expected to be alive beyond this period, which means that lifetime costs and effects are not included for all patients in the model. Nonetheless, the EAG considers a time horizon of 60 years to be sufficient to capture important differences in costs and effects between the intervention and comparator.

The EAG has significant concerns regarding the company's justification for the use of the non-reference case discount rate of 1.5% per annum. The NICE methods guide[20] provides criteria for the application of the non-reference case 1.5% discount rate. The EAG's critique of the company's justification for these criteria is discussed in turn below.

Vorasidenib is for people who would otherwise die or have a very severely impaired life.

The company states that this criterion is met based on established knowledge of outcomes for people living with LGG managed with current care (i.e., active observation), where patients experience the negative consequences of their disease at a much more rapid pace, especially when treated with RT/CT. The EAG has significant concerns regarding the company's position that patients would otherwise die or have a very severely impaired life without vorasidenib. First, the very fact that the relevant comparator in the model is active observation, and a placebo arm was considered ethical to include in the INDIGO trial, suggests that vorasidenib is not indicated for people who would 'otherwise die'. Vorasidenib is indicated for people with indolent, non-enhancing LGG, who are likely to have more stable disease, with inclusion criterion in INDIGO of ≥1 year but ≤5 years post-surgery and not in immediate need of RT or CT; therefore, vorasidenib is indicated for early stages of

the disease with better prognosis, where watch and wait is a viable alternative treatment option. Second, the predictions of OS from the model clearly indicate that vorasidenib is not for people who would otherwise die. The model predicts total life years (undiscounted) of 20.63 for active observation vs. 26.45 for vorasidenib. These estimates indicate high values of projected life expectancy, where the median OS is 15.26 years for active observation and 22.54 for vorasidenib. Throughout the CS, the company alludes to median OS for patients with IDH-mutant glioma of approximately 10 years and median survival for IDH-mutant Grade 2 astrocytomas ranging from between 5 to 8 years. At points for clarification, the EAG questioned the validity of the model predictions in light of the estimates reported in the CS for median OS (question B4b). The company clarified that the median OS of 10 years reported in the CS was specific to a population with IDH wildtype glioblastoma, not glioma, and therefore, not relevant to the target population. The company justified the model predictions in light of external data from Blonski et al., (2022) [21] and Bhatia et al., (2024)[22], which broadly support the model predictions (see response to EAG clarifications question B4b). The EAG considers the modelled median OS estimates for the comparator arm of active observation insufficient to justify the assertion that vorasidenib is indicated for people who would otherwise die. Furthermore, only one death has been recorded in the INDIGO trial.

The company's assertion that vorasidenib is indicated for people with a very severely impaired quality of life is also not supported by existing evidence. First, the EQ-5D utility values from INDIGO indicate a relatively good quality of life in both the vorasidenib and placebo arms compared to similar age- and sex-matched general population utility values, with a mean utility value of 0.744 for patients PF and receiving vorasidenib and a slightly higher mean utility value of 0.745 for patients PF on the placebo arm. For patients with progressed disease in INDIGO, the utility values were only slightly lower than PF and higher for the placebo arm than vorasidenib arm (mean utility of 0.730 in placebo arm and 0.678 in vorasidenib arm). Therefore, the evidence from the INDIGO trial suggests that health-related quality of life is associated with only a modest decrement compared to age- and sex-matched general population utility values and does not result in a 'very severely impaired life' from the perspective of the patient. Furthermore, it even suggests better quality of life in the placebo arm than the vorasidenib arm. The company justifies the severely impaired life based on potential acute adverse effects of RT, such as elevated intracranial pressure that can manifest as headaches and vomiting and the additional chronic side effects associated with RT. The EAG notes that while health-related quality of life is more likely to be impaired at later stages of disease when receiving subsequent treatments of RT/CT the evidence is not available to support severely impaired quality of life. In the absence of utility values required for health states linked to subsequent treatment lines in the model, a vignette study was conducted. This study produced low utility values associated with later stages of the disease (although it is subject to significant uncertainty – see Section 4.2.8.2), but no separate distinction was made in the model between utility values for patients on and off RT/CT,

which suggests that quality of life is dependent on disease stage rather than treatments received. Therefore, the evidence from the INDIGO trial and the lack of evidence from the wider literature suggests that vorasidenib is not indicated for people with 'severely impaired' life.

Vorasidenib is likely to restore them to full or near-full health.

The EAG has concerns regarding the company's position that vorasidenib restores patients to full or near-full health, both in terms of length and quality of life. First, even after surgical resection, IDH-mutant glioma remains incurable; therefore, vorasidenib cannot be demonstrated to represent a cure to 'full or near-full health'. Second, vorasidenib is demonstrated to slow progression in the INDIGO trial (with statistically significant PFS for vorasidenib relative to placebo) but there remains significant uncertainty regarding TTNI (see Section 4.2.6.2) and therefore the extent to which vorasidenib delays the time to RT/CT over and above active observation remains unknown. Furthermore, as discussed above, health-related quality of life in the placebo arm of INDIGO was greater than in the vorasidenib arm, which further confirms that vorasidenib does not offer improvements in quality of life, beyond potential delays to later stages of the disease. The vignette study was based on UK general population views on the description of NI of RT/CT and post-NI, and NI+ and post-NI+ health states, rather than from patients with glioma, which is one of the lowest forms of eliciting health-related quality of life utility values in the hierarchy of evidence outlined in NICE methods guide. As such, the evidence is not available to support the view that vorasidenib restores people to full or near-full health.

The benefits are likely to be sustained over a very long period.

As discussed in Section 3.2.2 and Section 4.2.6.2, the EAG considers there to be insufficient evidence to conclude with certainty that the benefits of vorasidenib are sustained over a very long period. PFS gains have been demonstrated to 30 months (but based on a limited number of patients at risk beyond 18 months), with no data beyond this period, and the outcome of TTNI is subject to significant uncertainties. No information on OS is yet available from INDIGO and no difference in the rates of malignant transformation have been shown for the vorasidenib and placebo arms of INDIGO. The long-term benefits of vorasidenib are built on the premise that the hazard ratios observed for PFS and TTNI will translate into OS gains through progression on subsequent treatment lines; however, this remains unknown and downstream effects on progression is a hypothesis that has not yet been demonstrated with evidence in this target population.

Vorasidenib will not commit the NHS to significant irrecoverable costs

The NICE guidance states that the "committee will need to be satisfied that any irrecoverable costs associated with the technology have been appropriately captured in the economic model or mitigated through commercial arrangements." [redacted]

[redacted]

[redacted]

In conclusion, the EAG considers there to be insufficient evidence to justify the application of the non-reference case discount rate of 1.5% per annum in the company's base case analysis and the EAG considers it more appropriate to use the reference case discount rate of 3.5% per annum.

4.2.6 Treatment effectiveness and extrapolation

4.2.6.1 Summary of company's submission

The model includes two elements relating to treatment effectiveness and extrapolation of effects by initial intervention (vorasidenib or active observation) based on outcomes from the INDIGO trial:

(i) Progression-free survival (PFS) or time to progression (TTP), i.e., time from initiation of intervention to first documented progressive disease (noting that only one death event was recorded in INDIGO, which occurred following progression; therefore, death events were not considered in the definition of PFS); and
(ii) Time to next intervention given progression (TTNI | P), i.e., time from first documented progression to next intervention.

Following progression and time to next intervention, outcomes for subsequent treatment lines and extrapolation of effects by treatment line are based on external sources to INDIGO:

(iii) Time to discontinuation of next intervention (NI), i.e., time from initiation of first line RT/CT (1L RT/CT) to discontinuation due to progressive disease; and
(iv) Time to discontinuation of next intervention plus (NI+), i.e., time from initiation of second and subsequent lines of RT/CT (2L+ RT/CT) to discontinuation due to progressive disease and transition to BSC.

Overall survival, i.e., the probability of all-cause death, is modelled the same as general population mortality risk, except for an excess mortality risk applied to the last line of treatment of BSC:

(v) Mortality risk for BSC.

In the absence of data for the proportion of people that opt out of further treatment, a proportion of 5% is assumed prior to initiation of NI and NI+.

The data sources informing each of these elements are summarised below.

Treatment effectiveness for initial interventions based on INDIGO (modelled health states S1 – S4)

The effectiveness of the initial interventions of vorasidenib and active observation is based on time-to-event data from INDIGO (07 March 2023 data cut). PFS data is extrapolated to inform the transitions from health state S1 (PF and on-vorasidenib) or S2 (PF and under active observation) to health state S4 (PD and off-treatment). Progression was determined as per RANO-LGG criteria, which defines progression as a ≥25% increase in the T2/FLAIR signal area of the tumour[10]. Parametric fitting of Kaplan-Meier (KM) data for PFS for the vorasidenib and placebo arms, using independent fitted models, was used to extrapolate PFS over time (see Figures 17 and 18 of CS for extrapolations of PFS in the vorasidenib and placebo arms, respectively). The selection of parametric model for the vorasidenib arm was based on goodness-of-fit statistics and feedback from one clinical expert of the long-term extrapolation, with the best fitted log-normal model selected for the base case analysis. For the placebo arm, the goodness-of-fit statistics were similar for the log-logistic, log-normal and gamma models and so the company selected the log-normal model for consistency with the vorasidenib arm.

In addition to the primary endpoint of PFS, time to next intervention (TTNI) was also assessed in the INDIGO trial, which measured the time until a patient continued onto their next anti-cancer therapy (i.e., NI). However, the outcome of TTNI was not used directly in the model. Instead, TTNI was disaggregated into different components that contribute to the decision for a patient to move onto their next treatment, such as progression and discontinuation of prior treatment. The model uses the conditional outcome of TTNI | P, which is the time to next intervention given the patient has progressed, as determined by the PFS curve. This conditional outcome is used to inform the duration of time spent in health state S4 with progression before moving to next intervention of 1L RT/CT. The outcome of TTNI | P is subject to cross-over concerns because participants in the placebo arm of INDIGO had the option to cross-over to vorasidenib when their disease progressed on placebo, with 42.9% crossed over to vorasidenib and 4.9% received subsequent anticancer therapy at the 07 March 2023 data cut. The company performed an exploratory analysis using multiple imputation for cross-over subjects, but the imputed analysis did not form part of the company's base case analysis. Parametric fitting of KM data for TTNI | P for the vorasidenib and placebo arms, using independent fitted models, was used to extrapolate TTNI | P over time (see Figures 20 and 21 of CS for extrapolations of TTNI | P in the vorasidenib and placebo arms, respectively). The parametric models in both arms provided very different long-term predictions of TTNI | P; therefore, modelled outcomes are sensitive to the distribution selected. For the base case analysis, the generalised gamma model was selected for both arms as the best fitted model based on goodness-of-fit statistics.

Treatment effectiveness for subsequent treatment lines from external sources (modelled health states S5 – S8)

The effectiveness of treatments for subsequent lines of therapy after patients have progressed and initiated their NI is based on published data sources external to the INDIGO trial. 1L RT/CT is considered the NI in health state S5. A study by Baumert et. al. (2016)[23] was selected by the company to provide PFS data to inform the time to progression and next subsequent intervention (NI+). Baumert et. al. (2016)[23] provides PFS for 477 patients (years 2005 – 2012, median follow-up of 4 years, international study from 19 countries) with grade 2 glioma (astrocytoma [35% of cohort], oligoastrocytoma [25%], oligodendroglioma [40%], WHO grade II) with at least one high-risk feature (age ≥ 40 years, progressive disease, tumour > 5 cm or crossing the midline, neurological symptoms) who were randomised to receive either conformal RT or chemotherapy of dose-dense temozolomide (TMZ) Baumert et. al. (2016)[23]. The KM estimates for PFS showed differences between the glioma subtypes (IDHmt co-deleted, IDHmt non-co-deleted, and IDH-wildtype). The numbers at risk at baseline of 104 IDH mutant co-deleted and 165 IDH mutated non-co-deleted in Baumert et. al. (2016)[23] was used to estimate the histological mix for patients with LGG entering health state S5, excluding patients with IDH-wildtype glioma, which resulted in a histological mix of 38.7% IDH mutant co-deleted and 61.3% non-co-deleted. This histological mix was used alongside the best-fitting PFS extrapolations for each glioma subtype (see Figures 25 and 26 of CS for extrapolations of PFS in IDHmt 1p/19q co-deleted LGG and 1p/19q non-co-deleted LGG, respectively) to estimate the duration of time spent in health states S5/S6 before moving to next subsequent intervention (NI+). However, the company considered that the study by Baumert et. al. (2016)[23] omits the possibility of some patients entering S5 with HGG. To account for this, 23.6% of patients were assumed to enter S5 with HGG based on a study by Hervey-Jumper et. al. (2023)[24], with a median survival estimate of 3.1 years based on a study by Juratli et. al. (2012)[25], which was used in the company's base case to re-weight the hazard of a progression event after initiation of NI.

Once patients progress following 1L RT/CT in health states S5/S6, they enter health state S7 for next intervention plus (NI+), where they receive second and subsequent treatment lines of RT/CT and remain in this health state based on time to progression before transitioning to BSC of planned palliative or supportive care at end of life. A study by Ma et. al. (2021)[26] was selected by the company to provide PFS/TTP data based on salvage therapies for recurrent IDH-mutant glioma after RT to represent the various treatments at 2L+ that a patient receives before moving onto BSC. Ma et. al. (2021)[26] provides TTP for 94 patients with recurrent IDH-mutant astrocytoma and 1p/19q codeleted oligodendroglioma after RT who received salvage systemic therapy (consisting of alkylating chemotherapy [TMZ, PCV or lomustine] or non-alkylating therapy [bevacizumab, immunotherapy, biological agents or tumour-treating field]) between 2001 and 2019 at a tertiary cancer center in the USA. The KM estimates for TTP showed differences between the glioma subtypes. The numbers at

risk at baseline in this study of 59 IDH mutant astrocytoma and 35 1p/19q codeleted oligodendroglioma was used to estimate the histological mix for patients entering health state S7 (62.7% astrocytoma and 37.2% oligodendroglioma). This histological mix was used alongside the best-fitting TTP extrapolations for each glioma subtype (see Figures 28 and 29 of CS for extrapolations of TTP in IDHmt astrocytoma and 1p/19q co-deleted oligodendroglioma, respectively) to estimate the duration of time spent in health state S7 before entering BSC.

Mortality risk associated with BSC

Upon progression with 2L+ RT/CT, patients transition to BSC to receive planned palliative or supportive care at end of life. OS data reported in Ma et. al. (2021)[26] based on salvage therapies for recurrent IDH-mutant glioma after RT (as discussed above) was used as a proxy for OS for patients who transition from health state S8 (BSC) to S9 (Dead). The histological mix at baseline in Ma et. al. (2021)[26] (62.7% astrocytoma and 37.2% oligodendroglioma) was used to represent the mix of patients by glioma subtype upon entry to health state S8. This histological mix was used alongside the best-fitting OS extrapolations for each glioma subtype (see Figures 31 and 32 of CS for extrapolations of OS in IDHmt astrocytoma and 1p/19q co-deleted oligodendroglioma, respectively) to estimate the probability of death on BSC.

Summary of time-dependent curves used in company's base case analysis

Table 7 provides a summary of the source of treatment effectiveness evidence used in the company's base case analysis for each intervention and line of treatment. Figure 4 and Figure 5 show the modelled time-dependent health state residency for vorasidenib and active observation in the base case analysis, respectively, while Table 8 summarises the total life years in health states (undiscounted) by intervention.

Table 7 Source of treatment effectiveness evidence used in the company's base case analysis for each intervention and treatment line

Parameter	Intervention /treatment line	Transition	Source selected	Extrapolation curve selected
PFS/TTP	Vorasidenib	S1->S4	PFS for vorasidenib arm of INDIGO	Log-normal
	Active observation	S2->S4	PFS for placebo arm of INDIGO	Log-normal
TTNI | P	Vorasidenib	S4->S5, separated by intervention	TTNI re-baselined at time of progression for vorasidenib arm of INDIGO	Generalised gamma
	Active observation		TTNI re-baselined at time of progression for placebo arm of INDIGO	Generalised gamma
NI	1L RT/CT	S5/6->S7	PFS for 1L RT/CT from Baumert et al., (2016), weighted by glioma subtype and combined with HGG median sPFS from [25]	IDH codeleted: Log-normal IDH non-codeleted: Gamma
NI+	2L+ RT/CT	S7->S8	TTP for salvage therapy from [26] as proxy for time to BSC, weighted by glioma subtype	Astro: Generalized gamma Oligo: Gompertz
	BSC	S8->S9	OS for salvage therapy from [26], weighted by glioma subtype	Astro: Log-normal Oligo: Log-normal

OS	NA	S1-S7->S9	General population lifetables – no excess mortality assumed, except for BSC	NA – general population mortality risk

Abbreviations: PFS, progression-free survival; TTP, time to progression; TTNI | P, time to next intervention following progression; NI, next intervention; OS, overall survival; RT, radiotherapy; CT, chemotherapy; BSC, best supportive care; sPFS, secondary progression-free survival (i.e., the time between first diagnosis of a HGG and first tumour recurrence or tumour progression); Astro, astrocytoma; oligo, oligodendroglioma; NA, not-applicable.

Figure 4 Time-dependent health state residency for vorasidenib in company's base case analysis

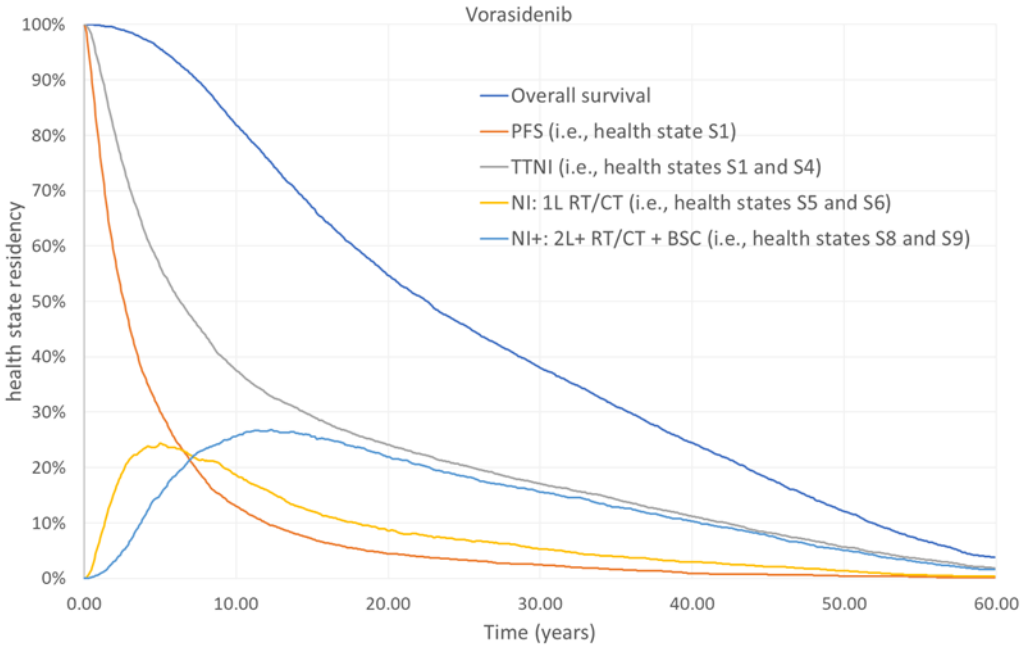


Figure 5 Time-dependent health state residency for active observation in company's base case analysis

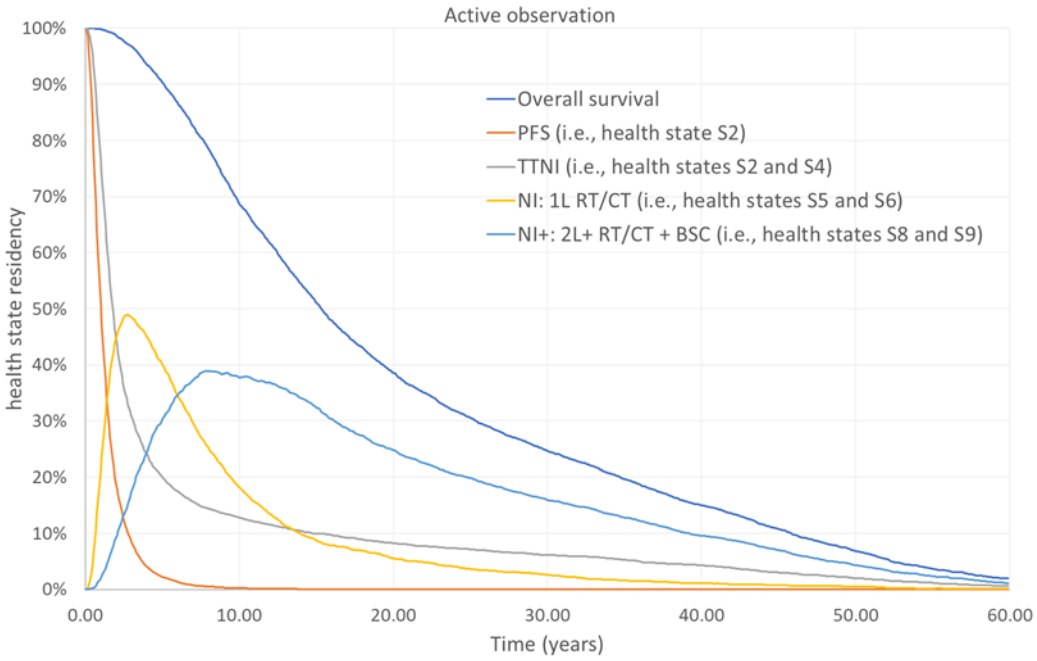


Table 8 Total life years in health states (undiscounted) by intervention

	OS	PFS	PD and off-treatment (S4)	NI (1L RT/CT)	NI+ (2L+ RT/CT + BSC)
Vorasidenib	26.45	5.22	8.58	4.53	8.11
Active observation	20.63	1.42	4.44	4.84	9.93
Difference (vorasidenib minus active observation)	5.81	3.80	4.14	-0.31	-1.82

4.2.6.2 Points for critique

The EAG has several concerns in relation to the treatment effectiveness evidence and assumptions used in the model, with a key concern relating to the approach used for TTNI | P, which significantly favours the cost-effectiveness of vorasidenib relative to active observation. These concerns relate to:

(i) The assumption that a surrogacy relationship holds for OS benefit in the absence of evidence in low-grade IDH mutant glioma.

(ii) Interpretation of the conditional outcome, TTNI | P, in light of cross-over in the placebo arm of INDIGO.

(iii) Duration of time spent in health state S4 based on TTNI | P curves.

(iv) Evidence used to model outcomes for subsequent treatment lines.

(v) Evidence used to inform the excess mortality risk applied at the last line of BSC.

Surrogacy relationship for OS benefit

In the absence of mature OS data from INDIGO, with only one death recorded post-progression at the 07 March 2023 data cut, the approach to modelling used in the CS relies on the relative effect of vorasidenib on PFS/TTP and time to next intervention given progression (TTNI | P) being predictive of its relative effect on OS. The use of a surrogacy relationship to infer OS may be valid provided there is good evidence that the relative effect of the intervention on the surrogate end point is predictive of its relative effect on the final outcome (NICE Methods Manual (2022)[27]). However, the company have not presented any evidence to support the validity of a surrogacy relationship between delaying PFS/TTP and TTNI | P and OS benefit for vorasidenib relative to active observation in the target population. In response to EAG clarifications (question B2a), the company acknowledged that there is no conclusive evidence for a surrogacy relationship between TTP (or PFS gain) and OS benefit in low-grade IDH mutant glioma. The company referred to supportive evidence from a study by Han et al., (2014)[28] of a meta-analysis of 91 clinical trials of populations in HGG (grade 3 and 4) with glioblastoma that showed a strong correlation ($R^2 = 0.92$; 95% CI, 0.71 –0.99) between PFS and OS hazard ratios for treatments with TMZ or bevacizumab containing regimens, with linear regression demonstrating that a 10% risk reduction for PFS would yield an 8.1% ± 0.8% risk reduction for OS. However, in the INDIGO trial a relationship between PFS and OS hazard ratios is not yet observed, with only one death reported in the trial despite a statistically significant difference in PFS for vorasidenib vs. active observation. Therefore, it remains unclear if PFS gains in LGG are likely to translate into comparable OS benefit in this population. The modelling approach adopted by the company is built on the premise that the hazard ratios observed for PFS and TTNI | P will ultimately translate into OS gains through progression on subsequent treatment lines rather than directly estimating OS based on a surrogacy of PFS. The EAG is particularly concerned about the use of TTNI | P as a surrogate for OS as this outcome is confounded by cross-over in the placebo arm. Importantly, however, no previous studies have demonstrated the validity of a surrogacy relationship between TTNI | P and OS in this population; therefore, the absence of OS data from INDIGO remains a key area of uncertainty.

Furthermore, the company have not provided evidence to show that vorasidenib reduces the likelihood or delays the transition from LGG to HGG, or transformation to malignant gliomas (secondary HGG), which is part of the natural progression of grade 2 gliomas and associated with increased mortality risk over an extended time horizon. The company's model captures progression to grade 3 or 4 indirectly using movement to subsequent treatment lines as a proxy for transitions to HGG, where standard treatments of RT/CT can induce tumour transformation to hyper-mutational

states linked to therapy resistance and rapid progression. However, it remains unknown which tumoral changes are potentially triggered by vorasidenib and how the disease will eventually behave after progression. The outcomes observed with vorasidenib in the INDIGO trial do not support a difference in the rates of malignant transformation (MT) for vorasidenib compared to placebo arm. In fact, MT occurred in both arms of the INDIGO trial with a slightly higher incidence in the treatment arm, with the rate of MT and time until onset consistent with published literature on the natural history of the disease population (response to EAG clarifications question A14). Thus, it remains unknown which, if any, of the downstream effects on progression are reversed with mutant IDH inhibition and whether that reversibility changes over the course of the disease.

In summary, in the absence of OS data from INDIGO, it remains difficult to judge and interpret the appropriateness of the implied OS hazard ratio of 0.69 for vorasidenib vs. active observation in the company's base case analysis. Furthermore, even with more mature OS data from INDIGO over a long follow-up period of time, the survival data will be difficult to interpret given the large percentage of patients in the placebo arm that crossed over to vorasidenib treatment upon progression. In addition, the extent to which a heterogeneous set of subsequent therapies impact on mortality will make interpretation of OS from INDIGO challenging.

Interpretation of the conditional outcome, TTNI | P

The model uses the conditional outcome of TTNI | P, which is the time to next intervention given the patient has progressed on their initial intervention of vorasidenib or active observation, and is used to inform the duration of time spent in health state S4 with progression before moving to the NI of 1L RT/CT. The EAG's primary concern with the use of this outcome is the fact that it is confounded by cross-over in the placebo arm of INDIGO, which makes the relative effect of vorasidenib vs. active observation on TTNI | P difficult to interpret. In the placebo arm, 42.9% of participants who had tumour progression crossed over to vorasidenib at the 07 March 2023 data cut, while only 4.9% received other subsequent anticancer therapies. This means that vorasidenib was administered to 90% of participants receiving next intervention in the placebo arm, which raises several issues for comparative efficacy for the outcome of TTNI | P used in the model. First, a high rate of cross-over limits interpretation of trial outcomes because differences between intervention arms are now confounded and based on post-randomised data, where participants in the placebo arm are likely to have moved to the next intervention quicker because they had access to a treatment that would otherwise not be available outside of the trial setting. The unblinding of trial randomisation occurred at the point of progression and the decision to cross-over upon progression, and the timing of this decision, is affected by the availability of vorasidenib and the desire to have access to a novel treatment for participants originally randomised to the placebo arm. In addition, the timing of progression differs between the arms of INDIGO, with later progressors on the vorasidenib arm

versus early progressors on the placebo armresulting in TTNI events more often censored in the vorasidenib arm as many patients' follow-up ended shortly after progression, which provides less time to capture TTNI events in the vorasidenib arm compared to the placebo arm. Second, vorasidenib is not currently available in the NHS; therefore, participants in the control arm of INDIGO had access to a treatment upon progression that is not currently available in the NHS, which limits the relevance of outcomes in the placebo arm to UK clinical practice. Furthermore, it is unclear if vorasidenib is the best treatment upon progression, and cross-over may have delayed access to other life prolonging therapies; as noted above, in the absence of OS data from INDIGO survival outcomes remain unknown and downstream effects on progression is a hypothesis that has not yet been demonstrated with evidence in this target population.

The company undertook an exploratory analysis to assess the impact of cross-over from placebo to vorasidenib on the outcome of TTNI by using a multiple imputation (MI) method that assumes that the option to cross-over to vorasidenib had not been available in the trial and imputes the missing data for cross-over subjects. In this analysis, the TTNI for the 70 participants who crossed over to vorasidenib in the placebo arm was imputed based on TTNI for participants who discontinued treatment for any reason in the vorasidenib arm. The company showed a visual comparison of the KM estimates for the outcome of TTNI for the placebo cross-over adjustment based on MI, the protocol placebo arm with cross-over, and the vorasidenib arm (see Figures 22 and 23 of CS for Sept 2022 and March 2023 data cut off, respectively). The company concluded that the visual overlay was similar between the placebo cross-over adjusted and unadjusted analysis, with the average TTNI slightly longer in the adjusted than unadjusted analysis and, therefore, the impact of cross-over was minimal. On this basis, the company determined it unnecessary to adjust the conditional outcome of TTNI | P used in the model. Consequently, the cross-over adjusted analysis did not form part of the company's base case.

The EAG has several concerns with the approach used by the company to conclude that cross-over adjustment was unnecessary in the placebo arm. First, the method of MI is not standard practice in HTA for cross-over adjustment. Typically, inverse-probability-of-censoring weighting (IPCW) is used to adjust for cross-over subjects that are censored, where the method compensates for censored subjects by giving more weight to subjects with similar characteristics who are not censored. Instead, the company have imputed the censored subjects with data on TTNI from the comparator arm of vorasidenib rather than the placebo arm. The EAG acknowledges that the company is likely to have had to use the comparator arm because of the very high cross-over in the placebo arm and therefore the significant amount of censoring and limited data for non-censored subjects in the placebo arm. However, the company's approach assumes that the reasons and timing for moving to next intervention in the vorasidenib arm and the placebo arm in censored subjects follow a similar pattern

by applying an exponential distribution fitted to data from vorasidenib patients who required subsequent therapy. This assumption contrasts with the need to use separate TTNI | P curves by intervention arm in the model that are fitted with independent distributions because the latter suggests that there are important differences for the pattern and timing of moving to next subsequent treatment by intervention arm. Second, the results of the company's cross-over adjusted analysis suggests that the average TTNI is longer for the placebo arm compared to the unadjusted analysis, which means that the relative efficacy of vorasidenib vs. active observation is more conservative for vorasidenib in the cross-over adjusted analysis; however, the unadjusted analysis, in favour of vorasidenib, is used in the company's base case. Third, the company have not adjusted the conditional outcome of TTNI | P, which is used in the model rather than TTNI; therefore, it is not possible to assess the magnitude of impact of cross-over on the cost-effectiveness results for vorasidenib vs. active observation in scenario analyses.

Duration of time spent in health state S4 based on TTNI | P curves

The model uses the conditional outcome of TTNI | P to determine the duration of time spent in health state S4 with progression before moving to the NI of 1L RT/CT, i.e., patients enter the modelled health state S4 upon disease progression with initial intervention (informed by the PFS/TTP curves by treatment arm of INDIGO) and remain in this health state off-treatment until TTNI | P. The EAG has several critical issues with the approach used to model time spent in health state S4. First, the conditional outcome of TTNI | P informing the duration of time spent in S4 is based on post-randomised data. Second, there is an important question about whether patients would be held in a progressed disease health state off-treatment rather than move directly to next intervention upon evidence of progression of their disease. The company argues that progression may not immediately trigger next intervention when taking account that LGG can be a slow progressing disease, and the difficult choice required to move to RT/CT. Furthermore, the company argues that treatment with vorasidenib in the INDIGO study leads to tumour shrinkage and, therefore, it is likely that patients have a smaller tumour at the time of progression than at baseline (company response to EAG clarifications question B5a). The EAG considers these statements as hypotheses which have not yet been supported by evidence from the INDIGO trial. As stated previously, it remains unknown which tumoral changes are potentially triggered by vorasidenib and how the disease will eventually behave after progression. The company have not shown data that tumour size is smaller at the time of progression than at baseline for vorasidenib. The EAG notes that although the focus of the INDIGO trial was on whether vorasidenib delays time until more aggressive treatments of RT/CT, the fact that 42.9% of participants who had disease progression in the placebo arm crossed over to vorasidenib indicates that the outcome of TTNI | P is not informing the time to 1L RT/CT (as required for the model) but instead informing the time to any subsequent therapy. A large percentage of participants in the vorasidenib arm (83.3% at the 07 March 2023 data cut) did not receive a subsequent treatment

despite having documented progressive disease (as assessed on imaging by blinded independent review according to the modified Response Assessment for Neuro-oncology for Low-Grade Gliomas [RANO-LGG]). The fact that not all participants in the trial received a subsequent treatment post-progression may support the hypothesis that some patients are deemed eligible for a watch and wait approach upon progression, but the cross-over in the placebo arm has confounded the interpretation of TTNI | P for a model that requires time to 1L RT/CT.

The company noted that the assumption that patients in NHS practice would not move directly to a subsequent treatment upon evidence of radiographic progression of disease with clinical deterioration is complicated by many factors, including risk of neurocognitive decline associated with RT/CT, impact on a person's daily activities, and desire to start a family. The EAG's clinical advisor suggested that there may be a subset of patients with slower albeit continuous growth in IDH-mutant LGG who have more favourable prognostic factors that could be monitored before proceeding to RT/CT. The EAG's clinical advisor also noted that the modified RANO-LGG criteria used to define progression (a ≥25% increase in the T2/FLAIR signal area of the tumour) in INDIGO may not be routinely used in NHS practice, and may lead to some differences in response to images where the RANO changes described by one radiologist may invoke a different response to a descriptive term of minimal progression by another radiologist. Thus, it remains unknown what proportion of patients, upon evidence of disease progression, are likely to remain off-treatment (under active observation) before moving to 1L RT/CT.

Third, the EAG is concerned about the extrapolation of the TTNI | P curves used in the model and the clinical plausibility of the predictions for average time to next intervention following disease progression. The company fitted independent parametric models to KM data for TTNI | P for the vorasidenib and placebo (unadjusted for cross-over) arms and applied a generalised gamma model as the best fitted model based on goodness-of-fit statistics. The EAG has no major concerns with the approach used by the company, but the EAG is concerned about the clinical plausibility of the resulting predictions. Figures 20 and 21 of CS show that the extrapolations of TTNI | P in the vorasidenib and placebo arms, respectively, are highly sensitive to the parametric distribution selected. The best fitted generalised gamma model based on goodness-of-fit statistics provides the most favourable predictions for TTNI | P in both arms. However, it must be noted that the numbers of patients at risk informing the KM estimates for TTNI | P is extremely low, with less than 11 patients informing this outcome at 12 months and one patient at 18 months (see Figure 19 of CS). The selected model predicts that approximately 21% of patients with documented progressive disease remain untreated at 20 years (i.e., remain off-treatment in health state S4 post-progression) following vorasidenib, while approximately 9% remain off-treatment at 20 years for active observation post-progression. While the EAG considers it plausible that a small subset of patients with progressive

disease but indolent, non-enhancing tumours, may not require immediate further treatment, the EAG does not consider it reasonable to assume that such large proportions of patients would remain untreated. As a result of the long-term extrapolation using the generalised gamma model, the company's base case assumes that over the model time horizon of 60 years a small proportion of patients will never progress to subsequent treatment lines, which effectively means that their disease never progresses (following post-progression on initial intervention) since movement to subsequent treatment lines is a proxy for disease progression in the model; note that this lack of progression to subsequent treatment lines is distinct from patient preference, where individuals may choose to defer treatment due to risks associated with further intervention or potential impact on quality of life, which is modelled separately through a percentage of patients that opt out of further treatment. Given the natural progression of the disease course over time, the EAG considers it implausible that a proportion of patients over the modelled time horizon will never transition to the subsequent health states in the model and are never subject to an excess mortality risk.

Importantly, the EAG does not consider the predictions from the TTNI | P extrapolated curves used in the company's base case analysis to be reasonable relative to the time spent PF in the model. The outputs of the company's model suggest that patients remain longer in health state S4, with PD and off-treatment, than in health states S1 and S2, where patients are PF and receiving initial intervention – see Table 8, where the total (undiscounted) life years in the PD state off-treatment are 8.58 years compared to 5.22 years in the PF state for vorasidenib, while the life years for active observation are over three times as much in the PD than PF state. The EAG considers the model predictions to lack face validity. The PFS data used in the model is prone to less bias than the TTNI | P outcome because it is based on randomised data and is more mature than the TTNI data. In contrast, the TTNI | P outcome is subject to several concerns as highlighted above, including cross-over in the placebo arm and limited KM data with high censoring, especially in the vorasidenib arm due to progression events occurring later compared to the placebo arm. Therefore, it is unlikely that the modelled TTNI | P curves accurately reflect the time to 1L RT/CT in either of the intervention arms, which taken together with the fact that it is unknown whether patients would remain off-treatment before moving directly to a subsequent treatment upon evidence of radiographic progression of disease creates significant uncertainty around the model predictions. In Section 6, the EAG considers the implications of using alternative models to extrapolate the TTNI | P curves, including the second best fitted curve of log-normal for both the vorasidenib and placebo arm of INDIGO, which produces more reasonable predictions with total life years in health state S4 lower than S1 and S2, and highlights the sensitivity of the cost-effectiveness results to the model predictions for TTNI | P. However, the inherent uncertainty with cross-over and lack of robust data for TTNI | P remains a key issue.

Fourth, the EAG is unclear why the conditional outcome of TTNI | P should be separated by treatment arm. At the point of entering health state S4, patients have documented progressive disease from initial intervention. The EAG is unclear why there would be a subsequent propensity to treat post-progression patients differently in health state S4 depending on whether they progressed on vorasidenib or progressed on active observation, especially when there are no differences assumed for subsequent treatment lines. The company argues that the difference observed for time to next intervention is because treatment with vorasidenib leads to tumour shrinkage and it is likely that patients have a smaller tumour at time of progression compared to active observation. The EAG agrees that the data from INDIGO indicates that vorasidenib was associated with a decrease in tumour volume compared to continued growth on the placebo arm. However, there is a direct correlation between tumour growth rate and PFS (see supporting evidence in Table 9 of CS); therefore, the statistically significant reduction in PFS for vorasidenib compared to placebo in INDIGO is likely to already reflect the benefits of vorasidenib vs. active observation on tumour size and volume, with fewer progression events in the vorasidenib arm reflecting the benefits associated with TGR, and, therefore, further accounting for tumour shrinkage is likely to risk double counting the benefits of vorasidenib. Therefore, it remains unclear why patients with documented progressive disease (defined based on the same criteria in both arms of INDIGO) would be managed differently post-progression depending on their initial intervention. Furthermore, the EAG notes that the health-related quality of life utility values by progression status and treatment arm of INDIGO indicates that patients with PD had better quality of life in the placebo arm (mean utility of 0.730) than the vorasidenib arm (mean utility of 0.678) – see Section 4.2.8.1.

In the absence of any evidence to support important ongoing effects of vorasidenib post-progression and the issues with the TTNI | P data (post-randomised, confounded by cross-over, high amount of censoring and immature data), the EAG considers it more reasonable to assume that a common TTNI | P curve, independent of intervention received, is appropriate post-progression. The EAG also considers this more aligned with the modelling of subsequent treatment lines where no differences in downstream effects are assumed by treatment, only a difference in the timing of entering the health states based on vorasidenib delaying time to progression. However, the EAG notes that it remains unclear which TTNI | P curve, independent of treatment arm, is most appropriate for use in the model because the curves from both arms of INDIGO have concerns. In Section 6, the EAG explores the implications of using the pooled TTNI | P curve across arms of INDIGO, fitted with alternative extrapolation models, in addition to using a common TTNI | P curve based on the vorasidenib arm of INDIGO, to assess the impact on the cost-effectiveness of vorasidenib relative to active observation.

Evidence used to model outcomes for subsequent treatment lines

To capture outcomes at subsequent treatment lines, effectiveness evidence from a range of different sources, external to the INDIGO trial, is used in the model. In particular, the modelling of subsequent treatment lines requires evidence on time to progression on 1L RT/CT, time to next intervention of 2L+ RT/CT, time to BSC, and death, in addition to evidence relating to change in glioma grade and histology over the course of disease progression. The selection of different survival models for these later health state transitions is permitted through the use of microsimulation that allows a 'new baseline' to be specified for a particular endpoint when a patient enters a specific health state. The EAG has no major concerns with the modelling approach used by the company, which tracks the pathway of patients as they transition through health states and allows for granular modelling of downstream costs and health effects over a lifetime horizon for the target population. However, the EAG is concerned about the reliance on multiple different literature sources from non-comparable populations and numerous assumptions required to inform long-term survival outcomes when there is a dearth of evidence for long-term outcomes in this target population and much ongoing debate around the management of LGG[21].

The company have provided limited justification for the choice of post-progression studies (Baumert et. al. (2016)[23], Ma et. al. (2021)[26], Juratli et. al. (2012)[25], Hervey-Jumper et. al. (2023)[24]) selected to model outcomes associated with subsequent treatment lines. The company confirmed in response to EAG clarifications (question B8) that no formal SLR was undertaken to inform transitions between later health states in the model and that the studies were identified through targeted, pragmatic searches, drawing on institutional knowledge and recommendations from clinical advisors. The company acknowledges the limitations of this approach but considers it proportionate to the timeline constraints of the appraisal.

The EAG's primary concern relates to the comparability of the populations (e.g., in terms of age, setting, radiological characteristics, tumour size, extent of symptoms, risk of malignant transformation, time since surgery or prior treatments) used in the post-progression studies and their relevance to the subsequent treatments used in INDIGO and NHS clinical practice. None of the studies are directly concerned with IDH mutant gliomas for adults in a UK setting, or specific to progression for patients who were previously not in need of immediate systemic therapy and within 1 to 5 years post-surgery. The studies selected report survival estimates baselined at the beginning of therapy. The study by Baumert et. al. (2016)[23] was selected for 1L RT/CT because it provided PFS data for grade 2 glioma for different subtypes (IDHmt co-deleted and IDHmt non-co-deleted) for treatments with RT or TMZ, where the PFS data was not separated by treatment arm. The EAG considers the choice of Baumert et. al. (2016)[23] to be reasonable in the context of providing survival estimates for 1L RT/CT. However, the EAG considers it more appropriate to undertake a SLR to identify the most relevant source of data, with clear criteria specified for study selection. The EAG

notes that the company presented an evidence network for studies reporting PFS and/or OS in IDH mutant grade 2 gliomas (Figure 4 of CS) as part of the company's review of clinical effectiveness evidence, but these studies were not further assessed by the company for relevance to inform long-term outcomes in the model.

The company makes several simplifying assumptions to include PFS from Baumert et. al. (2016)[23] in the model. First, the PFS curves include both progression events and death, whereas the transition from health states S5/S6 to next intervention is solely based on TTP. The company justified this assumption based on the study by Ma et. al. (2021)[26] for salvage therapies used at later treatment lines that reported TTP and PFS data and showed few deaths prior to progression. Therefore, the company assumed that the same holds for PFS reported in Baumert et. al. (2016)[23], i.e., that pre-progression deaths are rare and that TTP can be assumed equal to PFS. In the study by Baumert et. al. (2016)[23] it is reported that at a median follow-up of 4 years, 55% progression events and 25% deaths were recorded; therefore, deaths are known to have occurred in this study, but the timing of those deaths is not reported. The company's simplifying assumption means that deaths are not censored from the TTP curves used in the model for the transitions between health states S5/S6 and S7. This assumption may appear reasonable in light of the data in Ma et. al. (2021)[26], but the company is mixing and matching data from different populations and a histological mix that is unlikely to be comparable.

Second, the company had no information on the histological mix of patients entering health state S5, or the proportion of patients with HGG. In response to EAG clarifications (question B10), the company indicated that this information was not available from INDIGO because the design of the trial did not include grading upon initiation of next intervention. The company provided an exploratory statistical analysis for histological mix of astrocytoma and oligodendroglioma at TTNI event from INDIGO, but the sample size is small due to high censoring in this endpoint. Therefore, the company used the number of patients at risk at baseline from Baumert et. al. (2016)[23] to estimate the histological mix for patients with LGG. To account for the probability that a proportion of patients enter health state S5 with HGG, the company used a different source of evidence, Hervey-Jumper et. al. (2023)[24], which indicates that 23.6% of patients developed malignant transformation in a 20-year retrospective cohort of patients with newly diagnosed grade 2 astrocytoma IDH-mutant and oligodendroglioma IDH-mutant 1p19q codeleted, while the estimate of median survival for sHGG of 3.1 years was based on the study by Juratli et. al. (2012)[25]. The EAG considers the approach used by the company to re-weight the hazard of a progression event from Baumert et. al. (2016)[23] for sHGG to be reasonable given the modelled health states, but the EAG considers it more appropriate to explicitly model the health state of MT and incorporate PFS estimates for sHGG over time. However, the EAG's primary concern is that the survival estimates are based on sources of evidence from mixed

populations, settings, and treatments, and the relevance to the target population and NHS clinical practice is unclear.

In the absence of data for an outcome defined as 'time to BSC', a study by Ma et. al. (2021)[26] based on salvage therapies for recurrent IDH-mutant glioma after RT was used as a proxy for the time to discontinuation of next intervention of 2L+ RT/CT. This study provided TTP KM estimates for IDH mutant astrocytoma and 1p/19q codeleted oligodendroglioma, which were weighted by the histological mix at study baseline. The EAG has no major concerns with the approach used by the company, but the relevance of the study population to NHS clinical practice is uncertain. Ma et. al. (2021)[26] is based on a small US cohort and salvage systemic therapy consisted of both alkylating chemotherapy (TMZ, PCV or lomustine) and non-alkylating therapy, including bevacizumab that is not licensed for use in the UK for glioma. The costs of subsequent treatments in the model following progression reflect a range and distribution of treatments (including number of treatment lines) that is expected to be given in clinical practice (see Section 4.2.9.3), but the long-term survival outcomes informing the rate of subsequent progression are reflecting outcomes of specific treatments used in the selected studies rather than the different treatment modalities used in NHS clinical practice.

Evidence used to inform the excess mortality risk applied at the last line of BSC

The only excess mortality risk is applied at the last line of BSC in health state S8. This means that no excess deaths over and above all-cause general population mortality risk is assumed prior to the last line of BSC, where the timing of entry into S8 differs for vorasidenib and active observation due to the delay in progression and time to later treatment lines for vorasidenib compared to active observation. As noted above, whether this surrogacy relationship for OS holds remains a key area of uncertainty. In the absence of mature OS data to inform the transition from S8 to S9 (dead) for patients on BSC, the company used the OS data reported in Ma et. al. (2021)[26] for salvage therapies for recurrent IDH-mutant glioma after RT and applied a weighted approach to account for histological mix, with a new baseline upon entry to S8. The EAG's primary concern is the relevance of the study population for the modelled population receiving BSC, where BSC is defined in the model as patients who move to planned palliative or supportive care setting upon exiting salvage therapies at 2L+. The transition from S8 to S9 requires post-progression OS, whereas the OS curve from Ma et. al. (2021)[26] includes pre-progression deaths. The company justifies the use of Ma et. al. (2021)[26] because the TTP and PFS KM data in this study appears similar; therefore, the company considers that the OS curves are mostly based on post-progression deaths, with very few pre-progression deaths. Furthermore, the probability of death used in each model cycle takes account of the amount of time spent in health state S7 so that the survival hazard applied reflects time since baseline of S7. Nonetheless, the EAG notes that salvage systemic therapy used in the study does not represent BSC as defined in the model, in

addition to the concerns raised above about the relevance of the study to UK practice (e.g., small US cohort, therapies not licensed in UK).

4.2.7 Adverse events

4.2.7.1 Summary of company's submission

There are no adverse event (AE) management costs implemented in the model. Seizure is the only AE expected to incur substantial utility loss or costs, and the company proposes that these costs are captured sufficiently in the medical resource use and health state utility value components. The company have shown that based on data from patients with >=1 seizures at baseline or in on-treatment periods (response to EAG clarifications question A12a), the frequency and rate of seizures per person-year in the vorasidenib arm was 64% lower compared to the placebo arm of INDIGO (Table 19 of CS).

Safety at later lines is not expected to impact cost-effectiveness of vorasidenib since the choice of subsequent treatment is not dependent on whether patients previously received vorasidenib or not. The company lacks robust safety information for later-line subsequent treatment use and, therefore, AEs for subsequent treatments are not included in the model.

4.2.7.2 Points for critique

The EAG considers there to be no significant safety concerns with vorasidenib. The EAG's clinical advisor indicated that the AEs associated with vorasidenib are largely manageable; therefore, the lack of inclusion of non-seizure specific AE management costs is not expected to have a material impact on the cost-effectiveness results.

4.2.8 Health-related quality of life

4.2.8.1 Summary of company's submission

The CS considers health-related quality of life (HRQoL) relating to: (i) health state utility values for PF and PD associated with initial intervention received (i.e., for health states S1 to S4 in the model); and (ii) health state utility values for subsequent treatment lines (i.e., for health states S5 to S8 in the model). Health state utility values are applied to time spent in health states in the model to calculate quality-adjusted life years (QALYs) that reflect the improvement in HRQoL associated with treatment.

As part of EAG points for clarification (question B23), the EAG requested a summary of utility values from the published literature for the target population of interest. The company identified three studies: Garside et al. (2007) [29], Drewes et al.(2018)[30], and Bhanja et. al. (2024)[31]. The company also referred to a comprehensive literature review by Proescholdt et al. (2018)[32] of health utility values used in cost-effectiveness analyses in glioblastoma, which identified three publications and all of

them used utility values derived from Garside et al. (2007). The company considered that the identified studies were not relevant to the target population and health states included in the model.

EQ-5D-5L data were available from the INDIGO trial and used to inform the health state utility values for PF (health states S1 and S2) and PD (health state S4) based on a mixed-effects regression model with a progression variable to denote progression status, and with adjustment for baseline utility value. The baseline utility values were 0.847 for the placebo arm and 0.839 for the vorasidenib arm (see response to EAG clarifications question B13 and the report titled 'Utility Estimation in IDH mutant Glioma' submitted as an appendix to the CS [33]). For records where the date of progression was missing, the treatment discontinuation date or death/censoring (whichever came first) was used as a proxy for date of progression. A separation of progression status by treatment was not included in the company's base-case analysis. Therefore, the same utility value of 0.737 was used for the PF health states of S1 (on-treatment with vorasidenib) and S2 (off-treatment, active observation), and the same utility value of 0.728 was used for the PD health state of S4 (off-treatment with PD). In EAG clarifications (question B15), the EAG requested a summary of EQ-5D utility values for progression status by treatment arm of INDIGO (i.e., PF and PD utility values reported separately for the vorasidenib and placebo arms), which are provided in Table 9. While the utility values for PF were similar between vorasidenib (0.744) and placebo (0.745), the utility value for PD in the vorasidenib arm (0.678) was lower than in the placebo arm (0.730). The EAG considered it unclear from the CS whether crossover subjects to vorasidenib in the placebo arm of INDIGO were censored from the EQ-5D utility analysis and the impact of crossover on the utility values. Based on the company's response to EAG clarifications (question B14), the company states that the utility values were based on EQ-5D data reported between initiation of vorasidenib or placebo and subsequent anti-cancer therapy (i.e., the period before cross-over for patients on placebo).

Table 9 Utility values by treatment arm of INDIGO (response to EAG clarifications question B15)

	Vorasidenib, progression-free	Vorasidenib, progressed disease	Placebo, progression-free	Placebo, progressed disease
Number of observations	716	81	549	170
Mean utility (95% CI)	0.744 (0.731, 0.621)*	0.678 (0.621, 0.735)	0.745 (0.732, 0.758)	0.730 (0.707, 0.753)
SD	0.179	0.258	0.152	0.151
Median	0.777	0.742	0.777	0.774

Abbreviations: CI, confidence interval; SD, standard deviation.

*The EAG considers there to be an error reported in the 95% confidence interval.

To inform health state utility values for subsequent treatment lines (health states S5 to S8 in the model), the company conducted a SLR to identify studies reporting HRQoL for patients with grade 2

or 3 diffuse glioma (see Appendix F of CS for details about the SLR, including methodology, inclusion criteria and results). However, the company concluded that only one utility value was of potential relevance (i.e., a value for glioma recurrence with utility value of 0.60) and none of the other studies identified in the SLR provided suitable estimates for use in the model. The EAG's appraisal of health-related quality of life evidence identification is presented in Appendix 2. To derive utility values for subsequent treatment lines (health states S5 to S8), the company conducted a vignette study, which was a non-interventional study seeking to estimate utilities for vignettes describing the HRQoL of individuals with IDHmt glioma, using EQ-5D and time trade-off (TTO) valuation methods. The study consisted of two phases: 1) Development of vignettes, that is, descriptions of health states to describe the typical symptoms and HRQoL impacts experienced by individuals with IDHmt glioma, and 2) EQ-5D valuation survey and TTO interviews to elicit utility values using a sample of the general UK public. In the report "Utility Estimation in IDH mutant Glioma," which the company submitted as supplementary material to the CS, it states that the definition of each vignette was consistent with the definition of the health states in the cost-effectiveness model and a short summary of the model health states and definitions were provided. Although it states that the health state vignettes were designed to describe the symptoms, functioning and impact on HRQoL of a 'typical' patient in each health state in the cost-effectiveness model, the vignettes were not provided as part of the CS or supplementary material. The EAG requested the descriptions used in the vignettes at EAG points for clarification (question B18). The vignettes were prepared for four health states: next intervention (NI), post-next intervention (post-NI), NI+ and post NI+, and included a description of the following dimensions: 1) description of health state, 2) physical functioning/mobility, 3) pain, 4) seizures, 5) fatigue, 6) personality or behaviour changes, 7) cognitive impairment, 8) daily activities, 9) emotional wellbeing, 10) social functioning, and 11) treatment-related adverse events. The company states that the development of the health state vignettes was based on the SLR used to identified HRQoL utility values for glioma, a summary of HRQoL and patient-reported outcomes data from INDIGO (before starting on NI), a targeted literature review of qualitative studies on impact of glioma on patients' HRQoL, and a review of patient testimonials from brain tumour forum posts. Furthermore, the company states that the content of the vignettes was reviewed and approved as accurate by healthcare professionals (HCPs), patients and representatives of the patient advocacy group (PAG; The Brain Tumour Charity) in semi-structured qualitative interviews. The final health state vignettes were evaluated by members of the general public in the UK to estimate health state utilities.

The vignette study valued the vignettes using two methods: EQ-5D-5L and visual analogue scale (VAS; n=200) and time trade-off (TTO; n=100) methods. Eligibility criteria to participate in the online survey or the TTO interview included: age between 18-70 years old, currently living in the UK, able to read and speak English fluently, willing and able to give consent to take part in a 30-min

online survey or a 1-hour online interview, and not currently diagnosed with and currently receiving treatment for cancer. In the estimation of utility values, the EQ-5D data from the INDIGO study were used as reference values for the PF health states. The EAG notes that the INDIGO EQ-5D data were not used to anchor the vignette study by providing the participants with an understanding of the utility values for PF and PD in the population of interest. The INDIGO EQ-5D data were only used for the presentation of the vignette study results in the form of utility decrements relative to the PF and PD utility values from INDIGO. The sociodemographic characteristics of the participants who took part in the vignette study, both EQ-5D survey and TTO interview valuation, were similar in terms of age, sex and ethnicity when compared to the UK population. Participants had a mean age of 45.9 years (SD=14.6 years) in the EQ-5D survey and 48.2 years (SD=14.8 years) in the TTO interviews; the majority of participants were female and were employed full time. In the survey, participants were also asked to self-report their own health using the EQ-5D-5L and VAS.

Overall, the HRQoL of the survey sample was lower than the published UK population norm values (EQ-5D utility value of [redacted] vs 0.86 for UK population and VAS score [redacted] vs 82.80 for UK population). Mean health state EQ-5D-5L and TTO utilities for progressed IDHmt glioma health states obtained through the vignette study are presented in Table 10. For the health states informed by the vignette study, the company deemed it implausible for utility values to increase from health state NI on-treatment (health state S5) to NI off-treatment (health state S6) and then decrease for NI+ on-treatment (health state S7) and increase again for NI+ off-treatment (health state S8). The company assumed that HRQoL would be expected to worsen during and after RT/CT due to associated toxicities and would not recover after completion of treatment but instead would continuously decline over time. No supporting evidence was provided for this assumption in the CS. Consequently, for the base-case analysis, the company adjusted the EQ-5D utility values from the vignette study by averaging the estimates for on- and off-treatment with RT/CT (i.e., averaged the utility values for on- and off-treatment with 1L RT/CT in health states S5 and S6) and averaging the utility values for 2L+ RT/CT and BSC (i.e., averaged the utility values for on-treatment with 2L+ RT/CT and off-treatment with BSC in health states S7 and S8) and applied the same average utility value to both health states. The resultant utility values from the vignette study for each of the health states S5 to S8 used in the company's base case analysis are presented in Table 11.

Table 10 Mean health state EQ-5D-5L and TTO utilities for progressed IDHmt glioma health states from the vignette study

	EQ-5D-5L (N=200)		TTO (N=100)	
Health state description	**Mean (SD)**	**95% CI**	**Mean (SD)**	**95% CI**
Next intervention	0.40 (0.18)	[redacted]	0.61 (0.30)	[redacted]
Post next intervention	0.56 (0.13)	[redacted]	0.75 (0.22)	[redacted]

Next intervention+	0.26 (0.21)	[redacted]	0.42 (0.42)	[redacted]
Post next intervention+	0.42 (0.15)	[redacted]	0.61 (0.32)	[redacted]
Post-surgery	0.16 (0.23)	[redacted]	0.46 (0.39)	[redacted]
Best supportive care	-0.04 (0.21)	[redacted]	0.15 (0.48)	[redacted]

CI, Confidence intervals 95%; CT, Chemotherapy; n, number of observations; RT, Radiotherapy; SD, Standard deviation; SE, Standard error; TTO, time trade-off; VAS, visual analogue scale
Note: Higher utility scores indicate better HRQoL.

Table 11 Utility values from vignette study used in the company's base case analysis

Health state	Utility value for each health state				
	Base case (adjusted values)	Raw values (unadjusted values)	Lowest	Highest	Flat average
S5 – On NI	0.480	0.400	0.260	0.560	0.410
S6 – Off NI		0.560			
S7 – On NI+	0.340	0.260			
S8 – Off NI+ (BSC)		0.420			

Abbreviations: BSC, best supportive care; NI, next intervention.

Age-related utility decrements are included in the model to account for the decline in HRQoL associated with age. Utility values from the general population at each age were calculated using the algorithm by Ara and Brazier (2011)[34]. The utility multiplier was calculated per increase in age and applied in each cycle throughout the model time horizon. No AE disutilities were included in the model. The company assumed that the impact of seizures on HRQoL were implicitly captured in the health state utility values. A summary of the utility values for health states included in the company's base case is provided in Table 12.

Table 12 Summary of utility values used in the company's base case analysis

Health state	Utility value	Justification
S1 – PF and on tx	0.737	Regression model fitted to INDIGO data
S2 – PF and off tx	0.737	
S3 – PD and on tx	0.728	
S4 – PD and off tx	0.728	
S5 – On NI	0.480	Outputs from vignette study[33]
S6 – Off NI	0.480	
S7 – On NI+	0.340	
S8 – Off NI+ (BSC)	0.340	

4.2.8.2 Points for critique

The EAG considers the use of EQ-5D-5L instrument and mapping algorithm to 3L from Hernandez Alava et. al. (2018)[35] to represent the appropriate approach to estimate the utility values and in line with the 2022 NICE evaluation methods manual[27]. Given that the results of the company's SLR did not identify any relevant utility values for the population of interest, the EAG considers the use of

EQ-5D data from INDIGO as the appropriate source to derive HRQoL utility values for health states S1 to S4. Although the EAG considers the mixed-effect regression model used to derive the utility values to be appropriate, the EAG notes that very limited details on the methods are presented in the CS, which makes it challenging for the EAG to assess the appropriateness of the methods used. Although the EQ-5D data from INDIGO are considered the most appropriate source to inform utility values for health states S1 to S4, the EAG notes several concerns with these data. First, the EAG notes the very high baseline utility value by treatment arm, which is supportive of the view that the population of INDIGO is a stable population, which may not accurately reflect those patients who would be considered most suitable for vorasidenib in the NHS (see Section 4.2.3.2). The EAG further notes that the resulting EQ-5D estimates from INDIGO suggest a small decrement in EQ-5D utility for PD relative to PF (utility decrement of 0.009). Furthermore, the EAG notes that the EQ-5D utility values for PD in the vorasidenib arm of INDIGO were lower than in the placebo arm (i.e., 0.678 vs 0.730, respectively). Additionally, the EAG notes that the difference between PF health state and PD health state in each arm was more substantial than the difference assumed in the base-case analysis based on average values (difference of 0.067 in vorasidenib arm and 0.015 in placebo arm vs. 0.009 assumed in the company's base case analysis – see Table 9). Based on these results, the EAG considers the small decrement in EQ-5D utility values for PD relative to PF to be highly uncertain.

Utility values for health states S5 to S8 were informed by the vignette study. The EAG refers to the NICE health technology evaluations manual 2022 [27], which details the hierarchy of preferred HRQoL methods (Figure 4.1 of the NICE manual) and provides recommendations for circumstances when the EQ-5D is not available from relevant study or is considered to not be an appropriate measure. The EAG notes that in the flowchart providing the hierarchy of preferred HRQoL methods, the use of vignettes to estimate utility values is listed at the end of the flowchart when none of the other methods are possible. Consequently, the EAG notes that vignettes represent the lowest quality of evidence to inform utility values and should be used only if no other evidence is available. The EAG appreciates the scarce evidence available to inform the utility values for population in these health states and considers the vignette study to be in line with the 2020 DSU report on best practice recommendations (Rowen et al. 2020[36]). In line with the 2020 DSU report (Rowen et al. 2020[36]), the vignettes were valued indirectly by general population completing the EQ-5D for each vignette which was then scored using the appropriate and relevant value set for EQ-5D. The EAG notes several issues associated with the vignette study and obtained estimates. The vignette study did not include PF health states (health states S1 and S2) and PD health state (health state S4). Although the utility values used for these health states were informed using INDIGO data, inclusion of these health states in the vignette study would help anchor and understand the relation between the utility values for health states on NI and NI+ compared to the utility values for health states PF and PD, which are informed with INDIGO data. Not including these health states in the vignette study has led to a lack of evidence

to support the substantial drop in the utility values between health state S4 (off-treatment with PD) and health states S5 and S6 (on-and off-treatment with 1L RT/CT, respectively). The EAG considers the substantial drop in the utility value for subsequent treatment lines in the model to be highly uncertain. The company assumed that moving from PF to PD leads to a small decrement in utility value of 0.009 (i.e., from a mean utility value of 0.737 for PF to 0.728 for PD), while moving from the PD health state of S4 to next intervention of S5 is associated with a substantial decrease in utility value of 0.328 (i.e., from a mean utility value of 0.728 for health state S4 to 0.400 for health state S5). The EAG notes that moving from health state NI on-treatment (i.e., S5) to NI off-treatment (i.e., S6) leads to an increase in the utility value to 0.560 in the raw data from the vignette study. The EAG's clinical advisor indicated that while on RT/CT a decrease in utility value can be expected due to toxicities associated with treatment, but that the utility value would be expected to increase again once the patient comes off-treatment. The EAG notes that even after this increase, the utility value for NI off-treatment is still substantially lower than the utility value of the PD off-treatment health state of S4, which indicates that the use of different evidence sources to inform utility values for health states S1-S4 and health states S5-S8 may be misleading, and the assumed substantial drop in utility values based on the vignette study may not be plausible.

The EAG considers that the descriptions of the vignettes are broadly appropriate and in line with the DSU recommendations. However, the EAG notes that the health state vignette descriptions were quite general and did not separate symptoms by grade of IDH mutant gliomas and type (astrocytoma, 1p/19q-codeleted oligodendroglioma). The final utility values for health states S5-S8 used in the model were adjusted by the company by averaging the utility values on- and off-treatment to derive an average utility for NI and an average utility value for NI+. The EAG notes that the description of the vignette health states used to elicit utility values for on- and off-treatment differ in wording such that a worse health state is described whilst receiving NI and NI+ (on-treatment) compared to the health states described post-NI and post-NI+ (off-treatment) – see health state descriptions in response to EAG clarifications question B18. For example, the wording used for on-treatment reflects *"your condition has progressed"*, while the wording used for off-treatment reflects "*"your condition had progressed, but you are now stable*". Similarly, the on-treatment health state includes *"You may experience side effects such as itchy or red skin, hair loss vomiting/nausea, constipation, or diarrhoea"*, while the off-treatment health state does not include any treatment-related adverse events. Consequently, the EAG considers it inappropriate to use an average utility value across the on- and off-treatment health states at subsequent treatment lines given that the vignette health state descriptions used to elicit the utility values differentiate outcomes for on- and off-treatment. In Section 6, the EAG considers the implications on the cost-effectiveness of vorasidenib of using the unadjusted health state utility values for subsequent treatment lines from the vignette study. Furthermore, the EAG also undertakes an exploratory analysis using the utility values derived from

the TTO method to show the sensitivity of the cost-effectiveness estimates to the utility values assumed for subsequent treatment lines.

The EAG considers the source used for the age-adjusted utility decrements to be appropriate, given that it is used extensively in previous NICE technology appraisals but notes that it may be more consistent to use the general population utility values from Hernandez Alava et. al. (2018)[35] that were used in the severity modifier calculator. However, the EAG does not expect this to have a material impact on the cost-effectiveness results.

4.2.9 Resource use and costs

4.2.9.1 Summary of company's submission

The company's base case analysis includes resource use and costs relating to: (i) drug acquisition for vorasidenib; (ii) drug acquisition and administration for subsequent treatment lines of RT/CT; (iii) health state resource use consumption, including CT and MRI scans, hospitalisations and doctor visits, seizure management and debulking surgery; and (iv) end of life palliative care.

Table 13 summarises the costs included in the company's base case analysis.

Table 13 Costs used in the company's base case analysis

Item	Model	Description
Drug acquisition costs		
Vorasidenib	[redacted] per cycle (28 days) – 40mg	For patients weighing ≥40kg, the recommended dose of vorasidenib is 40 mg orally once daily, unless there [redacted]
CCNU (lomustine)	£780.82 per pack of 20, 40 mg capsules	The dosing of CCNU is 110mg per m^2, split over 3 days, after which patients will go on to receive 80−120 m
Procarbazine, CCNU and vincristine (PCV)	Procarbazine: £528.79 per 50, 50mg pack. CCNU: £780.82 per pack of 20, 40 mg capsules. Vincristine: £9.12 per 1, 1mg vial £25.38 per 5, 1mg vials £17.82 per 1, 2mg vial £33.89 per 5, 2mg vial	PCV has a 7-week treatment cycle. This regimen is "lomustine 110 mg/m^2 on Day 1, procarbazine 60 mg/m
Temozolomide (TMZ)	£137.51 per cycle	Costing TMZ appropriately is complex because there are six different unit sizes, and the drug is dosed based possible dose bands results gives an expected cost of £137.51 per model cycle.
Bevacizumab	£810.00 per 400mg/16 ml	The cost used for bevacizumab 400mg/16 ml concentrate for solution for infusion vials (pack size of 1 vial)

Item	Model	Description
	concentrate for solution for infusion vial	
Drug/treatment administration costs		
Vorasidenib	None	Drug administered orally so no administration costs included.
CCNU (lomustine)	None	Drug administered orally so no administration costs included.
PCV	None	Assumed zero, vincristine is an injection and the other two are oral
TMZ	None	Drug administered orally so no administration costs included.
Bevacizumab	£368.44	NHS reference costs 2021-2022: SB15Z - Deliver Subsequent Elements of a Chemotherapy Cycle
Health state resource use (progression-free and progressed disease)		
Unit costs Unit costs upon entering health state	CT scan - £117 MRI scan - £197 Hospital visit (unscheduled) -£873 Consultant doctor - £231 Seizure management - £203 GP appointment - £49 Home visitor - £28 Debulking surgery - £15,877.	Resource use costs are sourced from a combination of previous NICE appraisals, literature, the PSSRU and s Costs were applied based on estimated frequencies of use (Tables 43 and 44 of CS).
End of life palliative care costs		
Palliative care	£5,554 - one off cost	The transition to the death state in the model is associated with palliative care costs, which are based on Rou

4.2.9.2 Confidential pricing arrangements

The EAG notes that there are confidential commercial arrangements in place for one of the treatments delivered post-progression (bevacizumab) in the company's base case. In Sections 5 and 6 of this report the cost-effectiveness results [redacted].

Table 14 presents details of the treatments with confidential price which differ from the publicly available list price used to generate the results in this report. These prices were made available to the EAG and were used to replicate all analyses presented in the EAR for consideration by the Appraisal Committee. Details of all confidential pricing arrangements and all results inclusive of these arrangements are provided in the confidential appendix to this report. These prices are correct as of 3rd March 2025.

Table 14 Source of the confidential prices used in the confidential appendix

Treatment	Source of price/type of confidential arrangement
Vorasidenib	[redacted]
Bevacizumab	Simple PAS (mid-point across all brands considered)

4.2.9.3 Acquisition and administration costs of subsequent treatment lines

The subsequent treatments in health states S5 (1L RT/CT) and S7 (2L+ RT/CT) are based on a chemotherapy regimen of either procarbazine, CCNU and vincristine (PCV), temozolomide (TMZ), CCNU (lomustine) as a monotherapy, or bevacizumab. The proportion of patients on each treatment depends on the subsequent treatment line. The company used data from a French periodic synthesis report for ivosidenib in IDH1mutant LGG patients that are ineligible for surgery and progressing after and/or ineligible to RT and CT [38] to inform the proportion of patients that receive a given CT regimen, by treatment line, and modelled the costs of five subsequent treatment lines (Table 39 of CS). The company also made a simplifying assumption that the regimen 'Other' in the French periodic synthesis report referred to CCNU. The report includes the use of bevacizumab, which is not licensed in the NHS for the treatment of gliomas.

RT is given in conjunction with CT to a proportion of patients receiving treatment, and the remaining patients receive CT only. The proportion receiving CT and RT in conjunction varies by treatment line. In the absence of data informing the frequency of which patients are given RT in conjunction with CT, the company assumed that: (i) the proportion of patients who received RT in conjunction with CT as part of their first subsequent therapy (i.e. in health state S5 for 1L RT/CT) is 64% based on subsequent anticancer therapy use in INDIGO; and (ii) the proportion of patients who receive RT in conjunction with CT decreases in successive lines based on an approximate 50% reduction as patients move through each successive line (for example, for the 36% of patients who receive CT at 1L without RT, a 50% reduction in each successive line means that 18% receive RT in conjunction with CT in 2L, while 9% receive RT with CT at 3L, 5% at 4L and 2% at 5L). RT may be given before CT or initiated at the same time as appropriate for the CT regimen. The company's base case analysis assumes that RT is given in parallel with TMZ and bevacizumab and given in series for PCV and CCNU (i.e., RT is given first followed by PCV or CCNU as a follow-on therapy). Table 15 summarises the proportion of patients receiving CT with and without RT in each of the five successive treatment lines used to cost subsequent therapies in the company's base case analysis.

CCNU and PCV are costed in the NI and NI+ states based on expected packs of the drug required. The expected packs are calculated based on the dosing regimen (Table 13 above) and body surface area (BSA) of the patient on treatment. TMZ and bevacizumab are costed based on the percentage of

time on treatment in each cycle based on the treatment regimens described in Table 13 and in Section 3.5.1 of the CS. The unit costs for these subsequent treatments are outlined in Table 41 of the CS.

The CT treatments are all applied for a set duration. A one-cycle (28 days) grace period is assumed between completing one treatment and beginning the next (Table 40 of CS). CCNU and PCV are assumed to be given for a maximum of six 6-week cycles (9 model cycles) while a duration of 13 model cycles is assumed for bevacizumab. TMZ is assumed to be given for <= 6 cycles based on TA 121 (TMZ) [39].

RT costs are estimated based on a range of fractions assumed to be required for each CT regimen. The fractions required for CCNU and PCV are based on Buckner et. al. (2016)[40] which suggests 30 fractions over 6 weeks prior to CT, while TMZ is based on NG99 [9] which suggests 15 fractions taken in parallel within one 28-day model cycle. Bevacizumab is assumed to be the same as TMZ. RT costs are summarised in Table 46 of the CS.

Table 15 Proportion of patients receiving CT with and without RT in each line of treatment

Line and treatment	**Percentage of cohort within treatment line**		
NI: 1L	**With RT**	**Without RT**	**Total CT/RT**
PCV	4.28%	2.41%	6.69%
TMZ	22.38%	12.59%	34.97%
CCNU	37.33%	21.00%	58.33%
Total:	64%	36%	100%
NI+: 2L	**With RT**	**Without RT**	**Total CT/RT**
PCV	8.61%	39.25%	47.86%
TMZ	7.14%	32.52%	39.66%
CCNU	1.88%	8.55%	10.43%
Bevacizumab	0.37%	1.68%	2.05%
Total:	18%	82%	100%
NI+: 3L	**With RT**	**Without RT**	**Total CT/RT**
PCV	2.34%	23.64%	25.98%
TMZ	1.19%	11.98%	13.17%
CCNU	2.34%	23.64%	25.98%
Bevacizumab	3.14%	31.74%	34.88%
Total:	9%	91%	100%
NI+: 4L	**With RT**	**Without RT**	**Total CT/RT**
PCV	0.71%	13.41%	14.12%
TMZ	1.41%	26.83%	28.24%
CCNU	2.88%	54.77%	57.65%
Total:	5%	95%	100%
NI+: 5L	**With RT**	**Without RT**	**Total CT/RT**
PCV	0.67%	32.66%	33.33%
TMZ	0.33%	16.34%	16.67%
CCNU	0.33%	16.34%	16.67%
Bevacizumab	0.67%	32.66%	33.33%
Total:	2%	98%	100%

Abbreviations: L, line; NI, next intervention (health state S5 of model); NI+, next intervention for subsequent treatment lines (health state S7 of model); PCV, procarbazine, lomustine and vincristine; TMZ, temozolomide; CCNU, lomustine.

Points for critique

Data from a periodic synthesis report for ivosidenib in IDH1mutant LGG patients that are ineligible for surgery and progressing after and/or ineligible for RT and CT in France [38] was used to inform the proportion of patients receiving each subsequent treatment CT regimen. The EAG has several concerns with the use of this data. First, the EAG notes that market share data from France is unlikely to reflect treatment patterns in NHS clinical practice. The EAG's clinical advisor indicated that there are differences between the UK and other parts of Europe, where, for example, in other parts of Europe there is more use of TMZ rather than PCV as it is felt to have a better side-effect profile. For patients with glioma requiring treatment after surgery there is clinical trial evidence that RT and adjuvant CT improves PFS and OS. In most of these studies PCV is used. The EAG's clinical advisor also indicated that at 1L, PCV is used most in the UK in line with NG99[9] recommendations, whereas (the periodic synthesis report suggests only 25.6% use of PCV at 1L, with 43% use of TMZ). Consequently, the proportions of patients at 2L on each of PCV and TMZ are expected to differ because an alternative treatment would be considered post-progression. Second, the EAG notes that the sample size informing the market share data at each subsequent treatment line is small, ranging from n=60 at 1L to less than 10 patients receiving each treatment at 3L and only three patients at 5L. Third, the company makes the simplifying assumption that the regimen 'Other' in the market share data refers to CCNU, but there is no indication that it should be.

Importantly, a fourth concern is that the market share data from France includes the use of bevacizumab; however, bevacizumab is not licensed in the UK for the treatment of gliomas. Furthermore, contrary to statements made in the CS (page 85), NICE guideline NG99[9] does not make any suggestion that bevacizumab should be used in conjunction with CCNU in the treatment pathway for gliomas. The EAG notes that the NICE NG99[9] states: "*1.2.25 Do not offer bevacizumab as part of management of a newly diagnosed grade IV glioma (glioblastoma).", "1.2.33 Do not offer bevacizumab, erlotinib or cediranib, either alone or in combination with chemotherapy, as part of management of recurrent high-grade glioma."* Furthermore, clinical advice to the company, as outlined in the clinical insights reference, states that all three experts indicate that bevacizumab is not approved by NICE for gliomas and not commissioned for use in the NHS. The EAG notes that in the company's model, quite a large proportion of subsequent therapies include off-label bevacizumab (34.88% at 3L and 33.33% at 5L – see Table 15 above). The EAG does not consider it reasonable to include off-label bevacizumab use in subsequent treatment lines. In Section 6, the EAG considers a

scenario excluding the use of bevacizumab from subsequent treatment lines in the company's base case analysis and excludes its use in the EAG's preferred base case.

Furthermore, the EAG notes that the proportion of patients receiving RT in conjunction with CT is highly uncertain. The estimate of a 50% reduction in each successive treatment line is not based on any data. The company states that this estimate is broadly aligned with clinical feedback in the clinical insights reference, but the EAG notes that nearly all the clinical experts indicated that a large percentage would receive RT prior to receiving CT at 1L, but very few responses indicated the percentage who would receive RT at subsequent treatment lines. The clinical advisor to the EAG indicated that for glioma requiring further treatment after surgery, RT and CT are considered. At next relapse, consideration is given to offer re-irradiation based on location and size suitability versus offering 2L CT. The clinical advisor also noted that it would be uncommon to have a third course of RT after 1L treatment with RT and 2L re-irradiation.

The EAG also notes that the proportion of patients receiving each treatment in subsequent lines is not based on differentiating the histology mix of patients in health states S5 and S7. However, the progression and the survival outcomes are histology dependent (see Section 4.2.6.2).

The company's approach to the calculation of acquisition and administration costs for CCNU, PCV, TMZ and bevacizumab appears reasonable. The duration of treatment for CCNU and PCV, and TMZ appear reasonable based on NG99[9] and TA121 [39] guidance documents. The company's assumption of a one cycle grace period between treatment lines appears reasonable and is expected to have very minor impact on cost-effectiveness results.

4.2.9.4 Health state unit costs and resource use

Resource use and associated costs for health states in the model include frequencies of CT and MRI scans, unscheduled hospital visits, consultant doctor, GP appointments and home visitor appointments, seizure management, and debulking surgery. The frequencies for medical resource use (Tables 43 and 44 in CS) were estimated as below for each category:

- **CT scan**: Expected every three months prior to initiation of NI (i.e., for states S1, S2, S3, and S4). After initiation of NI, CT scans expected to be approximately twice as often. CT scans assumed to no longer be required once patients enter S8.
- **MRI scan**: Expected every six months prior to initiation of NI (i.e., for states S1, S2, S3, and S4). After initiation of NI, MRI scans expected to be approximately twice as often. MRI scans assumed to no longer be required once patients enter S8.
- **Hospital visit (unscheduled)**: Based on Boele et. al. (2020)[41], frequency of inpatient specialist care 1.1% per 4 weeks, assumed to apply for states S1, S2, S3, and S4. For S5 and

S7 (NI and NI+, respectively), unscheduled hospital visits assumed to be twice per model cycle, broadly in keeping with increased hospitalisation for patients receiving active treatment per NICE TA23 [42](PCV) [42] and TA121 (TMZ) [39]. For S6, same frequency assumed as per S1-S4. For S8, assumed same frequency as per S5 and S7.

- **Consultant doctor**: Boele et. al. (2020)[41] for 'outpatient specialist care'. Assumed to be the same frequency across all model health states after progression but assumed 50% of frequency for progression-free health states (i.e., S1 and S2).
- **GP appointment**: Boele et. al. (2020)[41] for 'GP'. Assumed to be the same frequency across all model health states after progression but assumed 50% of frequency for progression-free health states (i.e., S1 and S2).
- **Home visitor**: Boele et. al. (2020)[41] for 'home care'. Assumed to be the same frequency across all model health states.
- **Seizure Management**: Due to the complex nature of seizure management for glioma, the company focussed on secondary engagement (hospitalisation) costs rather than anti-seizure medication. Given a lack of data, the proportion requiring hospitalisation (10%) was assumed based on responses from clinicians (see company response to EAG clarifications, question B25 and Table 42 of CS). Seizure management costs are applied to health states. The rate of seizures (18.7 seizure events per person-year during seizure assessment period within progression-free state) was based on the INDIGO trial placebo arm. Based on a risk ratio of 0.36 (95% CI: 0.14, 0.89), the vorasidenib arm is modelled to have a reduced risk of seizures. The company expects that seizure severity worsens as the disease progresses and, therefore, the seizure management costs increase over time. Seizure management costs increase by 25% upon initiation of NI (movement to S5) and NI+ (S7) and following cessation of active treatment and movement to BSC (S8).
- **Debulking Surgery**: Palliative debulking surgery is considered in the model for patients entering health states S5 (NI) and S7 (NI+). The frequency is based on Brown et. al. (2022)[43] for glioblastomas, which suggests that 60% of patients had a debulking surgery. The 60% is assumed to be split evenly with 30% in S5 and another 30% in S7. Debulking surgery is costed upon entry to S5 and S7.

The unit costs associated with each resource use category can be found in Table 45 of the CS.

End-of-life care costs applied upon entry to health state S8 were sourced from a study by Round *et al.,* (2015)[37]. The lung cancer costs were deemed the most appropriate proxy given its aggressive progression and overlapping symptom burden. The total cost of health and social care from this study of £4,515 was inflated to 2022/23 prices, to give a total cost of £5,554 applied in the model.

Points for critique

The EAG considers the frequency of MRI scans to be reasonable. The EAG's clinical advisor indicated that CT scans are not used routinely for monitoring progression in NHS practice to avoid exposure to unnecessary radiation and only used in specific circumstances (e.g., for seizure management), but that MRI scans are the standard used to monitor progression. As a result, the EAG considers a scenario in Section 6 where the use of CT scans is removed from the company's base case analysis.

The company uses information from a Dutch study by Boele et. al. (2020)[41] to inform resource use for unscheduled hospital visits, consultant doctors, GP appointments, and home visitor costs, but it is not clear how generalisable the population in this study is to the target population in the NHS, where the study recruits patients with at least mild depressive symptoms and tracks their costs over a period of just 12 months. The EAG's clinical advisor considered the resource assumptions to be reasonable except for the inclusion of home visitor costs.

The company notes that seizures in INDIGO account for partial and generalised seizures (response to EAG clarifications question B25) and that resource use assumptions were subject to clinical validation including one UK expert. The company provided evidence of responses by clinical experts to questions on seizure management (response to EAG clarifications question B25) and the 10% of seizures assumed to require hospitalisation and resource use appears reasonable based on these responses. The company notes that in Table 19 of the CS (and confirmed in response to EAG clarifications question A12) that the vorasidenib arm had a reduced rate of seizures compared to the placebo arm of INDIGO. However, over the lifetime of the model, the vorasidenib arm has higher resource use associated with seizure management. This is driven largely by the costs incurred in health states S1 and S4 where patients on vorasidenib remain for longer compared to active observation.

The evidence from Brown et. al. (2022)[43] used to determine the proportion of patients that undergo debulking surgery (60%) appears reasonable in the absence of NHS data. However, the EAG notes that this study was primarily in patients with IDH-wildtype glioblastomas and only 11% of patients had IDH1 or IDH2 mutations. The company assumed that 30% of the surgeries each were done in health states S5 and S7. In response to EAG clarifications question B25, the EAG notes that [redacted] The EAG's clinical advisor indicated that for LGG the standard of care is early maximal safe resection, and that further surgery may be considered at progression of the LGG and is commonly followed with RT and CT. Intervention with surgery is less common after RT and CT if there is transformation to a HGG. The EAG's clinical advisor noted that the assumption of 2-3 debulking surgeries seems reasonable. The

EAG notes that changing the percentage or removing debulking surgery related resource use has minimal impact on the cost-effectiveness results.

5 COST EFFECTIVENESS RESULTS

5.1 Company's cost effectiveness results

5.1.1 Summary of company's submission

The cost-effectiveness results presented in the CS are based on [redacted]

A summary of the inputs and variables used in the company's base case analysis is presented in Section 3.9.1 of the CS and the assumptions used in the model are summarised in Section 3.9.2 of the CS.

At EAG clarifications, the company submitted a revised version of the economic model following a number of corrections required, as noted by the EAG. The key corrections to formulae in the model are:

1. Inconsistency in the application of transition probability formulae.
2. Error when choosing and running scenario for HR on TTNI | P.
3. Inaccurate cell references when running scenario for HR on TTNI | P.

The company presents base case cost-effectiveness results for vorasidenib compared with active observation. Table 16 shows the company's base case deterministic and probabilistic cost-effectiveness results. The deterministic and probabilistic ICERs for vorasidenib relative to active observation are [redacted], respectively. The results are inclusive of the non-reference case discount rate of 1.5% per annum and a severity weighting of 1.7 (see Section 7) as used in the company's base case analysis.

Table 16 Company's base case cost-effectiveness results

Technologies	Total costs	Total QALYs	Inc. costs	Inc. QALYs**	ICER** (£/QALY)
Deterministic analysis					
Active observation	[redacted]	7.74			
Vorasidenib	[redacted]	11.16	[redacted]	5.83**	[redacted]
Probabilistic analysis					
Active observation	[redacted]	7.50			
Vorasidenib	[redacted]	11.00	[redacted]	5.95**	[redacted]

Abbreviations: Incre., incremental; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years
*Includes x1.7 severity weighting applied to incremental QALYs based on the non-reference case discount rate of 1.5% per annum.

5.1.1.2 Points for critique

To aid understanding of the key drivers of the cost-effectiveness results, Table 17 and Table 18 provide a summary of the disaggregated costs by cost category and QALYs by modelled health states S1 to S8. The higher costs for vorasidenib are predominantly driven by the difference in drug acquisition costs prior to disease progression given that the comparator is active observation with no acquisition costs. This cost is offset slightly by costs incurred in the active observation arm in the NI and NI+ plus health states for all categories due to faster progression. The QALY gains for vorasidenib are driven mainly by the improvements in HRQoL associated with the longer time spent progression-free on vorasidenib (health state S1) compared to active observation (health state S2) and longer time spent in S4 (progressed disease, off treatment) for vorasidenib relative to active observation. The delay in progression also accentuates differences in QALYs since excess mortality is only applied in health state S8.

Table 17 Summary of the disaggregated costs in the company's deterministic base case results (Source: Electronic Model from CS)

Breakdown of costs		Vorasidenib		Active observation	
		Undiscounted	Discounted	Undiscounted	Discounted
Drug costs	Drug cost: vorasidenib	[redacted]	[redacted]	[redacted]	[redacted]
	Drug cost: NI	[redacted]	[redacted]	[redacted]	[redacted]
	Drug cost: NI+	[redacted]	[redacted]	[redacted]	[redacted]
AE costs	AE costs (total)	[redacted]	[redacted]	[redacted]	[redacted]
RT costs	RT costs: NI	[redacted]	[redacted]	[redacted]	[redacted]
	RT costs: NI+	[redacted]	[redacted]	[redacted]	[redacted]
Admin costs	Admin costs: NI	[redacted]	[redacted]	[redacted]	[redacted]
	Admin costs: NI+	[redacted]	[redacted]	[redacted]	[redacted]
EoL costs	EoL costs	[redacted]	[redacted]	[redacted]	[redacted]
MRU costs	Other MRU costs	[redacted]	[redacted]	[redacted]	[redacted]
	Costs: Total	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: NI, next intervention; NI+, next intervention plus; EoL, end of life; MRU, medical resource use; Admin, administration; RT, radiotherapy; AE, adverse event.

Table 18 Summary of the disaggregated QALYs in the company's deterministic base case results (Source: Electronic Model from CS)

	Vorasidenib		Active observation	
Health state	Undiscounted	Discounted	Undiscounted	Discounted
QALYs: S1	[redacted]	[redacted]	[redacted]	[redacted]
QALYs: S2	[redacted]	[redacted]	[redacted]	[redacted]
QALYs: S3	[redacted]	[redacted]	[redacted]	[redacted]
QALYs: S4	[redacted]	[redacted]	[redacted]	[redacted]
QALYs: S5	[redacted]	[redacted]	[redacted]	[redacted]
QALYs: S6	[redacted]	[redacted]	[redacted]	[redacted]

QALYs: S7	[redacted]	[redacted]	[redacted]	[redacted]
QALYs: S8	[redacted]	[redacted]	[redacted]	[redacted]
QALYs: AE loss	[redacted]	[redacted]	[redacted]	[redacted]
QALYs: Total	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: QALYs, quality-adjusted life years; AE, adverse event.

5.2 Company's sensitivity analyses

5.2.1 Summary of company's submission

The company reports deterministic one-way sensitivity analysis (OWSA) using the proposed list price for vorasidenib via tornado plots of the ten most influential parameters, where inputs were set in turn to their respective lower and upper limits, while all other parameters were maintained at their base case setting (Figure 38 of CS). Changes to the Standardized Mortality Ratio of patients with LGG vs the general population had the largest impact on the ICER. The uncertainty associated with parameters for modelling sPFS (PFS from Juratli et. al. (2012)[25] used in health state S5) and for opting out of further treatment prior to NI or NI+ were the next most impactful parameters.

The CS reports eighteen deterministic scenario analyses using the proposed list price for vorasidenib (Table 56 of the CS). The scenarios with the largest impact on cost-effectiveness results were changes to the parametric curves used for PFS and TTNI | P using data from the INDIGO study, the annual discount rate used for costs and effects, and reducing the model time horizon.

No subgroup analyses were conducted by the company.

5.3 Model validation and face validity check

5.3.1 Summary of company submission

The company did an internal validation of the outcomes (PFS and NI-free survival) compared to those from INDIGO (Appendix H of CS) and technical validation of the cost effectiveness analysis and the economic model. The CS states that quality-control procedures were undertaken via internal processes and via an economist not involved in the development process including reviewing the model for potential coding errors, inconsistencies, and checks on the plausibility of inputs.

5.3.1.1 Points for critique

The EAG considers the company's stated model technical validation procedure to be reasonable. The EAG notes that while there has been clinical consultation on some important parameters (Servier 2024 Clinical insights reports reference[44]) including vorasidenib arm long-term PFS and NI free, percentages of patients alive after 50 years, and survival time in BSC to NI, clinicians were often

unable to give clear answers or the answers suggest numbers different to those that seem to have been implemented in the model. In addition, the company presented very limited external validation of the outputs produced by the model with clinicians; however, in response to EAG clarifications the company undertook an advisory board meeting to gain clinical opinion and expert validation of the parameters and outputs of the cost-effectiveness model. The notes from this meeting were presented to the EAG in a separate document, UK Cost Effectiveness Model Advisory Board Report 2025[45], late in the process (approximately two weeks before finalising the EAR).

6 EXTERNAL ASSESSMENT GROUP'S ADDITIONAL ANALYSES

The EAG identified several limitations and areas of uncertainty in the company's cost-effectiveness analysis. These issues are identified and critiqued in Section 4.2. A number of alternative scenarios are presented in areas where the EAG considers an alternative approach to be more appropriate than the company's base case analysis, or where it is considered important to explore the impact of uncertainty.

A description of the exploratory analyses is described in Section 6.1 and the impact of these analyses on the company's base case are presented in Section 6.2. The EAG's preferred base case consists of the set of assumptions and model inputs that the EAG considers to be most appropriate for assessing the cost-effectiveness of vorasidenib relative to active observation. The effect of making changes simultaneously on elements that are considered to form part of the EAG's preferred base case are presented in Section 6.3.

6.1 Exploratory and sensitivity analyses undertaken by the EAG

The EAG conducted the following analyses on the corrected version of the company's model following EAG clarifications [redacted].

1. NICE reference case discount rate of 3.5% per annum, with the corresponding severity weighting of 1.2 rather than 1.7 used in the company's base case analysis.

As discussed in Section 4.2.5.2, the EAG has significant concerns regarding the company's justification for the use of the non-reference case discount rate of 1.5% per annum and the EAG considers it more appropriate to use the reference case discount rate of 3.5% per annum, in both the model and severity modifier calculations (Scenario 1).

In the EAG scenario analyses that follow, the EAG presents the cost-effectiveness results using a discount rate of 3.5% per annum. For completeness, Appendix 3 reports the EAG scenario analyses using the company's non-reference case discount rate of 1.5% per annum.

2. TTNI | P extrapolation curves, separated by treatment arm

As discussed in Section 4.2.6.2, the EAG has several concerns regarding the use of the conditional outcome of TTNI | P, which is used to determine the duration of time spent in health state S4 off-treatment with progression before moving to 1L RT/CT. One specific concern relates to the clinical plausibility of the model predictions from the TTNI | P extrapolated curve using a generalised gamma model relative to the predictions for PFS used in the company's base case analysis. The outputs of the company's base case suggest that patients remain longer in health state S4, with PD and off-treatment, than in health states S1 and S2, where patients are PF. The EAG considers the model predictions to lack face validity because it would seem unreasonable to believe that a patient would remain longer off-treatment with radiographic evidence of PD than in a PF health state; this includes significantly longer time in PD off-treatment than PF off-treatment for active observation (see Table 8 in Section 4.2.6.1). The TTNI | P outcome is subject to several concerns, including cross-over in the placebo arm and very limited KM data with a high amount of censoring, especially in the vorasidenib arm due to progression events occurring later compared to the placebo arm. Figures 20 and 21 of CS show that the extrapolations of TTNI | P in the vorasidenib and placebo arms, respectively, are highly sensitive to the parametric distribution selected. The best fitted generalised gamma model used in the company's base case provides the most favourable predictions for TTNI | P in both arms, with approximately 21% of patients with radiographic evidence of PD remain untreated at 20 years following vorasidenib, and a small proportion of patients never progress to subsequent treatment lines over the model time horizon (i.e., their disease never progresses following post-progression on initial intervention), while approximately 9% of patients remain off-treatment at 20 years for active observation post-progression.

Scenario 2 assesses the implications of using alternative models to extrapolate the TTNI | P curves on the cost-effectiveness of vorasidenib relative to active observation, including the second best fitted curve of log-normal for both the vorasidenib and placebo arm of INDIGO (Scenario 2a), and the exponential model that produces a much shorter time to next intervention (Scenario 2b). The EAG considers that the log-normal model produces more reasonable predictions with total life years in health state S4 (PD) lower than health states S1 and S2 (PF), while the exponential model produces more conservative estimates for time to 1L RT/CT given progression.

3. TTNI | P curve equal for both vorasidenib and active observation

As discussed in Section 4.2.6.2, there is no evidence to support a difference between vorasidenib and active observation following discontinuation of vorasidenib due to radiographic progression of disease. The EAG accepts that progression on imaging may not immediately trigger next intervention for a subset of patients when taking account that LGG can be a slow progressing disease, and the difficult choice required to move to RT/CT. However, it remains unknown which tumoral changes are potentially triggered by vorasidenib and how the disease will eventually behave after progression. The company have not shown data that tumour size is smaller at the time of progression than at baseline for vorasidenib. Furthermore, the outcome of TTNI | P is not informing the time to 1L RT/CT as required for the model but instead informing the time to any subsequent therapy, where 42.9% of participants who had progression on imaging in the placebo arm crossed over to vorasidenib rather than RT/CT. Therefore, the cross-over in the placebo arm has confounded the comparability of the interventions for the outcome of TTNI | P.

The EAG is unclear why there would be a propensity to treat post-progression patients (defined based on the same criteria in both arms of INDIGO) differently in health state S4 depending on whether they progressed on vorasidenib or progressed on active observation, especially when there are no differences assumed for subsequent treatment lines. Furthermore, the EAG notes that the health-related quality of life utility values by progression status and treatment arm of INDIGO indicates that patients with PD had better quality of life in the placebo arm (mean utility of 0.730) than the vorasidenib arm (mean utility of 0.678). In the absence of evidence to support important ongoing effects of vorasidenib post-progression and the issues with the TTNI | P data (post-randomised, confounded by cross-over, high amount of censoring and immature data), the EAG considers it more reasonable to assume that a common TTNI | P curve, independent of initial intervention received, is appropriate post-progression. The EAG also considers this more aligned with the modelling of subsequent treatment lines where no differences in downstream effects are assumed by treatment, where only a difference in the timing of entering the health states based on vorasidenib delaying time to progression.

Scenario 3 assesses the implications of using the same TTNI | P curve for both interventions (vorasidenib and active observation) on the cost-effectiveness of vorasidenib. However, the EAG notes that it remains unclear which TTNI | P curve is most appropriate for use in the model because both the vorasidenib and placebo arms of INDIGO have concerns; the placebo arm is confounded by cross-over, while the vorasidenib arm is subject to high censoring and small numbers of patients at risk to inform the long-term extrapolation. In the absence of a suitable alternative, the EAG explores the use of the pooled TTNI | P curve across arms of INDIGO and extrapolated using a generalised gamma model (Scenario 3a), a log-normal model (Scenario 3b) and an exponential model (Scenario

3c), in addition to using the TTNI | P curve for the vorasidenib arm of INDIGO with a log-normal model (Scenario 3d) that was considered to produce more plausible predictions as per Scenario 2.

4. Excluding the use of bevacizumab at subsequent treatment lines

As discussed in Section 4.2.9.3, the EAG does not consider it appropriate to include the use of bevacizumab at subsequent treatment lines because bevacizumab is not licensed in the UK for the treatment of gliomas. Furthermore, contrary to statements made in the CS (page 85), NICE guideline NG99 [9] does not make any suggestion that bevacizumab should be used in the treatment pathway for gliomas. This was further confirmed by the EAG's clinical advisor who indicated that off-label bevacizumab is not routinely used in the treatment of gliomas. The EAG notes that in the company's base case, quite a large proportion of subsequent therapies include off-label bevacizumab (34.88% at 3L and 33.33% at 5L), which has higher cost in the company's base case compared to the costs of RT/CT. Scenario 4 assesses the cost-effectiveness of vorasidenib excluding the use of bevacizumab from subsequent treatment lines.

5. Percentage of subsequent treatment use changed to reflect NHS practice

As discussed in Section 4.2.9.3, the EAG does not consider it appropriate to use market share data from France to reflect treatment patterns in NHS clinical practice. The EAG's clinical advisor indicated that there are important differences between the UK and other parts of Europe, for example, in Europe there is more scepticism around the use of PCV. The EAG's clinical advisor indicated that at 1L, PCV is used most in the UK in line with NG99 recommendations, whereas the periodic synthesis report based on French data suggests only 25.6% use of PCV at 1L. Consequently, the proportions of patients at 2L on each of PCV and TMZ are expected to differ because an alternative treatment would be considered post-progression. The EAG's clinical advisor also indicated that a higher percentage of patients would receive RT combined with adjunctive CT at 1L than assumed in the company's base case analysis, but that this would diminish at subsequent treatment lines as RT is typically given twice only.

In the absence of UK data, Scenario 5 aims to proxy NHS practice for subsequent treatment use based on NG99 [9] recommendations and clinical advice to the EAG. In scenario 5, the proportion of treatments used at subsequent lines are as follows:

- 1L: 100% PCV in conjunction with RT.
- 2L: 100% TMZ, in conjunction with % RT per company assumptions.
- 3L to 5L: Equal percentages of PCV, TMZ, and CCNU, with no RT.

Note that the company's model did not have sufficient flexibility to remove lines of treatment; therefore, equal percentages of PCV, TMZ, and CCNU were assumed at 3L+.

6. Excluding CT scans

As discussed in Section 4.2.9.4, the EAG's clinical advisor indicated that CT scans are not used routinely for monitoring progression in NHS practice to avoid exposure to unnecessary radiation (only used in specific circumstances such as presenting with a seizure), with MRI scans being the standard used to monitor progression. This also aligns with NG99 [9] recommendations and feedback from the company's UK Cost Effectiveness Model Advisory Board Report[45], which indicates that CT scans would not be done routinely. Scenario 6 assesses the cost-effectiveness of vorasidenib excluding the costs associated with CT scans.

7. Health state utility values for subsequent treatment lines

As discussed in Section 4.2.8.2, the EAG has several concerns relating to the health state utility values used for subsequent treatment lines. One specific concern relates to the adjustment made to the health state utility values from the vignette study for on- and off-treatment, where the company averaged the on- and off-treatment utility values to derive an average utility for NI (i.e., an average utility value for on- and off-treatment with 1L RT/CT in health states S5 and S6) and an average utility value for NI+ (i.e., an average utility value for on-treatment with 2L+ RT/CT and off-treatment with BSC in health states S7 and S8). The EAG notes that the description of the vignette health states used to elicit utility values for on- and off-treatment differ in wording such that a worse health state is described whilst receiving NI and NI+ (on-treatment) compared to the health states described post-NI and post-NI+ (off-treatment) – see health state descriptions in response to EAG clarifications question B18. For example, the wording used for on-treatment reflects *"your condition has progressed"*, while the wording used for off-treatment reflects "*"your condition had progressed, but you are now stable*". Similarly, the on-treatment health state includes *"You may experience side effects such as itchy or red skin, hair loss vomiting/nausea, constipation, or diarrhoea"*, while the off-treatment health state does not include any treatment-related adverse events. Consequently, the EAG considers it inappropriate to use an average utility value across the on- and off-treatment health states at subsequent treatment lines given that the vignette health state descriptions used to elicit the utility values differentiate outcomes for on- and off-treatment. Scenario 7 assesses the implications on the cost-effectiveness of vorasidenib of using the unadjusted health state utility values for subsequent treatment lines from the vignette study (see Table 19).

8. Health state utility values at subsequent treatment lines based on TTO responses to vignette study

As highlighted in Section 4.2.8.2, vignettes represent the lowest quality of evidence in the NICE hierarchy of preferred HRQoL methods. The company evaluated the vignettes using both EQ-5D and time trade-off (TTO) methods, which resulted in substantially different estimates of utility values for subsequent treatment lines (see Table 19). To show the sensitivity of the cost-effectiveness estimates to the utility values assumed for subsequent treatment lines, scenario 8 presents an exploratory analysis using the utility values derived from the TTO method.

Table 19 Health state utility values for subsequent treatment lines used in the company's base case and EAG scenarios 7 and 8.

	Mean utility value		
Health state	Company's base case (EQ-5D from vignette study; adjusted by averaging across on- and off-treatment)	EAG scenario 7 (EQ-5D from vignette study; unadjusted values)	EAG scenario 8 (TTO method used in vignette study; unadjusted values)
S5: On-treatment with 1L RT/CT	0.480	0.400	0.550
S6: Off-treatment post-1L RT/CT	0.480	0.560	0.700
S7: On-treatment with 2L+ RT/CT	0.340	0.260	0.330
S8: BSC	0.340	0.420	0.540

Table 20 provides a summary of the assumptions used in the EAG scenarios compared to the company's base case.

Table 20 Summary of EAG exploratory analyses

EAG scenario number	Company base case assumption	EAG scenario	Section in EAG report
1	Discount rate of 1.5% per annum	Discount rate of 3.5% per annum	4.2.5.2
2a	TTNI | P, separated by treatment arm: Generalised gamma model for both arms	TTNI | P, separated by treatment arm: Log-normal model for both arms	4.2.6.2
2b		TTNI | P, separated by treatment arm: Exponential model for both arms	
3a	TTNI | P, separated by treatment arm: Generalised gamma model for both arms	TTNI | P equal for both intervention arms based on pooled curve across arms: Generalized gamma model	4.2.6.2
3b		TTNI | P equal for both intervention arms based on pooled curve across arms: Log-normal model	
3c		TTNI | P equal for both intervention arms based on pooled curve across arms: Exponential model	
3d		TTNI | P equal for both intervention arms based on vorasidenib curve: Log normal model	
4	Includes the use of bevacizumab	Exclude the use of bevacizumab	4.2.9.3

	at subsequent treatment lines	at subsequent treatment lines	
5	Proportion of treatments used at subsequent lines based on market share data in France	Proportion of treatments used at subsequent lines a proxy for NHS practice	4.2.9.3
6	Includes monitoring costs using CT scans	Exclude monitoring costs associated with CT scans	4.2.9.4
7	Health state utility values at subsequent treatment lines adjusted based on averaging across on- and off-treatment	Health state utility values at subsequent treatment lines unadjusted	4.2.8.2
8	Health state utility values at subsequent treatment lines based on EQ-5D responses to vignette study	Health state utility values at subsequent treatment lines based on TTO responses to vignette study	4.2.8.2

6.2 Impact on the ICER of additional clinical and economic analyses undertaken by the EAG

Table 21 shows the results of the EAG scenarios for the comparison of vorasidenib with active observation (deterministic analysis). Note that it was not possible for the EAG to conduct all scenarios using a probabilistic analysis due to time constraints; each scenario using a probabilistic analysis had a run-time of over 5 hours.

Using the NICE reference case discount rate of 3.5% per annum, the company's base case ICER (without severity weighting) increases from [redacted] to [redacted]. When a discount rate of 1.5% per annum is used in the severity modifier calculations, a severity weighting of 1.7 is derived for the company's base case assumptions (see Section 7); however, using the reference case discount rate of 3.5% per annum results in a severity weighting of 1.2. With severity weighting, the company's base case ICER at the reference case discount rate of 3.5% per annum is [redacted].

For the majority of the EAG scenarios, the severity weighting of 1.2 holds. However, the weighting may change for scenarios depending on the magnitude of the total QALYs in the active observation arm that is used in the QALY shortfall calculations. For scenarios 3a (TTNI | P equal for both intervention arms based on pooled curve and generalized gamma model) and scenario 8 (utility values based on TTO method) a severity weighting of 1.0 is applied.

The scenarios with the largest impact on the cost-effectiveness of vorasidenib relative to active observation are scenarios 2 and 3 based on assumptions for the TTNI | P curve used in the model. Scenario 2 shows that the cost-effectiveness of vorasidenib is highly sensitive to the parametric distribution selected for the extrapolation of the TTNI | P curve in the vorasidenib and placebo arms of INDIGO. Using a log-normal model for the extrapolation compared to the generalised gamma increases the company's base case ICER (reference case discount rate) from [redacted] to [redacted], while the exponential extrapolation increases the ICER to [redacted]. Scenario 3 shows that the use of

differential TTNI | P curves for vorasidenib and active observation in the company's base case has a significant impact on the cost-effectiveness of vorasidenib. In the absence of evidence to support ongoing effects of vorasidenib post-progression, scenario 3 shows that the ICER increases substantially, ranging from [redacted] to [redacted], when the TTNI | P curve is set equal for both intervention arms, i.e., a common curve is assumed post-progression.

Scenarios 4 (excluding the off-label use of bevacizumab at subsequent treatment lines) and 5 (percentage of subsequent treatment use a proxy for NHS practice) have a moderate effect on the ICER, increasing it by around [redacted], while scenario 8 using the TTO estimates to inform the health state utility values at subsequent treatment lines has a significant effect, increasing the base case ICER by approximately [redacted]. Scenarios 6 (excluding the costs of CT scans) and 7 (unadjusted health state utility values) have a minimal effect on the ICER.

Table 21 Cost-effectiveness results of EAG scenario analyses for a discount rate of 3.5% per annum (deterministic analysis)

Scenario #	Description of scenario	Option	Total costs	Total QALYs	Inc. Costs	Inc. QALYs	ICER (/QALY)	Inc. QALYs (x1.0, x1.2* or x1.7** severity weighting)	ICER (x1.0, x1.2* or x1.7** severity weighting)
	Company's base-case results	Active observation	[redacted]	7.74					
	(1.5% annual discount rate)	Vorasidenib	[redacted]	11.16	[redacted]	3.43	[redacted]	5.83**	[redacted]
1	Discount rate of 3.5% per annum	Active observation	[redacted]	6.26					
	applied to company's base case assumptions	Vorasidenib	[redacted]	8.71	[redacted]	2.45	[redacted]	2.94*	[redacted]
2a	TTNI | P, separated by treatment arm: Log normal model for both arms	Active observation	[redacted]	5.32					
		Vorasidenib	[redacted]	7.32	[redacted]	2.00	[redacted]	2.40*	[redacted]
2b	TTNI | P, separated by treatment arm: Exponential model for both arms	Active observation	[redacted]	5.20					
		Vorasidenib	[redacted]	6.97	[redacted]	1.77	[redacted]	2.12*	[redacted]
3a	TTNI | P equal for both intervention arms based on pooled curve across arms: Generalized gamma model	Active observation	[redacted]	6.68					
		Vorasidenib	[redacted]	7.89	[redacted]	1.21	[redacted]	1.21*	[redacted]
3b	TTNI | P equal for both intervention arms based on pooled curve across arms: Log-normal model	Active observation	[redacted]	5.49					
		Vorasidenib	[redacted]	6.96	[redacted]	1.47	[redacted]	1.76*	[redacted]
3c	TTNI | P equal for both intervention arms based on pooled curve across arms: Exponential model	Active observation	[redacted]	5.28					
		Vorasidenib	[redacted]	6.78	[redacted]	1.50	[redacted]	1.79*	[redacted]
3d	TTNI | P equal for both intervention arms based on vorasidenib curve: Log normal model	Active observation	[redacted]	5.91					
		Vorasidenib	[redacted]	7.32	[redacted]	1.41	[redacted]	1.69*	[redacted]
4	Exclude the use of bevacizumab at subsequent treatment lines	Active observation	[redacted]	6.26					
		Vorasidenib	[redacted]	8.71	[redacted]	2.45	[redacted]	2.94*	[redacted]
5		Active observation	[redacted]	6.26					

	Proportion of treatments used at subsequent lines 1L: 100% PCV in conjunction with RT. 2L: 100% TMZ, in conjunction with % RT per company assumptions. 3L to 5L: Equal % of PCV, TMZ, CCNU, no RT	Vorasidenib	[redacted]	8.70	[redacted]	2.44	[redacted]	2.92*	[redacted]
6	Exclude CT scans	Active observation	[redacted]	6.26					
		Vorasidenib	[redacted]	8.71	[redacted]	2.45	[redacted]	2.94*	[redacted]
7	Unadjusted health state utility values for subsequent treatment lines	Active observation	[redacted]	6.47					
		Vorasidenib	[redacted]	8.88	[redacted]	2.41	[redacted]	2.90*	[redacted]
8	Health state utility values for subsequent treatment lines based on TTO utility values from vignette study	Active observation	[redacted]	7.44					
		Vorasidenib	[redacted]	9.62	[redacted]	2.18	[redacted]	2.18*	[redacted]

*Adjusted by applying a 1.2 severity weight
**Adjusted by applying a 1.7 severity weight

6.3 EAG's preferred assumptions

The EAG's preferred assumptions include the following changes to the company's base case (March 2023 data cut of INDIGO):

- NICE reference case discount rate of 3.5% per annum rather than the non-reference case discount rate of 1.5% per annum – Scenario 1.
- A common TTNI | P curve for both interventions based on the pooled curve across arms of INDIGO, with log-normal extrapolation, rather than TTNI | P curve separated by treatment arm (generalised gamma extrapolation) – Scenario 3b.
- Exclude the use of off-label bevacizumab at subsequent treatment lines – Scenario 4.
- Proportion of treatments used at subsequent treatment lines changed to proxy NHS practice rather than based on market share data from France – Scenario 5.
- Exclude the monitoring costs associated with CT scans – Scenario 6.
- Unadjusted health state utility values for subsequent treatment lines – Scenario 7.

Several important uncertainties remain, which cannot be adequately addressed with the available evidence:

- The absence of mature OS data from INDIGO and the assumption that the relative effect of vorasidenib on time to progression and time to next intervention given progression (TTNI | P) as predictive of its relative effect on OS remains unknown.
- The TTNI | P curve for both intervention arms of INDIGO are subject to concerns and not informing the time to 1L RT/CT required for the model; the placebo arm is confounded by a very high percentage of cross-over to vorasidenib (with limited data available from non-censored subjects to allow an adjustment for cross-over), and the vorasidenib arm has a significant amount of censoring due to progression events occurring later compared to the placebo arm and the numbers of patients at risk is extremely low at 12 months to extrapolate the curve over the long-term.
- The absence of survival outcomes for subsequent treatments relevant to the target population that reflect treatment modalities used in NHS clinical practice.
- The absence of health-related quality of life for subsequent treatment lines, with significant uncertainty in the estimates derived from the vignette study.

Table 22 summarises the cumulative impact of the EAG's preferred assumptions on the ICER for vorasidenib relative to active observation.

Table 22 Cost-effectiveness results of EAG preferred assumptions

Scenario #	Name	Option	Total costs	Total QALYs	Inc. Costs	Inc. QALYs	ICER (/QALY)	Inc. QALYs (x1.0, x1.2* or x1.7** severity weighting)	ICER (x1.0, x1.2* or x1.7** severity weighting)
	Company's base-case (1.5% annual discount rate)	Active observation	[redacted]	7.74					
		Vorasidenib	[redacted]	11.16	[redacted]	3.43	[redacted]	5.83**	[redacted]
1	Discount rate of 3.5% per annum	Active observation	[redacted]	6.26					
		Vorasidenib	[redacted]	8.71	[redacted]	2.45	[redacted]	2.94*	[redacted]
1 + 3b	+ TTNI | P equal for both intervention arms based on pooled curve across arms: Log-normal model	Active observation	[redacted]	5.49					
		Vorasidenib	[redacted]	6.96	[redacted]	1.47	[redacted]	1.76*	[redacted]
1 + 3b + 4	+ Exclude the use of bevacizumab at subsequent treatment lines	Active observation	[redacted]	5.49					
		Vorasidenib	[redacted]	6.96	[redacted]	1.47	[redacted]	1.76*	[redacted]
1 + 3b + 4 + 5	+ Proportion of treatments used at subsequent lines to proxy NHS clinical practice	Active observation	[redacted]	5.49					
		Vorasidenib	[redacted]	6.94	[redacted]	1.45	[redacted]	1.74*	[redacted]
1 + 3b + 4 + 5 + 6	+ Exclude CT scans	Active observation	[redacted]	5.49					
		Vorasidenib	[redacted]	6.94	[redacted]	1.45	[redacted]	1.74*	[redacted]
1 + 3b + 4 + 5 + 6 + 7	+ Unadjusted health state utility values for subsequent treatment lines [EAG base case – deterministic analysis]	Active observation	[redacted]	5.69					
		Vorasidenib	[redacted]	7.13	[redacted]	1.44	[redacted]	1.73*	[redacted]
1 + 3b + 4 + 5 + 6 + 7	EAG base case - probabilistic analysis	Active observation	[redacted]	5.72					
		Vorasidenib	[redacted]	7.22	[redacted]	1.51	[redacted]	1.81*	[redacted]

*Adjusted by applying a 1.2 severity weight
**Adjusted by applying a 1.7 severity weight

6.4 Conclusions of the cost effectiveness section

The company submitted a microsimulation decision model to assess the cost-effectiveness of vorasidenib compared with active observation (watch and wait) for a target population of people aged 12 years and over with grade 2 astrocytoma or oligodendroglioma with IDH1 or IDH2 mutations, who have had surgical intervention and not in immediate need of RT or CT. Vorasidenib is modelled to reduce the risk of progression and the time to RT/CT in patients with predominantly non-enhancing IDH-mutant gliomas. The model structure is based on health states relating to treatment status, where treatment-related milestones are used to signify stages of disease progression and the management of LGG. The EAG considers the model structure to be broadly appropriate for capturing the downstream effects of initial intervention but notes that it relies on two key structural assumptions to hold, which have not yet been proven with data: (1) subsequent treatments are a good surrogacy for progression of disease in terms of transitions to HGG (and type of gliomas) and malignant transformation; and (2) the relative effect of vorasidenib on time to progression and TTNI | P from INDIGO is predictive of its relative effect on OS. The company's base case uses a non-reference case discount rate of 1.5% per annum for both costs and health effects. The EAG has significant concerns regarding the company's justification for the use of a non-reference case discount rate and the EAG believes it does not meet NICE methods guide criteria (see Section 4.2.5.2)

The evidence informing the cost-effectiveness of vorasidenib is highly uncertain. In the absence of mature OS data from INDIGO, it remains unknown if the surrogacy relationship for OS assumed in the model holds (i.e., whether the relative effect of vorasidenib on time to progression and TTNI | P is predictive of its relative effect on OS). Furthermore, the TTNI | P curve for both arms of INDIGO are subject to concerns and not informing the time to 1L RT/CT as required for the model, where the placebo arm is confounded by a high percentage of cross-over to vorasidenib and the vorasidenib arm has a significant amount of censoring.

Following progression and TTNI, outcomes for subsequent treatment lines in the model are based on external sources to INDIGO. The modelling of subsequent treatment lines requires evidence on time to progression on 1L RT/CT, time to 2L+ RT/CT, time to BSC, and death, in addition to evidence relating to change in glioma grade and histology over the course of disease progression and HRQoL utility values. The EAG is concerned about the reliance on multiple different literature sources from non-comparable populations and numerous assumptions required to inform long-term survival outcomes for subsequent treatment lines when there is a dearth of evidence for long-term outcomes in this target population. None of the studies are directly concerned with IDH mutant gliomas for adults in a UK setting, or specific to progression for patients who were previously not in need of immediate systemic therapy and post-surgery, or reflecting outcomes of specific treatment modalities used in NHS clinical practice. There is also an absence of utility values for subsequent treatment lines of

RT/CT and BSC. The company undertook a vignette study to elicit utility values using both EQ-5D and TTO methods, valued by the UK general public, but the EAG considers vignettes to represent the lowest quality of evidence to inform utility values. The EAG also notes that the EQ-5D and TTO responses resulted in substantially different estimates of utility values, with EQ-5D producing lower utility values for subsequent treatment lines. Furthermore, the EQ-5D utility values from the vignette study produced substantially lower HRQoL compared to the EQ-5D utility values from INDIGO (e.g., a utility value of 0.728 from INDIGO was used for health state S4, off-treatment with PD, while a utility value of 0.480 was derived from the vignette study for health state S5 receiving RT/CT). The EAG considers the utility values for subsequent treatment lines to be highly uncertain and represent an unrealistic drop in utility when moving to RT/CT.

The modelling assumptions with the largest impact on the ICER are those relating to:

- The TTNI | P curve used in the model and its extrapolation over time. The TTNI | P curve affects the duration of time spent off-treatment with PD before moving to 1L RT/CT. The company's base case uses a generalised gamma model to extrapolate KM data for TTNI | P from INDIGO, separated by treatment arm. The use of alternative models of log-normal and exponential to extrapolate the KM data by treatment arm show that both incremental costs and QALYs are highly sensitive to the extrapolation model selected, with the company's base case ICER (with a 3.5% annual discount rate and severity weighting of 1.2) increasing from [redacted] (generalised gamma model) to [redacted] with log-normal model and [redacted] with exponential model.
- The TTNI | P curve separated by treatment arm used in the company's base case analysis. In the absence of evidence to support ongoing effects of vorasidenib post-progression and the issues with the TTNI | P data from INDIGO (post-randomised, confounded by cross-over, high censoring and immature data), the use of a common TTNI | P curve independent of initial intervention received (i.e., vorasidenib delays time to RT/CT by delaying time to progression, without assuming an additional effect associated with TTNI data from INDIGO) shows that the company's base case ICER (with a 3.5% annual discount rate and severity weighting of 1.2) increases substantially, ranging from [redacted] to [redacted] depending on extrapolation model selected.
- The health state utility values for subsequent treatment lines, where the total QALYs are highly sensitive to the utility values for RT/CT and BSC.
- The percentages of RT/CT and off-label bevacizumab used at subsequent treatment lines have a moderate effect on the ICER.

The EAG's preferred assumptions include the following changes to the company's base case: (i) NICE reference case discount rate of 3.5% per annum rather than the non-reference case discount rate

of 1.5% per annum; (ii) use of a common TTNI | P curve for both interventions based on the pooled curve across arms of INDIGO, with log-normal extrapolation, rather than TTNI | P curve separated by treatment arm (generalised gamma extrapolation); (iii) exclude the use of off-label bevacizumab at subsequent treatment lines; (iv) percentages of RT/CT used at subsequent treatment lines changed to proxy NHS practice rather than based on market share data from France; (v) exclude the monitoring costs associated with CT scans; and (vi) use the unadjusted EQ-5D utility values from the vignette study for subsequent treatment lines rather than the adjusted values that do not differentiate outcomes for on- and off-treatment.

7 SEVERITY MODIFIER

7.1 Summary of company submission

The CS presents the results of a QALY shortfall analysis using the R-Shiny tool by Schneider et. al. (2021)[46] for an average patient age of 40 years and proportion of females (44%) based on the baseline characteristics of INDIGO. The total QALYs for people living with the condition on current treatment is informed by the QALYs in the company's (corrected) base case analysis for active observation of 7.74, using a discount rate of 1.5% per annum. The expected total QALYs for the general population is based on the reference case values in Schneider et. al. (2021)[46] for population quality-adjusted life expectancy and discounted at a rate of 1.5% per annum. Table 23 summarises the results of the company's QALY shortfall analysis.

Table 23 Summary of the company's QALY shortfall analysis using a 1.5% annual discount rate

	Company base case			Reference case from QALY shortfall calculator (Schneider et. al. (2021)[46])			
Treatment	Start age	% of females	QALYs on SoC (output from model)	QALYs for general population	Absolute QALY shortfall	Proportional QALY shortfall	NICE severity weighting
Active observation	40	44%	7.74	25.93	18.19	0.70	1.7

Abbreviations: SoC, standard of care; QALYs, quality-adjusted life years.

The company concludes that the absolute QALY shortfall criterion for applying a 1.7 QALY weight is met. Therefore, the company applies a 1.7 QALY weight to the incremental QALYs for vorasidenib relative to active observation in its base case results, reported in Section 5.

7.2 Points for critique

The EAG's primary concern with the company's QALY shortfall analysis is the use of a non-reference case discount rate of 1.5% per annum for QALYs. The EAG notes that the NICE manual specifically states (section 6.2.17 of manual), "Absolute and proportional shortfall calculations should include discounting at the reference-case rate." The NICE reference case discount rate is 3.5% per annum. The EAG considers it appropriate to use consistent discounting for QALYs on standard of care and QALYs in the general population as the difference between these values is used to derive the QALY shortfall. Therefore, the EAG considers it appropriate to use a discount rate of 3.5% per annum in the QALY shortfall analysis to derive both the QALYs for the general population and the QALYs for active observation (current standard of care). The reference case discount rate for the severity calculations also aligns with the EAG's view that the company's justification for the use of a non-reference case discount rate does not meet the NICE methods guide criteria (see Section 4.2.5.2). Table 24 presents the QALY shortfall analysis for the company's base case assumptions using a 3.5% annual discount rate. With a 3.5% annual discount rate, the absolute QALY shortfall criterion for applying a 1.2 QALY weight is met. Therefore, the EAG considers it appropriate to use a severity weight of 1.2 rather than 1.7 in the company's base case analysis.

Table 24 QALY shortfall analysis for the company's base case assumptions using a 3.5% annual discount rate

	Company base case with a 3.5% discount rate			Reference case from QALY shortfall calculator (Schneider *et al.* 2021)			
Treatment	Start age	% of females	QALYs on SoC (output from model)	QALYs for general population	Absolute QALY shortfall	Proportional QALY shortfall	NICE severity weighting
Active observation	40	44%	6.26	18.65	12.39	0.66	1.2

The EAG also notes that when the results of scenario analyses are presented, which result in a change to the QALYs for standard of care, the severity weighting should be updated accordingly to accurately reflect the QALY shortfall based on the set of assumptions used in the specific scenario analysis. This was not done in the company's scenario analyses presented in Table 56 of CS, where a severity weighting of 1.7 was applied to the results of all scenario analyses. In the EAG's scenario analyses in Section 6, the EAG presents the corresponding severity weighting for each scenario.

In Section 6.3, the EAG presents their preferred base case assumptions that differ from the company's base case. Table 25 presents the corresponding QALY shortfall analysis for the EAG's preferred base case with a 3.5% annual discount rate. Under the EAG's preferred base case assumptions, the absolute

QALY shortfall criterion for applying a 1.2 QALY weight is met, which is applied to the EAG's base case.

Table 25 QALY shortfall analysis for the EAG's preferred base case assumptions with a 3.5% annual discount rate

	Company base case with a 3.5% discount rate			Reference case from QALY shortfall calculator (Schneider *et al.* 2021)			
Treatment	**Start age**	**% of females**	**QALYs on SoC (output from model)**	**QALYs for general population**	**Absolute QALY shortfall**	**Proportional QALY shortfall**	**NICE severity weighting**
Active observation	40	44%	5.69	18.65	12.96	0.69	1.2

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APPENDICES

Appendix 1 Systematic literature reviews – cost effectiveness and healthcare costs and resource use

Appendix E of the CS included the company searches to identify: i) economic evaluations of treatments for patients with grade 2 or 3 glioma and ii) healthcare cost and resource use studies in patients with grade 2 or 3 glioma.

The original searches were conducted in April 2023 with a further update search undertaken in May/June 2024.

The EAG found the searches were generally appropriate for identifying studies for both SLRs, with a few minor weaknesses outlined in Table 26

Table 26 EAG appraisal of evidence identification for SLR of cost-effectiveness and SLR of healthcare costs and resource use

Topic	EAG response	Note
Is the report of the search clear and comprehensive?	YES	Some of the search strategies were missing in the company submission but most were provided in the company response to the PFCs. A full search strategy for EconLit was not provided.
Were appropriate sources searched?	YES	Sources of published and unpublished literature were searched. Searching of relevant databases, conference proceedings, HTA agency websites and reference checking of included studies and relevant reviews and meta-analyses was undertaken. NHS Economic Evaluations Database, the HTA database and the INAHTA database were not searched.
Was the timespan of the searches appropriate?	YES	Databases: inception to 20th May 2024 Conference proceedings: 2020 to 3rd June 2024 HTA websites: to 4th June 2024 Supplementary sources: to 5th June 2024
Were appropriate parts of the PICOS included in the search strategies?	YES	**MEDLINE and Embase:** Population: astrocytoma OR oligodendroglioma (with IDH1 or IDH2 mutations) AND Outcomes: cost or resource use OR study design: economic evaluations **Conference proceedings and HTA agency websites:** Population: astrocytoma OR oligodendroglioma (with IDH1 or IDH2 mutations) **Supplementary sources CEA Registry, EconLit and EconPapers:** Population: astrocytoma OR oligodendroglioma (with IDH1 or IDH2 mutations)

		Google Scholar: Population: astrocytoma OR oligodendroglioma (with IDH1 or IDH2 mutations) AND Outcomes: cost or resource use OR study design: economic evaluations
Were appropriate search terms used?	YES	Search terms were generally appropriate. Missing truncation in the Embase.com search strategy – at line #3, tumor and tumour should have been truncated to cover tumors or tumours.
Were any search restrictions applied appropriate?	PARTLY	Conference abstracts were removed from the results from Embase.com.
Were any search filters used validated and referenced?	PARTLY	A bespoke search filter rather than a single previously validated search filter was used to limit retrieval to economic evaluations in MEDLINE and Embase. The bespoke filter was based upon terms from published Scottish Intercollegiate Guidelines Network(SIGN), with additional terms from Canada's Drug Agency (CDA) and NHS Economic Evaluations Database (NHS EED) economic filters. It is unclear how well this bespoke filter would have performed for the retrieval of all relevant economic evaluations and cost and resource use studies, but terms appeared to be comprehensive.

EAG response = YES/NO/PARTLY/UNCLEAR/NOT APPLICABLE

Appendix 2 Systematic literature reviews – HRQoL

Appendix F of the CS included the company searches to identify quality of life and utilities studies in patients with grade 2 or 3 diffuse glioma.

The original searches were conducted in April 2023 with a further update search undertaken in May/June 2024.

The EAG found the searches were generally appropriate for identifying studies for the SLR, with a few minor weaknesses outlined in Table 27

Table 27 EAG appraisal of evidence identification for SLR of HRQoL studies

Topic	EAG response	Note
Is the report of the search clear and comprehensive?	YES	Some of the search strategies were missing in the company submission but most were provided in the company response to the PfCs.
Were appropriate sources searched?	YES	Sources of published and unpublished literature were searched. Searching of relevant databases, conference proceedings, HTA agency websites, Glioma organisational websites, Google Scholar and reference checking of included studies and relevant reviews and meta-analyses was undertaken. NHS Economic Evaluations Database, the HTA database and the INAHTA database were not searched.
Was the timespan of the searches appropriate?	YES	Databases: inception to 20th May 2024 Conference proceedings: 2020 to 3rd June 2024 HTA websites: to 4th June 2024 Supplementary sources: to 4th June 2024
Were appropriate parts of the PICOS included in the search strategies?	YES	**MEDLINE and Embase:** Population: astrocytoma OR oligodendroglioma (with IDH1 or IDH2 mutations) AND Outcomes: Quality of life OR utilities **Conference proceedings, HTA agency websites, Glioma organisational websites:** Population: astrocytoma OR oligodendroglioma (with IDH1 or IDH2 mutations) **Google Scholar:** Population: astrocytoma OR oligodendroglioma (with IDH1 or IDH2 mutations) AND Outcomes: Quality of life OR utilities
Were appropriate search terms used?	YES	Search terms were generally appropriate. Missing truncation in the Embase.com search strategy – at line #3, tumor and tumour should have been truncated to cover tumors or tumours.

Were any search restrictions applied appropriate?	PARTLY	Conference abstracts were removed from the results from Embase.com.
Were any search filters used validated and referenced?	UNCLEAR	The search filter used to restrict retrieval to quality of life or utility studies was reported as the Scottish Intercollegiate Guidelines Network SIGN/ISSG filter. SIGN does not have such a filter on its website and the ISSG website has several quality of life and utility study filters. It is therefore unclear how well this search filter would have performed for the retrieval of all relevant quality of life or utility studies, but terms appeared to be comprehensive.

EAG response = YES/NO/PARTLY/UNCLEAR/NOT APPLICABL

Appendix 3 Cost effectiveness results with 1.5% annual discount rate for costs and health outcomes

Table 28 Cost-effectiveness results of EAG scenario analyses for a discount rate of 1.5% per annum (deterministic analysis)

Scenario #	Description of scenario	Option	Total costs	Total QALYs	Inc. Costs	Inc. QALYs	ICER (/QALY)	Inc. QALYs (x1.0, x1.2* or x1.7** severity weighting)	ICER (x1.0, x1.2* or x1.7** severity weighting)
	Company's base-case results	Active observation	[redacted]	7.74					
	(1.5% annual discount rate)	Vorasidenib	[redacted]	11.16	[redacted]	3.43	[redacted]	5.83**	[redacted]
2a	TTNI | P, separated by treatment arm: Log normal model for both arms	Active observation	[redacted]	6.36					
		Vorasidenib	[redacted]	8.97	[redacted]	2.61	[redacted]	4.43**	[redacted]
2b	TTNI | P, separated by treatment arm: Exponential model for both arms	Active observation	[redacted]	6.22					
		Vorasidenib	[redacted]	8.50	[redacted]	2.28	[redacted]	3.87**	[redacted]
3a	TTNI | P equal for both intervention arms based on pooled curve across arms: Generalized gamma model	Active observation	[redacted]	8.35					
		Vorasidenib	[redacted]	9.92	[redacted]	1.58	[redacted]	1.89*	[redacted]
3b	TTNI | P equal for both intervention arms based on pooled curve across arms: Log-normal model	Active observation	[redacted]	6.58					
		Vorasidenib	[redacted]	8.50	[redacted]	1.92	[redacted]	3.26**	[redacted]
3c	TTNI | P equal for both intervention arms based on pooled curve across arms: Exponential model	Active observation	[redacted]	6.31					
		Vorasidenib	[redacted]	8.26	[redacted]	1.95	[redacted]	3.31**	[redacted]
3d	TTNI | P equal for both intervention arms based on vorasidenib curve: Log normal model	Active observation	[redacted]	7.11					
		Vorasidenib	[redacted]	8.97	[redacted]	1.86	[redacted]	3.17**	[redacted]
4	Exclude the use of bevacizumab at subsequent treatment lines	Active observation	[redacted]	7.74					
		Vorasidenib	[redacted]	11.16	[redacted]	3.43	[redacted]	5.83**	[redacted]
5		Active observation	[redacted]	7.74					

	Proportion of treatments used at subsequent lines 1L: 100% PCV in conjunction with RT. 2L: 100% TMZ, in conjunction with % RT per company assumptions. 3L to 5L: Equal % of PCV, TMZ, CCNU, no RT	Vorasidenib	[redacted]	11.14	[redacted]	3.41	[redacted]	5.79**	[redacted]
6	Exclude CT scans	Active observation	[redacted]	7.74					
		Vorasidenib	[redacted]	11.16	[redacted]	3.43	[redacted]	5.83**	[redacted]
7	Unadjusted health state utility values for subsequent treatment lines	Active observation	[redacted]	7.99					
		Vorasidenib	[redacted]	11.39	[redacted]	3.40	[redacted]	4.08*	[redacted]
8	Health state utility values for subsequent treatment lines based on TTO utility values from vignette study	Active observation	[redacted]	9.22					
		Vorasidenib	[redacted]	12.39	[redacted]	3.17	[redacted]	3.80*	[redacted]

Table 29 Cost-effectiveness results of EAG preferred assumptions for a discount rate of 1.5% per annum (deterministic analysis)

Scenario #	Name	**Option**	**Total costs**	**Total QALYs**	**Inc. Costs**	**Inc. QALYs**	**ICER (/QALY)**	**Inc. QALYs (x1.0, x1.2* or x1.7** severity weighting)**	**ICER (x1.0, x1.2* or x1.7** severity weighting)**
	Company's base-case (1.5% annual discount rate)	Active observation	[redacted]	7.74	[redacted]				
		Vorasidenib	[redacted]	11.16	[redacted]	3.43	[redacted]	5.83**	[redacted]
3b	+ TTNI | P equal for both intervention arms based on pooled curve across arms: Log-normal model	Active observation	[redacted]	6.58					
		Vorasidenib	[redacted]	8.50	[redacted]	1.92	[redacted]	3.26**	[redacted]
3b + 4	+ Exclude the use of bevacizumab at subsequent treatment lines	Active observation	[redacted]	6.58					
		Vorasidenib	[redacted]	8.50	[redacted]	1.92	[redacted]	3.26**	[redacted]
		Active observation	[redacted]	6.58					

3b + 4 + 5	+ Proportion of treatments used at subsequent lines to proxy NHS clinical practice	Vorasidenib	[redacted]	8.48	[redacted]	1.90	[redacted]	3.23**	[redacted]
3b + 4 + 5 + 6	+ Exclude CT scans	Active observation	[redacted]	6.58					
		Vorasidenib	[redacted]	8.48	[redacted]	1.90	[redacted]	3.23**	[redacted]
3b + 4 + 5 + 6 + 7	+ Unadjusted health state utility values for subsequent treatment lines [EAG base case]	Active observation	[redacted]	6.81					
		Vorasidenib	[redacted]	8.72	[redacted]	1.91	[redacted]	3.25**	[redacted]

*Adjusted by applying a 1.2 severity weight
**Adjusted by applying a 1.7 severity weight

Single Technology Appraisal

Vorasidenib for treating astrocytoma or oligodendroglioma with IDH1 or IDH2 mutations after surgery in people 12 years and over [ID6407]

EAG report – factual accuracy check and confidential information check

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on 25 April 2025** using the below comments table.

All factual errors will be highlighted in a report and presented to the appraisal committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and information that is submitted as [redacted] should be highlighted in turquoise and all information submitted as '[redacted]' in pink.

Issue 1 Exclusion of patients that last surgery <1 or >5 years prior to randomization

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On page 15 of the EAR, the following is stated: *"An inclusion criterion in the INDIGO trial was that patients' last surgery had to have been between 1 and 5 years prior to randomization. This approach to*	Please amend to: *"An inclusion criterion in the INDIGO trial was that patients' last surgery had to have been between 1 and 5 years prior to randomization.* ***Per the anticipated marketing***	This requirement of 1 to 5 years after the last surgery was implemented to homogenize the enrolled patient population and allow for an adequate and robust assessment of radiographic disease progression. This window was used to identify patients who had already been	The text on p50 has been amended to make it clear that the EAG considers that there may be a selection effect.

recruitment means that patients with less stable disease may have been filtered out of the trial population." This does not adequately note that patients in immediate need of RT/CT would, by definition, not be eligible for vorasidenib. In addition, on page 50 of the EAR, the following is stated: *"The EAG is primarily concerned that the population of INDIGO is subject to selection effect, where participants with less stable disease (i.e., more likely to progress before randomisation) were excluded from the trial due to the inclusion criterion of surgery ≥1 year but ≤5 years at randomisation."* This is an opinion expressed as a fact. In this specific context, it could reasonably be argued that people with a time since surgery of <1 year have stable disease, but were simply not yet eligible for enrolment in the INDIGO study.	***authorization for vorasidenib, patients are in a period of active observation. Less stable patients with worse outcomes will be excluded by the label criterion 'not in immediate need of RT/CT'****."* And: *"The EAG is primarily concerned that the population of INDIGO* ***may be*** *subject to selection effect, where participants with* ***potentially*** *less stable disease (i.e., more likely to progress before randomisation) were excluded from the trial due to the inclusion criterion of surgery ≥1 year but ≤5 years at randomisation.* ***However, as per the anticipated marketing authorization for vorasidenib, patients are in a period of active observation. Less stable patients with worse outcomes will be excluded by the label criterion 'not in immediate need of RT/CT'****"*	under active surveillance for at least 1 year and were suitable candidates for a placebo-controlled study. It is not used in routine clinical practice to determine treatment eligibility. For example, EANO and NCCN criteria for defining the risk of progression are applied immediately after surgical intervention to identify patients for whom the benefits of initiating RT and CT immediately do not outweigh the risks. Patients anticipated in the marketing authorization are in a period of active observation. Less stable patients with worse outcomes will be excluded by the label criteria 'not in immediate need of RT/CT. The Company considers it most appropriate that there is a clear distinction between facts and opinions, and that this important context concerning need for RT/CT is provided.	

Issue 2 Evidence for patients not moving directly to subsequent treatment upon progression

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On page 65 of the EAR, the following is stated: *"The company was unable to provide clinical evidence to support the assumption that patients in NHS practice would*	Please amend to: *"The company noted that the assumption that patients in NHS practice would not move directly to a subsequent treatment upon evidence of*	An advisory board was held by Servier on 24th March and the report sent to the EAG on 27th March. At this all advisors agreed that progression on imaging wouldn't necessarily lead to the next intervention. If there has been tumour shrinkage previously or if the tumour has been classed as slow growing, even though it is progressing, this wouldn't	Text revised as suggested by the company.

not move directly to a subsequent treatment upon evidence of radiographic progression of disease but noted that the decision is complicated by many factors, including risk of neurocognitive decline associated with RT/CT, impact on a person's daily activities, and desire to start a family." This statement does not align with the expert opinion provided via the advisory board report shared as part of the submission.	*radiographic progression of disease is complicated by many factors, including risk of neurocognitive decline associated with RT/CT, impact on a person's daily activities, and desire to start a family."*	automatically trigger the next intervention. These patients are more likely to enter a period of active surveillance, especially if they have been on vorasidenib previously and the tumour has shrunk since treatment initiation. It was highlighted that radiotherapy and chemotherapy is a big step in this patients journey, and there is rarely an imperative to rush due to the acute and long term toxicities All advisors agreed that if enhancement is appearing or you have worries about transformation this would be different but not if we are talking small degrees of change. Advisors stated that if a patient were to progress on vorasidenib, if there was no enhancement, then effectively that patient goes back to the S2 state of active surveillance.	

Issue 3 Data for tumour size at time of progression

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On pages 20, 64,91 of the EAR, the following is stated: *"The company have not shown data that tumour size is*	Please remove this statement as company has now provided this data	Several post-hoc analyses of INDIGO indicate that patients who progress while receiving vorasidenib do so with more favorable features that allow for longer TTNI|P period, potentially allowing these patients to remain on active observation before further tumor growth or progression warrants initiation of a subsequent treatment. • [redacted] The change in log tumor volume from baseline to BIRC progression is [redacted] for patients treated with vorasidenib vs. placebo (Mean (95% CI): [redacted], Table 1). • Further, Figure 1 highlights that almost half of patients who received vorasidenib have a smaller tumor volume at progression than baseline.	This is not a factual inaccuracy. The company submission does not report this data. The data provided here does not show that tumour size is smaller at the time of progression than at baseline for vorasidenib. However, we have deleted a statement in the EAR

smaller at the time of progression than at baseline for vorasidenib," This data has now been provided.		*Table 1: Summary of Log Tumor Volume vs Baseline at PD per BIRC (Full Analysis Set)* |	Vorasidenib	Placebo
---	---	---
N	[redacted]	[redacted]
Mean Log Tumor Volume (Baseline)	[redacted]	[redacted]
Mean Log Tumor Volume (PD)	[redacted]	[redacted]
Mean Change (PD - BL) (95% CI)	[redacted]	[redacted]
Difference in Mean Change (95% CI)	[redacted]	
P-Value (vs Placebo)	[redacted]	| *Note: Mean change (PD – Baseline) is calculated at the individual subject level. Difference in Mean Change represents the difference in average change between Vorasidenib and Placebo. P-value is calculated from Wilcoxon test at 2-sided alpha level of 0.05.* *Figure 1: Box Plot of Change in Log Tumor Volume (PD per BIRC - Baseline) (Full Analysis Set)*	(p67) in relation to tumour growth from baseline to reflect this new data (i.e., deleted the statement "The company have not presented any evidence from INDIGO to show that tumour growth at the point of progression differs significantly between treatment arms").

		 Thus, as vorasidenib leads to more favourable tumour features at progression through tumour shrinkage and patients having smaller tumour burden at the time of progression than they did at baseline, it is reasonable to expect that subsequent treatment decisions could be delayed, as the reduced tumour size may allow people to remain clinically stable for longer. As a result, when progression eventually occurs, the tumour burden may remain relatively low, and progression may be sufficiently slow that it does not immediately trigger the need for NI. For example, in cases where only a small residual tumour remains following vorasidenib, subsequent progression may not reach a threshold for active treatment for an extended period. This rationale is supported by Bhatia et al., (2023), who demonstrated a clear relationship between tumour growth and risk of next intervention or death: for each 10% increase in MRI-based tumour volume, there was only a 5% increase in the risk of initiation of NI or death (95% CI: 3%–7%). This indicates that relatively modest increases in tumour size do not always prompt immediate further treatment, especially in the context of a previously reduced tumour burden.	

		Taken together, these considerations support the assumption that a higher proportion of patients treated with vorasidenib would remain untreated post-progression (i.e., reside in S4) compared to those under active observation, reflecting both the impact of tumour shrinkage and the natural variability in clinical management of slowly progressing disease.	

Issue 4 Data for surrogacy relationship

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On pages 18, 49, 61 of the EAR, the following is stated: However, the company have not presented evidence to support the validity of a surrogacy relationship between delaying PFS/TTP and TTNI | P and OS benefit for vorasidenib in the target population.	Please remove as the company has now provided this data	Although formal statistical validation of PFS or TTNI as consensually recognized surrogate endpoints for OS is currently lacking in mIDH gliomas, accumulating clinical evidence supports their relevance as markers of long-term prognosis and disease trajectory: Focusing exclusively on mIDH gliomas, Miller et al. (2019) provided valuable insights into the natural history and long-term progression dynamics of these tumors. The study included a large sample of 275 patients, evenly distributed between grade II (48.7%) and grade III (51.3%) gliomas as per the 2016 WHO classification. The primary objective was to characterize how tumor behavior evolves across successive recurrences, and to assess the implications of these changes on long-term outcomes such as overall survival (OS). In particular, the study aimed to quantify whether progression events (notably the first and second recurrences) are associated with acceleration in disease course. The study highlighted the marked shortening of progression-free survival (PFS) following initial recurrence: the median PFS from diagnosis to first progression (PFS1) was 5.7 years, while the interval from first to second progression (PFS2) decreased significantly to 3.1 years. Importantly, this shift in progression dynamics was paralleled by a substantial decline in OS. While the median OS from diagnosis was 18.7 years in the overall cohort, it dropped markedly to 8.3 years following first progression. This study reports that time to progression accelerates over time in IDH mutant glioma patients through acquisition of additional, tertiary genetic	This is not a factual inaccuracy. The statement is taken out of context of the previous sentence where the EAG is highlighting that the company have not presented evidence to show that the relative effect of vorasidenib on PFS/TTP and time to next intervention given progression (TTNI | P) is predictive of its relative effect on OS in the target population. We have revised the text to provide additional clarity that we are referring to relative effects in the target population.

		events, activating oncogenic pathways and emphasize that PFS can serve as a strong predictor of OS. This highlights the strong temporal and clinical correlation between delayed progression and improved survival, reinforcing the potential of PFS as a meaningful and valid surrogate endpoint for OS in patients with IDH-mutant gliomas. 1 Miller JJ, Loebel F, Cahill DP et al. Accelerated progression of IDH mutant glioma after first recurrence. Neuro Oncol. 2019 May 6;21(5):669-677. doi: 10.1093/neuonc/noz016.	

Issue 5 Datacuts from INDIGO study

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On pages 16 and 38 of the EAR the following is stated: *"The median follow-up of patients in INDIGO was only around 14 months."* This statement refers to the September 2022 data cut. Data were provided for the March 2023 data cut, comprising of an additional ~6 months of follow-up.	Please amend to: *"The median follow-up of patients in INDIGO was only around 14 months. However, a further data cut was provided with a further 6 month analysis."*	The March 2023 data cut was provided, as is used to inform the economic model. This added text clarifies the data available for this appraisal.	The EAG's text reflected what was reported in the submission and the EAG is unclear as to why the median follow up wasn't provided for the March 2023 data cut. Nevertheless, we have updated the text as suggested.

Issue 6 Description of TTNI | P outcome

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On page 38 of the EAR, the following is stated: *"The time to next intervention (TTNI) outcome, conditional on progression TTNI | P), was used in the cost-effectiveness modelling to represent time to receive RT/CT (which was not evaluated as an outcome in INDIGO)."* This is potentially misleading. TTNI is an outcome in INDIGO, but TTNI|P was not a pre-specified analysis (though is possible to evaluate).	Please amend to: *"The time to next intervention (TTNI) outcome, conditional on progression TTNI | P), was used in the cost-effectiveness modelling to represent time to receive RT/CT. This specific outcome (TTNI|P) was not a pre-specified analysis for the INDIGO study."*	The revised text more accurately describes the analysis performed using the INDIGO study data.	This is a misunderstanding. We have amended the text to make it clear that we mean that time to receive RT/CT was not evaluated as an outcome in INDIGO.

Issue 7 Decision for use of next intervention

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On page 38 of the EAR, the following is stated: *"This is because the clinical decision to treat placebo patients with vorasidenib (thus generating a 'next intervention' event) in INDIGO, in which patients have already been unblinded, is easier than the decision to commence RT/CT in progressed, unblinded patients in the vorasidenib arm, based on the perceived risks of administering these interventions (it should be noted that patients in the vorasidenib arm cannot continue to receive it following progression)."* This is an opinion expressed as a fact.	Please amend to: *"This is because the clinical decision to treat placebo patients with vorasidenib (thus generating a 'next intervention' event) in INDIGO, in which patients have already been unblinded, is,* ***in the opinion of the EAG,*** *easier than the decision to commence RT/CT in progressed, unblinded patients in the vorasidenib arm, based on the perceived risks of administering these interventions (it should be noted that patients in the vorasidenib arm cannot continue to receive it following progression)."*	It is most appropriate to ensure that there is a clear distinction between facts and opinions.	The relevant text has been amended to "….seems likely to be easier…..".

Issue 8 Incorporation of high-grade glioma in the economic model

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On page 49 of the EAR, the following is stated: *"The EAG is concerned that the company's model is not explicitly considering progression to high-grade disease and malignant transformation, which are key in the context of prognosis, HRQoL and survival."* This is not accurate. Within the base-case analysis, some patients are assumed to progress to HGG – this is described in Section 3.3.2: *"… To account for this, 23.6% of patients were assumed to enter S5 with HGG (based on a study by Hervey Jumper et al., [2023]83), and a median survival estimate of 3.1 years (based on a study*	Please amend to: *"The EAG is concerned that the company's model does not explicitly model progression to health states based on high-grade disease and/or malignant transformation, which are key in the context of prognosis, HRQoL and survival."*	This revised text more accurately describes the approach taken to account for HGG in the model. It is correct that the model does not consider health states related to HGG or malignant transformation. However, it is incorrect to state that the model does not consider progressions to HGG at all. This was explicitly considered as part of the transitions from the S5 health state.	Text revised as suggested by the company.

by Juratli et al., [2012]) to further re-weight the hazard of a progression event after initiation of NI."			

Location of incorrect marking	**Description of incorrect marking**	**Amended marking**
Give full details of inaccurate marking - document title and page number	Give details of incorrect confidential marking	Please copy the impacted section here, with your amended marking.

(Please add further lines to the table as necessary)

Single Technology Appraisal (STA)

Vorasidenib for treating astrocytoma or oligodendroglioma with IDH1 or IDH2 mutations after surgery in people 12 years and over [ID6407]

EAG addendum: review of company's additional evidence and analyses at Factual Accuracy Check (FAC)

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Declared competing interests of the authors

None.

Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

Note on the text

All commercial-in-confidence (CON) data have been highlighted in blue and underlined.

Table of Contents

1 OVERVIEW

This addendum to the External Assessment Report (EAR) report presents the External Assessment Group's (EAG) critique of the additional evidence and analyses provided by the company at Factual Accuracy Check (FAC) and submitted in a more detailed format on the 8th of May 2025.

The company presents two pieces of evidence:

1. New post-hoc analyses on tumour growth and volume at time of progression from INDIGO.
2. Additional literature regarding progression-free survival (PFS) surrogacy for overall survival (OS).

In Section 2, the EAG provides an overview of the evidence presented by the company in response to concerns raised in the EAR and the EAG provides a critique of the new information to address these concerns.

The EAG's position on the key issues outlined in the EAR remain unchanged.

2 DESCRIPTION AND CRITIQUE OF ADDITIONAL EVIDENCE

2.1 Tumour growth and volume at time of progression from INDIGO

The company submitted new post-hoc analyses on tumour growth and volume at time of progression from INDIGO in response to the following points made in the EAR:

- The time to next intervention given progression (TTNI | P) curve affects the duration of time spent off-treatment with progressive disease (PD) before moving to first line radiotherapy or chemotherapy (1L RT/CT) - Issue 7 of EAR.
- The EAG suggests using a common TTNI | P curve for both vorasidenib and active observation instead of separate curves by treatment arm - Issue 7 of EAR.
- No evidence supports managing patients differently post-progression based on initial intervention - Issue 7 of EAR.
- The follow-up for some vorasidenib patients may have ended before the next intervention could be given - Issues 3 and 6 of EAR.
- The company has not presented evidence to support the claim that vorasidenib treatment in the INDIGO study leads to tumour shrinkage, potentially resulting in smaller tumours at progression than at baseline, and the company has not demonstrated that tumour size is smaller at progression for vorasidenib - Issue 7 of EAR.

The new post-hoc analyses include:

- A box plot showing on-treatment tumour growth for participants in INDIGO by treatment arm for PD compared to non-PD (based on March 2023 data cut) – Figure 1 of the company's document named 'New analysis'.[1] The company highlights that this data shows that despite patients in the PD group exhibiting higher individual tumour growth compared to those in the non-PD group, patients who received vorasidenib show significantly lower individual tumour growth compared to placebo, including among patients with progressed disease ($p \leq 0.001$), which the company indicates supports the interpretation of a slower and more indolent progression with vorasidenib relative to placebo.
- A summary table showing the mean change in log tumour volume from baseline to PD for participants in INDIGO by treatment arm - Table 1 of company's document named 'New analysis'.[1] The company highlights that the mean change in log tumour volume from baseline to PD is substantially lower for patients treated with vorasidenib compared to placebo.
- A box plot showing the change in log tumour volume from baseline to PD for participants in INDIGO by treatment arm – Figure 2 of company's document named 'New analysis'.[1] The

company highlights that almost half of patients who received vorasidenib have a smaller tumour volume at progression than at baseline.

Taken together, the company considers this evidence sufficient to indicate that patients who progress while receiving vorasidenib do so with more favorable features that allow for a longer TTNI | P period compared to active observation, i.e., vorasidenib patients can remain on active observation following progression before initiation of a subsequent treatment for a much longer period than patients who progress on active observation.

The EAG's response

The new post-hoc analyses provides useful information on tumour growth for PD vs. non-PD and mean change in log tumour volume from baseline by treatment arm from INDIGO, which was not reported in the company's original submission. The individual on-treatment tumour growth, which is defined as the tumour volume (mL) change in individuals per every 6 months, clearly shows that PD exhibits higher individual tumour growth compared to non-PD, and a statistically significant difference in individual tumour growth for PD is observed between the vorasidenib and placebo arms of INDIGO (Figure 1 box plot[1]). The EAG agrees with the company that this information provides evidence of slower tumour growth in the vorasidenib arm relative to the placebo arm of INDIGO, which is also supported by a statistically significant difference in mean change in log tumour volume at PD from baseline for vorasidenib relative to placebo (Table 1 and Figure 2 box plot[1]). However, the EAG does not consider this evidence alone to be sufficient to address the EAG's concerns highlighted above. In particular, the evidence is insufficient to support a significantly longer TTNI | P period for vorasidenib compared to active observation for the following reasons:

- There is a direct correlation between tumour growth rate (TGR) and progression-free survival (PFS). The statistically significant reduction in PFS for vorasidenib compared to placebo included in the model is likely to already reflect the benefits of vorasidenib vs. active observation on tumour size and volume (i.e., the difference in mean log tumour volume at PD from baseline in Table 1 and Figure 2 box plot[1] is associated with fewer progression events in the vorasidenib arm compared to placebo arm that is included in the model). Therefore, further accounting for tumour shrinkage from baseline to PD is likely to risk double counting the benefits of vorasidenib.
- The mean log tumour volume at progression is almost the same for vorasidenib (9.24 mL) and placebo (9.25 mL) (Table 1[1]) and the EAG noted in the EAR that the health-related quality of life utility values from INDIGO indicates that patients with PD had better quality of life in the placebo arm (mean utility of 0.730) than the vorasidenib arm (mean utility of 0.678) (Section 4.2.8.1 of EAR). Therefore, it is not known whether patients would be managed differently at the point of progression and how the disease will behave after progression based on initial

intervention received. For example, the outcomes observed with vorasidenib in the INDIGO trial do not support a difference in the rates of malignant transformation (MT) for vorasidenib compared to placebo and showed a slightly higher incidence in the vorasidenib arm. Thus, it remains unknown how changes in tumour volume ultimately impact the downstream effects on progression.

- The EAG's key concern with over-interpreting the PD data from INDIGO and the outcome of TTNI | P, is the fact that it is confounded by cross-over in the placebo arm of INDIGO (42.9% of participants who had tumour progression crossed-over to vorasidenib, while only 4.9% received other subsequent anticancer therapies). This makes the difference between vorasidenib and placebo arms for PD in Figure 1 box plot[1] difficult to interpret. It also means that vorasidenib was administered to 90% of participants receiving next intervention in the placebo arm, which raises several issues for comparative efficacy for the outcome of TTNI | P used in the model, especially as this outcome for the placebo arm is not informing the time to 1L RT/CT, as required for the model, but instead informing the time to any subsequent therapy (predominantly vorasidenib for the placebo arm of INDIGO). Participants in the placebo arm are likely to have moved to the next intervention quicker because they had access to a novel treatment that would otherwise not be available outside of the trial setting.
- The vorasidenib TTNI | P curve is also not without issues. The numbers of patients at risk informing the Kaplan Meier estimates for TTNI | P is extremely low, with less than 11 patients informing this outcome at 12 months and one patient at 18 months (see Figure 19 of company submission). This is because the timing of progression differs between the arms of INDIGO, with later progressors on the vorasidenib arm versus early progressors on the placebo arm resulting in TTNI events more often censored in the vorasidenib arm as many patients' follow-up ended shortly after progression, which provides less time to capture TTNI events in the vorasidenib arm compared to the placebo arm. Therefore, the EAG holds the view that the follow-up for some vorasidenib patients may have ended before the next intervention could be given.
- Importantly, the EAG considers that any difference in tumour growth presented in the Figure 1 box plot[1] cannot equate to the substantial differences in life years between vorasidenib and active observation assumed in the model. The company's base case model predicts that approximately 21% of patients with PD remain untreated at 20 years following vorasidenib, while approximately 9% remain off-treatment at 20 years for active observation post-progression. While the EAG considers it plausible that a small subset of patients with PD but indolent, non-enhancing tumours, may not require immediate further treatment of 1L RT/CT, the EAG does not consider it reasonable to assume that such large proportions of patients would remain untreated over time. The EAG considers the model predictions to lack face

validity because the company's base case suggests that patients remain longer in a PD state off-treatment than in a progression-free (PF) state (undiscounted life years in the PD state off-treatment are 8.58 years compared to 5.22 years in the PF state for vorasidenib, while the life years for active observation are over three times as much in the PD than PF state).

The EAG suggests using a common TTNI | P curve for both vorasidenib and active observation instead of separate curves by treatment arm because it is unlikely that the modelled TTNI | P curves accurately reflect the time to 1L RT/CT in either of the intervention arms. In the absence of additional evidence for vorasidenib and the issues with the TTNI | P data from INDIGO (post-randomised data, confounded by cross-over, high censoring and immature data), the use of a common TTNI | P curve for both arms means that the relative effect of vorasidenib over active observation is modelled by delaying time to progression (and therefore time to 1L RT/CT), without assuming an additional effect associated with TTNI data from INDIGO. For the common TTNI | P curve, the EAG explores the implications of using the pooled data across arms of INDIGO, fitted with alternative extrapolation models, or a common TTNI | P curve based on data from the vorasidenib arm (not subject to cross-over but small sample), to assess the impact on the cost-effectiveness of vorasidenib relative to active observation.

In summary, with the additional post-hoc analyses on tumour growth and volume at the time of progression, the EAG's position on key issue 7 outlined in the EAR remains unchanged.

2.2 Additional literature regarding PFS surrogacy for OS

The company provided additional literature in the form of a paper by Miller *et al.* (2019)[2], which the company states provides valuable insight into the natural history and long-term progression of IDH mutant glioma and supports PFS as a meaningful and valid surrogate endpoint for OS in this population. This is in response to Issue 5 of the EAR on the surrogacy relationship for OS benefit.

The study by Miller *et al.* (2019)[2] is a retrospective analysis of 275 patients with IDH-mutant glioma (48.7% grade 2 and 51.3% grade 3) who were treated at a US institution between 1991 and 2017. The study examined PFS and OS from initial diagnosis to first progression, and then from first progression to second progression. The company highlights the following findings from the study[3]:

- The marked shortening of PFS into a more aggressive disease state following initial recurrence, where the median PFS from diagnosis to first progression (PFS1) was 5.7 years, while the interval from first to second progression (PFS2) decreased significantly to 3.1 years.
- The shift in progression dynamics was paralleled by a substantial decline in OS. While the median OS from diagnosis was 18.7 years in the overall cohort, it dropped markedly to 8.3 years following first progression (OS2). The company states that this nearly 10-year reduction

in expected survival following the first recurrence underscores that progression represents a clinically inflectional point in the disease course and highlights the prognostic significance of disease progression on long-term survival.

The company concludes that the findings of Miller *et al.* (2019)[2] demonstrate a strong temporal and clinical correlation between delayed progression and improved survival, thereby reinforcing the potential of PFS as a meaningful and valid surrogate endpoint for OS in patients with IDH-mutant gliomas.

The EAG's response

The paper by Miller *et al.* (2019)[2] demonstrates that PFS2 is a surrogate prognostic marker for identifying patients with poorer OS in a population that includes 51.3% grade 3 glioma compared to the target population of LGG for vorasidenib. The EAG's concern in Issue 5 of the EAR is whether the relative effect of vorasidenib (vs. active observation) on time to progression (TTP) and time to next intervention given progression (TTNI | P) from INDIGO is predictive of its relative effect on OS. The use of a surrogacy relationship to infer OS may be valid provided there is good evidence that the relative effect of the intervention on the surrogate end point is predictive of its relative effect on the final outcome (NICE Methods Manual, 2022[4]). The company's modelling approach assumes that the hazard ratios seen for PFS/TTP and TTNI | P from INDIGO will eventually lead to OS benefits through progression on later treatments. In the absence of OS data from INDIGO, the EAG considers it difficult to judge the validity of the company's implied OS hazard ratio of 0.69 for vorasidenib relative to active observation in their base case analysis.

The paper by Miller *et al.* (2019)[2] shows that PFS2 serves as a potentially valid surrogate endpoint for OS in patients with IDH-mutant gliomas (grade 2 and 3), but it does not formally model the effect of a change in PFS on the change in OS, with adjustment for patient characteristics such as grade, treatments received, and glioma type. In Miller *et al.* (2019), 33% of patients received no adjuvant therapy within 6 months, while the remaining patients received adjuvant treatment with RT alone (13%), combination of CT and RT (39%), or CT alone (11%). Although the study found a statistically significant difference in PFS based on treatment received (patients receiving any adjuvant radiotherapy RT had a median PFS of 7.6 years compared to 4.0 years for those who did not), the study does not report how this difference in PFS between treatments translates to an effect on OS. Notably, in this study, disease progression in any patient (using RANO criteria to determine progression events) led to the initiation of a salvage treatment, whereas in INDIGO a large percentage of participants did not receive a subsequent treatment despite disease progression (assessed using modified RANO-LGG), which limits the applicability of the study results to the INDIGO trial data.

The EAG is broadly in agreement with the company that PFS is likely to represent a valid surrogate endpoint for OS in patients with IDH-mutant gliomas, but the concerns raised in the EAR relate to the magnitude of the relative effects on OS. As noted above in relation to Issue 7 of the EAR, the EAG is particularly concerned about the use of TTNI | P as a surrogate for OS as this outcome is confounded by cross-over in the placebo arm. Furthermore, the company have not provided evidence to show that vorasidenib reduces the transformation to malignant gliomas, which is part of the natural progression of grade 2 gliomas and associated with increased mortality risk over an extended time horizon.

In summary, the absence of OS data from INDIGO makes it challenging to judge the validity of the company's implied OS hazard ratio of 0.69 for vorasidenib versus active observation in their base case analysis. Furthermore, even with more mature OS data from INDIGO over a long period of follow-up, the survival data will be difficult to interpret given the large percentage of patients in the placebo arm that crossed over to vorasidenib treatment upon progression. In addition, the extent to which a heterogeneous set of subsequent therapies impact on mortality will make interpretation of OS from INDIGO challenging.

3 REFERENCES

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Single Technology Appraisal (STA)

Vorasidenib for treating astrocytoma or oligodendroglioma with IDH1 or IDH2 mutations after surgery in people 12 years and over [ID6407]

EAG addendum: review of company's additional evidence prior to ACM1

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None.

Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

Note on the text

All commercial-in-confidence (CON) data have been [redacted]. Academic-in-confidence data have been [redacted] to coincide with the marking used in the company's response.

1 OVERVIEW AND CRITIQUE OF ADDITIONAL EVIDENCE

1.1 Overview and summary of company's additional evidence

This addendum to the External Assessment Report (EAR) report presents the External Assessment Group's (EAG) review of the additional evidence provided by the company in August 2025, prior to the first Appraisal Committee Meeting (ACM1).

The company provides evidence to support the ongoing effects of vorasidenib post-progression to address EAG key issue 7 of the EAR:

- No empirical evidence supports managing patients differently **post-progression** based on initial intervention received (vorasidenib or active observation), i.e., no evidence has been provided to support a significantly longer time to next intervention given progression (TTNI | P) for vorasidenib compared to active observation.

The new evidence provided by the company to support the ongoing effects of vorasidenib post-progression includes information from:

- A perioperative study that demonstrates that vorasidenib has an impact on tumour biology via 2HG suppression, and the genomic alterations seen in the study reflect the genomic changes seen in glioma progression. The company concludes that patients who have received vorasidenib are at a different place molecularly when they progress than those who have not had IDH mutation inhibition.
- [redacted]
- Outputs of TTNI|P (progression per BIRC) for vorasidenib arm of INDIGO segmented by tumour volume change from baseline (decrease, stable or in crease in tumour volume for threshold cut-offs of 25%, 10% and 0%) – presented in separate company files.
- Experimental analysis of a [redacted].

The company concludes that [redacted]

[redacted]

and that the results from INDIGO on tumour volume variation show that growing tumours have shorter TTNI|P than stable and shrinking tumours.

1.2 Critique of company's additional evidence

The additional evidence provided by the company provides useful information on the impact of vorasidenib on tumour biology and suggests that those with IDH mutation inhibition may be at a different place molecularly when they progress than those who have not had IDH mutation. However, the company has not provided new data that links this molecular change directly to improved patient outcomes. Specifically, it is not known if patients who progress on vorasidenib can remain on active observation for a significantly longer period before needing a subsequent treatment compared to patients who progress while on active observation. Therefore, while vorasidenib's effect on tumour biology may be clearer, its benefit to patients in terms of delaying subsequent treatments following progression on vorasidenib remains unknown.

In relation to the company's evidence on TGRs from INDIGO and changes in tumour volume variation, the EAG agrees with the company that this information provides evidence of slower tumour growth in the vorasidenib arm relative to the placebo arm of INDIGO, which is also supported by a statistically significant difference in tumour volume from baseline for vorasidenib relative to placebo. The variation in tumour volume change from baseline (decrease, stable or increase in tumour volume for threshold cut-offs of 25%, 10% and 0%) appears to confirm that a decrease in tumour volume leads to an improved survival probability of not requiring a next intervention. However, the EAG does not consider this evidence alone to be sufficient to address the EAG's primary concern highlighted above. As noted previously by the EAG in response to Factual Accuracy Check (FAC), there is a direct correlation between TGR and progression-free survival (PFS). The statistically significant reduction in PFS for vorasidenib compared to placebo included in the model is likely to already reflect the benefits of vorasidenib vs. active observation on tumour size and volume (i.e., the difference in tumour volume from baseline is likely to be associated with fewer progression events in the vorasidenib arm compared to placebo arm that is included in the model). Therefore, further accounting for tumour shrinkage from baseline is likely to risk double counting the benefits of vorasidenib.

Of the patients that progressed in the analysis of tumour volume change in the vorasidenib arm of INDIGO, the evidence does suggest that a decrease in tumour volume leads to longer time to next intervention. However, the data must be interpreted with caution because the numbers at risk are very small (less than 10 participants at risk with a decrease in tumour volume of greater than 25% and only

14 participants at risk with a decrease in tumour volume of greater than 10%). The fact that the numbers at risk of having a decrease in tumour volume from baseline in the vorasidenib arm are small may suggest that the effect on tumour volume is not as significant as suggested. The company have not provided the corresponding Kaplan-Meier curves of tumour volume change for the same thresholds in the placebo arm of INDIGO. Importantly, however, the outcome of change in tumour volume is not considered in the company's model and, therefore, this data can only be assessed qualitatively because the model is not structured on the link between changes in tumour volume and long-term progression outcomes.

The EAG noted in the EAR that the health-related quality of life utility values from INDIGO indicates that patients with progressive disease had better quality of life in the placebo arm (mean utility of 0.730) than the vorasidenib arm (mean utility of 0.678) (Section 4.2.8.1 of EAR. Therefore, it is not known whether patients would be managed differently at the point of progression and how the disease will behave after progression based on initial intervention received. Despite the changes in tumour volume, the outcomes observed with vorasidenib in the INDIGO trial do not support a difference in the rates of malignant transformation (MT) for vorasidenib compared to placebo and showed a slightly higher incidence in the vorasidenib arm. Thus, it remains unknown how changes in tumour volume ultimately impact the downstream effects on progression. The EAG's also cautions with over-interpreting the longer-term data from INDIGO because it is confounded by cross-over in the placebo arm of INDIGO (42.9% of participants who had tumour progression crossed-over to vorasidenib, while only 4.9% received other subsequent anticancer therapies).

While the EAG considers it plausible that a small subset of patients with progressive disease but indolent, non-enhancing tumours, may not require immediate further subsequent treatment following progression on vorasidenib, the EAG does not consider the company's base case reasonable to assume that such large proportions of patients would remain untreated over time following progression; the company's base case model predicts that approximately 21% of patients with progressive disease remain untreated at 20 years after initial treatment with vorasidenib, while approximately 9% remain off-treatment at 20 years for active observation post-progression. Furthermore, the EAG considers the model predictions to lack face validity because the company's base case suggests that patients remain longer in a progressive disease state off-treatment than in a progression-free (PF) state for vorasidenib.

In summary, with the additional evidence on tumour biology and volume, the EAG's position on key issue 7 of the EAR remains unchanged.

Committee Overview

Explanation

This page details the Managed Access Team's overall assessment on whether a medicine could be suitable for Managed Access and if data collection is feasible. The feasibility assessment does not provide any guidance on whether a medicine is a cost-effective, or plausibly cost-effective, use of NHS resources. This document should be read alongside other key documents, particularly the company's evidence submission and External Assessment Group (EAG) Report. Further detail for each consideration is available within the separate tabs.

The feasibility assessment indicates whether the Managed Access Team have scheduled to update this document, primarily based on whether it is undertaking actions to explore outstanding issues. There may be other circumstance when an update is required, for example when the expected key uncertainties change or a managed access proposal is substantially amended. In these cases an updated feasibility assessment should be requested from the Managed Access Team.

Topic name: **Vorasidenib for treating astrocytoma or oligodendroglioma with IDH1 or IDH2 mutations after surgery in people 12 years and over**
Topic ID: **ID6407**
Managed Access Lead: **Sarika Paul**
Date of assessment(s): **27/05/2025**

Feasibility of successful managed access	Comments / Rationale	
Committee judgement required	Rationale for rating	A managed access proposal has been submitted, and there may be value in further data collection to help resolve some uncertainties identified by the EAG. However there are limitations with that data that is available, primarily the unblinding of the trial, and cross over of participants, and the usefulness of SACT to answer the questions in the timeframe of a managed access agreement.
	Previous ratings and rationale for change	23/05/2025 - Following a meeting with the company on 20/05/2025, in which the feasibility of SACT/RTDS data collection was discussed with the company, an updated managed access proposal was submitted, and the ratings of some uncertainties were updated to reflect the company's agreement that SACT/RTDS data colection would be useful during a period of managed access. This changed the uncertainties and RWE ratings from medium, to high.

Managed Access Proposal	Yes	
Managed Access Team input at Committee meeting	High	As a proposal has been submitted NICE managed access colleagues will be at the committee meeting, and information will be presented.

Area	Rating	Comments / Rationale
Is the technology considered a potential candidate for managed access?	Yes	As a cancer drug, this technology is eligible for reimbursement through the CDF, and a proposal has been made to enable this.
Are there outstanding uncertainties that could be resolved with further data collection?	High	There is an ongoing trial which the company have proposed could provide additional data following a period in managed access. While this trial may help resolve some uncertainties, the populations have been unblinded, so a committee will need to decide whether or not this data is sufficient to help resolve decision making on exit. The company also suggest using SACT, RTDS and Blueteq to help resolve uncertainties where appropriate. The managed access team at NICE also believe there is value in collecting SACT and RTDS data to help resolve uncertainties related to time to next intervention and the time spent off treatment following progression, prior to next intervention.
Can data collection from ongoing clinical trials and RWE sources resolve relevant uncertainties?	Unclear	There is both an ongoing trial, and the technology would allow for SACT/RTDS data to be collected. There is a possibility that both of these data sources may help with resolving some of the uncertainties identified by the EAG, however there are also limitations for both of them. While the ongoing trial may help resolve some uncertainties, the populations have been unblinded, so a committee will need to decide whether or not this data is sufficient to help resolve decision making on exit. And SACT/RTDS data, may have limited usefullness in the 5 year time period of a managed access agreement, though it could help with providing useful information about the technology use within an NHS context.
Are there any other points to note that suggest RWE data collection may be beneficial or challenging in resolving uncertainties?	High	The company submitted an updated managed access proposal stating that SACT, RTDS and Blueteq data could be collected to help resolve uncertainties where appropriate. While committee discussion will be needed to ensure the timeframe of data collection is appropriate to help decision making, the managed access team think that this data could provide useful information follwoing a period of managed access.
Are there any other substantive issues (excluding price) that are a barrier to a MAA?	Yes - Minor	In order to obtain useful RWE it will be necessary to link the SACT and RTDS datasets as radiotherapy is a key 1L intervention in this population.

Key questions for committee if Managed Access is considered	
1	Would data on surgery pre-intervention aid in decision making at managed access exit?

2	Would commmittee like to collect data on surgery and/or radiotherapy post-treatment through SACT?
3	Is the interval between stopping vorasidenib and starting next treatment a suitable proxy for time off treatment?
4	Do committee believe there is enough time to collect data on subsequent treatments considering the length of time people are likely to stay on vorasidenib for?
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Highlighted uncertainties, other issues or ongoing Managed Access Team actions	
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Managed Access Ops Group Summary

Explanation

This page guides the discussion between the Managed Access Team and partner organisations at Managed Access Operational meetings. It provides a summary of the MAT's overall assessment on whether a medicine could be suitable for Managed Access and if data collection is feasible. It is updated with key issues raised by either MAT or the other participants in those meetings. This page is not aimed at the Committee or other readers, and may make points that seem irrelevant outside of the target audience, but should contain no confidential information. As with the overall feasibility assessment, it does not provide any guidance on whether a medicine is a cost-effective, or plausibly cost-effective, or use of NHS resources. This document should be read alongside other key documents, particularly the company's evidence submission and External Assessment Group (EAG) Report. Further detail for each consideration is available within the separate tabs.

Whilst a rationale is provided, in general the ratings for each area:
Green - No key issues identified
Amber - Either outstanding issues that the Managed Access team are working to resolve, or subjective judgements are required from committee / stakeholders (see key questions)
Red - The managed access team does not consider this topic suitable for a managed access recommendation.

The Managed Access Team may not assess other areas where its work has indicated that topic is not suitable for a managed access recommendation.

Topic name: **Vorasidenib for treating astrocytoma or oligodendroglioma with IDH1 or IDH2 mutations after surgery in people 12 years and over**

Topic ID: **ID6407**
Managed Access Lead: **Sarika Paul**
Date of assessment(s): **27/05/2025**

Feasibility of successful managed access	Comments / Rationale	
Committee judgement required	Rationale for rating	A managed access proposal has been submitted, and there is value in further data collection to help resolve some uncertainties identified by the EAG. There are some limitations with that data that is available, primarily the unblinding of the trial, and cross over of participants, and the usefulness of SACT to answer the questions in the timeframe of a managed access agreement. Therefore committee judgement will be required to determine which data should be collected in a managed access agreement.
	Previous ratings and rationale for change	23/05/2025 - Following a meeting with the company on 20/05/2025, in which the feasibility of SACT/RTDS data collection was discussed with the company, an updated managed access proposal was submitted, and the ratings of some uncertainties were updated to reflect the company's agreement that SACT/RTDS data colection would be useful during a period of managed access. This changed the uncertainties and RWE ratings from medium, to high.

Managed Access Proposal	Yes	
Managed Access Team input at Committee meeting	High	As a proposal has been submitted NICE managed access colleagues will be at the committee meeting, and information will be presented.

Area	Rating	Comments / Rationale
Is this technology eligible for managed access through the CDF or IMF?	Yes	As a cancer drug, this technology is eligible for reimbursement through the CDF, and a proposal has been made to enable this.
Are there outstanding uncertainties that could be resolved with further data collection?	High	There is an ongoing trial which the company have proposed could provide additional data following a period in managed access. While this trial may help resolve some uncertainties, the populations have been unblinded, so a committee will need to decide whether or not this data is sufficient to help resolve decision making on exit. The company also suggest using SACT, RTDS and Blueteq to help resolve uncertainties where appropriate. The managed access team at NICE also believe there is value in collecting SACT and RTDS data to help resolve uncertainties related to time to next intervention and the time spent off treatment following progression, prior to next intervention.
Can data collection from ongoing clinical trials and RWE sources resolve relevant uncertainties?	Unclear	There is both an ongoing trial, and the technology would allow for SACT/RTDS data to be collected. There is a possibility that both of these data sources may help with resolving some of the uncertainties identified by the EAG, however there are also limitations for both of them. While the ongoing trial may help resolve some uncertainties, the populations have been unblinded, so a committee will need to decide whether or not this data is sufficient to help resolve decision making on exit. And SACT/RTDS data, may have limited usefullness in the 5 year time period of a managed access agreement, though it could help with providing useful information about the technology use within an NHS context.
Are there any other points to note that suggest RWE data collection may be beneficial or challenging in resolving uncertainties?	High	The company submitted an updated managed access proposal stating that SACT, RTDS and Blueteq data could be collected to help resolve uncertainties where appropriate. While committee discussion will be needed to ensure the timeframe of data collection is appropriate to help decision making, the managed access team think that this data could provide useful information follwoing a period of managed access.
Are there any other substantive issues (excluding price) that are a barrier to a MAA?	Yes - Minor	In order to obtain useful RWE it will be necessary to link the SACT and RTDS datasets as radiotherapy is a key 1L intervention in this population.

Points raised by MAT	
1	Question related to EAG 1 - Looking at the SACT data set surgery pre-SACT administration is not captured in the data set and therefore SACT would not be able to help provide RWE to help resolve this uncertainty - Do NHSE colleagues agree?
2	Question related to EAG 2 - would start of radiotherapy be possible to collect within SACT?

3	Question related to EAG 7 - Looking at the SACT data set I don't think that time spent off treatment following progression on vorasidenib, before the administration of 1L SACT would be captured in the data set and therefore SACT would not be able to help provide RWE to help resolve this uncertainty - do NHSE colleagues agree?
4	Question related to EAG 8 - using SACT data to help this uncertainty might be possible, but it would be complex as it is related to the outcomes from subsequent treatments. Do NHSE colleagues have a view on the burden of collection of this data, as well as it's usefullness. Even with perfect data collection, the information would only help in the intervention arm due to the crossover in placebo arm.
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Points raised by managed access Ops Group	
1	NHSE answered the above questions and the comments have been captured next to the relevant uncertainties
2	NHSE colleagues highlighted that they believe if this drug does enter the CDF, the data collection period for SACT/RWE data items should extend beyond the 2028 trial end date, to maximise the time period for RWE NHS data collection
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Early Identification for Managed Access

Explanation on criteria
These criteria should be met before a technology can be recommended into managed access through the CDF or IMF. To give a 'high' rating, the Managed Access Team should be satisfied that it can be argued that the technology meets the criteria. Companies interested in managed access must engage early with NICE and demonstrate that their technology is suitable for managed access.

Date agreed with NHSE	22/04/2025

Is the technology a potential candidate for managed access?	
Rating	**27/05/2025**
Yes	As a cancer drug, this technology is eligible for reimbursement through the CDF, and a proposal has been made to enable this.

Uncertainties

Explanation

Likelihood data collection could sufficiently resolve key uncertainties?	
Rating	**Rationale**
High	There is an ongoing trial which the company have proposed could provide additional data following a period in managed access. While this trial may help resolve some uncertainties, the populations have been unblinded, so a committee will need to decide whether or not this data is sufficient to help resolve decision making on exit. The company also suggest using SACT, RTDS and Blueteq to help resolve uncertainties where appropriate. The managed access team at NICE also believe there is value in collecting SACT and RTDS data to help resolve uncertainties related to time to next intervention and the time spent off treatment following progression, prior to next intervention.

Key Uncertainties

Number	Title	Summary of issue	Impact on ICER	Data available to resolve uncertainty	Data collection in company proposal	Resolvable with managed access	Managed Access Team view on feasibility
EAG1	Restricted trial population compared to patients seen in the NHS	An inclusion criterion in the INDIGO trial was that patients' last surgery had to have been between 1 and 5 years prior to randomization. This approach to recruitment means that patients with less stable disease may have been filtered out of the trial population. The anticipated marketing authorization is not expected to place restrictions on how long ago surgery was (before patients can commence vorasidenib), yet the <1 year post-surgery patients may have worse outcomes than the population recruited in INDIGO. Patients with little or no visible residual disease were also excluded from INDIGO. These patients may have a better prognosis than the trial participants and, considering the baseline tumour diameter subgroup results for the progression free survival (PFS) analyses in INDIGO, vorasidenib may not be as effective. Therefore careful consideration should be given to the possible impacts on cost-effectiveness of both when patients should commence taking vorasidenib, and of treating patients with little or no visible residual disease post-surgery.	N/A	Likely that data from a range of NHS data sets could help - committee discussion required as to which characteristics they would like to capture.	Yes, the company propose using blueteq criteria to look at patient groups according to tumour size, type of surgery and time since surgery.	High	Blueteq criteria can also help characterise the demography of the patients who receive the technology, including information about prior surgery, providing key supporting information following a period of managed access. Surgery pre-SACT administration is not captured in the SACT data set a - however SACT can collect some information about demography (including weight as a different dose is given as to whether above or below 40Kg), time on treatment and overall survival. It will also be possible to collect via other databases the time to next treatment and what that treatment was as discussed for other uncertainties.
EAG2	Limited applicability of the progressed disease and time to next intervention (TTNI) INDIGO data to the NHS setting	In INDIGO, only around half of patients in the vorasidenib arm whose disease had progressed (based on modified response assessment for neuro-oncology for low-grade-gliomas (RANO-LGG) criteria) received a subsequent treatment. This might be a consequence of using the modified RANO-LGG criteria - one of the modifications was the removal of 'clinical deterioration' as an assessment criterion; although not considered in the trial, this would be considered as part of NHS disease progression assessments. The TTNI (Time to next intervention) outcome was judged by the EAG to have a high risk of bias due to lack of blinding. TTNI conditional on progression (TTNI | P) was used in the cost-effectiveness modelling to represent time to receive RT/CT (which was not evaluated as a trial outcome). However, for the majority of patients in the placebo arm, the next intervention was vorasidenib. The EAG considers that this created a bias in the TTNI data between the trial arms for several reasons. The clinical decision to treat placebo patients with vorasidenib (thus generating a 'next intervention' event) in INDIGO, in which patients have already been unblinded, is easier than the decision to commence RT/CT in progressed, unblinded patients in the vorasidenib arm; this being based on the perceived risks of administering these treatments. This is exacerbated by the use of the modified RANO-LGG criteria to assess progression in INDIGO, where a decision to commence RT/CT following progression will be less likely than would be expected in clinical practice, given that clinical deterioration was not part of the modified RANO-LGG criteria, and given that some INDIGO progression events will not have had any associated clinical deterioration. Using TTNI to represent time to receive RT/CT is therefore not appropriate and the TTNI results should not be considered as being applicable to the NHS setting. Moreover, vorasidenib is not currently available in the NHS, so it is not a relevant next intervention to consider in the placebo arm, with respect to the TTNI outcome.	See EAG 7 - this has a very large impact on the ICER, but as it remains above the upper NICE threshold of 30,000 it is unlikely to impact on decision making alone.	The INDIGO trial is ongoing and further data cuts will provide more mature data. Subsequent treatments can be collected in SACT/RTDS, and so this could be used to collect additional data about TTNI.	The company propose collecting SACT/RTDS data and using this in combination with the 2028 datacut from the INDIGO trial to inform this uncertainty.	High	As next treatment intervention may be either chemotherapy or radio therapy, work would need to be done to link SACT data about vorasidenib administration and RTDS data about radiotherapy delivery. As these data items are not mandated within the SACT dataset completeness may be an issue. Subsequent surgery has been added for previous topics in the CDF.
EAG3	Immaturity of the data reported in the company's submission	The median follow-up of patients in INDIGO was only around 14 months. Although the company proposes the use of the Cancer Drugs Fund to allow uncertainty to be resolved by further data collection, the EAG notes that some uncertainty could be resolved much sooner, in terms of progression-free survival and time to next intervention, if the company provided a more recent data cut than March 2023 i.e. a new data-cut could provide two years' more PFS and TTNI data. Also, since vorasidenib patients tended to progress at later timepoints than placebo patients, the follow-up for some vorasidenib patients may have ended (in terms of the data-cut) before the next intervention could be given. A more recent data-cut would help resolve this issue.	Unknown - UNASSESSED BY EAG	The INDIGO trial is ongoing and further data cuts will provide more mature data. SACT/RTDS may also be helpful in providing addittional information.	The company propose collecting SACT/RTDS data and using this in combination with the 2028 datacut from the INDIGO trial to inform this uncertainty.	High	SACT and RTDS do not collect information on progression, but it may be able to provide supporting information about time to next intervention, as discussed in EAG7 uncertainty.
EAG4	Non-reference case discount rate for costs and health effects	The company's base case uses a non-reference case discount rate of 1.5% per annum for both costs and health effects. The EAG has significant concerns regarding the company's justification for the use of a non-reference case discount rate and believes it does not meet NICE methods guide criteria: - Vorasidenib is indicated for people with indolent, non-enhancing low grade glioma, who have stable disease and not in immediate need of RT/CT, i.e., it is not indicated for people who would otherwise die; modelled median OS is 15.26 years for active observation and only one death recorded in INDIGO. - EQ-5D utility values from INDIGO suggests that HRQoL is associated with only a modest decrement compared to age- and sex-matched general population utility values. While HRQoL may be impaired at later stages of disease when receiving subsequent treatments of RT/CT the evidence is not available to support 'severely impaired quality of life'. - IDH-mutant glioma remains incurable; therefore, vorasidenib cannot be demonstrated to represent a cure to 'full or near-full health'. - Voraidenib is demonstrated to slow progression in INDIGO but the extent to which vorasidenib delays the time to RT/CT over and above active observation remains unknown. - No information on OS is yet available from INDIGO and no difference in the rates of malignant transformation have been shown for vorasidenib and placebo arms.	This has a large impact on the ICER, causing the CE estimate to change from the lower end of the NICE threshold range, to above 30,000 per QALY.	N/A - committee discussion required.	N/A - committee discussion required.	Low	
EAG5	Surrogacy relationship for OS benefit	In the absence of mature OS data from INDIGO, the approach to modelling relies on the relative effect of vorasidenib on PFS/TTP and time to next intervention given progression (TTNI | P) being predictive of its relative effect on OS. However, the company have not presented evidence to support the validity of a surrogacy relationship between delaying PFS/TTP and TTNI | P and OS benefit for vorasidenib in the target population. The EAG is particularly concerned about the use of TTNI | P as a surrogate for OS as this outcome is confounded by cross-over in the placebo arm, with the next intervention being any subsequent therapy rather than RT/CT as required for the model. Furthermore, the company have not provided evidence to show that vorasidenib reduces the likelihood or delays the transition from LGG to HGG, or transformation to malignant gliomas (secondary HGG). No difference in the rates of malignant transformation (MT) by treatment arm were observed in INDIGO. Therefore, it remains impossible to judge and interpret the appropriateness of the implied OS hazard ratio of 0.69 for vorasidenib vs. active observation in the company's base case analysis.	Unknown - Unassessed by EAG	The INDIGO trial is ongoing and could provide more mature OS data. However the EAG say "Even with more mature OS data from INDIGO over a long follow-up period, the survival data will be difficult to interpret given the large percentage of participants in the placebo arm that crossed over to vorasidenib at progression. In addition, the extent to which a heterogeneous set of subsequent therapies impact on mortality will make interpretation of OS from INDIGO challenging."	The company suggest using further data from INDIGO generated during a period of managed access. Survival data from SACT can also be collected, but due to the long life expectancy of this population, 5 years may not be sufficient for this information to be useful.	Medium	Committee discussion will be required to determine if the OS data from INDIGO remains useful despite unblinding.

EAG6	Interpretation of the conditional outcome of time to next intervention given progression (TTNI | P)	The model uses data from INDIGO for the conditional outcome of TTNI | P, separated by treatment arm, to inform the duration of time spent off-treatment with progression before moving to 1L RT/CT. The EAG's primary concern with this outcome is the fact that it is confounded by cross-over in the placebo arm, where participants in the placebo arm are likely to have moved to the NI quicker because they had access to a treatment that would otherwise not be available outside of the trial setting. Vorasidenib is not currently available in the NHS; therefore, NI in the placebo arm of INDIGO is not informing time to RT/CT as required for the model. In addition, the timing of progression differs between the arms of INDIGO, with later progressors on the vorasidenib arm versus early progressors on the placebo arm resulting in TTNI events more often censored in the vorasidenib arm as many patients' follow-up ended shortly after progression.	Unknown - Unassessed by EAG	SACT/RTDS data could help inform this uncertainty, if the typical timeframe to next intervention was <5 years. The INDIGO trial is not set up to directly help answer this question, as it measures TTNI, which could be vorasidenib, and not time to RT/CT.	The company propose collecting SACT/RTDS data and using this in combination with the 2028 datacut from the INDIGO trial to inform this uncertainty.	High	Clinical input will be needed to determine the typical time to next intervention following surgery and if the MA period of 5 years is sufficient to resolve this uncertainty. If so work would need to be done to link SACT data about vorasidenib administration and RTDS data about radiotherapy delivery. This has been done for previous topics in the CDF.
EAG7	Duration of time spent off-treatment with progression before moving to 1L RT/CT	The model uses the conditional outcome of TTNI | P to determine the duration of time spent off-treatment with progression (in health state S4) before moving to 1L RT/CT. The EAG has several critical issues with the approach used: - TTNI | P is based on post-randomised data and not informing time to 1L RT/CT as required for the model (issue 6). - It is unclear whether patients would be held in a progressed disease health state off-treatment rather than move directly to NI upon evidence of radiographic progression. The company have not shown data that tumour size is smaller at the point of progression than at baseline for vorasidenib, and it remains unknown which tumoral changes are potentially triggered by vorasidenib and how the disease will eventually behave after progression. - Clinical plausibility of the modelled predictions for average time to RT/CT given progression. The selected model predicts that ~21% of patients with PD remain untreated at 20 years for vorasidenib, while ~9% remain off-treatment at 20 years for active observation post-progression. The EAG does not consider the predictions reasonable relative to the time spent PF in model, where patients remain longer off-treatment with PD than PF (e.g., life years for active observation are over three times as much in the PD than PF health state). - It is unclear why the outcome of TTNI | P should be separated by treatment arm, i.e., evidence has not been presented to show that patients should be managed differently post-progression (where progression has been defined using the same criteria in both arms of INDIGO) depending on initial intervention, especially when there are no differences assumed for treatments at subsequent lines. Furthermore, the EAG notes that the HRQoL utility values by progression status and treatment arm of INDIGO indicates that patients with PD had better quality of life in the placebo arm than the vorasidenib arm. The EAG considered scenario analyses to explore this, however in the absence of evidence to support important ongoing effects of vorasidenib post-progression and the issues with the TTNI | P data (post-randomised, confounded by cross-over, high censoring and immature data), the EAG considers it more reasonable to assume a common TTNI | P curve post-progression, independent of initial intervention received (i.e., vorasidenib delays time to RT/CT by delaying time to progression, without assuming an additional effect associated with TTNI data from INDIGO).	This has a very large impact on the ICER, but as it remains above the upper NICE threshold of 30,000 it is unlikely to impact on decision making alone.	SACT/RTDS data could help inform this uncertainty, if the typical timeframe to next intervention was <5 years. The INDIGO trial is not set up to directly help answer this question, as it measures TTNI, which could be vorasidenib, and not time to RT/CT.	The company propose collecting SACT/RTDS data and using this in combination with the 2028 datacut from the INDIGO trial to inform this uncertainty.	High	Progression is not explicitly recorded in SACT or RTDS. However, as vorasidenib is stopped following progression, the time between final vorasidenib cycle, and start of next treatment can be used to infer time spent off treatment with progression before moving to 1L RT/CT
EAG8	Evidence used to model outcomes for subsequent treatment lines	To capture outcomes at subsequent treatment lines, effectiveness evidence from a range of different sources, external to the INDIGO trial, is used. The EAG is concerned about the reliance on multiple sources from non-comparable populations and several assumptions required to inform long-term survival outcomes where there is a dearth of evidence for the target population of LGG. In particular, the EAG expresses concern about: - The limited justification for the choice of post-progression studies and relevance to NHS practice. None of the studies are directly concerned with isocitrate dehydrogenase (IDH) mutant gliomas for adults in a United Kingdom (UK) setting, or specific to progression for patients who were previously not in need of immediate systemic therapy and post-surgery. - The company makes several simplifying assumptions to include PFS from these studies, but the company is mixing and matching data from different populations and histological mix that is unlikely to be comparable. - The costs of subsequent treatments in the model reflect a range and distribution of treatments (including number of treatment lines) that is expected to be given in clinical practice, but the long-term survival outcomes informing the rate of subsequent progression are reflecting outcomes of specific treatments used in the selected studies rather than the different treatment modalities used in NHS clinical practice. - The excess mortality risk applied to the last line of BSC is based on OS data for salvage systemic therapy that does not represent BSC as defined in the model, in addition to concerns about the relevance of the study to UK practice (e.g., small United States (US) cohort, with therapies not licensed in UK, and include pre-progression deaths).	This has a very large impact on the ICER, but as it remains above the upper NICE threshold of 30,000 it is unlikely to impact on decision making alone.	Uncertain - committee discussion required.	The company propose using collated retrospective RWE to inform real world outcomes and treatment patterns for patients in a matched population. The company accept SACT being collected as part of a MA agreement.	Medium	Clinical input into the outcomes for subsequent treatments can help committee decision making. The company propose using collated retrospective RWE to inform real world outcomes and treatment patterns for patients in a matched population - committee discussion will be needed to ensure this data is appropriate for decision making on exit. Using SACT data to help this uncertainty might be possible, but it would be complex as it is related to the outcomes from subsequent treatments. Also the timelines from vorasidenib admin, to progression, to outcomes from subsequent treatments is likely to be >5 years for a significant proportion of people in the SACT cohort - which again will impact the appropriateness of using SACT for this uncertainty.
EAG9	Off-label bevacizumab use at subsequent treatment lines	In the company's base case, a large proportion of subsequent therapies include off-label bevacizumab (34.88% at third line and 33.33% at fifth line), which is associated with a higher cost compared to the costs of RT/CT. The EAG does not consider it appropriate to include the use of bevacizumab at subsequent treatment lines because bevacizumab is not licensed in the UK for the treatment of gliomas. The EAG's clinical advisor confirmed that off-label bevacizumab is not routinely used in the treatment of gliomas.	This has a moderate impact on the ICER, but as it remains above the upper NICE threshold of 30,000 it is unlikely to impact on decision making alone.	N/A - committee discussion required.	N/A - committee discussion required.	Low	
EAG10	Percentages of RT/CT used at subsequent treatment lines	In the company's base case, market share data from France was used to inform the proportion of patients receiving each CT regimen, while the proportion of patients receiving RT in conjunction with CT was based on assumptions. The EAG does not consider it appropriate to use market share data from France to reflect treatment patterns in NHS clinical practice. The EAG's clinical advisor indicated that there are important differences between the UK and other parts of Europe, e.g., in the use of procarbazine, CCNU (lomustine) and vincristine (PCV). The EAG's clinical advisor indicated that at first line, PCV is used most in the UK in line with NICE guideline NG99 recommendations, whereas the periodic synthesis report based on French data suggests only 25.6% use of PCV at 1L. The EAG's clinical advisor also indicated that a higher percentage of patients would receive RT combined with adjunctive CT at 1L than assumed in the company's base case analysis, but that this would diminish at subsequent treatment lines as RT is typically given twice only. In the absence of UK data, an EAG scenario analysis aims to proxy NHS practice for subsequent treatment use based on NG99 recommendations and clinical advice to the EAG. In EAG scenario 5, the proportion of treatments used at subsequent lines are as follows: - 1L: 100% PCV in conjunction with RT. - 2L: 100% temozolomide (TMZ), in conjunction with % RT per company assumptions. - 3L to 5L: Equal percentages of PCV, TMZ, and CCNU, with no RT.	This has a moderate impact on the ICER, but as it remains above the upper NICE threshold of 30,000 it is unlikely to impact on decision making alone.	N/A - committee discussion required.	N/A - committee discussion required.	Low	
EAG11	Health state utility values for subsequent treatment lines	In the absence of utility values for subsequent treatment lines of RT/CT and BSC, the company undertook a vignette study to elicit utility values using both EQ-5D and time trade-off (TTO) methods, valued by the UK general public. The EAG notes that vignettes represent the lowest quality of evidence in the NICE hierarchy of preferred HRQoL methods. The EQ-5D and TTO responses resulted in substantially different estimates of utility values for subsequent treatment lines, with EQ-5D producing lower utility values. Furthermore, the EQ-5D utility values from the vignette study produced substantially lower HRQoL compared to the EQ-5D utility values from INDIGO (e.g., a utility value of 0.728 from INDIGO was used for health state S4, off-treatment with PD, while a utility value of 0.480 from the vignette study was used for health state S5 receiving RT/CT). The EAG considers the utility values for subsequent treatment lines to be highly uncertain and represent an unrealistic drop in utility when moving to RT/CT. The EAG also notes that the company adjusted the EQ-5D utility values from the vignette study by averaging the estimates for on- and off-treatment with RT/CT. However, the wording used in the health state descriptions of the vignettes clearly distinguish between on- and off-treatment, e.g., on-treatment includes "You may experience side effects such as itchy or red skin, hair loss vomiting/nausea, constipation, or diarrhoea", while off-treatment excludes treatment-related adverse events. Therefore, the EAG considers it inappropriate to use an average utility value across the on- and off-treatment health states at subsequent treatment lines given that the vignette health state descriptions differentiate outcomes for on- and off-treatment.	The company's base case ICER with a 3.5% annual discount rate and severity weighting of 1.2 (see Issue 4) marginally increases with the unadjusted EQ-5D utility values from the vignette study. However, when the TTO utility values from the vignette study are used instead of the EQ-5D responses, the ICER increases by a large amount. In all scenarios the CE limit is abover 30,000.	N/A - committee discussion required.	N/A - committee discussion required.	Low	
EAG12	Monitoring with CT scans	The company's base case includes monitoring costs associated with CT scans, in addition to MRI scans. The EAG's clinical advisor indicated that CT scans are not used routinely for monitoring progression in NHS practice (only used in specific circumstances such as presenting with a seizure), with MRI scans being the standard used to monitor progression. This also aligns with NICE guidelines NG99 recommendations and feedback from the company's UK Cost Effectiveness Model Advisory Board Report, which indicates that CT scans would not be done routinely.	This has a small impact on the ICER and is unlikely to impact decision making	N/A - committee discussion required.	N/A - committee discussion required.	Low	

Data Collection

What data sources are available for data collection during a managed access period? Will these sources feasibly resolve the key uncertainties?	
Rating	**Rationale**
Unclear	There is both an ongoing trial, and the technology would allow for SACT/RTDS data to be collected. There is a possibility that both of these data sources may help with resolving some of the uncertainties identified by the EAG, however there are also limitations for both of them. While the ongoing trial may help resolve some uncertainties, the populations have been unblinded, so a committee will need to decide whether or not this data is sufficient to help resolve decision making on exit. And SACT/RTDS data, may have limited usefullness in the 5 year time period of a managed access agreement, though it could help with providing useful information about the technology use within an NHS context.

Existing or proposed clinical trials	
Name and registry ID of trial	27/05/2025
Is trial proposed for managed access?	Yes
Link to clinicaltrial.gov	https://clinicaltrials.gov/study/NCT04164901
Start date	Jan-21
Anticipated completion date	May-28
Data cut presented to committee	primary analysis (IA2; data cut-off date: 06 September 2022) ad-hoc analysis (data cut-off date: 07 March 2023)
Data collection timeline	Further data cuts are expected in May 2025, and May 2028.
Description of trial	Study AG881-C-004 is a phase 3, multicenter, randomized, double-blind, placebo-controlled study comparing the efficacy of vorasidenib to placebo in participants with residual or recurrent Grade 2 glioma with an IDH1 or IDH2 mutation who have undergone surgery as their only treatment. Participants will be required to have central confirmation of IDH mutation status prior to randomization. The primary end point of the trial was progression-free survival, which was defined as the time from randomization to the first documented progressive disease (as assessed on imaging by blinded independent review according to the modified Response Assessment for Neuro-oncology for Low-Grade Gliomas [RANO-LGG]30) or death from any cause, whichever occurred earlier. The key secondary end point was the time to next intervention, which was defined as the time from randomization to the initiation of the first subsequent anticancer therapy (including vorasidenib, for patients in the placebo group who subsequently crossed over to receive vorasidenib) or death from any cause. Secondary end points included objective response and safety, as well as tumour growth rate according to volume (determined on the basis of blinded independent review), health-related quality of life, and overall survival (not reported here). Objective response was determined on the basis of blinded independent review according to the modified RANO-LGG. Patients who had been randomly assigned to the placebo group were eligible to cross-over to vorasidenib treatment if they had imaging-based disease progression confirmed on blinded. Cross-over from placebo to vorasidenib upon centrally confirmed progressive disease (PD) was included in the study following feedback from clinicians and patients/advocates based on ethical considerations for subjects who were already on active surveillance being randomised to placebo. If PD was confirmed by Blinded Independent Review Committee (BIRC), unblinding was performed and physicians thus had the option to offer the possibility for patients to cross-over to vorasidenib if their disease progressed on placebo. If unblinded patients were on vorasidenib treatment, continuation of vorasidenib was not permitted and patients were offered the next possible intervention such as surgery, RT and/or CT or as per investigator discretion. As per protocol, the trial was unblinded after IA2 (data cutoff September 6, 2022) following recommendation of the data and safety monitoring committee based on early demonstration of efficacy by vorasidenib. After unblinding, patients on placebo were given the option of cross-over to vorasidenib. IA2 is the final analysis due to early demonstration of efficacy and unblinding, therefore there will be no FA data cut.
Link(s) to published data	

NHS registry data	
Name of registry	SACT - Systemic anti-cancer therapy database
Is registry proposed for managed access?	The company suggest using SACT, RTDS and Blueteq to help resolve uncertainties where appropriate. The managed access team at NICE also believe there is value in collecting SACT data to help resolve uncertainties related to time to next intervention and the time spent off treatment following progression, prior to next intervention. Discussions with NHSE confirmed this position.
Mandated data collection?	Yes
Available to use?	Yes
Data items already collected	As discussed in relation to specific uncertainties, the mandatory data items collected in SACT will help provide addittional information to help resolve uncertainties.
Issues raised by committee or stakeholders	
Data collection timeline	NHSE colleagues highlighted that they believe if this drug does enter the CDF, the data collection period for SACT data items should extend beyond the 2028 trial end date, to maximise the time period for RWE NHS data collection

NHS registry data	
Name of registry	RTDS - radiotherapy data set
Is registry proposed for managed access?	The company suggest using SACT, RTDS and Blueteq to help resolve uncertainties where appropriate. The managed access team at NICE also believe there is value in collecting RTDS data to help resolve uncertainties related to time to next intervention and the time spent off treatment following progression, prior to next intervention. Discussions with NHSE confirmed this position.
Mandated data collection?	Yes
Available to use?	Yes - however in order to make use of this data set, work will need to be done to link vorasidenib admisistration in SACT to delivery of radiotherapy treatment for individuals.

Data items already collected	As discussed in relation to specific uncertainties, the mandatory data items collected in RTDS will help provide addittional information to help resolve uncertainties.
Issues raised by committee or stakeholders	
Data collection timeline	NHSE colleagues highlighted that they believe if this drug does enter the CDF, the data collection period for SACT/RWE data items should extend beyond the 2028 trial end date, to maximise the time period for RWE NHS data collection

Non-NHS registry data	
Name of registry	N/A - non proposed
Is registry proposed for managed access?	
Mandated data collection?	
Available to use?	
Country in use	
Data items already collected	
Issues raised by committee or stakeholders	
Data collection timeline (future data cuts, proposed end of data collection…)	

Data collected in clinical practice	SACT

Is RWE data collection within managed access feasible?		
Overall Rating		**Rationale/comments**
High		The company submitted an updated managed access proposal stating that SACT, RTDS and Blueteq data could be collected to help resolve uncertainties where appropriate. While committee discussion will be needed to ensure the timeframe of data collection is appropriate to help decision making, the managed access team think that this data could provide useful information follwoing a period of managed access.

Data Source		
Relevance to managed access		
Existing, adapted, or new data collection	Existing	NHS England's SACT dataset is an established mandatory dataset
Prior experience with managed access	High	NHS England's SACT Team have extensive experience with managed access in the Cancer Drugs Fund
Relevance of existing data items	High	Surgical timing or outcomes and radiotherapy administration will need to be added to the mandatory SACT items.
If required, ease that new data items can be created / modified	High	It is thought likely that the addition of surgical timing and radiotherapy administration will be able to be added.
How quickly could the data collection be implemented	Normal timelines	SACT is an existing mandatory dataset. No additional time is required to implement data collection in clinical practice
Data quality		
Population coverage	High	SACT is an existing mandatory dataset that will capture the entire population treated with the medicine in clinical practice
Data completeness	High	Surgical timing or outcomes and radiotherapy administration will need to be added to the mandatory SACT items. NHS England's SACT team have established processes in place to ensure high data completeness. Cohort of interest is identified by Blueteq records and NHS Digital follow-up with trusts where data is missing.
Data accuracy	High	SACT is an established mandatory dataset and there is a good understanding of using SACT in clinical practice. NHS England's SACT Teaml have a dedicated help desk and follow-up with trusts where data submitted is ambiguous or lacks face validity
Data timeliness	High	Trusts submit records to the SACT dataset monthly
Quality assurance processes	Yes	Dedicated SACT data liaison officers and SACT helpdesk. Established process to ensure data quality available at: http://www.chemodataset.nhs.uk
Data availability lag	Low	Four months are required from data collection to allow for data to be uploaded to SACT, follow-up of missing data, and analysis and production of NHS England's SACT Team's report
Data sharing / linkage		
New data sharing arrangements required?	No	Data sharing agreements between NHSE, SACT, blueteq and Personal Demographics Service (vital status) have been previously established
New data linkages required?	No	Data linkage has been previously established to allow NHSD to link blueteq applications to SACT activity to identify the cohort of interest.
If yes, has the governance of data sharing been established	Not applicable	0
Analyses		
How easily could collected data be incorporated into an economic model	High	0
Existing methodology to analyse data	Yes	Established methodology available here: http://www.chemodataset.nhs.uk
If no, is there a clear process to develop the statistical analysis plan	Not applicable	0
Existing analytical capacity	High	Established analytical capacity
Governance		
Lawful basis for data collection	Yes	6(1)e of the United Kingdom General Data Protection Regulations (UK GDPR). Statutory authority to process confidential patient information (without prior patient consent) afforded through the National Disease Registries (NDRS) Directions 2021
Privacy notice & data subject rights	Not applicable	Mandated dataset as part of the Health and Social Care Information Standards
Territory of processing	Yes	UK
Data protection registration	Yes	0
Security assurance	Yes	0
Existing relevant ethics/research approvals	Not applicable	0
Patient consent	Yes	No prior patient consent required

Funding		
Existing funding	Yes	Established partnership between NHS Englands CDF team and SACT team (part of NDRS)
Additional funding required for MA	No	0
If yes, has additional funding been agreed in principle	Not applicable	0
Service evaluation checklist - registry specific questions		
HRA question 2. Does the study protocol demand changing treatment/care/services from accepted standards for any of the patients/service users involved?		
Does data collection through registry require any change from normal treatment or service standards?	No	Established mandatory dataset. Surgical timing or outcomes and radiotherapy administration will need to be added to the mandatory SACT items.
Are any of the clinical assessments not validated for use or accepted clinical practice	No	Assessments are not likely to change even though additional data items will be added.
HRA question 3. Is the study designed to produce generalisable or transferable findings?		
Would the data generated for the purpose of managed access be expected to be used to make decisions for a wider patient population than covered by the marketing authorisation / NICE recommendation	No	Data collection mandated by a Data Collection Agreement would be used for the purpose of the NICE guidance update
Additional considerations for managed access		
Are the clinical assessments and data collection comparable to current clinical practice data collection?	Yes	Established mandatory dataset. Surgical timing or outcomes and radiotherapy administration will need to be added to the mandatory SACT items.
Burden		
Additional patient burden	No	Existing mandated data set. No additional burden of data collection within managed access
Additional clinical burden	No	Established mandatory dataset. Surgical timing or outcomes and radiotherapy administration will need to be added to the mandatory SACT items, but this is not considered burdensome.
Other additional burden	No	0

Other issues	SACT

Explanation

This page details the Managed Access Team's assessment on whether there are any potential barriers to agreeing a managed access agreement and that any potential managed access agreement operates according to the policy framework developed for the Cancer Drugs Fund and Innovative Medicines Fund.

The items included are informed by the relevant policy documentation, expert input from stakeholders including the Health Research Authority, and the Managed Access team's experience with developing, agreeing and operating managed access agreements. Additions or amendments may be made to these considerations as further experience is gained from Managed Access.

Are there any substantive issues (excluding price) that are a barrier to a MAA	
Overall rating	**Rationale/comments**
Yes - Minor	In order to obtain useful RWE it will be necessary to link the SACT and RTDS datasets as radiotherapy is a key 1L intervention in this population.

		Rating	Rationale / comments
Burden	Expected overall additional patient burden from data collection?	Low	Data collection in clinical practice through existing mandated data set. No additional burden of data collection within managed access
	Expected overall additional system burden from data collection?	Low	As above
	Do stakeholders consider any additional burden to be acceptable	Not applicable	0
	Would additional burden need to be formally assessed, and any mitigation actions agreed, as part of a recommendation with managed access	Not applicable	0

		Rating	Rationale / comments
Patient Safety	Have patient safety concerns been identified during the evaluation?	No	No additional patient safety concerns identified
	Is there a clear plan to monitor patient safety within a MA?	Yes	No additional patient safety concerns identified
	Are additional patient safety monitoring processes required	No	No additional patient safety concerns identified

		Rating	Rationale / comments
Patient access after MAA	Are there are any potential barriers to the agreed exit strategy for managed access, that in the event of negative NICE guidance update people already having treatment may continue at the company's cost	Yes	It the event of negative NICE guidance at the end of managed access it is expected, in line with principles of the Innovative Medicines Fund and Cancer Drugs Fund, that patients will continue to be able to receive the treatment until such time that the patient and the treating clinician determines it is no longer clinically appropriate.
	If yes, have NHS England and the company agreed in principle to the exit strategy	Yes	0

		Rating	Rationale / comments
Service implementation	Is the technology disruptive to the service	No	0
	Will implementation subject the NHS to irrecoverable costs?	No	0
	Is there an existing service specification which will cover the new treatment?	Yes	0

		Rating	Rationale / comments
Patient eligibility	Are there specific eligibility criteria proposed to manage clinical uncertainty	No	It is expected that the entire eligible patient population, as recommended by NICE, will be able to access the medicine. Detailed blueteq criteria will be developed by NHSE prior publication of any positive draft final NICE guidance
	If yes, are these different to what would be used if the technology had been recommended for routine use?	Not applicable	-

		Rating	Rationale / comments
Service evaluation	HRA question 1. Are the participants in your study randomised to different groups?		
	Will the technology be available to the whole recommended population that meet the eligibility criteria?	Yes	As above
	HRA question 2. Does the study protocol demand changing treatment/care/services from accepted standards for any of the patients/service users involved?		
	Will the technology be used differently to how it would be if it had been recommended for use?	No	0

checklist	Any issues from registry specific questions	No	0
	HRA question 3. Is the study designed to produce generalisable or transferable findings?		
	Any issues from registry specific questions	No	0
	Additional considerations for managed access		
	Is it likely that this technology would be recommended for routine commissioning disregarding the cost of the technology?	Yes	0
	Any issues from registry specific questions	No	0

		Rating	Rationale / comments
Equality	Are there any equality issues with a recommendation with managed access	No	There are not expected to be any equality issues from a recommendation for use with managed access compared to a recommendation for routine use.

		Rating	Rationale / comments
Timings	Likelihood that a Data Collection Agreement can be agreed within normal FAD development timelines	Yes	It is expected that a data collection agreement could be agreed within normal FAD development timelines (35 days) if committee make a recommendation for use in managed access