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

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

Contents:

The following documents are made available to stakeholders:

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

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

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on **Tuesday 4 November 2025**. Please submit via NICE Docs.

Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly.

The Appraisal Committee is interested in receiving comments on the following:

- has all of the relevant evidence been taken into account?
- are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- are the provisional recommendations sound and a suitable basis for guidance to the NHS?

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations:

- could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology;
- could have any adverse impact on people with a particular disability or disabilities.

Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced.

Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Servier Laboratories
Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	N/A
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	**Data Sources** Page 9 states the company submitted results from a data cut in September 2022 (median follow up 14 months) and an ad-hoc analysis in March 2023 (median follow up unknown). Median follow up at March 2023 data-cut was 20 months.
2	**Generalisability of the population**

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	Page 12 of the DG refers to how the clinical experts explained at the ACM that the INDIGO trial used an older World Health Organization (WHO) classification criteria for LGG than is used in clinical practice. Because of this, a small proportion of people with astrocytoma in the INDIGO trial would likely be classed as having HGG under the new criteria. The Committee noted that these people would not be eligible for vorasidenib in clinical practice and were likely to have disease progression sooner than people with LGG. This may well have led to an underestimation of the treatment effect for vorasidenib in the full population, and therefore should also be referred to in the uncaptured benefit section
3	**Company's modelling approach** Section 3.8 on page 14, states the company developed a microsimulation model based on key treatment milestones to evaluate the cost effectiveness of vorasidenib. The base-case model included 8 health states: • progression free, on treatment, where people having vorasidenib entered the model • progression free, off treatment, where people having placebo entered the model • progressed disease, off treatment • first-line chemotherapy or radiotherapy, on treatment • first-line chemotherapy or radiotherapy, off treatment • second-line chemotherapy or radiotherapy onwards, on treatment • best supportive care • death. To avoid any confusion, Servier align the states mentioned in the draft guidance with the health state numbers as S3 is not used: • S1: progression free, on treatment, where people having vorasidenib entered the model • S2: progression free, off treatment, where people having placebo entered the model • *S3: not used in the company or EAG base-case analyses* • S4: progressed disease, off treatment • S5: first-line chemotherapy or radiotherapy, on treatment • S6: first-line chemotherapy or radiotherapy, off treatment • S7: second-line chemotherapy or radiotherapy onwards, on treatment • S8: best supportive care (i.e., no further active treatment) • S9: dead
4	**TTNI-P as a proxy for time off treatment with progressed disease** Section 3.10 of the DG on page 16 explains how in the company base case model at ACM1, twenty one per cent of people having vorasidenib and 9% having placebo had had no further treatment 20 years after their disease progressed, implying a cure, which they believed to be not plausible given the disease characteristics Servier has now revised its base-case analysis to take this in to consideration (please see details in section 6). The revised base-case analysis now estimates 7% of people having vorasidenib and 0% having placebo (active observation) receiving no further treatment 20 years after their first disease progression. Clinical feedback to Servier is that this is aligned with expectations for certain patients with low-risk disease oligodendrogliomas with indolent disease that the risk of RT/Chemo outweighs not moving to the next intervention. This is plausible due to the indolent nature of the disease and slow progressing tumours, coupled with the tumour shrinkage seen with vorasidenib.
5	**TTNI-P as a proxy for time off treatment with progressed disease**

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	Section 3.10 on page 16 states that in the initial company base case, people in the vorasidenib and placebo arms spent considerably more time with progressed disease off treatment than in the progression-free health state, which the EAG considered implausible. Servier has revised its base-case analysis (please see details in section 6), to address this concern. The revised estimates are as follows: • people in the vorasidenib arm spend 5.22 years in the progression-free, on treatment health state (S1), and 2.19 years in the progressed disease, off treatment health state (S4) • people in the active observation arm spend 1.42 years in the progression-free health state (S2) and 0.43 years progressed disease, off treatment health state (S4) This difference is explained by the tumour size data previously presented (and further presented throughout this document) in both arms both at the start of treatment/active observation, and then at first PD. Clinician feedback to Servier is that these are plausible values. The clinical consensus is that around two years after cessation of vorasidenib and having progressed, but not yet receiving Rt/Ct, is a reasonable point in time where next intervention would be initiated for people previously treated with vorasidenib due to the molecular change in disease from being on vorasidenib. They also state that if a patient was on active observation, following progression, they would wait to do another scan to assess the rate of growth before intervening with the next intervention. Clinical feedback to Servier was that this would be undertaken around 6 months after progression.
6	**TTNI-P as a proxy for time off treatment with progressed disease** In Section 3.10 of the DG, the committee preferred to apply the INDIGO vorasidenib data to both arms in the model. The committee agreed that the company should provide a full exploration of the bestfitting parametric curve using this approach at consultation. and requested that the company explore alternative ways to plausibly model a TTNI-P benefit for vorasidenib as a scenario. Servier agrees that using the vorasidenib data for both arms would likely overestimate the TTNI-P for people managed with active observation. However, despite this concern, the model can be run using vorasidenib for TTNI|P across both arms. When running this in the model, the modelled next intervention free survival (NIFS – i.e., how many people are both alive and still residing in either S2 or S4) on the active observation arm is around 2.22 years. When comparing with external evidence that was provided at the clarification stage, the following estimates are obtained:

Source	Median TTNI (years)	Rebaselined* TTNI (years)
Tran 2023[1]	4.4	1.8
Huang 2020[2]	3.06	0.46
Bhatia 2024[3]	3.9	1.3
INDIGO[4]	-	1.675
CEM using vorasidenib TTNI|P	-	2.22

[1] Tran S, Thomas A, Aliouat I, et al. A threshold for mitotic activity and post-surgical residual volume defines distinct prognostic groups for astrocytoma IDH-mutant. Neuropathol Appl Neurobiol. 2023;49(4):12928.
[2] Huang RY, Young RJ, Ellingson BM, et al. Volumetric analysis of IDH-mutant lower-grade glioma: a natural history study of tumour growth rates before and after treatment. Neuro-Oncol. 2020;22(12):1822–30.

[3] Bhatia A, Moreno R, Reiner AS, Nandakumar S, Walch HS, Thomas TM, Nicklin PJ, Choi Y, Skakodub A, Malani R, Prabhakaran V, Tiwari P, Diaz M, Panageas KS, Mellinghoff IK, Bale TA, Young RJ. . Tumor Volume Growth Rates and Doubling Times during Active Surveillance of IDH-mutant Low-Grade Glioma. Clin Cancer Res. 2024;30(1):106–15.
[4] Mellinghoff, I. K., van den Bent, M. J., Blumenthal, D. T., Touat, M., Peters, K. B., et al. Vorasidenib in IDH1- or IDH2-Mutant Low-Grade Glioma. 389(7): 589-601. N Engl J Med. (2023b);389(7):589–601

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*Note: *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.*

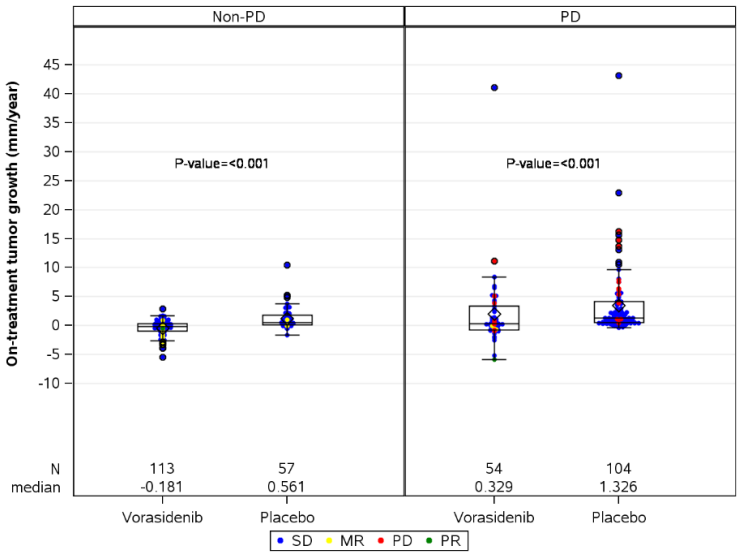
The table above demonstrates that using TTNI|P from the vorasidenib arm as a proxy for TTNI|P for the active observation arm leads to markedly longer estimates for how long patients are expected to spend on active observation (i.e., in health states S2 and S4) before initiating Rt/Ct.

In the DG on pg 18 section 3.10 the committee agreed that using the vorasidenib data for both arms may overestimate the TTNI-P for people managed with active observation. Therefore, we have provided scenarios applying HRs to the vorasidenib arm to produce estimates of TTNI|P that exhibit greater face validity based on how long patients are expected to remain on active observation after progression until initiation of Rt/Ct – in other words, how long patients on the active observation arm are expected to reside in S4 of the model.

Several post-hoc analyses of INDIGO indicate that patients who progress while receiving vorasidenib do so with more favorable features that allow for a relatively longer TTNI|P period, compared to patients managed with active observation. This longer period of time where Rt/Ct is not immediately required means that some people will be able to remain on active observation before unequivocal progression identified through higher tumor growth or volume warrants initiation of a subsequent treatment.

The Box Plot of On-Treatment Tumor Growth by PD vs non-PD based on the Mar-23 DCO below highlights 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 tumor growth compared to placebo, including among patients with progressed disease (p≤0.001), supporting the interpretation of a slower and more indolent progression.

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



Note: 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.

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The change in log tumor volume from baseline to BIRC progression is substantially lower for patients treated with vorasidenib vs. placebo (Mean (95% CI): -0.27 (-0.38, -0.16), p<0.0001, see table below).

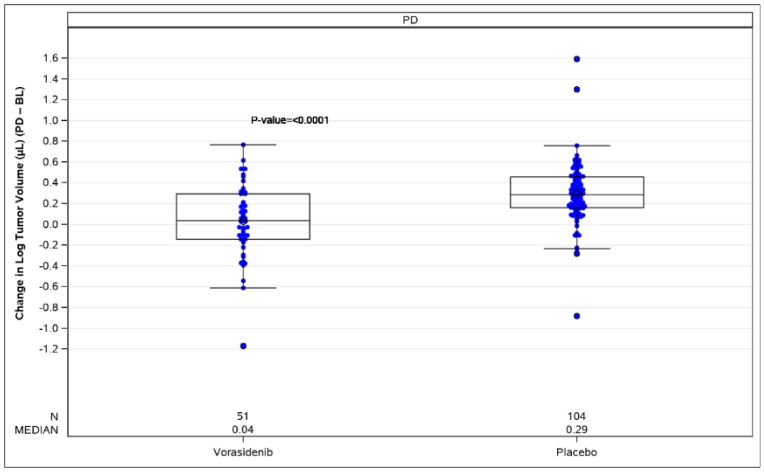
Summary of Log Tumor Volume vs Baseline at PD per BIRC (Full Analysis Set)

	Vorasidenib	Placebo
N	54	104
Mean Log Tumour Volume (Baseline)	9.21	8.95
Mean Log Tumour Volume (PD)	9.24	9.25
Mean Change (PD - BL) (95% CI)	0.03 (-0.06, 0.13)	0.30 (0.25, 0.36)
Difference in Mean Change (95% CI)	-0.27 (-0.38, -0.16)	
P-Value (vs Placebo)	<0.0001	

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, the figure below highlights that almost half of patients who received vorasidenib have a smaller tumor volume at progression than baseline.

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



Relating to this reduction in tumour volume then resulting in a longer TTNI, Servier provides a Cox regression model which shows that 1 unit increase in the log tumour volume is associated with an increase in the hazard (risk of TTNI event) by approximately 56.0%, at a given time while holding all other covariates constant. This substantial increase in hazard (as indicated by the 95% CI and p value<0.0001) highlights the clear association between tumour volume and TTNI.

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TTNI Cox regression include repeated log-volume measurements

The PHREG Procedure

Analysis of Maximum Likelihood Estimates

Parameter		DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	95% Hazard Ratio Confidence Limits		95% Hazard Ratio Profile Likelihood Confidence Limits		Label
TRT01P	AG-881	1	-1.32136	0.22797	33.5960	<.0001	0.267	0.171	0.417	0.168	0.411	Planned Treatment for Period 01 AG-881
log_aval		1	0.44491	0.10803	16.9610	<.0001	1.560	1.263	1.928	1.262	1.928	

Servier also provides outputs of TTNI|P (progression per BIRC) segmented by tumour volume variation vs. baseline. Different cutoffs were applied in three analyses presented below:

- 1: an analysis with: decreased volume=25% decrease; stable=-25 to +25% variation; increased volume=+25% increase
- 2: an analysis with: a cutoff of 10%
- 3: an analysis with: only 2 groups: increase vs. decrease volume.

These results confirm Servier's expectation that TTNI|P is linked with tumour volume variation with growing tumours having shorter TTNI|P than stable and shrinking tumours. The effect of IDH mutation in shrinking the tumours is intrinisically connected to the tumour biology molecularly being in a different place, which was heard from experts at the committee meeting. This would affect the rate of progression and the time to TTNI vs those that progress on active observation.

Figure 1.1.3

Kaplan-Meier Plot of TTNI-P per BIRC for Vorasidenib by Tumor Volume Change from Baseline to PD with Threshold 0%

(Full Analysis Set Without Japanese Subjects)

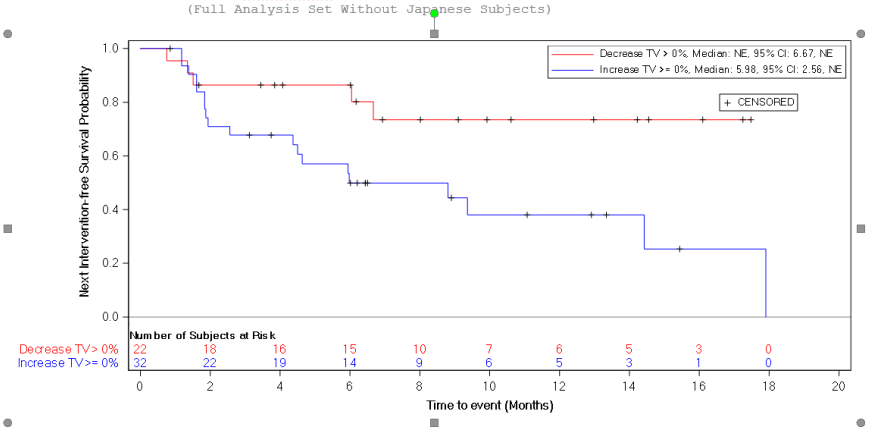

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Figure 1.1.2
Kaplan-Meier Plot of TTNI-P per BIRC for Vorasidenib by Tumor Volume Change from Baseline to PD with Threshold 10%
(Full Analysis Set Without Japanese Subjects)

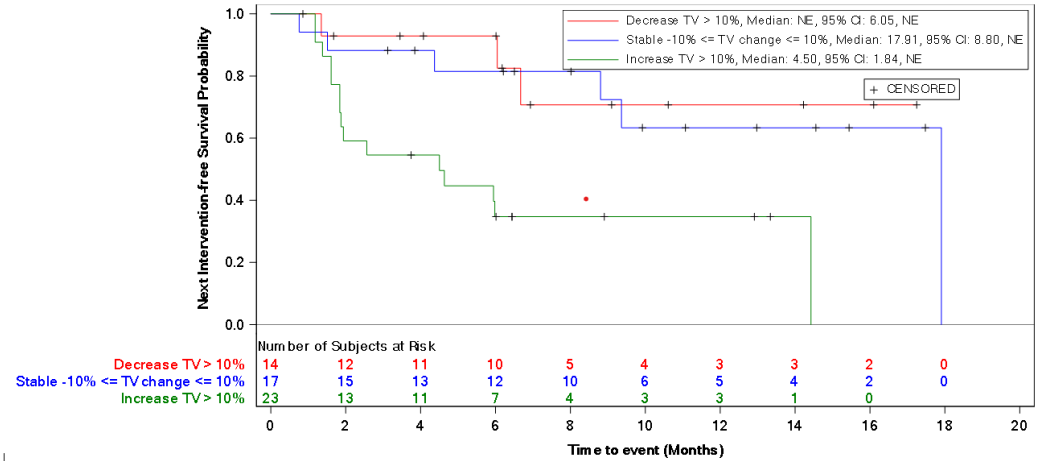
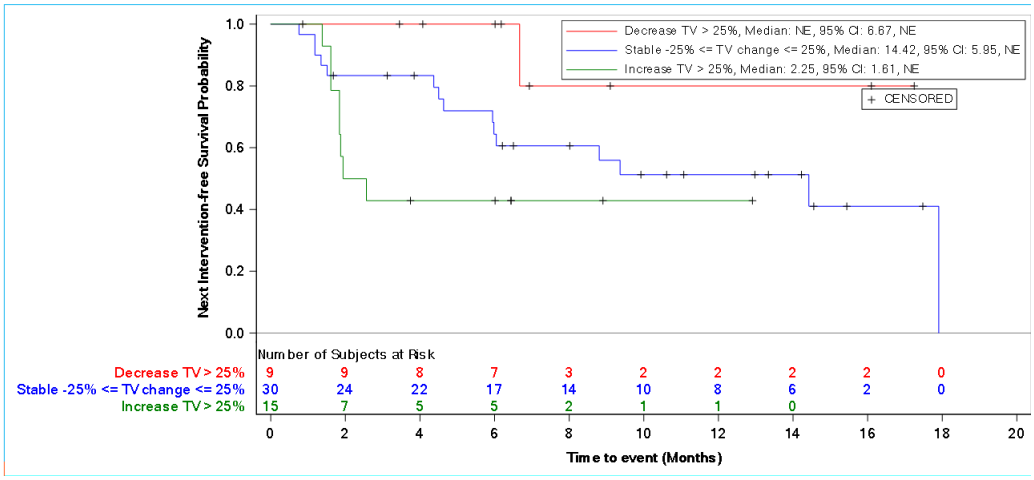


Figure 1.1.1
Kaplan-Meier Plot of TTNI-P per BIRC for Vorasidenib by Tumor Volume Change from Baseline to PD with Threshold 25%
(Full Analysis Set Without Japanese Subjects)



Taken into consideration with the perioperative study[5]

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

- 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 mIDH 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:

[5] Mellinghoff, I. K., Lu, M., Wen, P. Y., Taylor, J. W., Maher, E. A., et al. Vorasidenib and ivosidenib in IDH1-mutant low-grade glioma: a randomized, perioperative phase 1 trial. Nat Med. 2023;29(3):615–22.

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	• 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 tumours. However, the recurrent IDH1 mutation affecting Arg132 was never lost during glioma progression and remained clonal in all progressed tumours. • 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. The question remains on what a clinically reasonable difference between vorasidenib TTNI|P and active observation TTNI|P is, for use in the model. To determine this, Servier sought input from clinicians and data from the Australian brain registry. **Australian brain registry** The report utilises a real-world patient cohort model derived from the BRAIN registry to gain insights about treatment outcomes for patients diagnosed with grade 2 IDH-mutant glioma, with reference to the INDIGO placebo arm cohort. Data was extracted from the BRAIN registry in May 2024 for all patients with IDH-mutant grade 2 glioma diagnosed from 2009-2024. Only patients who met the key inclusion criteria for the INDIGO trial were included in this analysis. This included known IDH-mutant status, at least 1 surgery occurring between 1 and 5 years prior, and recurrent or residual disease. Patients were excluded if they had received radiotherapy or chemotherapy within 1 year of surgery, or if they remained disease-free more than 5 years after surgery. Survival outcomes were estimated using the Kaplan Meier method. Progression-free survival (PFS) was defined as time from date of surgery to date of progression/recurrence or death, or last known follow up. TTNI was defined as time from date of surgery to date of next intervention or death from any cause. Note that this is a different baseline to the economic model (and so these outcomes should be interpreted with caution, and are not able to be directly applied within the economic model). When considering independent review committee assessed progression, median PFS was 42.7 months in the BRAIN real-world cohort. Median TTNI was 48.4 months in the BRAIN real-world cohort. This gives an estimated difference between the medians of around 6 months. This report has been provided separately to NICE as an attachment. **Clinicians** In addition, Servier has spoken to clinicians who highlight that it makes sense to want to monitor the patient after progression on vorasidenib. They state that they would not be in any rush to initiate Rt/Ct immediately after stopping treatment with vorasidenib. The clinicians explained that disease is fundamentally different between the two groups (i.e., those managed with active observation versus those treated with vorasidenib). The clinical consensus is that around two years after cessation of vorasidenib and having progressed, but not yet receiving Rt/Ct, is a reasonable point in time where next intervention would be initiated for people previously treated with vorasidenib due to the molecular change in disease from being on vorasidenib. They also state that if a patient was on active observation, following progression, they would wait to do another scan to assess the rate of growth before intervening with

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<table>
<tr><td></td><td>the next intervention. Clinical feedback to Servier was that this would be undertaken around 6 months after progression. This aligns with the data from the brain registry.

<u>Application in the model</u>
Both data from the Australian brain registry and opinion from clinical experts suggested an average time of 6 months would be reasonable for patients managed with active observation to spend after progression before receiving Rt/Ct. Therefore, the model was updated to allow for the specification of a hazard ratio (HR) to the vorasidenib TTNI|P, with the goal of determining a suitable value such that the time spent in the S4 health state on the active observation arm was around 6 months.

Three different HRs were considered:
• an HR of 2.5, which yielded an average time of 6.53 months for AO patients in S4
• an HR of 3.0, which yielded an average time of 5.12 months for AO patients in S4
• an HR of 3.5, which yielded an average time of 4.11 months for AO patients in S4

Servier’s revised base-case analysis applies an HR of 3.0 to TTNI|P on the vorasidenib arm, which gives a time in the progressed disease off treatment state (i.e., S4) for the active observation arm of 5.12 months. This value was chosen as a midpoint between the values of 2.5 and 3.5 which were considered to be plausible bounds based on the combination of the data and feedback described above.</td></tr>
<tr><td>7</td><td><u>TTNI-P as a proxy for time off treatment with progressed disease</u>

On Pg 17 of the DG, it is also noted that people with progressed disease in INDIGO reported higher quality-of-life results in the placebo arm than the vorasidenib arm, which did not support a longer TTNI-P for vorasidenib.

Since the original company submission, health-related quality-of-life data are now available for the March 2023 data cut off (DCO). The same regression analyses were run as per the values described in the company submission run on an earlier DCO (see section 8 of this response). In addition, summary results are presented in the table below (noting that these values are not based on a formal regression analysis):
<table>
<tr><th rowspan="2">Treatment arm</th><th rowspan="2">Progression status</th><th colspan="2">UK EQ-5D-3L, DSU cross-walked: Mean (95% CI)</th></tr>
<tr><th>INDIGO utility analyses Sept 2022 DCO</th><th>Updated INDIGO utility analyses March 2023 DCO</th></tr>
<tr><td rowspan="2">Vorasidenib</td><td>Progression-free</td><td>0.744 (0.731, 0.757)</td><td>0.746 (0.735, 0.758)</td></tr>
<tr><td>Progressed</td><td>0.678 (0.621, 0.735)</td><td>0.709 (0.667, 0.751)</td></tr>
<tr><td rowspan="2">Placebo</td><td>Progression-free</td><td>0.839 (0.826, 0.853)</td><td>0.748 (0.737, 0.760)</td></tr>
<tr><td>Progressed</td><td>0.730 (0.707, 0.753)</td><td>0.732 (0.714, 0.750)</td></tr>
</table>
These indicate a narrower difference between arms versus the Sep 2022 DCO (Δ PD = 0.023 versus Δ PD = 0.052 respectively). This difference can be explained by a combination of the vorasidenib arm having a lower average utility at baseline compared to the placebo arm, and that there are fewer observations of utility for vorasidenib patients that progressed versus placebo owing to the follow-up period available from INDIGO. Relatedly, an ‘average’ patient that has progressed after being treated with vorasidenib is likely to have a poorer prognosis than an average patient treated with vorasidenib who may or may not have progressed over the period of trial follow up. Overall, Servier considers any differences in the average utility for progressed patients by treatment arm to be related to the data collection in INDIGO, and does not consider it plausible that placebo patients have a greater utility upon progression versus vorasidenib patients.</td></tr>
<tr><td>8</td><td><u>Source of utility values</u></td></tr>
</table>

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Section 3.13 of the DG noted that the company's literature search had identified a utility value of 0.60 that was used for glioma recurrence in TA23. It thought that using the utility value of 0.60 for first-line chemotherapy and radiotherapy in the model, and applying the relative difference between health-state utilities in the unadjusted EQ-5D vignette applied for later health states, would result in a more plausible set of utility values. This was because it would capture the burden of treatment from subsequent treatments but remove the implausible drop in utility when moving to subsequent treatments.

Servier notes that the utility value of 0.60 comes from TA23 (published in 2001), which considered a population described as having 'recurrent malignant glioma'. In the report produced by Wessex Institute for Health Research and Development, it is noted that *"…, no reliable utility data were available.*" (Dinnes *et al.*, summary section, p.7, link). It is Servier's view, therefore, that the value of 0.60 should be interpreted with caution. Despite this concern, Servier has undertaken an analysis based on the approach proposed in the draft guidance – namely, using a value of 0.60 for first-line Rt/Ct (i.e., S5), and then applying relative differences between health-state utilities in the unadjusted EQ-5D vignette for later health states (i.e., S6, S7, and S8). This led to the values presented in the table below:

State	EAG base-case	NICE request (TA23)
5	0.400	0.600
6	0.560	0.840
7	0.260	0.390
8	0.420	0.630

*Note: *Not used in base-case analysis*

Servier does not consider these values to be plausible, as a utility value for S6 (post-1L Rt/Ct) should not be higher than baseline (S1/S2), when considering overall impact of progression of the disease, and the neurocognitive decline that is associated with use of Rt/Ct. To address this issue, but to still make use of the value of 0.60, an alternative analysis was undertaken by applying it to the S6 health state, and then using the relative differences per the vignette in the same way for health states S5, S7, and S8. This led to the values in the table below:

State	EAG base-case	Amended NICE request (TA23)
5	0.400	0.429
6	0.560	0.600
7	0.260	0.279
8	0.420	0.450

*Note: *Not used in base-case analysis*

When using the 0.60 value for S6 instead, this provides more plausible utility values. Overall, the values are similar to those from the vignette study, and Servier maintains its preference for these values given that they come from a single source, and the derivation of these values was undertaken specifically in consider of the health economic model used to inform this appraisal.

In addition, Servier has looked at TA977 which provides alternative utility values. The appraisal is in children but has utilised adult utility values. From this appraisal, utility values may be constructed using a combination of age- and sex- population norms, impacts of having LGG, impacts of progression events, and impacts of chemotherapy-related disutility. Servier has developed a TA977-based scenario using the values from this appraisal in the following way:

- baseline utility in the model is approximately 0.90
- impact of LGG is -0.155

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• impact of each progression is -0.06
• impact of Rt/Ct is -0.187
• the number of progressions associated with each health state was assumed as follows: S1 and S2: 0; S3 (not used in base case) and S4: 1; S5: 2; S6: 3; S7: 5; and S8: 6

Combined, this led to the following values:

State	EAG base-case	TA977 based values
1	0.737	0.745
2	0.737	0.745
3*	0.728	0.685
4	0.728	0.685
5	0.400	0.438
6	0.560	0.565
7	0.260	0.258
8	0.420	0.385

*Note: *Not used in base-case analysis*

Outside of the utility values from other source, Servier has re-run the utility regression model using data from a later DCO of INDIGO (March 2023). These are provided in the updated model, and are used in preference to the values from the earlier DCO:

State	Previous DCO	Updated DCO
1	0.737	0.742
2	0.737	0.742
3*	0.728	0.720
4	0.728	0.720

*Note: *Not used in base-case analysis*

Cost-effectiveness results using a range of utility value scenarios are provided towards the end of this response. Four scenarios were considered in total, summarised below:

State	EAG base-case at ACM1	Updated DCO + raw vignette	Updated DCO + TA23 based values	TA977 based values
1	0.737	0.742	0.742	0.745
2	0.737	0.742	0.742	0.745
3*	0.728	0.720	0.720	0.685
4	0.728	0.720	0.720	0.685
5	0.400	0.400	0.429	0.438
6	0.560	0.560	0.600	0.565
7	0.260	0.260	0.279	0.258
8	0.420	0.420	0.450	0.385

*Note: *Not used in base-case analysis*

In terms of the comment in the DG that the committee agreed with the EAG that the large drop between the INDIGO and vignette utility values may not be plausible and noted it was amplifying the impact of the TTNI-P difference between arms, applying these values prevents such a large drop. However, a drop remains as patients experience side effects from Rt/Ct, such as fatigue, alopecia, nausea, headaches, constipation, loss of appetite, rash, peripheral neuropathy, and brain fog, as well as the symptoms that occur due to tumour progression. These also include general symptoms due to increased intracranial pressure, such as headaches, nausea, drowsiness, confusion, blurred vision, and focal neurological symptoms such as motor loss, numbness, speech difficulties.

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

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9	Section 3.11 of the DG refers to the surrogacy relationship between PFS, TTNI-P and overall survival being uncertain and not supported by data. Surrogacy relationship between PFS and OS 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)[6] 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 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. These conclusions are further supported by evidence from high-grade glioma (HGG) populations, in which the correlation between PFS and OS has been more formally investigated. In a meta-analysis of 91 clinical trials including patients with HGG, Han et al. reported a strong correlation between hazard ratios for PFS and OS ($R^2 = 0.92$), with a Pearson correlation coefficient of 0.42.[7] Additionally, a targeted literature review (TLR) was conducted by Servier to explore the relationship between tumor volume, tumor growth, and clinical outcomes—particularly OS—in patients with IDH-mutant WHO grade 2 gliomas. This focused review enabled a comprehensive mapping and critical appraisal of the available literature specific to this population. A total of 56 publications were identified and analyzed, providing a consistent and convergent body of evidence supporting a strong inverse correlation between tumor size (including volume) and growth parameters with OS. Specifically, Bhatia et al. 2024[8] analyzed a cohort of mIDH gliomas that were in active observation after surgical resection and demonstrated that one natural logarithm tumor volume increase resulted in more than a 3-fold increase in risk of death. Additionally, three post-hoc analyses on the INDIGO trial data were conducted to explore the relationship between volume, tumor growth rate (TGR) and PFS:

[6] 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.
[7] Han K, Ren M, Reardon DA *et al*. Progression-free survival as a surrogate endpoint for overall survival in glioblastoma: a literature-based meta-analysis from 91 trials. Neuro Oncol. 2014;16(5):696–706
[8] Bhatia A, Moreno R, Young RJ *et al*. Tumor Volume Growth Rates and Doubling Times during Active Surveillance of IDH-mutant Low-Grade Glioma. Clin Cancer Res. 2024 Jan 5;30(1):106-115. doi: 10.1158/1078-0432.CCR-23-1180.

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

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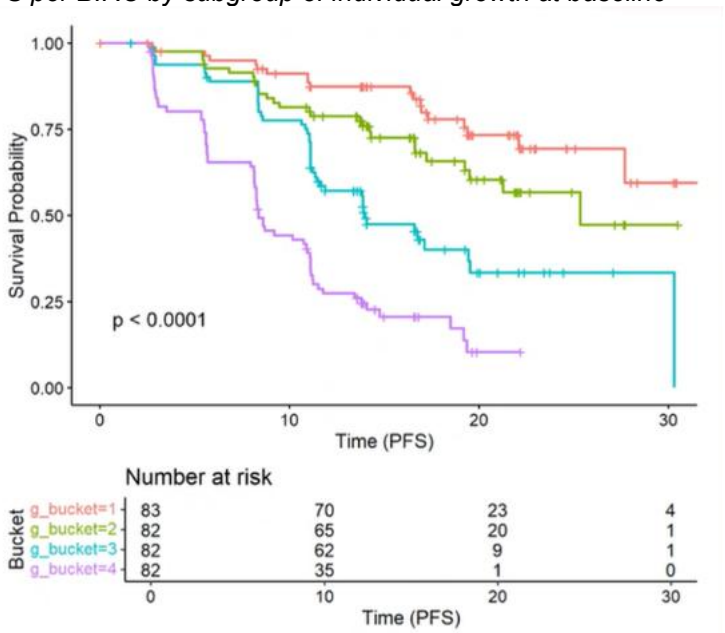
	Quantile-based analysis of individual TGR (Figure 3): PFS was examined across four predefined groups based on tumor growth velocity. *PFS per BIRC by subgroup of individual growth at baseline*  Analysis of tumor growth in the first 6 months: PFS was analyzed according to two distinct growth patterns — early growth (tumor volume increased at month 6 compared to baseline) and early shrinkage (tumor volume decreased at month 6 compared to baseline). *Kaplan-Meier Plot for Progression-Free Survival (PFS) per BIRC by Early Tumour Growth Until Study Unblinding (Full Analysis Set)*

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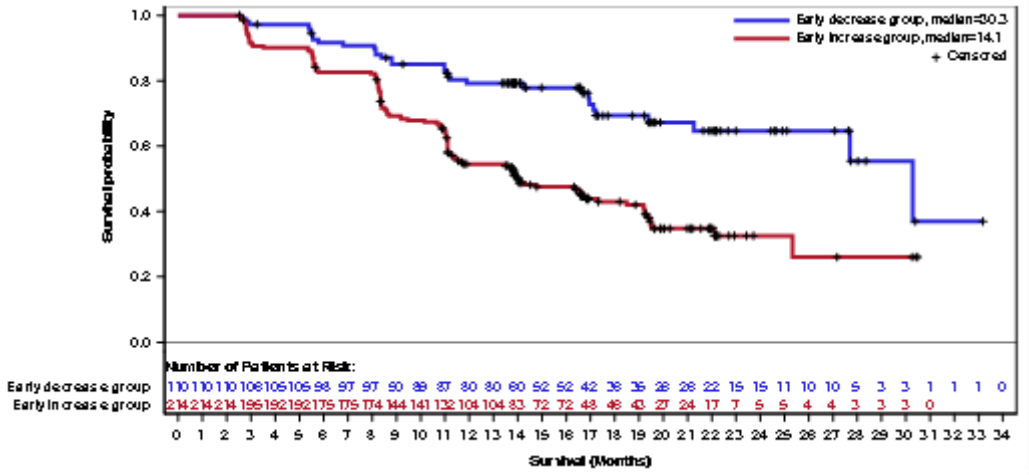

Cox regression analysis with repeated volume measurements.

Summary of Progression-Free Survival (PFS) per BIRC with Repeated Tumour Measurements from Cox Regression Model Until Study Unblinding (Full Analysis Set)

	Overall (n=328)
Log tumor size	
Hazard ratio (95% CI)	1.22 (1.02, 1.45)
P-value	0.027

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.
Interpretation: The HR for log tumor volume is 1.22, meaning that 1 unit increase in log tumor volume increases the risk of progression by 22%.

All 3 analyses highlighted the predictive nature of tumor volume for PFS: patients with faster-growing tumors had the highest risk of progression and the poorest PFS, while those with early shrinkage experienced better PFS and a lower risk of progression, indicating that, through its correlation with TGR and volume, PFS is expected to correlate with OS.

These findings confirm that PFS can serve as a surrogate for OS in patients with IDH-mutant grade 2 gliomas.

In conclusion, Miller et al. (2019) established that disease progression significantly impacts long-term survival, validating PFS as a proxy for OS. The INDIGO trial showed TGR and volume data are predictors of PFS, with faster-growing tumours leading to earlier progression and poorer outcomes. Furthermore, findings from the TLR reinforce the association between tumor size and growth parameters with OS, supporting the clinical relevance of PFS as a surrogate endpoint for OS. This is particularly relevant in the context of limited long-term survival data and the clinical need for early indicators of therapeutic benefit in this indication.

Surrogacy relationship between TTNI and OS

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	In the context of IDH-mutant WHO grade 2 gliomas, where the disease often follows an initially indolent but ultimately progressive course, delaying clinical deterioration and deferring the need for subsequent therapeutic intervention represents a meaningful clinical objective. As an endpoint, TTNI offers a pragmatic measure of disease control and serves as an implicit predictor of long-term outcomes: First, TTNI is mechanistically linked to OS through its dependence on disease progression (TTP or PFS). In the natural history of mIDH gliomas, unequivocal progression is the primary driver of therapeutic decision.[9] [10] By delaying progression, vorasidenib defer the need for next-line therapies (RT/CT or secondary surgery). TTNI therefore captures a clinically meaningful milestone, reflecting both disease biology and treatment decision-making in clinical practice. The established body of evidence demonstrating a strong correlation between PFS and OS in mIDH patients[11] [12] [13] therefore supports the transitive relevance of TTNI to OS. Since progression commonly triggers therapeutic intervention, and PFS is strongly correlated with OS, it follows that TTNI—which lies downstream of progression—also correlates with OS. In this sense, TTNI functions as an indirect but practical surrogate for survival, integrating the clinical consequence of progression with subsequent management patterns. Second, specifically in the context of diffuse mIDH grade 2 gliomas, standard post-surgical management relies on a limited range of non-specific cytotoxic therapeutic options—namely radiotherapy (RT) and/or chemotherapy (CT) with PCV and Temozolomide as the only 2 recommended regimens—which have been shown to provide comparable overall survival (OS) benefit whether administered at an early or delayed stage: This was most notably demonstrated in the EORTC 22845 trial, which reported no statistically significant difference in OS between patients who received immediate postoperative RT and those who underwent delayed RT at the time of progression. As such, the postponement of therapeutic intervention—as captured by TTNI—does not compromise the efficacy of subsequent RT, but instead preserves their survival benefit for future use.[11] Although EORTC 22845 focused solely on RT, its findings are transposable to the current standard of combined RT and CT (RT/CT), as the patient populations in the RT arm of EORTC 22845 and the RT/CT arm of the RTOG 9802 trial share comparable clinical characteristics, including histology, age, and performance status, together with comparable median PFS and OS at ~ 8 years.[12] Indeed, results from the observational arm of RTOG 9802 highlighted how patients with favorable prognostic factors can be safely managed by delaying RT/CT and their acute and long-term side effects for several years.[14] Together, these trials support the notion that delaying the initiation of RT (alone or in combination with CT) does not diminish its efficacy when administered after progression. Accordingly, a

[9] NICE. Brain tumours (primary) and brain metastases in over 16s - NICE guideline [NG99] [Internet]. 2021; Available from: https://www.nice.org.uk/guidance/ng99

[10] Weller M, van den Bent M, Preusser M, et al. EANO guidelines on the diagnosis and treatment of diffuse gliomas of adulthood. Nat Rev Clin Oncol 2021;18(3):170–86.

[11] van den Bent MJ, Afra D, Karim AB *et al*. Long-term efficacy of early versus delayed radiotherapy for low-grade astrocytoma and oligodendroglioma in adults: the EORTC 22845 randomised trial. Lancet. 2005 Sep 17-23;366(9490):985-90. doi: 10.1016/S0140-6736(05)67070-5.

[12] Buckner JC, Shaw EG, Curran WJ Jr *et al*. Radiation plus Procarbazine, CCNU, and Vincristine in Low-Grade Glioma. N Engl J Med. 2016 Apr 7;374(14):1344-55. doi: 10.1056/NEJMoa1500925.

[13] Shaw EG, Berkey B, Mehta M *et al*. Recurrence following neurosurgeon-determined gross-total resection of adult supratentorial low-grade glioma: results of a prospective clinical trial. J Neurosurg. 2008 Nov;109(5):835-41. doi: 10.3171/JNS/2008/109/11/0835.

[14] Iwamoto F, Polley MY, Minesh PM. CTNI-16. NRG-RTOG 9802 OBSERVATION ARM - LONG TERM RESULT. Neuro-Oncology. 24. vii73-vii73. 10.1093/neuonc/noac209.282.

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	therapeutic strategy that extends PFS and, as a result, defers the need for RT and/or CT—as captured by TTNI—is expected to preserve the therapeutic potential of these interventions without compromising OS. In this setting, TTNI captures a clinically relevant milestone that reflects both disease control and preservation of future treatment benefit. Together with the strong correlation established between PFS and OS, these elements provide a coherent rationale for the use of TTNI as a pragmatic and meaningful surrogate endpoint for OS in patients with mIDH WHO grade 2 gliomas. In addition, further support for the clinical relevance of TTNI as a surrogate for OS arises from the study by Blonski *et al.* (2022)[15], which explored long-term outcomes in patients with diffuse low-grade glioma treated with initial PCV chemotherapy followed by RT. Among 20 patients, 12 deaths (60%) were reported: six were directly attributed to tumor progression, five to treatment-related neurotoxicity (notably cognitive decline and severe leukoencephalopathy in the absence of radiological progression), and one due to both causes. These findings highlight TTNI as a meaningful proxy for survival, illustrating that both the biological course of the disease and the timing and burden of subsequent therapies contribute directly to overall mortality. This evidence supports TTNI as a valid surrogate for OS in patients with mIDH grade 2 gliomas. Disease progression prompts subsequent treatment, and delaying progression extends TTNI, with strong evidence linking PFS to OS, reinforcing TTNI's relevance. Furthermore, historical data, including the EORTC 22845 and RTOG 9802 trials, showed similar long-term OS outcomes for early versus delayed RT/CT, suggesting the survival benefit associated with these therapies can be preserved until unequivocal progression warrants their initiation. Additionally, findings from real world series indicate that although most deaths result from tumour progression, many can be attributed to treatment-related toxicity, highlighting TTNI's role in survival. In conclusion, Miller et al. emphasized that delaying the first progression is essential for successfully controlling mIDH glioma, especially as the second progression is challenging to manage due to the limited success of salvage therapy which VORANIGO is expected to delay through its effect on PFS in a pre-RT/CT context, as shown in the INDIGO study. Additionally, studies like EORTC 22845 and RTOG9802 highlighted that RT/CT remains very effective when postponed until unequivocal progression warrants their initiation. Thus, the effect of the RT/CT combination as a subsequent treatment is likely to add to the progression-free survival (PFS) benefit provided by vorasidenib. Therefore, the incremental benefit of vorasidenib on PFS and TTNI is expected to carry over to OS, as patients will be able to benefit from the highly efficacious RT/CT regimens when unequivocal progression arises.
10	**<u>Acceptable ICER</u>** Section 3.18 of the DG states the committee concluded that an acceptable ICER would be around £20,000 per QALY. In the final guidance for TA977 also in a LGG population it states that the committee noted that there were several sources of uncertainty. Servier note that some of these uncertainties mirror that for this appraisal. The committee for TA977 highlighted: • the comparative efficacy of dabrafenib plus trametinib in HGG was based on indirect comparison • the progression-free survival extrapolations were uncertain and based on KM data from a small number of people

[15] Blonski M, Obara T, Taillandier L *et al*. Initial PCV Chemotherapy Followed by Radiotherapy Is Associated with a Prolonged Response but Late Neurotoxicity in 20 Diffuse Low-Grade Glioma Patients. Front Oncol. 2022 Mar 4 ;12 :827897. Doi : 10.3389/fonc.2022.827897.

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	• the likely duration of treatment with dabrafenib plus trametinib that would be used in NHS clinical practice is unclear • the utility decrements used in the model were sourced from adults But the committee also recalled the statements from the clinical and patient experts that children and young people with BRAF V600E mutation-positive glioma would highly value a new treatment option. It also recalled that they would particularly welcome a treatment that would allow them to live a less restricted life with fewer visits to the hospital. It also noted that because of the rarity of BRAF V600E mutation-positive glioma, the decision risk to the NHS was low. So, the committee concluded that an acceptable ICER would be around £30,000 per QALY. Section 3.18 states that utility values are higher than other appraisals but TA977 (see point 8 above) does not show this to be true. Servier urges that the cost effectiveness threshold is re-explored in the light of additional analysis presented and the other issues raised throughout this response, especially taken into consideration with the uncaptured benefits covered in point 11 below.
11	**Uncaptured benefits** The uncaptured benefits have not been discussed fully in the draft guidance. It is not clear how the committee considered the uncaptured benefits of vorasidenib in its decision making by accepting a higher level of uncertainty, as stated in section 3.17 of the DG. Ability to drive. In 3.17 of the DG, it states that given the median PFS of 22.1 months in the vorasidenib arm, it considered it unlikely that many people having vorasidenib would be seizure-free for an entire year to allow them to return to driving. However, the median PFS was not reached in the vorasidenib arm. Patient Pathway Study[16] Servier have carried out a qualitative study exploring the patient pathway and disease burden for people living with mIDH1/2 diffuse glioma, their caregivers, and PAG representatives. This included 6 patients from the UK, 2 caregivers and 2 Patient group representatives. A copy of this report has been provided as an attachment to NICE. A perceived benefit of active observation included the fact that, despite the fatigue and burden of antiseizure medication, some patients were able to return to work, exercise, or even travel when the necessary adaptations were made to make the activity more accessible. 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. A PAG representative stated how this was the “worst period” because of the lack of an “action plan”. Caregivers agreed and

[16] Gatellier et al 2024 100310- COT-27 UNDERSTANDING THE BURDEN OF MIDH1/2 DIFFUSE GLIOMA AND THE COMPLEXITY OF NAVIGATING THE PATIENT PATHWAY: INSIGHTS FROM PATIENTS AND CAREGIVERS - PMC

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	outlined that they struggled to comprehend why a more "proactive" treatment plan was not being offered. 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. A minority of patients had to stop CT before the end of their treatment cycle because of allergic reactions and side effects. 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. Caregivers reported feeling fear, panic, and trauma when patients first began experiencing symptoms. This was followed by sadness, confusion, and more fear when patients were diagnosed. Caregivers were fearful about the risks of surgery and post-surgical care, and experienced anxiety and frustration during the active observation period, in addition to the fear of the patient relapsing. Caregivers witnessed personality changes in patients, with some describing their relative as being more irritable and sensitive, and having less patience. Other caregivers noticed the opposite: patients became more reserved and emotionally detached during their disease journey. Practical burdens on caregivers were very specific. Just as for patients, their life plans, including holidays and various projects, were subject to change. Caregivers had to increase or decrease hours at work to meet extra financial burdens or support patients, some of whom needed constant care. They had more responsibilities in the household or with their children, and provided support to patients receiving RT/CT, such as attending appointments with them and helping them to manage side effects. <u>Burden of glioma on economic productivity</u> In addition, Servier has also generated real-world evidence on the burden of glioma – specifically regarding days absent from work – by use of Danish administrative registers. This clearly shows the burden of progressing disease and RT/CT to pts and on the economy with a median 4.4 weeks absent from work per month when on RT/CT, equating to a productivity loss per pt of €3,750 calculated using the human capital approach (value=salary+taxes)[17]. <u>Paediatric patients</u> In addition, Vorasidenib is licensed for those over the age of 12 and Servier does not feel that the paediatric population has been referred to in terms of the uncaptured benefits. Incidence figures are particularly hard to identify although Ostrom <u>https://doi.org/10.1093/neuonc/noac202</u> provides the following figures Age 12-14: incidence 0.5 per 100,000 population

[17] Lukacova et al 2025. Evaluating work activity and societal burden in patients with grade 2 IDH-mutant glioma Neuro-onc Practice. 1–11, 2025; https://doi.org/10.1093/nop/npaf092.Advance Access date 1 September 2025

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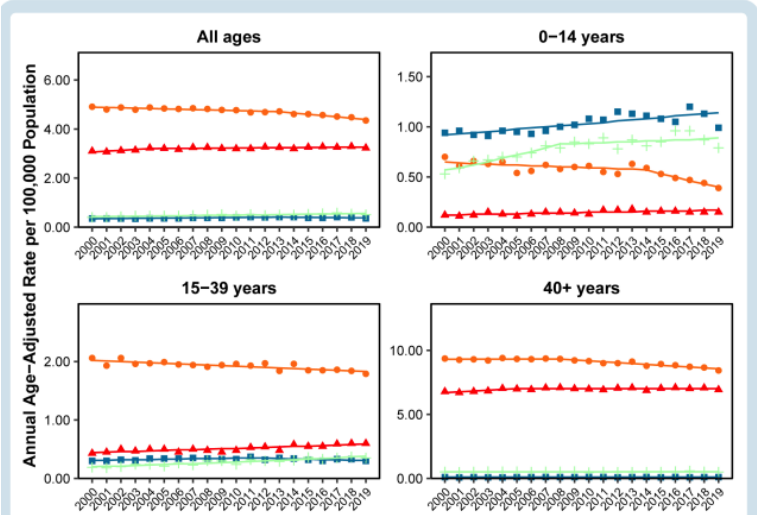
	Age 15-39: incidence of 2 per 100,000 population Therefore, paediatric patients would be eligible for vorasidenib. Delaying RT in children is very important to stress due to the cognitive effect on the brain and the effect on skull growth in the adolescent years. In addition, there is also a huge uncaptured benefit to society. These individuals are going through core education years. Being able to remain in education at this stage yields long term returns and education in this age band is one of the most cost-effective drivers of GDP in the long run. The paediatric patients eligible will contribute to future workforce and productivity as well as demographic and economic stability.  a. Rates are per 100,000 and are age-adjusted to the 2000 US standard population. Abbreviations: CBTRUS, Central Brain Tumor Registry of the United States; NPCR, National Program of Cancer Registries; SEER, Surveillance, Epidemiology, and End Results Program. Fig. 8 Annual Age-Adjusted Incidence Rates[a] of Primary Brain and Other Central Nervous System Gliomas and Incidence Trends by Age Group at Diagnosis, CBTRUS Statistical Report: US Cancer Statistics – NPCR and SEER, 2000-2019 Underestimation of treatment effect for Vorasidenib Page 12 of the DG refers to how the clinical experts explained at the ACM that the INDIGO trial used an older World Health Organization (WHO) classification criteria for LGG than is used in clinical practice. Because of this, a small proportion of people with astrocytoma in the INDIGO trial would likely be classed as having HGG under the new criteria. The Committee noted that these people would not be eligible for vorasidenib in clinical practice and were likely to have disease progression sooner than people with LGG. This may well have led to an underestimation of the treatment effect for vorasidenib in the full population, and therefore should also be referred to as an uncaptured benefit.
12	**Managed Access**

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	Section 3.22 states that collecting more evidence during a managed access period is unlikely to resolve the key uncertainties in the evidence. So, vorasidenib cannot be used with managed access. Servier disagrees with this comment based on the expected DCO from INDIGO in May 2028. This will certainly help with the shape of the PFS and TTNI curve in the vorasidenib arm. In terms of disease progression, in the March 2023 DCO, there were only 54 PFS events in the vorasidenib arm (CS, Table 15) and 28 TTNI events in the vorasidenib arm (CS, Table 17). The 2028 data-cut should therefore be held in mind as a source of significantly more events. In addition, entry to the CDF would allow for more time of exploration of RWE datasets to retrospectively collect data on the active observation arm, specifically on outcomes such as TTNI-P time Servier are already aware of datasets that could perhaps allow this to be done, and could collate, where appropriate,RWE from other countries, seeking prospective HRQOL/utility data collections for the various health states in the model. Servier have already begun to investigate this but unfortunately cannot provide the analysis within the timeframe of the second committee meeting. Servier have specifically been in contact with Birmingham, Cardiff and Kings, London to assess the feasibility of investigating specific questions through their registries, and are prepared to work with NICE/NHSE to align the data collected moving forward. This would involve 158 grade 2 patients across 3 centres. Feedback received from the managed access feasibility assessment conducted highlights 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. As this is one of the key uncertainties affecting cost effectiveness, the company believes strongly that this should be considered and time on treatment. The CDF could collect: Patient demography Histology mix (oligo vs astro) Time from first diagnosis Time from surgery Size of tumour at CDF entry Time on treatment Next intervention and when (chemo, RT, surgery etc) With a Data cut in 2028, CDF entry could be until 2029 or for longer if the committee wanted more mature RWE in the NHS of vorasidenib use especially re TTNI. There are also patients in a named patient supply that have already been on the treatment for 18 months which would help collate real world evidence on TTNI, treatment duration etc to help resolve this issue.
13	**<u>Model results</u>** The company's revised base-case analysis is presented below, which includes the following settings: • starting from the EAG's preferred base-case analysis (including x1.2 modifier) • vorasidenib data used for vorasidenib arm to inform TTNI|P (log-normal model, per EAG base-case)

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• apply an HR of 3.0 to the vorasidenib TTNI|P to obtain clinically plausible TTNI|P for the AO arm (mean time spent in S4: 5.12 months)
• update utility values for S1 to S4 using latest DCO data from INDIGO
• apply a revised price of vorasidenib equivalent to [redacted] per pack of 30 x 40mg vorasidenib tablets

Arm	Costs	QALYs	d(cost)	d(QALYs)	ICER
Vorasidenib	[redacted]	7.50			
AO	£260,670	5.33	[redacted]	2.60	[redacted]

As described earlier in this response, scenarios were also investigated using different HRs to obtain an estimate of TTNI|P for the placebo arm (HRs of 2.5, 3.0, and 3.5); plus different utility scenarios (the EAG's base-case analysis, updated DCO values from INDIGO, and using values reported in TA23 and TA977). The ICER associated with each combination of these scenarios, building on Servier's revised base-case analysis presented above, is provided in the table below.

HR applied to TTNI|P	EAG base-case utility values	Updated INDIGO DCO + raw vignette values	Updated INDIGO DCO + TA23 (0.60) values	TA977 values
2.5	[redacted]			
3.0				
3.5				

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about funding from the company and links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into one response. We cannot accept more than one set of comments from each organisation.
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- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

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NICE National Institute for Health and Care Excellence

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

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on **Tuesday 4 November 2025**. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Astro Brain Tumour Fund

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Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	Astro Brain Tumour Fund has received a total of £788 from company Servier in the past year. This is in respect of charity trustee Mary Burton's appointment as one of the authors of the manuscript of a project undertaken by Servier titled "Glioma Patient Pathway". This is project is not in any way related to the product vorasidenib. It is ongoing at present. Astro Brain Tumour Fund, along with other charities, is part of a group to raise awareness of low grade gliomas. The secretariat is provided by Servier. This group's work is not related to Vorasidenib and Astro Brain Tumour Fund has not received any monies from Servier .
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	1. **Has all the relevant evidence been taken into account?** **A. No – please see comments below.** The Health and Social Care Act 2012 requires NICE to have regard to the degree of **need** of persons for health services in England.

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	A. The draft guidance does not adequately reflect the **UNMET** need of low grade glioma (LGG) **patients** or their **families**, including the profound psychosocial, cognitive and practical impacts of living with the disease. With an LGG diagnosis comes devasting effects that reach much further than the patient. The consequential effect on the patient's own families, both for those that have children themselves, or the parents, siblings, and wider family members has not been fully recognised The current care pathway is, after surgery, watch and wait or subsequent toxic therapies. These are not alternatives, radio/chemotherapy is recognised as a treatment of last resort, described by one neurologist as the 'nuclear option'. So what treatment is there on offer for this group of patients within the current health service? Sadly, the answer is NONE. Vorasidenib is a desperately needed treatment - a treatment, as recognised by the committee, that **"increases how long people have before their cancer gets worse"**. There is currently no equivalent treatment. This is one of the most significant **unmet** needs faced by this group of generally young patients i.e. the **lack of a current treatment**. With the current lack of treatment for this group of patients the following **needs** are **unmet**, including very poor quality of life, mental health issues, anxiety, depression. The experience of our patients is that these needs are not addressed in the current care pathway. Patients and their families have to try and cope, often resorting to charities offering 'support groups', and whilst offering some help this cannot meet the overriding complex mental and health needs. Some of our patients have been fortunate to access Vorasidenib via the '**early access**, **named patient programme**', so can speak first hand of experience of watch and wait and how Vorasidenib has **positively impacted their quality of life.** The psychological impact of the diagnosis on the **wider family** and how a loved one accessing Vorasidenib, has a positive impact on their own unmet needs, is also captured by their accounts below. B. With **lack of a treatment** option, this group of patients suffer as their **tumour will grow** and this in turn will have **physical** effects , including personality changes, headaches, speech - these patients desperately need access to a treatment that will **slow that growth** and hence avoid for the longest period possible these physical changes that come with the tumour growing. The committee accept Vorasidenib extends the time to the cancer getting worse (progression free survival). This **unmet** need i.e. the need to stop the cancer progressing can be met by making Vorasidenib available through the NHS. C. **With a lack of treatment options**, unfortunately even with anti-seizure medication -some LGG patients continue to experience **seizures**, patients report the very negative effects on their mental and physical health - there is a

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	desperate need for patients to experience less seizures , with a reported 64% reduction in seizures in the Vorasidenib group, this need can to a much greater extent be met. D. **lack of treatment option** to **avoid radio/chemotherapy for as long as possible**-it is well accepted that toxic treatment should be avoided as long as deemed clinically appropriate - there is no treatment currently available on the NHS that achieves this. **Short term** effects i.e. year of treatment were considered by the committee. Some of the **longer term** effects (albeit not all, were noted - cognitive problems). **Medium term** effects were not considered sufficiently – Astro Brain Tumour Fund refers to our earlier written submission and further below. The current **unmet** need is to avoid toxic treatments for as long as possible, we would submit that need would be met by Vorasidenib being available on the NHS. We consider also that the short, medium and long term effects on **family members** have not been adequately considered (If further data is needed to address 'time to next intervention') , Astro Brain Tumour Fund would urge the committee to refer to p20EAG- 'additional data to be collected May 2028' – importantly the EAG stated this would help reduce the uncertainty about 'progression free survival' and 'time to next intervention.' To help the committee to better understand the effects of living with this complex and life altering disease and the resultant **unmet** needs experienced by these patients and their families, we list below comments from LGG patients and carers at various stages of their treatment. These accounts also support the increase quality of life for those patients in receipt of Vorasidenib. **PLEASE ALSO SEE THE ADDITIONAL "PATIENT EXPERIENCES" DOCUMENT WHICH HAS BEEN SENT TO NICE SEPARATELY PER THEIR AGREEMENT** • **WATCH AND WAIT** **Patients:** The fear of "watch and wait" made the whole family constantly anxious" "The idea of taking a pill rather than going through more treatments would be a life saver – the prospect of more invasive treatments has already given my daughter suicidal thoughts" **Carers:** "I have had to have counselling because of my daughter's diagnosis in order to come to terms with this additional need in her life" "Watch and Wait made the whole family anxious".

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	"I hid my anxiety from my son and would go to the bathroom to weep. I took unpaid leave to support him". "My son is now 18 years old, having first surgery at age of 8, he's now had 3 surgeries and now on watch and wait. The anxiety and impact on the carers' mental health is debilitating at times" "During the initial watch and wait period, our whole family lived under a shadow of constant fear" • **VORASIDENIB PATIENTS AND CARERS** At para 3.15 (p.26) the committee concluded that Vorasidenib did not restore "near full health". We ask the committee to reconsider this, in light of the following comments from patients and the clinical evidence that tumour progression was halted for a significant period of time, which equates to "near full health". However, it must be noted that Astro Brain Tumour Fund and Brain Tumour Research, in their written submissions, did give patients' accounts of this. These accounts have not been referred to by the committee in its draft guidance and as such this has not been adequately considered. We ask for the following patient/carers' statements be taken into account: **Patients:** "I have been taking the drug for 5 years and have remained stable. My oncologist recommends I stay on the drug as long as possible due to its success." "Since my diagnosis, this is the most 'normal' I have felt having been on Vorasidenib since May 2024". "What Vorasidenib does for me certainly is allow me to live a full life as much as anyone can with a looming terminal illness". "I am now on Vorasidenib which has given me hope, enabling me to help people and fundraise. I cannot understand why the NHS cannot fund life changing treatment for brain cancer patients who have gone through so much already" "I am now on vorasidenib – I couldn't imagine the difficulty of going straight into radiotherapy and chemotherapy after the trauma of surgery and the impact that it would have on our young family". **Carers:** "To remove Vorasidenib from my daughter would have a disastrous effect on our lives". "Prior to my daughter receiving Vorasidenib it felt we were living with little hope and I suffered extreme anxiety" "Vorasidenib has given us our lives back as a family to a considerable degree – given us much needed hope". "We all feel anxious and involved at every point of my son's journey. Since taking Vorasidenib he has been working to support himself and his daughter financially".

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	"Vorasidenib has given our son hope for the future. After his diagnosis, we were left crushed and helpless. We were all broken. For the first time we can dare to be optimistic for the future". "We are alarmed and bewildered by the recent news that NICE has declined to recommend that Vorasidenib be made available through the NHS. The decision does not adequately reflect how the quality of life for carers is affected". "Why would anyone just wait for chemotherapy and radiotherapy to destroy their bodies and even further damage my husband's brain when there are other options?" "Preparations were being made for our son to commence radio/chemotherapy. The negative impact on him was immense. Then he was offered Vorasidenib. It has given him hope, something none of us had before". "Our son has been given a growing sense of optimism for his future, and he is pinning his hopes of having continued access to Vorasidenib". "My son has returned to being more positive and happier, almost the son I knew prior pre 2019 (diagnosis). We envisage his positive attitude will disappear if Vorasidenib is withdrawn". "Vorasidenib has given my son hope that he will have longer to work and to enjoy his life" "The moment our son was granted early access to vorasidenib the atmosphere in our family shifted from despair to cautious optimism". "Vorasidenib has, in our experience, been the single most important factor in restoring hope and quality of life to our son and to those who love him". • **RADIOTHERAPY/ CHEMOTHERAPY PATIENTS & THEIR CARERS** At the committee meeting, the patient experts were asked about the effect on **quality of life for patients that underwent radio/chemotherapy** - neither was able to help the committee with this. **Patients:** "After six weeks of radiotherapy and 12 months of chemotherapy, I am left with memory loss, lack of focus, poor attention span, increased seizures and infections. The fatigue is relentless**"** "I've had radiotherapy and am now living with the side effects including having frequent falls and forgetting what I was saying mid-sentence – the list goes on" "I've had radiotherapy and chemotherapy. I now have some degree of memory loss and suffer from bouts of fatigue, headaches and mood swings". "I have just completed chemo and radiotherapy and experience extreme fatigue, other physical side effects plus mental stress. Ruling patients out (of Vorasidenib) like myself is very frustrating. Once again it seems low grade patients get less priority than high grade but we are no less important".

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	Carers: "My wife has had chemo/radiotherapy, it was very stressful with anxiety, fatigue, extensive travel, taking time off work, it now ongoing with periods of anxiety impacting our quality of life significantly" "I do not sleep at night worrying in case my son has another life-threatening seizure. We have had no release from worry and fear; the future brings more of the same without any let-up. Living day-to-day like this is incredibly challenging. If only my son had been allowed just a couple more years for him to enjoy his life before brutal radiotherapy and chemotherapy" "My husband had to take six weeks of unpaid leave to take our son to the hospital every day during this challenging time so our income has been impacted. I have not been able to work now for many years due to my younger son's also having needs, and now there is little prospect of me being able to work again" "My daughter has had surgery, radiotherapy and chemotherapy treatment which left her unable to work for two years" "My son has been unable to regrow his hair after the radiotherapy and chemotherapy, his confidence is rock bottom and he will not even answer the door without wearing a cap at all times in public. He has become extremely nervous and riddled with anxiety. He tires easily more since his radiotherapy and chemotherapy and it affected his liver function" • **SEIZURES** The committee has failed to consider the effect of **seizures** on patients and their families. Vorasidenib demonstrates a significant reduction in **seizures**. This in turn affects the mental health of the patient and their own family and their ability to care for their own family if they have children of their own. This also affects the ability to work. The **physical effect** of experiencing a seizure has not been adequately considered. The financial implications both for the family and the cost to the NHS is not reflected in the draft decision. The committee state they think the fact of not being able to drive for a year after a seizure "is not of particular relevance", as they suggest it's unlikely to have any real life implications because of how the disease progresses. No tangible evidence has been referred to support this assumption, and we have not received reported outcomes that support this assumption. **Following are seizure experiences of patients who are taking Vorasidenib:** **Patients** "Immediate improvements were infrequent seizures" "My anxiety has improved as have my seizures" "I've had no seizures being on Vorasidenib" "I have had seizures whilst on Vorasidenib but they have not been severe. I'd had massive tonic-clonic seizures where I've needed Hospital treatment, been injured and lost consciousness. Since Vorasidenib they have generally been short/focal seizures and I've not needed to go into hospital or got hurt from them"

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	"I have had no seizures over the last year since starting Vorasidenib" "The seizures have significantly decreased since I'm on Vorasidenib and now I no longer have any" **Carers' experience of seizures** "I do not sleep at night worrying in case my son has another life-threatening seizure". "My son suffered seizures following his craniotomy, the first witnessed by his dad and his partner, the second by his partner alone. Witnessing a seizure was traumatic for them, particularly for his partner, who found it difficult to be alone with my son, particularly at night, and had difficulty sleeping. She would be watching out for signs that he might have another seizure and worrying about how to cope and how to keep him safe if he did. She spent some weeks sleeping in a different room and accessed talking therapy to help her cope with the trauma". "The fear of my son (28 years) having a seizure and the physical and mental toll that comes with it, is indescribable. It's almost as bad as the fear and anxiety that comes from a brain tumour diagnosis. We dare not leave him on his own in case he had a seizure, he stopped going out because he was so frightened and stopped work. We had to stand by and watch him going through this turmoil. The only relief from the constant, relentless terror that has invaded our family life since our son's diagnosis, is since he has been receiving Vorasidenib . His mental health has improved immeasurably and as a result we have been able to cope better. He has not had any seizures in the last year, this is such a massive relief, we dare to 'breathe again'". **PLEASE ALSO SEE THE ADDITIONAL "PATIENT EXPERIENCES" DOCUMENT WHICH HAS BEEN SENT TO NICE SEPARATELY PER THEIR AGREEMENT**
2	**Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** **No.** A. The committee's decision does not put sufficient weight on the clinical evidence or patient impact. The committee accepts that the rarity of low-grade glioma makes long-term data collection extremely difficult but then rejects the treatment on that basis. This appears to penalise rare cancer patients simply because of their small numbers. B. Inconsistent treatment of "uncertainty". In recent evaluations of rare cancers (e.g. CDF-DCA-TA658) NICE has accepted managed access arrangements to gather further evidence while allowing patients immediate benefit. The committee states that 'collecting more evidence is unlikely to resolve uncertainties' - yet also requests further analysis which appears contradictory. Real-world access can generate the evidence the committee suggest is missing and the **Cancer Drugs Fund** would allow further data collection.

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	C. Patients on watch and wait often live with constant fear, unable to plan families, careers, or drive. The INDIGO study showed fewer seizures and better stability - outcomes that directly translate to independence and mental health. These factors are inadequately reflected in the economic model's utility values. The impact on carers - parents\carers watching their child, partner or family member deteriorate while waiting for the next scan - is not captured at all. D. Low-grade glioma patients in the UK face a unique injustice: after surgery they are told to wait until the tumour worsens before receiving any active treatment. That 'watch and wait' approach might have been acceptable when no other option existed. But with Vorasidenib, there is now a safe, targeted therapy proven to delay progression. For many families, this drug represents the difference between years of meaningful life and early neurological decline. To deny access on cost-modelling grounds while accepting its clinical effectiveness is not just a technical issue - it is an ethical one. NICE's own principles include equity and proportionality. The decision as drafted risks reinforcing a sense that brain tumour patients are treated as less deserving than those with other cancers that benefit from modern targeted drugs (see equality further below). E. At para 3.15 p25 the committee refer to the EAG assessment that there was “only a small decrease in quality of life between the public and people in INDIGO whose glioma was progression free”. This statement does not reflect the fact that those patients in INDIGO would either be on treatment or believe there was a very good chance they were on treatment, therefore their mental health would be much improved. This is colloquially known as the “placebo effect” where a person’s belief can trigger a response that improves their symptoms.
3	3. **Are the provisional recommendations sound and a suitable basis for guidance to the NHS?** **No.** Clinical benefit is clear but undervalued. The INDIGO trial showed a doubling of progression-free survival compared with placebo (median 27.7 months vs 11.4 months) with a favourable safety profile. Patients remained stable for longer, needed less intensive treatment, and experienced fewer seizures. These outcomes are highly meaningful in a disease where quality time and cognitive function are everything. The draft guidance states that survival benefit is 'uncertain' because the data is immature. That is true of every emerging therapy for rare, slow-growing cancers. Mature survival data will take years - but the progression benefit is real today. **Managed Access/Cancer Drugs Fund:**

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	We believe the Committee has rejected the Managed Access/Cancer Drugs Fund scheme too easily. The committee listed key uncertainties in the model including; A. **Time to Next Intervention (TTNI):** o The Committee suggested the TTNI evidence was uncertain because people in the placebo arm were later offered Vorasidenib. The Committee found collecting more evidence during MAA period would be unlikely to resolve the uncertainty (para 1.2 p4). However (para 3.11 p20) the Committee acknowledged the EAG thought the additional data expected in May 2028 would "reduce the uncertainty around Progression free survival and TTNI'. B. **Overall Survival (OS):** o Given the slow and progressive nature of the disease, answering this question would require long-term follow-up over many years. There have been past examples of NICE approving an MAA despite finding MAA could not resolve uncertainties relating to overall survival. (Ref TA658.) C. **Quality of Life (QoL):** o The quality of life data is already well documented in literature and this could be strengthened by additional data collection of people from patients from the clinical trial, patients from the named patient programme currently running, and extra data collected via CDF. We also note the Committee did **not find it impossible** for more data to be collected - only that it might not be sufficient. In any event we suggest that existing data on disease progression, time to malignant transformation (already noted by the Committee at para 3.1 p5) and overall survival can be used for assessing treatment benefit. We ask the Committee to have regard to the NICE, "Our Principles" as we believe these are very relevant to the NICE decision. In particular; • **Principle 8 – Support innovation:** NICE aims to encourage and support innovative treatments that address **unmet** needs and advance care. • **Principle 9 – Reduce health inequalities:** Guidance should offer particular benefit to the most **disadvantaged** groups, ensuring fair access to effective treatments.

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	• **Principle 11 -Research and Data Collection:** NICE explicitly supports proposing **new research questions** and **data collection efforts** to **resolve uncertainties** in the evidence. So whilst the committee expressed doubts that managed access data collection would fully resolve uncertainties about Vorasidenib, existing evidence and the potential for real-world data suggest that **targeted data collection** could meaningfully **reduce uncertainty.** This would be consistent with NICE's principles of supporting innovation, reducing inequalities, and encouraging research to fill evidence gaps.
4	**4. EQUALITY;** The NHS constitution recognises the NHS has a duty to each and every individual that it serves and must respect their human rights. **At the same time, it has a "wider social duty to promote equality through the services** it provides and to pay **particular attention to groups or sections of society where improvements in health and life expectancy are not keeping pace with the rest of the population."** NICE published principles provide focus on the morals ,ethics and values that underpin recommendations: **'Our Principles 9** ; '**Reduce inequalities** ', '**offering particular benefit to the most disadvantaged'** - this group of mainly young people facing a devasting diagnosis without recourse to a treatment , unlike other cancers, brain cancer is not keeping pace with health and improvements in life expectancy , hence this group of mainly young people are some of the most **disadvantaged** in the current health regime . **AGE** The committee acknowledges that many people with LGG IDH1 and IDH2 mutation may be young and that 'Age' is a protected characteristic under the Equality Act 2010". The guidance states that the 'recommendation' does not restrict access to treatment for some people over others" (thus concluding there were 'no equality issues relevant to the recommendations'). However, as the condition is common in young people – it is not clear the committee considered; a) the differential impacts on the group who share the protected characteristic of 'Age', by not supporting NHS funding and b) how they have addressed their duty under s149 (1) (b) Equality Act to promote equality between protected groups. In particular, the effect of denying NHS treatment to a protected group (age) while other groups are better supported by funded technologies

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	and treatments across the NHS patient population. Brain cancer is the biggest killer of children and young people under 40.
5	**5. INNOVATION.** NICE has a statutory responsibility under the *Health and Social Care Act 2012* to have regard to the desirability of promoting **innovation** in the provision of health services. We are concerned that the current recommendation does not sufficiently reflect this obligation. **Principle 8 of NICE's "Our Principles" commits NICE to supporting innovation,** recognising the importance of encouraging the development and adoption of new and promising health technologies that address **unmet needs**. Vorasidenib represents precisely the kind of innovation that **Principle 8** seeks to promote — a targeted therapy for people with IDH-mutant gliomas, a condition with very limited existing treatment options. By concluding that further data collection through a managed access agreement would be unlikely to resolve key uncertainties, despite acknowledging that it is possible to collect more data, the committee's decision risks discouraging innovation and delaying access to a treatment that could meaningfully improve patients' lives. A managed access approach would have allowed evidence gaps to be addressed in real-world settings while supporting **innovation**, consistent with both NICE's statutory duties and its own ethical principles. **CONCLUSION** **We request the Committee reconsider its decision and recommend Vorasidenib to be used to treat grade 2 astrocytoma or oligodendroglioma with a susceptible isocitrate dehydrogenase (IDH) 1 or IDH 2 mutation in people 12 years and over who do not need immediate chemotherapy or radiotherapy after surgery.** **Alternatively, recommend Vorasidenib be used with managed access.**

Insert extra rows as needed

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ASTRO BRAIN TUMOUR FUND
NICE COMMITTEE MEETING 20TH NOVEMBER 2025
APPENDIX TO DRAFT GUIDANCE STAKEHOLDER COMMENTS FORM
ADDITIONAL INFORMATION TO ITEM 1
PATIENT EXPERIENCES

WATCH AND WAIT PATIENTS AND THEIR CARERS/FAMILY MEMBERS

K

"My [redacted] is [redacted] and suffers immensely with waiting and then visiting hospitals and not knowing what treatment she will have in respect of her LGG. She is currently on watch and wait until Jan 2026. The idea of taking a pill rather than going through all other treatment would be life changing as currently she thinks her only options going forward will be operations and chemo or radiotherapy. More invasive treatments have already given her suicidal thoughts and she has suffered deep depression and anxiety as a result. Vorasidenib would and does give us hope she can get through this with as little mental health issues as possible".

K

"I cannot express how much it takes it out of us every time we have a hospital appointment booked.
As a carer of an [redacted] person receiving any medical appointments we must plan and organise so far in advance due to my [redacted]'s massive anxiety. We must think about the language we use, the level detail we go into, the meeting length. We often must have 2 of us take her as we don't know how she will react to news. We both must take time off work to do this and often meetings at the hospital can take longer due to my daughter anxiety, meltdowns etc. it has a huge effect on our mental wellbeing too as it is very tiring and can wipe out a whole day for us whereas a person with no mental health needs can come and go to an appointment in the allotted time And probably get on with their day. We unfortunately don't have that as it takes us time to talk events through my daughter after or give her rest time after to process things. If her mental state is not good, she sometimes has to stay with us overnight until she feels less anxious. As a result of this both my husband I and must plan our work around appointments and plan to work at home or work outside of work hours to make up for lost time. I have had to have counselling because of my daughters diagnosis to come to terms with this additional need in her life".

VORASIDENIB PATIENTS AND THEIR CARERS/FAMILY MEMBERS

J

"As a parent of a young woman using vorasidenib it would be catastrophic for her to have this withdrawn from NHS use. My daughter had anxiety and depression on diagnosis of the tumour. After the operation to remove some of the tumour she physically recovered and through work, which is to her a meaning to live, much of the anxiety and depression reduced and with the use of vorasidenib so gained a normal quality of life uplifted by working and gaining friends, so much so she trains people in physical exercise. Removal of this drug would mean, giving up her job, and spiralling back into depression, for she would prematurely have to have radio therapy and chemotherapy. This besides losing her wages, and claiming benefits would destroy her mentally. Vorasidenib has given my daughter a life back for as long as this drug is available to remove it would make her as a shell of a person and would have a disastrous effect on me and her".

M

After diagnosis and on watch & wait for 8 months, I had surgery in 2020 to qualify for the trial drug, Vorasidenib, as it was highly recommended by my oncologist at my cancer clinic in Canada. I have been taking the drug for 5 years now, and I have remained stable. This has allowed me to remain on watch & wait, return to work successfully and raise my family with few limitations from the disease. Immediate improvements were infrequent seizure and headaches and a small reduction in tumour size over a 12 month period. The results of the trial have been very successful and it is currently the preferred drug for me and many other clinics for low grade tumour patients. My oncologist recommends I stay on the drug for as long as possible due to its success. My kids are almost through high school and if the drug allowed me to raise my family through this stage of life, and well beyond, our family is truly grateful for its availability at our clinic". "

S

"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, [redacted] 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".

C

"I was diagnosed with a brain tumour after several episodes of losing consciousness in October 2021. I was determined to carry on working as a [redacted] until I fell off a high stage after [redacted] a spin class and hurting myself. I was forced to give up my passion and being self-employed I lost my income overnight. From then on, I had to move back in with my Dad.

I was referred to the local neurology centre in who recommended my best long-term outcome was to undergo surgery to remove as much of the tumour as possible, with it being in my motor area they couldn't remove it all without permanent paralysis. I had surgery January 2022 waking up unable to move my right side at all. I sunk into a deep depression and did not want to live if I was paralysed. However, my surgeon gave me some hope and told me I could get most movement back if I really worked at physio. Which I did, initially learning to walk, eat and care for myself again. It took 18 months of rehab where I fought tooth and nail to get myself back to a place where I was finally able to work again in a part employed role, this made all the hard work worthwhile, as I just want to help people and help others feel better.

In 2024 I qualified as a [redacted]. For example, one of my [redacted] is returning to activity after partial lobectomy of a lung due to lung cancer. I also aim to push myself physically and raise awareness of brain tumours.

Unfortunately, In May this year I suffered a seizure, and a subsequent MRI showed tumour regrowth. My oncologist applied for me to go onto targeted medication Vorasidenib. Which allowed me to continue living independently, caring for my elderly parents, and working. This gave me

hope and helped my passion for helping people, fundraising, and demonstrating what people with cancer and or disabilities can achieve. For example, obtained the mixed doubles world record of the deadly dozen fitness race. None of this would be possible without Vorasidenib treatment.

The only alternative treatment if Vorasidenib was not available would be for me to have radiotherapy and a year of chemotherapy. As you are well aware these are aggressive and debilitating treatments, especially when targeted onto the brain, I would likely have right sided movement loss, requiring me to be in 24 hour care, unable to look after my parents, be unable to work and having no quality of live.

Overall, I think I am emotionally strong and somewhat resilience to setbacks. But the news about Vorasidenib not getting NHS NICE approval due to financial reasons has shaken me to the core. It really made me question if it is worth fighting anymore. I can't understand why the NHS funds cosmetic surgery for psychological reasons, nicotine replacement and weigh loss injections yet cannot fund life changing treatment for brain cancer patients who have gone through so much trauma already".

J

"Having Vorasidenib has given us a huge part of our life back. Prior to my daughter receiving the drug it felt like we were living with little hope and I suffered from extreme anxiety. She was 27 when diagnosed and our world shattered.

'Watch and Wait' is so incredibly damaging to our mental health as a family. You live from scan to scan, you get more and more terrified as the scan approaches and sob with relief if the scan result shows no change. This is not a sustainable existence for any family and it is incredibly harmful. With Vorasidenib, our anxiety levels reduced considerably. I felt like there was more chance of my daughter living a normal life and avoiding chemo/radio for some years and the damage such treatments can cause. While the drug is in its early days, it gave us hope. We could get back to work, we could all concentrate and focus better, which we needed to do to live our lives productively. We've even been able to organise her wedding which we couldn't even dream of before the drug was prescribed.

Put simply, Vorasidenib has given us our lives back as a family to a considerable degree and given us much needed hope. We're now all functioning, economically active family members with more stable mental health. If Vorasidenib was taken from us I fear for our future and whether we would cope at all.

My daughter's neurosurgeon has explained to us the harm chemo/radio therapy can cause and how Vorasidenib is hopefully able to delay these treatments for an unknown (potentially indefinite) period of time. To remove the drug effectively condemns my daughter to a far higher chance of facing chemo/radio therapy and the damage that we desperately want to avoid.

My daughter is bright, active and works as a senior [redacted] at a [redacted] but if she were to go through chemo/radio it is quite likely that the cognitive impairment she would sustain could end her career".

M

“I’m a pragmatic person and appreciate death is a part of living, I will caveat that with this though, quality of life is more important than quantity.

What Vorasidenib does, for me certainly, is allow me to live a full life as much as anyone can with a looming terminal illness. I can work and crucially I can avoid the trauma, both physical and mental, of the alternative treatments and I am allowed hope.
To have to tell my daughter and those I love and am loved by that this lifeline will be cut off is the hardest part of conveying your decision”.

To me the decision feels somewhat like when a person chooses to cross the road when they see someone less fortunate asking for help in a brutal world avoiding helping when they easily could. I’m sure if it were your brother, mother, son, daughter or even friend you’d do anything to will a positive result for them, as we all would. That is what being human is.
It’s an incredible feat these researchers have pulled off creating a drug that can cross the blood/brain barrier and it is a testament to our innovative spirit as a species. We all deserve a chance to live the best life we can, this disease is not a self inflicted condition. It’s a ticking time bomb and this drug is the safety mechanism that prevents the explosion. I truly hope you consider the ripple effects of a decision like this.

A

“My son had his first seizure last November and was subsequently diagnosed as having a large brain tumour. This came as a massive shock not only to him but to every family member. My son is a father, a beloved son and brother. We were told that this tumour was most likely Grade 3 with the expectation that it may have already moved towards being Grade 4 or was at the point of doing so. My son had a Craniotomy during which approximately 80% of the tumour was removed. We were all massively thankful for his successful outcome and to the wonderful team. Even more so when it was confirmed that it was still Grade 2 ,an Astrocytoma with IDH mutant gene although this could turn to a higher grade at any point.

My son recovered well and was given the opportunity to take Vorasidenib- which we were all supportive of. Chemo and Radiotherapy have very damaging long term effects on the brain meaning patients often have cognitive difficulties with motor difficulties too.

My son recovered well and has been working to support himself financially and his daughter. He still has to cope with fatigue and seizures - for which he takes medication - but Vorasidenib gives him the hope of a longer and productive life.

As a family we have seen the huge effort he puts in to keeping a healthy lifestyle to ensure that he remains alive and thriving in the face of this devastating illness. We all feel anxious and involved at every point on his journey.

Unless they walk in our shoes the NICE members will never know how cruel and backward their decision is - to literally take away years of life from our loved ones.

Vorasidenib is the only drug to successfully cross the blood brain barrier and prove effective in halting growth for LGG brain tumour patients. The benefits for all brain tumour patients are being explored but if it is not passed because of financial considerations it is a complete travesty and belittling of our NHS -which we all pay for”.

J

“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 given the stomach lurching diagnosis of a brain tumour by the local hospital. The emotional pain and shock were and are indescribable. Our son's diagnosis was 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. The crass and callous comments of the consultant at the local hospital made our son feel even more anxious and afraid. We were left feeling crushed and helpless. There was no relief from the nightmare.

The impact on him and us was and is beyond words. I hid my anxiety from my son and would go to the bathroom to weep. I could not sleep or eat and was in no fit state to work and so took unpaid leave in order to process my son's diagnosis and to support him. I was unable to emerge from my private grief and make proper contact with friends and other family members. There was a feeling of disbelief as you are so consumed by pain and yet the rest of the world is carrying on oblivious to your devastation. As a family we could not share one another's feelings; there was no emotional room left over to even acknowledge them. We were all broken.

Our son withdrew. He started to train excessively and finally admitted he did this as the pain of exercise was the only time he was not thinking about the brain tumour. I wondered if his depression and anxiety and difficulty in planning and organising were all linked to the frontal lobe tumour. I sensed his feeling of fear, isolation and vulnerability.
The next few weeks were a blur of scans, tests and worry. Another admission to the local hospital brought with it bleak moments of despair.

Having been referred on to hospital our son underwent tumour resection in February 2020, and biopsy later identified the tumour as an astrocytoma. 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. We needed hope otherwise there was only darkness.
As a parent it is like waking up in a nightmare with no way out. There is no relief from the anxiety and sadness. It is all consuming. It is the first thing you think of when you wake up, and having struggled throughout the day, the last thing you think of at night. 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.

In 2022 an MRI scan showed evidence of tumour regrowth and our son was referred to the local neuro centre where there followed a period of ‘watchful waiting’, a state of uncertainty which was frustrating and stressful and made us feel constantly anxious. 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. In the meantime, we had become aware of the Indigo trial and the success of Vorasidenib however, although our son was clinically eligible to participate, the trial had closed. This was obviously hugely disappointing.

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 a highly active and competitive athlete, and the prospect of these treatments had an immediate detrimental effect on his physical, psychological and emotional wellbeing. Plans he had made would have to be cancelled and his life put on hold. Then, immediately prior to commencing radiotherapy, the hospital offered our son access to Vorasidenib on a compassionate

use basis. Our son was ecstatic, as were we! His quality of life would now not be affected by arduous radiotherapy and chemotherapy treatments and its side effects, and instead of the onerous regime of daily travelling to the hospital, he could take oral medication at home. This was an immense relief. He could now carry on with his everyday life and reinstate his plans.
Our son has now been taking Vorasidenib every day since May 2024. He has been having MRI scans at three monthly intervals and thankfully the tumour has remained stable with no further regrowth. Additionally, four weekly 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.

So NICE, in a nutshell, would rather all these (mainly young) people go through the rigours of both the short term and long term effects of radiotherapy and chemotherapy instead of getting on with their lives by taking oral medication daily all because of cost. Also NICE are not prepared to consider that Vorasidenib may delay/stop these hideous tumours from growing and are denying hope to all those affected.

Vorasidenib improves quality of life and gives hope when previously there was none. By giving hope, this new drug manages to reduce anxiety for both the patient and his/her family, who previously felt powerless and desperate, living with the relentless fear of the unknown and wondering when and how fast the tumour would progress. There is now a possibility that tumour growth will be halted.
'Watchful waiting' results in a state of uncertainty and continuous stress just waiting for the time bomb to explode.

Radiotherapy and chemotherapy cause anxiety due to the worry of both short term and long term side effects of both, particularly a decline in cognitive function. The fear of tumour progression and undergoing existing treatments cause physical, psychosocial and emotional distress. The list is endless but includes:-

General anxiety
Scan anxiety
Insomnia
Anorexia
Low mood
Depression
Sadness
Helplessness (there is a feeling of living in a perpetual nightmare with no way out)
Despair
Isolation (as others are carrying on oblivious to your devastation)
Negative impact on work, causing financial loss and hardship
Unable to drive, causing loss of independence and, in some cases, employment
Loss of self esteem because of the above
Adverse effects on partner, children and family

When undergoing radiotherapy and chemotherapy:
Plans cancelled and life put on hold
Unable to participate in competitive sport

Unable to attend social events including weddings

Vorasidenib mitigates some of the above and enables a return to normal life. The development of Vorasidenib means there is optimism for the future for the first time".

H

In November 2019 our son, then 25, was diagnosed with a Grade 2 Astrocytoma IDH2 brain tumour. The news was obviously devastating. In February 2020 he underwent surgery during which most of the tumour was successfully removed.

Regular MRI scans over the following two years showed no tumour regrowth, but in 2023, following a referral, regrowth began to become apparent and was confirmed as being definite in February 2024.

Our son was consequently in the process of clinical preparation for radiotherapy and chemotherapy when we received notification that the drug Vorasidenib had become available on a humanitarian, named-patient basis. This news was immensely encouraging, both for our son and for his partner and for us, his family; we had all been dreading the considerable downsides of the standard treatments. We had heard about Vorasidenib and the optimism it had generated in the USA but had hitherto been under the impression that it was unavailable in the UK. So, this was great news, and the neuro oncologist promptly changed our son's course of treatment from radiotherapy and chemotherapy to a daily oral dose of Vorasidenib. Since then, regular scans at three monthly intervals have shown complete stability and no tumour regrowth. Monthly blood tests have shown our son to be very tolerant of the drug with minimal, if any, side effects.
We wrote earlier this year that the then four stable MRI scan results since he commenced taking Vorasidenib had given our son a growing sense of optimism for his future and he is pinning his hopes on having continued access to this excellent treatment which is, on the strong and growing evidence of our personal experience, showing signs of being effective at slowing or halting tumour progression.

Over the last 18 months, our son's emotional state has continued to follow a cautious but upward trajectory as each three-monthly scan has delivered good news. In the last six months he and his partner have purchased their first property, and their small businesses are beginning to thrive. We can say with near certainty that none of this would be happening without the intervention of Vorasidenib. Furthermore, our son has only last week been informed that his MRI scans will, from now on, be every six months. This has further boosted his and our confidence in Vorasidenib and elevated our hopes for the future.
We fully appreciate that this medication is currently not a cure, but we know that it is effective and, furthermore, that there are emerging methods by which that effectiveness may be improved. For instance, we are active fund raisers for Astro Brain Tumour Fund, a charity currently giving financial support for research into the use of focused ultrasound to improve the uniformity of delivery of Vorasidenib to tumour tissue. We fear that if the drug becomes unavailable then this research will become pointless

As a family, we have been daring to hope that Vorasidenib may soon begin to deliver a reduction in the size of our son's tumour. We understand that our optimism is shared by many families in the brain tumour 'community'.

We are alarmed and bewildered by the recent news that the National Institute for Clinical Excellence has declined to recommend that Vorasidenib be made available through the NHS. Apparently, the reason for this determination is lack of evidence of cost-effectiveness. In response, we would ask how can a decision based on cost-effectiveness be made when evidence of that very cost-effectiveness continues to accumulate? As our son progresses free of tumour regrowth, does not the evidence that Vorasidenib is cost-effective become more compelling?
This determination has put us in a state of very high anxiety. We urge NICE to reconsider its decision and allow the NHS to make Vorasidenib available to this group of very vulnerable patients"

G
"My son started this journey in August 2019 at the age of 37 having had a one off seizure at work; a craniotomy leaving residual tumour that was classified as a Grade 2 oligodendroglioma IDH mutant 1p 19q co-deleted . After six years of continuous stress, anxiety and uncertainty we were finally offered some hope when Vorasidenib came along. Since taking it for over 12 months, he has had only one seizure while before we were constantly on tenterhooks when these had become monthly. Vora has provided an amazing improvement to our mental wellbeing. The thought of returning to the previous worry, sleepless nights and nightmares with the consequential physical and mental health implications, leaves us devastated".

A
"My son has returned to being more positive, chatty and so much more fun and happier. Almost the son I knew of pre 2019. He is planning a ski/ snowboarding trip for January which he has been reluctant to do for quite a while due to the seizures..

He has chosen 'Watch & Wait' twice now after second opinions from experts and I cannot contemplate how he would deal with the consequences of chemoradiotherapy and am not sure he would go through with this. He is determined 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.

We, his parents, are 77 early next year and the future for all of us, after the negative NICE decision, now feels again very bleak and uncertain.

I consider that it is too early with the curtailed trials to predict the long term positive effects of the drug. We read that it is so far showing reduction in seizures and even stopping the growth or reducing the tumour. It does seem to be doing this in my sons's case. We are bewildered that this possibility will be lost if unavailable to the small number of sufferers in England. Other family members and friends will be very sad if he has to return to the previous non Vorasidenib regime. He still works full time and travels abroad with a top trades events company; continues to live independently; socialises well and supports his friends and their families as well as ourselves. We are proud that he is independent and hasn't claimed any state benefits so far. We envisage his positive attitude will disappear if Vorasidenib is withdrawn and he is eventually forced into chemoradiotherapy.

These are some of the effects that this disease has had on my son and our family. Constant anxiety, uncertainty, lack of sleep, not being able to live a full life, stress, fractured family relationships, frustration of being unable to help him, happiness becoming rare or non existent and sadness. Life has not been the same for any of us involved since August 2019. His surgeon warned us!"

H

“This is something that is close to my heart after being diagnosed with a Grade 2 Astrocytoma on 24th July 2025, at the age of 33, when my first baby was only 6 weeks old. I went into A&E on 13th July 2025 with persistent headaches, double vision and vomiting, was transferred to a neuro oncology centre and had a craniotomy on 16th July, the day before my baby turned 5 weeks old. We returned home on 19th July.

I started Vorasidenib on 27th September via the Early Access scheme. Given the positive feedback from people on the drug (including that their tumours have shrunk in some cases) and the INDIGO trial results, it is therefore disappointing to see that NICE have issued a draft that it won't be recommended for use on the NHS. It feels like they are not only saying that my life isn't worth it, but also that my son deserves to grow up without a mum. All I've ever wanted to do was work hard in a job I enjoyed, so that I could make a positive contribution to society and support a family of my own. To have this ripped away by a brain tumour that I've done nothing to cause is heart-wrenching. To have NICE reject Vorasidenib, when all other treatments negatively affect quality of life, feels like the final nail in the coffin”.

L

“My partner of 11 years was diagnosed with an astrocytoma grade 2 IDH mutant, we are traumatised by this news but he underwent surgery and was offered vora - we saw light at the end of this dark tunnel, now our hopes have been shattered that he will only get it for 18 months. He is 39 years old. How can you put a price on someone’s life? It’s gut wrenching. Robbing us of precious time. Please give us all hope again. We have a mortgage and he hasn’t worked since February, our world has been shattered. He wants to work again but it’s a ticking timebomb. Why would anyone just wait for chemotherapy and radiotherapy to destroy their bodies and even further damage his brain when there are other options? Please have compassion. From a heartbroken 33 year old mum who needs her husband”.

D

“As parents of a 27-year-old son diagnosed in mid-2024 with a low-grade oligodendroglioma (IDH mutant), we have lived through the extreme anxiety and uncertainty that accompanies the “watch and wait” approach. Our son is a [redacted] working on serious and complex [redacted] — a job that demands sharp cognitive function, emotional resilience, and focus. Following his diagnosis and partial resection, we were told that further surgery, chemotherapy or radiotherapy would almost certainly result in lasting neurological and cognitive impairment, likely ending his career and dramatically reducing his quality of life.

During the initial watch and wait period, our whole family lived under a shadow of constant fear. Each MRI appointment brought weeks of mounting anxiety, sleeplessness, and intrusive thoughts about what the next scan might show. There was a pervasive sense of helplessness — knowing that a tumour was present but that no safe or effective treatment option was available. For our son and his wife, newly married and both in the early years of their careers, this uncertainty was devastating. For us as parents, it was heartbreaking to see their future clouded by fear rather than hope.

Everything changed when our son was granted early access to vorasidenib in January 2025. From that moment, the atmosphere within our family shifted from despair to cautious optimism. The knowledge that he was receiving a targeted treatment, supported by promising clinical trial results, gave him something profoundly important: *hope* — hope of delaying tumour progression, hope of

avoiding the debilitating effects of radio- or chemotherapy, and hope of maintaining his ability to live a full and meaningful life.

The positive impact on his mental health has been striking. He has regained his confidence, his motivation, and his sense of purpose. The fog of anxiety that hung over him (and, by extension, us) has lifted to a great extent. He is once again able to concentrate fully on his demanding work and to plan ahead — something that had seemed impossible only months earlier. As parents, we have seen a visible and emotional transformation not only in him but also in his wife and siblings. There is a renewed sense of stability and normality in their lives.

The thought that this treatment, grounded in science, might now be withdrawn is deeply distressing. To take away a therapy that has provided such tangible improvement in wellbeing — without any alternative of similar effectiveness or tolerability — would be cruel and profoundly damaging, not only to patients but to their families who share every step of this journey.

Vorasidenib has, in our experience, been the single most important factor in restoring hope and quality of life to our son and to those who love him. Its continued availability would not just be a medical decision — it would be a humane one”.

C

“My son, age 29, was diagnosed with a grade 2 astrocytoma last year and underwent a craniotomy in February. He was accepted for Vorasidenib on the managed access programme. Had he not, there would have been no further treatment, just watch and wait - worrying for him and us. He so pleased to have this drug to delay regrowth of his tumour. It has given him hope that he will have longer to work and to enjoy his life. He is now really anxious that he will not be able to take the drug after the managed access program ends and that this may mean that his disease progresses more quickly, affecting his quality of life and ability to work”.

R

"We discovered my wife had an astrocytoma just over a year ago. We have 2 young [redacted] (aged 4 and 2) and I have a very busy job as a [redacted] of a local [redacted].
With the use of Vorasidenib we have been able to keep things as normal as possible for the boys, though it’s not been easy. It’s been so valuable for her to not have gone through chemo or radiotherapy at this stage of family life."

E

"I am a 30 year-old mum to a 4 year-old and an adopted 2 year-old. I was diagnosed with an astrocytoma last August and it radically changed my life.
I had surgery in November 2024 with a slow recovery. I still need family support to get through a day on my own with the [redacted]. I am now on vorasidenib and I couldn’t imagine the difficulty of going straight into radiotherapy and chemotherapy after the trauma of surgery and the impact that it would have on our young family.
Every day that I live without the long term effects that radiotherapy and chemotherapy have on the brain is another day where I can give as much of myself as I can to my [redacted]."

PATIENTS WHO HAVE HAD CHEMO AND/OR RADIOTHERAPY & FAMILY MEMBERS

B

“My wife has a grade 2 oligodendroglioma. She was on watch and wait for over 10 years before a year of radio and chemotherapy in 2019. Treatment was a very stressful year, provoking considerable anxiety and fatigue, and needing extensive travel and time off work for both of us across the year. Now back on watch and wait, it is an ongoing period of anxiety and impacts our quality of life significantly, with no further treatment available unless the tumour progresses”.

C

“I have a diffuse grade 2 astrocytoma and had surgery in May 2023. They were only able to remove 40% so I then had 6 weeks of daily radiotherapy followed by 12 months of chemotherapy. The treatments have left me with memory loss, lack of focus, reduced ability to retain information, poor attention span, increased seizures, increased infections, balance problems, nausea, IBS, anxiety and depression. The fatigue is relentless and I have been unable to return to my old job as a [redacted]”.

A

“So, I can’t have surgery, I can’t get hold of VORASIDENIB and my Oncologist is one of those who is giving it out on compassionate grounds, I’m not suitable for LITT and I’ve had my dose of R/T and am now living with the side effects of having no balance so my walking is shot so now use a walking stick and hold on to my husband, frequent falls, frequently forget what I was saying mid sentence and the list goes on”.

M

“I was diagnosed with an inoperable right parietal oligdendroglioma in 2018. My primary treatment was 6 rounds of PCV which controlled the tumour for 5 years. Last year a routine scan showed some minor growth so I had 30 radiotherapy sessions followed by adjuvant Temozolomide chemotherapy. Both types of chemo affected me badly(severe allergic reactions, constipation and fatigue) and had to be reduced. The radiotherapy has caused some improvement but I have a degree of short term memory loss and some slight visual deterioration since the RT. I currently suffer from bouts of fatigue, headaches and dizziness likely caused by the tumour. My mental health is ok, albeit with some mood swings”.

P

“As someone who has just completed chemo and radiotherapy I have experienced extreme fatigue at times alongside other side effects, not to mention the mental stress of the diagnosis and treatment.

No trials have been done as far as I am aware on patients who have had PCV chemo, but I think one is in progress for the drug in combination with TMZ (which isn't the standard of care in the UK for my tumour which is a Grade 2 Oligodendroglioma)
Ruling patients out like myself is very frustrating as the drug does seem to delay progression in those who have it.
It does feel once again low grade patients get less research priority than those with higher grades which on some levels is obviously understandable, but we are no less important”.

L

“My son is now 18 years old and 2 years tumour-free and having regular scans
After a first and then second surgery when he was 8 and 9 years old to completely resect a grade 1 PA, my son was on watch & wait from the age of 11 to 15 when the MDT decided to operate for a 3rd time to remove the recurrent growth. He didn’t know - we managed to keep it from him - but it traumatized me. I was diagnosed with general anxiety disorder. It takes over your life - worrying if every headache, stumble, feeling ill means it’s become symptomatic and will urgently need removing. And the worry of whether he’d survive a 3rd surgery and the impact another surgery will have on the quality of his life, on his education, on his future. At a time when I should have been watching his independence grow, I hated him being out of my sight for fear of what might happen to him - had it now grown large enough to start causing seizures? What if he fell and hurt himself? What if his vision suddenly went blurred (like it did the very first time he was diagnosed)? What impact would that have on a teenager? He wasn’t left alone for worry - I would meet him from school to walk home with him if he had no friend to walk with, one of us would hang around outside the bathroom when he was showering just in case. The anxiety and impact on the carers mental health is debilitating at times”.

P

“My daughter was diagnosed with a grade 2 Astrocytoma 3 years ago. Although much of it was removed she still needed radiotherapy and chemotherapy. This treatment left her unable to work for 2 years due to fatigue, learning to use her hand & arm again and learning to speak again. she is only recently started to build up her stamina. She is 39 and has a young child, all the family needed to help look after her, and her daughter. We are extremely worried as we have been told it will start to grow again, She has 3 monthly scans. What will happen when it does start to grow. I’m not sure she can go through the trauma and physical anguish of chemo & radiotherapy and I am now in my seventies and will not be able to care for her and my granddaughter easily. Vorasidenib is our only hope that it will stop the tumour growing and allow my daughter to look forward to a future where she will be able to continue working as a [redacted] and look after her 4 year old daughter. Please approve vorasidenib and give hope to our family”.

G

“I urge to NHS NICE committee to please think again about recommending Vorasidenib.
My daughter has a grade II astrocytoma IDH mutant. She has had surgery, and this removed much of the tumour, and this was followed by radiotherapy and chemotherapy. However we are told it is likely to grow back, and that the only long-term solution is with Vorasidenib. After much effort with speech and physiotherapists, [redacted] has now gone back to work. She pays her taxes. Please reconsider your decision on Vorasidenib. It may be her only hope”.

S

“We had no choice but to have our son undergo brain surgery that would last eight hours. He bravely accepted this, saying, ‘I am not brave; I have no choice’. He was and remains stoic. I am in awe of his resiliency and courage.

The weeks leading up to my son's surgery made my stomach turn. I couldn’t believe my young boy would have to undergo a procedure to open his skull and remove a vicious tumour. To make matters worse, he was paralysed on one side for several weeks afterwards and had to learn to walk and use his right arm again, regaining full use only after many months. Four years later, he still feels that his right foot does not have the same dexterity it once had.

I was so proud and loved that he was born with the most perfect beautiful round head—. I know this sounds strange but I was. However, during his recovery, he developed a bone infection at the site where the skull had been opened, necessitating another surgery to remove the infected area. This left him with a literal large hole in the top of his head. We lived in constant fear of something falling on him or him bumping his head during this time. I was devastated; to me, it felt as if the surgery had disfigured him.

He eventually had a third surgery to place a prosthesis to replace the skull flap. I have two other children: one is autistic and has psychosis. The time my husband and I had to devote to our son impacted our ability to care for them both as well, which directly affected the well-being of our son with psychosis, leading to the threat of his mental health deteriorating further. If we had time and a respite period before further interventions we could have given more time (if we were not attending hospital appointments for chemo and radiotherapy)to our other children and our sons mental health may not of spiralled further.

One year and 3 surgeries later including a variety of cocktails of antibiotics later post-surgery. Sadly his 3 monthly routine scan only to discover that his tumour had started to I grow. We were advised to have intensive daily radiotherapy and six months of chemotherapy. At that time we had discussed the drug Vorasidenib but could not get access via any means or trials. We were devastated and my son’s worst fears of having to endure Radiotherapy and Chemotherapy were now the only option available unless you follow the tortuous cruel ‘watch and wait’ mantra to cast its devastation to strike its brutal invasion without warning. What a choice for a 22yr old young man who has already been through a year of experiencing continuous antiquated and barbaric treatments. He should have been making plans for his future not another year of being violently sick, scan after scan, blood tests, endless tireless hospital appointments and being further isolated and falling behind his peers and missing all the millstones every young wants to achieve in life. Losing any confidence he had and left with extreme anxiety. Another blow he would have to lose his driving license for even longer after radiotherapy. Due to our son’s high possibility of having further nocturnal tonic-clonic seizures we slept for more than a year on a mattress on his bedroom floor as we were so fearful after witnessing him unconscious several times previously and scared he would not recover and wake up. I regularly may hear a noise and get up to check my son is breathing.

I do not sleep at night worrying in case he has another life threatening seizure.

My husband had to take six weeks of unpaid leave to take him to the hospital every day during this challenging time so our income has been impacted. I have not been able to work now for many years due to my younger sons also have needs, and now there is little prospect of me being able to work again. We live very simple lives and rarely go out or take holidays we have not had a

holiday for 7years. My son has a various gaps in his work history due to several years of treatment.

The radiotherapy and surgeries have left him with a large scar extending from above his ear to the upper left of his crown. He has been unable to regrow his hair after the radiotherapy.and chemotherapy his confidence is rock bottom and will not even answer the door without wearing a cap at all times in public. I can't deny that his appearance has changed, and it saddens me that he has had to face this as a young man. We also notice that he is not as sharp mentally as he once was, and he tends to forget small things and gets tired very easily. He lost his independence as no longer able to drive relying on us for transportation. He has become extremely nervous and riddled with anxiety. He tires easily more since his radiotherapy and chemotherapy and it affected his liver function.

We have had no release from worry and fear; the future brings more of the same without any let-up. Living day-to-day like this is incredibly challenging. If only he had been were allowed just a couple more for him to years to enjoy his life before brutal radiotherapy and chemotherapy. Also for a young man he missed on so many opportunities and the ability to build up more work experience, if he had his prospects now would be much better. That is why I am so angry that this wealthy country can be so shortsighted as to not support Vorasidenib, denying young people the chance to enjoy their lives a bit before they have to face the mountain of pain he has had to endure. NICE are Taking away all Hope purely on an assessment based around accountancy"

Brain Tumour Research – Vorasidenib – response to consultation on the draft guidance 04/11/25

- We must be clear here that the choice for a patient is Vorasidenib or 'Watch and Wait' (Active Surveillance) "a concept I found unbearable" – which essentially means it is Vorasidenib or nothing.
- The Lancet Oncoloy 29 October 2025 - Vorasidenib in IDH1-mutant or IDH2-mutant low-grade glioma (INDIGO): secondary and exploratory endpoints from a randomised, double-blind, placebo-controlled, phase 3 trial.Interpretation: Vorasidenib reduced tumour growth rate and improved seizure control compared with placebo, with no observed negative effects on HRQOL or neurocognition. Additional follow-up supported the robustness of progression-free survival and time to next intervention in patients with grade 2 IDH1/2-mutant diffuse glioma. These findings support the use of Vorasidenib in patients with grade 2 IDH1/2-mutant gliomas who only had surgical intervention and are not in immediate need of radiotherapy or chemotherapy.
- How might the treatment landscape change for these patients following a Vorasidenib enabled period of Progression Free Survival? What innovation for these patients is around the corner that following a period of PFS they are then able to access?
- There isn't the maturity of data to demonstrate average time to further interventions or how patients react to these interventions is influenced by being previously on Vorasidenib – to accumulate that could take a decade plus. Do we wait for that? – there are precedents (e.g. in breast cancer) where NICE have said no – we don't wait. Can we do that in the case of Vorasidenib?
- According to one neuro oncologist who has 22 patients on the Servier managed access programme – "they are all doing well"
- What further opportunities are there for Vorasidenib to teach us more about other forms of brain cancer including the transition for low to high grade glioma and applications post, or in combination with, chemotherapy and radiotherapy
- If there is ambiguity about time to next intervention could this ever be standardised as each patient is different. Is this looking for data that is not only not ready now but in reality will never be available?
- "I'm currently too young to be considered for harsher treatments such as chemotherapy or radiotherapy." The disproportionate impact on younger patients means that much of the feedback received from Patient Advocacy Groups such as Brain Tumour Research is from parents. Many of these may then have to curtail their working hours to support child care. They may also be poorly affected by the level pain and distress only a sick child can bring.
- **Patient experience:**

"Vorasidenib became a shining beacon of hope.

Since then, taking the medication has been simple. I have experienced absolutely no side effects and have felt completely well. Even better, I've now had two MRI scans showing that the small portion of tumour left behind (to preserve function on my left side) has remained completely stable and unchanged.

The relief of having access to this medication cannot be overstated. Living under "active surveillance" is incredibly anxiety-inducing, and that would be my reality again if I lost access to Vorasidenib. Instead, I now approach MRI scans with calm and even optimism — sometimes

even excitement at the thought that perhaps this will be the scan that shows a little shrinkage, if I'm lucky enough to experience that

This drug has given me my life back.

Vorasidenib may only work for me for a few years — but those years will be ones where I am living, working, raising my children to become wonderful adults, and enjoying life as a wife and daughter.

This drug is everything to me and my family. Every morning when my early alarm rings so I can take my tablet, I feel grateful — grateful that despite the terrible luck of developing a brain tumour, it happened to be one that could be treated with this incredible medication."

- **Patient Experience:**

"After surgery I lost 40 years' worth of nerve connections, so e.g. my balance is at the level of a2-year-oldd and I have falls fairly frequently, but with an adult weight! - Obviously Vorasidenib would have been vastly preferable!"

- **Parent Experience**

"More invasive treatments have already given my daughter suicidal thoughts, and she has suffered deep depression and anxiety as a result. Vorasidenib would and does give us hope she can get through this with as little mental health issues as possible".

"Much of the anxiety and depression my son suffered reduced with the use of Vorasidenib so he gained a normal quality of life uplifted by working and gaining friends"

- **Parent Experience**

Radiotherapy and chemotherapy cause anxiety due to the worry of both short term and long-term side effects of both, particularly a decline in cognitive function. The fear of tumour progression and undergoing existing treatments cause physical, psychosocial and emotional distress. This is how distress manifests itself:

I. *General anxiety, Scan anxiety, Insomnia, Anorexia, Low mood, Depression, Sadness*
II. *Helplessness (there is a feeling of living in a perpetual nightmare with no way out),*
III. *Despair, Isolation (as others are carrying on oblivious to your devastation), Negative impact on work, causing financial loss and hardship*
IV. *Unable to drive, causing loss of independence and, in some cases, employment*
V. *Loss of self-esteem because of the above*
VI. *Adverse effects on partner, children and family*
VII. *When undergoing radiotherapy and chemotherapy - Plans cancelled and life put on hold, Unable to participate in competitive sport, Unable to attend social events including weddings"*

"We were advised to have intensive daily radiotherapy and six months of chemotherapy. At that time, we had discussed the drug Vorasidenib but could not get access via any means or trials.

We were devastated and my son's worst fears of having to endure Radiotherapy and Chemotherapy were now the only option available unless you follow the tortuous cruel 'watch and wait'. We notice that he is not as sharp mentally as he once was, and he tends to forget small things and gets tired very easily. He lost his independence as no longer able to drive relying on us for transportation. He has become extremely nervous and riddled with anxiety. He tires easily more since his radiotherapy and chemotherapy, and it affected his liver function"

- **In the draft guidance we don't think seizures were adequately considered.**

The Vorasidenib data says the drug reduces seizures by 64%.

- Seizures take a heavy toll on patient mental and physical health.
- They have distressing effects on family members.
- There are resultant costs for the NHS.

From a carer

Vorasidenib is *"A treatment where one didn't exist before. Not a better treatment, the only treatment. A new and targeted, innovative treatment, a treatment that delays the time until the cancer gets worse, a treatment to be set against the woeful landscape for brain cancer patients."*

- Overall survival data - is always going to be difficult with a relatively slowly progressing disease but if rejected on that basis no drug for this group of patients would ever be available unless a trial was run over 15-20 years.
- This isn't just about life years lost but loss of 'life' years – normal life - life meaning working, driving, playing, being a parent, contributing, avoiding anguish and uncertainly. What price these 'life' years. Not just being alive but having a life.

I know I have added quite a bit of content from patients and their families and that some of it is similar to that inputted into the original call for evidence however there is such strength of feeling and the need is so great that I would be remiss in my role not to provide at least a taste of the content I have been receiving since the first NICE decision was made public.

I am leaving the final word to the parents of another young patient:

The committee's draft decision undervalues meaningful benefits demonstrated by vorasidenib and mischaracterises the nature of uncertainty in the evidence.

The INDIGO trial showed a clear, clinically significant improvement in progression-free survival (PFS) and an even larger gain in time to next intervention (TTNI) - a direct measure of how long patients can safely defer radiotherapy or chemotherapy. In low-grade glioma, deferring genotoxic therapy is a recognised treatment goal because it preserves cognition, fertility, and quality of life over potentially decades of survival. The absence of a proven overall survival (OS)

gain is not surprising in a cross-over trial with long post-progression survival; OS is the wrong metric in this setting and should not be treated as a failure of evidence.

The economic model appears to undervalue quality-of-life gains from reduced seizure frequency, delayed neurocognitive decline, and avoidance of fertility damage. These are tangible outcomes with NHS cost implications - fewer emergency admissions, less long-term rehabilitation, and lower need for assisted reproduction or hormone therapy. Moreover, the model's assumptions about time to new treatment contradict the INDIGO data, biasing results against vorasidenib.

International regulators (MHRA, EMA, FDA) have already accepted these benefits and approved vorasidenib. The NHS now risks becoming an outlier, denying access to a therapy that changes the disease trajectory for predominantly young adults.

The appropriate path forward is conditional adoption under managed access. This would generate UK-specific real-world data on TTNI, seizure control, quality of life, and resource use—precisely the evidence the committee finds lacking - while giving patients timely access.

Vorasidenib demonstrably delays disease progression and toxic treatment. It offers patients more normal years of life, which the NHS should value. Conditional approval with evidence collection, not rejection, is the rational and ethical choice.

Vorasidenib doesn't just buy months of PFS; it buys time off chemo and radiotherapy with fewer seizures - benefits regulators have already accepted and which the draft model under-prices. Those "uncertainties" are precisely what a targeted managed-access scheme would answer, so the right call is conditional NHS adoption, not a blanket "no."

NICE National Institute for Health and Care Excellence

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

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on **Tuesday 4 November 2025**. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	British Neuro Oncology Society (BNOS)

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Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	Has all of the relevant evidence been taken into account?

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	We cannot identify any additional relevant clinical data since the literature review of May 2024.
2	Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? Trial Data Limitations: Several comments were made on the lack of Overall Survival (OS), Quality of Life (QoL), and cognitive function data reported directly from the INDIGO trial. It is recognised that the trial's focus on primarily on PFS – (Progression-Free Survival) without evidencing direct patient benefits in these crucial areas is a limitation of the available data.
3	The crossover of placebo patients to Vorasidenib treatment after progression is noted as making long-term OS data from the trial less helpful.
4	Comment was also made about lack of data on the incidence of malignant transformation (progression to higher grade disease) in the different treatment groups and lack of information about how many of the patients were treated on the basis of significant residual disease after surgery vs evidence of recurrence.
5	Comments on NICE's Modelling and Underestimation of Benefits: Many commentators state that they believe that NICE's model, particularly around Time to Next Intervention (TTNI), underestimates Vorasidenib's economic and clinical benefits.
6	There is a strong argument that the model does not adequately capture the full benefits of delaying radiotherapy/chemotherapy, including avoiding costly and debilitating side effects, preserving QoL, maintaining cognitive function, and reducing the need for care support.
7	One comment raises the issue of 'distribution of subsequent treatments' in the model which suggests 100% of patients get radiotherapy as first line and then 50% as second line, suggesting a re-irradiation rate of 50% which seems very high and not in line with UK practice.
8	Concerns are raised that some model assumptions may be based on high-grade glioma (HGG) data, which is inappropriate for low-grade glioma (LGG) patients who have a different disease course and different expected patterns of QoL deterioration.
9	The sudden decrease in QoL after the next intervention, which NICE finds unlikely, is argued may be a plausible reality due to the immediate effect of radiotherapy/chemotherapy, however this is hard to gauge in the longer term when later effects of treatment, which will also clearly impact on QoL, appear not to have been addressed.
10	Real-World Clinical Benefits and QoL Impact: The nursing representative on the clinical committee specifically highlights substantial real-world benefits of treatment with Vorasidenib: excellent QoL, ability to work full-time, to drive, to enjoy family life, and travel with minimal to no side effects compared to the impact of radiotherapy/chemotherapy.
11	The nurse representative also notes from personal experience, that patients on Vorasidenib often don't require corticosteroids, maintain cognitive function, and have fewer MRI scans (6 monthly vs. 3 monthly), benefiting both patients and NHS services.

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	These points are seen as crucial but not adequately captured in the company's submission or NICE's model. *Patient on active surveillance also rarely need steroids , we have to acknowledge Vora is proven beneficial in patient for whom wait and watch deemed appropriate.* *I thought MAP suggested having MRI scan every 3 monthly but NICE guidelines suggests that From 0 to 2 years, a scan at 3 months, then every 6 months. So in fact its more scans with Vora.*
12	However it is also relevant that patients on treatment require weekly bloods if LFTs are deranged, which represents about 40% of patients from INDIGO trial data
13	Although people with uncontrolled seizures were not included, it was noted there was a 64% reduction in seizure rate in patients with ≥1 seizure (p=0.026) and not having seizures would have a clear and direct benefit to QoL.
14	Are the recommendations sound and a suitable basis for guidance to the NHS? The lack of transparency regarding the cost per QALY makes it difficult to assess how far Vorasidenib exceeds NICE's £30,000 threshold in an NHS context.
15	International Context and NICE as an Outlier: Several individuals point out that major regulatory bodies (FDA, EMA, MHRA) have approved Vorasidenib based on the INDIGO dataset, suggesting NICE is an outlier. This raises questions about whether NICE is considering the rapidly evolving international standard of care and the rarity of the condition.
16	Are there any aspects of the recommendations that need consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation? Concerns are raised about potential unlawful discrimination, particularly against younger patients with decades of life ahead who stand to lose the most from delayed treatment, face greater socioeconomic impact, and have significant QoL considerations (e.g., fertility, work, family).
17	The availability of Vorasidenib privately post-MHRA approval also creates socioeconomic inequity for UK patients.
18	It is noted that the NICE committee applied a standard cost-effectiveness threshold with minimal flexibility for a rare condition, despite its own manual suggesting it should do otherwise.
19	Suggestions for Resolution: A request to revisit the TTNI model to better account for the costs and harms of earlier radiotherapy/ chemotherapy is suggested. The idea of a Managed Access Programme (MAP) or similar evaluative commissioning scheme is proposed to collect real-world UK data on QoL, cognition, and long-term outcomes, though it's clarified that suggesting a MAP is typically the company's role.

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	There's a strong sentiment that biological plausibility and patient-reported outcomes (e.g., impact of seizures, ability to work) deserve greater weight in decision-making.

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about funding from the company and links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into one response. We cannot accept more than one set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- In line with the NICE Health Technology Evaluation Manual (sections 5.4.4 to 5.4.21), if a comment contains confidential information, it is the responsibility of the responder to provide two versions, one complete and one with the confidential information removed (to be published on NICE's website), together with a checklist of the confidential information. 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 submit a second version of your comments form with that information replaced with asterixis and highlighted in black.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, 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 during our consultations 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.

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Submitted by [redacted], for and on behalf of the International Brain Tumour Alliance (IBTA), a registered stakeholder.

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Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	We confirm that neither the IBTA nor its officers or directors have any past, current, direct or indirect links to the tobacco industry. The IBTA has not received any funding from the tobacco industry.
Name of commentator person completing form:	[redacted], for and on behalf of the International Brain Tumour Alliance (IBTA)

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1.1	Thank you for the opportunity to comment on the draft guidance for vorasidenib for treating astrocytoma or oligodendroglioma brain tumours characterised by IDH1 or IDH2 mutations. The International Brain Tumour Alliance (IBTA) believes that it is appropriate

Please return to: **NICE DOCS**

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	for NICE to recommend vorasidenib for use on a reimbursed basis 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 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 in patients. **(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, epileptic 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. NICE's draft guidance for vorasidenib seems to entirely avoid a mention of the importance of supporting access to innovative treatments like vorasidenib despite NICE's own principle to "Support innovation in the provision and organisation of health and social care services" (Principle 8 - https://www.nice.org.uk/about-us/our-principles). **(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. In short, we believe that vorasidenib addresses a substantial unmet need for people suffering from IDH-mutant, grade 2 astrocytoma or oligodendroglioma and should be recommended for use on the National Health Service in England**. (7)** We also make the point as to the value of a therapy such as vorasidenib in helping people to contribute to society by allowing them to continue to feel well enough to work in light of the fact that vorasidenib delays progression and provides a window of opportunity for patients (especially young adults) to be contributing members of society rather than consuming healthcare resources. The productivity lost to society when the patient may not be able to work is substantial.
1.2	NICE's draft guidance states that "Vorasidenib is not required to be funded and should not be used routinely in the NHS in England for the condition and population in the recommendations. This is because the available evidence does not suggest that vorasidenib is value for money in this population." We disagree. There is a fundamental benefit that vorasidenib extends "how long people have before their cancer gets worse compared with placebo". For NICE to assert that the evidence does not suggest that vorasidenib is value for money in this population denies the significance and vital importance to every patient of extending their progression free period by being able to have access to this medication. We believe that to ignore this

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	crucial contribution is unacceptable and illogical. A progression-free existence for patients is a justified treatment goal in itself.
3.5	Regarding bullet point 1 in the Results section of the draft Guidelines documents which says: "The Committee noted that this would not occur in NHS clinical practice because vorasidenib is not available." This statement appears to be meaningless in the context of the Committee seeking to justify a rejection of vorasidenib. Regarding the statement in the NICE Draft Guidance document: "Data from the March 2022 data cut showed a 64% lower rate of seizures in the vorasidenib arm than the placebo arm (ratio of rates 0.36 [95% CI 0.14 to 0.89])." Seizures in people with low grade glioma are a major challenge. The NICE document also states in Section 3.1 that: "The physical symptoms of the condition [low-grade glioma] can be challenging, especially seizures, which can cause anxiety and affect independence by limiting the ability to drive." It's clear that these aspects can negatively affect the quality of life experienced by low-grade glioma patients. The NICE committee has not sufficiently considered how vorasidenib appears to contribute to a reduction in seizures and, by extension, a reduction in anxiety suffered by patients with low-grade glioma. Reductions in seizures can also result in, for example, savings for the NHS in relation to the costs of hospital admissions, treatment for injuries sustained in falls from seizures and, in some cases, costs of resuscitation during seizure activity in people with low-grade glioma.
3.6	We do not understand how it is possible for the Committee to assert that the exclusion of a group of patients who have had recent resection or who have only a very small tumour will enhance the positive rate of progression postponement for patients who are included in the INDIGO trial. We understand that the patients who have been excluded would be very unlikely to experience progression in the short term. Their exclusion means that those who are included in the trial are more likely to be a valid test of the positive effect of having vorasidenib available to them than if a group of patients with little likelihood of progression during the trial period were to be included within the INDIGO trial.
3.15	The INDIGO trial shows that vorasidenib helps delay progression for low-grade glioma patients. It does not claim to be able to reverse progression that has occurred. However, by achieving a delay in progression, it follows that as an entirely reasonable proposition delayed progression will assist in reducing the anxiety of patients living with an inevitably progressive disease. This positive aspect will also impact on caregivers who bear a substantial burden in supporting their loved ones on the low-grade glioma journey.
3.17	With regard to uncaptured benefits, we agree that it will be important for the company to provide further evidence. In response to the assertion in paragraph 3.17 of insufficient evidence to support return to close to a normal life and the return to work and participation in social events, such further evidence, we agree, would be very helpful as an additional reinforcement of the argument to make vorasidenib available on the NHS. The points the Committee makes in paragraphs 3.17 are essentially criticising vorasidenib as a medication for not achieving longer overall survival. We are not saying vorasidenib can ultimately prolong life but it provides a significantly longer progression-free life. That in itself, we believe, is sufficient to justify the economic cost of making vorasidenib available. Every patient deserves to have the opportunity for a longer progression-free survival. To ignore this benefit for patients with low-grade glioma does

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	not make sense. Vorasidenib could revolutionise the progression-free period of low-grade glioma patients and must not be dismissed because it has not been established that in addition it extends overall survival.
	Thank you again for this opportunity to submit a consultation response.

Insert extra rows as needed

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- Combine all comments from your organisation into one response. We cannot accept more than one set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
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- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Royal College of Pathologists

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Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	[Insert disclosure here] No links to Tobacco industry, in the past or present
Name of commentator person completing form:	[redacted]

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.

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Example 1	We are concerned that this recommendation may imply that ……..
1	I am concerned that Vorasidenib is available through private healthcare, but not in the NHS. This will inevitably create a disparity between people of different socio-economic backgrounds.
2	I am concerned that the Indica trial excludes patients with little or no radiologically detectable residual disease (section 3.6). Diffuse astrocytomas do not stop at the respectable border and due to the infiltrative nature of these tumours there will ALWAYS be residual tumour, even if it cannot be detected by imaging and cannot be assessed into operatively by the surgeon. Residual tumour cells migrate into the adjacent normal appearing brain. Therefore, I believe that a treatment with Vorasidenib would also benefit patients with no "detectable" residual disease, and may indeed delay recurrence was in this patient cohort. This is something the evaluation committee should look into. A prospective clinical trial could investigate this as follows: following a perceived gross total resection or supra-maximal restriction should include small (0.5 x 0.5 cm) samples from the margin. These marginal samples, from the assumed "tumour free" area can easily be tested for the presence of infiltrating tumour cells by means of an Immunostaining for mutant IDH1 (R132H). The antibody is positive in 90% of IDH-mutant gliomas (the remaining tumours have rarer mutations which are not detectable by the antibody).
3	If I understand correctly, progression is assessed by imaging parameters, not by other parameters. (Section 3.7). Even though these are relatively objective and quantifiable measurements, how much do other parameters (epilepsy, other clinical parameters) influence the decision to call a tumour progressing?
4	Assessment of grade: IDH-mutant astrocytomas of the CNS WHO grades 2 and 3 are assessed solely by histological parameters in most centres. However, there are more subtle and refined ways of assessing the molecular underpinnings that influence the tendency to progress. Specifically, a publication (PMID 29687258) has shown that the cumulative copy number variation (CNV) can be an additional/adjunct tool to establish the risk for progression, or, assist in a more objective grading. We perform these tests routinely on all IDH-mutant astrocytomas and report the cumulative CNV in our molecular pathology report of IDH-mutant astrocytomas that do not have a CDKN2A/B deletion. (Briefly, a cumulative CNV of below 350 mega bases showing outcome more akin to CNS WHO grade 2, whilst those above 350 MBases have an outcome more akin to WHO grade 3). Notably, this applies only to IDH-mutant astrocytomas, not to oligodendrogliomas. It may be worthwhile to retrospectively test all IDH-mutant astrocytomas that went into the trial with this method (methylation array, copy number output), to get a better understanding as to why some of these astrocytomas progress faster and some others progress slower, and put this into the context of treatment and outcome (also taking into account the extent of resection). Given the cost of treatment and the health economic assessment, the cost for such investigation is comparatively minor. Another important component is the assessment of copy number changes in the CDKN2A/B locus. This is not entirely consistently assessed across all centres. Some histological grade 2 tumours show an incipient CDKN2A/B deletion, which can be seen on copy number assays derived from methylation arrays, but is often not confirmed/reported on NGS, due to the definition of cut off values. Reassessment of the astrocytoma cohort in the INDIGO trial (using the same methodology as above) might be useful to understand progression of some and non-progression of other tumours with or without treatment.
6	

Insert extra rows as needed

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	The Brain Tumour Charity

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	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/
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	The Brain Tumour Charity does not have any direct or in-direct links to the tobacco industry.
Name of commentator person completing form:	[redacted]

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	The Brain Tumour Charity are concerned that the high unmet need and potential benefit has not been considered as part of the production of this draft guidance. Following the publication of the draft guidance, we asked our community to share their experiences and views through a survey. We have shared this information as part of this response. The survey was available online from Wednesday 15th October to Wednesday 22nd October. **Insights** • 1,316 total responses • 73% (958/1316) responses were from individuals personally affected by their or their loved one's low-grade glioma diagnosis • 28% (370/1316) responses were from individuals who were not personally • affected by a low-grade glioma diagnosis. When asked 'Do you want vorasidenib to be available on the NHS? • 99% (1309/1316) said yes.

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	• 1% (7/1316) said no. Of those personally affected who chose to answer additional questions– • 33% (223/678) were diagnosed with a low grade-glioma • 67% (455/678) were a carer, family member or friend of someone diagnosed with a low-grade glioma. When asked 'Do you think there is an unmet need for patient with this condition (e.g, gaps in treatment or support? • 86% (542/627) said yes • 1% (5/627) said no • 13% (80/627) said unsure
2	Our community shared their experiences of taking vorasidenib, highlighting how this treatment contrasts with traditional approaches and the meaningful difference it can make to daily life. Patients and families describe it as gentler, more manageable, and less disruptive than chemotherapy or radiotherapy, allowing for greater independence, emotional wellbeing, and normalcy. Through their own words, they emphasise both the physical and psychological benefits, the hope it brings, and the urgent need for broader, equitable access. This section draws directly from the lived experiences of patients and families, showing how vorasidenib is already changing lives and offering a vision of care that preserves quality of life while addressing unmet needs. **Experience of using vorasidenib** • Gentler, kinder treatment: Perceived contrast between the harshness of chemotherapy or radiotherapy and the relative gentleness of vorasidenib. Described as "kinder", "non-invasive", "no major side effects" and helping people "feel normal" • Vorasidenib: Oral administration allows for greater normalcy in daily life and "means people can return to an almost normal life." It is viewed as having fewer adverse effects compared to traditional treatments. • Preserving quality of life: The drug offers the potential to delay or avoid more aggressive treatments, helping patients maintain independence, emotional wellbeing, and daily functioning for longer. • Need for broader access: There is a strong desire for wider availability of promising new drugs like vorasidenib, which offer fewer side effects and a more routine-friendly, home-based alternative to hospital-based care. *"I'm in work whilst taking, I'm not having side effects, I'm running, driving, I'm living a near normal life. I don't think you'd get that with chemotherapy, radiotherapy or surgery and those would be my only other options."* *"With my tumour close to essential motor function, I have been told surgery currently isn't a viable treatment as I would need chemotherapy and radiotherapy anyway. I am utterly shocked and disappointed that this novel targeted drug is not going to be approved and very much hope this decision will be overturned. Or at least allowed to be accessed whilst more data is made available to produce an informed decision in the real world."* **Lived Experience and Evidence**

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	• First-hand improvement: Patients in early access or trials report reduced seizures, tumour stability, and tangible improvements in daily life. • Psychological boost: Even before physical improvements, access to Vorasidenib brings profound relief, optimism, and restored mental health for patients and families. • Desire for parity: People emphasise that other targeted cancer therapies are funded by the NHS; low-grade glioma patients deserve the same equitable access.
3	Our community shared the profound impact that a low-grade brain tumour has, not only on the patient, but on their families and loved ones. Through their own words, they describe the emotional, social, and practical challenges of living with ongoing uncertainty, disrupted daily life, and gaps in support. Families speak of shared responsibility and advocacy, while patients describe the strain of navigating treatment pathways, managing work and finances, and coping with the emotional and psychological toll. This section highlights their lived experiences, emphasising the urgent need for care, treatments, and support that truly address both medical and everyday realities. **Family and relational impact** • Shared emotional weight: Many accounts are rooted in relationships – parents, partners, children, siblings and friends highlighting that brain tumours affect entire families. The emotional burden is shared between patients and their loved ones. • Advocacy by loved ones: Many responses are written by family members or friends, reflecting collective concern and advocacy. The impact of denial is not only felt by patients by everyone who loves them. • Shared burden and loss of independence: Illness often leads to reliance on others for daily tasks, medical appointments and childcare. Family involvement is frequently required for transport and support, adding to the emotional and practical strain. *"I live with a constant reminder that I will die a lot sooner than I and everyone around me expected. It saddens me that my parents have to go through this and that I can no longer follow the career I worked so hard for. I am not from a privileged background which increases the anxiety when it comes to affording treatment and being out of work during recovery."* *"It also strains family life and friendships. Loved ones share the worry, adjust routines, and carry emotional burdens that are hard to articulate. Social life often suffers because energy and mental focus are limited and explaining what's happening to others can be exhausting and emotionally painful."* **Navigating without a clear path forward** • Continued uncertainty and impact: Many patients described the emotional toll of living with constant uncertainty, feeling unable to plan or envision the future. This is often experienced as a trauma or a forced acceptance of new, limiting reality. • Living with a shadow: The persistent presence of worry, fear, anticipation and loss affects daily functioning and emotional wellbeing. The feeling of not knowing the next steps makes it difficult to shape one's life or future. • Life-limiting opportunities: Reduced opportunities, time and ability to build a future are common. Many patients are navigating critical life stages – particularly in their 20s and 30s, when they would otherwise be building careers, relationships and independence.

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	• Financial and employment strain: Ongoing costs of living and unequal access to private care create financial pressure. Side effects and uncertainty often prevent people from working or sustaining a career, despite a strong desire to contribute and reengage with society. • Biopsychosocial effects: The impact of illness spans physical health, mental wellbeing, and social life often overlapping and compounding. Patients express a need for care that acknowledges and addresses this full spectrum of experience. *"Every morning, I wake up and have about 5 seconds of bliss when I do not remember that I have a brain tumour. Then, I suddenly remember, and I feel a huge weight on my shoulders. I am self-employed and I need to work but I am demotivated because my future is so uncertain. I may live for one more year. I may live for 20 more years, I just do not know. I am constantly very worried about the tumour growing and my seizures starting again."* **Emotional and Psychological toll** • Loss of independence and social withdrawal: Illness can lead to reliance on others for daily tasks and medical appointments, contributing to feelings of isolation and reduced self-worth. • Gaps in psychological and social support: Many patients and families report minimal access to counselling, specialist services and peer support. There is a clear need for psychological care and emotional support throughout the treatment journey and beyond. • Inconsistent and insufficient care across the pathway: Patients experience a lack of follow up post treatment, absence of dedicated clinical nurse specialists and inconsistent clinical guidance. Rehabilitation is often not sustained long term. • Need for holistic, long-term support: Support must extend beyond active treatment into survivorship and long-term care. Low-grade brain tumours require sustained monitoring and care that addresses both medical and emotional needs. • Practical support and advocacy gaps: Patients need clearer guidance on managing work, benefits, and financial strain. There is a call for advocacy around employment rights and adjustments, as well as better information about diagnosis and treatment options. *"Life as you know it changes the moment you receive this diagnosis. There's not a day goes by that it's not on your mind. Every little symptom, from a mild headache to fatigue to concentration issues, becomes a trigger. A trigger for negative thoughts - has my tumour grown? How long do I have until my scan to get an update? We're constantly searching for reassurance that we're still ok. We know it will return, it's only a matter of time. That's a difficult thing to know, a difficult way to go through life knowing that it's waiting on the horizon. I live my life as best I can, but there's a constant niggle in the back of your mind, wondering when things are going to change for the worse, again."* **Burden of current care** • Significant side effects and long-term risks: Current treatments such as radiotherapy and chemotherapy can cause fatigue, seizures, anxiety, cognitive decline, and physical deterioration. Younger patients are especially vulnerable to long-term cognitive and emotional changes.

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	• Daily emotional strain of "watch and wait": The watch and wait approach causes ongoing trauma and emotional distress. Scans become life-defining moments, with patients putting life on hold while awaiting appointments and results. • Disruption to life for younger patients: Treatments often interrupt education, careers, parenting, and social development. Mental health challenges are exacerbated by delayed or avoided treatment due to age-related risks, and support tailored to young adults is limited. • Practical and logistical burden: Frequent hospital visits disrupt work and family life. Travel for treatment adds financial and emotional strain, especially when advanced care is not locally available. These challenges compound the stress of managing illness. *"Low grade glioma is a confusing diagnosis for patients. You are told that it is not aggressive, yet it remains incurable with the treatments that are available to us now. You live dreading your next scan, worried that it will be the one to reveal significant growth or progression. In addition, there is still no true consensus on the treatment of these tumours, as current options are either treat very aggressively, or watch and wait. Life with a low-grade glioma can oftentimes feel like waiting for things to get worse."*
4	Some healthcare professionals and researchers also shared their perspective in response to this survey. **Healthcare Professional Perspective** • Visible clinical benefit: Nurses and clinicians describe clear improvements in patients' wellbeing and stability, with minimal side effects and better quality of life. • Delaying harsher treatments: Vorasidenib enables patients to delay radiotherapy and chemotherapy, avoiding their significant side effects and loss of independence. • Preserving function and contribution: Patients remain able to drive, work, and participate in family and community life - vital for a young patient group. • Reduced burden on services: The treatment avoids the costly rehabilitation and additional medication needs associated with chemo and radiotherapy. • Ease of delivery: Vorasidenib can be provided effectively through nurse-led clinics, making it efficient and sustainable for NHS services. • Professional disappointment: Healthcare professionals express deep concern and sadness that this promising, well-tolerated drug may not be available to their patients, describing it as a missed opportunity to transform care. *"I am a therapeutic radiographer, I see brain tumour patients every day. Radiotherapy is good however not a cure. This gives real light and hope and positive treatment to all patients who are eligible. We work hard to help these patients, but their survival is one of the lowest of all cancers. Why can we not try and improve that with this new medication, be leading edge in brain tumour treatments and see how we can positively help this patient group."* *"I am writing as a brain tumour researcher who is deeply disappointed and frustrated by the decision not to approve vorasidenib for NHS use in the treatment of low-grade glioma. For grade 2 gliomas, a condition where treatment options are limited and the impact of interventions like surgery, radiotherapy, and chemotherapy can be profoundly life-altering, vorasidenib represents meaningful clinical benefit, both in terms of survival and quality of life. If such results are not deemed "value for money," what message does that send to researchers, clinicians, and, most*

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	importantly, patients? How are we meant to maintain their trust, their hope, and our motivation to keep pushing for progress, when the system itself devalues outcomes that clearly matter"
5	The approval of vorasidenib represents far more than access to a new treatment. For people living with low-grade gliomas, it symbolises long-overdue progress, renewed hope, and the possibility of a more normal life. After decades with little advancement, this drug offers the first real sense that change is within reach - not only medically, but emotionally and socially too. The testimonies gathered from patients, families, and healthcare professionals highlight the profound human impact that approval would have - restoring dignity, protecting quality of life, and addressing long-standing inequalities in brain tumour care. **Hope** • Renewed hope: There is a strong sense of optimism after decades without progress, often described as "first hope in 25 years" and a "breakthrough moment". Hope feels real and achievable, not abstract. **Frustration with Lack of Progress** • Perceived neglect: Repeated comments about "no progress in 40 years" and a sense that research into brain tumours is underfunded, overlooked, and deprioritised compared to other cancers. Patients feel left behind and express frustration that brain tumours are seen as "too hard" or low priority. • Anger and disappointment: Strong feelings of frustration that treatment options lag far behind those available for other cancers. There is a sense of injustice and abandonment within the community. • Systemic impact and opportunity: Recognition that the NHS is under pressure, and that oral treatments like vorasidenib could reduce hospital visits and ease system burden. Approving new treatments could also drive visibility, research momentum, and future investment. **Unmet Need, Systemic inequality and financial injustice** • Limited and outdated treatment options: Patients with low-grade gliomas often face only three choices of surgery, radiotherapy, or chemotherapy, despite these being invasive and largely unchanged for decades. There is a lack of proactive or preventative treatments before disease progression, and some tumours are inoperable, with repeat surgeries carrying significant emotional strain. • Reactive rather than anticipatory care: Many patients feel they only receive help once their condition deteriorates. This reactive approach contributes to a sense of abandonment and delays access to potentially life-changing interventions. • Unjust divide and health inequality: Deep frustration exists around access being dependent on wealth. Patients feel it is fundamentally wrong that treatment availability is determined by personal finances rather than clinical need. "Health shouldn't be a financial lottery." There is a strong sense of exclusion and unfairness, with those unable to self-fund being left behind despite having the same right to care and hope.

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Insert extra rows as needed

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	The Society of British Neurological Surgeons

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Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	No funding, direct or indirect links to the tobacco industry.
Name of commentator person completing form:	[redacted]

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	Question from NICE 1. Has all of the relevant evidence been taken into account? No new studies presenting new data identified in the last 18 months

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2	Question from NICE: 2 Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
3	We are concerned that NICE did not effectively consider the significant cognitive, social and QOL impact of radio and chemotherapy on this group of patients.
4	We are concerned that as patients on Vorasidenib are more likely to work for longer, need less financial support, and continue paying taxes, this has also not been considered.
5	We are concerned that the effects of improved epilepsy control of patients on treatment on the above do not appear to have been taken into account.
6	It is difficult to comment on cost effectiveness when the final figures are not presented
7	NICE should consider if subgroups within this population do reach the predetermined limit
8	With the significant cross-over of placebo into the treatment arm, and the long term survival of patients, OS data is likely to be limited in the future from the INDIGO trial group. This is a concern for the future evaluation of this drug.
9	Because of the overall survival of patients, and the successful acceptance of vorasidenib in the treatment paths of most other similar health care economies, it is unlikely that survival data, in anything other than simple cohort studies, will be available in the future. There may also be some delay to this data being available. Again the delay in getting the data that NICE is suggesting it needs is s concern for the future approval of the drug.
10	Question from NICE: 3 Are the recommendations sound and a suitable basis for guidance to the NHS?
11	There is concern that with the underestimation of effects of current chemo-radiotherapeutic treatments that the recommendations are not sound.
12	The recommendations appear to based purely on the monetary value ascribed to the treatment, rather than the clinical evidence, and the level of that cost is not given.
13	It is hard therefore to support the guidelines as clinicians.
14	Question from NICE 4: Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation? No additional comments.

Insert extra rows as needed

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Association British Neurologists Specialist Interest Group

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Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Nil
Name of commentator person completing form:	[redacted]

Comment number	**Comments**

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1	We are concerned that this assessment focusses primarily on the impact of Vorasidenib on overall survival. Up to 85% of those with an IDH1/2 mutated astro/oligodendroglioma experience seizures, either at presentation or during their disease course. Existing chemotherapy has been shown to reduce seizure frequency – see data on Temozolamide as an example[1]. Seizure reduction is positively correlated with progression free survival. Seizures are additionally independently associated with reduced QOL and reduced productivity (including secondary to the inability to drive) in this population. Although change in seizure frequency was not a primary endpoint in the INDIGO trial, a second interim analysis of exploratory endpoints suggested a favourable trend towards seizure reduction with Vorasidenib[2]. It can therefore be anticipated that, in line with other chemotherapeutic agents, Vorasidenib may benefit seizure control while potentially delaying time to intervention and associated late effects. [1]Koekkoek JAF, Dirven L, Heimans JJ*, et al* Seizure reduction in a low-grade glioma: more than a beneficial side effect of temozolomide. *Journal of Neurology, Neurosurgery & Psychiatry* 2015;**86:**366-373 [2]Vorasidenib in IDH1-mutant or IDH2-mutant low-grade glioma (INDIGO): secondary and exploratory endpoints from a randomised, double-blind, placebo-controlled, phase 3 trial. Cloughesy TF, van den Bent MJ, Touat M et al. The Lancet Oncology, 2025.
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Insert extra rows as needed

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Patient Expert

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Name of commentator person completing form:	SHAY EMERTON

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	HAS ALL THE RELEVANT EVIDENCE BEEN TAKEN INTO ACCOUNT? **NO** I do not believe all the significant **unmet needs** faced by LGG patients and their families have been fully taken into account.

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	Vorasidenib is the first innovative treatment for LGG's in decades. There is a **need** for a targeted approach to suppress the mutant enzyme IDH – there is a **need** for a treatment that can be delivered by a convenient oral therapy. The HSC Act 2012 (p9 of NICE health technology manual) requires NICE to have regard to the degree of need of persons for health services in England. **Unmet needs** result from the lack of treatment. The choice for LGG patients like me after surgery is stark, watch and wait for the inevitable progression (with the unimaginable anxiety that goes along with that) or RT/ CT, which is gruelling and will have a major impact on quality of in the short, medium and long term. Watch and wait is **not** a treatment. What patients like me need is a treatment that meets our **unmet needs**. A treatment that slows tumour growth, reduces tumour volume, delays the time to toxic therapy and results in fewer seizures. There is a treatment that the committee has found 'increases how long people have before their cancer gets worse compared with placebo'. Simply consigning patients to Watch and Wait when there is now a treatment is **not** acceptable. Without a treatment being made available emotional distress, depression, psychological, financial, and physical wellbeing needs are not being addressed at all. **Unmet Needs** The current needs of patients on watch and wait are not met because they receive **no** treatment. a) Progression of the tumour can have **physical** effects on speech, personality changes, ability to concentrate. For me progression\growth in my tumour will mean my movement is likely to be affected as my tumour is in my motor strip. Watch and wait does not address this. Without treatment the tumour will grow, the physical and cognitive effects will only become worse. The importance of delaying progression in terms of the **physical** effects of progression is not fully acknowledged by the committee. Vorasidenib addresses the need to stop/slow growth of the tumour. b) Tumour **shrinkage**, this has not been adequately considered. Watch and wait does not address this - I do not think the guidance captures the **physical unmet need** to control and reduce if possible the tumour without resorting to further surgery or more toxic therapies. c) The **mental health** issues surrounding 'watch and wait' being the extreme uncertainty and emotional stress caused by knowing you are **receiving no treatment** have not been fully recognised nor has the immense improvement in my mental health and that of others on Vorasidenib. The recognised condition of "**Scanxiety**" is not mentioned in the guidance. Trying to live life between scans, "Scanxiety" (recognised as a condition by clinicians), is the debilitating fear experienced on watch and wait. When I was receiving no treatment each scan and waiting for the results was terrifying. There is no treatment currently offered to address this. Receiving Vorasidenib and knowing I am on a treatment has alleviated this. d) The data shows there is a 64% lower rate of **seizures** in the Vorasidenib group than in the placebo group. The only reference to seizures in the guidance is at P6 where it is acknowledged seizures can cause 'anxiety and affect independence 'and the reference to p27\28 relating to driving and seizures. Insufficient consideration has been given to this. There is a considerable and **unmet need** for LGG patients to experience fewer seizures.

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	A reduction in seizures will have a considerable positive impact on the quality of life including mental health, work and social life. Seizures also significantly impact families and carers – this has not been considered. • The **fear** of having a seizure. It is not simply suffering from a seizure but almost worse is the **fear** of having a seizure, eg the fear of having a seizure and spoiling best friend's wedding nearly meant I did not go. Vorsidenib has given me far more confidence about the likelihood of a seizure not occurring. This is not captured at all by the decision. • **Actual** seizure. It is the most horrible frightening experience knowing for a split second that you are going to lose control of body and mind. After a seizure you do not physically or mentally recover for days. I would not be able to return to work or anything like normality for quite a period of time The mental and physical effects do not just leave you once the seizure is over. Having a seizure compounds the anxiety because the thought is so vivid you are terrified of having another one, it is a horrible spiral. The references at pages 6,27 and 28 do not in any way reflect this. • **Driving** - at page 28, 'But, given the median PFS of 22.1 months in the Vorasidenib arm it considered it unlikely that many people having Vorasidenib would be seizure free for an entire year to allow them to return to driving '. This comment assumes that progression of the tumour would result in an automatic increase in seizures. Progression could be a very small growth, the patient continuing on Vorasidenib. (Additional data could be collected as part of the CDFMAA -please see below). I have been seizure free for over a year. • Effect of seizures on Carers; - My family never wanted to be away from me in case I had a seizure when alone. This is not referred to in the guidance There is a much wider effect than that captured at P's 6, 26 and 27. • Cost to the NHS - I do not think this has been reflected in the decision. By way of example when seizures (full loss of consciousness) occur paramedics were called and admission to hospital can follow. These costs to the NHS have not been taken into account. (para 1.13 NICE Manual) e) **Caregivers physical and psychological**- even though my family try to hide it from me they face anxiety stress, and exhaustion every single day. We have been left to work it out for ourselves how we try and manage; I do not think the emotional and financial burden on families has been considered adequately. My mental health has a direct impact on their ability to cope. They would never tell me, but I believe they are only just about coping. It is very difficult to say these things in a meeting when I know it would upset my family for me to acknowledge their pain. My brother has been directly impacted as has my partner; it is hard to explain this as my family/partner put on a "face" that they are coping but I know it is a charade. My mum worked for 30 years at a job she loved, stopped work when I was diagnosed. My dad also stopped work and drove me around My parents would never be far away in case I had a seizure, or had a 'bad day'. Since my mental health has improved by being on Vorasidenib I can see my family/partner are in a much better place than they were and dad has returned to work. These significant **unmet needs** are not addressed at all by

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	watch and wait. The committee found LGG's "significantly impact lives of people affected, their families and carers", but proceed to reject a treatment that meets those impacts. f) **Socio Economic Benefits**: Since being on Vorasidenib I have been able to return to full time work. This crosses over with the control of seizures and being able to drive. My parents' ability to work has had a significant socio-economic benefit. I can only speak anecdotally but I know the cost of getting help for LGG patients with their own young children is very relevant but was not fully considered. I also think the committee has failed to consider the needs of children to have their parent with a LGG in the best health possible for as long as possible. **Other points of evidence** which I believe have not been taken into account or not given sufficient consideration;. **Radio\chemo** (P6) The committee found that LGGs 'significantly impact the lives of people affected, their families and carers and the committee noted the aims of treatment of glioma include 'delaying progression and improving neurological function and quality of life'. Delaying RT/CT, means impacts that will follow from those treatments are not experienced until much later if at all. The negative effects of those treatments need to have been given more weight. As a general point I note the committee decision does not refer to how serious the effects of RT are **in particular** when applied to the brain compared to any other part of the body. (If the committee believe there is uncertainty as to how long it will be until TTNI (RT/CT) and therefore they don't have enough data on this, I would refer to p20, the EAG thought the additional data collected in May 2028 - 'would reduce uncertainty about PFS and TTNI ', and I would ask the committee to give further consideration to data collection through the CDF/MAA see below). **Short term effects of RT/CT;** The committee acknowledged fatigue, hospital visits and unable to work. The committee did not comment on how undergoing this treatment for a year would impact on LGG patients with young families ie with their own caring responsibilities or how a LGG patient would cope with the regime without a supportive network. How financially a family would be impacted, or how a single parent would cope with young children. **Medium term effects-** p23 reference to 'quality of life is likely to improve after treatment". Whilst the quality of life after the year of horrendous treatment might be better than when in treatment (i.e. for that year), it would be still very badly affected. I cannot speak to this personally and the other patient expert did not, however, I see in stakeholders' written submissions that were lodged with the committee that clear accounts were provided of patients' experiences of their quality of life following RT/CT but these patients' accounts are not reflected in the draft guidance. **Long term effects of RT/CT** The committee noted the long term side effects 'like cognitive decline ', but I do not think other long term effects such a radiation necrosis and migraine attacks were given sufficient consideration. Servier list (P 16/145) the **side effects** of RT/CT. Neither has sufficient consideration been given to the effect of RT on the **biology** of the tumour in that RT may result in the deletion of CNKN2A. When I received my pathology report my neurologist surgeon stated it was very good that the CNKN2A was intact. It would have been grade 4 tumour if that was deleted. (WHO Classification)

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

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	RT may result in deletion of CNKN2A and as such means the tumour would be classified as a grade 4. This is really important but not noted in the decision at all. (This should also be seen in the context of one clinical expert explaining that by inhibiting the effects of IDH mutation this may lead to a more favourable tumour biology on progression and less immediate need for RT\CT). (Further data can be collected through the CDF/MAA).
2	ARE THE SUMMARIES OF CLINICAL AND COST EFFECTIVENESS REASONABLE INTERPRETATIONS OF THE EVIDENCE? **NO** **P12** - "**more stable group'** - I do not think EAG have presented a very balanced argument. They refer to those that were excluded from the trial and conclude therefore the group included in INDIGO was more "stable" than the general LGG population. To provide a balanced view EAG should have acknowledged that if the trial had included those with gross total resection or very small tumour volume, the trial would have included more stable LGG patients than the INDIGO group. **P12**- the committee recognised this is a rare disease and the difficulty recruiting patients for a clinical trial. I also think that brain tumour patients generally are hard to recruit to trials where there is a placebo arm, because of the very serious nature of the disease they are frightened they might receive a placebo. An alternative method, eg using external data should be considered and may be relevant when collecting further data via CDF/MAA. **P20** the committee noted there 'was no data to suggest a delayed transition to HGG or malignant glioma with Vorasidenib compared to active surveillance '. At p5 the committee state ''up to 70% of LGGs may progress to high grade or become malignant within 10 years '. If the CDF/MAA is utilised there would be the possibility to compare the people on Vorasidenib with the generally accepted data that currently 70% progress. The trial has data for approx. 4 years already and a further time under the MAA would give another 5-7 years for collection. At **p4** the committee state because of the uncertainties in the economic model, including a key identified uncertainty namely, 'how long people who had Vorasidenib or placebo wait before starting a new treatment' it was not possible to determine the most likely cost effectiveness estimates for Vorasidenib, so it should not be used routinely in the NHS. The committee went on to determine collecting more evidence during the managed access period would be 'unlikely to resolve key uncertainties' so concluded, "vorasidenib cannot be used with managed access" At p20 the committee state the EAG thought the additional data available from May 2028 would reduce the uncertainty over PFS and TTNI. The Committees' reason to reject a MAA at p 4 of the draft guidance makes no reference to this. I believe CDF/MAA has too readily been rejected. **P25** The committee accepted LGG patients have severely impaired quality of life as the disease progresses. The EAG suggesting there was only a small decrease in quality of life between the public and people in INDIGO whose glioma was progression free. EAG also suggest there was no 'significant improvements in health related quality of life between the two arms'. I do not think this statement properly reflects that those on

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	INDIGO were or believed they were on treatment so their mental health was better than it would have been otherwise. If I had been on the trial, even if unbeknown to me I was on the placebo, I believe my mental health would have been positively enhanced because I would believe I was 'doing something'. **P26** - the committee recounted I said my anxiety was greatly lowered but not eliminated completely so the committee found Vorsidenib 'did not restore people to full or near full health'. However, the committee notes that (p27) that since starting Vorasidenib my mental health had improved considerably to the point where I could live a "close to normal life". So, I do not agree with the finding at p26 that Vorasidenib did not restore to 'near full health'. Physically the tumour is not progressing as demonstrated by scans, my mental health is such that I'm living 'close to a normal life 'which I believe equates to **'near full health'**. **P26** The committee say the long term benefits for Vorasidenib including overall survival are unknown because of the high level of uncertainty about the benefit in TTNI -P but discount collecting further data via the Managed access fund to help with this, despite EAG recognising as above, that additional data would reduce the uncertainty over PFS and TTNI (p 20) **P27 -uncaptured benefits – please see my comments on unmet needs above.**
3	ARE THE PROVISIONAL RECOMMENDATIONS SOUND AND A SUITABLE BASIS FOR GUIDANCE TO THE NHS **NO** **Cancer Drugs Fund/Managed Access Agreement.** I understand this is specifically designed to provide access to promising new treatments, while further evidence is collected. I do not feel that the Committee has properly explored the option of a MAA. The draft guidance contains many references to uncertainties in data modelling, yet the Committee seems to have closed the door too readily to a MAA. NICE accept that there was information that could be collected to resolve some of the uncertainty however because there was "no plausible potential for cost effectiveness" for Vorasidenib the "criteria" for a MAA was not met. I don't think it is a requirement that Vorasidenib has to be cost effective to qualify for a MAA. I thought the purpose was to provide interim funding for a promising cancer drug when there was not enough evidence to prove its cost effectiveness. I have looked at some other NICE decisions where a MAA has been agreed. In appraisal Ref TA400 NICE stated that whilst it could not draw any firm conclusion on overall survival benefit from the data available the clinical treatment under consideration "looked promising". In appraisal TA658 the Committee concluded "there may not be enough time for meaningful data on subsequent treatments to be collected". In both examples it was still decided to proceed with a MAA It was also stated at the NICE meeting that the MAA period could extend to 7 years. As NICE are required to exercise its functions with a desirability of **promoting innovation** in the provision of health services in England how can this decision be considered to be promoting innovative treatments for this disease? (see further below). 64,000 patients have been able to access new treatments through the MAA regime while

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	further data is collected, presumably because the "cost effectiveness" of the treatment was not proven at the time of the application. Why on the basis of natural justice and rational consideration is the same approach not being followed by NICE in this instance? **INNOVATION-** I have read at p160 para 6 of the NICE Health Technology Manuel that the Health and Social Care Act 2012 requires NICE when exercising its functions to have regard to the desirability of promoting **innovation** in the provision of health services or of social care in England. I have also read the NICE 'Our Principles'. I see **Principle 8** is to support innovation in the provision and organisation of health services. Vorasidenib has innovative status because it is the only treatment that targets mutant IDH 1 and IDH2 genetic mutations. Vorasidenib crosses the "blood brain" barrier. NICE aims to support innovation by encouraging interventions "…..that may not be captured by QALY's and further 'to mitigate the risk….' NICE can recommend its use in the context of a MAA. I also see **Principle 11** provides for the collection of data to resolve uncertainties. The draft guidance does not demonstrate that NICE has had regard to Principles 8, 9 (below) and or 11. **Equality** The Committee acknowledges that many people with LGG IDH1 and IDH2 mutation may be young and that 'Age' is a protected characteristic under the Equality Act 2010. The draft decision states there are no equality issues as the draft guidance does not restrict access to Vorasidenib for some people over others. The equality issue is wider than that and I ask the committee whether they have considered 1. the differential impacts on the group who share the protected characteristic of 'Age', by not supporting NHS funding and if so 2. can they provide details of how they have addressed their duty under s149 (1) (b) Equality Act to promote equality between protected groups. In particular the effect of denying an NHS treatment to a protected group (protected by Age) while other groups are better supported by funded technologies across the NHS patient population. (ie - other cancers). The NHS constitution provides: The service is designed to improve, prevent, diagnose and treat both physical and mental health problems with equal regard. It has a duty to each and every individual that it serves and must respect their **human rights**. **At the same time, it has a wider social duty to promote equality through the services** it provides and to pay **particular attention to groups or sections** of society where improvements in **health and life expectancy are not keeping pace** with the rest of the population." I believe LGG patients' treatments **have not** kept pace with treatments for other cancers. LGG patients are generally young and are most disadvantaged in the healthcare system as they have no current treatment available to them after surgery other than watch and wait (not a treatment) and subsequently as last resort then resort to RT/CT upon progression.

NICE National Institute for Health and Care Excellence

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

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	See **Principle 9** – reduce health inequalities) – brain cancer kills more children and young people under 40 than any other cancer. **CONCLUSION** I would ask the Committee to grant Vorasidenib for use in the NHS having regard to all of the above, its constitution and its 'Our Principles' to support innovation (Principle 8), reduce health inequalities (Principle 9) and if deemed necessary collect further data to help resolve any uncertainties in the evidence (Principle 11 – intervention showing promise of being better than existing alternatives but for which the evidence is limited). It is acknowledged by government that brain tumour patients have 'limited options' and it is acknowledged that brain cancer remains one of the 'hardest to treat' cancers. To refuse Vorasidenib for use on the NHS or via CDF/MAA is contrary to the morals, ethics and values that should underpin a NICE recommendation

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about funding from the company and links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into one response. We cannot accept more than one set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- In line with the NICE Health Technology Evaluation Manual (sections 5.4.4 to 5.4.21), if a comment contains confidential information, it is the responsibility of the responder to provide two versions, one complete and one with the confidential information removed (to be published on NICE's website), together with a checklist of the confidential information. 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 submit a second version of your comments form with that information replaced with asterixis and highlighted in black.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

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

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Note: We reserve the right to summarise and edit comments received during consultations, 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 during our consultations 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.

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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]

Comments on the draft guidance received through the NICE website and by email

Name	[redacted]
Organisation	
Conflict	
Comments on the DG:	

Are the summaries of clinical and resource savings reasonable interpretations of the evidence?

"No. The summaries fail to reflect the full clinical and real-world impact of vorasidenib. The committee underestimated the therapy's transformative benefit for patients with IDH-mutant gliomas and omitted key evidence on quality-of-life and functional outcomes. Vorasidenib prolongs progression-free survival (PFS) by 61 percent (INDIGO Phase III trial) and reduces seizure frequency by 64 percent. These are not marginal improvements; they represent major clinical and socioeconomic value.

Resource savings were not realistically modelled. The current pathway of "watch and wait" followed by toxic radiotherapy or chemotherapy leads to cognitive disability, hospitalisations for seizure-related injuries, mental-health deterioration, and long-term unemployment among young adults. These generate far greater costs to the NHS than vorasidenib therapy. The model ignored these downstream effects and the savings from preserving cognition, delaying radiotherapy, and maintaining productivity.

Overall, the clinical and economic summaries are not reasonable interpretations of the evidence because they focus narrowly on drug price rather than long-term societal and healthcare value."

Has all of the relevant evidence been taken into account?

"No. The assessment did not sufficiently consider key data or patient-reported outcomes. The INDIGO trial clearly demonstrated that vorasidenib reduces disease progression and seizure frequency and, in some cases, causes measurable tumour shrinkage. These benefits were under-weighted in the evaluation.

The model excluded evidence on mental-health improvement, cognitive preservation, and quality-of-life gains. It also failed to capture the catastrophic harms of existing options such as PCV chemotherapy and

radiotherapy, which cause cognitive destruction, infertility, and secondary malignancies, with one in twenty PCV patients developing fatal secondary cancer.

The committee also did not account for the real-world link between PFS and overall survival. In slow-growing gliomas, overall survival data may take 15 to 20 years to mature, but longer PFS directly translates to longer life. Each month of stability is a month without tumour progression, without radiation-induced damage, and with preserved neurological function. Waiting for final OS data is unrealistic and would delay access for an entire generation of patients.

The evaluation also ignored statutory considerations under the Health and Social Care Act 2012 requiring NICE to have regard to the degree of health need. Patients with IDH-mutant gliomas currently have no effective therapy, meaning their need is absolute."

Are the recommendations sound and a suitable basis for guidance to the NHS?

"No. The draft recommendations are unsound and not a suitable basis for NHS guidance because they disregard clinical evidence, statutory duties, and the lived experience of patients.

Vorasidenib is safe, effective, and well tolerated, with no significant side effects reported in my own case and many others. It offers the first genuine disease-modifying option for this population in over forty years. To deny NHS access is inconsistent with NICE's own Principles 8, 9, and 11: supporting innovation, reducing health inequalities, and promoting data collection to resolve uncertainty.

Rejecting vorasidenib will create an unjust two-tier system where patients already on treatment continue while others are refused. This cannot be considered a fair or stable foundation for NHS guidance.

Furthermore, "watch and wait" is not a treatment; it is the absence of one. Surgery is often deadly, radiotherapy causes cognitive destruction, and PCV chemotherapy carries a risk of fatal secondary cancer. To claim that this represents acceptable care is ethically indefensible.

Compared to vorasidenib, these methods are barbaric and outdated. To proceed with this decision would be an unfathomable failing on NICE's behalf and would send a message that the lives of young brain-tumour patients hold little value. The progression-free survival benefit is overwhelmingly clear, and the recommendation must proceed on this evidence rather than wait decades for overall survival data."

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender

reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

"Yes. The current recommendation discriminates against patients on the basis of age and disability. IDH-mutant gliomas overwhelmingly affect younger adults, typically between 20 and 45 years old, who are otherwise healthy, working, and capable of long, productive lives. Denying them access to vorasidenib condemns them to neurological decline and loss of cognitive ability during their most formative years.

This group faces unique disadvantages: they are too young for palliative approaches but too high-risk for surgery or radiotherapy. Excluding them from access to a safe, targeted therapy violates the principle of equitable treatment under the Equality Act 2010 and NICE's own Principle 9 on reducing health inequalities.

The draft guidance would also deepen inequality by creating a split between patients who already receive vorasidenib and those newly diagnosed. NICE should amend the guidance to prevent this discriminatory disparity by approving the drug under a Managed Access Agreement for all eligible patients."

Has all of the relevant evidence been taken into account?

"No. The document does not fully reflect the available clinical, economic, or patient-reported evidence. It omits the psychological and functional toll of "watch and wait," underplays seizure reduction and cognitive preservation, and fails to recognise the direct link between longer progression-free survival and longer overall survival.

In this condition, delaying progression directly extends life expectancy. Each additional year of stability defers radiotherapy and chemotherapy and prevents neurological damage that shortens life. Waiting for final OS data, which may take up to 20 years, would effectively deny treatment to an entire generation of patients.

NICE has a statutory duty under the Health and Social Care Act 2012 to consider the degree of health need and the desirability of promoting innovation. Failing to act on the clear evidence supporting vorasidenib breaches those obligations.

Vorasidenib is safe, clinically effective, and represents hope for thousands of patients. Approving it would uphold the value of life and align NICE's decision-making with its founding principles of innovation, equality, and compassion."

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

"No. The summaries in the draft guidance underestimate both the clinical significance and economic value of vorasidenib. The INDIGO Phase III trial clearly showed that vorasidenib reduced the risk of progression or death by 61 percent and increased median progression free survival from 11.1 months to 27.7 months. It also reduced seizure frequency by 64 percent and in some cases produced measurable tumour shrinkage. These are major therapeutic benefits that have not been properly reflected.

The cost effectiveness model fails to consider real world outcomes such as preservation of cognitive function, reduction in seizure related hospital admissions, and the ability of patients to continue working, studying and contributing to society. It also overlooks the substantial downstream costs of radiotherapy and chemotherapy, including long term cognitive disability, secondary cancers and psychological illness.

Progression free survival is not an isolated measure. Each month of stability preserves neurological integrity and delays the need for toxic therapies. In this disease, extended PFS inevitably translates to longer overall survival because the brain remains intact and functional for longer. Waiting for mature overall survival data, which may take up to twenty years to obtain, is unrealistic and unethical. The summaries therefore do not reasonably interpret the evidence and fail to reflect the true clinical and societal value of vorasidenib."

Are the recommendations sound and a suitable basis for guidance to the NHS?

"No. The draft recommendations are not sound and cannot form a suitable basis for NHS guidance. They disregard clinical evidence, patient outcomes and NICE’s own statutory duties.

Vorasidenib is the first targeted treatment in more than forty years to address the genetic driver of IDH mutant gliomas. It is safe, effective and well tolerated. I have personally experienced complete stabilisation of my tumour with no side effects at all. To deny this treatment to others is to deny access to a life preserving therapy that already meets the highest standards of efficacy and safety.

The guidance instead promotes “active surveillance”, which is not a treatment. It leaves patients living in fear while their tumours grow. Surgery would likely cause death or severe disability in many cases, radiotherapy causes irreversible cognitive decline and secondary cancer, and PCV chemotherapy is toxic and life shortening. Continuing to endorse these outdated approaches when a targeted oral therapy exists is medically and morally indefensible.

NICE’s own principles require it to support innovation, reduce inequality and collect further data to resolve uncertainty. Rejecting vorasidenib contradicts these principles and the organisation’s statutory duty under the Health and Social Care Act 2012 to have regard to the degree of health need. The

current recommendations therefore cannot be considered a fair or evidence based guide for the NHS."

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

"Yes. The draft recommendations indirectly discriminate against patients based on age and disability. IDH mutant gliomas predominantly affect younger adults who are otherwise healthy and in the prime of their lives. Denying access to vorasidenib forces this group into years of mental distress and functional decline while they await inevitable progression. This is a form of age and disability discrimination that contradicts the Equality Act 2010.

The decision would also create an unfair two tier system in which patients already receiving vorasidenib can continue, while new patients with identical diagnoses and needs are excluded. This inconsistency directly undermines equality of access within the NHS.

These patients are young, ambitious members of society who could live for decades if their disease is stabilised. NICE's current recommendation removes that opportunity. Approving vorasidenib for NHS use, at least through a Managed Access Agreement, would ensure fairness and compliance with the Equality Act while restoring dignity, hope and equal value to the lives of all people affected by this disease."

"This comment responds to the draft NICE recommendation regarding Vorasidenib for the treatment of IDH mutant grade 2 gliomas. It is structured as follows:

1. Personal case study and lived experience
2. Limitations and risks of current recommended management
3. Evidence, unmet need and statutory obligations
4. NICE principles and duty to support innovation
5. Equality considerations and concluding summary

The aim of this submission is to provide both a personal and evidence-based perspective on why the current recommendation fails to reflect the available data, the lived reality of patients, and NICE's legal and ethical duties.

1. Personal Case Study and Lived Experience

My name is [redacted], a [redacted] patient with three inoperable oligodendrogliomas distributed across both hemispheres of my brain, the largest measuring approximately 10 by 5 centimetres. I was diagnosed in May 2024 and since that moment I have lived in a constant state of fear, anxiety, depression and uncertainty. I am not a weak person.
[redacted]

[redacted] I have a loving family, a supportive partner and ambitions to make a positive contribution to society. The current system of care leaves people like me abandoned. Surgery would almost certainly leave me dead or severely disabled due to the location and extent of my tumours. Radiotherapy would destroy cognitive function, leaving me unable to think or work normally and exposing me to the long-term risk of radiation induced malignancy. PCV chemotherapy, the only other option, carries serious toxicity. Approximately one in twenty people who receive it die from secondary cancers such as leukaemia. Following biopsy, I was placed on active surveillance, which in reality means no treatment at all. Living with an untreated brain tumour is psychologically unbearable. Every day brings the same thought: my cancer is still growing and there is nothing I can do to stop it. The toll this takes on mental health, family stability and social wellbeing cannot be overstated. By early 2025, imaging showed that my largest tumour had begun to grow more quickly and to display a new enhancing focus in its centre, consistent with aggressive transformation. I fought across three separate health boards to access Vorasidenib, which I eventually began taking in July 2025. I am writing this on the 4th of November 2025, one day after receiving my most recent MRI results. After three months on Vorasidenib, my tumour growth has completely halted, and the enhancing lesion has almost entirely disappeared. I have had no side effects at all. For the first time since my diagnosis, I have clear evidence that my treatment is working. My quality of life has returned. I can study, train and plan my future. Vorasidenib has not only stopped my disease but given me hope. It allows me to live as myself again.

2. Limitations and Risks of Current Recommended Management

The committee's statement that active surveillance is the appropriate care pathway for patients who do not require immediate chemotherapy or radiotherapy fails to recognise that this is not a treatment. It offers no therapeutic benefit and leaves patients at risk of physical and psychological harm as their disease continues unchecked.

The alternatives are unacceptable. Surgery is often impossible and frequently fatal when tumours infiltrate both hemispheres. Radiotherapy causes progressive cognitive destruction, damages healthy brain tissue and carries a lifetime risk of secondary cancer. PCV chemotherapy is highly toxic and only modestly effective, especially when used without radiotherapy. The side effects of these treatments include cognitive decline, severe fatigue, neuropathy and the development of secondary malignancies. These harms extend beyond the individual patient to families, carers and the healthcare system itself through increased admissions, rehabilitation and mental health costs.

To continue recommending such outdated and damaging approaches when a safe and effective targeted therapy exists is inconsistent with both scientific progress and ethical care. Compared to vorasidenib, the other treatments are barbaric and backwards. Continuing to promote them while withholding an available modern therapy represents a profound moral and clinical failing.

3. Evidence, Unmet Need and Statutory Obligations
Under the Health and Social Care Act 2012, NICE must have regard to the degree of need for health services. The need for patients with IDH mutant gliomas is profound. They are predominantly young adults facing decades of life with a slowly advancing cancer and no effective or tolerable treatment options.
The INDIGO Phase III trial demonstrated that Vorasidenib reduced the risk of progression or death by 61 percent compared with placebo and extended median progression free survival from 11.1 to 27.7 months. The drug also reduced seizure frequency by 64 percent and improved overall neurological stability. Reports of tumour shrinkage confirm that the therapy can not only slow but, in some cases, reverse disease activity. These findings are clinically significant and consistent across subgroups. The benefits extend far beyond radiographic measures: patients experience greater independence, reduced seizure burden and a dramatic improvement in quality of life.
The economic model used in the draft guidance underestimates these effects. It fails to capture the long-term costs avoided by preserving cognitive function, maintaining employment and preventing hospital admissions for seizures or treatment complications.
The committee's insistence on mature overall survival data is misplaced. In slow-growing brain tumours such as these, overall survival can take 15 to 20 years to measure. Waiting for this data before allowing treatment would mean denying an entire generation of patients the chance to live well. Progression free survival is not a disconnected endpoint; it is intrinsically linked to overall survival. Each month that a tumour does not progress is a month where the brain remains functional, where radiotherapy and chemotherapy can be delayed, and where survival potential is extended. A patient who remains stable for five or ten extra years through Vorasidenib will inevitably live longer than one whose tumour progresses unchecked. To suggest otherwise ignores basic oncology principles and the lived outcomes already observed in the real world.
NICE cannot afford to wait for final overall survival data, as patients are likely to live for more than twenty years precisely because of the early disease control that Vorasidenib provides. The progression free survival benefit is overwhelmingly clear and must form the principal evidence base for recommendation.

4. NICE Principles and Duty to Support Innovation
The draft recommendation is inconsistent with multiple NICE principles and statutory duties. Principle 8 requires NICE to support innovation. Vorasidenib is the first therapy in over forty years to address the molecular cause of IDH mutant gliomas and the first to cross the blood brain barrier effectively. Principle 9 commits NICE to reducing health inequalities. The current recommendation entrenches inequality by excluding a group of predominantly young adults from a safe treatment that can preserve their ability to live, work and contribute to society. Principle 11 requires NICE to promote research and data collection to resolve uncertainty. Managed Access Agreements exist precisely for this purpose. The assertion that

more data would not resolve uncertainty contradicts NICE's own mandate and the approach taken for other rare and slow growing cancers.

5. Equality Considerations and Concluding Summary
This decision would create an unequal system in which patients already on Vorasidenib can continue treatment while newly diagnosed individuals with identical conditions are denied access. This breaches the Equality Act 2010 and creates unjust disparity within a small and vulnerable patient community.
Vorasidenib is safe, effective and transformative. It prolongs progression free survival, reduces seizures, delays radiotherapy and chemotherapy, and preserves cognitive function. It restores quality of life and the ability to contribute to society. Compared with Vorasidenib, the current alternatives are barbaric and outdated. To move forward with the decision not to implement the use of Vorasidenib would be an unfathomable failing on NICE's behalf and sends a clear message about the value placed on the lives of patients like me. The purpose of healthcare is to preserve and enhance life, not to withhold it on the basis of imperfect economic projections. Each day on Vorasidenib gives patients time, time to live, to love, to work and to remain themselves. The true measure of value is not cost per QALY but the preservation of human potential.
NICE should reconsider its draft recommendation and approve Vorasidenib for NHS use, ideally through a Managed Access Agreement to enable ongoing data collection. This would align with NICE's principles of supporting innovation, addressing unmet need and reducing inequality. If NICE refuses to act, patients like me will be left to watch our tumours grow while knowing that an effective treatment exists but has been withheld. Such an outcome would represent a failure not only of policy but of compassion, reason and humanity."

Name	[redacted]
Organisation	Brain Tumour Support
Conflict	
Comments on the DG:	

"We write on behalf of the patients, families and carers supported by Brain Tumour Support to comment on the draft NICE guidance on Vorasidenib for the treatment of grade 2 astrocytoma or oligodendroglioma with IDH1 or IDH2 mutation in people aged 12 years and over.

We note with deep disappointment the draft recommendation that Vorasidenib "should not be used routinely" on the NHS at this time. We believe that while we respect NICE's rigorous appraisal process, the draft position does not sufficiently recognise the urgency, unmet need and lived experience of people with low-grade gliomas.
For many of those diagnosed with low-grade gliomas, the standard management often involves a period of "watch and wait" after surgery, followed by radiotherapy and/or chemotherapy when progression occurs. These treatments can have profound and lasting effects on cognition, memory, fatigue, and overall quality of life. Because low-grade gliomas

frequently affect younger adults, who are studying, building careers, raising families or caring for others, the long-term consequences of early radiotherapy or chemotherapy can be life-altering. They may include difficulties returning to work or education, loss of independence, and significant emotional and financial strain on families. The draft guidance does not sufficiently reflect how delaying the need for further treatment can itself represent a meaningful benefit in preserving life opportunities, independence, and quality of life for this younger patient population.
The clinical evidence available (for example the INDIGO trial) shows that Vorasidenib significantly delays tumour progression and the time to next intervention.

We therefore believe that the value of delaying the need for radiotherapy/chemotherapy (and the associated side-effects) should be given greater weight in the appraisal, from the patient/family perspective.

The voice of patients and families:

From [redacted]:

My name is [redacted], I wanted to share my story.

Last August, my [redacted] was camping with her family and had a seizure out of the blue. She was taken to hospital via ambulance and so started the journey to a diagnosis of low grade glioma.

The word glioma was first mentioned quite early and a quick google showed the words “uniformly fatal”. I was 38 weeks pregnant, preparing to give birth any day and read that my sister may have a condition that she would certainly die from. To say I was devastated would be an understatement.

My nephews were [redacted] when [redacted] was admitted to hospital for the first time. One of them was [redacted], and [redacted] had to battle with the anxiety and worry of his attachment process to his [redacted] as well as the normal (and horrible) anxiety of separation from your children for the first time. My [redacted] had to abruptly stop breastfeeding, not only did his mum have to spend extensive time away from him, but that feeding journey was brought to an end without any preparation or gradual weaning that would normally happen.

The process to diagnosis was gradual, first she was out of hospital and on anti-seizure meds. Then she was told she had a brain tumour. Noone had mentioned the word cancer to her until she got a letter through her door saying ""support for those facing a cancer diagnosis"". Crying, she showed me this letter ""does this mean i have cancer?"". Yet on she ploughs, as she has [redacted] to look after. Surgery is next, which means she has to endure a long, torturous surgery where she was awake the whole time, and experienced 2 seizures and a stroke during. Brain surgery like this requires

extensive psychologist support as it is an extremely traumatic experience and has induced flashbacks and ptsd like symptoms. Following surgery she could not talk, and had to spend months developing the ability to speak and read again. That is months of not being able to sing to her [redacted], read bedtime stories, not even able to spend long chunks of time with them due to limited energy reserves.

After surgery recovery, she had an appointment with her oncologist where it was revealed she has an astrocytoma, and her life expectancy would be limited.

Bad news after bad news, a previously healthy [redacted] was told that she had cancer, that it was incurable, and finally, that it would kill her. She will likely never get to see her children have children, never get to be the amazing grandma I know she would be.

After months of surgery recovery, she was faced with a future of chemotherapy and radiotherapy, both of which would mean more time away from her [redacted] more horrible side effects, and poor outcomes as radiotherapy leads to cognitive decline.

After this, there was a glimmer of hope. A new drug. Vorasidenib. Promising to delay the need for chemo/radiotherapy and so stay off the nasty side effects. She has started on this drug with the named patient scheme and has done brilliantly on it.

What has it meant for my [redacted]? Energy to invest in her [redacted] time to make memories to last a lifetime. She chooses to use her limited time and energy to help out at our church doing admin, overseeing the children's groups, helping with youth groups and encouraging all members of the church young and old alike. She can now care for her [redacted] on her own, take them swimming, read them stories, be present at bedtime, be there for her [redacted], take them to the park, teach them how to bake cookies.

What has it meant for my [redacted] At this crucial time in their life, children need to build strong attachments with their parents, especially when children are adopted and have had a rough start in life. [redacted] have been separated from their mother enough. If vorasidenib can give them a few more months or years of a healthy mother before chemo and radiotherapy are needed, that may be the difference that gives them the emotional resilience and secure foundation that they will need to face the awful future to come of losing their [redacted] way too young. They need their [redacted] able to operate at her best possible capacity, as she can through vorasidenib, so that they can look back and remember their [redacted] as she truly was.

What has it meant for me? My [redacted] is my best friend, the person I turn to when I need a hug or a cry. She was there at the birth of my son even a week after coming out of hospital. Having a [redacted] with brain cancer has meant that a lot of time and energy has gone into caring for her and for her

[redacted], which is an honour and a privilege. Even more tears have been shed for the future. As I was recovering from birth, a lot of time was spent crying over my [redacted] and my [redacted] who need their [redacted] so much. In a time of my life where my [redacted] would usually be supporting and caring for me, I was lying in bed trying to hurry my recovery so that I could help her. Pretending I've got it all sorted so that they would let me help out with the [redacted] as I felt so helpless. [redacted] (and very loved) baby because I wasn't able to be there for my [redacted] as I would have liked to have been in this awful time. I wasn't able to visit my [redacted] in hospital following her surgery as [redacted] and they wouldn't allow children onto the ward.

After my son and [redacted] saw my [redacted] have a seizure, I watched them act out '[redacted] lying on the floor making noises' later that day. [redacted] process a lot through play, yet seeing [redacted] having to deal with such heavy and complex things was heartbreaking.

As I think about the future, I worry about how we will navigate chemo and radiotherapy as a family. How will I explain to my sons what is happening? How will we support my [redacted], her husband and my [redacted] as they face another period of separation while their [redacted] isn't able to care for them as much? How will they process seeing their [redacted] unwell during treatment, and the cognitive decline that often occurs after radiotherapy? Having a [redacted] with a brain tumour is tough. Being told that there is a treatment that could help, could definitely prolong her time of a good quality of life before stronger therapies, and possibly even extend her already short life is amazing news in a very very dark story. Being told that that treatment won't be funded is more than a blow, its life shattering. Thinking about how much money we could raise if we sold our home, gave up our savings, our car, yet still the reality is that privately funding for any length of time is impossible.

My [redacted] deserves better. My [redacted] deserve better. I don't know how we can face my [redacted] and say, yes there was an option that could have helped your [redacted] but the NHS didn't think it was worth the money. He has already [redacted]. He has now found another, who will be taken from him as well.

Throughout this my [redacted] has been an absolute star. She just wants to live her life well, love her family well, and serve her community well. And thankfully, vorasidenib has allowed her peace of mind and physical ability to do those things for longer. Please reconsider and allow my [redacted], and many others like her, to have time that counts with their families.

Hello, I'm [redacted] and I am writing this in light of NICEs draft decision to not to recommend Vorasidenib for use on the NHS as of October 15th 2025.

I want to start by saying how detrimental this will be and how devastating a blow this is for so many of us that have waited for Vorasidenib to be approved.

Glioma is an incurable cancer and for many of us aggressive treatments have been the only way forward before its arrival.

Vorasidenib gave us time to stave off such treatments and allow us a peaceful gap with a higher quality of life between diagnoses and surgery and then the eventually of Chemotherapy and/or Radiation Therapy.

To paint the picture of how Vorasidenib has changed my life this past year I need to explain how difficult is was beforehand:

In short, [redacted] ago my health began to decline rapidly. As some of you may be aware getting diagnosed with a brain tumour can be an incredibly difficult process. In February this year it was brought to the governments attention that 70% of brain tumour patients, in Scotland alone, need to present to A&E in order to receive a correct diagnoses like I did. That is another problem all in itself… however what this means is pre-diagnosis, like me, many people end up on vast amounts of prescription drugs to combat the various symptoms they have developed over the years in an attempt to try and have some semblance of a normal day to day.

At my worst I was on a cocktail of 14 different medications.

And by the time of my diagnoses I was living anything but a normal day to day. I was essentially “living” in my bed… sleeping through the night with an additional 6-10 hours during the day due to extreme fatigue. If I wasn’t sleeping I was vomiting and in the few moments of clarity I’d maybe manage to eat causing horrific nausea despite the medication.

I had to give up my career and, with being self employed and without a formal diagnoses, my family [redacted] had little support outwith my wives earning.

The dangers of this is that, again like me, many people can have adverse side effects to these drugs - such as severe weight gain.

This weight gain can then mean that when finally diagnosed surgery is too risky an option either meaning waiting too long for the individual to loose weight (often meaning the tumour has grown exponentially and maybe become a Grade 3) or taking said risk.

I was lucky to get the surgery. But over the 5 years to that point I went from a [redacted] at 85kg to 150kg (managing to get to 140kg by the time of surgery).

Now out of a successful surgery in October 2024 - removing 80% of my tumour - I was prepared to start Chemotherapy and Radiotherapy which, while it would “hopefully” prevent further growth, would not allow me to return to the man I was before. Not in the short term anyway. If anything my quality of life would be little more than it was pre surgery for another year.

Even with a positive outcome in my surgery the thought of aggressive treatment was somewhat torturous. I thought I had no good options and mentally I was already beaten down to a point where I saw little to no light.

This is not to mention what this does to those around you. Your friends who loose time with you, your [redacted] who don’t know their [redacted] or are able to understand what is happening to him, a wife turned carer and parents facing the potential loss of their child.

However I was presented with an alternative:

Vorasidenib.

At that point there was only the clinical studies to go off of as the Early Access Program - that I am on - was only just then being presented to a number of eligible patients.

One thing stood out for me in those studies: 86% of participants on Vorasidenib saw no progression in 22 months. Almost 2 years!

2 years I could have a normal life with no thought of aggressive treatment if Vorasidenib worked for me.

It was an easy choice.

Now a year on Vorasidenib what can I say:

- My tumour has not grown.
- I have had no seizures.
- I have returned to [redacted].
- That cocktail of drugs has gone from 14 to 3!
- We have a new home that I have been personally decorating and renovating.
- I’ve lost another 10kg and more on the way now I can lift weights again.
- I have been learning two languages to combat the Aphasia I had from surgery.
- I have got to be a [redacted], a husband and a friend again.
- I can eat without the fear of nausea

I am slowly getting to be the [redacted] I new before this all began.

Do I still get bad days? Yes! But living with Glioma, controlled or not is a challenge.

But it's a challenge that has become bearable both physically and mentally thanks to Vorasidenib.

In a weeks time I get the results of my next MRI. A result - given how my health has continued to improve - I can say with confidence will be good.

However now that result is somewhat tainted…

Why?

Because while NICE say that "The draft guidance does not impact those already accessing Vorasidenib and will still be able to access it as part of their treatment" this is not entirely true.

Since yesterday already those on the Early Access Program have been told by their oncologists that if the final decision in November is made; that Vorasidenib will not be available on the NHS, they will only receive 1 more year of this life changing medication.

1 year… only 2 extra months from that incredible statistic I gave before.

I have not yet mentioned that during this last year of the Early Access Program there has been numerous cases that Patients on Vorasidenib have seen their tumour Shrink… SHRINK! A sentence that I couldn't have imagined being uttered to me a year ago.

This isn't a cure… no… but it's a preventative.

It's a key to a good life amongst the battles we with Glioma are faced with.

This letter to NICE is as much for those that may be denied the opportunity of Vorasidenib in the future as it is for me and the others Vorasidenib will be taken away from.

And why do NICE not see it as a valid treatment?

It isn't "Cost Effective."

In their eyes patients "in their lifetime" on Vorasidenib will still need Chemotherapy and or Radiotherapy. So why spend money on Vorasidenib.

And unfortunately the data they have used in draft is just from the clinical trials.

And worse the next pull of data is in 2028… by then many could be taken off Vorasidenib and many could die without access to this drug.

There is now more people taking Vorasidenib worldwide than there was in the trials… yet their stories and results are not part of the equation.

Well… I believe they should be, and that is my I am sharing my positive experience with Vorasidenib in the hope that NICE can overturn this decision for all of us battling Glioma.

A cure can't come soon enough…

But for now… those with Glioma have a means to a life we all deserve. And those around them get to spend more time with the one they love.

And that is way it should be considered "Cost Effective"

In closing, we understand that NICE must balance evidence, cost-effectiveness and NHS resource constraints. We urge that in this case the evidence of meaningful benefit, the nature of the disease (younger adults, long life expectancy, substantial life-impact), and the broader value to patients/families be given full weight. We believe that a recommendation against routine use of Vorasidenib at this time risks disadvantaging a small but very important patient group who face limited options and significant long-term consequences.

Thank you for the opportunity to comment on this draft guidance."

Name	[redacted]
Organisation	
Conflict	
Comments on the DG:	

In February 2022, I was diagnosed with Oligodendroglioma, Grade 2 with IDH1 mutation. I can't explain how devastating it is to be diagnosed with a brain tumour at [redacted] years of age. Having recently got engaged, I was planning my wedding and looking forward to building a family and suddenly, I had brain cancer. In March, I underwent a craniotom/y to remove the tumour, which was highly successful. My amazing neurosurgeon was able to provide great results and I began to feel optimistic about the future. However, I then realised that this is not something that can simply be removed and you get on with your life. This is a tumour that will return. Maybe in 3 years, maybe in 20 - but we know if will return. Like every other patient diagnosed with this life-limiting illness, I desperately searched for a way to maximise my time before reoccurrence but with limited research into brain cancer, I wasn't optimistic. Amazingly, I came across the INDIGO trail and I can't tell you the impact it's had on my life to know there's a drug out there that could give me more time. More time to spend with my husband, with [redacted] More time to make memories as a family. For my [redacted] to have both parents by her side. To hear that this drug may not be approved for use on the NHS is beyond devastating. This drug has become a beacon of hope for all patients who are suffering daily, wondering if the next scan will show regrowth. Wondering when they will need to begin

aggressive treatments, chemotherapy and radiotherapy, and the impacts those harsh treatments may have on their cognitive abilities. I'm terrified of these treatments. If my cognitive functions are affected, will I still be able to work? Will my personality change? How will that affect my family? Will I be able to look after my [redacted]? These questions torment those who see these treatments as part of their future. Our only hope in prolonging our lives as we know them is through the phenomenal results that have come out of the INDIGO trial. The hope that using Vorasidenib will give us more time to spend with our families, making memories and living normal lives, before aggressive treatments become necessary.

Name	[redacted]
Organisation	
Conflict	
Comments on the DG:	

"I am writing to urge NICE to reconsider its draft decision not to recommend vorasidenib for NHS use.

Vorasidenib represents a vital breakthrough for people living with IDH-mutant low-grade glioma. It is the first targeted treatment designed specifically for this rare type of brain tumour, and clinical trials have shown that it can significantly delay tumour progression and postpone the need for chemotherapy and radiotherapy. This means more years of good quality life for patients who are often young adults — people working, studying, raising families and contributing to society.

Current treatments such as surgery, chemotherapy and radiotherapy can lead to lifelong side effects including fatigue, cognitive decline and memory loss. Delaying these treatments is not just clinically meaningful but life-changing for patients and their families.

The decision to reject vorasidenib appears to be based primarily on cost rather than clinical effectiveness. I urge NICE, the Department of Health and Servier to work together to find a fair and sustainable pricing solution so that patients in England and Wales can benefit from this therapy.

People with IDH-mutant gliomas deserve hope, time, and access to modern, evidence-based care. NICE has the opportunity to ensure that they are not left behind. Please reconsider this decision and approve vorasidenib for use on the NHS.

Thank you for your consideration.

This comment is supported by a public petition titled “Urge NICE to Reverse Its Decision on the Life-Saving Drug Vorasidenib” on Change.org, which has received over 2,900 signatures from patients, families, and supporters across the UK.

Petition link: https://www.change.org/p/urge-nice-to-reverse-its-decision-on-the-life-saving-drug-vorasidenib"

Name	[redacted]
Organisation	
Conflict	
Comments on the DG:	
"Before my Awake Craniotomy my health declined massively over 6 years. Getting diagnosed was horrifically difficult and I was put on a cocktail of drugs to deal with my symptoms. However even with these drugs I found myself bedridden and lost my career. I put on massive amounts of weight making surgery almost an unviable and risky option. After a fortunately successful surgery I started Vorasidenib. That cocktail of 14 drugs - to live a below average quality of life - has now become 2 drugs: Vorasidenib and an Anti-epileptic. I have been able to work again, be a [redacted] and life an incredible fruitful life. I have lived more this past year than the previous 5. Losing Vorasidenib would be incredible heartbreaking. Chemotherapy and Radiotherapy is a preventative measure yes… but an extremely aggressive one. And having either I don't think I'd be living as well as I am on Vorasidenib. To hear that it's hasn't been deemed as "cost effective" is heartbreaking. This isn't stocks and shares we are talking about this is peoples lives. I had no quality of life before this was granted to me. I don't want to have my children see me like that again. I hope this decision is reversed and many like me can see a change in their lives due to this drug. I see the current choice as nothing more than a disregard for the positive stories and life changing experiences that Vorasidenib has brought."	

Name	[redacted]
Organisation	
Conflict	
Comments on the DG:	
Are the summaries of clinical and resource savings reasonable interpretations of the evidence? As a lay person i cannot comment. **Has all of the relevant evidence been taken into account?**	

More information from patients and their families is needed. The psychological, health and economic impact has not been sufficiently explored

Are the recommendations sound and a suitable basis for guidance to the NHS?

The recommendation not to prescribe is flawed. See above.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

"Restricting this drug so that, in particular, women of child bearing age cannot have it is potentially indirectly discriminatory.

Women of child bearing age are more likely to have children if they believe there is a greater chance of survival with vorasidinib. Without the drug women are less likely to have children due to fear of dying sooner.

I gave seen my [redacted] go through this terrible thought process.

According, restricting vorasidinib as proposed is likely to be indirectly discriminatory to women as per the terms of the Equality Act 2010"

The psychological impact of LGG cannot be over emphasised. Since my [redacted] has had vorasidenib she has returned to work successfully and remains positive and economically active. My wife also been able to work and be economically active due to seeing her [redacted] improve. Without the hope this drug brings the mental health of our family shatters. Things have been desperate and our whole collective health suffers. LGG diagnosis is an ongoing misery and stress, vorasidenib gives hope to families and enables them to lead far better lives, which benefits them and society as a whole

Name	[redacted]
Organisation	
Conflict	
Comments on the DG:	

"I am reaching out concerning the recent draft guidance from NICE regarding the non-availability of Vorasidenib to eligible patients through the NHS. I urge you to reconsider this decision. It overlooks the significant unmet needs of a group of predominantly young patients who have no

alternative treatments. Vorasidenib has demonstrated impressive efficacy, showing nearly double the progression-free survival compared to the placebo group—27 months versus 11 months—with minimal side effects. While the committee noted a lack of data on its impact on overall survival, it's unrealistic to conduct clinical trials for progressive diseases over a short timeframe. This raises concerns about whether future drugs in this class will face similar rejection as we await long-term outcomes.
Delaying the adverse effects of radio-chemo treatment is crucial, particularly for younger individuals who may be balancing university, work, or family responsibilities. The negative impacts extend beyond the patient to their families, affecting their ability to work and care for young children, leading to broader economic and practical issues.
Moreover, the committee appears to have overlooked the significant reduction in seizures provided by Vorasidenib, which plays a vital role in improving both the mental health of patients and the well-being of their families. The assertion that restrictions on driving after a seizure are irrelevant due to the disease's progression lacks substantial evidence.
This decision affects not only low-grade glioma patients but also all brain tumour patients, potentially discouraging pharmaceutical investment in the UK. It dismisses the innovation Vorasidenib represents as the first drug to effectively cross the blood-brain barrier amidst a dire landscape for brain tumour research funding.
Notably, Vorasidenib was part of Project Orbis, aimed at expediting patient access to promising new drugs. If NICE prevents its availability in the NHS, the purpose of such initiatives is called into question.
The investment in research for astrocytomas over the past decade has been disappointingly low, with only £407,665 allocated to three projects and £632,742 for low-grade gliomas. Disturbingly, no specific funding for astrocytoma research was provided by the MRC from 2020 to 2025.
The NICE committee must consider this background and the ongoing unmet needs of these patients as they reassess their decision. The unmet needs these patients face."

Name	[redacted]
Organisation	
Conflict	
Comments on the DG:	

Are the summaries of clinical and resource savings reasonable interpretations of the evidence?

I am not able to comment given my limited access to knowledge

Has all of the relevant evidence been taken into account?

No further patient information is required on quality of life and should include family/carer impact.

Are the recommendations sound and a suitable basis for guidance to the NHS?

Further patient and carer experience data needed

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

None that I am able to comment on given limited information

"My [redacted] diagnosed, resected [redacted] 2023 has been taking this drug since July 2024. Since starting this drug She lived a full life as a [redacted].

The psychological impact on her and the entire family was huge. All of us developed mental health issues eg severe anxiety and depression and this directly impacted our ability to function. In particular we all were prescribed medication, had significant absence periods from work etc. the added anxiety of financial pressure overlaying the already stressful situation.

My [redacted] mental state has improved substantially since starting this drug. Her scans which were uncertain upon starting in [redacted] 2024 have given reassurance of no progression (possible shrinkage). She has been able to marry, concentrate on her career. Her husband has also achieved promotion and as a family we have been able to feel we can move forward again with life. We have been able to either reduce anxiety and depression medication or stop completely. We are all working fully and making active contributions to society. This drug has been significant in this shift in our collective mental state.
Before only doing surveillance created heightened anxiety living scan to scan. It is an extremely difficult way to live, psychologically knowing you are not actively treating /preventing tumour recurrence.

Vorasidenib has been a game changer. It allows her to avoid/ defer the established complications of lasting deterioration from Radiotherapy and Chemo and this resulting in It being likely that she would no longer [redacted] by age [redacted]. In [redacted] 2024 the area of possible growth made this SOC sadly her only option. She was faced with balancing her future quality of life against survival. Vorasidenib as the alternative is giving her the chance to delay invasive treatments and a better chance of being a fully functional adult at [redacted]. With the added hope of a family/child.

The alternative treatment pathways are destabilising, require significant carer input from family and likely to causes multiple mental health issues for the whole family, which leads to the likely absences from work and the inability to live a normal life day to day.

This drug is not just ‘hope’ that it is preventing tumour growth, it is also helping to prevent the addition of further health issues for her both cognitive and mentally and for our entire family."

Name	[redacted]
Organisation	
Conflict	
Comments on the DG:	

"We had no choice but to have our [redacted] undergo brain surgery that would last eight hours. He bravely accepted this, saying, “I am not brave; I have no choice.”

The weeks leading up to my [redacted] surgery made my stomach turn. I couldn’t believe my [redacted] would have to undergo a procedure to open his skull and remove a vicious tumour. To make matters worse, he was paralysed on one side for several weeks afterwards and had to learn to walk and use his right arm again, regaining full use only after many months. Four years later, he still feels that his right foot does not have the same dexterity it once had.

I was proud of his beautiful, round head—I know it sounds strange, but I truly was. However, during his recovery, he developed a bone infection at the site where the skull had been opened, necessitating another surgery to remove the infected area. This left him with a literal hole in the top of his head. We lived in constant fear of something falling on him or him bumping his head during this time. I was devastated; to me, it felt as if the surgery had disfigured him.

He eventually had a third surgery to place a prosthesis to replace the skull flap[redacted]. The time my husband and I had to devote to our [redacted] impacted our ability to care for them, which directly affected the well-being of our son with psychosis, leading to the threat of him being sectioned unless he resumed his medication.

Our [redacted] remained well for one year post-surgery, only for us to discover that he needed urgent daily radiotherapy and six months of chemotherapy. My husband had to take six weeks of unpaid leave to take him to the hospital every day during this challenging time. I have not been able to work for many years due to my younger son’s needs, and now there is no prospect of me being able to work again. We live very simple lives and rarely go out or take holidays. My [redacted] has a five-year gap in his work history due to several years of treatment. He is eager to work; however, in every interview he has had, the feedback has been that he appeared very nervous and unsure.

We are now in a constant state of uncertainty, never knowing when this dreadful tumour will return. We have been told that, when it does, it will be more aggressive and require urgent surgery again. The radiotherapy and surgeries have left him with a large scar extending from above his ear to the upper left of his crown. He has been unable to regrow his hair after the

radiotherapy. I can’t deny that his appearance has changed, and it saddens me that he has had to face this as a young man. We also notice that he is not as sharp mentally as he once was, and he tends to forget small things.

We have had no release from worry and fear; the future brings more of the same without any let-up. Living day-to-day like this is incredibly challenging. If he were allowed just a few years to enjoy his life while young and build up more work experience, his prospects would be much better. That is why I am so angry that this wealthy country can be so shortsighted as to not support Vorasidenib, denying young people the chance to enjoy their lives a bit before they have to face the mountain of pain he has had to Endure prematurely.
I am reaching out concerning the recent draft guidance from NICE regarding the non-availability of Vorasidenib to eligible patients through the NHS. I urge you to reconsider this decision. It overlooks the significant unmet needs of a group of predominantly young patients who have no alternative treatments. Vorasidenib has demonstrated impressive efficacy, showing nearly double the progression-free survival compared to the placebo group—27 months versus 11 months—with minimal side effects.

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Notably, Vorasidenib was part of Project Orbis, aimed at expediting patient access to promising new drugs. If NICE prevents its availability in the NHS, the purpose of such initiatives is called into question.

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£632,742 for low-grade gliomas. Disturbingly, no specific funding for astrocytoma research was provided by the MRC from 2020 to 2025.

The NICE committee must consider this background and the ongoing unmet needs of these patients as they reassess their decision. The unmet needs these patients face."

Name	[redacted]
Organisation	
Conflict	
Comments on the DG:	

To whom it may concern,

I wanted to express my feelings of utter desperation over your decision to reject Vorasidenib as a treatment for low grade IDH mutation gliomas on the NHS even though it is being used in common practice all over the world.

I was diagnosed with a brain tumour after several episodes of losing consciousness in [redacted]. I was determined to carry [redacted] until I fell of a high stage after [redacted] and hurting myself. I was forced to give up my passion and being self-employed I lost my income overnight. From then on, I had to move back in with my Dad.

I was referred to the [redacted] who recommended by best long-term outcome was to undergo surgery to remove as much of the tumour as possible, with it being in my motor area they couldn't remove it all without permanent paralysis. I had surgery January 2022 waking up unable to move my right side at all. I sunk into a deep depression and did not want to live if I was paralysed. However, my surgeon gave me some hope and told me I could get most movement back if I really worked at physio. Which I did, initially learning to walk, eat and care for myself again. It took 18 months of rehab where I fought tooth and nail to get myself back to a place where I was finally able to work again in a part employed role, this made all the hard work worthwhile, as I just want to help people and help others feel better.

In 2024 I qualified as a [redacted]. For example, on of my clients is returning to activity after partial lobectomy of a lung due to lung cancer. I also aim to push myself physically and raise awareness of brain tumours.

Unfortunately, In [redacted] this year I suffered a seizure, and a subsequent MRI showed tumour regrowth. My oncologist at [redacted] applied for me to go onto targeted medication Vorasidenib. Which allowed me to continue living independently, caring for my elderly parents, and working. This gave me hope and helped my passion for helping people, fundraising, and demonstrating what people with cancer and or disabilities can achieve.

For example, obtained the mixed doubles world record of the deadly dozen fitness race. None of this would be possible without Vorasidenib treatment.

The only alternative treatment if Vorasidenib was not available would be for me to have radiotherapy and a year of chemotherapy. As you are well aware these are aggressive and debilitating treatments, especially when targeted onto the brain, I would likely have right sided movement loss, requiring me to be in 24 hour care, unable to look after my parents, be unable to work and having no quality of live.

Overall, I think I am emotionally strong and somewhat resilience to setbacks. But the news about Vorasidenib not getting NHS NICE approval due to financial reasons has shaken me to the core. It really made me question if it is worth fighting anymore. I can't understand why the NHS funds cosmetic surgery for psychological reasons, nicotine replacement and weigh loss injections yet cannot fund life changing treatment for brain cancer patients who have gone through so much trauma already. I have always praised the NHS for the care I received, but am now deeply ashamed coming from a country where the health system which shows such a negligence of care and lack of dignity for brain cancer patients.

Thank you for reading and I look forward to hearing your thoughts

Whilst I appreciate you putting together justifications on your opposition to funding Vorasidenib treatment in the current economic role. I do question some of your reasoning:

How long Vorasidenib extends how long people live. There is currently no data available to show this because it is such a new treatment. The study was only published in June 2023 (1) furthermore within this study patients on the placebo were unblinded, as it was deemed unethical to without treatment which was showing such clinically significant improvement. Which to me speaks volumes. Hence there is now no (published) control to compare this to.

Whether Vorasidenib treatment leads to a better quality of life. In my opinion without doubt physical Vorasidenib treatment leads to better quality of life. Vorasidenib is an oral tablet taken once a day requiring monthly hospital appointment for 3 cycles and then 3 monthly after that. The alternative is 6 weeks of radiotherapy which will involve travelling to hospital 5 days a week noting patients will have to surrender their driving licence for a year at this point and will be unable to work, take care of family etc. After this a year of chemotherapy regular visits to hospital for infusions and monitoring, with a high probability of being hospitalised due to the damaging side effects of treatment.
Recent additional data from the INDIGO study indicate that vorasidenib allows the preservation of HRQoL (2). Seizures have a huge impact of quality of life and low grade gliomas harbouring an IDH1/2 mutation exhibit a much higher seizure rate than wildtype gliomas (3)(4) due to the non-

function of IDH enzyme resulting in the toxic compound of oxidative respiration 2' HG which can contribute to seizures, without even taking into account the actual physical tumour. There has shown to be a clinically and significant impact on the personalized management of glioma-associated epilepsy, improving seizure control using IDH inhibitors (5)(6). Targeting IDH1/2 with Vorasidenib (or other IDH inhibitors) is/are the first successful attempt to apply “precision oncology” in low-grade gliomas harbouring an IDH1/2 mutation, has huge positive implications. Namely, IDH1/2 inhibition recession or stalls growth (1) and my person case also shows that and dedifferentiation mechanisms/progression to higher grade tumour ; furthermore delaying radiotherapy implies delaying the onset of neurocognitive disorders over time, which significantly compromise young patients’ quality of life and social relationships(7)(8), which my person case demonstrates (as detailed in my first email)
As with all the evidence above I ask on the behalf my myself and so many other patients who benefit and would benefit from Vorasidenib to reconsider your decision. I have a [redacted], so if any of this is unclear, please feel free to ask.

Yours sincerely

[redacted]

1) Vorasidenib in IDH1- or IDH2-Mutant Low-Grade Glioma
Authors: Ingo K. Mellinghoff, M.D., Martin J. van den Bent, M.D., Deborah T. Blumenthal, M.D., Mehdi Touat, M.D., Katherine B. Peters, M.D., Jennifer Clarke, M.D., M.P.H., Joe Mendez, M.D., +23 , for the INDIGO Trial Investigators

2) Peters K, Mellinghoff I, van den Bent M, Blumenthal D, Touat M, Clarke J, et al. QOL-26. A RANDOMIZED, DOUBLE-BLIND PHASE 3 STUDY OF VORASIDENIB VS PLACEBO IN PATIENTS WITH MUTANT IDH1/2DIFFUSE GLIOMA (INDIGO): ANALYSIS OF HEALTH-RELATED QUALITY OF LIFE, NEUROCOGNITION AND SEIZURES. Neuro-Oncology (2023) 25(Supplement_5):v254–v5. doi: 10.1093/neuonc/noad179.0978

3) Li Y, Shan X, Wu Z, Wang Y, Ling M, Fan X. IDH1 mutation is associated with a higher preoperative seizure incidence in low-grade glioma: A systematic review and meta-analysis. Seizure (2018) 55:76–82. doi: 10.1016/j.seizure.2018.01.011

4)Chen S, Xu D, Fan L, Fang Z, Wang X, Li M. Roles of N-methyl-D-aspartate receptors (NMDARs) in epilepsy. Front Mol Neurosci (2021) 14:797253. doi: 10.3389/fnmol.2021.797253

5) Vo AH, Ambady P, Spencer D. The IDH1 inhibitor ivosidenib improved seizures in a patient with drug-resistant epilepsy from IDH1 mutant oligodendroglioma. Epilepsy Behav Rep (2022) 18:100526. doi: 10.1016/j.ebr.2022.100526

6) Tejera D, Kushnirsky M, Gultekin SH, Lu M, Steelman L, de la Fuente MI. Ivosidenib, an IDH1 inhibitor, in a patient with recurrent, IDH1-mutant glioblastoma: a case report from a Phase I study. CNS Oncol (2020) 9(3):Cns62. doi: 10.2217/cns-2020-0014

7)Douw L, Klein M, Fagel SS, van den Heuvel J, Taphoorn MJ, Aaronson NK, et al. Cognitive and radiological effects of radiotherapy in patients with low-grade glioma: long-term follow-up. Lancet Neurol (2009) 8(9):810–8. doi: 10.1016/S1474-4422(09)70204-2

8) Gondi V, Paulus R, Bruner DW, Meyers CA, Gore EM, Wolfson A, et al. Decline in tested and self-reported cognitive functioning after prophylactic cranial irradiation for lung cancer: pooled secondary analysis of Radiation Therapy Oncology Group randomized trials 0212 and 0214. Int J Radiat Oncol Biol Phys (2013) 86(4):656–64. doi: 10.1016/j.ijrobp.2013.02.033

Name	[redacted]
Organisation	
Conflict	
Comments on the DG:	

My [redacted], was diagnosed with a brain tumour (Grade 2 Astrocytoma) in July this year. She had a near total (≥95 %) resection with good pathology (detailed below) which can give her a 7-10 year survival (involving 3 more resections, chemotherapy and radiotherapy). Vorasidenib as you know is a revolutionary new drug trialed to slow or stem tumour growth delaying resections and therapy. It changes the landscape of brain tumour survival. It is being considered by NICE and I understand the initial response is to not allow NHS funding.

My daughter is only [redacted], has an impressive career as a [redacted] bringing in 40% tax for Government funding. She would have had 30+ more years continuing to pay a higher rate of tax, support her Country, and yet now in her time of need it seems her Country can show little compassion.

I have been here before; her [redacted] in 2007; no drug was available for him, sadly another successful young adult lost. I was a strong, young single parent determined to raise my two young children to be educated upstanding adults. I have urged their independence, supported their learning and been self sufficient.

Why do those suffering from these tumours not deserve access to this drug which, from my understanding, has trial data supporting up to 7 years extra time before resections? (7 years so far proven in trials however this could be more as we receive data going forward)? Is it purely cost? How can this be when Vorasidenib delays the need for expensive resection, and delays the unpleasant chemotherapy and radiotherapy which severely reduces quality of life. In addition this drug alleviates the need for time spent on

social benefits and palliative care; saving the Government more funds. Instead those diagnosed would be able to continue, in my [redacted] case, to be self sufficient and paying high taxes! Cost effectiveness I understand should not be a consideration and surely in this case Vorasidenib instead provides better quality of life and extends that life for at least 7 years or more between resections. We are an aging population do we not be supporting successful young lives?

Is it possible that having a brain tumour becomes a manageable condition with Vorasidenib not a life sentence? Yes it is! I know the Government has pledged to raise the very low survival figures from brain tumours, therefore, please support all the those facing this not just my [redacted] and let's increase that low survival rate to a much higher figure.
Thank you for your time.

[redacted]

Name	[redacted]
Organisation	
Conflict	
Comments on the DG:	

I am writing as a patient advocate for those living with low-grade brain tumours to urgently request a full and compassionate review of the interim decision not to approve vorasidenib for NHS use in England.

This decision directly affects patients with grade 2 astrocytoma or oligodendroglioma harbouring IDH1 or IDH2 mutationsvpeople who are often young, working, raising families, and living with the immense uncertainty that their disease will progress without warning.

The case for reconsideration
Global precedent: Vorasidenib has been approved in both the United States and Europe, where regulators recognised its clear clinical benefit and potential to delay radiotherapy or chemotherapy treatments that are effective but often life-altering in their long-term side effects.

Human impact: "Low-grade" does not mean "low impact." These tumours rob individuals of memory, speech, and independence. Every year of clear cognitive function and normal life matters deeply to patients, families, and society.

Economic and ethical value: The NHS rightly considers cost-effectiveness, but delaying severe disability and preserving productivity, autonomy, and emotional stability are also vital forms of value. Denying access risks higher long-term social and medical costs and profound personal suffering.

A respectful request
As you approach your next committee meeting on 20 November 2025, I respectfully ask NICE to:

Reassess all international and real-world data now available following approvals abroad.

Consider the wider value to patients and society, beyond traditional cost-effectiveness thresholds.

Include patient voices directly in the appraisal discussion, ensuring lived experience shapes this crucial decision.

Vorasidenib offers something rare in brain tumour care: time with quality, time to live, think, work, and love before the harsher realities of advanced treatment. The UK must not fall behind when hope and evidence already exist.

Please do not leave brain tumour patients behind.

With hope and your sincere consideration,

[redacted]
Patient Advocate

Name	[redacted]
Organisation	
Conflict	
Comments on the DG:	

Question 1. Vorasidenib should not be used to treat grade 2 astrocytoma or oligodendroglioma with a susceptible isocitrate dehydrogenase (IDH) 1 or IDH2 mutation in people 12 years and over who do not need immediate chemotherapy or radiotherapy after surgery.

Answer 1. Our [redacted] had a Glioma of which 80% to 90% was removed. She had a seizure during the surgery and a stroke so was unable to communicate sufficiently having lost speech to safely get it all. After a long recovery she recovered most skills and is functioning as a [redacted]. The consultant offered her a choice of traditional treatment for the rest of the tumour or application for Vorasidenib which the family accepted so she could be actively parenting and involved in their development. This has proved very successful and enabled her to support the oldest into school. The monitoring via scans and by blood tests at the Oncology unit has shown no growth of the Glioma and no side effects. She wants to continue this treatment to avoid any further interventions that have side effects and restrictions on family life. The Vorasidenib was initially for 18 months sponsored by the company monitored by the NHS.

Question 2. This recommendation is not intended to affect treatment with vorasidenib that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS healthcare professional consider it appropriate to stop. For young people, this decision should be made jointly by the healthcare professional, the young person, and their parents or carers.

Answer2. If this is true then she would be happy but as indicated the Vorasidenib was sponsored by the company with NHS support. As the NHS agreed this option we feel she should be able to continue and hopefully avoid invasive treatments, allow her to see her children grow even sufficiently to understand more of the Glioma and its impact and have a relatively normal childhood.

Question 3, Usual care for astrocytoma or oligodendroglioma with IDH1 or IDH2 mutations for people who do not need immediate chemotherapy or radiotherapy after surgery is active surveillance. The clinical trial evidence shows that vorasidenib increases how long people have before their cancer gets worse compared with placebo. But it is unclear if vorasidenib affects how long people with the condition live.
You have unsaved changes

Answer 3. As indicated, they could not remove all the Tumour safely without a communicating patient. The Vorasidenib created another option to monitor recovery and either use alternate treatments or more surgery. The impacts of these can affect the person's ability to function and at this stage in her life and for the childrens benefit she needs to function as close to normal as possible. The evidence on long term impact cannot be measured until more research arrives on longer term users as would occur with all new drugs. I talk of human impacts that can be measured now and in the longer term. Uncertainties in the economic model are financial cost but as indicated there is a human cost and not just to the patient it includes family.

Question 4 . Because of the uncertainties in the economic model it is not possible to determine the most likely cost-effectiveness estimates for vorasidenib. So, vorasidenib should not be used routinely in the NHS. Collecting more evidence during a managed access period is unlikely to resolve the key uncertainties in the evidence. So, vorasidenib cannot be used with managed access.
You have unsaved changes

Answer 4. I cannot follow the logic in the economic model you refer to. Quality of life for our [redacted] and family is good at present. Okay if you want longer term research then you must continue using Vorasidenib to gain evidence. When my [redacted] ask me in some years why their [redacted] died when they were so young shall I quote your economic model, or should I say well you got much longer than we thought. If Vorasidenib has so few side effects, shall I explain to them that the economic model meant [redacted] had

to have all that radiotherapy and Chemotherapy which you witnessed because of an economic model.

Yours with thanks.
[redacted]

Name	[redacted]
Organisation	
Conflict	
Comments on the DG:	

I am writing as a mother and Patient advocate whose [redacted] will be directly affected by the recent NICE interim decision to refuse approval of Vorasidenib for NHS use

My [redacted], is living with an astrocytoma (IDH mutant) following surgery earlier this year to remove as much of the tumour as safely possible. Like many patients with low-grade gliomas, parts of the tumour remain inoperable due to their location. These tumours can evolve into higher-grade cancers at any time, leaving patients in a constant state of uncertainty. Patients families live every step of this anxiety with them.

Vorasidenib is the first drug proven to cross the blood–brain barrier, stop tumour growth with an enzyme inhibitor which specifically targets this type of tumour. It offers patients real hope of many extra years of productive life—something that has been desperately lacking for decades in brain tumour treatment. NICE has only considered the original Indigo trials and not the fact that many on that trial are still taking Vorasidenib now and still benefitting from no further tumour growth and in some cases reductions in tumour size. Vorasidenib is used widely in the U.S now through Insurance funding and also for patients after chemo and radiotherapy. We in the UK are brought up to believe in our NHS and to think that in case of serious illness we will be getting the best available drugs and care.

NICE’s refusal, mainly based on cost considerations rather than clinical efficacy or full recent data , feels devastatingly short-sighted. This decision:

Undermines innovation by signalling to pharmaceutical companies that investment in UK trials is not worthwhile.

Contradicts the aims of Project Orbis, the international collaboration designed to accelerate access to promising cancer drugs. Vorasidenib has already been approved in the US and Canada, and other partner nations. In the UK it has been approved by the MHRA already.

Disregards the human and social cost of denying NHS patients access to the only available targeted therapy for LGG's. Undermining trust in our NHS.

The UK already faces a “woeful” landscape for brain tumour research and treatment access—the lowest survival improvements among all major cancers. Refusing this drug now not only affects patients today but jeopardises future progress in collaboration with commercial research companies- this is contrary to the views expressed in Lord Shaughnessy's review of commercial clinical trials - of such monetary value to the U.K.

We urgently ask for your help :

To write to the Health Minister, Wes Streeting, and Ashley Dalton Parliamentary Under Secretary for Health and Social Care urging a review of NICE’s cost–benefit approach for rare and hard-to-treat cancers;

And to support efforts calling for continued access to Vorasidenib pending full reassessment.

This is not simply about one drug—it is about the future of brain tumour patients and maintaining the UK’s position as a place of medical progress and compassion.

Thank you very much for your attention and please pass this letter on for consideration to the panel.

Yours sincerely,

To the Commitee and Team considering whether Vorasidenib be allowed for NHS patients.

My [redacted] is living with an Astrocytoma Grade 2 with IDH mutation. He is being treated with Vorasidenib currently on 'compassionate care' basis through the [redacted] Hospital and he is doing well ,living a productive life on it. He will be deprived of valuable years if funding is not approved.

He and the other patients who are living with this rare cancer - approximately 300 - I believe across the UK will suffer not only physically but their mental health will also be put under immense stress . The families and loved ones will match the pain felt by their loved ones too.

Ivosidenib - also manufactured by Servier - also an IDH inhibitor drug - has been recommended for use with patients with Bile Duct Cancer and Myeloid leukemia .The costs involved are very similar to those of Vorasidenib and outcomes show a similar life extension pattern - although Vorasidenib has now been shown to also shrink some tumours the longer patients take it.

Why then should Vorasidenib be not funded when the latest ,up to date data shows excellent results with patients still thriving on it from the original Indigo trial 3 years on.

This is the cutting edge of progress now and money must not rule decisions which affect lives of NHS patients. Especially cruel when if patients have private insurance or huge funds it can be obtained.

Is it going to be one way for the rich and the rest left behind ? Shame.

Please consider my points and balance funding, compassion and progress in your decision making.
Yours sincerely

Name	[redacted]
Organisation	
Conflict	
Comments on the DG:	

Dear TAT ,
Would you please pass the following to the committee members . I understand the deadline is slightly extended .

When my bright , beautiful [redacted] year old [redacted] was ,completely out of the blue, diagnosed with a brain tumour , our world fell apart .
Some how we got through all the tests before his operation , the scans and the meetings , the actual operation , (that for 7 days afterward left him unable to use his left side or speak) , through lifting him to the toilet , to drying his tears . We got through a further admission to hospital for an infection and returning to London everyday for 3 weeks for intravenous anti biotics . We got through waiting for pathology to reveal it was a grade 2 Astrocytoma .
Then reality hit - this was our life now , - But with all the medical advances surely there would be a treatment ? We searched high and low looking for anything . What we quickly learnt was there was nothing , absolutely nothing but to watch and wait knowing the tumour would grow and almost inevitably transform .
My [redacted] hit the bottom of a well , a cavern of darkness and despair and our family followed .
I believe there is no greater pain as a parent you can suffer than seeing your [redacted] suffer . I would have changed places in a heart beat .
Existing in this world for 2 years was almost impossible , but we had no choice , we kept going believing something would happen , there would be a breakthrough . And then it came , an offer to receive Vorasidenib .
This gave our [redacted] belief , hope that he was at last on a treatment. His seizures stopped . He returned to work as did my husband , and we climbed out of that black hole , it was as though a life line had been offered to us .
We know it's not a cure but what it is giving us all cannot be measured or even adequately explained . Please NICE don't take that lifeline away .
And when you come to make your decision please consider this, Can you imagine at [redacted] years being told you have brain cancer , that treatments have not moved in decades , that there's no cure , and brain cancer is second from bottom for 5 year survival rates.(slightly above pancreatic cancer)

Those other cancers that have risen up the ‘rankings’ are because treatments have become available . This is a first treatment for this group of young patients ,that doesn’t involve horrendous radio and chemo (which people endure but they will not be cured by it) Brain cancer needs NICE’s help . Please let’s get it up the rankings , embrace and celebrate this moment of innovation ,and hope and let the NHS be proud to offer it Thankyou From a [redacted]

Name	[redacted]
Organisation	
Conflict	
Comments on the DG:	

Dear TATeam,

I ask the committee to take into account the following and reverse their decision.

1) Vorasidenib needs to be set against the woeful landscape for brain cancer patients. Treatments have not changed in years and survival rates, unlike other cancers, have barely moved.

2) A new breakthrough - a drug that crosses the blood brain barrier, that is taken as a tablet at home with very good efficacy and minimal side effects. A drug that the committee acknowledge prolongs the time to the patients’ cancer getting worse. A drug that addresses the unmet needs of this group of mainly young patients.

3) ‘Watch and wait’ for the tumour to grow, progress and impact physical and mental wellbeing, experience more seizures and live knowing absolutely nothing is being done for you. This is NOT a treatment. But there is a treatment if approved by NICE, take Vorasidenib, stop or substantially slow progression of your cancer getting worse, and delay the time when you will endure radio and chemotherapy (which by the way won’t cure you).

4) There is a statutory duty on NICE to consider health needs when making an evaluation (it’s in the NICE manual) Health and social care Act 2012. Unmet needs of this group of patients, have not been adequately considered. The unmet need arises because for this group of patients, they receive no treatment. That results in unmet needs including:

- The physical effects of a slowly growing tumour
- Mental wellbeing - patients on watch and wait suffer acute anxiety
- Seizures - Vorasidenib reduces seizures by 64%. Insufficient consideration given to the toll on mental health, physical health, effects on wider family, resultant costs to NHS - falls, injuries, hospital admissions on occasions.

5) No reference in the decision to the committee considering the principles that govern NICE. NICE ‘Our principles’ - particularly, principles 8, 9 and 11:

- **Principle 8 – Support innovation:** NICE aims to encourage and support innovative treatments that address **unmet** needs and advance care.
- **Principle 9 – Reduce health inequalities:** Guidance should offer particular benefit to the most **disadvantaged** groups, ensuring fair access to effective treatments.
- **Principle 11 -Research and Data Collection:** NICE explicitly supports proposing **new research questions** and **data collection efforts** to **resolve uncertainties** in the evidence.

6) Innovation - In addition to 'Our principle' (8), there is a statutory duty in this regard, see Health and Social Care Act 2012, to have regard to the desirability of promoting **innovation** in the provision of health services. We are concerned that the current recommendation does not sufficiently reflect this obligation.

INNOVATION: this is the first drug in decades , a truly innovative drug that is targeted and crosses the blood brain barrier.
It would be completely against NICE principles above and their duty to promote innovation if NICE refuse this.
This group of patients are generally young in prime of their life - they are severely disadvantaged in current health care system.
NICE should recommend on NHS or if still concerned about data they can approve Vorasidenib through 'managed access arrangement / cancer drug fund' - purpose of MAA is to assess cost effectiveness of drug once further data collected.

Given all of the above I would ask for NICE to reconsider their initial decision.

Best wishes

Name	[redacted]
Organisation	
Conflict	
Comments on the DG:	

Hello Team,
I'm writing in order to share my thoughts as the sister of an astrocytoma IDH mutant patient.
[redacted] is my [redacted] ([redacted] with lovely [redacted]), initially diagnosed with 2 x IDH mutant grade 2 astrocytoma tumours in April 2025. He has had quite the journey, including multiple operations, steroid reaction, brain bleed, seizure and so on, and has just started radio and chemo following regrowth of one tumour (now grade 4)
I have closely followed the UK position on listing this drug since his diagnosis - as it represents a rare glimmer of hope, not just for patients but for those supporting them. I am a trained scientist by background (studied at Oxford university) and so am aware of the likely health economic arguments and difficulty in evaluating the cost:benefit of backing drugs not just at the

individual level but also the societal one. It is not easy and even harder when examining drugs that likely prolong progression free survival rather than being an outright cure. That said, some things can not easily be quantified or measured. Hope is one of them. Hope for patients and their carers of a well tolerated drug that can give back quality time. The lost opportunity cost of not having hope or being at the forefront for future studies seems as if it may not have been factored into the 'calculations'. If we have UK patients on vorasidenib then we will play our part in further building the research base, which doesn't just impact patient lives but the whole system through which the UK stands to advance outcomes in brain cancers. Lastly, in my darling [redacted]'s case we know that we are potentially playing a game of time...vorasidenib seems to offer more of an opportunity to achieve a lengthening of quality time. It appears better tolerated than many of the standard of care treatments (radio, chemo, resection) all of which feel like a huge roll of the dice for patients and families - as these treatments can themselves cause cognitive declines long term adding to a need for carer involvement at an earlier stage. Again I wonder if the indirect costs of carers (close family members of peak working age given the young age of many of these patients) needing to give up work or starting to claim additional benefits and support from the NHS were 'costs' that were also considered in the calculations, beyond the patients themselves being unable to work. Additional months of progression free survival also potentially mean more productive 'working months' for both patients and carers, adding to UK tax revenues in the process.
I've attached some photos of my [redacted] at the amazing charity auction he organised last week in which he raised over £42000 for charities. I can only hope for lengthened 'progression free survival' in which he can do more of this...
Thank you for listening and taking a sufficiently broad view in evaluating this drug - there are qualitative and moral reasons, as well as quantitative ones which point for a need for NICE to review the availability of this drug in the UK to patients.
King regards,

Name	[redacted]
Organisation	
Conflict	
Comments on the DG:	

Please pass this vital medication for use on the NHS. It is a lifeline for hundreds of people who have low grade brain tumours.
My [redacted], who is [redacted] with [redacted] children has an inoperable Oligodendroglioma. Surgery failed as it is deep in his motor region. He would have been paralysed if it wasn't for the monitoring during the operation. Vorasidenib is keeping [redacted] stable and preventing the tumour developing. Many are in the same position, it's the best solution in an otherwise terrible prognosis. Hopefully there will be further developments in the future. Until then, lets keep the treatment going.
Yours sincerely,

Name	[redacted]
Organisation	
Conflict	
Comments on the DG:	

Hello,

I have been asked by the Astro Brsin Tumour Fund to submit my experience of living with a Brain tumour in relation to the recent discussion of the drug Vorasidenib and its failure to be made available to LGG patients.

My [redacted] was diagnosed with an oligoastrocytoma in [redacted], age [redacted]. At the time our [redacted] children were still in full time education and we ran a business together employing [redacted] people.

The treatment protocol was 'watch and wait' which has since been re-branded as 'active surveillance'. Regular MRIs were completed at [redacted] Hospital to monitor changes.

A second opinion was sought from [redacted] , a specialist brain hospital in [redacted], and the decision was taken to proceed to surgery in [redacted].

On the advice of the neuro-oncology team [redacted] was treated with 6 weeks of targeted radiotherapy starting immediately in [redacted], and 6 rounds of PCV chemotherapy over the 36 weeks from [redacted].

Histology showed that [redacted]'s LGG with the 1p19q IDH1 co-deletions reclassified it as an oligodendroglioma . His specific diagnosis is important as we have been monitoring the development and trial of the new drug from Servier Vorasidenib closely and are aware that it is successful in treating this tumour type, slowing the progression into a more aggressive higher grade.

After building the business together in design and manufacturing over 30 years, and with at the time of surgery some 20 trained in-house skilled workers, we made the difficult decision to walk away from the business after surgery, losing our income.

My [redacted] had worked hard to stay fit, eat well and attend his annual scans, which have stayed stable over the last 10 years , for which we are grateful for the work of his neurosurgeon [redacted] at [redacted].

However we always knew that things would progress, and on [redacted] this year he was taken to [redacted] Hospital having suffered his first grand mal tonic-clonic seizure, quickly followed by more in the ambulance and A&E. He then had another 35+ seizures over the next 48 hours and was treated in the Acute Medical Unit for 12 days to stabilise him. MRIs showed that he now has tumour progression to a higher grade . This is devastating

news for all of us. Due to the anti-epileptic drugs he now has to be on as a result of the fits, he has had to surrender his driving license , cannot swim (or even take a bath alone) , use power tools , cycle- the list goes on. This for a man who drove to southern Europe for the last 3 years, [redacted] 30 years ago, is a [redacted]) . Benign it most certainly is not.

What we need is a drug that will offer some hope, that will slow down the inevitable progression , that will give patients more time with their children and grandchildren. Our youngest [redacted] is a [redacted] and works in [redacted] in the [redacted] for [redacted], where there is a whole host of drugs for so many [redacted] cancer types. We have none. Vorasidenib is our only hope, and if we are denied it as we have been given adjunctive treatments that were standard at the time, we should not be penalised if it becomes available.

We have given a lot to our community through creating employment, I care for my [redacted] mother alongside offering daily childcare for grandchildren. We feel that we are not being given a fair chance. I need my [redacted] to survive.

Please help . Do all you can to recognise the pain of this diagnosis and offer us a lifeline.

Name	[redacted]
Organisation	
Conflict	
Comments on the DG:	

To whom it may concern,

I am emailing to ask for the decision that Vorasidenib will not be made available on the NHS to be reconsidered.

My [redacted], a young, fit and healthy man in his twenties suffered a seizure completely out of the blue. Rushed to hospital, a scan revealed a brain tumour. It was the worst news possible.

At the time, he was fit and active, confident, funny, easy going and buoyant young man, making his way in life, starting a business and looking to settle down. From that day, that all changed.

He underwent a long brain surgery, removing a substantial amount of the brain tumour - but not all of it. Recovery saw him face mobility and speech issues in a long rehab process. Thankfully after a lot of work, mentally and physically, he regained his speech and movement (with only minor mobility issues remaining).

Although physically he was ‘ok’ (albeit with some of the tumour remaining), mentally, the shock of sudden seizure and diagnosis, plus surgery and the long road of rehab and recovery, he was *far* from ok.

With some tumour remaining, the future was/is still uncertain. Being an Astrocytoma Grade 2, we were told the tumour would continue to grow and spread, and not only mean his physical health would deteriorate, but the worst news (we thought) of all- the tumour would inevitably transform to a faster growing, more aggressive, high grade tumour - it was just a matter of time.

What in fact turned out to be the worst news, was learning there was absolutely no treatment on offer - meaning no cure.

Earth shattering. And cruel.

Whilst some options such as radiotherapy and chemotherapy were talked about, it was made clear these would not cure him, and not only mean he would spend time undergoing such gruelling treatments, they could also cause additional issues with memory and thinking skills, and even worse longer term effects.

‘Watch and wait’ is not a treatment.

I was with my [redacted] and his immediate family during all of this time, helping with rehab, helping try to bring him out of anxiety attacks and deep depression, and ever since he has not been the same.

The Vorasidenib named patient programme came along, and this meant a *huge* shift in his life- both day to day, and his long term prospects.

Whilst not a cure, this offered hope. With the tumour remaining ‘stable’ and unlikely to progress.

This changed everything.

We have seen him somewhat come back to life, and whilst nowhere near living care free, he is so much lighter, with more and more of his old self coming back. Things that should be standard for a young man in his twenties.

To deny him this treatment - and other young people in similar positions - is nothing short of cruel.

This is the only drug that works in this way - and for brain cancers being especially hard to treat with drugs - it is heartbreaking that there is something that *actually works* - plus can be taken at home with no side effects - and these young people are being denied it.

Denying them of this drug would not only mean these patients are to face

the physical effects that come from a growing tumour - but means they will live in fear, with severe impact on their mental health.

This is the chance for brain cancer to follow the improving survival rates of other cancers. This could be the change.

The decision needs to be reconsidered, urgently.

Thank you for reading.

Name	[redacted]
Organisation	
Conflict	
Comments on the DG:	

Vorasidenib for treating astrocytoma or oligodendroglioma with IDH1 or IDH2 mutations after surgery in people 12 years and over [ID6407]
Reference number: GID-TA11498

Recommendations
Comments

Subsection 1.1

Comment:
Vorasidenib is in its early days but it represents the only breakthrough ever to treat this very rare disease that affects so few people. It has offered a glimmer of hope to those taking it and evidence is showing it has improved the lives of patients as well as their families and friends. To snuff this out without collecting further evidence and negotiation would be unreasonable. It would also negate/ fend off future research possibilities into treatment for such a small population if it is declined by NICE.

Sub section 1.2
There are uncertainties in the economic model, including assumptions on how long people who had vorasidenib or placebo wait before starting a new treatment after their cancer gets worse if vorasidenib extends how long people live the quality of life of people in the model.

Comment:
it is very early days to expect certainty and all the answers. However the drug provides a welcome action while 'watching & waiting' that seems to be having positive results on tumour stability and perhaps even regression. Certainly for the 14 months of taking Vorasidenib, our [redacted] seizures have decreased from monthly to just the one 12 months ago. The constant anxiety; uncertainty; lack of sleep; inability to live a full life; fractured family relationships have diminished. Positivity and happiness is returning for all with planning for some previously enjoyed activities like snowboarding. Only

further data collection will answer the question of uncertainty. Otherwise we will never know the outcome.

1.2
This recommendation is not intended to affect treatment with vorasidenib that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS healthcare professional consider it appropriate to stop. For young people, this decision should be made jointly by the healthcare professional, the young person, and their parents or carers.
Comment:
this needs far more clarification to alleviate anxiety for those already taking the drug. Those already taking Vorasidenib are on different schemes eg one through a Trust Clinic mentions availability for only 18 months after a possible decline by NICE! And if the drug is still paid for will the additional MRI scans and blood tests be covered. There are unnecessary crossed messages.

I came across this update on Friday which provides more evidence. Perhaps it is already known to the advisory group but if not I would be grateful if you could share somehow:
https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(25)00472-3/abstract?rss=yes

https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(25)00491-7/abstract

Questions on Consultation

1. Are the summaries of clinical and resource savings reasonable interpretations of the evidence?

Probably not as I don't feel all the evidence has been collected especially on seizures and quality of life

2. Has all of the relevant evidence been taken into account?

There is new evidence that I hope has been looked at as it seems important
https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(25)00472-3/abstract?rss=yes

https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(25)00491-7/abstract

I understand that the stakeholder Charities have also submitted theirs

3. Are the recommendations sound and a suitable basis for guidance to the NHS?

There has so far been little to no thorough study/ collection of views of the effects on quality of life for the patient. family and friends from before and after taking Vorasidenib especially the hope that it gives and space for other treatments to manifest themselves. If declined totally, surely further managed schemes with data collection would be very appropriate.

4. Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Access to this drug via different schemes has been confusing and complicated and possibly impossible for some applicants to struggle through. It has been a post code lottery in that some clinical teams were unaware of these schemes

Nov 4th 2025

An addition. Hope the attached is being taken into account when NICE considers Vorasidenib. Oligodendroglioma is a **very rare disease** according to NICE

https://www.gov.uk/government/news/major-change-for-rare-disease-treatments-on-way-signals-mhra?utm_source=Brain+Tumour+Research+Campaigning+Update&utm_campaign=4496f05e94-campaigning_251107&utm_medium=email&utm_term=0_-93c33a2ad6-276303745&mc_cid=4496f05e94&mc_eid=d7519dec52

Also

https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(25)00472-3/abstract?rss=yes

https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(25)00491-7/abstract

Many thanks

Name	[redacted]
Organisation	
Conflict	
Comments on the DG:	
Vorasidenib Question on Consultation:	

Are the summaries of clinical and resource savings reasonable interpretations of the evidence?

Response:
No. The economic model appears to undervalue quality-of-life gains from reduced seizure frequency, delayed neurocognitive decline, and avoidance of fertility damage. These are tangible outcomes with NHS cost implications - fewer emergency admissions, less long-term rehabilitation, and lower need for assisted reproduction or hormone therapy. Also, the model's assumptions about time to new treatment contradict the INDIGO data, biasing results against Vorasidenib.

Question on Consultation:
Has all of the relevant evidence been taken into account?

Response:
Not properly, and not equitably. The INDIGO trial showed a clear, clinically significant improvement in progression-free survival (PFS) and an even larger gain in time to next intervention (TTNI), which is a direct measure of how long patients can safely defer radiotherapy or chemotherapy. In low-grade glioma cases, deferring genotoxic therapy is a recognised treatment goal because it preserves cognition, fertility, and quality of life over potentially decades of survival. The absence of a proven overall survival (OS) gain is not surprising in a cross-over trial with long post-progression survival; OS is the wrong metric and should not be treated as a failure of evidence.

Question on Consultation:
Are the recommendations sound and a suitable basis for guidance to the NHS?

Response:
No, the recommendations are unsound, principally because they use the incorrect metric for interpretation – see my comment below.

Question on Consultation:
Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Response:
Yes. The decision discriminates against the young as it is denying access to therapy for a disease that predominantly affects young people.

Document title:

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

Comment on Document:

COMMENT BY [redacted] -

The committee's draft decision undervalues meaningful benefits demonstrated by Vorasidenib and misrepresents the nature of uncertainty in the evidence.
The INDIGO trial showed a clear, clinically significant improvement in progression-free survival (PFS) and an even larger gain in time to next intervention (TTNI), which is a direct measure of how long patients can safely defer radiotherapy or chemotherapy. In low-grade glioma cases, deferring genotoxic therapy is a recognised treatment goal because it preserves cognition, fertility, and quality of life over potentially decades of survival. The absence of a proven overall survival (OS) gain is not surprising in a cross-over trial with long post-progression survival; OS is the wrong metric and should not be treated as a failure of evidence.
The economic model appears to undervalue quality-of-life gains from reduced seizure frequency, delayed neurocognitive decline, and avoidance of fertility damage. These are tangible outcomes with NHS cost implications - fewer emergency admissions, less long-term rehabilitation, and lower need for assisted reproduction or hormone therapy. Also, the model's assumptions about time to new treatment contradict the INDIGO data, biasing results against Vorasidenib.
International regulators (MHRA, EMA, FDA) have already accepted these benefits and approved Vorasidenib. The NHS now risks becoming an outlier, denying access to a therapy that changes the disease trajectory for predominantly young adults.
The appropriate path forward is conditional adoption under managed access. This would generate UK-specific real-world data on TTNI, seizure control, quality of life, and resource use - precisely the evidence the committee finds lacking - while giving patients timely access.
Vorasidenib demonstrably delays disease progression and toxic treatment. It offers patients more normal years of life, which the NHS should value. Conditional approval with evidence collection, not rejection, is the rational and ethical choice.
Vorasidenib doesn't just buy months of PFS; it buys time off chemo and radiotherapy with fewer seizures - benefits regulators have already accepted and which the draft model under-prices. Outstanding uncertainties would be progressively addressed by a targeted managed-access scheme, so the correct decision is surely conditional NHS adoption, not an absolute 'no.'

Submitted

[redacted]
4.11.25

Additional submission on Vorasidenib from parent of patient

Statistical models are an investigative tool, not an end in themselves. It is surely wrong to focus on curves on graphs while taking less notice of the living experience of patients. The real impact of Vorasidenib is measured not only in months of progression-free survival, but in the absence of decline. Please consider what does *not* occur for a patient on Vorasidenib: cognitive slowing, memory loss, fatigue, and the slow attrition that pushes people out of work, out of family life, and out of noisy rooms.

As Professor Martin van den Bent of Erasmus MC, Rotterdam, recently said:

'Having a brain tumour is like having two diseases - the cancer and the neurological effects. Vorasidenib postpones radiation and chemotherapy, thereby preserving quality of life in a way we have not achieved before. What comes next will test where vorasidenib optimally sits: maintenance after chemoradiation; combination with radiation and temozolomide; and, crucially, how early treatment influences the long game.
We need long-term follow-up – 10 to 20 years. We're setting up registries. Many of these patients can live a very long time; we must learn how early IDH inhibition shapes overall survival and subsequent therapies.'
(OncoDaily, Oct 2025)

The emphasis must be on the long term. Care and innovation feed each other: making Vorasidenib available on the NHS will sustain this progressive cycle, enabling real-world evidence collection and refinement of treatment strategies. Conversely, refusing access will stifle learning, weaken collaboration between clinicians and researchers, and delay our ability to tailor therapy for individual patients.

Vorasidenib does not just extend progression-free survival; it extends human capability and independence, it enables patients to have self-respect and lead a normal life, free from the toxic and debilitating effects of radio and chemotherapy.

Please change your decision and make Vorasidenib available on the NHS.

Evidence Summary in support of previous (7.11.25) additional submission on Vorasidenib from parent of patient

1. Quality of Life (QoL) Outcomes

a. Cognitive and functional preservation

The major clinical benefit is the avoidance of neurocognitive decline associated with early radiotherapy and chemotherapy.

Studies show that radiotherapy in low-grade glioma causes progressive deficits in working memory, attention and executive function *(Taphoorn et al., 2007; Douw et al., 2009).*

INDIGO patient-reported outcomes demonstrated stable global health status, cognitive functioning and seizure control throughout follow-up *(Neuro-Oncology 2024 SNO abstract IND-23-102).*

b. Seizure control and independence

Seizure frequency is a critical determinant of quality of life and employability. Fewer seizure-related adverse events were recorded with Vorasidenib than placebo, consistent with prolonged disease control.

NHS reference data *(Epilepsy Society, 2019)* estimate seizure-related admissions at £6000 - £8000 per episode; reduced frequency provides measurable cost savings.

c. Fertility and family life

Avoiding alkylating chemotherapy and cranial radiotherapy preserves fertility, particularly relevant as median patient age is about 40 years, with many significantly younger.

Fertility preservation and hormone-replacement costs average £4000 - £6000 per patient (NHS tariff 2023), representing a quantifiable avoided cost.

2. Registry and Evidence-Generation Potential

A managed-access or conditional-reimbursement framework would allow robust UK real-world data collection to address modelling uncertainty.

Proposed dataset:

- Clinical: PFS, TTNI, OS (crossover-adjusted), seizure incidence, corticosteroid use.
- QoL: EQ-5D-5L, EORTC BN20 cognitive sub-scale, fertility/sexual-health modules.
- Health-economic: Resource use (visits, imaging, admissions), occupational status.
- Follow-up horizon: ≥ 10 years, aligned to long natural history of IDH-mutant glioma.
- Governance: Could utilise the Tessa Jowell Brain Matrix infrastructure with data flow through the SACT dataset to NICE.

3. Summary of Value

- Clinical: Clear delay in progression and next intervention.
- Patient: Maintained independence, cognition and fertility - benefits uncaptured by short-term survival metrics, improved quality of life.
- Economic: Reduced downstream NHS spending on rehabilitation, seizure care and endocrine management; lower productivity loss through ability to work, thus benefitting both patients and dependent families.
- Scientific: Unique opportunity to generate 10 to 20-year registry data clarifying survival and sequencing questions NICE identified.

4. Conclusion

Vorasidenib fills a critical gap in IDH-mutant Grade 2 glioma care: patients for whom “watch-and-wait” is no longer appropriate. Its benefits - fewer cognitive deficits, improved seizure control and delayed need for toxic therapy - translate into both human and economic value. Introducing Vorasidenib within a managed-access framework would resolve the very uncertainties currently preventing approval, whilst continuing to preserve patients’ quality of life as progress is achieved.

Submitted.

Name	[redacted]
Organisation	
Conflict	
Comments on the DG:	

Are the summaries of clinical and resource savings reasonable interpretations of the evidence?

"NO

1) There has been insufficient weight placed on the cost burden to NHS and care services and social support services, by the impact on the wider family. There has also been insufficient consideration of the whole of life Quality of Life impact on the whole wider family.

1a) Most LGG patients are young adults and many have young children; some stages of disease and its treatment makes them unable to care for their own children. The long term impact on the children's mental and social wellbeing will bring costs to public services. There are life long benefits to a young child of having an extra 3 -5 years with their mum still well enough to interact before harsher therapies, [slide 26 of Public Committee Slides ACM1] [see Alexander et al 2023, The Psychosocial Effect of Parental Cancer: Qualitative Interviews with Patients’ Dependent Children]

1b) Caring for a patient's children impacts the work and personal lives of the wider family. In our personal experience this takes the family's care capacity away from elderly relatives who then burden NHS and care services.

1c) Also in our personal experience, the considerable stress of caring for 4 generations at once, causes family to lose work capacity and lose quality of life and have significant stress related illness which leads to use of more NHS services. See Schulz and Sherwood 2009 Physical and Mental Health Effects of Family Caregiving

2) Impact on seizure control has not adequately been addressed. Vorasidenib can hold a patient for longer in a lower disease state, with fewer seizures.

Reduced seizure control has wider economic benefit through reducing healthcare use and improving ability to contribute to work life, community life and family life.

Seizure control also fundamentally changes ability to look after one's own children. See point 1a), 1b) and 1c) above.

Cloughesy et al Oct 2025 Vorasidenib in IDH1-mutant or IDH2-mutant low-grade glioma (INDIGO): secondary and exploratory endpoints from a randomised, double-blind, placebo-controlled, phase 3 trial - The vorasidenib group had lower rates of seizures than the placebo group

Bruno et al Oct 2025 EARLY SEIZURE CONTROL WITH [18F]-DOPA PET RESPONSE AFTER IDH INHIBITION WITH VORASIDENIB ""Over a median treatment duration of 6.6 months, 9/10 patients experienced seizure reduction without changes in antiseizure medication: 8/10 achieved early seizure freedom within 2 cycles.""

Value for Money requires a broader viewpoint than what has been used. Initiatives such as the Highly specialised technologies assessment route aim to address underfunded areas of rare cancers, and the UK does encourage more research. But as stated in Commercial clinical trials in the UK: the Lord O'Shaughnessy review 2023, [https://www.gov.uk/government/publications/commercial-clinical-trials-in-the-uk-the-lord-oshaughnessy-review/commercial-clinical-trials-in-the-uk-the-lord-oshaughnessy-review-final-report#part-3-transforming-how-the-uk-does-clinical-trials]
the UK needs to improve end to end policies to get treatments from bench to bedside, and the UK need to provide more for unmet needs - like LGG which kills more young adults than other cancers but attracts less than1% of cancer research funding.

Many millions have been spent [links 1, 2, 3 below] bringing new cancer therapies to point of use, why then deny their use? In Vorasidenib we have research that has cost the UK no research funds -done by Servier - with a

proven outcome, yet it is being denied to young patients with unmet need. This does not seem to be ""value for money""

1] Gov.uk Project Orbis Published Dec 2020, updated Oct 2025 www.gov.uk/guidance/guidance-on-project-orbis

2] Gov.uk Cancer Healthcare Goals Updated 14 October 2025 www.gov.uk/government/publications/life-sciences-healthcare-goals/cancer-healthcare-goals

3] Commons Library Debate on research and treatment of brain tumours Research Briefing Published Tuesday, 06 May, 2025 commonslibrary.parliament.uk/research-briefings/cdp-2025-0094/"

Has all of the relevant evidence been taken into account?

"No.

1) Recent evidence from Cloughesy et al Oct 2025 [Vorasidenib in IDH1-mutant or IDH2-mutant low-grade glioma (INDIGO): secondary and exploratory endpoints from a randomised, double-blind, placebo-controlled, phase 3 trial]
Vorasidenib reduced tumour growth rate and improved seizure control compared with placebo, with no observed negative effects on HRQOL or neurocognition.

2) Recent evidence from Bruno et al OCt 2025 [EARLY SEIZURE CONTROL WITH [18F]-DOPA PET RESPONSE AFTER IDH INHIBITION WITH VORASIDENIB]
Over a median treatment duration of 6.6 months, 9/10 patients experienced seizure reduction without changes in antiseizure medication: 8/10 achieved early seizure freedom within 2 cycles ...(1 patient seizures got worse)
Also, seizure improvement correlated with decreased F-DOPA PET uptake despite stable disease on conventional MRI, supporting the value of F-DOPA PET as a more sensitive tool for assessing treatment efficacy.

3) Overall Survival Benefit. The recommendations have glossed over a key point about Overall Survival Benefit, and any uncertainties have, wrongly, led to a sweeping dismissal of this key benefit.

3a) Public Committee Slides ACM1, slide 27, Clinical Experts said: ""Expect vorasidenib improves life expectancy in people with LGG by delaying need for 2nd surgery, CT and RT and their associated toxic effects."" In the Committee Papers, several clinical experts said the same and commented that understanding what IDH inhibitors do on a molecular level will likely give OS benefit. But this crucial point seems to have been dismissed in the Draft guidance document.

3b) Public Committee Slides ACM1, slide 27. The same key point, that delaying disease progression will very likely improve overall survival, is also put by the company with evidence to back it up [Miller et al. (2016): Retrospective analysis of 275 with IDH-mutant glioma treated in US 1991 - 2017], and this too has not been given sufficient weight in the draft guidance consultation document.

3c) Public Committee Slides ACM1 , slide 26 has a graph of ""Time spent in health states"" and in that both the company's base case and the EAG base case both show significant improvement of OS for Vorasidenib over existing treatment pathways. Slide 26 also has a table showing again that both the company's and EAG's base cases show significant Overall Survival Benefit for Vorasidenib of 5.81 and 3.12 Life Years. This vital information seems to be unmentioned in the draft guidance despite being of utmost importance.

Failing to pass into the draft guidance document these very important points, makes the recommendations unsound.

3d) Delaying disease progression is very likely to delay mortality, because it is disease progression that leads to mortality. This obvious logic seems to have been lost in the detail.

3e) The aim of Low Grade Glioma care is to delay disease progression, and this is what Vorasidenib does.

3f) Vorasidenib is ""Another tool in the toolbox [that] offers hope." [Vorasidenib Treatment Shows Promise for Some Low-Grade Gliomas, National Cancer Institute June 2023]. Vorasidenib gives the patient extra time with little to no harm. Existing therapies also buy extra time but are harmful. A safe effective tool in the toolbox is needed.

3g) Laack et al 2017, in ""Radiation Therapy Oncology Group 9802: Controversy or Consensus in the Treatment of Newly Diagnosed Low-Grade Glioma?"" a phase III randomized trial comparing RT alone with RT and 6 cycles of adjuvant procarbazine, CCNU, vincristine (PCV), demonstrated an unprecedented 5.5-year improvement in median overall survival.
This lends support to the logic that adding yet another tool to delay disease progression will improve Overall Survival.

3h) Bruno et al Oct 2025 [EARLY SEIZURE CONTROL WITH [18F]-DOPA PET RESPONSE AFTER IDH INHIBITION WITH VORASIDENIB] demonstrated seizure improvement which also ""correlated with decreased F-DOPA PET uptake despite stable disease on conventional MRI, supporting the value of F-DOPA PET as a more sensitive tool for assessing treatment efficacy."" These findings lend more support to the overall survival benefit of Vorasidenib."

Are the recommendations sound and a suitable basis for guidance to the NHS?

"NO:
See my answers above to NICE ""Question: Has all of the relevant evidence been taken into account?"" Regarding Overall Survival benefit and evidence.

Also:

1a) Comparing Vorasidenib versus watch and wait is not relevant for estimating effect on Health Related Quality of Life. Because Vorasidenib changes the patient's FUTURE more than it changes the patient's PRESENT.
The comparison for QoL needs to be between people whose disease progression happens sooner, versus patients whose disease progression happened 3-5 years later [Public Committee Slides ACM1, slide 26] . And that extra time in a more healthy state has even more added value because of the patients being economically and socially active young adults in an active life stage, often parenting young children. [see Alexander et al 2023, The Psychosocial Effect of Parental Cancer: Qualitative Interviews with Patients' Dependent Children]

1b) INDIGO trial was not focussing on HRQoL. So other sources must be used to assess QoL impact. There is ample evidence that radiotherapy, chemotherapy and earlier cancer progression have a negative impact on QoL, especially to young adults in active life stages, many of whom have young children. [Halkett et al 2022, Brain cancer patients' levels of distress and supportive care needs over time]

2) The assessment requires more flexibility in use of economic models especially the discount rate applied. A severe life limiting disease with rapid progression is more favourably assessed. A slower progressing but not life limiting disease is more favourably assessed. LGG is falls into an unusual gap between these: severe and life limiting, but slowly progressing.

3) Astrocytoma patients have a median survival of only 5-8 years, and are young. Giving them 2-5 extra years before disease progression is transformative to them and their families. The reality of this fact is lost in the detail of modelling.

3a) Vorasidenib is a major breakthrough in brain cancer care, and early results are showing increasing benefits. Not only delaying disease progression, but also shrinking tumours and reducing seizures. [Cloughesy et al Oct 2025 Vorasidenib in IDH1-mutant or IDH2-mutant low-grade glioma (INDIGO): secondary and exploratory endpoints from a randomised, double-blind, placebo-controlled, phase 3 trial and [Bruno et al OCt 2025 EARLY SEIZURE CONTROL WITH [18F]-DOPA PET RESPONSE AFTER IDH INHIBITION WITH VORASIDENIB]

Our [redacted] experience is echoed by other patients on Vorasidenib: after a few months on Vorasidenib she has fewer seizures, less neurological deficits, more energy. This returns her ability to care for her children and take them out (with help) to participate in social life. It reduces care burden on her husband and other family which benefits their workplaces. It returns family carers to their lives.

For such an innovative drug with such promising early results, and for a devastating disease in young people, it is not appropriate to reject a Managed Access Arrangement or use of the Cancer Drug Fund whilst awaiting more results. Even more so when Low Grade Glioma is the biggest cancer killer of young adults, yet dreadfully underrepresented in research, and here is potentially the best news ever in glioma care."

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

"Age:
Low Grade Glioma Patients are young, and adding between 3.12 and 5.81 extra years [Public Committee Slides ACM1 slide 26] to a young life is significant. More significant to someone in their 20s than typical cancer patients in say their 60s or 70s.

The economic modelling assumes that dying after 20 years is not so bad. That may be the case for a 60 year old but not for a 25 year old.

The recommendations do not seem to put enough weight on the impact on a patients' children, who are likely to be very young. To the young children of the glioma patient, 3 to 6 extra years with a parent is life changing. Even more so when Vorasidenib can hold that parent in the early disease stage for longer with better brain function and less treatment side effects. [see Alexander et al 2023, The Psychosocial Effect of Parental Cancer: Qualitative Interviews with Patients' Dependent Children]

From a bereaved mother of a young cancer victim: ""Every extra day means the world to loved ones.""

Socioeconomic status:
Socioeconomic inequality arises if NICE do not approve this life changing drug that has no safe alternatives, then the very wealthy can access it privately and most people cannot. Others might sell homes and cars and cash in pensions to fund it privately, leading to sudden poverty that will affect the wider family.

Age and Socioeconomic status:

Chemotherapy is more risky when sharing a home with young children who bring community germs into the home. Delaying chemo until the patient's children are older does make chemo less risky. Also, poorer families are less likely to have second bathroom to make chemo safer, and less likely to be able to afford childcare and domestic help to reduce contact during chemo with children coming home from preschool with community germs. For our [redacted], if she can wait until her little boys are older and better at washing their hands and wiping their own bottoms and noses, it will increase her chance of successfully coming through chemotherapy. Small houses with small children, a small kitchen, no dishwasher and only one bathroom are not ideal for chemotherapy patients.

Unusual disease progression not being given flexibility of modelling, is discriminatory against a disability(disease):
LGG fall into a hole in NICE's economic models, this discriminates against patients with a particular type of slow but deadly disease:

Cost effectiveness model gives preference to people who have a less serious disease that will not kill them, so they get a better discount rate. and to those with a more serious disease who will die quickly therefore not need the treatment for so long. so they get a better discount rate

But the NEEDS of patients with a slowly progressing disease that eventually kills, falls into a gap between those. This is discriminatory. This discrimination also happens to research funding into LGG, which ultimately progress to High grade and is the biggest cancer killer of under 40s, yet receives 1% of cancer research funding.
[https://www.braincancerjustice.org/]"

"1. The Highly Specialised Technology Route should be more seriously considered. The sole reason for disregarding that is uncertainty in the number of patients who would be suitable for Vorasidenib [see HST checklist Vorasidenib]

NICE PMG37 Highly Specialised Technologies Programme in chapter 7.2.5 states that ""NICE has the discretion to apply some flexibility in these cases based on information and evidence gathered by the scoping exercise."" This consultation does not appear to have applied flexibility to this uncertainty.

HST was designed for situations like this:
Long disease progression making long term outcomes difficult to gather data on.

Rare disease with serious effects.

Gives significant benefit over other treatment options.

Young patients for whom harsher therapies have more impact:

Especially long term cognitive decline after radiotherapy, this is more risky to younger brains [Rube et al 2023 Radiation-Induced Brain Injury: Age Dependency of Neurocognitive Dysfunction Following Radiotherapy] and more problematic if you are in an active life stage working and raising children, and more problematic for young patients who have many years left to live for the cognitive decline to irreversibly progress. The longer radiotherapy can be delayed, the better for the patient.

Chemotherapy has more impact on younger adults who often live with their own young children so cannot isolate from sources of community infection."

"2. There has been insufficient weight placed on the cost burden to NHS and care services and social support services, by the impact on the wider family. There has also been insufficient consideration of the whole of life Quality of Life impact on the whole wider family.

3. Most LGG patients are young adults and many have young children; some stages of disease and its treatment makes them unable to care for their own children. The long term impact on the children's mental and social wellbeing will bring costs to public services. There are life long benefits to a young child of having an extra 3 -5 years [slide 26 of Public Committee Slides ACM1] with their mum still well enough to interact before harsher therapies, [see Alexander et al 2023, The Psychosocial Effect of Parental Cancer: Qualitative Interviews with Patients' Dependent Children]

4. Caring for a patient's children impacts the work and personal lives of the wider family. In our personal experience this takes the family's care capacity away from elderly relatives who then burden NHS and care services.

5. Also in our personal experience, the considerable stress of caring for 4 generations at once, causes family to lose work capacity and lose quality of life and have significant stress related illness which leads to use of more NHS services. See Schulz and Sherwood 2009, Physical and Mental Health Effects of Family Caregiving"
"6. Impact on seizure control has not adequately been addressed. Vorasidenib can hold a patient for longer in a lower disease state, with fewer seizures.

Reduced seizure control has wider economic benefit through reducing healthcare use and improving ability to contribute to work life, community life and family life.

Seizure control also fundamentally changes ability to look after one's own children. See points 2, 3, 4 and 5 above.

*Cloughesy et al Oct 2025 Vorasidenib in IDH1-mutant or IDH2-mutant low-grade glioma (INDIGO): secondary and exploratory endpoints from a randomised, double-blind, placebo-controlled, phase 3 trial - The vorasidenib group had lower rates of seizures than the placebo group

*Bruno et al Oct 2025 EARLY SEIZURE CONTROL WITH [18F]-DOPA PET RESPONSE AFTER IDH INHIBITION WITH VORASIDENIB ""Over a median treatment duration of 6.6 months, 9/10 patients experienced seizure reduction without changes in antiseizure medication: 8/10 achieved early seizure freedom within 2 cycles."""

"7. Value for Money requires a broader viewpoint than what has been used. Initiatives such as the Highly specialised technologies assessment route aim to address underfunded areas of rare cancers, and the UK does encourage more research. But as stated in [Commercial clinical trials in the UK: the Lord O'Shaughnessy review 2023], the UK needs to improve end to end policies to get treatments from bench to bedside, and the UK need to provide more for unmet needs - like LGG which kills more young adults than other cancers but attracts less than1% of cancer research funding.

Many millions have been spent [see 1, 2, 3 below] bringing new cancer therapies to point of use, why then deny their use? In Vorasidenib we have research that has cost the UK no research funds -done by Servier - with a proven outcome, yet it is being denied to young patients with unmet need. This does not seem to be ""value for money""

1] Gov.uk Project Orbis Published Dec 2020, updated Oct 2025

2] Gov.uk Cancer Healthcare GoalsUpdated 14 October 2025

3] Commons Library Debate on research and treatment of brain tumours Research Briefing Published Tuesday, 06 May, 2025"

"""Usual care for astrocytoma or oligodendroglioma with IDH1 or IDH2 mutations for people who do not need immediate chemotherapy or radiotherapy after surgery is active surveillance.""

Comment: This as an opening statement is misleading because it suggests that active surveillance is an acceptable option for an incurable cancer in young patients; this opening statement is also misleading because it fails to mention the fact that glioma patients do all in the end progress to needing radiotherapy and chemotherapy; and fails to mention that the progression leads to debilitating fatigue, increased seizures, neurological deficits and then dying young.

A more truthful opening statement would continue thus:
...active surveillance until progression is shown radiologically or neurologically. This progression is inevitable and the timing of it unpredictable. Upon progression, the only existing treatments are:
1. brain radiotherapy which causes long term irreversible cognitive loss
2. chemotherapy with its risks and side effects
3. for some, further surgery with risks of damaging vital brain functions
4. and even after all of these, the patient will at some point suffer tumour progression to higher grade which leads, usually within a few months, to

neurological deficits, worsening seizures, cognitive deficits, then death at a young age.

Vorasidenib is an exciting and safe new option that is proven to delay the progression of the tumour and therefore delay the young person's suffering of the events listed above 1 to 4. For the mostly young adult patient population, vorasidenib buys extra time with their families who often include young children - before the disease makes them too unwell to participate in normal life."

"""But it is unclear if vorasidenib affects how long people with the condition live.""

Comments:
i. It is reasonable and logical that delaying the time until the tumour progresses, will extend length of life, because it is tumour progression that leads to higher grades, more neurological deficits, and death.
ii. The key to successful Low Grade Glioma care is in delaying that progression.
iii. Delaying chemotherapy in young adults allows patients to move into life stages where chemotherapy is less risky. Young adults are often unable to prevent exposure to community germs – potentially fatal during chemotherapy - due to their small children bringing germs into the home as well as the youthful lifestyles of their spouse and family carers. Therefore even if Vorasidenib only delays the need for harsher treatments for a few years, that can in itself extend life by making chemotherapy safer.
iv. Brain radiotherapy risks causing other cancers, so postponing for longer can improve Overall survival.
Not taking this into account is discriminatory against young patients.
v. Vorasidenib has only been in use for around 3 years, therefore length of life data that NICE are requiring cannot be available yet. INDIGO trial's next planned data cut in May 2028 will be too late for many young patients if they are denied access now.
vi. Other innovative therapies such as anti tumour immunotherapy, are being developed, [Rizwani et al Med Oncol 2025 Unlocking glioblastoma: breakthroughs in molecular mechanisms and next-generation therapies] especially for high grade glioma which these patients will progress to. If Vorasidenib can keep young adults free from tumour growth and malignant transformation even for only a few more years, they can still be here and healthy to access future options to increase quality of life and length of life - without needing to damage their cognition with brain radiotherapy."

"""...uncertainties in the economic model, including assumptions on...
if vorasidenib extends how long people live""

Comments:
There is evidence about Overall survival, which needs more consideration:

1) Recent evidence from Cloughesy et al Oct 2025 Vorasidenib in IDH1-mutant or IDH2-mutant low-grade glioma (INDIGO): secondary and

exploratory endpoints from a randomised, double-blind, placebo-controlled, phase 3 trial. Vorasidenib reduced tumour growth rate and improved seizure control compared with placebo, with no observed negative effects on HRQOL or neurocognition.

2) Recent evidence from Bruno et al OCt 2025 EARLY SEIZURE CONTROL WITH [18F]-DOPA PET RESPONSE AFTER IDH INHIBITION WITH VORASIDENIB Over a median treatment duration of 6.6 months, 9/10 patients experienced seizure reduction without changes in antiseizure medication: 8/10 achieved early seizure freedom within 2 cycles ...(1 patient seizures got worse)
Also, seizure improvement correlated with decreased F-DOPA PET uptake despite stable disease on conventional MRI, supporting the value of F-DOPA PET as a more sensitive tool for assessing treatment efficacy.

Knowing the molecular biology of Vorasidenib's effects, adding that to this evidence, it is likely that Overall Survival will benefit, as stated by your own clinical experts.

3a) Public Committee Slides ACM1, slide 27, Clinical Experts said: ""Expect vorasidenib improves life expectancy in people with LGG by delaying need for 2nd surgery, CT and RT and their associated toxic effects.""
This expert opinion was echoed several times in the Committee papers section 5 from several clinical experts. This crucial pint needs to be given more weight.

3b) Public Committee Slides ACM1, slide 27. The same key point, that delaying disease progression will very likely improve overall survival, is also put by the company with evidence to back it up [Miller et al. (2016): Retrospective analysis of 275 with IDH-mutant glioma treated in US 1991 - 2017], and this too has not been given sufficient weight.

3c) Public Committee Slides ACM1 , slide 26 has a graph of ""Time spent in health states"" and in that both the company's base case and the EAG base case both show significant improvement of OS for Vorasidenib over existing treatment pathways. Slide 26 also has a table showing again that both the company's and EAG's base cases show significant Overall Survival Benefit for Vorasidenib of 5.81 and 3.12 Life Years. This vital point again seems to under-represented in the draft guidance despite being of utmost importance.

Failing to adequately pass into the draft guidance document these very important points, makes the recommendations unsound.

3d) Delaying disease progression is very likely to delay mortality, because it is disease progression that leads to mortality. This obvious logic seems to have been lost in the detail.

3e) The aim of Low Grade Glioma care is to delay disease progression, and this is what Vorasidenib does.

3f) Laack et al 2017, in Radiation Therapy Oncology Group 9802: Controversy or Consensus in the Treatment of Newly Diagnosed Low-Grade Glioma?"" a phase III randomized trial comparing RT alone with RT and 6 cycles of adjuvant procarbazine, CCNU, vincristine (PCV), demonstrated an unprecedented 5.5-year improvement in median overall survival.
This lends support to the logic that adding yet another tool to delay disease progression will improve Overall Survival. Especially with such a well tolerated treatment which will reduce patient drop out due to side effects.

3g) Cloughesy et al Oct 2025 Vorasidenib in IDH1-mutant or IDH2-mutant low-grade glioma (INDIGO): secondary and exploratory endpoints from a randomised, double-blind, placebo-controlled, phase 3 trial demonstrated reduced seizures and reduced tumour growth rate.

Bruno et al Oct 2025 EARLY SEIZURE CONTROL WITH [18F]-DOPA PET RESPONSE AFTER IDH INHIBITION WITH VORASIDENIB demonstrated seizure improvement and decreased F-DOPA PET uptake.

The molecular biology of gliomas and IDH inhibitors, together with these findings, all add support to the overall survival benefit of Vorasidenib. Is it ethical to deny this to patients until several more years of data have been collected to prove what we already know?"

"""...the quality of life of people in the model""

Comments:

a) Comparing Vorasidenib versus Watch and Wait is not relevant for estimating effect on Health Related Quality of Life. Because Vorasidenib changes the patient's FUTURE more than it changes the patient's PRESENT.

b) The comparison for QoL needs to be between people whose disease progression happens sooner, versus patients whose disease progression happened 3-5 years later [Public Committee Slides ACM1, slide 26]

c) The aim of Low Grade Glioma care is to delay progression, and this is exactly what Vorasidenib does. HRQoL gets worse as glioma progresses through harsh treatments and to higher grade glioma. [Halkett et al 2022, Brain cancer patients' levels of distress and supportive care needs over time]
d) NICE have failed to put enough weight on the negative impact on life functioning and brain health of the only alternatives: brain radiotherapy, chemotherapy and further brain surgery.
e) Using the comparator from the INDIGO trial of QoL during Active Surveillance versus QoL during IDH inhibitor treatment, is not ideal for assessing impact on Quality of Life. Because this fails to capture

Vorasidenib's benefits to FUTURE HRQoL by delaying tumour progression and all that comes with it.

f) NICE have failed to put enough weight on the typical age and life stage of low grade glioma patients. Most are in their 20s, 30s and 40s, and at crucial stages of education, career, relationships and parenting. At this stage of life, a few extra years of healthy life with a fully functioning brain makes a big difference not only to quality of life of the patient, but also to their children, spouses, siblings, parents and communities. [Schulz and Sherwood 2009 Physical and Mental Health Effects of Family Caregiving]

g)
h) NICE have not factored in the full and life long effects on the patients' children - who are often very young - of their parent having their brain damaged by radiotherapy and further surgery, or of their parents as the tumour progresses having increase in neurological deficits, cognitive deficits and seizures. This will cost the NHS more in the long term as those children grow up with resulting issues with mental health and social and emotional damage. [see Alexander et al 2023, The Psychosocial Effect of Parental Cancer: Qualitative Interviews with Patients' Dependent Children]

i) Vorasidenib can hold the patient in a lower care need phase for longer, which reduces burden on the whole family and community; the consultation did not seem to adequately take this into account. Spouses, siblings and parents can becomes unable to work or pursue normal lives due to caring for the patient and their children, and this demand increases as the tumour progresses and as more harsh therapies take their toll. Diseases of the brain affect the level of care needed to a greater extent than diseases of the body. Cancer in young people brings higher care need than in the elderly because we are trying to facilitate some form of socially active life. All of these were not adequately considered in this assessment of QoL impact on the wider family.

j) Knowing that there is a proven, safe and effective therapy available, but being denied it due to cost, adds significant distress to the whole family and this will increase as the disease progresses.

k) If the next data cut in May 2028 - or later ones - backs up the likely outcome that delaying tumour progression also extends total life, the distress to grieving families will be immense knowing the drug was available but denied and now it is too late for them."

""""Because of the uncertainties in the economic model it is not possible to determine the most likely cost-effectiveness estimates for vorasidenib. So, vorasidenib should not be used routinely in the NHS.""

Comments:

NICE state that lack of data about long term survival benefits is needed, but this data cannot be collected without giving the drug to patients. Managed

Access Arrrangements and use of the Cancer Drug Fund has been dismissed too readily.

The INDIGO study data on disease progression for glioma is for median age 40, and there is ample evidence [Lanese et al 2018, The Risk Assessment in Low-Grade Gliomas: An Analysis of the European Organization for Research and Treatment of Cancer (EORTC) and the Radiation Therapy Oncology Group (RTOG) criteria] that, under all treatment options, younger glioma patients do better. This surely must enhance ""value for money.""

NICE have failed to adequately take into account the impact on future brain tumour research funding, of not approving the biggest breakthrough in years.

Glioma is the biggest cause of cancer deaths in adults under 40 years, but brain tumours only receive 1% of cancer research funding. This area of unmet need warrants a more flexible approach to economic modelling.

It seems counterproductive to invest heavily in funding cancer healthcare research, funding brain tumour research, and fast tracking the licensing of new cancer therapies via Project Orbis, for then NICE to refuse patients access to the life enhancing technologies that result from such costly processes.

Oral tablet with few side effects is less costly to the overall health service than supporting a patient through radiotherapy, chemotherapy, and the side effects of those.

Add in the wider follow on costs of the patient's family with the increased care burden of supporting through Radiotherapy and chemotherapy: - time off work, reduced capacity to care for other family eg elderly relatives and children, mental health needs, stress and burnout leading to more healthcare visits.

Farther down the road will be mental health and social care needs of the children whose parent is being taken by this disease. In the life of a child 3-5 years extra time with a parent [Public Committee Slides ACM1, slide 26] has a lifelong benefit and will reduce their burden on services for mental and social well being. [see Alexander et al 2023, The Psychosocial Effect of Parental Cancer: Qualitative Interviews with Patients' Dependent Children] Whilst being given more time with a parent in a lower disease state, will help children to grow up more economically productive.
These value for money impacts have not been adequately taken into consideration. The economic modelling requires more flexibility."

"""Collecting more evidence during a managed access period is unlikely to resolve the key uncertainties in the evidence. So, vorasidenib cannot be used with managed access.""

Comments:
Managed access will collect more data. There are already reports of reduced seizures and tumours shrinking; time is needed to gather the data. It is not ethical to let young adults progress beyond treatment suitability whilst awaiting more data.

More data cannot be collected without giving the drug to patients."

Price

This is beyond the reach of most people privately, raising an inequality in access to healthcare by wealth status.

"We really hope and pray that Servier and the NHS can get together to agree an acceptable price for the best available treatment for a devastating disease.

Let us not lose sight of real people, young mums and dads, leaving their children bereaved at a young age."

"""The committee thought that the full impact of vorasidenib on mental health may not be captured in the model.""

Comment:

As a parent and carer of a patient, I absolutely agree that the impact on mental health has been massively underestimated Vorasidenib is the only good news in the rollercoaster ride of LGG. This affects also the patient's children, spouse, siblings and parents, whose whole futures are affected by what happens to the patient. Reading the growing evidence for the benefits that Vorasidenib can bring, then being told its supply to our [redacted] might stop, brings extreme distress to the whole family. This impacts our health with costs to the NHS, our employers with costs to the economy, our capacity to care for elderly relatives with costs to NHS and care services, our volunteering roles, hobbies and social lives with costs to communities.

When our [redacted] children grow up and learn that [redacted] might have lived longer and healthier if we had Vorasidenib supplied, the effect on their mental health will be lifelong. The same for her [redacted] who are all heavily involved in caring for her and her toddlers.

Economic models can lose sight of real people."

"""It concluded that it was uncertain whether the full quality-of-life benefit from reducing seizures had been captured in the model.""

Comment:

There is more to reduced seizures and independence than a driving licence. Especially for young patients. Needing supervision to look after one's own small children. Having to avoid: busy places, conversations even within the household, sports, noise and over exertion have massive impacts on QoL for patient and their family, more so because the patients are young.

Recent evidence from Cloughesy et al Oct 2025 Vorasidenib in IDH1-mutant or IDH2-mutant low-grade glioma (INDIGO): secondary and exploratory endpoints from a randomised, double-blind, placebo-controlled, phase 3 trial Vorasidenib reduced tumour growth rate and improved seizure control compared with placebo.

Recent evidence from Bruno et al OCt 2025 EARLY SEIZURE CONTROL WITH [18F]-DOPA PET RESPONSE AFTER IDH INHIBITION WITH VORASIDENIB Over a median treatment duration of 6.6 months, 9/10 patients experienced seizure reduction without changes in antiseizure medication: 8/10 achieved early seizure freedom within 2 cycles."

Acceptable ICER

"Comparing Vorasidenib versus Active Surveillance is not relevant for estimating effect on Health Related Quality of Life. Because Vorasidenib changes the patient's FUTURE more than it changes the patient's PRESENT.

The comparison for QoL needs to be between people whose disease progression happens sooner, versus patients whose disease progression progress later.

Compare having RT and CT sooner or postponing them until later. That extra time in a more healthy state has even more added value because of the patients being economically and socially active young adults in an active life stage, often parenting young children. [see Alexander et al 2023, The Psychosocial Effect of Parental Cancer: Qualitative Interviews with Patients' Dependent Children]"

"Overall Survival Benefit:

Overall Survival Benefit evidence requires more consideration:
1) Recent evidence from Cloughesy et al Oct 2025 Vorasidenib in IDH1-mutant or IDH2-mutant low-grade glioma (INDIGO): secondary and exploratory endpoints from a randomised, double-blind, placebo-controlled, phase 3 trial Vorasidenib reduced tumour growth rate and improved seizure control compared with placebo, with no observed negative effects on HRQOL or neurocognition.

2) Recent evidence from Bruno et al OCt 2025 EARLY SEIZURE CONTROL WITH [18F]-DOPA PET RESPONSE AFTER IDH INHIBITION WITH VORASIDENIB Over a median treatment duration of 6.6 months, 9/10 patients experienced seizure reduction without changes in antiseizure medication: 8/10 achieved early seizure freedom within 2 cycles ...(1/10 patient seizures got worse)
Also, seizure improvement correlated with decreased F-DOPA PET uptake despite stable disease on conventional MRI, supporting the value of F-DOPA PET as a more sensitive tool for assessing treatment efficacy.

3) Overall Survival Benefit. The recommendations have glossed over a key point about Overall Survival Benefit, and any uncertainties have, wrongly, led to a sweeping dismissal of this key benefit.

3a) Public Committee Slides ACM1, slide 27, Clinical Experts said: ""Expect vorasidenib improves life expectancy in people with LGG by delaying need for 2nd surgery, CT and RT and their associated toxic effects."" But this crucial point seems to have been ignored in the Draft guidance document.

3b) Public Committee Slides ACM1, slide 27. The same key point, that delaying disease progression will very likely improve overall survival, is also put by the company with evidence to back it up [Miller et al. (2016): Retrospectiveanalysis of 275 with IDH-mutant glioma treatedin US 1991 - 2017], and this too is not mentioned in the draft guidance consultation document, suggesting it has not been given sufficient weight.

3c) Public Committee Slides ACM1 , slide 26 has a graph of ""Time spent in health states"" and in that both the company's base case and the EAG base case both show significant improvement of OS for Vorasidenib over existing treatment pathways. Slide 26 also has a table showing again that both the company's and EAG's base cases show significant Overall Survival Benefit for Vorasidenib of 5.81 and 3.12 Life Years. This vital point again seems to be unmentioned in the draft guidance despite being of utmost importance.

Failing to pass into the draft guidance document these very important points, makes the recommendations unsound.

3d) Delaying disease progression is very likely to delay mortality, because it is disease progression that leads to mortality. This obvious logic seems to have been lost in the detail.

3e) The aim of Low Grade Glioma care is to delay disease progression, and this is what Vorasidenib does.

3f) Vorasidenib is ""Another tool in the toolbox [that] offers hope." [Vorasidenib Treatment Shows Promise for Some Low-Grade Gliomas, National Cancer Institute June 2023]. Vorasidenib gives the patient extra time with little to no harm. Existing therapies also buy extra time but are harmful. A safe effective tool in the toolbox is needed.

3g) Laack et al 2017, in Radiation Therapy Oncology Group 9802: Controversy or Consensus in the Treatment of Newly Diagnosed Low-Grade Glioma?"" a phase III randomized trial comparing RT alone with RT and 6 cycles of adjuvant procarbazine, CCNU, vincristine (PCV), demonstrated an unprecedented 5.5-year improvement in median overall survival. This lends support to the logic that adding yet another tool to delay disease progression will improve Overall Survival.

3h) Bruno et al OCt 2025 EARLY SEIZURE CONTROL WITH [18F]-DOPA PET RESPONSE AFTER IDH INHIBITION WITH VORASIDENIB demonstrated seizure improvement which also ""correlated with decreased F-DOPA PET uptake despite stable disease on conventional MRI, supporting the value of F-DOPA PET as a more sensitive tool for assessing treatment efficacy."" These findings lend more support to the overall survival benefit of Vorasidenib."

"""So, the committee concluded that an acceptable ICER would be around £20,000 per QALY.""

Comment:

Unusual disease progression:
LGG fall into a hole in NICE's economic models, this discriminates against patients with a particular type of slow but deadly disease:

Cost effectiveness model gives preference to people who have a less serious disease that will not kill them, so they get a better discount rate; and to those with a more serious disease who will die quickly therefore not need the treatment for so long, so they get a better discount rate.

But the NEEDS of patients with a slowly progressing disease that eventually kills, falls into a gap between those two more common scenarios. This requires a more flexible approach to the economic models especially the discount rate.

The Highly Specialised Technology Route is designed for such unusual cases, and has been dismissed on uncertain sources for patient numbers, but HST is supposed to be applied with flexibliity to patient numbers.

Low Grade Glioma Patients are young, and adding between 3.12 and 5.81 extra years [Public Committee Slides ACM1 slide 26] to a young life is significant. More significant to someone in their 20s than typical cancer patients in say their 60s or 70s.

The economic modelling assumes that dying after 10 or 20 years is not so bad. That may be the case for a 60 year old but not for a 25 year old.

The recommendations do not seem to put enough weight on the impact on a patients' children, who are likely to be very young. To the young children of the glioma patient, 3 to 6 extra years with a parent is life changing. Even

more so when Vorasidenib can hold that parent in the early disease stage for longer with better brain function and less treatment side effects. [see Alexander et al 2023, The Psychosocial Effect of Parental Cancer: Qualitative Interviews with Patients' Dependent Children]

NICE are allowed to use flexibility in applying guidance, and this case certainly requires more of that. Felxiblity in discount rate, flexibility in using the Highly Specialised Technology Route, and flexibility in accepting the existing evidence and expert opinions for Overall Survival benefit."

The assessment requires more flexibility in use of economic models especially the discount rate applied. A severe life limiting disease with rapid progression is more favourably assessed. A slower progressing but not life limiting disease is more favourably assessed. LGG is falls into an unusual gap between these: severe and life limiting, but slowly progressing. NICE are allowed to apply the guidelines with flexibility, and this case requires that.

"Did the QALY adequately take into account the young patient population? And the impact on the young children, spouses, siblings and parents of patients? As an example, an extra 2, 5 or 7 years of healthy brain function before radiotherapy and chemotherapy is of more value to a [redacted] year old mother of 3 than to a 66 year old retiree.

Astrocytoma patients have a median survival of only 5-8 years, and are young. Giving them 2-5 extra years before disease progression is transformative to them and their families. The reality of this fact is lost in the detail of modelling."

Uncertainties to explore further in the modelling

"1a) Comparing Vorasidenib versus watch and wait is not relevant for estimating effect on Health Related Quality of Life. Because Vorasidenib changes the patient's FUTURE more than it changes the patient's PRESENT.
The comparison for QoL needs to be between people whose disease progression happens sooner, versus patients whose disease progression happened 3-5 years later [Public Committee Slides ACM1, slide 26] . And that extra time in a more healthy state has even more added value because of the patients being economically and socially active young adults in an active life stage, often parenting young children. [see Alexander et al 2023, The Psychosocial Effect of Parental Cancer: Qualitative Interviews with Patients' Dependent Children]

1b) INDIGO trial was not focussing on HRQoL. So other sources must be used to assess QoL impact. There is ample evidence that radiotherapy, chemotherapy and earlier cancer progression have a negative impact on QoL, especially to young adults in active life stages, many of whom have young children. [Halkett et al 2022, Brain cancer patients' levels of distress and supportive care needs over time]

1c) Vignette studies have not compared the relevant populations which should be those with significantly delayed disease progression and those with earlier disease progression. Also, vignette studies must not be used to override common sense: Taking a tablet that is shown to be well tolerated, and delaying progression of cancer. Versus cancer getting worse and needing radiotherapy, chemotherapy and more surgery."

"""Grade 3 and 4 gliomas, referred to as high-grade glioma (HGG), grow quickly. Consequently, HGG is associated with worse outcomes than LGG. Up to 70% of LGGs may progress to high grade or become malignant within 10 years.""

Comment: This statement is misleading in that it fails to make clear that all LGG do at some point progress to HGG, with fatal outcomes. 10 years is not long to give to someone in their 20s who leaves behind children."

"""Symptoms of IDH-mutant astrocytoma and oligodendroglioma (from here, referred to as LGG) include headaches, seizures, difficulty thinking or remembering and changes in vision.""

Comment: this statement underplays the real life impact of gliomas. Patients progressively lose brain function for example debilitating fatigue, losing the ability to find words, speak, swallow, or control their movements, increasing seizures and having to limit activities to avoid triggering seizures. Vorasidenib can delay all of these distressing losses."

"""Patient-organisation submissions highlighted the large impact on quality of life of living with LGG, which affects social life, education and work. The physical symptoms of the condition can be challenging, especially seizures, which can cause anxiety and affect independence by limiting the ability to drive. ""

Comment: Seizures have more impact than is mentioned here. Our daughter is afraid to swim or kayak or cycle in case of seizure. Before Vorasidenib improved her energy levels and reduced her seizures, she could not socialise without hours of rest before and after, because getting over tired makes her seizure. A bad cold or noise from conversation and noise from her own children made her seizure. Her seizures and fatigue, facial weakness and swallowing difficulties have all gradually reduced the longer she has been on Vorasidenib. She even looks more like her old self with facial expression and demeanour.

Recent evidence: Cloughesy et al Oct 2025 Vorasidenib in IDH1-mutant or IDH2-mutant low-grade glioma (INDIGO): secondary and exploratory endpoints from a randomised, double-blind, placebo-controlled, phase 3 trial Vorasidenib reduced tumour growth rate and improved seizure control compared with placebo, with no observed negative effects on HRQOL or neurocognition.

Bruno et al OCt 2025 EARLY SEIZURE CONTROL WITH [18F]-DOPA PET RESPONSE AFTER IDH INHIBITION WITH VORASIDENIB Over a median treatment duration of 6.6 months, 9/10 patients experienced seizure reduction without changes in antiseizure medication: 8/10 achieved early seizure freedom within 2 cycles ."

"""Chemotherapy and radiotherapy are also associated with debilitating side effects such as cognitive decline and fatigue.""

Comment: it is necessary to include here that the cognitive decline caused by brain radiotherapy is permanent, progressive, and life changing. Therefore delaying brain radiotherapy is a wonderful option that vorasidenib gives."

"""So, the committee concluded that active surveillance was the relevant comparator but the exact population for which vorasidenib would be used in clinical practice was unclear.""

Comments:
Active surveillance is not the relevant comparator: progression to the need to radiotherapy and chemotherapy is the relevant comparator, since this is what vorasidenib significantly delays. Moreover, data may show -if given time and opportunity- that vorasidenib might indefinitely postpone the need for radiotherapy and chemotherapy.

This approach fails to state or address the fact that active surveillance, unlike vorasidenib, does not prevent growth of the glioma or progression to higher grade. The wording of 3.3 of the report is indeed quite misleading. The committee needs to be more aware of these points:

There are patients for whom surgical resection is incomplete and yet there are good reasons to delay radiotherapy and chemotherapy. However, whether a patient has partial resection, complete resection, or supramaximal resection, it cannot be ethical to deny an innovative new treatment if the patient's oncologist and neurosurgeon deem it to be beneficial to that individual.

It is correct to say that use of different treatment options needs to be on a case by case basis. Amount of resection and size and location of a brain tumour are more variable than for tumours in other organs, making individualised decisions pertinent. Individualised decisions cannot be made when the best available treatment is denied."

"""There were no significant improvements in neurological function or health-related quality of life between arms (see section 3.13).""

Comments:

The issue is not the present QoL and function in each arm, rather it is what difference is made to the patient's future.

Also, recent evidence from Cloughesy et al Oct 2025 and Bruno et al Oct 2025 show reduction in tumour growth, reduction in seizures, and reduction in F-DOPA PET uptake.
All of these will have positive effects on QoL: practically by reducing seizures, and psychologically for the present and future by slowing disease progression."

"Individualised care is paramount in brain tumours because glioma locations and sizes vary widely and different parts of the brain vary in their sensitivity to damage by tumour growth and by surgery.

Although some individuals might have more benefit from vorasidenib and other less benefit, this is not an ethically acceptable reason to deny treatment to all patients.

A more appropriate approach would be to offer oncologists and multidisciplinary teams the option to prescribe this groundbreaking new safe treatment for suitable patients, rather than remove the option from suitable patients because there are some unsuitable patients."

"Vorasidenib does not claim to cause neurological improvement; rather it is significantly delays progression, which will delay neurological deterioration.

Recent evidence also demonstrates reduction in tumour growth rate, reduction of seizures, and improvement of PET scans. [Cloughesy et al Oct 2025 Vorasidenib in IDH1-mutant or IDH2-mutant low-grade glioma (INDIGO): secondary and exploratory endpoints from a randomised, double-blind, placebo-controlled, phase 3 trial] and [Bruno et al OCt 2025 EARLY SEIZURE CONTROL WITH [18F]-DOPA PET RESPONSE AFTER IDH INHIBITION WITH VORASIDENIB]"

""""It also noted that people with progressed disease in INDIGO reported higher quality-of-life results in the placebo arm than the vorasidenib arm, which did not support a longer TTNI-P for vorasidenib.""

Comment:

Does this include people who progressed in placebo arm then crossed over to vorasidnib arm? Their QoL will be adversely affected by knowing that they might not have had disease progression if they had been in the treatment group.

""So, the EAG believed that the company's TTNI-P curves lacked face validity and that using separate curves was likely inappropriate. Because of this, it preferred to fit the same curve to both arms, that is, to assume no benefit in TTNI-P for vorasidenib.""

Comment:

That is a very big assumption to make."

"""The committee noted that this approach did not assume a TTNI-P benefit for vorasidenib. It acknowledged that a different time to next treatment after progression on placebo and vorasidenib may be plausible, because of vorasidenib's effect on tumour biology.""

Comment:

This is an important point that needs to be given more weight. Especially in light of recent evidence that demonstrates reduction in tumour growth rate, reduction of seizures, and improvement of PET scans.

[Cloughesy et al Oct 2025 Vorasidenib in IDH1-mutant or IDH2-mutant low-grade glioma (INDIGO): secondary and exploratory endpoints from a randomised, double-blind, placebo-controlled, phase 3 trial]

and [Bruno et al OCt 2025 EARLY SEIZURE CONTROL WITH [18F]-DOPA PET RESPONSE AFTER IDH INHIBITION WITH VORASIDENIB]"

"""...the company submitted data from Miller et al. (2019), a retrospective analysis of 275 people with IDH-mutant glioma who had treatment in the US between 1991 and 2007. This suggested that delaying the time to first and second progression improved overall survival. ""

Comment:

This is a very important point that needs to carry more weight."

"""The clinical experts explained that it was difficult to directly translate improvements in PFS to overall survival without further evidence, but that this might be plausible.
They noted that treatment options for LGG are limited, so a poorer overall survival would be expected in people whose disease progressed quickly through treatments.""

Comment:
It is not possible to have this data for some years yet, due to the long term nature of LGG progression.
So instead we can use the data that is possible to have:
a) vorasidenib increases time to disease progression,
b) rapid disease progression leads to earlier mortality;
c) delaying disease progression therefore increases time to mortality and
d) recent evidence that demonstrates reduction in tumour growth rate, reduction of seizures, and improvement of PET scans.
[Cloughesy et al Oct 2025 Vorasidenib in IDH1-mutant or IDH2-mutant low-grade glioma (INDIGO): secondary and exploratory endpoints from a randomised, double-blind, placebo-controlled, phase 3 trial]

and [Bruno et al OCt 2025 EARLY SEIZURE CONTROL WITH [18F]-DOPA PET RESPONSE AFTER IDH INHIBITION WITH VORASIDENIB]"

"""The committee noted that there was no data to suggest a delayed transition to HGG or malignant glioma with vorasidenib compared with active surveillance.""

Comment:

Disease progression leads to transition to higher grade. Delaying disease progression will delay transition to Higher Grade. This is simple logic! I am a veterinary surgeon and we use simple logic every day!"

"""The company explained that an additional data cut from INDIGO was expected in May 2028.""

Comment:

That date will be too late for the current patient group, hence why a Managed Access Arrangement would be suitable."

"""But it [the EAG] acknowledged that collecting data to inform a progression-based model would be challenging given the rarity of LGG and the lack of published evidence on the condition.""

Comment:
Which is why the HST appraisal route is appropriate."

"""the committee thought that the unadjusted vignette utilities may not have captured the long-term impacts of chemotherapy or radiotherapy.""

Comment:

I agree and want to add that the long term impacts of cognitive decline from radiotherapy must carry more weight due to the young patient population. Firstly because younger brain are more sensitive to radiation damage [Rube et al 2023, Radiation-Induced Brain Injury: Age Dependency of Neurocognitive Dysfunction Following Radiotherapy]

Secondly because younger patients have more potential years ahead of them for the progressive cognitive decline to impact.

Also the risk of fatal infections during chemo is increased for young patients who live with children and other young people, with increased unavoidable exposure to community germs.

This risk increases for less wealthy people with only one toilet at home and who cannot afford childcare help during chemo cycles so have to take the risk of community germs brought into their hom by their own children."

""""It concluded that the utility values from the vignette study were highly uncertain, and that further analyses should be presented at consultation.""

Comment:

Vignette studies will be inaccurate, therefore when discussing impact on Quality of Life of the threat of or presence of disease progression, more weight should be given to Real World Experience from oncologists, patients and their families and carers."

"Comment:

The assessment requires more flexibility in use of economic models especially the discount rate applied. A severe life limiting disease with rapid progression is more favourably assessed. A slower progressing but not life limiting disease is more favourably assessed.

LGG is falls into an unusual gap between these: severe and life limiting, but slowly progressing.

NICE are allowed to apply the guidelines with flexibility, and this case requires that."

"Did the QALY adequately take into account the young patient population? And the impact on the young children, spouses, siblings and parents of patients? As an example, an extra 2, 5 or 7 years of healthy brain function before radiotherapy and chemotherapy is of more value to a 27 year old mother of 3 than to a 66 year old retiree.

Astrocytoma patients have a median survival of only 5-8 years, and are young. Giving them 2-5 extra years before disease progression is transformative to them and their families. The reality of this fact is lost in the detail of modelling."

"The key to Low Grade Glioma care is delaying tumour progression, and Vorasidenib does this. Delaying disease progression will improve Overall Survival. Public Committee Slides ACM1 slides 26 and 27 provide 4 different sources that indicate improved Overall Survival - why has this not carried weight in the committee discussion ?

Recent evidence demonstrates tumour shrinkage, decreased seizures and improvement in PET scans, these are good indicators that Vorasidenib not

only delays progression but has other emerging effects that will improve overall survival.

Cloughesy et al Oct 2025 Vorasidenib in IDH1-mutant or IDH2-mutant low-grade glioma and Bruno et al Oct 2025 EARLY SEIZURE CONTROL WITH [18F]-DOPA PET RESPONSE AFTER IDH INHIBITION WITH VORASIDENIB

Waiting years for more data on this will be too late for the current patient group. Is it ethical do deny such a groundbreaking safe effective treatment whilst awaiting more data?"

"Age:

Low Grade Glioma Patients are young, and adding between 3.12 and 5.81 extra years [Public Committee Slides ACM1 slide 26] to a young life is significant. More significant to someone in their 20s than typical cancer patients in say their 60s or 70s.

The economic modelling assumes that dying after 20 years is not so bad. That may be the case for a 60 year old but not for a 25 year old.

The recommendations do not seem to put enough weight on the impact on a patients' children, who are likely to be very young. To the young children of the glioma patient, 3 to 6 extra years with a parent is life changing. Even more so when Vorasidenib can hold that parent in the early disease stage for longer with better brain function and less treatment side effects. [see Alexander et al 2023, The Psychosocial Effect of Parental Cancer: Qualitative Interviews with Patients' Dependent Children]

From a bereaved mother of a young cancer victim: ""Every extra day means the world to loved ones."""

"Age:

Low Grade Glioma Patients are young, and adding between 3.12 and 5.81 extra years [Public Committee Slides ACM1 slide 26] to a young life is significant. More significant to someone in their 20s than typical cancer patients in say their 60s or 70s.

The economic modelling assumes that dying after 10 or 20 years is not so bad. That may be the case for a 60 year old but not for a 25 year old. For Astrocytoma near the eloquent area - as our daughter has - they might only have 5-7 years, and then Vorasidenib adding 3-5 years is amazing!

The recommendations do not seem to put enough weight on the impact on a patients' children, who are likely to be very young. To the young children of the glioma patient, 3 to 6 extra years with a parent is life changing. Even

more so when Vorasidenib can hold that parent in the early disease stage for longer with better brain function and less treatment side effects. [see Alexander et al 2023, The Psychosocial Effect of Parental Cancer: Qualitative Interviews with Patients' Dependent Children]

From a bereaved mother of a young cancer victim: ""Every extra day means the world to loved ones.""

Socioeconomic status:

Socioeconomic inequality arises if NICE do not approve this life changing drug that has no safe alternatives, then the very wealthy can access it privately and most people cannot. Others might sell homes and cars and cash in pensions to fund it privately, leading to sudden poverty that will affect the wider family.

Age and Socioeconomic status:

Chemotherapy is more risky when sharing a home with young children who bring community germs into the home. Delaying chemo until the patient's children are older does make chemo less risky. Also, poorer families are less likely to have second bathroom to make chemo safer, and less likely to be able to afford childcare and domestic help to reduce contact during chemo with children coming home from preschool with community germs. For our daughter, if she can wait until her little boys are older and better at washing their hands and wiping their own bottoms and noses, it will increase her chance of successfully coming through chemotherapy. Small houses with small children, a small kitchen, no dishwasher and only one bathroom are not ideal for chemotherapy patients."

"Unusual disease progression:
LGG fall into a hole in NICE's economic models, this discriminates against patients with a particular type of slow but deadly disease:

Cost effectiveness model gives preference to people who have a less serious disease that will not kill them, so they get a better discount rate. and to those with a more serious disease who will die quickly therefore not need the treatment for so long. so they get a better discount rate

But the NEEDS of patients with a slowly progressing disease that eventually kills, falls into a gap between those. This is discriminatory. This discrimination also happens to research funding into LGG, which ultimately progress to High grade and is the biggest cancer killer of under 40s, yet receives 1% of cancer research funding.
[https://www.braincancerjustice.org/]"

Name	[redacted]
Organisation	Add details here
Conflict	Add details here
Comments on the DG:	

Are the summaries of clinical and resource savings reasonable interpretations of the evidence?

"In the INDIGO trial, active surveillance in the placebo group is used as a comparator for the vorasidenib group. This is an appropriate comparator for assessing clinical effectiveness, however when comparing quality of life between the two groups, the faster progression to CT/RT in the placebo group with associated impact on health-related quality of life should be considered. The quality-of-life comparison should be between vorasidenib and active surveillance plus CT/RT, with associated negative side effects. This comparison is reflected in the clinical expert statements in the committee paper who place an emphasis on the benefits of delaying CT/RT with vorasidenib to improve overall quality of life.
NICE also stated that the INDIGO trial has shown that vorasidenib increases progression free survival but does not show that it increases the length of life. Clinical expert opinion is recorded in the public committee slides ACM1 slide 27 to say that they expect vorasidenib will increase the life expectancy due to delaying need for second surgery and CT/RT with associated side effects. Current treatment aims to delay tumour progression through tumour debulking surgery and CT/RT, therefore another drug that works to this aim like vorasidenib can provide a similar effect without the quality of life impacting side effects linked to surgery or CT/RT
The base case models of both Servier and the EAG predict a possible increase (between 3-5 years) in overall survival. The clinical expert opinions in the committee papers in favour of the drug have not been sufficiently considered or reflected in the consultation document.
Requiring concrete evidence for overall survival before NICE approval when a drug is newly developed where concrete information is impossible to access disadvantages those currently suffering from the disease. As this drug has shown promising beginnings, there should be access given and evidence reviewed over time to assess outcomes."

Has all of the relevant evidence been taken into account?

"Evidence regarding quality of life for people with LGG e.g. quality of life for those on vorasidenib vs. quality of life for those undergoing active surveillance, and progressed disease related interventions such as radiotherapy and chemotherapy has not adequately been considered. Further evidence on the quality-of-life impact of the condition must be considered to inform this discussion. Young et al. (2023) found that between half to three quarters of people with brain tumours experience a behavioural health disorder as a result of their diagnosis, with 16% of LGG patients diagnosed with PTSD within 3 months of surgery, and 60% of primary brain tumour patients reporting elevated stress. Anxiety and severe anxiety were found in 80% and 55% of patients. Hao, Huang & Xu (2021) found that

depression and anxiety in glioma patients negatively impacted overall survival. If living with untreated disease increases depression and anxiety, then using vorasidenib could have additional benefits by reducing the mental health effects of living with an untreated serious disease.
Heffernan et al. (2023) found that quality of life for those with LGG is an under researched field, they discovered that two thirds of LGG patients had difficulty thinking, speaking and memory, and quality of life was significantly reduced compared to the general population or those with other less severe brain tumours.
Further, 36.5% caregivers were found to have anxiety or depressive symptoms (Chen et al., 2021). Finocchiaro et al. (2012) also found a clinically significant impaired quality of life for caregivers of those with brain tumours. Patient and patient group statements in the committee papers also showed a big impact on the lives of carers and family members and showed that the effect of LGG care was lessened on vorasidenib compared to current pathways.
The psychological impact on children whose parents have LGG has not been adequately considered. Children whose parents have cancer are at increased risk of various psychosocial, emotional and behavioural problems (Alexander, O'Connor & Halkett, 2023). The impact of having more higher quality-of-life years with a parent on child lifelong mental and emotional stability needs to be further addressed. Better mental and emotional wellbeing due to less parental side effects will improve child outcomes.
Cancer parents with minor children experience parenting concerns that cause significant psychological distress. Due to the young age of LGG patients, and the high proportion that would then have young families, it is important to factor in the additional impact to quality of life that parenting concerns would have. Jing-ling, Qin and Ning (2024) said that healthcare professionals should pay attention to the special needs of cancer parents raising minor children and develop and support targeted interventions that may relieve psychological stress and impact to the family unit.
Vorasidenib would delay the need for CT/RT and associated side effects, which have been shown to increase distress in children of cancer patients. CT and RT increase time away from children and increase negative symptoms that would affect parents' ability to be active in their child's care.
The positive impact of vorasidenib on patient and carer wellbeing should be explored through real world patient and carer feedback through the early access scheme.
Alexander ES, O'Connor M, Halkett GKB. The Psychosocial Effect of Parental Cancer: Qualitative Interviews with Patients' Dependent Children. Children (Basel). 2023 Jan 15;10(1):171. doi: 10.3390/children10010171. PMID: 36670721; PMCID: PMC9857104.
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Heffernan AE, Wu Y, Benz LS, Verhaak RGW, Kwan BM, Claus EB. Quality of life after surgery for lower grade gliomas. Cancer. 2023 Dec 1;129(23):3761-3771. doi: 10.1002/cncr.34980. Epub 2023 Aug 20. PMID: 37599093; PMCID: PMC10872908.
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Jing-Ling Li, Qin Ye, Ning Liu. Cancer parents' experiences of parenting concerns about minor children: A meta-synthesis of qualitative studies, International Journal of Nursing Studies Advances, Volume 6, 2024, 100210, ISSN 2666-142X, https://doi.org/10.1016/j.ijnsa.2024.100210. (https://www.sciencedirect.com/science/article/pii/S2666142X24000377)
Young JS, Al-Adli N, Sibih YE, Scotford KL, Casey M, James S, Berger MS. Recognizing the psychological impact of a glioma diagnosis on mental and behavioral health: a systematic review of what neurosurgeons need to know. J Neurosurg. 2022 Nov 4;139(1):11-19. doi: 10.3171/2022.9.JNS221139. PMID: 36334288; PMCID: PMC10413205."

Are the recommendations sound and a suitable basis for guidance to the NHS?

"No. Low grade gliomas are an under researched area, denying innovative treatment may dissuade other companies from investing in research in this area. Brain cancers have attracted only 1% of national cancer funding, despite being the highest cause of cancer death of those under 40 in the UK according to Brain Cancer Justice.org. There has been no prior evolution in LGG care for the last 2 decades and vorasidenib marks a hopeful change in this under researched cancer. Discouraging developmental and new therapies stunts the evolution of cancer care in the UK.
Assessing vorasidenib under the Highly Specialised Technologies criteria should be reassessed. The drug met criteria for all but eligible population size, but data around the actual UK population eligible for vorasidenib was vague and uncertain.
The NICE technical team recognised their figure in the HST criteria assessment was likely overestimated as a patient is unlikely to be on vorasidenib for their lifetime. Perhaps the models by the company and EAG could be used to predict length of time on vorasidenib for the population with IDH mutant LGG and therefore get a more accurate picture of numbers per year eligible for vorasidenib.
The study by Wanis et al.(2021) used to calculate numbers in the HST assessment checklist looked at data between 1995-2017 before the updated WHO classification on types of LGG. Recalculating numbers based on this classification may result in less people predicated to be eligible for vorasidenib per year and thus make it more likely to fall under HST eligibility.

According to the Highly Specialised Technologies Programme, NICE has the discretion to apply some flexibility in cases where population size is over 300 based on information and evidence gathered by the scoping exercise. Due to the agreed likely overestimation of eligible population size, NICE could exercise discretion in allowing vorasidenib under HST criteria due to the lack of other effective treatments currently available. Active surveillance is not a treatment, and CT/RT are delayed due to negative side effects. Vorasidenib is currently the only available and suitable treatment for this progressive disease.
Further, LGG is a rare disease that is slowly progressing. A disease with better treatment options and a possibility of cure would be favoured in the cost-benefit assessment by achieving a lower discount rate because patients could be restored to near or full health. A disease with faster progression would be favoured in the cost-benefit analysis because patients would be on treatments for a shorter duration. Are we missing a vital patient group who fall between these two categories and denying funding to those who have a devastating, albeit slow progressing, diagnosis? Perhaps this is why LGG care has fallen behind many other cancer types, and no new treatments have been developed for the past two decades.
Further, the word slow is used to describe the disease, yet for those who are in their 20s and 30s and 40s, a disease that has a median survival of 5 to 8 years for astrocytomas and 7.2 to 17 years for oligodendrogliomas certainly won't feel slow progressing.
The models used to assess acceptable cost thresholds are not tailored to recognise the increased negative impact of a 5-20 year survival to a young adult versus a elderly adult.
In light of the young age of patients, the lack of development and innovation for this cancer type and the gap in funding for diseases with these characteristics, flexibility should be applied to cost analysis models."

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

"For a young adult, a prognosis of 5 to 20 years represents a significantly greater loss of potential life compared to an older individual with the same life expectancy. For a disease that primarily affects young adults, the cost-benefit analysis models used do not function appropriately to assess the impact of a 5-20 year prognosis on a young adults life.
Due to the holes in funding mechanisms for diseases that are incurable and yet slowly progressing to death, I believe that there is an unmet need for LGG patients which is not reflected in the models used. Diseases with rapid progression often qualify for greater funding due to their shorter treatment durations and lower cumulative costs to the NHS, while more curable conditions benefit from favorable cost-effectiveness assessments owing to the potential for full or near-full recovery and the application of lower discount rates.

Why should those with slowly progressing, life limiting and increasingly debilitating diseases fall through the gaps and not be eligible for higher funding thresholds to improve treatment pathways and quality of life?
A lack of funding for diseases that fall within this category is a discrimination based on disability."

This is because the available evidence does not suggest that vorasidenib is value for money in this population.

"The current eligible patient group in the UK is likely small, particularly considering the use case for the drug, which means a lower total cost to the NHS.
Low grade gliomas are an under researched area, denying innovative treatment may dissuade other companies from investing in research in this area. Discouraging developmental and new therapies stunts the evolution of cancer care in the UK.

Brain tumours have attracted only 1% of UK cancer funding, according to Brain Cancer Justice.org, despite being one of the highest cause of cancer death in those under 40. Therefore, LGG glioma care has an area of unmet need that should be prioritised for funding.

Assessing vorasidenib under the Highly Specialised Technologies criteria should be reassessed. The drug met criteria for all but eligible population size, but data around the actual UK population eligible for vorasidenib was vague and uncertain.

The impact on quality of life for the primarily young patient population and their families has not been adequately considered when assessing value for money."

But it is unclear if vorasidenib affects how long people with the condition live.

"Vorasidenib has not been around long enough to show whether it extends total life, however, death for LGG sufferers is caused by tumour progression, progressing the disease to HGG and then death. Therefore, it is plausible that delaying tumour progression can extend life. Requiring evidence that it extends life without factoring in the plausibility of delaying disease progression disadvantages the current cohort of those with LGG, for whom it may be too late by the time concrete evidence comes that may show vorasidenib can extend life.
Current treatments (surgery & chemo/radiotherapy) are centred around reducing tumour size and progression, so its plausible that another drug that can effectively inhibit tumour growth would extend life.
Further, In the supporting documents, public committee slides ACM1, slide 26 outlines the company and EAG models of overall survival, between the placebo group and the vorasidenib group. The company base-case model

shows a difference in 5.81 life years, and the EAG base-case shows a difference in 3.12 life years.
If these models are right, an increase in a few years for patients already facing a shorter life expectancy would make a vast difference.
Slide 27 of the public committee slides ACM1 also states that clinical experts expect that vorasidenib improves life expectancy in people with LGG by delaying need for second surgery and CT/RT with associated side effects."

Collecting more evidence during a managed access period is unlikely to resolve the key uncertainties in the evidence. So, vorasidenib cannot be used with managed access

"Data from the INDIGO trial does not make clear the impact on quality of life for those with vorasidenib, however, there are many people around the world on vorasidenib and qualitative data could be gathered through surveys or listening to feedback from the brain tumour charities to hear about the real impact on quality of life.
All of this could be done to increase the evidence base for decision making.
Moreover, allowing access or managed access until further data from the INDIGO study emerges would give those who are currently suffering from LGG a better chance.
Further, more research into anti-tumour drugs is happening, and if vorasidenib can maintain LGG patients in a healthier stage of disease progression for longer, they will be still here and healthier to access future options that may further increase quality and length of life."

The committee recalled the psychological impact of LGG (see section 3.1). A patient expert at the meeting explained that, since starting vorasidenib, their mental health had improved considerably, to the point where they could live a close-to-normal life and had returned to work and social events. The committee thought that the full impact of vorasidenib on mental health may not be captured in the model.

More data should be considered to assess the full impact on quality of life that vorasidenib makes. Patient and carer stories gathered during consultation period should be factored in.

The committee recalled that the seizures associated with LGG stop people from driving, which can limit their independence (see section 3.1). The clinical experts explained that people needed to have not had a seizure for 12 months to restore driving eligibility. It noted that the INDIGO trial reported a reduction in the number of seizures compared with placebo, and that this reduction had been included in the model (see section 3.5). But, given the median PFS of 22.1 months in the vorasidenib arm, it considered it unlikely that many people having vorasidenib would be seizure-free for an entire year to allow them to return to driving. It concluded that it was uncertain whether the full quality-of-life benefit from reducing seizures had been captured in the model.

"Seizures affect much more than stopping people from driving. Seizures may affect ability to carry out work roles, and may result in having to stop jobs that involve risky procedures or operating heavy machinery. For those who rely on incomes from such careers this would have a big impact.
The unpredictable nature of seizures can cause people anxiety about going into public places and social gatherings.
Parents with seizures may not be able to care for children independently, bathe children or cook meals without another adult present due to risks of harm if a seizure were to occur.
Parents will often experience increased anxiety about impact to children if the children witness a seizure."

The patient experts highlighted the socioeconomic benefits of increasing the time before people have chemotherapy and radiotherapy for people with LGG. Postponing the associated debilitating side effects extends the time people can function at their best, both professionally and personally. The committee recalled that people who would have vorasidenib are often in the middle of their careers and have young families to support (see section 3.1). It agreed that the socioeconomic benefits of vorasidenib may not be captured in the modelling.

"Children whose parents have cancer are at increased risk of various psychosocial, emotional and behavioural problems (Alexander, O'Connor & Halkett, 2023). The impact of having more higher quality-of-life years with a parent on child lifelong mental and emotional stability needs to be further addressed. Better mental and emotional wellbeing due to less parental side effects will improve child outcomes.
Cancer parents with minor children experience parenting concerns that cause significant psychological distress. Due to the young age of LGG patients, and the high proportion that would then have young families, it is important to factor in the additional impact to quality of life that parenting concerns would have. Jing-ling, Qin and Ning (2024) said that healthcare professionals should pay attention to the special needs of cancer parents raising minor children and develop and support targeted interventions that may relieve psychological stress and impact to the family unit.
Vorasidenib would delay the need for CT/RT and associated side effects, which have been shown to increase distress in children of cancer patients. CT and RT increase time away from children and increase negative symptoms that would affect parents ability to be active in the care of their children.

Alexander ES, O'Connor M, Halkett GKB. The Psychosocial Effect of Parental Cancer: Qualitative Interviews with Patients' Dependent Children. Children (Basel). 2023 Jan 15;10(1):171. doi: 10.3390/children10010171. PMID: 36670721; PMCID: PMC9857104.

Jing-Ling Li, Qin Ye, Ning Liu. Cancer parents' experiences of parenting concerns about minor children: A meta-synthesis of qualitative studies, International Journal of Nursing Studies Advances, Volume 6, 2024, 100210, ISSN 2666-142X, https://doi.org/10.1016/j.ijnsa.2024.100210.

(https://www.sciencedirect.com/science/article/pii/S2666142X24000377)"

"For a person who is only expected to live 5-20 years following diagnosis, a few years with a better quality of life makes a bigger impact on them and their families. This should be reflected in the cost assessment.

LGG as a disease falls between two funding categories: It is not curable, so has not been assessed as eligible for a lower discount rate as treatments cannot restore people to full or near-full health. It is also not fast progressing, so patients are expected to be on treatments for a longer time, thus again lowering the acceptable cost threshold.
Allowance should be made for diseases that fall between these two groups. LGG is a disease that will progress to a malignant and highly life impacting disease resulting in death. However, because this transformation doesn't always happen within the time thresholds allowed in cost analysis models, delaying progression for LGG patients is not made a priority."

"With a condition that always progresses to a higher grade, it is important to factor in the symptoms those suffering would experience as the disease progresses, such as debilitating fatigue, an increase in seizures, a loss of speech or motor function, and eventually premature death. The reason the care currently revolves around preventing disease progression through surgery and chemo/radiotherapy is to prolong time before these symptoms become a reality for those with LGG. Vorasidenib increases time to disease progression which allows more time with less symptoms.

The impact of disease progression and further treatments on quality of life of patients and their families should be considered."

The physical symptoms of the condition can be challenging, especially seizures, which can cause anxiety and affect independence by limiting the ability to drive.

"To add, it is important to note that seizures increase as the disease progresses, thus prolonging time before disease progression can mitigate some of these symptoms.

Seizures also can prevent parents from caring for their children on their own, cycling with their children, swimming, bathing children without help and cooking. All of which massively impact the lives of the family."

LGG in their 20s, 30s, and 40s and so may have young families
With young families, if the parent progresses to chemotherapy sooner, they are less able to shield from bacteria or viruses that may be harmful in their immunocompromised state due to children being active in school or nursery. Prolonging time before chemotherapy, and so ensuring children are older and more aware of infection prevention, may reduce chemotherapy associated illness/death.

The patient expert explained that treatments for LGG have a large effect on quality of life. The psychological burden of active surveillance for a progressively enlarging tumour can lead to substantial anxiety.

"Hao, Huang & Xu (2021) found that depression and anxiety in glioma patients negatively impacted overall survival. If living with untreated disease increases depression and anxiety, then using vorasidenib will have additional benefits by reducing the mental health effects of living with an untreated serious disease.

The impact on those currently on vorasidenib through the early access scheme should be considered. For people currently given hope through vorasidenib and doing well on the drug to have their treatment withdrawn and return to an untreated, active surveillance state would massively increase anxiety and stress for patients and their family. Subsequently this would impact overall survival rates and also impact stress related health conditions in family, thus increasing cost to NHS.

Hao, A., Huang, J. & Xu, X. Anxiety and depression in glioma patients: prevalence, risk factors, and their correlation with survival. Ir J Med Sci 190, 1155–1164 (2021). https://doi.org/10.1007/s11845-020-02374-5"

One clinical expert explained that, although uncertain, a longer time to next treatment for people who had vorasidenib was plausible. This was because, by inhibiting the effects of the IDH mutation early, vorasidenib changes the downstream effects of tumour development, leading to more favourable tumour biology on progression and less immediate need for chemotherapy and radiotherapy.

"Another factor in favour of allowing access to this drug while more evidence is gathered. If vorasidenib can have more impact than currently understood, denying access to those currently suffering from LGG would leave their families devastated if future research comes out and reverses NICE's decision. By then it would be too late for those currently suffering. This possibility should not be underplayed - if vorasidenib can render the tumour more favourable even after progression that could massively impact subsequent care."

"In the supporting documents, public committee slides ACM1, slide 26 outlines the company and EAG models of overall survival, between the placebo group and the vorasidenib group. The company base-case model shows a difference in 5.81 life years, and the EAG base-case shows a difference in 3.12 life years. However, in this consultation document, the figures from this model are not mentioned. This data should be included in the consultation.
For patients who are already experiencing a disease that will take them away from their families at a young age, the possibility of a few more years of life is paramount.

Slide 27 also states that clinical experts expect that vorasidenib improves life expectancy in people with LGG by delaying need for second surgery and CT/RT with associated side effects.
This clinical expert opinion should also be included in the committee consultation report.

Younger patients who have children in school and nursery would be at increased risk of contracting illnesses during chemotherapy that may lead to adverse outcomes. Treatment such as vorasidenib that can delay the need for chemotherapy until patients have left this life stage may decrease adverse events due to immunocompromised states while receiving chemotherapy."

The company explained that the quality-of-life data in INDIGO was collected relatively close to disease progression and was based on very small numbers. So, by the time people started chemotherapy or radiotherapy they would be expected to have a poorer quality of life than was recorded in the trial.

"There is substantial research on how chemotherapy and radiotherapy negatively affect quality of life, and research on the impact for children when their parent or carer is undergoing chemo/radiotherapy. There is not enough emphasis in this report on the impact of these treatments on quality of life, and therefore the beneficial impact of vorasidenib delaying these treatments.

Further, more accurate information on quality of life for those with LGG and those on vorasidenib could be gathered from feedback and personal stories through the Brain Tumour Charity and Astrofund. This qualitative data is important to make a decision based on all available evidence.

https://pmc.ncbi.nlm.nih.gov/articles/PMC9857104/
Alexander ES, O'Connor M, Halkett GKB. The Psychosocial Effect of Parental Cancer: Qualitative Interviews with Patients' Dependent Children. Children (Basel). 2023 Jan 15;10(1):171. doi: 10.3390/children10010171. PMID: 36670721; PMCID: PMC9857104."

"As quoted from the NICE health technology evaluations manual:
The committee may consider analyses using a non-reference-case discount rate of 1.5% per year for both costs and health effects, if, in the committee's considerations, all of the following criteria are met:

""The technology is for people who would otherwise die or have a very severely impaired life.""

- LGG patients have severely impaired quality of life not only as the disease progresses to HGG, but as they are undergoing CT/RT and experiencing associated side effects and long term effects of these treatments. Without Vorasidenib, CT/RT would be used sooner, and the quality of life would drastically reduce for patients and their families. Increase of seizures due to

disease progression also decreases quality of life. Anxiety and stress of having an untreated disease during active surveillance also decreases quality of life.

""It is likely to restore them to full or near-full health.""

- Information from those currently on vorasidenib should be gathered to assess impact on health. Although they cannot be restored to full health, compared to living with a progressive disease that is untreatable, those on vorasidenib massively benefit from knowing that they are on treatment that should slow the growth of their tumour.

""The benefits are likely to be sustained over a very long period.""

- Benefits of delaying further treatment are amplified in a young patient group due to the impact on young families. Benefits to children of having a parent more able to care for them during early years will last a lifetime. Cost related to mental, emotional and behavioural problems for children of LGG patients throughout their lifetime will be reduced if children have a secure attachment with their caregiver in formative years, enabled by increased years of better physical and mental/emotional capacity given by vorasidenib.
Although data on overall survival is unclear, there is a plausible mechanism to improve overall survival due to delayed tumour progression and even more favourable tumour properties on progression. For those facing a diagnosis of LGG, this chance should not be taken away from them."

The EAG also highlighted that there was also only a small decrease in quality of life between the public and people in INDIGO whose glioma was progression free after surgery.

"Using data from the INDIGO trial to base an assessment on quality of life is not enough. Listening to patient voices, and the voices of carers, children, friends and family members of those with LGG, it is hard to believe there is only a small decrease in quality of life between the public and people with progression free glioma after surgery.
Further evidence on quality of life impact of the condition must be considered to inform this discussion.
Young et al. (2023) found that between half to three quarters of people with brain tumours experience a behavioural health disorder as a result of their diagnosis, with 16% of LGG patients diagnosed with PTSD within 3 months of surgery, and 60% of primary brain tumour patients reporting elevated stress.
Heffernan et al. (2023) found that quality of life for those with LGG is an underesearched field, but they found that two thirds of LGG patients had difficulty thinking, speaking and memory, and quality of life was significantly reduced compared to the general population or those with other brain tumours.
Further, 36.5% caregivers were found to have anxiety or depressive symptoms (Chen et al., 2021). Finocchiaro et al. (2012) also found a

significantly impaired quality of life for caregivers of those with brain tumours.

Finocchiaro, C.Y., Petruzzi, A., Lamperti, E. et al. The burden of brain tumor: a single-institution study on psychological patterns in caregivers. J Neurooncol 107, 175–181 (2012). https://doi.org/10.1007/s11060-011-0726-y

Chaoyi Chen, Haorun Wang, Liying Zhang, Ke Wang, Lin Jiang, Shenjie Li, Wei Xiang, Li Song, Shasha Hu, Changmei Yang, Jie Zhou,
Clinical study of preoperative psychological distress and its related factors in the primary caregivers of patients with glioma,
Clinical Neurology and Neurosurgery,
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ISSN 0303-8467,
https://doi.org/10.1016/j.clineuro.2020.106364.
(https://www.sciencedirect.com/science/article/pii/S0303846720307071)

Young JS, Al-Adli N, Sibih YE, Scotford KL, Casey M, James S, Berger MS. Recognizing the psychological impact of a glioma diagnosis on mental and behavioral health: a systematic review of what neurosurgeons need to know. J Neurosurg. 2022 Nov 4;139(1):11-19. doi: 10.3171/2022.9.JNS221139. PMID: 36334288; PMCID: PMC10413205.

Heffernan AE, Wu Y, Benz LS, Verhaak RGW, Kwan BM, Claus EB. Quality of life after surgery for lower grade gliomas. Cancer. 2023 Dec 1;129(23):3761-3771. doi: 10.1002/cncr.34980. Epub 2023 Aug 20. PMID: 37599093; PMCID: PMC10872908."

So, the committee agreed that people would not have a severely impaired quality of life or otherwise die at the point in the treatment pathway where vorasidenib would be used.

Again, it is not fitting to compare quality of life on active surveillance alone to quality of life on vorasidenib as active surveillance would lead to CT/RT with associated impact on quality of life than vorasidenib.

"Vorasidenib could be considered for managed access if data is gathered from early access scheme and INDIGO. Other data could also be gathered from other countries who are approving and using this drug.

Further, on plausibility for cost effectiveness, a flexibility in ceiling figure per QALY could be adopted due to the unmet needs of the patient group.

A firm denial of this drug would negatively affect those currently accessing vorasidenib through the early access scheme. The negative mental and emotional effects of being on active surveillance would be amplified by the removal of a drug that is currently in use for them.

Similarly, for LGG family members and carers, the knowledge that a treatment is being removed, and the tumour has returned to being untreated and inevitably progressive, anxiety and depression would certainly increase.

Stress related health conditions in family members should also be factored into the cost analysis, as mental health and physical health conditions triggered by periods of extreme stress around treatment withdrawal will end up costing the nhs money."

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EAG ADDENDUM

Review of the company's response to Consultation on the Draft Guidance Document: Vorasidenib for treating astrocytoma or oligodendroglioma with IDH1 or IDH2 mutations after surgery in people 12 years and over [ID6407]

Produced by
York Technology Assessment Group, University of York, Heslington, York, YO10 5DD

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None.

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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.

Note on the text

All commercial-in-confidence (CON) data have been [redacted].

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1 OVERVIEW OF THE COMPANY'S RESPONSE TO THE DRAFT GUIDANCE DOCUMENT

The company provided 13 comments in response to the Consultation of the Draft Guidance Document (DGD). The EAG have excluded four of these from further discussion here:

- Three comments (1, 2, and 3) relate only to the wording used in the draft guidance (DG).
- One comment (10) refers to what constitutes an acceptable ICER for NICE decision-making, which the EAG deems a committee consideration and not a relevant critique point.

The remaining comments relate to:

- The use of TTNI-P as a proxy for time off treatment with progressed disease (comments 4 - 7)
- Source of utility values (comment 8)
- Surrogacy relationship for OS (comment 9)
- Uncaptured benefits (comment 11)
- Managed access (comment 12)
- Company's revised base case assumptions and additional scenario analyses (comment 13)

Within the short timelines available to the EAG (five working days), the EAG provides a critical evaluation of the company's response to the DG. This evaluation focuses on new evidence or analyses provided by the company and identifies areas where clarification is required from the EAG. The EAG critique should be read in conjunction with the company's DG response document, and the Evidence Assessment Report (EAR).

2 CRITIQUE OF THE COMPANY'S COMMENTS IN RESPONSE TO THE DRAFT GUIDANCE DOCUMENT

2.1 Comments 4-7: TTNI-P as a proxy for time off treatment with progressed disease (DGD Section 3.10)

2.1.1 Summary of committee considerations

A key issue in the appraisal of vorasidenib is the interpretation of the outcome data from INDIGO for time to next intervention given progression (TTNI-P) and, consequently, the duration of time spent off treatment following progression before initiating first line RT/CT. DGD Section 3.10 highlights the committees concerns, specifically that the TTNI-P data from the placebo arm of INDIGO was not

suitable for decision making, while the extrapolations of TTNI-P data from the vorasidenib arm were limited by a small number of events, leading to uncertainty in long-term TTNI-P. The committee heard the EAG's concerns that the company's chosen parametric curves lacked face validity because 21% of people having vorasidenib and 9% having placebo had no further treatment 20 years after their disease progressed, and that people in the vorasidenib and placebo arms spent considerably more time with progressed disease off treatment than in the progression-free health state, while people with progressed disease in INDIGO reported higher quality-of-life results in the placebo arm than the vorasidenib arm. The company justified the long TTNI-P as plausible in people with progressed disease after vorasidenib because these people may have more favourable features on progression than people who had placebo and supported this with a perioperative study suggesting that vorasidenib caused molecular changes in the tumour. The committee acknowledged that a different TTNI-P on placebo and vorasidenib may be plausible because of vorasidenib's effect on tumour biology; however, the size of this difference was uncertain, and the committee had not been presented with any plausible ways to accurately capture the TTNI-P in the placebo arm. The committee requested that the company provide a full exploration of the best fitting parametric curve, applying the INDIGO vorasidenib TTNI-P data to both arms in the model, at consultation. The committee also requested that the company explore alternative ways to plausibly model a TTNI-P benefit for vorasidenib as a scenario.

2.1.2 Summary of company's response

The company's response to the issues raised in DGD Section 3.10 are covered in comments 4, 5, 6, and 7. Comments 4 and 5 address revised estimates derived from the company's updated base case analysis, where comment 4 refers to the revised estimate of the percentage of people off treatment with progressed disease at 20 years, while comment 5 refers to the revised estimate of the duration of time spent with progressed disease off treatment relative to time spent progression-free. Comment 6 provides a detailed response to the committee's preference to apply the INDIGO vorasidenib TTNI-P data to both arms in the model and explores the application of alternative hazard ratios (HRs) to model a TTNI-P benefit for vorasidenib for the company's revised base case and scenario analyses. Comment 7 provides new health-related quality of life data for the March 2023 data cut off (DCO) from INDIGO and responds to the concern that people with progressed disease in INDIGO reported higher quality-of-life results in the placebo arm than the vorasidenib arm.

For comment 6, the company shows that using vorasidenib TTNI-P data as a proxy for TTNI-P for the active observation arm leads to markedly longer estimates for how long patients are expected to spend on active observation before initiating RT/CT, which the company argues overestimates the TTNI-P for people managed with active observation. Therefore, the company have provided scenarios applying HRs to the vorasidenib arm to produce lower estimates of TTNI-P for the active observation

arm. The company justifies this approach based on post-hoc analyses of INDIGO, which indicates that people who experience progression while receiving vorasidenib exhibit more favourable disease features, with molecular changes in tumour biology, that, in turn, allows for a relatively longer TTNI-P compared to people managed with active observation. However, the company acknowledges that a question remains regarding the magnitude of a clinically reasonable difference in TTNI-P between the vorasidenib and active observation arm for use in the model. To determine this, the company sought input from clinicians and data from an Australian brain registry. The company states that both data from the Australian brain registry(1) and opinion from clinical experts suggested an average time of 6 months would be reasonable for patients managed with active observation to spend after progression before receiving RT/CT. Therefore, the company provides a revised base case that allows for the specification of a HR to the vorasidenib TTNI-P arm, with the goal of determining a suitable HR value such that the duration of time spent in the progressed health state off treatment (model health state S4) in the active observation arm was approximately 6 months.

The company's revised base case includes the vorasidenib TTNI-P data (with log-normal extrapolation) for the vorasidenib arm and application of a HR of 3.0 to derive the TTNI-P curve for the active observation arm, yielding an average time of 5.12 months for active observation in health state S4. This HR was chosen as a midpoint between the values of 2.5 and 3.5, yielding an average time of 4.11 months (HR = 2.5) to 6.53 months (HR = 3.5) for active observation. The HRs of 2.5 and 3.5 were included as company scenario analyses.

The company's revised base case also includes the new health-related quality of life data for the March 2023 DCO from INDIGO (comment 7), which shows a narrower difference between arms for the utility values for progressed disease compared to the September 2022 DCO used in the original base case, but the quality-of-life results for the placebo arm remain higher than the vorasidenib arm for progressed disease.

2.1.3 EAG critique

The EAG critique for comments 4 – 7 focuses on the company's response to the committee requests and the new evidence (Australian brain registry and opinion from clinical experts) and analyses provided by the company. The company has provided several post-hoc analyses of INDIGO data on tumour growth, but the EAG notes that this data and evidence has been presented previously by the company before the first appraisal committee meeting (ACM1). The EAG provided an addendum to the EAR critiquing this additional evidence and analyses on tumour volume variation and growth provided by the company at Factual Accuracy Check (FAC) and submitted in a more detailed format on the 8th of May 2025. This information formed part of the committee papers for ACM1 and was

discussed in the committee slides at ACM1. Therefore, the EAG does not provide a further critique of this evidence.

Critique of the additional evidence from the Australian brain registry

This study sought to use a real-world patient cohort, derived from the Australian BRAIN registry(2) (n=100), to gain insights about treatment outcomes in grade 2 IDH-mutant glioma patients when compared to the INDIGO placebo arm cohort (n=163). The study found no significant difference in PFS between the INDIGO placebo arm and BRAIN registry cohorts, and a statistically significant difference in median time to next intervention (but not for the means), favouring the INDIGO placebo cohort.

The study also reported the following outcomes just for the BRAIN registry cohort(2) (i.e. no comparison): PFS2, overall survival, 'residual' overall survival, and 'residual' next intervention overall survival. The median overall survival was 161 months for the BRAIN registry cohort. At the time of progression, for the BRAIN registry cohort, the most common next interventions were surgery followed by observation (28 patients, 40%), and combination chemo-radiotherapy with or without surgery (22 patients, 31%). Overall, 49 patients (70%) underwent surgery. Of these, 21 patients (43%) received further anti-cancer therapy.

The EAG's concerns with this study relate to uncertainties about how the population was selected from the BRAIN registry and the lack of matching or adjustment of the two cohorts for imbalances in prognostic factors, especially given that IPD were available for both groups. More specifically:

1) Although the report stated that only patients who met the key inclusion criteria for INDIGO were included in BRAIN, the EAG is uncertain how patients were selected. The BRAIN cohort(2) utilised data for all patients with IDH-mutant grade 2 glioma diagnosed from 2009-2024 using a criterion of patients having "*at least 1 surgery occurring between 1 and 5 years prior*". It is unclear what the "*prior*" relates to. The study's appendix further confuses the issue by comparing INDIGO and BRAIN using bar charts for *Time from initial diagnosis (in months) to randomisation date for INDIGO placebo patients* and *Time from initial diagnosis (in months) to "randomisation date" in BRAIN*, even though there was no such date in BRAIN. These bar charts are notably different in their distributions, suggesting population differences.

2) In order to be similar to the INDIGO exclusion criteria, the BRAIN registry cohort(2) excluded patients who remained disease-free more than 5 years after surgery. However, it is unclear how this was done, given that Figure 1 of the BRAIN study report shows data for patients who have not progressed after 5 years. Moreover, although a 5-year exclusion criterion may be appropriate for comparisons with the INDIGO placebo cohort, it may have limited applicability to the NHS setting when considering outcome data for the BRAIN cohort in isolation (such as TTNI-P). This is because

i) in NHS practice it will not be possible to predict which patients will not progress within 5 years post-surgery and ii) vorasidenib's license does not exclude those patients. The study does not report how many patients were excluded based on the 5-year criterion.

3) In INDIGO patients had to be '*not in need of immediate treatment*' whereas this (or a similar criterion) was not specifically required for the BRAIN registry cohort. Patients were excluded though if they had received radiotherapy or chemotherapy within one year of surgery.

4) It appears that no methods were used to match the two cohorts or otherwise adjust for imbalances in prognostic factors. The EAG notes that although co-deletion status was not available for 43% of BRAIN registry patients, where testing was done it showed a 20% difference in the presence of the chromosomal 1p/19q co-deletion between the INDIGO (52%) and BRAIN (32%) cohorts. This co-deletion is associated with a better prognosis, so is likely to produce a bias, favouring INDIGO.

In conclusion, the EAG considers the Australian BRAIN registry data(2) to have limited generalisability to the INDIGO population.

Critique of the company's response to committee requests and new analyses provided by company

The company did not provide a full exploration of the best fitting parametric curve when applying the INDIGO vorasidenib TTNI-P data to both arms in the model, as the committee had requested. Instead, the company selected the log-normal extrapolation to the vorasidenib TTNI-P data to inform the vorasidenib arm and justified the application of a HR of 3.0 to derive the TTNI-P curve for the active observation arm. In Figure 1, the EAG shows the alternative parametric distribution fits to the INDIGO vorasidenib TTNI-P data, extrapolated over time. The alternative parametric models can be grouped based on their varying long-term survival estimates: least optimistic (exponential, Weibull and gamma models), most optimistic (generalised gamma and Gompertz models) and mid-range (log-normal and log-logistic models). Of these, the generalised gamma model is identified as the best-fitting model to the Kaplan-Meier data, based on statistical goodness-of-fit AIC/BIC criterion. The log-normal model represents the second best-fitting model.

In the company's original base case, the generalised gamma model was selected for the vorasidenib arm, which provides the most optimistic long-term extrapolation for TTNI-P, with 21% of people in the vorasidenib arm having no further treatment 20 years after their disease progressed. In the company's updated base case, the company selected the log-normal model for the vorasidenib TTNI-P extrapolation, which results in 1.5% of people in the vorasidenib arm having no further treatment 20 years after their disease progressed. Note that in response to comment 4, the company states that their revised base case results in 7% of people in the vorasidenib arm having no further treatment 20 years after their disease progressed; however, the EAG considers this to be an error in response to comment

4, where the company appears to be reporting TTNI given progression or discontinuation of treatment.

As discussed in the EAR, the EAG does not consider it reasonable to assume that people with progressed disease spend considerably longer off treatment relative to the time spent in the progression-free health state. Therefore, the EAG considers this an important consideration when selecting the most appropriate extrapolation for TTNI-P data. Of the models presented in Figure 1, the most optimistic of generalised gamma and Gompertz fail this criterion, while all the other models, including the log-normal, provide lower estimates of time spent off treatment with progressed disease relative to the progression-free state. Therefore, the EAG considers the company's selection of the log-normal curve for vorasidenib TTNI-P data extrapolation to be reasonable based on two factors: the model produces a lower time in progressed disease health state compared to the progression-free health state, and it represents the second best-fitting curve based on the statistical AIC/BIC criterion. Furthermore, the EAG notes that the predicted long-term survival estimates from the selected curve (log-normal) in the company's revised base case lies between the company's original base case (generalised gamma) and the EAG's original base case (log-normal using pooled TTNI-P data across arms of INDIGO), in line with the committee considerations (Figure 2).

Figure 1 Alternative parametric distribution fits to extrapolated vorasidenib TTNI-P data

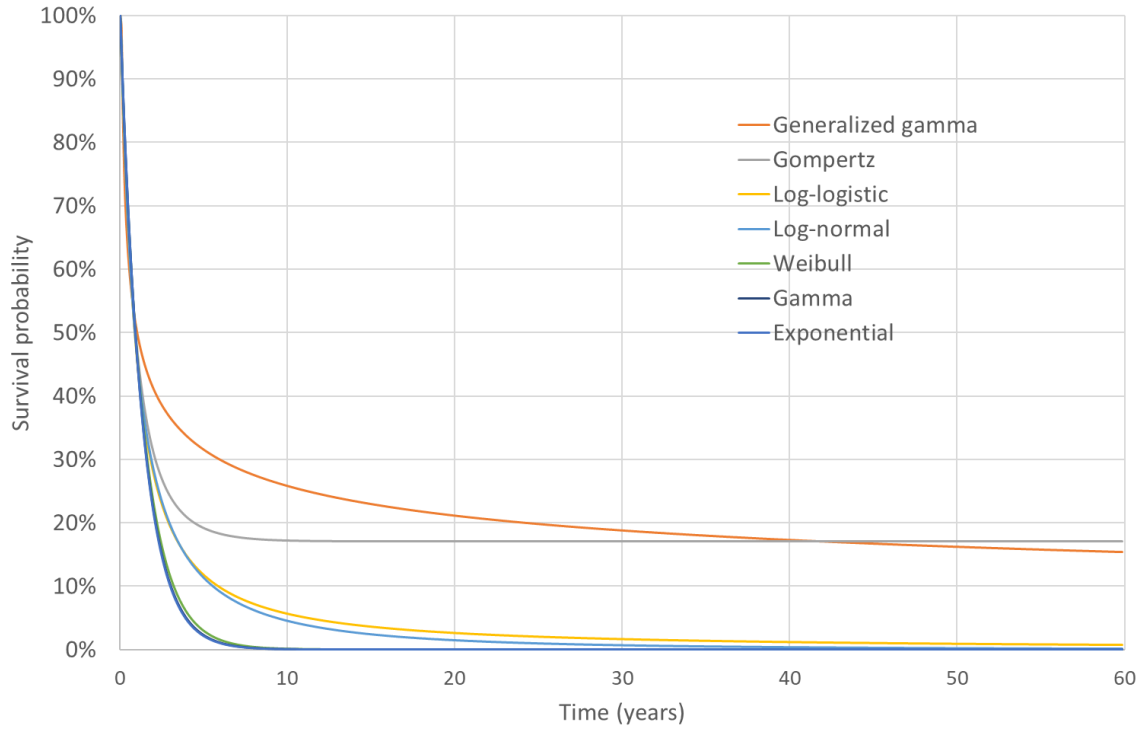
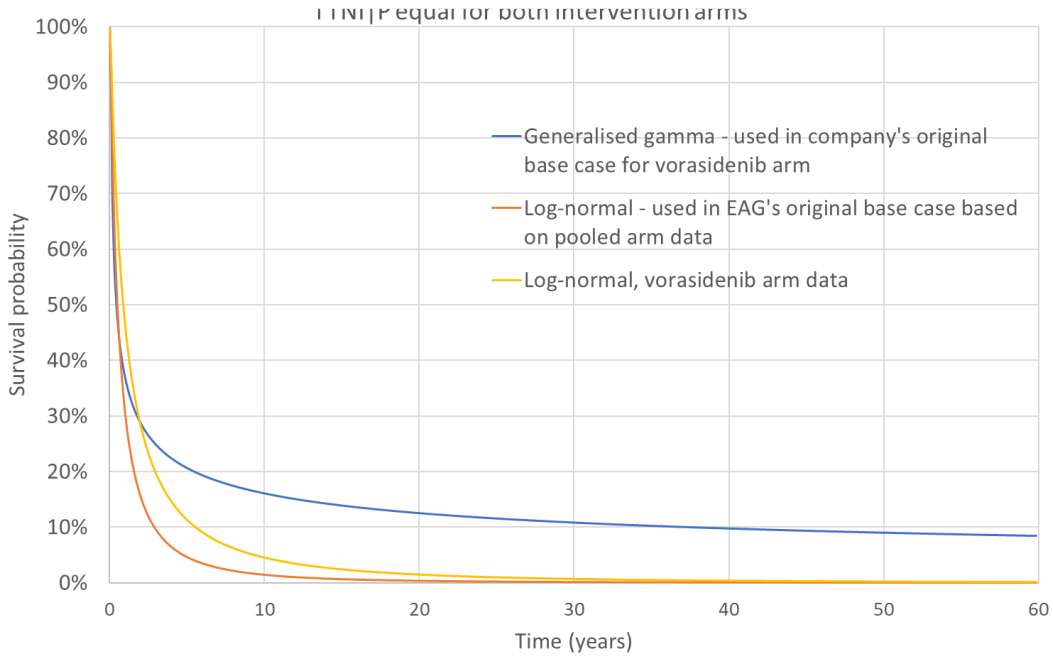


Figure 2 Comparison of curve used in the company's updated analysis for vorasidenib arm (log-normal) and company's original base case (generalised gamma) and EAG's original base case (log-normal based on pooled arm data)



The company did not agree with the committee preference to apply the INDIGO vorasidenib TTNI-P data to both arms in the model because this is likely to overestimate the TTNI-P for people managed with active observation. The company states that using the TTNI-P data from the vorasidenib arm as a proxy for the active observation arm leads to markedly longer estimates for the expected duration patients spend on active observation before initiating RT/CT, which the company notes is not supported by external evidence(3-5). In the absence of robust external evidence for people with grade 2 astrocytoma or oligodendroglioma (with a susceptible IDH1 or IDH2 mutation) who do not require immediate RT/CT after surgery, and given the known issues with the INDIGO TTNI-P data (i.e., post-randomised data, confounded by cross-over in the placebo arm, high censoring and immaturity), the EAG considers the use of a common TTNI-P curve for both arms in the model to be a reasonable choice. However, the EAG agrees with the company that using the vorasidenib TTNI-P data for both arms (implying a HR of 1.0 for the active observation arm) leads to longer estimates for the expected duration people spend on active observation before initiating RT/CT. In fact, the resulting duration of time spent off treatment with progressed disease for the active observation arm (2.3 life years, undiscounted) is longer than the time spent off treatment in the progression-free health state (1.42 life years, undiscounted) – see Table 1. Therefore, the EAG agrees with the company that using the vorasidenib TTNI-P data (log-normal model) for the active observation arm may not be appropriate. The EAG notes that applying the vorasidenib TTNI-P data to both arms but using an exponential model for the extrapolation leads to lower estimates for the expected duration people spend on active

observation before initiating RT/CT. Specifically, the resulting duration of time spent off treatment with progressed disease for the active observation arm (1.26 life years, undiscounted) is lower than the time spent off treatment in the progression-free health state (1.42 life years, undiscounted). Thus, applying a HR of 1.0 for the active observation arm can produce plausible estimates of TTNI-P for this arm; however, these estimates are sensitive to the specific extrapolation curve used for the vorasidenib TTNI-P data.

Table 1 Total life years in the modelled health states (undiscounted) by intervention arm when the same vorasidenib TTNI-P curve (log-normal model) is used for both arms

	OS	PFS (S1 or S2)	PD and off-treatment (S4)	NI (1L RT/CT, S5)	NI+ (2L+ RT/CT + BSC)*
Vorasidenib	22.66	5.22	2.19	5.38	9.87
Active observation	19.70	1.42	2.30	5.18	10.79
Difference (vorasidenib minus active observation)	2.96	3.80	-0.11	0.20	-0.93

* NI+ is the sum of health states S7 and S8.

The committee acknowledged that a difference in TTNI-P between the active observation and vorasidenib arms may be plausible, given vorasidenib's effect on tumour biology. Consequently, the committee requested that the company explore alternative ways to plausibly model a TTNI-P benefit for vorasidenib as a scenario analysis. The company did this by applying a HR to the selected vorasidenib TTNI-P curve (log-normal extrapolation) to determine a suitable TTNI-P curve for the active observation arm, such that the average time spent in the progressed disease off treatment health state (S4) was approximately 6 months. The approximate 6-month value was based on two factors. First, it was derived from the difference between the median TTNI of 48.4 months and the median PFS of 42.7 months observed in the Australian BRAIN registry cohort data(2). Second, this value was supported by clinical feedback to the company, which indicated that if a patient on active observation experienced progression, clinicians would typically wait approximately six months after progression to perform another scan and assess the rate of tumour growth before initiating the next intervention. Consequently, a HR of 3.0 was chosen to yield an average time of 5.12 months for active observation in health state S4, while HRs of 2.5 and 3.5, yielding average times of 4.11 months and 6.53 months, respectively, were included in scenario analyses.

The EAG considers the approach used by the company to be reasonable. However, the evidence supporting a six-month average duration spent in the progressed disease off treatment health state for the active observation arm is limited. As noted above, the Australian BRAIN registry data (2)is considered to have limited generalisability to the INDIGO population. Nonetheless, the EAG confirms that a HR of 3.0 yields an approximate duration of six months for the time off treatment after progression before initiating RT/CT on the active observation arm. Crucially, the EAG considers it

important to not only assess the average time spent in health state S4 but also to consider the implied difference between the vorasidenib and active observation arms. Figure 3 shows the TTNI-P curves for the vorasidenib arm (log-normal model) and active observation arm (HR = 3.0 applied to vorasidenib arm) used in the company's revised base case. The difference in median TTNI-P between arms is 0.61 years, while the difference in average TTNI-P between arms is approximately 1.9 years. The corresponding percentages of people off treatment with progressed disease over the long-term are shown in Table 2.

Figure 4 illustrates the company's revised base case with alternative HRs for the active observation arm. For HRs of 1.5 and above, the EAG notes that the corresponding duration of time spent off treatment with progressed disease for the active observation arm is lower than the time spent off treatment in the progression-free health state. The EAG considers these resulting durations to represent plausible values, which contrasts with the duration obtained when a HR of 1.0 is used for the active observation arm, applying the vorasidenib TTNI-P log-normal curve.

For completeness, Figure 5 illustrates the company's revised base case utilising the generalised gamma model for the vorasidenib TTNI-P curve and a HR of 3.0 used for the active observation arm. Separately, Figure 6 illustrates the revised base case utilising the exponential model for the vorasidenib TTNI-P curve, also with a HR of 3.0 used for the active observation arm.

In summary, the EAG considers the company's selected log-normal vorasidenib TTNI-P curve to be a reasonable choice, with a HR applied to derive a TTNI-P benefit for vorasidenib. However, the magnitude of the difference between the vorasidenib and active observation arms remains uncertain, with HRs between 1.5 and 3.0 leading to substantially different durations of time spent off treatment with progressed disease.

Figure 3 TTNI-P curves for the vorasidenib and active observation arms used in the company's revised base case

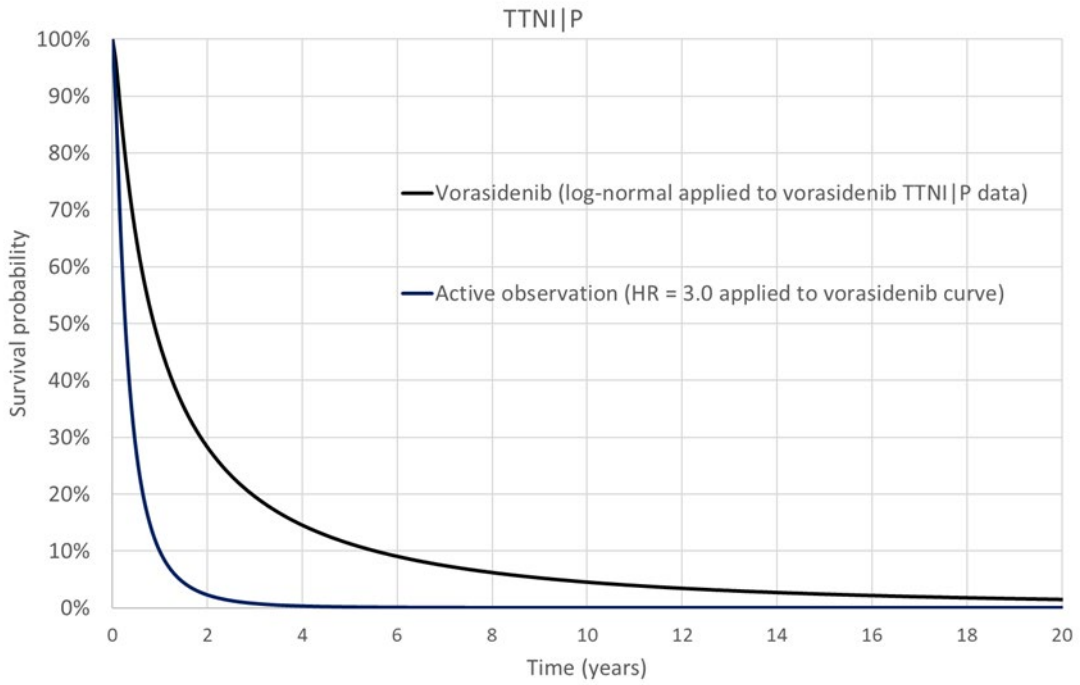


Table 2 Percentages of people off treatment with progressed disease over the long-term in the company's revised base case

% off treatment with progressed disease in:	Time (years)			
	5	10	20	30
Log-normal vorasidenib arm	11%	4.5%	1.5%	0.72%
HR = 3 applied to vorasidenib curve (log-normal) for active observation arm	0.15%	0.01%	0%	0%

Figure 4 Company's revised base case with alternative HRs for the active observation arm

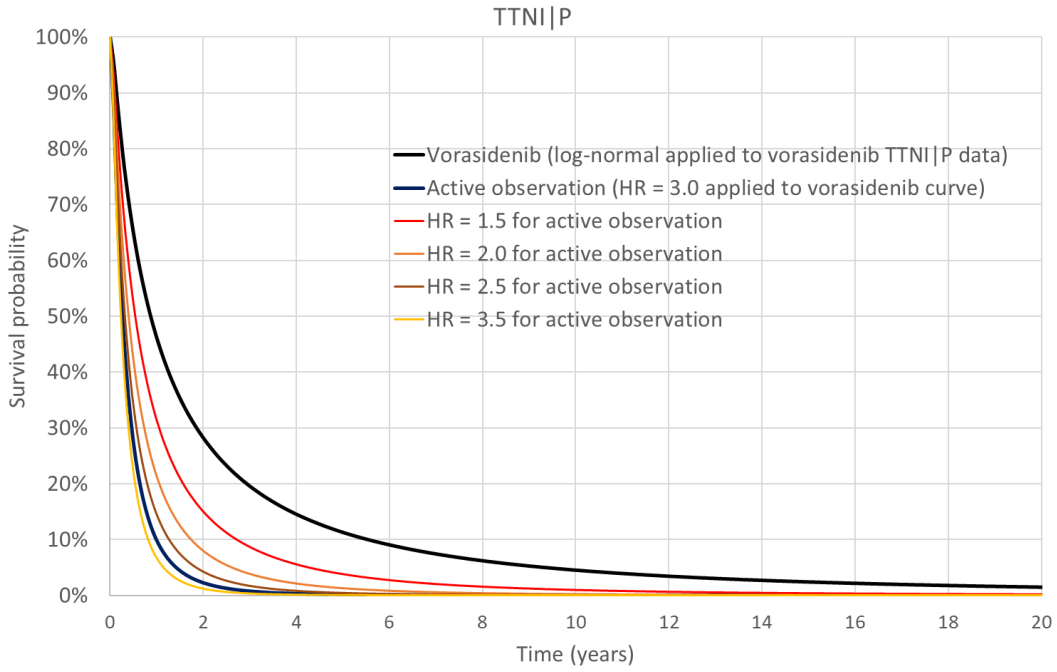


Figure 5 Company's revised base case with generalised gamma model for vorasidenib TTNI-P

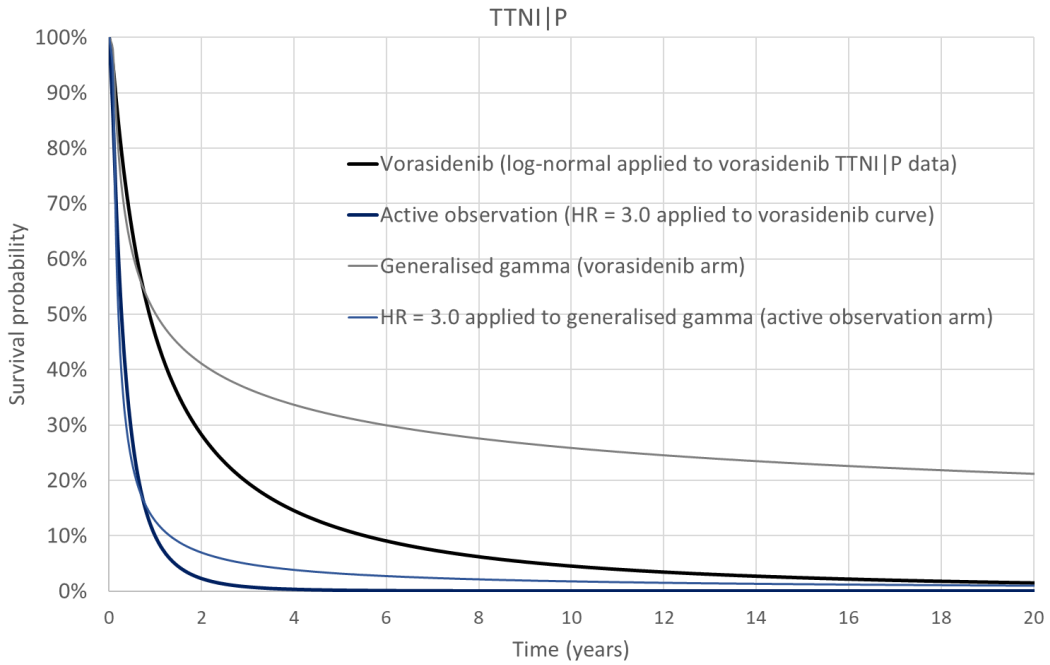
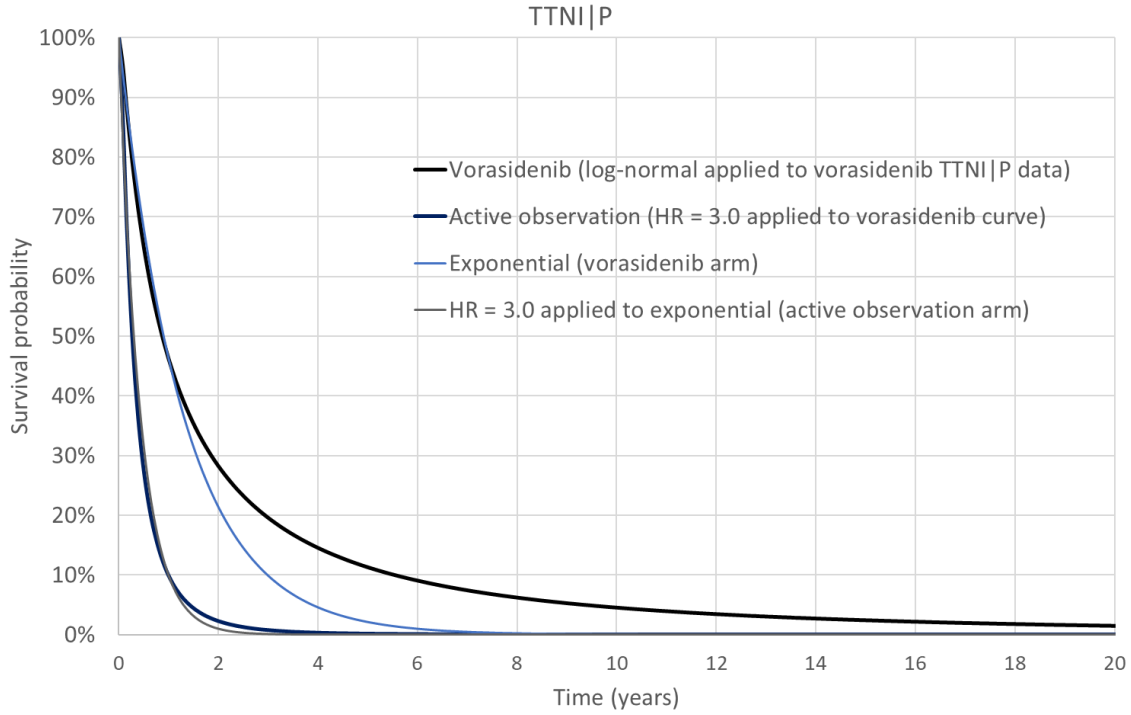


Figure 6 Company's revised base case with exponential model for vorasidenib TTNI-P



Critique of the company's updated health-related quality of life data for progression status

Comment 7 provides updated health-related quality of life data for the March 2023 data cut off (DCO) from INDIGO using the same regression analyses as per the original company submission. While the mean utility values for both the progression-free and progressed health states were higher in the active observation arm than the vorasidenib arm in the September 2022 DCO, the updated DCO shows that the mean utility values for progression-free are similar across both arms and the mean utility values for progressed disease remain slightly higher for the active observation arm compared to the vorasidenib arm. Therefore, the clinical benefits of vorasidenib observed in the INDIGO trial (improvements in PFS and anticipated improvements in TTNI-P) do not translate in improved health-related quality of life utility values.

The company justifies the higher utility value for active observation in progressed disease by stating that an 'average' patient that has progressed after being treated with vorasidenib is likely to have a poorer prognosis than an average patient treated with vorasidenib who may or may not have progressed over the period of trial follow up. The EAG does not consider this justification to be sufficient, as it implies that patients who progress while on vorasidenib have a poorer prognosis. This implication contradicts the company's arguments regarding the vorasidenib TTNI-P benefit over the active observation arm.

2.2 Comment 8: Source of utility values (DGD Section 3.13)

Section 3.13 of the DG notes that the committee concluded that the utility values derived from the vignette study were highly uncertain and requested that further analyses be presented at consultation. The committee suggested using the utility value of 0.60 from TA23(6) for first-line RT/CT in the model and then applying the relative difference between health-state utilities in the unadjusted EQ-5D vignette for later health states, to remove the implausible drop in utility when moving to subsequent treatments.

The company undertook the analyses requested by the committee but noted the limitations of the source of utility value of 0.60 from TA23 in its response to DG. The EAG agrees with the noted limitations of the source data used to inform the 0.60 value for first-line RT/CT. In addition, applying the relative difference between health-state utilities derived from the unadjusted EQ-5D vignette data to later health states produces implausibly high utility values for later health states. For example, using a value of 0.6 for first-line RT/CT (health state S5) and the relative difference from the vignette study for later health states produces a utility value of 0.84 for S6 (1L RT/CT off treatment), which is higher than the progression-free and progressed disease health state utility values of 0.742 and 0.720, respectively. The EAG considers this outcome to be a consequence of the issues with the vignette study (detailed in Section 4.2.8.2 of the EAR); specifically, the vignette study did not include descriptions of the progression-free and progressed-disease health states that could be used to anchor the values for the later health states to the INDIGO utility values. To overcome the issue of an implausibly higher utility value for health state S6, the company amended the NICE committee request by applying the utility value of 0.60 from TA23 to S6 (1L RT/CT off treatment) and then using the relative difference from the vignette study for the other health states. This produced more plausible estimates. Notably, the estimates resulting from this approach are not dissimilar to the unadjusted EQ-5D vignette values used in the EAG's original base case. The company maintains its preference to use the vignette study because it was specifically undertaken to inform the health economic modelling for the vorasidenib appraisal.

In response to DG, the company also considered NICE TA977 (7) as a potential source for alternative utility values. Although this appraisal focused on children and young people, it utilised adult utility values. The utility values reported in TA977 are presented as a decrement applied to successive progression events (e.g., a mean utility decrement of 0.06 is applied relative to the previous health state for each progression, and a mean utility decrement of 0.155 is applied to HGG relapsed/refractory relative to patients without the condition), rather than being linked directly to subsequent lines of therapy, as used in the company's model. The company developed a TA977-based scenario for use in this appraisal, starting with a baseline utility (general population) of 0.90, a utility decrement of 0.155 for LGG pre-progression, a utility decrement of 0.06 for each progression, and a

utility decrement of 0.187 for chemotherapy, based on the utility values reported in TA977. For the company's model, the company applied the LGG pre-progression disutility (-0.155) to the baseline utility (0.90) to derive a progression-free utility value of 0.745 for health states S1 (vorasidenib) and S2 (active observation) in the model. For the progressed disease health state S4, the company applied the disutility (-0.06) to the progression-free (PF) utility to obtain the progressed disease utility value of 0.685. For 1L RT/CT on-treatment (S5), the company applied two progression disutilities to PF and added the chemotherapy disutility (-0.187) to derive a utility value of 0.438 for health state S5. For 1L RT/CT off-treatment (S6), the company removed the chemotherapy disutility but applied three progression disutilities to produce a utility value of 0.565. For 2L+ RT/CT (S7), the company applied five progression disutilities and a chemotherapy disutility to produce a utility value of 0.258. For BSC (S8), the company applied six progression disutilities to produce a utility value of 0.385.

The EAG notes that the estimates resulting from the company's alternative approach utilising TA977 utility decrements are not significantly dissimilar to the values used in the EAG's original base case. The EAG also notes a limitation associated with the utility values derived from TA977. These values are sourced from Vera et al (2023)(8), which is a retrospective cohort study of 336 patients with malignant glioma in the US National Cancer Institute Neuro Oncology Branch Natural History Study. The utility values are determined using the US value set for EQ-5D. Transferring these decrements presents additional uncertainty because the source data comes from a US population and the decrements are based on progression events, while the company's model is built around lines of therapy. Furthermore, the patient population in subsequent lines of therapy in the model is a mix of LGG, HGG, and secondary HGG (malignant transformation), further complicating the transferability of the utility values.

In summary, the EAG does not consider the alternative estimates derived from either TA23 or TA977 to be useful for reducing the uncertainty in the utility values used in the company's or EAG's original base case.

The company has used the updated utility values from the INDIGO trial's March 2023 DCO for the progression-free (health states S1 and S2) and progressed (health state S4) health states, and the unadjusted vignette utility values for subsequent treatments, in its revised base case. The EAG considers this approach to be appropriate.

2.3 Comment 9: Surrogacy relationship for OS (DGD Section 3.11)

The company's base case assumes a benefit in OS for vorasidenib compared with active observation, which is driven by improvements in PFS and TTNI-P. Section 3.11 of the DG discusses the EAG concerns that the surrogacy relationship between PFS, TTNI-P and OS was uncertain and not supported by data.

The company acknowledged the lack of statistical validation of PFS or TTNI as surrogate endpoints for OS in mIDH gliomas. However, the company provided some clinical evidence to support the importance of PFS and TTNI as surrogate endpoint for OS.

Surrogacy relationship between PFS and OS:

Regarding using PFS as a surrogate for OS, the company cited three published studies and conducted some post-hoc analysis. The company cited the work by Miller et al, 2019 which concluded that PFS2 was a surrogate prognostic marker, identifying patients with poorer overall survival in a population of natural history of grade 2 (48.7%) and grade 3 (51.3%) glioma. The company cited a study by Han et al(9) which investigated the correlation between PFS and OS. The study concluded that there is a strong and positive correlation 0.92 (95% CI, 0.71–0.99) between the hazard ratio of PFS and OS in patients with glioblastoma; and there is a good positive relationship between mPFS and median OS 0.70 (95% CI, 0.59–0.79). Concluding that PFS **may be** an appropriate surrogate for OS. The company also cited a target literature review (TLR) by Bhatia et al(5). which investigated the tumor volume growth rate (TVGR) in a population of IDH-mt WHO grade 2 gliomas patients in active observation after surgical resection. The study showed that one natural logarithm tumor volume increase resulted in more than a 3-fold increase in risk of death and concluded that TVGR **may be** used as an earlier measure of clinical benefit and correlates well with the WHO 2021 molecular classification of gliomas and survival. The company conducted three pot-hoc analysis using the INDIGO trial to show that the tumour growth rate (TGR) and volume data are predictors of PFS.

The EAG agrees that there could be some plausible relationship between PFS and OS. However, there are still uncertainties in translating the PFS benefit to OS benefit in grade 2 glioma. Firstly, the study by Miller et al showed that the surrogacy relationship is between PFS2 and OS in a combination of grade 2 and grade 3 natural history population. However, INDIGO did not report PFS 2 as an endpoint even after the EAG requested it in the PFC (A15). Secondly, the study by Han et al(9) investigated the surrogacy relationship between PFS and OS in HGG patients. Thus, evidence from Hans et al could be limited to HGG population. Moreover, 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. The TLR by Bhatia et al(5) and post-hoc analysis from INDIGO focused on relationship between tumour volume and growth rate and PFS not PFS and OS. Hence, the EAG notes that the evidence and post-hoc analysis submitted by the company do not remove the uncertainties of using PFS as a surrogate endpoint for OS.

Surrogacy relationship between TTNI-P and OS:

In the DG the committee was also concerned about the use of TTNI-P as a surrogate marker for overall survival, because it was highly uncertain and was likely confounded by crossover. The company argues that TTNI is mechanistically linked to OS through its dependence on disease progression (TTP or PFS). The company points to a body of evidence that demonstrates a strong correlation between PFS and OS in mIDH patients, which they indicate supports the transitive relevance of TTNI to OS. They argue that TTNI functions as an indirect but practical surrogate for survival. To support this the company also refer to the EORTC 22845 trial(10), which reported no statistically significant difference in OS between patients who received immediate postoperative RT and those who underwent delayed RT at the time of progression. The company also stated that the observational arm of RTOG 9802(11) had comparable clinical characteristics and median PFS and OS at 8 years to EORTC 22845. A further study by Blonski et al(12) is also given to support the surrogacy relationship which explored long term outcomes in patients with diffuse low-grade glioma treated with initial PCV chemotherapy followed by RT. Among 20 patients, 12 deaths were reported: six were directly attributed to tumor progression, five to treatment-related neurotoxicity, and one due to both causes. The company state that "TTNI captures a clinically relevant milestone that reflects both disease control and preservation of future treatment benefit. Together with the strong correlation established between PFS and OS, these elements provide a coherent rationale for the use of TTNI as a pragmatic and meaningful surrogate endpoint for OS in patients with mIDH WHO grade 2 gliomas."

Again, the EAG agrees that there could be some plausible relationship between TTNI-P and OS, but the studies reported do not statistically assess the surrogacy relationship and instead it is inferred from 'no statistically significant difference in OS' between patients that had immediate treatment versus delayed treatment at progression and comparable results with the combined RT/CT arm of RTOG 9802(11). In the INDIGO trial, a relationship between TTNI-P and OS is not yet observed with only one death reported in the trial and issues with the TTNI-P outcome. Data from Blonski et al(12) is only a small sample size and does not conclusively specify a surrogacy relationship between TTNI-P and OS. The company also 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 in response to EAG clarifications (B2a). In addition, TTNI-P is still confounded by cross-over in the placebo arm of the INDIGO trial. Therefore, the EAG's concerns remain that the surrogacy relationship between TTNI-P and OS is uncertain and not supported by data.

2.4 Comment 11: Uncaptured benefits (DGD Section 3.17)

Section 3.17 of the DG noted that there are some potential benefits of vorasidenib which may not have been fully captured in the company's model. These uncaptured benefits included: the impact of vorasidenib on the mental health of patients with LGG (i.e., psychological benefits), seizures

associated with LGG (which directly impact a patient's ability to drive), the physical and psychological impacts on carers and family members, and the socio-economic benefits of increasing the time before people require CT/RT. Hence, the committee considered these uncaptured benefits of vorasidenib in its decision making by accepting a higher level of uncertainty.

The company's response and EAG's comments on the uncaptured benefits are summarised below:

Ability to drive:
The company noted that Section 3.17 of the DG states that "given the median PFS of 22.1 months in the vorasidenib arm, it considered it unlikely that many people having vorasidenib would be seizure-free for an entire year to allow them to return to driving". The company noted that the median PFS was not reached in the vorasidenib arm.

The EAG agrees with the company that the median PFS was not reached (95% CI: 22.1, NE) for the vorasidenib arm as of March 2023 DCO. However, this does not translate that patients on vorasidenib are likely to be seizure-free for an entire year to allow them to return to driving. Hence, the EAG considers that the benefit of vorasidenib relating to the ability to drive remains uncertain among patients on the vorasidenib arm.

Patient Pathway Study:
The company noted that they carried out a qualitative study(2) exploring the patient pathway and disease burden for people living with mIDH1/2 diffuse glioma, their caregivers, and PAG representatives. In the report, they highlighted the perceived benefits for patients on active observation compared to those receiving RT/CT. These benefits included the ability to return to work, resume normal daily lives, and travel given necessary adaptations, and the avoidance of the side effects (both emotional and physical burden and long-term effects) associated with RT/CT.

The EAG agrees with the company that there could be some potential benefits accruing to the active observation group over the CT/RT group especially relating to the avoidance of RT/CT side effects and the ability of patients to return to work after the initial surgery. However, the study did not include patients receiving vorasidenib. Thus, the benefit or side effect profile of vorasidenib was not explored in this study, which prevents an understanding of how it impacts the patient pathway. Therefore, the EAG still considers the benefit of vorasidenib relating to the patient pathway to be highly uncertain among patients in the vorasidenib arm.

Burden of glioma on economic productivity:
The company used the Danish administrative register to generate real-world evidence(13) on the burden of glioma on patients and the economy. The company noted that the median time absent from work due to RT/CT is 4.4 weeks per month, which equates to a productivity loss of €3,750 per patient.

The EAG agrees with the company that the impact of the burden of glioma on economic productivity is large, especially with RT/CT treatment. Hence, the EAG considers that any treatment that can significantly slow the disease progression after initial surgery (taking into consideration the cost-effectiveness of the therapy) could help to reduce the burden of glioma economically. However, the EAG notes that in the Danish study, RT/CT was not offered to patients as an alternative (or comparator) to active observation, but rather as a treatment option administered upon disease progression, which is a similar practice in the NHS. Therefore, RT/CT would still be administered to patients on vorasidenib when their disease progresses. Consequently, the EAG still considers that the benefit of vorasidenib relating to the economic burden of glioma to be uncertain among patients in the vorasidenib arm.

Paediatric patients

The company noted that there are uncaptured benefits of vorasidenib in the paediatric population who are eligible for vorasidenib that the company felt were not considered. The company noted that this population would contribute to the work force of the economy in the future increasing the economy GDP and productivity. Therefore, the company noted that delaying the RT/CT treatment in paediatric patients would have significant effect on the cognitive effect on the brain and skull development and would enable them to remain in education.

The EAG agrees with the company that delaying CT/RT treatment in the paediatric population would reduce the long-term effect of CT/RT on their brain development. However, contributing to the work force futuristically depends on long-term progression and survival outcomes. Currently, there is no mature OS data available from the INDIGO trial to remove the uncertainties surrounding the overall survival of grade 2 glioma patients receiving vorasidenib. Moreover, in the INDIGO trial only one paediatric patient below 18 years was recruited in the trial. With this very small sample size, the EAG considers that the benefit of vorasidenib relating to the pediatric population to be highly uncertain.

Underestimation of treatment effect for vorasidenib

The company noted that the treatment effect from the INDIGO trial could be underestimated given that the trial used the older World Health Organization (WHO) classification criteria for LGG. Consequently, a small proportion of people may have been misclassified as HGG instead of LGG. The company suggests this likely led to an underestimation of the treatment effect for vorasidenib in the full population and should therefore also be considered as an uncaptured benefit.

The EAG agrees that there is a difference in how LGG is diagnosed based on the older WHO criteria (2016) versus the newer WHO criteria (2021). Consequently, there is a possibility that using the newer WHO criteria could lead to the misdiagnosis and misclassification of patients, which may undermine the estimated treatment effect. However, the precise proportion of misdiagnosed patients is

unknown. Moreover, the same WHO criteria (2016) used in the recruitment and classification of patients at the start of the trial were used at each data cut off to classify patients as progressed or stable. Therefore, the EAG still considers that the uncaptured benefit of vorasidenib regarding the underestimated treatment effect to be highly uncertain.

In summary, the EAG agrees with the company that there may be uncaptured benefits that are not quantified in the model. However, the EAG considers that the uncaptured benefits specifically attributable to vorasidenib are highly uncertain.

2.5 Comment 12: Managed access (DGD Section 3.22)

The company disagrees with the committee's statement in Section 3.22 of the DG, which concluded that "collecting more evidence during a managed access period is unlikely to resolve the key uncertainties in the evidence. So vorasidenib cannot be used with managed access".

The company noted that it is expecting mature data from the INDIGO trial by the May 2028 data cut-off and, if granted entry into the CDF (until 2029 or beyond), this would help generate more data that could shape the PFS and TTNI curves for vorasidenib; thereby, addressing the key uncertainties in the cost effectiveness analysis. Furthermore, the company noted that feedback from the managed access feasibility assessment from the NICE managed access team indicates that there is value in collecting SACT and RTDS data to help resolve uncertainties related to TTNI and time spent off treatment following progression and prior to the next intervention.

The EAG agrees with the company that providing mature data with a later data cut off than May 2023 would offer more evidence that could potentially resolve some of the uncertainties in the cost-effectiveness analysis. However, 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 in the placebo arm. Even with more mature OS data from INDIGO over a longer 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.

3 CRITIQUE OF THE COMPANY'S REVISED COST-EFFECTIVENESS ANALYSES

3.1 Summary of the company's base case analysis

The company presents revised base-case results following DG. The company's revised base-case assumptions include the following committee preferred assumptions (DGD Section 3.20):

- use the baseline characteristics for the population from INDIGO.
- use the PFS data from INDIGO for vorasidenib and placebo, using a log-normal distribution.
- use the vorasidenib TTNI-P data to model the time off treatment with progression for both vorasidenib and placebo but exploring alternative approaches – the company applies a log-normal curve using the vorasidenib TTNI-P data for the vorasidenib arm. For the active observation arm the company applies a HR of 3.0 to the vorasidenib TTNI-P curve (see below).
- use the company's modelling of overall survival while noting the uncertainty in this approach but would assess outputs from updated analyses – note no updated analyses provided.
- use the EAG's preferred distribution of subsequent treatments, informed by clinical experts and NG99.
- exclude the cost for using bevacizumab as a subsequent treatment.
- exclude the cost of using CT scans for monitoring for vorasidenib and placebo.
- use a discount rate of 3.5% for health benefits and costs.
- add a severity weight of 1.2 to the QALYs.

In addition to the committee's preferred assumptions, the company's revised base case includes:

- A revised PAS price for vorasidenib ([redacted] PAS discount, equivalent to a price of [redacted] per pack of 30 x 40mg vorasidenib tablets).
- Updated data cut (March 2023) for utility values from INDIGO for health states S1 to S4 and use of unadjusted vignette utility values for subsequent treatments.
- Application of a HR of 3.0 to the TTNI | P curve (based on vorasidenib TTNI-P data and log-normal model) for the active observation arm.

3.2 Critique of the company's base case results

The EAG validated the company's revised base case results and model implementation. The EAG shows the incremental impact of the company's additional changes to the committee preferred assumptions (Table 1) and the probabilistic results of the company revised base case (not reported in company's response to DG).

The EAG has checked the appropriate severity weighting for the company's revised base case results and agrees with the weighting of 1.2 applied to all analyses in Table 3.

Table 3 Results of company revised base case following DG

Name	Option	Total costs	Total QALYs	Inc. Costs	Inc. QALYs	ICER* (£/QALY)
Committee preferred assumptions (with revised PAS price for vorasidenib)	Active observation	[redacted]	6.11			
	Vorasidenib	[redacted]	7.49	[redacted]	1.65	[redacted]
+ Updated data cut (March 2023) for utility values from INDIGO and unadjusted vignette values	Active observation	[redacted]	6.11			
	Vorasidenib	[redacted]	7.50	[redacted]	1.67	[redacted]
+ Application of a HR = 3.0 to vorasidenib TTNI | P for the active observation arm of the model [Company base case – deterministic]	Active observation	[redacted]	5.33			
	Vorasidenib	[redacted]	7.50	[redacted]	2.60	[redacted]
Company base case - probabilistic	Active observation	[redacted]	5.36			
	Vorasidenib	[redacted]	7.60	[redacted]	2.24	[redacted]

Abbreviations: ICER: incremental cost-effectiveness ratio; QALYs: quality-adjusted life years.
*Adjusted by applying a 1.2 severity weight

3.3 Summary of the company's scenario analyses

The committee noted that there was considerable uncertainty surrounding the cost effectiveness of vorasidenib for the target population. The committee requested that the company (DGD Section 3.21):

- explore alternative ways to model TTNI-P, including but not limited to:
    - providing full parametric distributions for TTNI-P, applying data from the INDIGO vorasidenib arm to both vorasidenib and active surveillance in the model.
    - exploring alternative ways to plausibly model a benefit in TTNI-P for vorasidenib without using data from the placebo arm of INDIGO as a scenario.
- model the quality-of-life burden for subsequent treatments by applying the relative difference between health-state utilities in the unadjusted EQ-5D vignette study to the value for glioma recurrence from TA23 and consider alternative quality-of-life decrements moving from progression-free disease to progressed disease.

In response to the first of these committee requests, the company did not provide full parametric distributions for TTNI-P, by applying vorasidenib data to both arms in the model; however, the company did explore the application of different HRs (2.5 and 3.5) to the TTNI | P curve (based on vorasidenib TTNI-P data and log-normal model) for the active observation arm.

For the second of these committee requests, the company explored different utility scenarios: (i) EAG base case utility values, (ii) use of the updated DCO utility values and unadjusted vignette values when alternative HRs are applied to the TTNI-P curve, (iii) utility values from TA23, and (iv) utility values from TA977 (see Section 2.2 above).

3.4 Critique of the company's scenario analyses results

The EAG validated and confirmed the results of the company's scenario analyses. Table 4 presents the results of the company's scenario analyses for the alternative HRs of 2.5 and 3.5 applied to the vorasidenib TTNI-P curve to derive the active observation arm, and with updated INDIGO DCO utility values and unadjusted vignette utility values for subsequent treatments. The EAG refers the reader to the company's response to the DG for the ICERs generated using the alternative utility values derived from TA23 and TA977 in the model.

The EAG has checked the appropriate severity weighting for the company's scenarios and agrees with the weighting of 1.2 applied.

Table 4 Results of company scenario analyses following DG (deterministic)

Name	Option	Total costs	Total QALYs	Inc. Costs	Inc. QALYs	ICER* (£/QALY)
Company revised base case	Active observation	[redacted]	5.33			
	Vorasidenib	[redacted]	7.50	[redacted]	2.60	[redacted]
HR = 2.5 applied to vorasidenib TTNI-P for active observation, with updated INDIGO DCO + raw vignette values	Active observation	[redacted]	5.38			
	Vorasidenib	[redacted]	7.50	[redacted]	2.54	[redacted]
HR = 3.5 applied to vorasidenib TTNI-P for active observation, with updated INDIGO DCO + raw vignette values	Active observation	[redacted]	5.29			
	Vorasidenib	[redacted]	7.50	[redacted]	2.65	[redacted]

Abbreviations: ICER: incremental cost-effectiveness ratio; QALYs: quality-adjusted life years.
*Adjusted by applying a 1.2 severity weight

4 EAG ADDITIONAL ANALYSES

The committee requested full parametric distributions for TTNI-P, applying data from the INDIGO vorasidenib arm to both the vorasidenib and active observation arms in the model. The EAG presents the cost-effectiveness results in Table 5 when a HR of 1.0 is used for the active observation arm, i.e. the same TTNI-P curve is used for both arms and alternative parametric models (log-normal, generalised gamma and exponential, corresponding to mid-range, most optimistic and least optimistic predictions of long-term survival, respectively) used to extrapolate vorasidenib TTNI-P data.

The EAG also presents results in Table 5 for alternative values of the HR (1.5, 2.0, 2.5 and 3.0), which include a vorasidenib TTNI-P benefit relative to active observation. These alternative HRs are also presented for alternative parametric models used to extrapolate vorasidenib TTNI-P data.

Note, in all scenarios presented in Table 5 the updated INDIGO DCO utility values and unadjusted vignette utility values for subsequent treatments are included, as per the company's revised base case.

Of the results presented in Table 5, the EAG considers that the following scenarios provide plausible estimates of the duration of time spent off treatment with progressed disease (PD) relative to the time spent progression-free (PF):

- HR = 1.0 applied to vorasidenib TTNI-P with **exponential** extrapolation (undiscounted life years: vorasidenib PD = 1.22, vorasidenib PF = 5.22, active observation PD = 1.26, active observation PF = 1.42). Note that both the log-normal and generalised gamma models produce greater duration of time spent off treatment in PD compared to PF for the active observation arm, which the EAG considers lacks face validity.
- HR = 1.5 applied to vorasidenib TTNI-P with **log-normal** extrapolation (undiscounted life years: vorasidenib PD = 2.19, vorasidenib PF = 5.22, active observation PD = 1.18, active observation PF = 1.42).
- HR = 2.0, 2.5 or 3.0 applied to vorasidenib TTNI-P with **log-normal** extrapolation (reducing the undiscounted life years for active observation PD to 0.75, 0.54 and 0.43, respectively).
- HR = 1.5, 2.0, 2.5 or 3.0 applied to vorasidenib TTNI-P with **exponential** extrapolation (undiscounted life years: vorasidenib PD = 1.22, vorasidenib PF = 5.22, active observation PD ranges from 0.83 with HR = 1.5 down to 0.39 with HR = 3.0, active observation PF = 1.42).

The appropriate severity weighting for the scenarios in Table 5 is 1.2, except for the scenario with HR = 1.0 applied to vorasidenib TTNI-P with generalised gamma extrapolation, where there is no QALY shortfall (i.e., severity weighting = 1.0). Removing the severity weighting for this scenario from Table 5 produces an ICER of [redacted].

Table 5 Results of EAG additional scenario analyses

Name	Option	Total costs	Total QALYs	Inc. Costs	Inc. QALYs	ICER* (£/QALY)
Company's revised base case	Active observation	[redacted]	5.33			
	Vorasidenib	[redacted]	7.50	[redacted]	2.60	[redacted]
HR of 1.0 for active observation arm and alternative extrapolations for vorasidenib TTNI-P data						
HR = 1.0 applied to vorasidenib TTNI-P with log-normal extrapolation	Active observation	[redacted]	6.11			
	Vorasidenib	[redacted]	7.50	[redacted]	1.67	[redacted]
HR = 1.0 applied to vorasidenib TTNI-P with generalised gamma extrapolation	Active observation	[redacted]	7.69			
	Vorasidenib	[redacted]	8.84	[redacted]	1.39	[redacted]
HR = 1.0 applied to vorasidenib TTNI-P with exponential extrapolation	Active observation	[redacted]	5.71			
	Vorasidenib	[redacted]	7.17	[redacted]	1.75	[redacted]
HR of 1.5 for active observation arm and alternative extrapolations for vorasidenib TTNI-P data						
HR = 1.5 applied to vorasidenib TTNI-P with log-normal extrapolation	Active observation	[redacted]	5.66			
	Vorasidenib	[redacted]	7.50	[redacted]	2.20	[redacted]
HR = 1.5 applied to vorasidenib TTNI-P with generalised gamma extrapolation	Active observation	[redacted]	6.62			
	Vorasidenib	[redacted]	8.84	[redacted]	2.67	[redacted]
HR = 1.5 applied to vorasidenib TTNI-P with exponential extrapolation	Active observation	[redacted]	5.52			
	Vorasidenib	[redacted]	7.17	[redacted]	1.98	[redacted]
HR of 2.0 for active observation arm and alternative extrapolations for vorasidenib TTNI-P data						
HR = 2.0 applied to vorasidenib TTNI-P with log-normal extrapolation	Active observation	[redacted]	5.48			
	Vorasidenib	[redacted]	7.50	[redacted]	2.42	[redacted]
HR = 2.0 applied to vorasidenib TTNI-P with generalised gamma extrapolation	Active observation	[redacted]	6.01			
	Vorasidenib	[redacted]	8.84	[redacted]	3.40	[redacted]
HR = 2.0 applied to vorasidenib TTNI-P with exponential extrapolation	Active observation	[redacted]	5.42			
	Vorasidenib	[redacted]	7.17	[redacted]	2.10	[redacted]
HR of 2.5 for active observation arm and alternative extrapolations for vorasidenib TTNI-P data						
HR = 2.5 applied to vorasidenib TTNI-P with log-normal extrapolation	Active observation	[redacted]	5.38			
	Vorasidenib	[redacted]	7.50	[redacted]	2.54	[redacted]
HR = 2.5 applied to vorasidenib TTNI-P with generalised gamma extrapolation	Active observation	[redacted]	5.67			
	Vorasidenib	[redacted]	8.84	[redacted]	3.81	[redacted]
HR = 2.5 applied to vorasidenib TTNI-P with exponential extrapolation	Active observation	[redacted]	5.36			
	Vorasidenib	[redacted]	7.17	[redacted]	2.17	[redacted]
HR of 3.0 for active observation arm and alternative extrapolations for vorasidenib TTNI-P data						
HR = 3.0 applied to vorasidenib TTNI-P with log-normal extrapolation (i.e., the company revised base case)	Active observation	[redacted]	5.33			
	Vorasidenib	[redacted]	7.50	[redacted]	2.60	[redacted]
HR = 3.0 applied to vorasidenib TTNI-P with generalised gamma extrapolation	Active observation	[redacted]	5.49			
	Vorasidenib	[redacted]	8.84	[redacted]	4.03	[redacted]

HR = 3.0 applied to vorasidenib TTNI-P with exponential extrapolation	Active observation	[redacted]	5.32			
	Vorasidenib	[redacted]	7.17	[redacted]	2.22	[redacted]

Abbreviations: ICER: incremental cost-effectiveness ratio; QALYs: quality-adjusted life years.
*Adjusted by applying a 1.2 severity weight

4.1 EAG preferred base case

The EAG's preferred base case aligns with the committee's preferred assumptions. The committee accepted all of the EAG's original base case assumptions, except that they preferred the vorasidenib TTNI-P data from the INDIGO trial over the pooled TTNI-P data across arms. The EAG's preferred base case incorporates the vorasidenib TTNI-P data with log-normal extrapolation (second best-fitting curve) and incorporates the revised PAS price for vorasidenib and the updated INDIGO DCO utility values and unadjusted vignette utility values for subsequent treatments (consistent with the EAG's original base case).

The benefit in TTNI-P for vorasidenib remains unknown. To account for a potential benefit, the EAG considers HRs of 1.5 to 3.0 applied to the vorasidenib TTNI-P data with log-normal extrapolation to derive the active observation arm to be plausible scenarios.

Table 6 presents the results of the EAG base case and scenarios.

Table 6 EAG base case and scenarios

Name	Option	Total costs	Total QALYs	Inc. Costs	Inc. QALYs	ICER* (£/QALY)
EAG base case	Active observation	[redacted]	6.11			
	Vorasidenib	[redacted]	7.50	[redacted]	1.67	[redacted]
Scenarios						
HR = 1.5 applied to vorasidenib TTNI-P with log-normal extrapolation	Active observation	[redacted]	5.66			
	Vorasidenib	[redacted]	7.50	[redacted]	2.20	[redacted]
HR = 2.0 applied to vorasidenib TTNI-P with log-normal extrapolation	Active observation	[redacted]	5.48			
	Vorasidenib	[redacted]	7.50	[redacted]	2.42	[redacted]
HR = 2.5 applied to vorasidenib TTNI-P with log-normal extrapolation	Active observation	[redacted]	5.38			
	Vorasidenib	[redacted]	7.50	[redacted]	2.54	[redacted]
HR = 3.0 applied to vorasidenib TTNI-P with log-normal extrapolation (i.e., the company revised base case)	Active observation	[redacted]	5.33			
	Vorasidenib	[redacted]	7.50	[redacted]	2.60	[redacted]

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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, with a data cut in 2028. This trial has limitations due to the unblinding of populations and the high degree of crossover. 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. The managed access team view on feasibility has been updated following ACM1.
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 that 5 years of data collection in managed access is beneficial in reducing uncertainty about the 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): **07/11/2025**

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 following ACM1. 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, with a data cut in 2028. This trial has limitations due to the unblinding of populations and the high degree of crossover. 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. The managed access team view on feasibility has been updated following ACM1.
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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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, with a data cut in 2028. This trial has limitations due to the unblinding of populations and the high degree of crossover. 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. The managed access team view on feasibility has been updated following ACM1.

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
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 large impact on the ICER, and may impact decision making.	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. During ACM1 the committee noted their reservations about the usefullness of longer term data from the trial, due to crossover, however the issue was not fully resolved.
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. During ACM1 the committee noted their reservations about the usefullness of longer term data from the trial, due to crossover, however the issue was not fully resolved.
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	Following ACM1 committee preferred using data from the vorasidenib arm for both the treatment and placebo arm, but wanted to see further modelling approaches from the company. This uncertainty links closely to uncertainty EAG6, discussed below.

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. However further analysis conducted by the company following ACM1 show that patients who progress while receiving vorasidenib do so with more favorable features that allow for a relatively longer TTNI|P period, compared to patients managed with active observation. - 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. 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 large impact on the ICER, and may impact decision making.	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	Following ACM1 the committee concluded that the company approach of using TTNI-p could be used to model time off treatment with progression, for both treatment arms, but they requested further analyses. Clinical input at ACM1 said that people with astrocytoma, have disease which is likely to have progressed within 5 years, while oligodrendroglioma has a more stable disease course. They also state that in clinical practice roughly twice as many people will have astrocytoma. Therefore an MA period of 5 years may be sufficient to resolve this uncertainty. Blueteq criteria, collected as part of a managed access agreement can collect tumour type, and so would be able to provide information separately for astrocytoma and glioma. 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. 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. The possibility of linking to surgical datasets is also being explored with NHSE. The company have also been in contact with NHS registries, from multiple trusts, to investigate feasibility of clinical data collection, and believe that they could collect data from up to 158 patients.
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.	Medium	Following ACM1 this remains an area of uncertainty, however the company mentioned in discussions with the managed access team at NICE that they would be willing to explore health utilities data collection as part of a managed access agreement. Collecting utilities data is often complicated during a managed access agreement, and therefore the managed access team do not believe that entry into the CDF should be based on this uncertainty alone, but it may provide supporting information if this technology entered due to other clinical uncertainties.
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	Resolved at ACM1 - committee decided to use the companies approach to modelling OS, while also asking for updated analyses. The committee concluded that post progression data cuts remaining from the trial are biased due to the high cross over of patients, and that even with remaining trial data cuts an OS benefit is unlikely to be seen in the available period of managed access
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	Resolved at ACM1 - the committee preferred to use baseline characteristics from the INDIGO trial. However a period in managed access may provide additional information to support this decision. 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.

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	Uncertainty resolved at ACM1.

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.

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
	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?		

Service evaluation checklist	Will the technology be used differently to how it would be if it had been recommended for use?	No	0
	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