National Institute for Health and Care Excellence

Health Technology Evaluation

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

Response to stakeholder organisation comments on the draft remit and draft scope

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Comment 1: the draft remit and proposed process

Section	Stakeholder	Comments [sic]	Action
Appropriateness of an evaluation and proposed evaluation route	Servier	Servier believes that Vorasidenib fulfils the criteria for highly specialised technology evaluation. The criteria and its applicability has been addressed in the criteria checklist uploaded in to NICE docs.	Thank you for your comment. This evaluation has been scheduled into the Technology Appraisal programme. The topic was considered against the criteria for Highly Specialised Technologies and criterion 2 (Normally no more than 300 people in England are eligible for the technology in its licensed indication and no more than 500

Section	Stakeholder	Comments [sic]	Action
			across all its indications) was considered not to be met. Please see the HST checklist for further detail.
	ABN Neuro-oncology advisory group	Appropriate evaluation given poor prognosis and limited curative treatment options for this condition.	Thank you for your comment. This evaluation has been scheduled into the Technology Appraisal programme.
	Astro Brain Tumour Fund	We feel that evaluation of Vorasidenib is essential as current treatments for LGG are limited and this new technology offers an alternative, innovative, less invasive and potentially very effective option. Following surgery, those patients that 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. A treatment that can halt or delay the need for radio/chemotherapy is desperately needed. These conventional treatments are harsh and invasive and should be avoided if at all possible. They have possible devastating side effects (see additional comment section), of particular significance to LGG patients as they are often young and desperate to lead ‘normal’ lives.	Thank you for your comment. This evaluation has been scheduled into the Technology Appraisal programme.

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		Further, radiotherapy can cause long term cognitive effects and necessitates daily hospital visits for a number of weeks and this, with follow up of chemotherapy, can greatly impact on the patients' ability to participate fully in their daily life of education/work and family life, causing a great negative effect on their mental health and well-being - with feelings of isolation and desperation. Additionally, the side effects of the treatments greatly impact on the daily life of family members/carers of the patient. In our opinion, a treatment that is both kinder and less risky is desperately needed for all.	
	British Neuro-oncology Society	It is appropriate	Thank you for your comment. This evaluation has been scheduled into the Technology Appraisal programme.
	International Brain Tumour Alliance	Thank you for the opportunity to comment on the draft scope document for a health technology evaluation of vorasidenib for treating astrocytoma or oligodendroglioma characterised by IDH1 or IDH2 mutations. The International Brain Tumour Alliance (IBTA) believes that it is appropriate for NICE to evaluate vorasidenib in the above setting for a number of reasons: **(1)** Vorasidenib is a first-in-class, targeted treatment for people with IDH mutant low grade glioma (astrocytoma and oligodendroglioma). An international, randomised, placebo-controlled, double-blinded, phase 3 clinical trial ("INDIGO"), involving 331 patients has shown that progression-free survival was more than doubled in the vorasidenib arm versus placebo (median progression-free survival, 27.7 months versus 11.1 months). **(2)** The INDIGO trial also revealed that not only did vorasidenib significantly improve	Thank you for your comment. This evaluation has been scheduled into the Technology Appraisal programme.

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		progression-free survival, but it also delayed time to the next intervention/treatment for these glioma patients. **(3)** Therefore, vorasidenib delays the administration of radiation therapy which can have significant cognitive side effects. **(4)** Although astrocytoma and oligodendroglioma generally have longer survival times than highly malignant glioblastoma brain tumours, there are still a great deal of unmet needs experienced by people diagnosed with low grade glioma. These tumours are not yet curable; they grow continuously and for patients and their families, they represent an ever-present “sword of Damocles” hanging over their heads. These patients are also frequently from the young adult population who are at a time in their lives when they are just starting careers and families. People with astrocytoma or oligodendroglioma may often have significant chronic impairments including cognitive deficits, seizures, fatigue and other side effects of their tumour. 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 IDH-inhibitor. **(5)** Additionally, vorasidenib is an innovative, first-in-class dual mutant IDH1/IDH2 inhibitor with increased brain penetration and a good safety profile. **(6)** 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. We believe that the single technology appraisal (STA) route for vorasidenib is the most appropriate pathway to approval.	
	Society of British Neurological Surgeons	It is appropriate	Thank you for your comment. This evaluation has been scheduled into the Technology Appraisal programme.

Section	Stakeholder	Comments [sic]	Action
	The Brain Tumour Charity	We believe given the current eligibility criteria, the routing decision is correct.	Thank you for your comment. This evaluation has been scheduled into the Technology Appraisal programme.
Wording	Servier	Servier does not feel the wording accurately reflects the population and suggests alternative wording: To appraise the clinical and cost effectiveness of vorasidenib within its marketing authorisation [redacted]	The remit cannot be confidential at this stage. The wording of the remit has been kept broad to ensure that it captures possible wording of the marketing authorisation.
	Astro Brain Tumour Fund	The FDA has approved Vorasidenib “following surgery including biopsy, sub-total resection, or gross total resection”, we think it prudent to include this description	Thank you for your comment. The wording of the remit has been kept broad to ensure that it captures possible wording of the marketing authorisation.
	British Neuro-oncology society	To appraise the clinical and cost effectiveness of vorasidenib for treating astrocytoma or oligodendroglioma with IDH1 or IDH2 mutations after surgery	Thank you for your comment. The technology will be evaluated within its marketing authorisation.

Section	Stakeholder	Comments [sic]	Action
			No change to the scope required.
	International Brain Tumour Alliance	We believe that the wording of the remit is acceptable.	Thank you for your comment. No change to the scope required.
	Society of British Neurological Surgeons	Suggest the following wording: To appraise the clinical and cost effectiveness of vorasidenib for treating astrocytoma or oligodendroglioma with IDH1 or IDH2 mutations after surgery	Thank you for your comment. The technology will be evaluated within its marketing authorisation. No change to the scope required.
	The Brain Tumour Charity	We believe that the wording is reflective and have no further comment	Thank you for your comment. No change to the scope required.
Additional comments on the draft remit	ABN Neuro-oncology advisory group	Urgent given the limited treatment options and impact of disease on quality of life.	Thank you for your comment. This evaluation has been scheduled into the Technology Appraisal programme.
	Astro Brain Tumour Fund	The technology will offer a new pharmacological option which will relieve the burden to the NHS currently only able to offer radio/chemotherapy to patients whose tumour has progressed and will result in more successful immediate outcomes without the need for that further treatment (which comes with life changing impacts on patients quality of life). NHS treatment options are	Thank you for your comment. This evaluation has been scheduled into the

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		currently very limited and compare poorly with the treatment options and outcome profiles and statistics for other types of cancer. Accordingly; For those patients following surgery that are on active surveillance, a treatment option that can halt/delay the growth of the tumour (and in some instances may shrink the tumour) is vital. Halting or delaying progression to higher grade is very urgent –a tumour can grow or transform at any time. LGG patients do not have the luxury of time. The effect of this technology means that radio/chemotherapy (with their long term side effects) can be halted or delayed. A technology that can halt or delay more invasive treatments which is well tolerated is desperately needed to improve the quality of life for these young patients.	Technology Appraisal programme.
	International Brain Tumour Alliance	It is urgent that this evaluation of vorasidenib be started as soon as possible and once begun, proceed as rapidly as possible to conclusion. Brain tumour patients do not have the luxury of time. Patients need to have the opportunity to increase the time to their next treatment intervention after receiving surgery. 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.	Thank you for your comment. This evaluation has been scheduled into the Technology Appraisal programme.
	The Brain Tumour Charity	We believe that this evaluation should be prioritised due to the lack of development of brain tumour treatments. Other than the approval for dabrafenib and trametinib in a select group of paediatric gliomas, there has been no new treatments approved in brain tumours for two decades. This means that any potential treatment to impact this neglected disease should be assessed as a matter of priority.	Thank you for your comment. This evaluation has been scheduled into the Technology Appraisal programme.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Servier	Suggest to remove the information on grade 3 tumours as according to the proposed license and the population studied within the clinical trial for Vorasidenib, grade 3 is not relevant	Thank you for your comment. The scope has been updated.
	Astro Brain Tumour Fund	For completeness we suggest the background information should include the following; 1. The high degree of clinical need of these patients to access a treatment. This is an area of "unmet need" 2. The lack of current options 3. This disease mainly affects young people in the prime of education, working and family life 4. Adverse long term effects of radiotherapy in terms of cognitive decline – future health of patient of particular importance given the young age of patients who may live with the disease for long periods. Toxicity associated with conventional treatment. 5. Potential long term benefits to NHS of this innovation 6. The patient's mental and social wellbeing in living with the disease including the burden and mental health effects on the patient's family and care giver and the burden on the NHS from health related behaviours such as anxiety and depression	Thank you for your comment. The background section of the scope is only intended to briefly describe the disease in the remit, prognosis associated with the condition, epidemiology and treatments currently used in the NHS.
	British Neuro-oncology society	Typos: 1.Isocitrate rather than idocitrate (line 7 of background) 2. Ref 2 IDH rather than ISH. Background Line 1 They develop from glial stem cells. Glia have many roles, which supporting the nerve cells of the brain and spinal cord.	Thank you for your comments. The background section of the scope is only intended to briefly describe the disease in the remit, prognosis associated with the

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		Line 2 there are many types of glioma including astrocytoma (IDH mutant), oligodendroglioma(IDH mutant), glioblastoma (IDH wild type), and ependymoma. Line 4. For the purpose of this appraisal, only grade 2,3 and 4 astrocytomas will be reviewed. Third paragraph in background Line 4 'recommends that all gliomas are usually treated with surgery if possible Line 7 '…postoperatively, and the symptoms, people could be offered radiotherapy, followed by up to 6 cycles of PCV, Temozolomide, or active monitoring.' Fourth paragraph. Line 6. Carmustine implants are rarely if ever used, suggest this statement is deleted.	condition, epidemiology and treatments currently used in the NHS. The scope has been updated in line with some of your comments.
	International Brain Tumour Alliance	The Background information provided is useful but we believe that it does not adequately-enough reflect the huge challenges for patients diagnosed with astrocytoma or oligodendroglioma. It is a matter of fact that these tumours, even at the low grade level, cause significant and increasing deficits in patients over a number of years. As already mentioned, some of these patients are quite young and, as a result of their diagnosis, face a marathon of challenges with their mental acuity, physical abilities, and a whole raft of other side effects which can be caused by an astrocytoma or oligodendroglioma. This situation can also profoundly affect the patient's family who sometimes need to give up their own careers to support their loved one through their diagnosis and treatment. The productivity lost to society when both the patient and their family members may not be able to work is substantial. Additionally, we suggest that paragraph 2 in the Background section needs to be clarified. The Draft Scope states that: "There are around 12,700 new cases of brain tumour each year in the UK." We suggest that this sentence is amended to read: "There are around 12,700	Thank you for your comment. The background section of the scope is only intended to briefly describe the disease in the remit, prognosis associated with the condition, epidemiology and treatments currently used in the NHS. The descriptions of the statistics are consistent with the reference source.

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		new cases of primary brain tumour each year in the UK." This is to make sure that people understand we are talking about primary brain tumours and not metastatic brain tumours (for which the incidence statistics are much higher). The third sentence in this paragraph beginning "10-year survival for people…" should also be clarified as to whether this refers to the "10-year survival" for low-grade gliomas specifically.	
	Society of British Neurological Surgeons	Typos identified: 1.Isocitrate rather than idocitrate (line 7 of background) Line 1 They develop from glial stem cells. Glia have many roles, which supporting the nerve cells of the brain and spinal cord. Line 2 there are many types of glioma including astrocytoma (IDH mutant), oligodendroglioma(IDH mutant), glioblastoma (IDH wild type), and ependymoma. Line 4. For the purpose of this appraisal, only grade 2,3 and 4 astrocytomas will be reviewed. Third paragraph in background Line 4 'recommends that all gliomas are usually treated with surgery if possible Line 7 '…postoperatively, and the symptoms, people could be offered radiotherapy, followed by up to 6 cycles of PCV, Temozolomide, or active monitoring.' Fourth paragraph. Line 6. Carmustine implants are rarely if ever used, suggest this statement is deleted.	Thank you for your comments. The background section of the scope is only intended to briefly describe the disease in the remit, prognosis associated with the condition, epidemiology and treatments currently used in the NHS. The scope has been updated in line with some of your comments.
	The Brain Tumour Charity	We believe the background information could express limited detail around the impact of a brain tumour diagnosis, including their potential quality of life impact.	Thank you for your comments. The background section of the scope is only

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		This could include information from The Brain Tumour Charity's 2015 quality of life report, Losing Myself, that states: - 61% participate in less social activity - 3 in 4 have had their / their partner's working life affected - 1 in 2 experience financial difficulty - 2 in 5 have difficulty with personal care Source: https://assets.thebraintumourcharity.org/live/uploads/2016/08/losing_myself_the_reality_of_life_with_a_brain_tumour.pdf?_gl=1*hv9200*_gcl_au*MjAyOTE5MDYwMS4xNzI3MDgxNDY3*_ga*OTQ0MTU5NDI2LjE3MjcwODE0NjU.*_ga_1119S81MP1*MTcyNzEwNjg0My4yLjEuMTcyNzEwNjk2MC40OC4wLjc3OTY3NjI3	intended to briefly describe the disease in the remit, prognosis associated with the condition, epidemiology and treatments currently used in the NHS. The scope has been updated in line with some of your comments.
Population	Servier	Servier suggests the population is more clearly [redacted]	Thank you for your comment. The population cannot be confidential at this stage. The wording of the population has been kept broad to ensure that it captures possible wording of the marketing authorisation.

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	British Neuro-oncology society	Yes	Thank you for your comment. No change to the scope required.
	International Brain Tumour Alliance	Yes, this definition reflects the data in the INDIGO clinical trial and subsequent published paper in the New England Journal of Medicine reporting on this study.	Thank you for your comment. No change to the scope required.
	Society of British Neurological Surgeons	Yes	Thank you for your comment. No change to the scope required.
	The Brain Tumour Charity	We believe the population is defined appropriately	Thank you for your comment. No change to the scope required.
Subgroups	Brain Tumour Research	The younger patient cohort - Please see additional comments on the draft scope	Comment noted.
	British Neuro-oncology Society	Yes IDH mutant astrocytoma grade 2 IDH mutant astrocytoma grade 3 IDH mutant oligodendrogliomas grade 2 /3 Any IDH mutant high grade glioma with no enhancing disease Patients who have had biopsy vs sub total resection vs total macroscopic resection.	Thank you for your comment. The scope has been updated.

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	International Brain Tumour Alliance	We understand that subgroups were defined in the INDIGO trial for analyses of progression free survival (PFS) and for time to next intervention. The subgroups included: age; sex; geographic region; location of tumour at initial diagnosis; time from last surgery to randomisation; number of previous surgeries; chromosome 1p/19q codeletion status and longest diameter of tumour at baseline. The vorasidenib paper published in the New England Journal of Medicine (https://www.nejm.org/doi/pdf/10.1056/NEJMoa2304194) states that: “The results of the subgroup analyses of progression-free survival and the time to next intervention favoured vorasidenib across most of the subgroups.”	Thank you for your comment. The committee may consider evidence presented on subgroups throughout the evaluation.
	Society of British Neurological Surgeons	Yes IDH mutant astrocytoma grade 2 IDH mutant astrocytoma grade 3 IDH mutant oligodendrogliomas grade 2 /3 Any IDH mutant high grade glioma with no enhancing disease Different surgical groups, so patients who have had biopsy vs sub total resection vs total macroscopic resection.	Thank you for your comment. The scope has been updated.
	The Brain Tumour Charity	We have no comment	Thank you for your comment. No change to the scope required.
Comparators	Servier	Servier considers the established clinical management without vorasidenib in the population studied to be “watch and wait”	Thank you for your comment. In the course of the evaluation, the committee will consider what is established clinical management in

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			the NHS. No change to the scope required.
	Astro Brain Tumour Fund	For those Patients where radio/chemotherapy are deemed inappropriate, the standard care is active monitoring. The comparator is no treatment vis-a-vis Vorasidenib (that can halt or delay tumour growth, recurrence and or transformation for a meaningful period). For those Patients who following surgery where (given the lack of alternatives) radio/chemotherapy may be considered (following relapse or progression) given the long term cognitive effects of radiotherapy on their future health and the brutal chemotherapy regime – a treatment that can avoid/delay this is essential. This technology would provide clinicians with an alternative option whilst maintaining patients quality of life.	Thank you for your comment. In the course of the evaluation, the committee will consider what is established clinical management in the NHS. No change to the scope required.
	British Neuro-oncology society	Yes	Thank you for your comment. No change to the scope required.
	International Brain Tumour Alliance	The vorasidenib trial used matched placebo for a comparator. The Draft Scope lists the comparator as “Established clinical management without vorasidenib” so this statement should be amended.	Thank you for your comment. In the course of the evaluation, the committee will consider what is established clinical management in the NHS. No change to the scope required.

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	Society of British Neurological Surgeons	Yes	Thank you for your comment. No change to the scope required.
	The Brain Tumour Charity	We believe this to be accurate	Thank you for your comment. No change to the scope required.
Outcomes	Servier	• Progression Free Survival • Time to Next Intervention • Overall Survival • adverse effects of treatment • health-related quality of life.	Thank you for the comment. The scope has been updated.
	ABN Neuro-oncology advisory group	Yes	Thank you for your comment. No change to the scope required.
	Astro Brain Tumour Fund	No The outcome measures listed do not capture the health related benefit of the “time to next intervention”, which is a different outcome measure to “progression free survival”. “Time to next intervention” encompasses the situation where the disease may have progressed in terms of there being some growth of the tumour whilst on treatment, but that growth is not such that radio/chemotherapy needs to be administered Ie growth has been slowed down by the treatment such that no other intervention is needed.	Thank you for the comment. The scope has been updated.

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	British Neuro-oncology society	Yes but suggest add Effects on fertility and implications for women of childbearing age Time to next treatment (surgery, radio, other chemo) Ability to stay at work It is essential that the economic analysis take into consideration the significant socioeconomic effects of current treatments (chemo and radiotherapy) on quality of life, the ability to work, chronic fatigue, hospital attendances and admissions, as well as the financial benefit to the NHS from delaying these treatments.	Thank you for your comments. NICE health technology evaluations consider all health effects, and consider an NHS and personal social services perspective on costs. See NICE health technology evaluations: the manual. The scope has been updated in line with some of your comments.
	International Brain Tumour Alliance	The outcome measures to be considered by the Draft Scope include: (1) Overall survival – this was included in the INDIGO trial as a secondary endpoint but has not yet been reported. (2) Progression free survival – yes, this should be included. This was the primary endpoint of the INDIGO trial. (3) Response rates – yes, this should be included and was a secondary endpoint in the INDIGO trial. (4) Adverse effects of treatment – yes, this should be included. Safety was a secondary end point of the INDIGO trial. (5) Health-related quality of life – yes, this should be included as it was a secondary endpoint in the INDIGO trial. ADDITIONALLY…	Thank you for your comments. The draft scope has been updated.

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		(1) The Draft Scope should also include as an endpoint “Time to next intervention”. This was the key secondary endpoint of the INDIGO trial (2) Tumour growth rate according to volume was also a secondary endpoint of the INDIGO trial	
	Society of British Neurological Surgeons	Yes but suggest add Time to next treatment (surgery, radio, other chemo) Ability to stay at work Epilepsy (control, effects on) It is essential that the economic analysis take into consideration the significant socioeconomic effects of current treatments (chemo and radiotherapy) on quality of life, the ability to work, chronic fatigue, hospital attendances and admissions, as well as the financial benefit to the NHS from delaying these treatments.	Thank you for your comments. NICE health technology evaluations consider all health effects, and consider an NHS and personal social services perspective on costs. See NICE health technology evaluations: the manual. The scope has been updated in line with some of your comments.
	The Brain Tumour Charity	We believe the listed outcomes to be comprehensive.	Thank you for your comment. No change to the scope required.
Equality	Servier	No equality concerns	Thank you for your comment. No change to the scope required.

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	Astro Brain Tumour Fund	Age is a protected characteristic in the Equality Act 2010. Given this condition mainly effects the younger age group not carrying out the evaluation would have a disproportionate negative impact on young people. As gliomas disproportionately impact a younger age group more profoundly, age is a relevant consideration which should be taken into account in this evaluation – see NICE technology appraisal guidance 977 (BRAF mutated gliomas).	Thank you for your comment. The committee will consider vorasidenib within its marketing authorisation.
	British Neuro-oncology society	Patients who struggle to attend hospital appointments because of socioeconomic disadvantage may not be able to attend every month.	Thank you for your comment. The committee will consider whether its recommendations could have a different impact on people protected by the equality legislation than on the wider population.
	International Brain Tumour Alliance	Based on the Equality Act's list of "protected characteristics" it is against the law to discriminate against anyone because of age; gender reassignment; being married or in a civil partnership; being pregnant or on maternity leave; disability; race; religion or belief; sex; and sexual orientation. We don't think that the draft remit and scope contravene these requirements.	Thank you for your comment. No change to the scope required.
	Society of British	Patients who struggle to attend hospital appointments because of socioeconomic disadvantage may not be able to attend every month.	Thank you for your comment. The committee will consider whether its

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	Neurological Surgeons		recommendations could have a different impact on people protected by the equality legislation than on the wider population.
	The Brain Tumour Charity	We have no further comment.	Thank you for your comment. No change to the scope required.
Other considerations	Brain Tumour Research	Please see additional comments on the draft scope	Comment noted.
	Astro Brain Tumour Fund	The severity of the condition. All health effects of living with the condition for patients, family and carers including direct and indirect effects anxiety / depression. All future health lost by patients living with the condition Degree of unmet need for the patients Significant immediate quality of life gains Toxicity of radio/chemotherapy – particularly given the young age group that these tumours affect – we would suggest the effect of these treatments on a young person education/university or working life are relevant.	Thank you for your comments. The committee will consider the health effects in line with the reference case described in NICE health technology evaluations: the manual. Where appropriate the committee may also consider uncaptured benefits and non-health factors. No change to the scope required.

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	British Neuro-oncology society	Appropriate timing of treatment Should a registry of all patients treated be considered?	Thank you for your comments. Creating a registry of patients is not within the remit of the NICE committee. No change to the scope required.
	Society of British Neurological Surgeons	Should a registry of all patients treated be considered? Appropriate timing of treatment.	Thank you for your comments. Creating a registry of patients is not within the remit of the NICE committee. No change to the scope required.
	The Brain Tumour Charity	We have no further comment.	Comment noted.
Questions for consultation	Servier	Q. Where do you consider vorasidenib will fit into the existing care pathway for astrocytoma or oligodendroglioma with IDH1 or IDH2 mutations? 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. IDH1/2 mutational testing is routine clinical practice for diagnosing glioma patients. Although most patients progress to a more aggressive disease state, there are several prognostic factors that aid in identifying patients at potentially higher risk of malignant transformation who may benefit from early adjuvant	Thank you for your comments. No change to the scope required. The committee will consider any uncaptured benefits and non-health factors as appropriate throughout the evaluation.

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		RT/CT. These factors include age greater than 40 years, subtotal resection/biopsy only, 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.[1,2.] However, more recently, the modest association between age and outcome of patients with IDH-mutant glioma does not warrant the use of guidelines of a strict age criterion of 40 years for the identifcation of patients at risk for a poor outcome[3].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, and this is where Vorasidenib fits within the patient pathway. Q. Are radiotherapy and PCV (procarbazine, CCNU [lomustine] and vincristine) chemotherapy relevant comparators? • As per the license indication, Vorasidenib is only for those not in immediate need of radiotherapy or chemotherapy, and therefore radiotherapy and PCV are not relevant comparators. The median time spent on surveillance before randomisation in to the INDIGO study was 2.4 years, clearly highlighting the population for Vorasidenib. Q. Is vorasidenib likely to be used for high grade gliomas? • No, as per license indication and trial population in INDIGO Q. Please select from the following, will vorasidenib be: A. Prescribed in primary care with routine follow-up in primary care B. Prescribed in secondary care with routine follow-up in primary care	

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		C. Prescribed in secondary care with routine follow-up in secondary care D. Other (please give details): • Vorasidenib will be prescribed in secondary care with routine follow-up in secondary care Q. For comparators and subsequent treatments, please detail if the setting for prescribing and routine follow-up differs from the intervention. • The only comparator is watch and wait but this involves regular scans which will be carried out in secondary care. Subsequent treatment will be prescribed in secondary care with routine follow up in secondary care Q. Would vorasidenib be a candidate for managed access? • Yes, potentially. Q. Do you consider that the use of vorasidenib can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation? The benefits of a targeted treatment to delay progression go beyond what is measured in a cost effectiveness model. IDH-mutant glioma is associated with high indirect costs, related to loss of productivity, inability to work, early retirement, and premature mortality[4]. 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[5]. The potential acute	

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		adverse effect of RT, such as elevated intracranial pressure, can manifest as headaches and vomiting[6]. 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[7]. All advisors at an advisory board held by Servier expressed that the societal benefits of vorasidenib by delaying RT/Chemo will be marked, such as continuing to work due to a lack of neurological deficit. 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[8]. 1. Mellinghoff, I. K., Chang, S. M., Jaeckle, K. A. and Van Den Bent, M. (2022). Isocitrate Dehydrogenase Mutant Grade II and III Glial Neoplasms. Hematology/Oncology Clinics of North America 36(1): 95-111. 2. Schaff, L. R., Ioannou, M., Geurts, M., van den Bent, M. J., Mellinghoff, I. K. and Schreck,K. C. (2024). State of the Art in Low-Grade Glioma Management: Insights From Isocitrate Dehydrogenase and Beyond. American Society of Clinical Oncology Educational Book 44(3): e431450. 3. Van den Bent, M et al. The biological signifcance of tumor grade, age, enhancement, and extent of resection in IDH-mutant gliomas: How should they inform treatment decisions in the era of IDH inhibitors? 1–18, 2024 | Neuro-Onc. https://doi.org/10.1093/neuonc/noae107 | Advance Access date 24 June 2024 4. Frances, S. M., Velikova, G., Klein, M., Short, S. C., Murray, L., et al. Long-term impact of adult WHO grade II or III gliomas on health-related quality of life: A systematic review. Neurooncol Pr. 2022;9(1):3–17. 5. Boele, F. W., Meads, D., Jansen, F., Verdonck-de Leeuw, I. M., Heimans, J. J., et al. Healthcare utilization and productivity loss in glioma patients and	

Section	Consultee/ Commentator	Comments [sic]	Action
		family caregivers: the impact of treatable psychological symptoms. J Neurooncol. 2020;147(2):485–94. 6. Pérez-García, V. M., Bogdanska, M., Martínez-González, A., Belmonte-Beitia, J., Schucht, P. and Pérez-Romasanta, L. A. Delay effects in the response of low-grade gliomas to radiotherapy: a mathematical model and its therapeutical implications. Math Med Biol. 2015;32(3):307–29. 7. Brook, I. Late side effects of radiation treatment for head and neck cancer. Radiat Oncol J. 2020;38(2):84–92. 8. Servier. Servier UK advisory board. 2024.	
	ABN Neuro-oncology advisory group	Vorasidenib recommended for prescribing in tertiary care setting, for routine monitoring in tertiary care	Thank you for your comment. No change to the scope required.
	Astro Brain Tumour Fund	This is a first in time drug which specifically targets the mutation in the tumour – the desirability of promoting innovative healthcare by the NHS is a factor we would ask is taken into account at consultation.	Thank you for your comment. The committee will consider any uncaptured benefits and non-health factors as appropriate throughout the evaluation.
	British Neuro-oncology society	Vorasidenib will fit in the treatment path after first surgical treatment, once all the results are known and these are discussed at the MDT to consider suitability. Chemotherapy comparators. Should also include temozolomide.	Thank you for your comments. Chemotherapy has not been included as a comparator because vorasidenib is expected to be used before chemotherapy is

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		The use of vorasidenib should be considered for high grade gliomas with no contrast enhancement on contrast enhanced T1 weighted MRI. We would suggest that current pathways would support C. prescribed and followed up in secondary care. (preferably by oncologists) Health related benefits. As stated above, any economic impact needs to take into account the significant socioeconomic effects of current treatment pathways. Radio and chemotherapy over an extended period often mean people cannot work, are significantly limited by side effects (fatigue etc), and will have more hospital attendances and inpatient episodes, (complications such as infections, low blood counts, etc) as well as the implications on fertility.	required. The committee will consider any uncaptured benefits and non-health factors as appropriate throughout the evaluation. No change to the scope required.
	Society of British Neurological Surgeons	Vorasidenib will fit in the treatment path after first surgical treatment, once all the results are known and these are discussed at the MDT to consider suitability. Chemotherapy comparators. Should also include temozolomide. The use of vorasidenib should be considered for high grade gliomas with no contrast enhancement on contrast enhanced T1 weighted MRI. We would support C. prescribed and followed up in secondary care.	Thank you for your comments. Chemotherapy has not been included as a comparator because vorasidenib is expected to be used before chemotherapy is required. The committee will consider any uncaptured benefits and non-health factors as appropriate throughout the

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		Health related benefits. As stated above, any economic impact needs to take into account the significant socioeconomic effects of current treatment pathways. Radio and chemotherapy over an extended period often mean people cannot work, are significantly limited by side effects (fatigue etc), and will have more hospital attendances and inpatient episodes, (complications such as infections, low blood counts, etc) as well as the implications on fertility.	evaluation. No change to the scope required.
	The Brain Tumour Charity	We have no further comment on this.	Comment noted.
Additional comments on the draft scope	Brain Tumour Research	Brain Tumour Research is a research funding and campaigning charity regularly communicating with, and taking the views of, the stakeholders in the UK brain tumour community. Our input into this consultation response has been collated with the support of three stakeholders. **Firstly a Consultant Neuro-oncologist:** 1.There is a clear need for better, kinder treatments for patients with lower grade tumours 2.Vorasidenib offers the potential to delay other treatments, thereby delaying some of the side-effects of chemotherapy and radiotherapy 3.However, the access to Vorasidenib is still difficult: there is a bureaucratic process to apply, and some trusts are worried about the fact that the company won't guarantee long-term access to the drug. At the moment, some trusts have agreed to take part in the MAP, and some haven't; this means that patients face a postcode lottery to access the drug.	Thank you for your comments. No change to the scope required. NICE welcomes the participation of stakeholders throughout the evaluation process and will invite relevant stakeholders to submit information to the committee as part of the evaluation.

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		4.Managed Access Programs sound attractive but MAPs are not funded, and are often a lot of work for pharmacy. Given the national shortage of chemotherapy-trained pharmacists, asking them to take on additional, unfunded work is not feasible. 5.For all of those reasons, MAPs are not a replacement for proper NICE assessment and NHS-funded approval for treatments **Secondly the mother of a low grade glioma (LGG) patient;** The draft / scope should include: 1)The mental health side of living with this disease and that patients can live with it for a comparatively 'long ' period 2) This disease mainly affects young people in the prime of life 3) There is an unmet need with no current pharmaceutical treatment. The only thing on offer is radiotherapy/ chemotherapy - and radiotherapy to the brain brings a risk of long term cognitive impairment **The experience with her son has taught her:** 1) There is currently no treatment offered to LGG patients after surgery, that are placed on watch and wait (active surveillance) 2) This puts a tremendous strain on the mental health of the patient , carer and family (and this consequentially calls on NHS services dealing with anxiety, depression and associated conditions) 3) There are 2 measures demonstrated positively by the trial are 'progression free survival' and 'time to next intervention'	

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		4) The Vorasidenib clinical trial demonstrated meaningful improvement in progression free survival period meaning a first in class treatment can now be made available to a group of patients who previously had to just wait for the inevitable progression of their tumour . 5) These tumours affect mainly younger generation so factors for consideration are; I. Radiotherapy to brain is to be avoided if at all possible because of the long term future cognitive effects (of particular importance as this group of patients can 'live ' with the disease for a comparatively long period) II. Radiotherapy necessitates daily visits to hospital for approx. 6 weeks - making schooling/work impossible III. Chemotherapy is a brutal regime over a 9 -12 month period and the side effects are well documented. The impact of this intervention, not only on physical health, but on family life, the inability to take part in 'normal' social activities for example, leads to feelings of isolation IV. The Vorasidenib trial demonstrated that the time to next intervention (radio/chemo) needing to be started was considerably delayed (in fact at the close of the trial - it had not been reached) In other words , there may have been some growth in the tumour but it had been slowed so considerably that radio and chemo was not deemed a necessary intervention 6) Apart from the obvious benefits to the patients i.e. being treated for their tumour as opposed to the 'doing nothing' and waiting for the likely inevitable, there is a huge benefit to the NHS as Vorasidenib will relieve the burden of	

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		NHS currently only being able to offer 'no treatment'(watch and wait) or radio/ chemo , it will result in more successful immediate outcomes, without the need for further treatment with invasive treatments that can cause life changing impacts . **Her son explains his story in his own words;** *"On the 9th April 2021 I was a young healthy regular 24 year old. 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*	

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		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.* *"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 part 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.* *"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 knew on the 9th April 2021.* *"Hope. It's amazing at what it can do. Vorasidenib is just that. 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*	

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		accessed Vorasidenib I feel like those thoughts are lighter. Where now I think at least I'm fighting back. One tablet in the morning and the days don't seem so dark. I am able to smile properly for the first time in years and not have to put a face on, with the knowledge I'm taking something which allows me to live a nearer 'normal' life. *"It's allowed me to think about all the things a healthy person in their 20s should be thinking about. It is at last an option for treatment alongside what is already out there. If it means I have longer without my tumour progressing and have the ability to put off chemotherapy and radiotherapy I feel like I have control back in my life which is the most amazing feeling. Having options is the biggest contributor to hope for the future, and that is what I have. I don't know exactly what the future holds but instead of being fearful of the future, there is now excitement in building what I thought my life would look like before diagnosis."* **This is the story of another patient again told to us by his mother;** *"**** suffered an unexpected seizure in July 2019 and a scan showed a large brain tumour that was operated on and removed ten days later. Some tumour remains. Histology and further sequencing pronounced it as an Oligodendroglioma IDH mutant and 1p 19q co-deleted (WHO grade 2). That was five years ago and he has been closely monitored with scans since. Fortunately these have shown little to no change but his oncologist suggested, a few months ago, that he now receive radiotherapy but with no particular rationale for this. Coincidentally the success of Vorasidenib was,*	

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		around the same time, reported on in the USA and we have been avidly following its progress since. *"At the start of this journey he declined the recommended radio/ chemotherapy offered by his local clinical team after taking a second opinion from an expert on Oligodendrogliomas who recommended '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 anxious and trying to avoid radiotherapy that might, as he gets older, affect his cognitive function and his ability to work. Of course this would also be a cost to the state.* *"He decided to return to the same consultant a few months ago to discuss 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 rather than radiotherapy. He has been on the drug now for around 3 weeks with no problems. However he has been told basically that this will only be supplied by Servier for 18 months if acceptance into the NHS is not forthcoming.* *"**** is now 42 and almost immediately after his craniotomy returned to full time employment as a web developer for a trade events company and still manages to travel abroad. He has a wide network of friends who all support each other and he is also much needed by them. He lives alone without any help and has never needed benefits during these health issues. We, his parents, are in our mid-seventies and he is there for us too, enjoying taking us out for meals and theatre etc. He 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*	

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		funded, and especially if it is successfully arresting further tumour growth, is causing unnecessary anxiety to him, his family and friends. And no doubt worry to the other patients who might be benefiting from early access . *"So an effective and efficient route through all the processes would be so much appreciated with a decision made on provision as soon as possible. This drug is so far a unique ground breaker so we must try to make use of it after all these years of lack of progress for brain tumour sufferers."*	
	Astro Brain Tumour Fund	YES - to delay progression of this disease and to delay radio and chemotherapy for this group of younger patients is vital and we ask that the draft scope for the evaluation takes into account the real life effects of radio and chemotherapy . This is an extract from a first hand account of a LGG patient who has experienced radiotherapy and is nearing the end of a round of chemotherapy treatments: "PHYSICAL SIDE EFFECTS Radiotherapy: Hair loss, extreme fatigue, lack of mental clarity, seizures, clicking type of sensation in my head Chemotherapy: Nausea, constipation, increased appetite some of the time, but when the nausea is at its peak then I have no appetite and can't eat. I get abdominal pains and daily exhaustion -needing to sleep in the daytime as well as night time, and still feel tired. I try to get some fresh air and go for short walks, but most days I can't face it and stay in the house. This is partly due to lack of motivation and partly due to exhaustion. (I used to go to the gym most days). I am covered in bruises and have itchy skin. Even scratching an itch makes me bruise badly.	Thank you for your comments. No change to the scope required. NICE welcomes the participation of stakeholders throughout the evaluation process and will invite relevant stakeholders to submit information to the committee as part of the evaluation.

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		I've been having recurring bacterial vaginosis, and whilst my oncologist isn't sure if it's caused by the chemo, there is talk that it could be all the meds I'm on, including ones to combat the constipation and nausea, and seizures. This perhaps might explain the hormonal imbalance down there. I never suffered with this previously. It's very embarrassing because the main symptom is the smell. So sometimes it makes me want to stay in the house on my own, affecting me physically as well as mentally. MENTAL SIDE EFFECTS I have brain fog, low mood and anxiety. Inability to complete basic tasks some days, like cooking or keeping on top of chores. I can't focus for very long any more. I had a recent cognition test in my home by occupational health, and she concluded that my attention span and focus is one of the main problems. I had to do a series of tests and I lost my train of thought and struggled to complete the tasks. I struggle badly with memory loss and recall of events, and have to ask people to explain things. And I do feel a gradual decline overall. I feel the cumulative effects of the chemotherapy building. One of my joys in life is playing the piano, something I struggle with now because my left side has been impacted. I have forgotten some things and my left hand and fingers can't keep up with the right. I feel this was slightly worse after radiotherapy….I seem to lack coordination. I've also become clumsier. I've had a few falls and trip up quite frequently or become disoriented and veer. I also struggle to tolerate lots of noise, in particular clashing noises. For example, a friend took me to a restaurant and I couldn't tolerate the music or the people talking. If I'm in the house and the tv is on, I dislike people talking at the same time and I'll have to go into another room. I used to enjoy swimming, but I can't do it because I'm worried my wig will fall off in the water, and I'm too self-conscious to not wear a wig	

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		Whilst previously working as a trainee psychological practitioner with 3 months left to go to be fully qualified and earn my postgrad diploma, I don't feel that I will ever be able to complete this or return to the job I loved. This is due to the fatigue, the inability to focus, and the forgetfulness, not to mention the deterioration in my own mental health. As a single mother of 4, this adds even more stress and anxiety to me, as I have to consider how I will provide for them if I can't work. The additional seizures are continuing to delay me being able to get my driving license returned to me. Money from a return to work shouldn't be something to burden me with, when I'm already distressed by the diagnosis itself and how my children are coping and how they will cope when I die".	
	International Brain Tumour Alliance	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. We hope that the process for appraising vorasidenib proceeds in a swift, timely way and look forward to contributing to the process by providing the patient and caregiver perspective in the forthcoming stages of the single technology assessment for this new therapy.	Thank you for your comments.
	Society of British Neurological Surgeons	The treatment is clearly of benefit, but the trial data is limited follow up. Could a managed access pathway be considered (for at least some of the indications), as this would aid data collection? It would have to be of long enough duration to provide the data necessary to understand the longer term implications of treatment.	Thank you for your comments. The committee can make a managed access recommendation in some circumstances and this will be considered throughout the course of the evaluation.

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	The Brain Tumour Charity	We have no further comment.	Thank you for your comments.

The following stakeholders indicated that they had no comments on the draft remit and/or the draft scope

None