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

Technology appraisal committee HST [20th November 2025]

Single Technology Appraisal: Second Committee Meeting

For projector – contains no CON information

Chair: Paul Arundel

Lead team: Annett Blochberger (clinical lead), Ed Wilson (cost lead), Tina Garvey (lay lead)

External assessment group: York (NETSCC)

Technical team: Emma Douch, Alan Moore, Richard Diaz

Company: Servier Laboratories

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

- ✓ **Recap to background and key issues**
- ❑ Summary of consultation comments
- ❑ Company's new evidence
- ❑ Other considerations
- ❑ Summary

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Vorasidenib (Voranigo, Servier Laboratories)

Oral treatment for people who do not need immediate further treatment after surgery

Marketing authorisation	• Vorasidenib is indicated for the treatment of Grade 2 astrocytoma or oligodendroglioma with a susceptible isocitrate dehydrogenase-1 (IDH1) mutation or isocitrate dehydrogenase-2 (IDH2) mutation in adults and paediatric patients 12 years and older, who are not in need of immediate chemotherapy or radiotherapy following surgical intervention • MA granted September 2025
Mechanism of action	• Inhibits the IDH1 and IDH2 mutant enzymes, reducing proliferation of tumour cells.
Administration	Administered orally (40mg) once daily for people weighing at least 40kg For people who weigh less than 40kg, a 20mg dose is recommended
Price	• List price per pack: 30 x 40 mg £15,000, 30 x 10 mg £7,500 • List price for 12 months of treatment: £[redacted] • A confidential patient access scheme is agreed for vorasidenib

Link to supplementary appendix: Background to LGG

Kg, kilogram; MA, marketing authorisation; MHRA, Medicines and Healthcare products Regulatory Agency; mg, milligrams

Summary of appraisal to date

Recommendation after ACM1: 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.

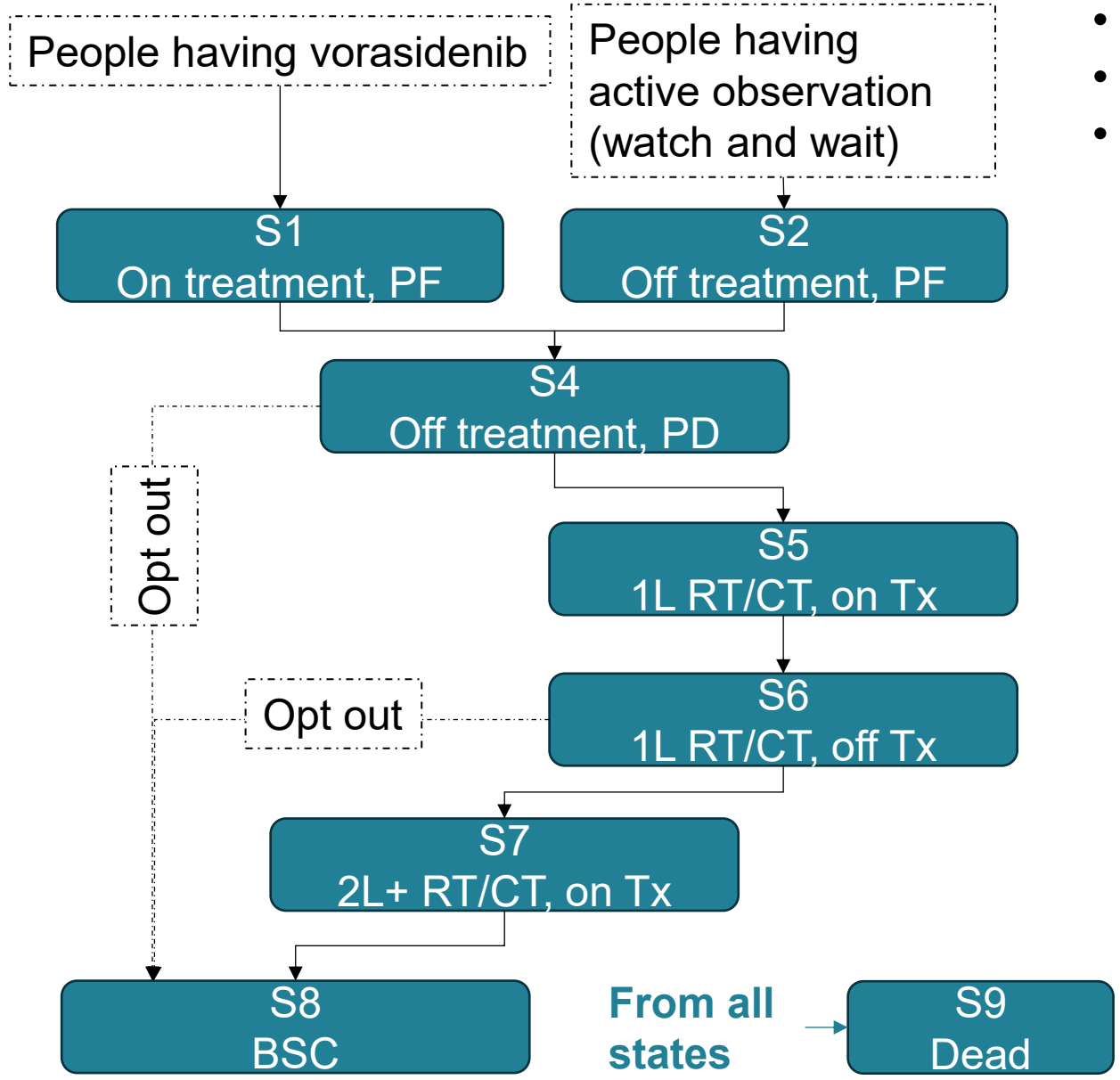
Issue	Committee conclusion
Population	People with tumours not in need of immediate RT/CT; may include people with supramaximal or complete resection
Comparator	Active surveillance
Key clinical evidence	INDIGO RCT: vorasidenib 40 mg daily (N = 168) vs placebo (N = 163) • On progression, treatment unblinded and people could have next intervention (NI): RT/CT or, for placebo arm, vorasidenib **Results:** vorasidenib improves PFS vs. placebo, but high uncertainty in TTNI and OS as 90% (N = 70) in placebo arm crossed over to vorasidenib after progression
Generalisability of INDIGO	• INDIGO population narrower than licence and may have more stable glioma vs NHS population (see supplementary slides: generalisability of INDIGO 1 and 2) • INDIGO used old WHO classification → may include some now classed as HGG ❖ Trial population considered acceptable for decision making given rarity • Use of vorasidenib as subsequent treatment makes TTNI results in placebo arm highly uncertain and unsuitable for decision making

ACM, appraisal committee meeting; CT, chemotherapy; HGG, high grade glioma; N, number; OS, overall survival; PFS, progression free survival; RCT, randomised controlled trial; RT, radiotherapy; TTNI, time to next intervention; WHO, World Health Organisation. Link to supplementary slides: LGG pathway, INDIGO design, results 1 and 2

Company's base case model overview, ACM1

Company developed de novo model based on key treatment-related milestones

Model structure



- Cycle length: 28 days with half cycle correction
- 60-year time horizon
- Microsimulation → individual characteristics vary on per-patient basis: mean age = 40 years old

Committee conclusion: prefer model based on disease progression status but model acceptable for decision making given the limited available data

Notes: a) state S3 (on treatment, PD) not in base case so not shown here. b) General population mortality applies to all health states but S8 (BSC).

Link to supplementary appendix: Model inputs, ACM1

BSC, best supportive care; CT, chemotherapy; PD, progressed disease; PF, progression free; RT, radiotherapy; Tx, treatment;

Summary of appraisal to date (cost effectiveness) (1)

RECAP

Table: Committee considerations from ACM1

Issue	Committee conclusion	Further information requested	Company updated?
Time to next intervention after progression (TTNI | P)	TTNI | P benefit for vorasidenib vs placebo plausible but uncertain → TTNI | P from INDIGO placebo arm unfit for decision making due to crossover	Alternative modelling for TTNI | P: • full parametric distributions using INDIGO vorasidenib arm for both treatments • scenarios with plausible TTNI | P benefit for vorasidenib without using placebo INDIGO data	Yes – for discussion
Overall survival	No OS data available from INDIGO so company uses benefits in PFS & TTNI | P as proxy → may be suitable but need to reevaluate post-consultation		Yes – for discussion
Utility values	• large difference between utilities from INDIGO and vignette implausible • requested alternative approaches to calculating utility values	• subsequent treatments: apply relative difference between utilities in unadjusted EQ-5D vignette to value for glioma recurrence in TA23 • consider alternative utility decrements moving from PF to PD	Partially – for discussion

ACM, appraisal committee meeting; OS, overall survival; PD, progressed disease; PF, progression free; PFS, progression free survival; TA, technology appraisal; TTNI, time to next intervention; TTNI | P, time to next intervention given progression. TA23: temozolomide for recurrent malignant glioma

Summary of appraisal to date (cost effectiveness) (2)

RECAP

Table: Committee considerations from ACM1

Issue	Committee conclusion	Company updated?
Subsequent treatments	Prefer EAG's base case distribution informed by expert advice/NICE guideline and exclude bevacizumab (unavailable in NHS)	Yes: resolved
Costs	Exclude cost of CT scans to align with clinical practice	Yes: resolved
Discount rate	Criteria for applying 1.5% discount rate not met → use 3.5% discount rate for costs and benefits	Yes: resolved
Severity	x 1.2 based on current ACM1 analyses (to be reconsidered based on updated analysis)	For discussion
Uncaptured benefits	Socioeconomic benefits, impact: a) on carers, b) on mental health, c) from reducing seizures	For discussion

ACM, appraisal committee meeting; CT, computerized tomography

Equality considerations

Stakeholders raised equalities issues related to age, pregnancy and travel

ABTF, BNOS, Patient expert:

Gliomas disproportionately impact a younger age group who:

- generally, have young families to support
- stand to gain most from delaying RT/CT
- face greater socioeconomic impact and have significant QoL considerations (e.g., fertility, work, family, travel)

- Are there any inequalities that need to be considered for this topic?

NICE

ABTF, Astro Brain Tumour Fund; BNOS, British Neuro Oncology Society; CT, chemotherapy; RT, radiotherapy; QoL, quality of life

Key issues for discussion

KEY: Change from base case ICER: small: < £5,000, moderate: £5,000 to £10,000, large: > £10,000

Issue	Impact
Appropriate data source for TTNI | P and resulting duration of time off treatment with progressed disease	Large
Surrogacy relationship for OS benefit	Unknown
Plausibility of health state utility values from vignette	Small
Uncaptured benefits in the modelling	Unknown
Appropriate severity weighting	N/A
Appropriateness of managed access	N/A

CT, computed tomography; ICER, incremental cost-effectiveness ratio; OS, overall survival; TTNI I P, time to next intervention given progression

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Consultation comments to draft guidance

- Comments received from:

Company	Servier
Patient and professional organisations	• Astro Brain Tumour Fund (ABTF) • The Brain Tumour Charity • Royal College of Pathologists • British Neuro Oncology Society (BNOS) • Society of British Neurological Surgeons (SBNS) • International Brain Tumour Alliance (IBTA)
Experts	• Patient expert
Web comments	24 web comments

All stakeholder comments provided for committee consideration → key themes summarised here but further comments can be found in the supplementary appendix

Consultation comments to draft guidance

Diagnosis of LGG is "devastating"

- "Low grade" not low impact: seizures / strokes impair memory, speech, movement, independence
- Constant uncertainty as tumours inevitably return → each year of normal life is profoundly valuable
- Immense psychological toll. Anxiety and depression affecting daily life and financial stability
- People with LGG often young, building careers, and raising families → symptoms may force patients to stop working, leading to lost income and independence

Significant unmet need for treatment options post-surgery for LGG:

- Currently treatments limited and outdated → no current options slow time to post-surgery progression
- Watch and wait not a treatment
  - Can cause "debilitating" anxiety and distress → patients report living "under a shadow of constant fear" between scans
- RT/CT side effects "serious" and "aggressive" → not fully captured in model (see health state utilities)

Large impact on carer and family quality of life

- Carers/families "share the emotional weight" → mental health impacted by watching loved ones suffer
- Financial strain or burden of care may impact employment and independence for carers
- Full impact on carers not captured in the model

CT, chemotherapy; LGG, low grade glioma; RT, radiotherapy

Consultation comments to draft guidance

Vorasidenib is a "game changer" in treatment for LGG:

- INDIGO trial showed vorasidenib delays PFS with minimal side effects → vital in maintaining independence, fitness, work, and caring or parenting duties
- Clear clinical benefit and potential to delay life-altering long-term side effects of RT/CT
- "Gentler, kinder" alternative with minimal side effects, enabling near-normal life and more family time
- Relief from anxiety and depression due to tumour stability and active treatment plan
- Potential for nurse-led delivery, easing NHS burden

Stakeholders disappointed in negative recommendation and requested committee consider:

- Uncaptured benefits for vorasidenib including socioeconomic benefits, impact on seizures, mental health, reduced treatment burden and avoidance of RT/CT side effects (see uncaptured benefits)
- Rarity of condition
- International and real word data to support effectiveness of vorasidenib
- Innovation → first drug to cross the blood–brain barrier and target LGG directly
- Unmet need: little research in LGG with lowest survival gains amongst all major cancers
- Patient voices and lived experiences of using vorasidenib
- Consider a MAA to allow data collection while providing access (see MAA slides).

CT, chemotherapy; LGG, low grade glioma; MAA, managed access agreement; PFS, progression free survival; RT, radiotherapy

Consultation comments to draft guidance

"Cognitive decline caused by brain radiotherapy is permanent, progressive, and life changing."

"Since being on Vorasidenib I have been able to return to full time work"

" 'Scanxiety'…is the debilitating fear experienced on watch and wait."

"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…."

"Tumour shrinkage…has not been adequately considered. Watch and wait does not address this"

"NICE have failed to put enough weight on the typical age and life stage of low-grade glioma patients."

"Treatments have not moved in decades, that there's no cure, and brain cancer is second from bottom for 5-year survival rates"

"'Watch and wait' is not a treatment.."

"The constant anxiety; uncertainty; lack of sleep; inability to live a full life; fractured family relationships have diminished [with vorasidenib]"

"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."

"Delaying chemo until the patient's children are older does make chemo less risky"

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Key issue: TTNI | P, time with progression before NI (1)

Committee requested alternative approaches to TTNI | P due to bias in INDIGO placebo arm

Background: TTNI | P (TTNI given progression) used for time off treatment with PD in model → difference between PFS (proxy for time to progression) and TTNI in INDIGO (supplementary appendix).

Used by	Approach	Distribution	Justification
Company ACM1	Separate curves for each arm	Generalised gamma (best fitting)	TTNI | P benefit for vorasidenib seen in INDIGO plausible → more favourable features on progression vs placebo
EAG ACM1	Pooled data used for both arms	Log normal (best fitting that results in longer time in PF than PD, off tx)	Company's curves implausible as: • result in longer time in PD, off tx than PF. • TTNI | P for placebo underestimated - high crossover to vorasidenib → no evidence that PD managed differently in each arm • higher HRQoL for PD in INDIGO placebo vs vorasidenib arm

Committee conclusion: approach to TTNI | P driver of cost effectiveness. Some benefit for vorasidenib plausible but size of difference uncertain as INDIGO placebo arm unfit for decision making. Requested:

- ❖ Full parametric distributions for TTNI-P, using INDIGO vorasidenib arm data for both modelled arms
- ❖ Scenario using alternative ways to plausibly model a TTNI-P benefit for vorasidenib without using data from INDIGO placebo arm

ACM, appraisal committee meeting; HRQoL, health related quality of life; PD, progressed disease; PF, progression free; PFS, progression free survival; TTNI, time to next intervention; TTNI | P, time to next intervention given progression

Key issue: TTNI | P, time with progression before NI (2)

Company support longer TTNI | P in vorasidenib arm

Company: vorasidenib data overestimates TTNI |P for people having active observation → maintain plausibility of longer TTNI |P in vorasidenib arm supported by:

1. Tumour data from INDIGO and perioperative study (both from ACM1) suggest favourable features when progressed on vorasidenib → longer time before tumour growth/volume needs treating
   - Cox regression model (new for ACM2) suggests 1 unit increase in log tumour volume = 56.0% increase in risk of TTNI event
2. Vorasidenib TTNI | P applied to placebo arm increases TTNI vs when using placebo TTNI | P and TTNI estimates from external evidence for active observation (mix of grade 2 and 3 glioma)
   → 2.22 years v 1.3 – 1.8 years
3. Australian BRAIN registry data (submitted at clarification), IDH-mutant grade 2 glioma diagnosed 2009-2024, ≥ 1 surgery "between 1-5 years prior", recurrent or residual disease
   - ❖ Median PFS: 42.7 months, median TTNI (time from surgery to NI) 48.4 months → estimated TTNI | P ~ 6 months
   - ❖ Interpret with caution as different definition of TTNI to INDIGO (time from surgery, not randomisation, to NI)

Comparison of TTNI values from INDIGO study and literature

Source	Rebaselined* TTNI (years)
Tran 2023	1.8
Bhatia 2024	1.3
INDIGO data	**TTNI (years)**
- Placebo for PF and PD	1.68
- Placebo for PF, vorasidenib for PD	2.22

*reported median TTNI from last surgery in literature - mean time from last surgery to randomization in INDIGO placebo arm.

ACM1, appraisal committee meeting; IDH, isocitrate dehydrogenase; NI, next intervention; PD, progressed disease; PF, progression free; PFS, progression free survival; TTNI, time to next intervention; TTNI | P, time to next intervention given progression

Key issue: TTNI | P, time with progression before NI (3)

Company cont. 4. Clinical experts to company:

- plausible some having vorasidenib off tx at 20 years based on tumour shrinkage and indolent, slowly progressive nature of oligodendrogliomas (risk of RT/CT may outweigh risk of staying off tx with PD)
- Reasonable to assume average TTNI | P of:
  - ❖ 6 months for active observation → NI would start after 6 monthly scan to assess growth rate
  - ❖ 2 years for vorasidenib due to the molecular change in disease

5. Updated HRQoL data (March 2023): narrower difference between vorasidenib and placebo (Δ PD = 0.023 vs. 0.052) → difference between arms likely due to INDIGO data collection (vorasidenib arm had lower average baseline utility baseline and less PD HRQoL data)

Base case: Vorasidenib: INDIGO vorasidenib arm using log normal distribution (TTNI | P = 2.19 years)

- Active observation: HR of 3.0 applied to vorasidenib arm → gives average TTNI |P = 5.12 months → aligns with expert advice and BRAIN registry that suggest TTNI |P of around 6 months

Scenarios: vary HRs for active observation to limits considered plausible by clinical experts:

a) HR of 2.5, average TTNI | P = 6.53 months, b) an HR of 3.5, average TTNI | P = 4.11 months

Stakeholders: Web comments, SBNS, IBTA, The Brain Tumour Charity, ABTF:

- INDIGO trial: vorasidenib significantly delays time to RT/CT in IDH1/2-mt LGG
- TTNI meaningful endpoint—delaying genotoxic therapy preserves cognitive function and QoL, especially in younger patients
- Consider updated INDIGO data cut or MAA to provide more data on TTNI

ABTF, Astro Brain Tumour Fund; CT, chemotherapy; HR, hazard ratio; HRQoL, health related quality of life; IBTA, International Brain Tumour Alliance; IDH, isocitrate dehydrogenase; LGG, low grade glioma; MAA, managed access agreement; NI, next intervention; PD, progressed disease; RT, radiotherapy;

SBNS, Society of British Neurological Surgeons TTNI, time to next intervention; TTNI | P, time to next intervention given progression; QoL, quality of life; tx, treatment

Key issue: TTNI | P, time with progression before NI (4)

EAG comments: note that much of the company's information previously critiqued. For new data:

1. BRAIN registry has limited generalisability to NHS: unclear how patients selected, especially:

BRAIN study included people:	EAG comment
With ≥1 surgery 1 to 5 years prior	unclear what "prior" relates to → comparison of BRAIN and INDIGO "time from diagnosis to randomisation graphs" suggests different populations, although unclear meaning of "randomisation" in BRAIN study
Who weren't disease free 5 years after surgery	• Unclear how excluded and how many • People disease free after 5 years included in BRAIN study report • Limited applicability to NHS setting as: a) cannot predict who will progress within 5 years, b) vorasidenib's licence includes these people
In need of immediate treatment	• Excluded from INDIGO but no corresponding criterion stated in BRAIN (though excluded if had RT/CT within 1 year)

- No methods used to match cohorts or adjust for imbalances in prognostic factors: e.g. chromosomal 1p/19q co-deletion (associated with better prognosis): INDIGO 52%, BRAIN 32% (status unavailable for 43% population)

CT, chemotherapy, RT, radiotherapy

Key issue: TTNI | P, time with progression before NI (5)

EAG (cont.): Interpret supporting data for TTNI | P with caution:

1. Tumour shrinkage from baseline captured in model through direct correlation between tumour growth/volume and PFS → modelling further benefits risks double counting
2. Mean log tumour volume at PD similar for vorasidenib and placebo
3. Analysis suggest reduced tumour volume = longer TTNI | P with PD on vorasidenib in INDIGO. But:

- N at risk small (<N = 10 with >25% reduction in tumour volume) → smaller effect than suggested?
- No comparative data for placebo and change in tumour volume not in model → assess qualitatively

4. Link between reduced tumour volume and risk of malignant transformation not supported by INDIGO
5. Higher QoL with PD in placebo vs vorasidenib arm of INDIGO

Company did not fully explore best fitting vorasidenib curve for both arms as requested at ACM1

- Log-normal for vorasidenib arm appropriate → best fitting curve with lower time in PD than PF state → predicted survival falls between company and EAG ACM1 base cases (committee preference)
- Vorasidenib TTNI | P data may overestimate TTNI | P for placebo → people having active observation spend longer in PD state (2.3 years) than PF state (1.42 years), but no robust data to inform
- Limited evidence supporting 6-month average TTNI | P for active observation → applying different HRs leads to substantially different TTNI | P estimates

Base case: log normal for vorasidenib arm but unclear what HR should be applied for active observation

Scenarios: vary HR for active observation (1.0, 1.5, 2.0, 2.5, 3.0) using log normal, generalised gamma and exponential for vorasidenib arm (see supplementary appendix for parametric distributions 1 and 2)

ACM, appraisal committee meeting; HR, hazard ratio; N, number; PD, progressed disease, PF, progression free; PFS, progression free survival; TTNI, time to next intervention; TTNI | P, time to next intervention given progression; QoL, quality of life; tx, treatment

Key issue: TTNI | P, time with progression before NI (6)

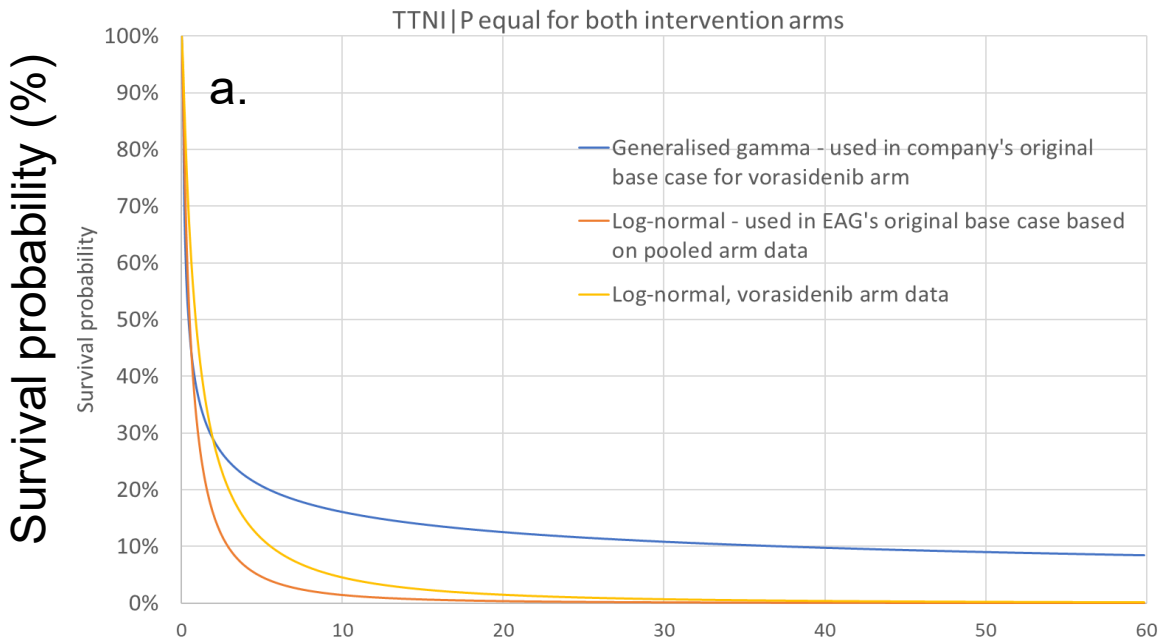
Life years in PD, off treatment health state using varying approaches

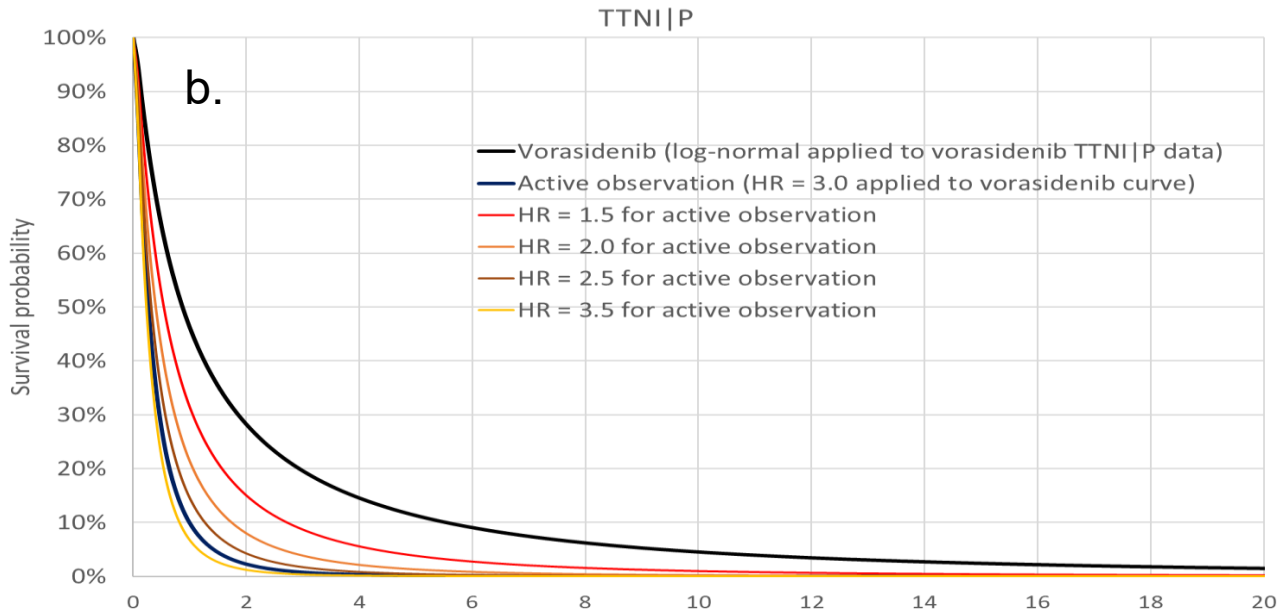
Analysis	Vorasidenib	Active observation
PFS, company and EAG base case ACM1 and 2, log normal	5.22	1.4
PD, off Tx (TTNI | P)		
Generalised gamma, fitted separately (Company base case ACM1)	8.58	4.44
Log normal, pooled (EAG base case ACM1)	1.21	1.25
New for ACM2:		
Log normal vorasidenib + HR 3.0 for placebo (Company base case)	2.19	0.43
EAG scenarios varying HR for active observation applied to log normal curve for vorasidenib		
Log normal vorasidenib for both arms (HR 1.0)	2.19	2.30
HR 1.5 for active observation		1.18
HR 2.0 for active observation		0.75
HR 2.5 for active observation		0.54
EAG scenarios varying HR for active observation applied to exponential curve for vorasidenib		
Exponential vorasidenib for both arms (HR 1.0)	1.22	1.26
HR 1.5 for active observation		0.83
HR 3.0 for active observation		0.39

ACM, appraisal committee meeting; HR, hazard ratio; PD, progressed disease, PFS, progression free survival;; TTNI | P, time to next intervention given progression; tx, treatment

Key issue: TTNI | P, time with progression before NI (7)

a) Comparison of company's updated analysis for vorasidenib arm and company and EAG base cases ACM1, b) Company's revised base case with alternative HRs for the active observation arm





Time (years)

- Which parametric curve best represents expected TTNI | P for LGG NHS population?
- Should a HR to be applied to the placebo arm (is there a benefit in TTNI | P for vorasidenib)?

% off treatment with PD:	Time (years)			
	5	10	20	30
Log-normal vorasidenib	11%	4.5%	1.5%	0.72%
HR = 3 for active observation	0.15%	0.01%	0%	0%

HR, hazard ratio; LGG, low grade glioma; PD, progressed disease; TTNI | P, time to next intervention given progression.
N.B. Company response to DG states 7% in vorasidenib arm off treatment with progressed disease at 20 years in error

Key issue: Modelling overall survival (1)

Company assumes PFS and TTNI benefits for vorasidenib translate to survival benefit

Background: No mature OS data for vorasidenib → only 1 death in INDIGO (placebo arm)

- Vorasidenib OS benefit in model comes from delaying time to BSC through better PFS/TTP and TTNI | P vs active observation
- Company's ACM1 base case had much larger OS benefit for vorasidenib vs EAG, driven by differences in TTNI | P approach
- Excess mortality from LGG applies only to BSC health state → supported by clinical experts at ACM1

Committee conclusion: company's approach to OS highly uncertain because used uncertain model inputs but may be acceptable for decision making

- Additional OS / TTNI | P data from INDIGO also hard to interpret due to crossover in placebo arm

Company: Evidence supports use of TTNI and PFS as surrogates for OS

PFS as surrogate for OS: Supported by:

1. Miller et al. (2016) in mIDH glioma (presented ACM1, see supplementary appendix) suggests shorter time to next progression and reduced OS after initial progression
2. Han et al. reported strong correlation between hazard ratios for PFS and OS in HGG ($R^2 = 0.92$*), with a Pearson correlation coefficient of 0.42^
3. Bhatia et al. 2024: link between tumour volume and OS: 1 natural logarithm tumour volume increase resulted in > 3-fold in risk of death in mIDH gliomas in active observation after surgery

* A R^2 value closer to 1 than 0 suggests a large percentage of the data fits the regression model, and the model is a better representation of the data.
^ A Pearson coefficient of 0 to +1 suggests a positive correlation (as one variable increases, the other also increases), with values closer to 1 showing better correlation
ACM1, appraisal committee meeting; BSC, best supportive care; HGG, high grade glioma; LGG, low grade glioma; mIDH, mutant isocitrate dehydrogenase; OS, overall survival; PFS, progression free survival; TTNI | P, time to next intervention given progression; TTP, time to progression

Key issue: Modelling overall survival (2)

Company provides data and justification to support surrogacy relationship

Company (cont.): 4. New post-hoc analyses of INDIGO data (full analysis set) supports predictive nature of tumour volume and growth rate for PFS, which is expected to correlate with OS:

- Longer PFS in people with slower vs faster tumour growth velocity
- Worse PFS at month 6 vs. baseline in people whose tumor volume increased vs. those whose tumor volume decreased
- Cox regression model showed HR for log tumour volume of 1.22 (p value 0.027) (i.e. 1 unit increase in log tumour volume increases the risk of progression by 22%)

TTNI as surrogate for OS: WHO G2 gliomas often indolent but always progressive → delaying RT/CT meaningful objective and TTNI pragmatic measure of disease control. Surrogacy supported by:

1. TTNI mechanistically linked to OS through dependence on disease progression (TTP or PFS) which drives therapeutic decision → clinically meaningful milestone
   - Established strong correlation between PFS and OS supports transitive relevance of TTNI (downstream of progression) to OS
2. EORTC 22845 and RTOG 9802 suggest RT (alone or with CT) provides comparable OS benefits whether administered early or delayed → postponing NI does not compromise OS
3. Blonski et al. (2022): 5 of 12 deaths in diffuse LGG treated with PCV + RT attributed to treatment-related neurotoxicity rather than tumour progression → suggests delaying TTNI can improve OS

CT, chemotherapy; HR, hazard ratio; G, grade; NI, next intervention; LGG, low grade glioma; OS, overall survival; PCV, Procarbazine, Lomustine, Vincristine; PFS, progression free survival; RT, radiotherapy; TTNI, time to next intervention; TTNI | P, time to next intervention given progression; TTP, time to progression

Key issue: Modelling overall survival (3)

EAG comments: some plausible relationship but new evidence does not resolve uncertainty for:

1. **PFS and OS**: but still uncertainty about translating benefit to G2 glioma:
- Miller at al. showed relationship between PFS2 and OS but INDIGO did not report PFS2
- Han et al. in HGG patients → unclear if transferable to LGG
- Bhatia et al and post hoc INDIGO analyses focus on relationship between tumour volume and growth rate, not PFS, with OS

2. TTNI | P and OS: Studies reported do not statistically assess TTNI | P and OS → instead inferred from "no statistically significant difference in OS" for delayed and immediate RT/CT after progression

- Blonksi et al. small sample size and not conclusive of surrogacy relationship
- TTNI | P from INDIGO still confounded by crossover in placebo arm
- Company acknowledge lack of conclusive evidence that TTNI | P is a surrogate for OS

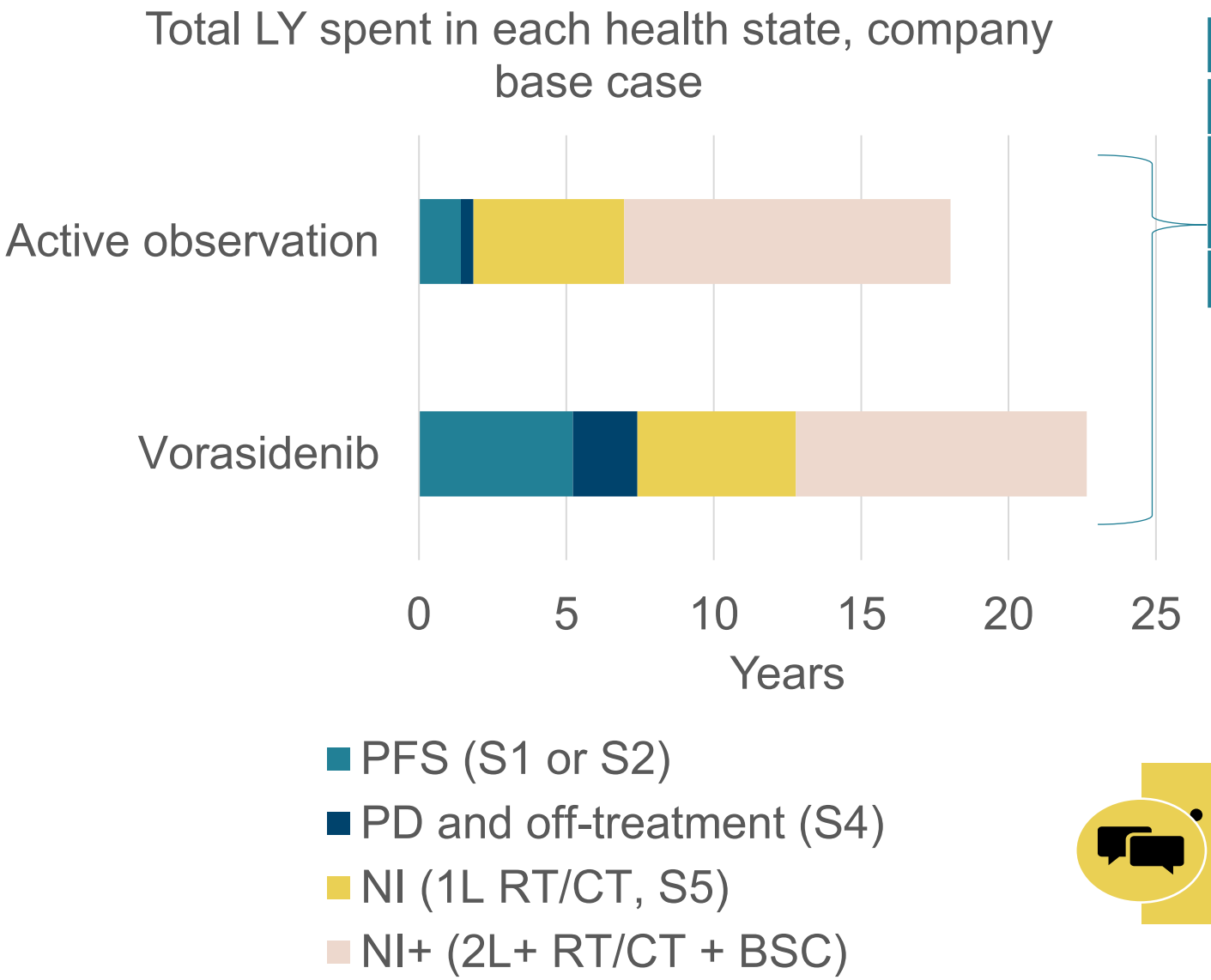
No relationship between PFS or TTNI | P and OS observed yet in INDIGO as only 1 death despite statistically significant difference in PFS vorasidenib vs active observation

Stakeholders: Web comments, SBNS, IBTA, ABTF:

- OS unrealistic to measure in short-term trials for progressive diseases:
  - Likely that only future OS data will be simple cohort studies → waiting for this would delay access to treatment unnecessarily. Lack of OS data should not preclude approval

ABTF, Astro Brain Tumour Fund; CT, chemotherapy; G, grade; HGG, high grade glioma; IBTA, International Brain Tumour Alliance ; LGG, low grade glioma; OS, overall survival; PFS, progression free survival; RT, radiotherapy; SBNS, Society of British Neurological Surgeons; TTNI | P, time to next intervention given progression

Key issue: Modelling overall survival (4)



	OS (LY)
Vorasidenib	22.66
Active observation	18.03
Difference	4.63

Removing TTNI | P benefit for vorasidenib (log normal curve for vorasidenib with HR = 1.0 for active observation) increases OS for active observation of 19.70 years (difference 2.96 years)

- Is the method and the OS benefit estimated robust and appropriate?

BSC, best supportive care; Ct, chemotherapy; LY, life years; NI, next intervention; OS, overall survival; PD, progressed disease; PFS, progression free survival; RT, radiotherapy; TTNI | P, time to next intervention given progression

Key issue: Health state utilities, subsequent treatments (1)

Company base case ACM2 uses updated INDIGO EQ-5D data

S1: PF, on tx
S2: PF, off tx
S4: PD, off tx
S5: On NI
S6: Off NI
S7: On NI+
S8: BSC

Background: Company model ACM1 used:

a) INDIGO EQ-5D-5L mapped to 3L for health states linked to initial treatment (S1-4)

b) Company vignette (general public) using EQ-5D for next intervention health states (S5 onwards)

- ❖ Company averaged on/off tx EQ-5D utilities, EAG preferred unadjusted values

Committee conclusion: large drop in utility from INDIGO to vignette values implausible. Requested alternative ways to model quality-of-life on subsequent treatments:

- Applying relative difference between utilities in the unadjusted EQ-5D vignette study to the value for glioma recurrence from TA23, temozolomide for recurrent malignant glioma (0.60)
- Consider alternative quality-of-life decrements moving from PF to PD (as values very similar)

Company: PF and PD health states (S1 – 4): Updated base case to include utility values from later data cut of INDIGO (March 2023) see supplementary appendix for full details

- Company justifies lower QoL for PD in vorasidenib arm vs placebo: average patient progressed on vorasidenib likely to have a poorer prognosis than average patient who may or may not have progressed on vorasidenib over the period of trial follow up

Subsequent treatment health states (S5 onwards): HRQoL drops when move from S4 to S5 because of a) RT/CT side effects and b) symptoms of progressive disease

ACM1, appraisal committee meeting; CT, chemotherapy; HRQoL, health related quality of life; NI, next intervention; OS, overall survival; PD, progressed disease; PF, progression free; RT, radiotherapy; TA technology appraisal; QoL, quality of life

Key issue: Health state utilities, subsequent treatments (2)

Company explores alternative approaches to health state utilities for subsequent treatments

Company (cont.): Explored alternative approaches to generate more plausible utilities for subsequent treatments:

1. Using 0.6 for S5 → glioma recurrence in TA23:

- Interpret with caution: TA23 included people with recurrent malignant glioma and EAG did not consider utilities reliable
- Utilities using TA23 value for S5, on NI (committee preferred approach) lack face validity:
  - ❖ Resulting utility for S6 (off tx) higher than baseline from INDIGO (0.742) → implausible given progressive condition and neurocognitive decline from RT/CT

Health state		Utility
S1, S2: PF on and off Tx (new DCO)		0.742
S4, PD, off Tx		0.720
	TA23 for S5	**TA23 for S6 (scenario)**
S5: On NI	**0.600**	0.429
S6: Off NI	0.840	**0.600**
S7: On NI+	0.390	0.279
S8: BSC	0.630	0.450

Scenario: INDIGO utilities for PF and PD, with TA23 (0.6) for S6, off NI. Other utilities calculated based on relative difference to S6 in EQ-5D unadjusted vignette

2. Based on TA977 (Dabrafenib with trametinib for BRAF V600E mutation-positive glioma)

- TA in children but uses adult utilities
- ***Scenario***: new utilities for all health states generated based on TA977 values. Assumes:
  - ❖ baseline utility ~ 0.90 with disutilities: -0.155 for LGG, -0.06 for each progression, -0.187 for RT/CT
  - ❖ Number of progressions: S1 & S2: 0; S4: 1; S5: 2; S6: 3; S7: 5; S8: 6

Base case: maintains preference for vignette EQ-5D values → single source derived specifically for TA

BSC, best supportive care; CT, chemotherapy; DCO, data cut off; LGG, low grade glioma; NI, next intervention; PD, progressed disease; PF, progression free; RT, radiotherapy; TA technology appraisal; Tx, treatment; QoL, quality of life. TA23, temozolomide for recurrent malignant glioma

Key issue: Health state utilities, subsequent treatments (3)

Stakeholder support low QoL with RT/CT and highlight long-term side effects

EAG comments:

1. INDIGO utilities: Appropriate to include updated utilities but company's explanation of higher QoL in placebo arm lacks face validity → suggests people who progress on vorasidenib have poorer prognosis vs progression on placebo
2. Company's alternative approaches for subsequent treatments do not resolve uncertainty:
   a. Agree committee approach to applying TA23 utility leads to implausibly high value for NI, off Tx
      - Linked to vignette issues, no description of PD/PF states anchoring vignette + INDIGO utilities
   b. Concerns about transferability of TA977 utility values:
      - Sourced from Vera et al (2023) using US value set for EQ-5D and US population
      - Decrements based on progression events, not lines of treatment (as modelled)
      - Subsequent lines are a mix of LGG, HGG and secondary HGG (malignant transformation)
   c. Notes company's utility values based on TA977 and TA23 (adjusted) similar to unadjusted vignette EQ-5D values

Base case: As per company at ACM2 (updated INDIGO utilities for PF and PD + unadjusted EQ-5D utilities for subsequent treatments)

ACM, appraisal committee meeting; HGG, high grade glioma; LGG, low grade glioma; NI, next intervention; PD, progressed disease; PF, progression free; TA technology appraisal; Tx, treatment; QoL, quality of life. TA23, temozolomide for recurrent malignant glioma

Key issue: Health state utilities, subsequent treatments (4)

Stakeholder support low QoL with RT/CT and highlight long-term side effects

Stakeholders: BNOS, ABTF, SBNS, IBTA, The Brain Tumour Charity, Patient expert, Web comments:

RT/CT: NICE underestimated cognitive, social and QoL impacts, especially of RT to the brain:

1. Short-term: fatigue, hospital visits or admissions, inability to work, disruption to family life
2. Medium-term: persistent cognitive and emotional effects even after treatment ends
3. Long-term: cognitive decline, radiation necrosis, and transformation to HGG or development of secondary malignancies (both can shorten life)

- Plausible:
  - Sudden drop in QoL when starting NI, due to immediate effects of RT/CT
  - QoL after RT/CT would likely improve, but may still be badly affected by long-term side effects → not clearly addressed in modelling
- Impact on carers: mental health burden, economic strain and social disruption for carers/families from RT/CT side effects. RT especially burdensome for carers → may reduce work to provide support/transport

Active observation: "Constant fear" and anxiety on active observation between scans not modelled:

- Trauma for parents\carers watching child, partner or family member deteriorate before next scan
- Limits patients' quality of life and ability to plan long term

ABTF, Astro Brain Tumour Fund; BNOS, British Neuro Oncology Society; CT, chemotherapy; HGG, high grade glioma; IBTA, International Brain Tumour Alliance; QoL, quality of life; RT, radiotherapy; SBNS, Society of British Neurological Surgeons

Key issue: Health state utilities, subsequent treatments (5)

Summary of potential utility value sources

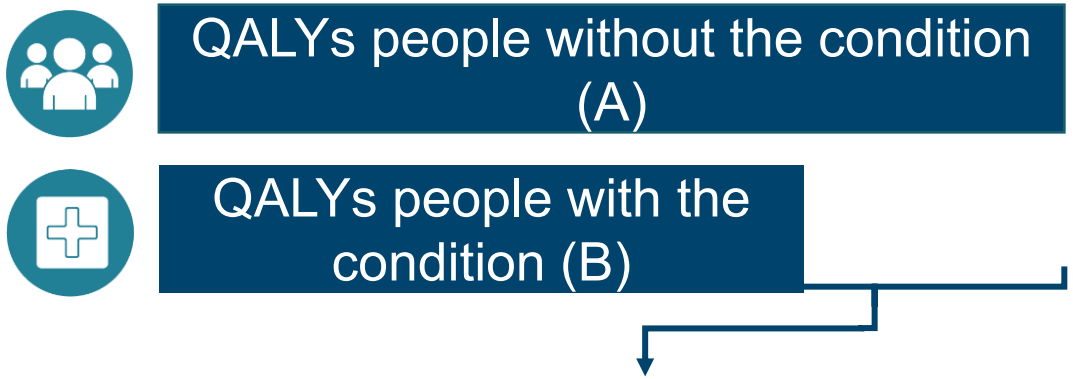
	Regression model fitted to INDIGO EQ-5D-5L			TA977 based values (New)
Health state	**Sep 2022 DCO (ACM1)**	**March 2023 DCO (New)**		
S1: PF, on tx	0.737	0.742		0.745
S2: PF, off tx	0.737	0.742		0.745
S4: PD, off tx	0.728	0.720		0.685
Health state	**Vignette EQ-5D adjusted (ACM1)**	**Vignette EQ-5D unadjusted (ACM1)**	**TA23 company adjusted (New)**	
S5: On NI	0.48	0.40	0.429	0.438
S6: Off NI	0.48	0.56	0.600	0.565
S7: On NI+	0.34	0.26	0.279	0.258
S8: BSC	0.34	0.42	0.450	0.385
Base case?	Company ACM1	Company and EAG ACM2	Company scenario	Company scenario

What are the most appropriate health state values?

ACM, appraisal committee meeting; NI, next intervention; PD, progressed disease; PF, progression free; TA technology appraisal; Tx, treatment;. TA23, temozolomide for recurrent malignant glioma, TA977, Dabrafenib with trametinib for BRAF V600E mutation-positive glioma

QALY weightings for severity (1)

Severity modifier calculations and components:



Health lost by people with the condition:

- Absolute shortfall: total = A – B
- Proportional shortfall: fraction = (A – B) / A
- *Note: The QALY weightings for severity are applied based on **whichever of absolute or proportional shortfall implies the greater severity**. If either the proportional or absolute QALY shortfall calculated falls on the cut-off between severity levels, the higher severity level will apply

QALY weight	Absolute shortfall	Proportional shortfall
1	Less than 12	Less than 0.85
X 1.2	12 to 18	0.85 to 0.95
X 1.7	At least 18	At least 0.95

Technical team: NICE health technology evaluations: the manual states that *"Absolute and proportional shortfall calculations should include discounting at the reference-case rate (3.5%)."*

QALY, quality-adjusted life year

QALY weightings for severity (2)

QALY, quality-adjusted life year; TTNI | P, time to next intervention give progression

Background: Company updated base case (using 3.5% discount rate) meets criteria for applying 1.2 x severity weight

All company and EAG scenarios meet 1.2 x severity weight except:
- No TTNI | P benefit for placebo, using generalised gamma extrapolation for the vorasidenib arm (no severity weight applies)

Baseline characteristics used in company's calculation of QALY shortfall

Factor	Value
% female	44%
Starting age	40 years

Base case ACM2 (using 3.5% discount rate)	QALYs without condition (trial population characteristics)	QALYs with condition on current treatment	Absolute QALY shortfall (must be >12)	Proportional QALY shortfall (must be >0.85)	Severity weight applied
Updated company base case	18.65	5.33	13.32	0.71	X1.2
EAG scenario (log normal vorasidenib data for both arms)	18.65	6.11	12.54	0.67	X1.2

Is it appropriate to apply a QALY weighting for severity?

Uncaptured benefits for vorasidenib (1) - Stakeholder comments

Seizure Control: Vorasidenib showed 64% reduction in seizure rates vs placebo in INDIGO.

- Seizure reduction improves quality of life, independence, and reduces fear before and during seizures
- Patient/clinical experts indicate % having vorasidenib seizure free for 1 year - regained ability to drive
- Reduced NHS burden and costs from seizure related hospital admissions, injuries or resuscitation

NICE Technical team: *Reduced seizures for vorasidenib vs. active observation modelled as cost & resource use (ratio of rates vs placebo from INDIGO: 0.36). Seizures in vignette health state descriptions*

Tumour shrinkage: not accounted for appropriately → benefit not achieved by active observation

Wider value: delays disability, preserves independence, productivity, and family mental health

Impact on carers: less support needed → improved quality of life on vorasidenib

Mental health and psychological stability: Delaying progression reduces anxiety and depression

- ≥75% with brain tumours experience behavioural health disorder as a result of diagnosis

Socioeconomic: people having vorasidenib likely work (and pay taxes) longer

Avoidance of RT/CT side effects: including cognitive dysfunction, and need for corticosteroids, plus costs for rehabilitation and concomitant medication

Vorasidenib likely benefits people with no radiological residual disease: diffuse astrocytoma's always leave residual tumour even if radiologically undetectable

Innovation: first treatment to cross the blood brain barrier

CT, chemotherapy; RT, radiotherapy

Uncaptured benefits for vorasidenib (2)

Company: unclear how committee accepted higher level of uncertainty for uncaptured benefits below

Cost effectiveness threshold should be re-examined in light of new analyses and uncaptured benefits

- Similar uncertainties in TA977 (comparative efficacy, PFS extrapolations, treatment duration and utilities). Acceptable ICER ~£30,000 due to unmet need, reduction in hospital visits and low decision risk due to rarity

	Company's uncaptured benefit	EAG: uncaptured benefit is:
Driving	Median PFS not reached in INDIGO, so plausible that some people having vorasidenib seizure free for 1 year (so have ability to drive)	Uncertain: Median PFS being unreached does not translate into seizure-freedom
Productivity loss	Company RWE from Danish administrative registers shows over 50% with LGG not working when on RT/CT = productivity loss per patient of €3,750	Uncertain: Agree large economic productivity impact but people who progress on vorasidenib still have RT/CT (not a comparator to active observation)

CT, chemotherapy; ICER, Incremental Cost-Effectiveness Ratio; LGG, low grade glioma; PFS, progression free survival; RT. radiotherapy; RWE, real world evidence; TA technology appraisal; Tx, treatment;. TA977, Dabrafenib with trametinib for BRAF V600E mutation-positive glioma

Uncaptured benefits for vorasidenib (3)

Treatment burden

Company's uncaptured benefit	EAG:
New company patient pathway study captures burden of care: • Poor QoL on active observation → uncertainty linked to risk of recurrence between scans, despite perceived benefits (return to work, exercise and travel) ❖ difficult to plan ahead/find purpose, especially study or work ❖ carers experience anxiety and frustration due to lack of "proactive" treatment plan • RT/CT: many with mIDH gliomas survive long enough for treatment-induced physical & cognitive deficits to manifest later ❖ RT/CT burdensome for patients and carers because of: ▪ side effects and allergic reactions (can halt treatment) ▪ logistical difficulties of hospital trips and associated travel expenses, especially if cannot drive due to seizures • Carers: symptoms & diagnosis cause profound emotional distress for carers (panic, fear, trauma); personality changes difficult to witness ❖ Practical challenges: managing increased household responsibilities and adjusting work hours to provide constant care and mitigate financial burden	Agree potential benefits of active observation vs RT/CT but Burden of Care study did not include people having vorasidenib • no exploration of benefit or side effect profile for vorasidenib so unclear how impacts patient pathway

CT, chemotherapy; mIDH, mutant isocitrate dehydrogenase; QoL, quality of life; RT, radiotherapy

Uncaptured benefits for vorasidenib (4)

	Company's uncaptured benefit	EAG: uncaptured benefit is:
Treatment effect	INDIGO used older WHO classification, likely included some HGG under new criteria → HGG = faster disease progression → underestimates vorasidenib's treatment effect in model	Highly uncertain: % misdiagnosed uncertain. Older WHO criteria also used to classify progression.
Paediatric patients	Not fully considered. Licence includes people age 12+ (incidence age 2-14: 0.5 per 100,000) so some children will have vorasidenib in NHS. Delayed RT/CT in children important to: ❖ avoid cognitive effects on brain and improve skull growth in adolescent years ❖ continue education → huge uncaptured societal benefit with long term returns	Highly uncertain: Agree delaying RT/CT in this population reduces long term effects of RT/CT on brain development but contribution to future workforce relies on long term progression and OS → not supported by mature data from INDIGO (which only included 1 person <18 years old)

- Are there uncaptured benefits relevant for decision making?
- What proportion of people with LGG are aged between 12 and 18 years old?

CT, chemotherapy; HGG, high grade glioma; LGG, low grade glioma; OS, overall survival; RT. radiotherapy; WHO, World Health Organisation

Summary of company and EAG base case assumptions

Assumption	Committee preferred ACM1	Company base case ACM2	EAG base case ACM2
TTNI | P curves	Explore alternative ways to model TTNI|P including vorasidenib data for both arms	Vorasidenib INDIGO data (log normal) with a HR of 3.0 applied to active observation arm	Vorasidenib INDIGO data (log normal) → unclear on appropriate HR to apply for placebo
Overall survival	Highly uncertain due to use of placebo data for TTNI | P	• Maintains use of PFS and TTNI | P as proxy for OS but removed placebo data from TTNI | P calculations	As per company's approach
EQ-5D utilities values	Explore alternative methods for subsequent treatment lines	• PF and PD: updated INDIGO utilities (March 2023) • Subsequent treatments: unadjusted EQ-5D vignette from ACM1	As per company's approach

ACM, appraisal committee meeting; OS, overall survival; HR, hazard ratio; PD, progressed disease; PF, progression free; PFS, progression free survival; TTNI | P, time to next intervention given progression

Cost-effectiveness results

Summary of company base case

Cumulative cost-effectiveness deterministic results, company's base case, with PAS price for vorasidenib

Name	Option	Total costs	Total QALYs	Inc. Costs	Inc. QALYs	ICER (£/QALY)
Committee preferred assumptions (revised PAS for vorasidenib)	Active observation	[redacted]	6.11			
	Vorasidenib	[redacted]	7.49	[redacted]	1.65	[redacted]
+ Updated INDIGO DCO (March 2023) for utility values + unadjusted vignette values	Active observation	[redacted]	6.11			
	Vorasidenib	[redacted]	7.50	[redacted]	1.67	[redacted]
+ HR = 3.0 for active observation [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]	2.69	[redacted]

DCO, data cut off, HR, hazard ratio; PAS, patient access scheme; QALY, quality adjusted life-year; ICER, incremental cost-effectiveness ratio;

EAG scenario analyses

EAG's deterministic scenario analysis varying the HR for active observation, PAS price for vorasidenib

Scenario	Option	Total costs	Total QALYs	Inc. Costs	Inc. QALYs	ICER (£/QALY)
Scenarios varying HR for active observation applied to vorasidenib TTNI | P with log-normal extrapolation						
HR = 1.0 (no benefit for vorasidenib)	Active observation	[redacted]	6.11			
	Vorasidenib	[redacted]	7.50	[redacted]	1.67	[redacted]
HR = 1.5	Active observation	[redacted]	5.66			
	Vorasidenib	[redacted]	7.50	[redacted]	2.20	[redacted]
HR = 2.0	Active observation	[redacted]	5.48			
	Vorasidenib	[redacted]	7.50	[redacted]	2.42	[redacted]
HR = 2.5	Active observation	[redacted]	5.38			
	Vorasidenib	[redacted]	7.50	[redacted]	2.54	[redacted]
HR = 3.0 (company base case)	Active observation	[redacted]	5.33			
	Vorasidenib	[redacted]	7.50	[redacted]	2.60	[redacted]

HR, hazard ratio; PAS, patient access scheme; QALY, quality adjusted life-year; ICER, incremental cost-effectiveness ratio; TTNI | P, time to next intervention given progression

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

- ❑ Recap to background and key issues
- ❑ Summary of consultation comments
- ❑ Company's new evidence
- ✓ **Other considerations**
- ❑ Summary

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Managed access

Background: ACM1: committee concluded, based on evidence presented, vorasidenib did not meet managed access criteria:

- Preferred ICER unknown but likely above preferred threshold of £20,000 per QALY → no plausible potential for cost effectiveness
- Available data sources (updated INDIGO DCO, early access scheme, existing registries) would not resolve key issues of TTNI | P and OS benefits for vorasidenib and subsequent treatment utilities
- MAA team ACM1: may be value in collecting data from SACT/ RTDS to resolve TTNI and TTNI | P but will need to link databases to obtain useful data (full MAA insights in supplementary appendix)

Company: disagree uncertainties cannot be resolved in CDF

- Updated INDIGO data cut in May 2028 could provide data for PFS and TTNI in vorasidenib arm → March 2023 DCO: 54 PFS and 28 TTNI events in vorasidenib arm
  - ❖ CDF entry could be until 2029, or longer if more mature NHS RWE (especially TTNI) needed
- Would allow more time to explore RWE datasets, including registries from UK and other countries, to provide TTNI data for active observation and utility data for modelled health states
- CDF could collect data on 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)
- Named patient supply also includes 18 months follow up → data on TTNI and treatment duration

ACM, appraisal committee meeting; CDF, cancer drug fund; DCO, data cut off; MAA, managed access arrangement; OS, overall survival; RT, radiotherapy; RTDS, Radiotherapy Data Set; RWE, real world evidence; SACT, Systemic Anti-Cancer Therapy; TTNI, time to next intervention; TTNI | P, time to next intervention given progression

Managed access

Stakeholders: ABTF, BNOS, Patient experts: Recent evaluations of rare cancers (e.g. TA658) routed to CDF despite considerable uncertainties (including OS)

- Real-world access and further data collection in CDF can generate data on QoL, cognitive outcomes, long-term effect
- Managed access would align with NICE's own principles of supporting innovation, reducing inequalities, and encouraging data collection to resolve uncertainty.
- Could collect data on seizure frequency to support uncaptured benefit

EAG comments: Later INDIGO data cut would provide more evidence that could potentially resolve some uncertainties but crossover in placebo arms means uncertainties will remain in time to RT/CT and OS data (interpretation also challenged by heterogeny in subsequent treatment used)

NICE MAA team, ACM2: may be value in further data collection in CDF but limitations with data:

- Unblinding of trial and cross over to vorasidenib arm
- SACT, RTDS and Blueteq data is available to help resolve uncertainties related to TTNI and the TTNI | P but usefulness within timeframe of MAA uncertain → committee discussion needed to make sure timeframe of data collection appropriate

- Should managed access be considered for vorasidenib?

ABTF, Astro Brain Tumour Fund; ACM, appraisal committee meeting; BNOS, British Neuro Oncology Society; CDF, Cancer Drugs Fund; CT, chemotherapy; OS, overall survival; QoL, quality of life; RT, radiotherapy; RTDS, Radiotherapy Data Set;; SACT, Systemic Anti-Cancer Therapy; TTNI, time to next intervention; TTNI | P, time to next intervention given progression. TA658: Isatuximab with pomalidomide and dexamethasone for treating relapsed and refractory multiple myeloma

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

- ❑ Recap to background and key issues
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- ❑ Other considerations
- ✓ **Summary**

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Key issues for discussion

KEY: Change from base case ICER: small: < £5,000, moderate: £5,000 to £10,000, large: > £10,000

Issue	Impact
Appropriate data source for TTNI |P and resulting duration of time off treatment with progressed disease	Large
Surrogacy relationship for OS benefit	Unknown
Plausibility of health state utility values from vignette	Small
Uncaptured benefits in the modelling	Unknown
Appropriate severity weighting	N/A
Appropriateness of managed access	N/A

CT, computed tomography; ICER, incremental cost-effectiveness ratio; OS, overall survival; TTNI I P, time to next intervention given progression

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

Supplementary appendix

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Background: IDH1/IDH2-mutant astrocytoma & oligodendroglioma [48]

- Types of glioma → brain tumour that originates in glial cells

Classification: appraisal focuses on grade 2 astrocytoma & oligodendroglioma:

1. low grade glioma (LGG): Grade 1 or 2, not currently growing or grow slowly → limited symptoms
2. high grade glioma (HGG): Grade 3 or, for astrocytoma, 4, fast-growing

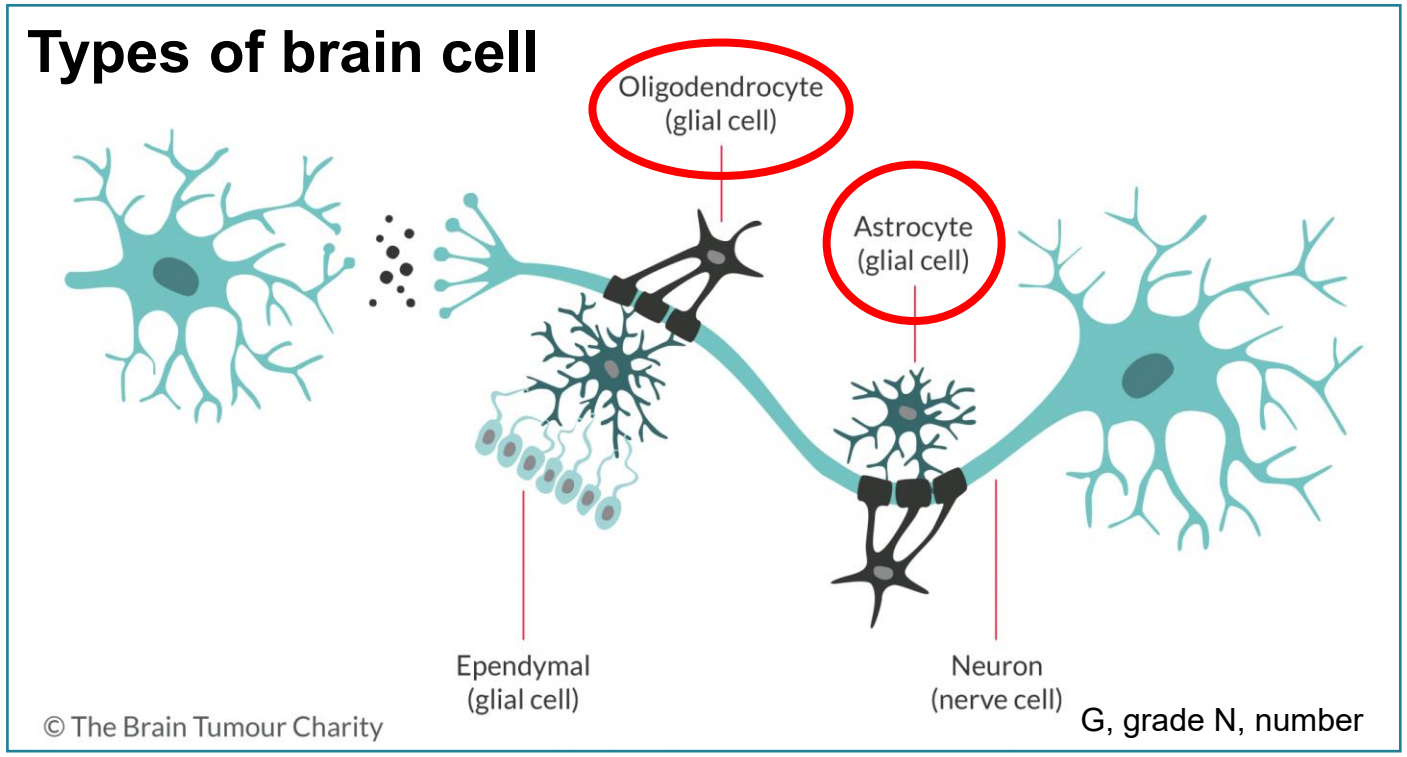
- ~70% LGG may progress into HGG or become malignant within 10 years
- Key genetic alterations in gliomas include isocitrate dehydrogenase (IDH1 and 2) mutations and 1p/19q co-deletion → both generally associated with better prognosis than wild-type

Epidemiology:

	Incidence per 10,000 people in England*	N in UK
Oligodendroglioma	~0.5	~1,440
Astrocytoma	~1.12	~4,500

- IDH mutations: ~ 80% G2 or 3 LGG

Symptoms: headaches, seizures, difficulty thinking/remembering, changes in vision **Median adult survival after diagnosis^:** oligodendroglioma (G2): >5 years, astrocytoma (G1 and 2): ~7 years



Source: *Wanis, H.A. et al. (2021), ^The Brain Tumour Charity

Link to main deck: Technology

Further stakeholder comments

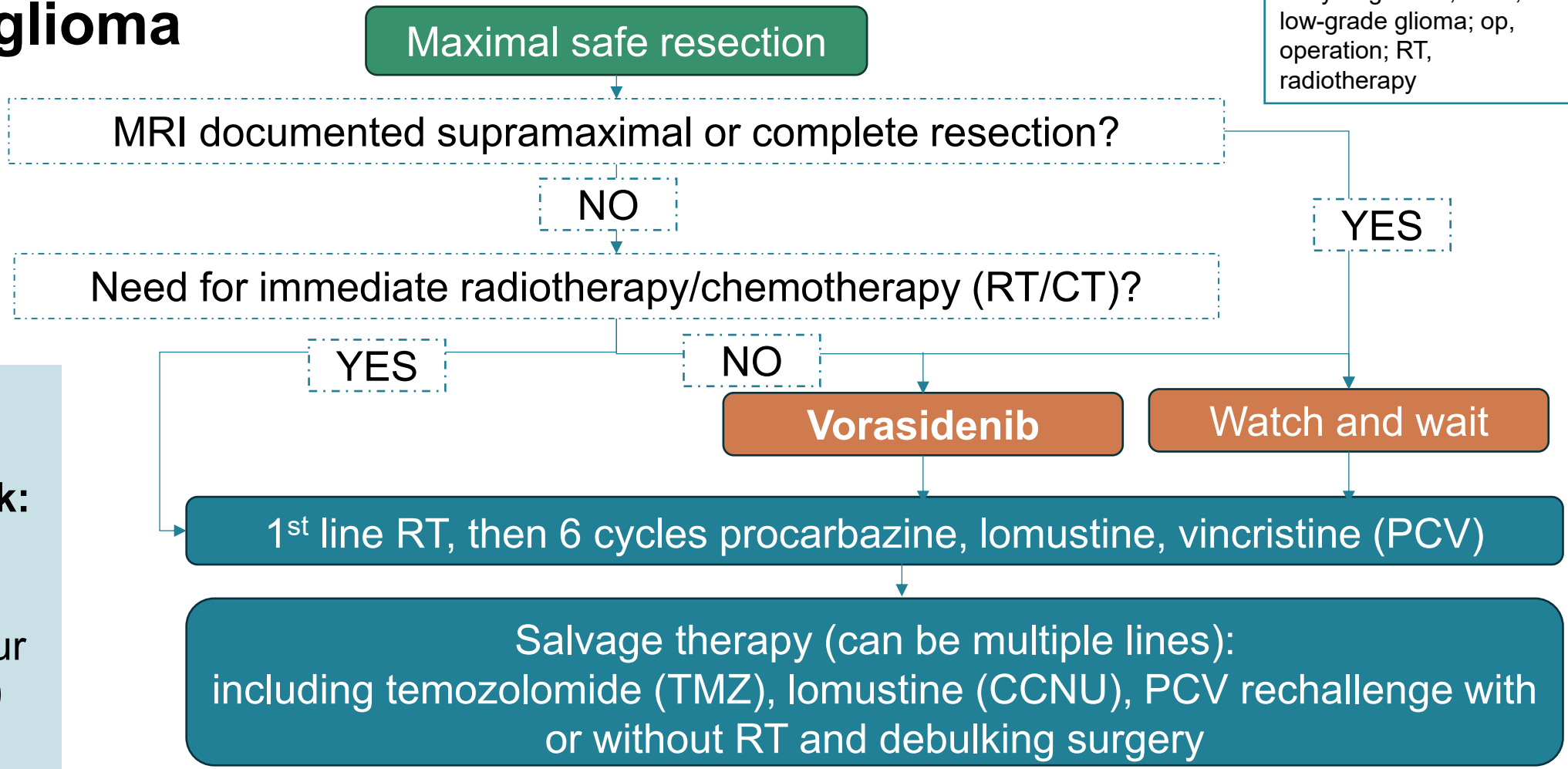
Theme	Comments
INDIGO trial	• **Population:** Appropriate to exclude people with little to no radiological disease who are unlikely to progress within trial follow up period • **Outcomes**: current classification based on histology, but cumulative copy number variation (CNV) and CDKN2A/B locus changes also predict outcomes — retrospective analysis could offer deeper insights.
Pathway and treatments	• Surgery associated with lasting effects (paralysis, cognitive decline, disfigurement, infection risk) • Care across LGG pathway insufficient, especially mental health & post treatment follow up • Treatment of symptoms can also affect quality of life
Cost effectiveness	• NICE should consider if subgroups within this population do reach the predetermined limit • Recommendations based purely on monetary value of treatment, rather than clinical evidence • Negative recommendation risks potential deterrent of pharma investment and delaying access to transformative therapies • Committee applied a standard cost-effectiveness threshold with minimal flexibility for a rare condition, contradictory to NICE health technology evaluations: the manual
Vorasidenib	• ~40% of patients require weekly blood tests due to liver function abnormalities • Early vorasidenib use supports independence, employment, and family life by postponing aggressive treatments

CDKN2A/B, cyclin-dependent kinase inhibitor 2A/B; LGG, low grade glioma;

Link to main deck: Summary of consultation comments

Treatment pathway: G2 IDH1/IDH2-mutant astrocytoma & oligodendroglioma

CT, chemotherapy; G, grade; IDH, isocitrate dehydrogenase; LGG, low-grade glioma; op, operation; RT, radiotherapy

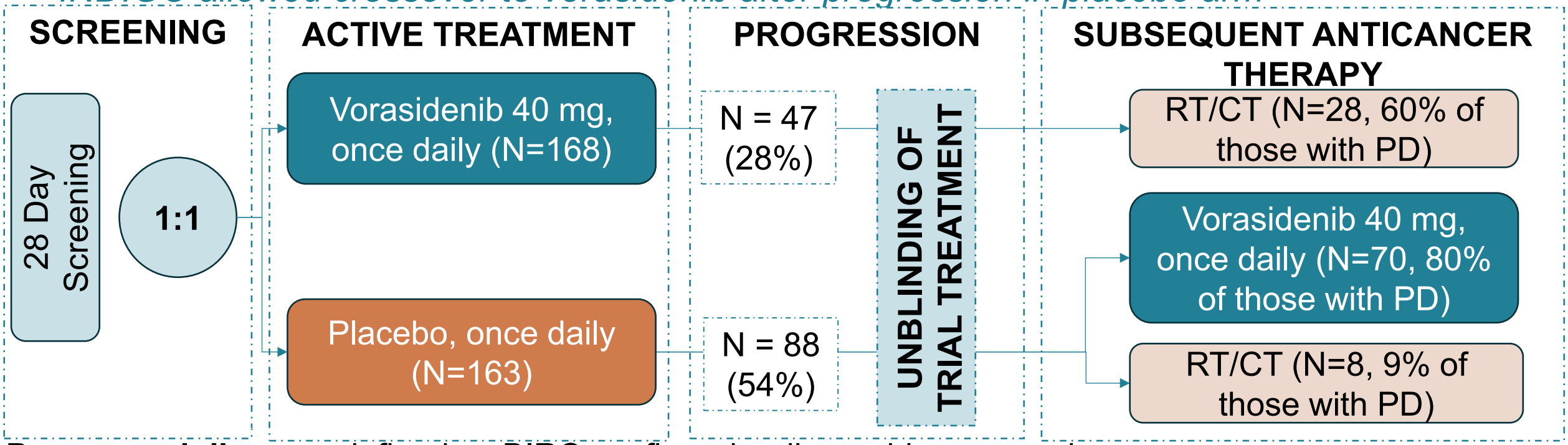


Watch and wait favoured if low progression risk: minimal post-op tumour volume, low pre-op tumour growth, under 40 years old

Clinical expert: treatments for LGG non-curative → aim to slow tumour growth or progression and delay time to next intervention

Key clinical trial: INDIGO trial design

INDIGO allowed crossover to vorasidenib after progression in placebo arm



Progressed disease: defined as BIRC confirmed radiographic progression

Vorasidenib withdrawal criteria: confirmed PD; unacceptable toxicity; need for CT, RT or anticancer therapy; pregnancy

- Inclusion criteria: ≥12 years old, no high-risk features, ≥1 surgery for glioma (last surgery 1 to 5 years from randomisation) no other anti-cancer therapy, measurable, non-enhancing disease on MRI (≥1 target lesion measuring ≥1 cm x ≥1 cm) confirmed by blinded review
- Stratified by: 1p/19q status (co-deleted or non-co-deleted), baseline tumour size (longest diameter ≥2 cm or <2 cm)

BIRC, blinded independent review committee; CT, chemotherapy; LGG, low-grade glioma; mg, milligram; MRI, Magnetic Resonance Imaging; N, number; PD, progressed disease; RT, radiotherapy. Link to main deck: Summary of appraisal, clinical effectiveness

INDIGO trial: Key clinical outcomes

Results suggest vorasidenib improves PFS compared to placebo; crossover to vorasidenib biased TTNI outcome

BIRC assessed PFS: data cut-off March 2023 (ad-hoc analysis)	Vorasidenib N = 168	Placebo N = 163
N events, %	54 (32)	104 (64)
Median PFS, months (95% CI)	NE (22.1, NE)	11.4 (11.1, 13.9)
HR (95% CI)	0.34 (0.23, 0.50)	
P-value	0.00000000013	
TTNI (March 2023)		
Event	28 (17%)	78 (48%)
Median, months (95% CI)	NE (NE, NE)	20 (18, 27)
HR (95% CI)	0.25 (0.16, 0.40), p<0.05	
Subsequent anticancer therapy (March 2023)		
Vorasidenib	N/A	70 (43%)
Other	28 (17%)	8 (5%)

Note: 90% of people having next intervention in placebo arm had vorasidenib

BIRC, blinded independent review committee; CI, confidence interval; FAS, full analysis set; N, number; NE, not evaluable; HR, hazard ratio; PFS, progression free survival; PD, progressed disease; TTNI, time to next intervention. Link to main deck: Summary of appraisal, clinical effectiveness

INDIGO trial: Other key clinical outcomes

Outcome	Sep 22	Mar 23	Vorasidenib N = 56	Placebo N = 67	In model?
Objective response rate*, n (%)		✓	12% (7%, 18%)	3% (1%, 6%)	
Odds ratio (95% CI)				5 (2, 17)	
Specific response rates	✓		High rates stable disease across arms (vorasidenib 83%, placebo 88%). Vorasidenib higher rate of minor response (10% vs 3%) and lower rate of PD (6% vs 9%). 0% complete response in both arms.		
Mean tumour volume change every 6 months (95% CI)	✓		-2.5% (-4.7%, -0.2%)	13.9% (11.1%, 16.8%)	
Seizures		✓	64% lower seizure rate with vorasidenib vs placebo: ratio of rates **0.36** (95% CI 0.14, 0.89; P= 0.026 → not clinically meaningful).		✓
Neurocognitive function	✓		No changes suggesting treatment effect in psychomotor function, attention, executive function, verbal learning, working memory		
N with malignant transformation (EAG requested at clarification)		✓	6 (4%). Median onset 44 months from diagnosis	2 (1%). Median onset 25 months from diagnosis	
HRQoL	✓		No significant differences between treatment groups for **EQ-5D-5L** or FACT-Br (Functional Assessment of Cancer Therapy – Brain).		✓

*Best overall response of CR, PR, or MR assessed by Investigator and BIRC using modified RANO-LGG criteria. **Bold** = in model.

BIRC, blinded independent review committee; CI, confidence interval; CR, complete response; HRQoL, health related quality of life; N, number; mRANO-LGG, modified Response Assessment in

REACP ACM1: Generalisability of INDIGO trial to NHS

Anticipated MA wider than trial population

Background: INDIGO trial:

- Only included people with prior surgery between 1 and 5 years before randomisation
- Excluded people with: a) high-risk features (uncontrolled seizures, brain-stem involvement, tumour related functional or neurocognitive deficits) b) little to no residual disease

Company: Restricted time to surgery to ensure enrolled population sufficiently similar for robust assessment of radiographic PD → will not apply in clinical practice.

EAG comments: vorasidenib may not be as effective in wider LGG NHS population vs. trial

- People with surgery within 1 year may have worse outcomes → less stable disease
- People with little or no residual disease may have better prognosis than trial participants
- PFS subgroup analyses suggest vorasidenib may be less effective for smaller baseline tumours

Clinical expert 1: interpret INDIGO results with caution: a) no OS benefit yet, b) may be differences in extent of surgery and tumour location, c) no evidence for use directly after surgery, d) max eligible tumour volume unknown, e) N=1 under 18 and N=3 ≥65 years old, f) neurocognitive effects unknown.
Clinical expert 2: INDIGO reflects UK clinical practice and aligns with real world evidence

LGG, low grade glioma; N, number; OS, overall survival; PD, progressed disease; PFS, progression free survival

RECAP ACM1: Outcomes in INDIGO trial

Clinical relevance of PD and TTNI outcomes in INDIGO may not be generalisable to NHS

Background: Key clinical outcomes in the INDIGO trial included:

- Progressed disease (PD) assessed using modified (m)RANO-LGG criteria (imaging only)
- Time to next intervention (TTNI): randomisation to 1st subsequent anticancer therapy

Company: Clinical deterioration subjective → removed from RANO-LGG to minimise bias

- TTNI appropriate proxy for time to RT/CT (next treatment used).

EAG: INDIGO population stable with predominantly non-enhancing LGG with slower tumour-growth than expected in clinical practice

RANO-LGG: EAG's clinical advisors: clinical deterioration assessed in NHS with imaging to inform progression. More likely to start RT/CT in clinical practice vs INDIGO trial.

- Only ~50% with PD in vorasidenib arm had subsequent treatment using mRANO-LGG criteria → no clinical deterioration = less willing to start CT/RT after vorasidenib (avoid neurocognitive side effects)?
- No neurocognitive function or HRQoL improvements for vorasidenib → PD results clinically relevant?

***TTNI*:** Bias created by crossover: 90% having NI in placebo arm had vorasidenib

- Easier decision to start vorasidenib in placebo arm than RT/CT in vorasidenib arm
- Placebo arm: time to vorasidenib = proxy for time to RT/CT in model → inappropriate as vorasidenib not available on NHS
- INDIGO data immature: little TTNI data for vorasidenib as delayed PD vs placebo

CT, chemotherapy; HRQoL, health related quality of life; LGG, low-grade glioma; (m)RANO-LGG, modified Response Assessment in Neuro-Oncology for LGG; NI, next intervention; PD, progressed disease; RT, radiotherapy; TTNI, time to next intervention

RECAP ACM1: How company incorporated evidence into model

INDIGO data for initial treatment effectiveness and utilities, excess mortality in BSC state only

Input	Assumption and evidence source
Baseline	INDIGO baseline characteristics
Efficacy	• Before progression: INDIGO PFS • After progression: INDIGO TTNI | P, multiple literature sources • Opt out rate to BSC prior to next intervention: assumption (5%)
Utilities	INDIGO trial EQ-5D for PF and PD, EQ-5D vignette for subsequent treatment lines
Costs	No administration costs except for bevacizumab Seizure management costs increase 25% on starting NI or BSC One off costs for debulking surgery (when start 1L & 2L+ NI) and palliative care
Resource use	Healthcare visit frequency: Boele et. al. (2020) Seizures: rate from INDIGO, % hospitalised from clinical expert opinion Rate of debulking surgery: Brown et. al. (2022)
Subsequent treatments	Equal across arms. Patients remain on treatment until progression
Mortality	General population for S1-S7, excess mortality risk for BSC (S8) from Ma et. al. (2021)

BSC, best supportive care; L, line; NI, next intervention; PD, progressed disease; PF, progression free; PFS, progression free survival; TTNI | P, time to next intervention given progression

Link to main deck:
Company base case model

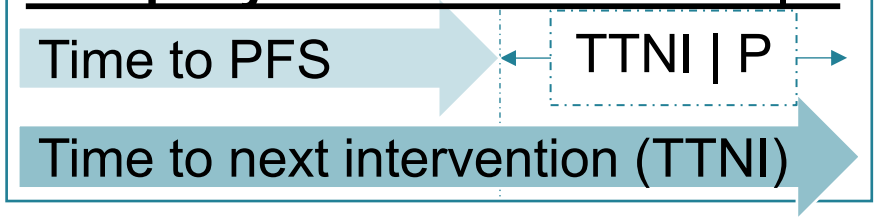
REACP ACM1: TTNI | P, time with progression before NI:

Company calculates conditional outcome from PFS and TTNI to inform time to NI with PD

Background: Time to next intervention (TTNI) from INDIGO not used in model → TTNI | P (TTNI given progression) used for time spent off treatment with progressed disease. Company:

1) Calculated relative difference between INDIGO PFS and TTNI
   - PFS = proxy for time to progression (TTP) as no deaths on treatment in INDIGO
   - median TTNI | P (months): 14.4 vorasidenib, 3.9 placebo

Company calculation of TTNI | P



2) Independently fitted parametric curves to each arm to extrapolate the INDIGO TTNI | P KM data (full extrapolations in supplementary appendix). Generalised gamma chosen for best fit.

- Based on TTNI | P, model predicts:
  - ❖ 21% vorasidenib and 9% active observation arm off treatment with PD at 20 years
  - ❖ a small % of people with PD in vorasidenib arm never progress to NI in company model

Link to main deck: TTNI | P, background

NI, next intervention; KM, Kaplan-Meier; PD, progressed disease; PF, progression free; PFS, progression free survival; TTNI, time to next intervention; TTNI | P, time to next intervention given progression

REACP ACM1: TTNI | P by change in tumour volume

Perioperative study: vorasidenib impacts tumour biology via 2HG suppression:

- reduced tumour cell proliferation & reversal of gene expression programs typical for IDH mutations
- 2HG reduction associated with induction of genes associated with antitumor immunity and modest increase in tumour infiltration with CD8+ T cell
- reversal of ‘proneural’ gene expression signature (molecular hallmark of mIDH gliomas), downregulation of genes linked to stem cell properties in a variety of cancers

2HG, 2-hydroxyglutarate; BIRC, blinded independent review committee; CI, confidence interval; DCO, data cut off; IDH, isocitrate dehydrogenase; m, mutant; NE, not evaluable; PD, progressed disease; TTNI, time to next intervention; TTNI | P, time to next intervention given progression; TV, tumour volume. Link to main deck: TTNI | P, company response

Link to main deck: TTNI | P, company response

RECAP ACM1: INDIGO trial: Change in tumour volume

Tumour Volume statistics (FAS), provided after FAC

	Vorasidenib (N=[redacted])	Placebo (N=[redacted])
Mean Log Tumour Volume, March 2023 DCO		
Baseline	[redacted]	[redacted]
PD (BIRC)	[redacted]	[redacted]
Mean change at PD vs. baseline (95% CI)	[redacted]	[redacted]
Difference (95% CI)	[redacted]	
Change in tumour volume (cohort level modelling of TGRs)		
Mean change every 6 months, Sep 2022 (95% CI)	2.5% (-4.7%, -0.2%),	13.9% (11.1%, 16.8%).

Tumour volume change in vorasidenib arm 6, 12 & 24 months:

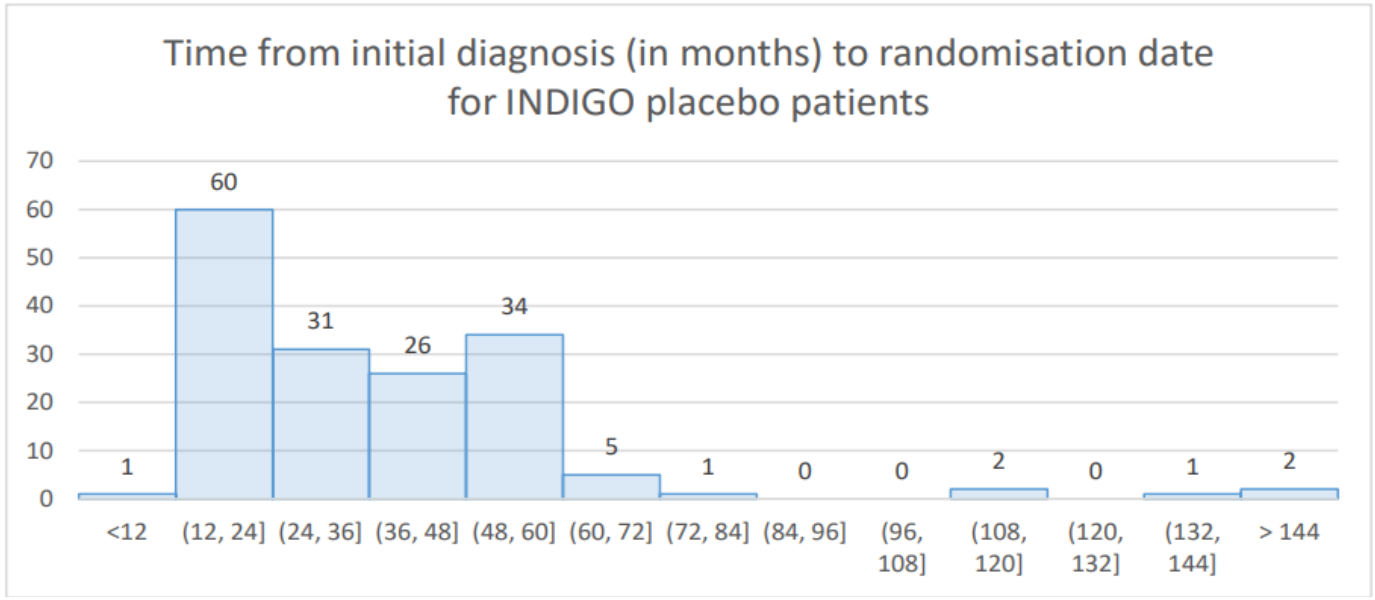
- [redacted]
- [redacted]

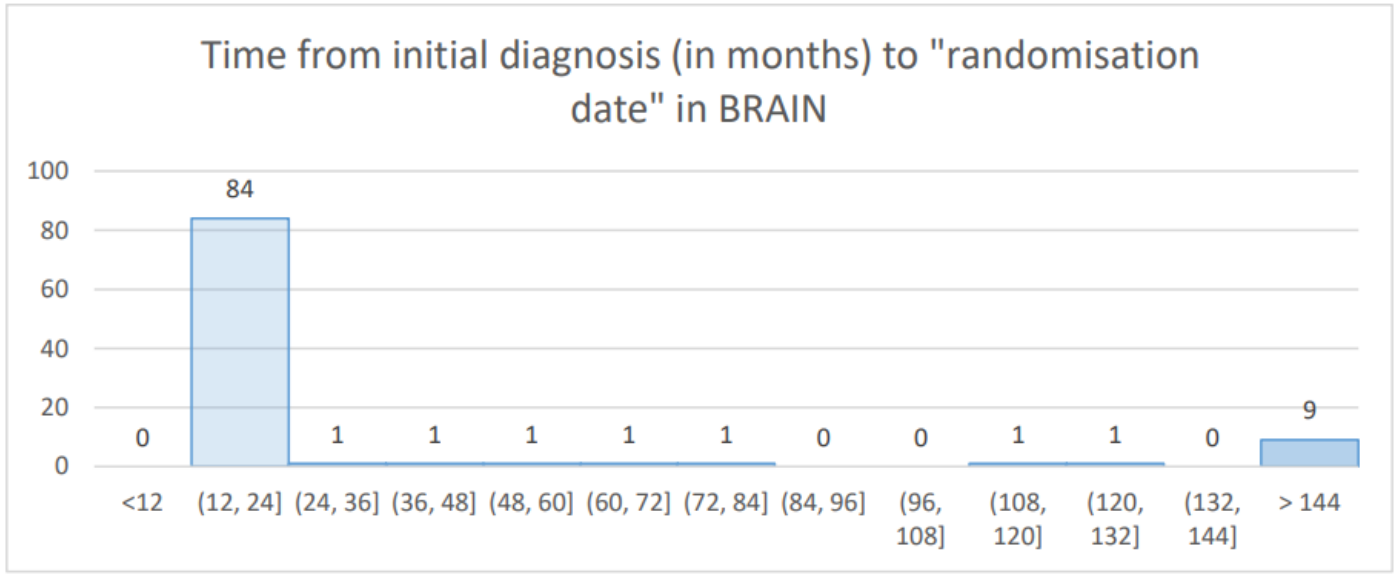
Box Plot of Change in Log Tumour Volume at PD (per BIRC) vs Baseline, March 2023 DCO (FAS)

[redacted]

BIRC, blinded independent review committee; BL, baseline; CI, confidence interval; DCO, data cut off; FAC, factual accuracy check; FAS, full analysis set; PD, progressed disease; N, number; TGR, tumour growth rate; TV, tumour volume

BRAIN registry: time from diagnosis to randomisation

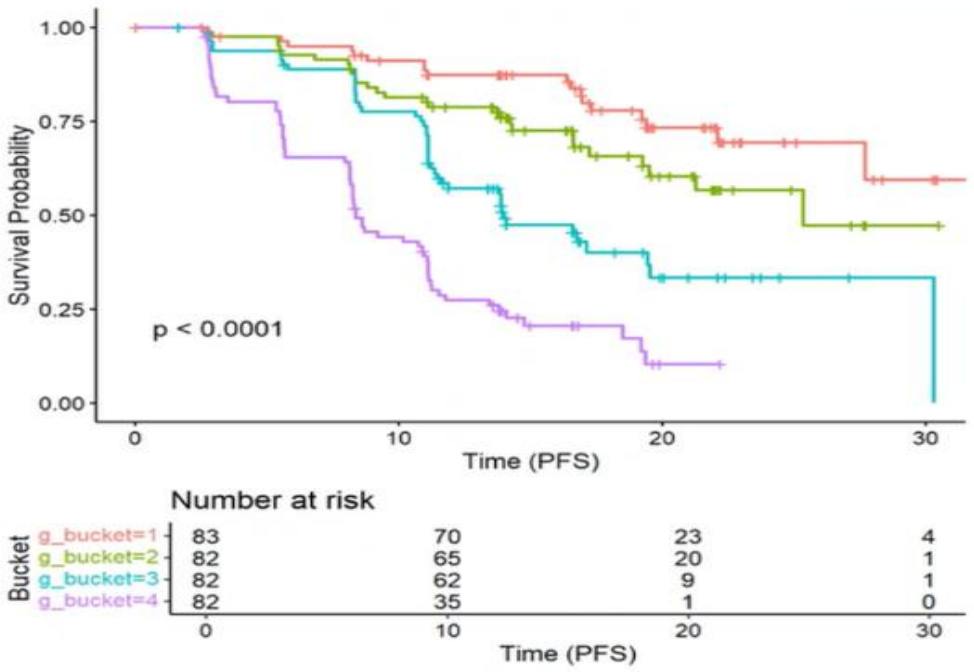




Data to support surrogacy relationship for PFS and OS

New post-hoc INDIGO analyses

PFS per BIRC by subgroup of individual growth at baseline



PFS per BRIC with repeated tumour measurements from Cox regression model until study unblinding (FAS)

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

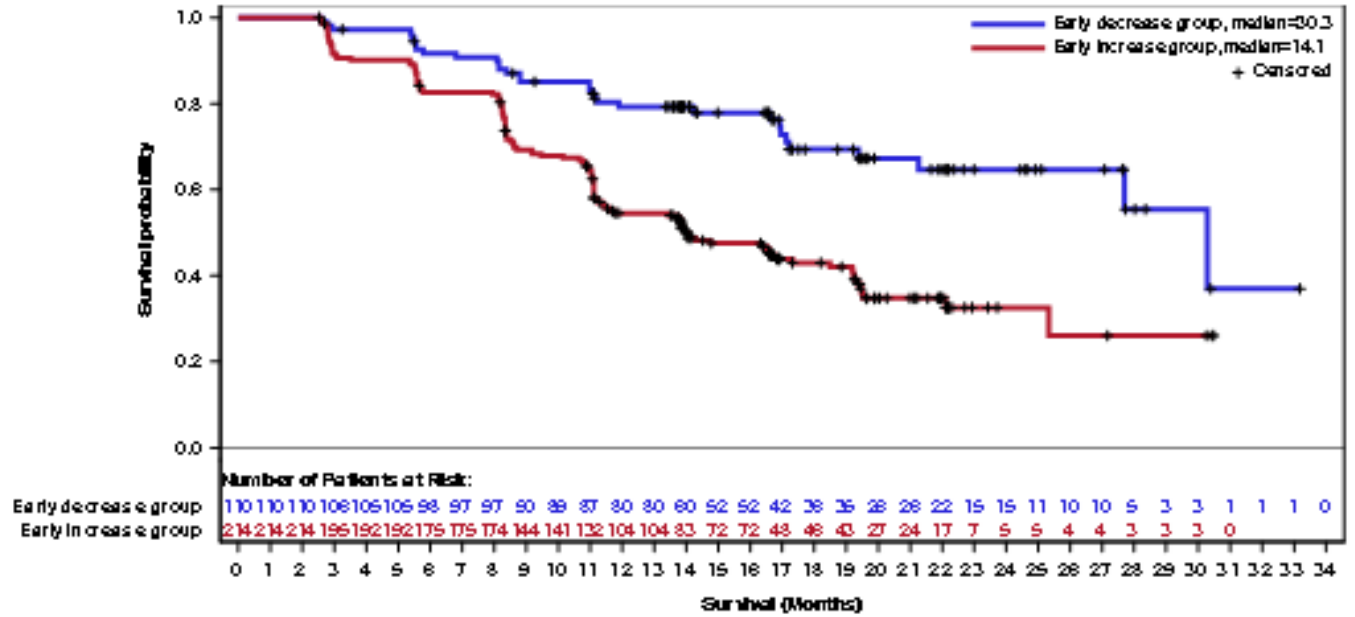
Link to main deck: Modelling OS

PFS & OS from Miller et al (2016)

Retrospective analysis of 275 with mIDH glioma treated in US 1991 -2017

	Median years to endpoint
PFS	• Diagnoses for 1st progression (PFS1): 5.7 • 1st to 2nd progression (PFS2): 3.1
OS	• 18.7 in overall cohort • 8.3 after PFS1

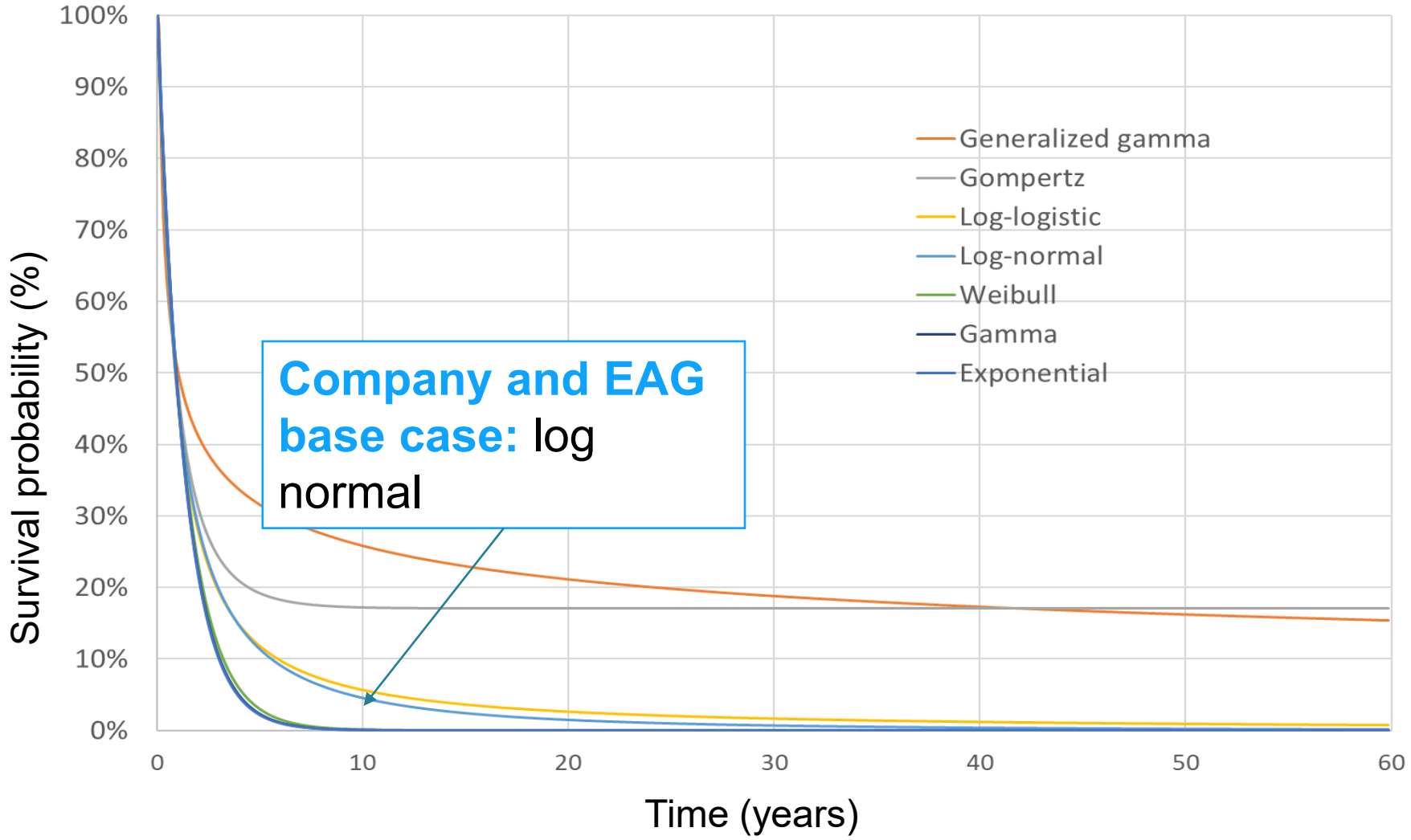
Kaplan-Meier Plot for PFS per BIRC by Early Tumour Growth Until Study Unblinding (FAS)



BIRC, blinded independent review committee; CI, confidence interval; mIDH, mutant isocitrate dehydrogenase; OS, overall survival; FAS, full analysis set; PFS, progression free survival

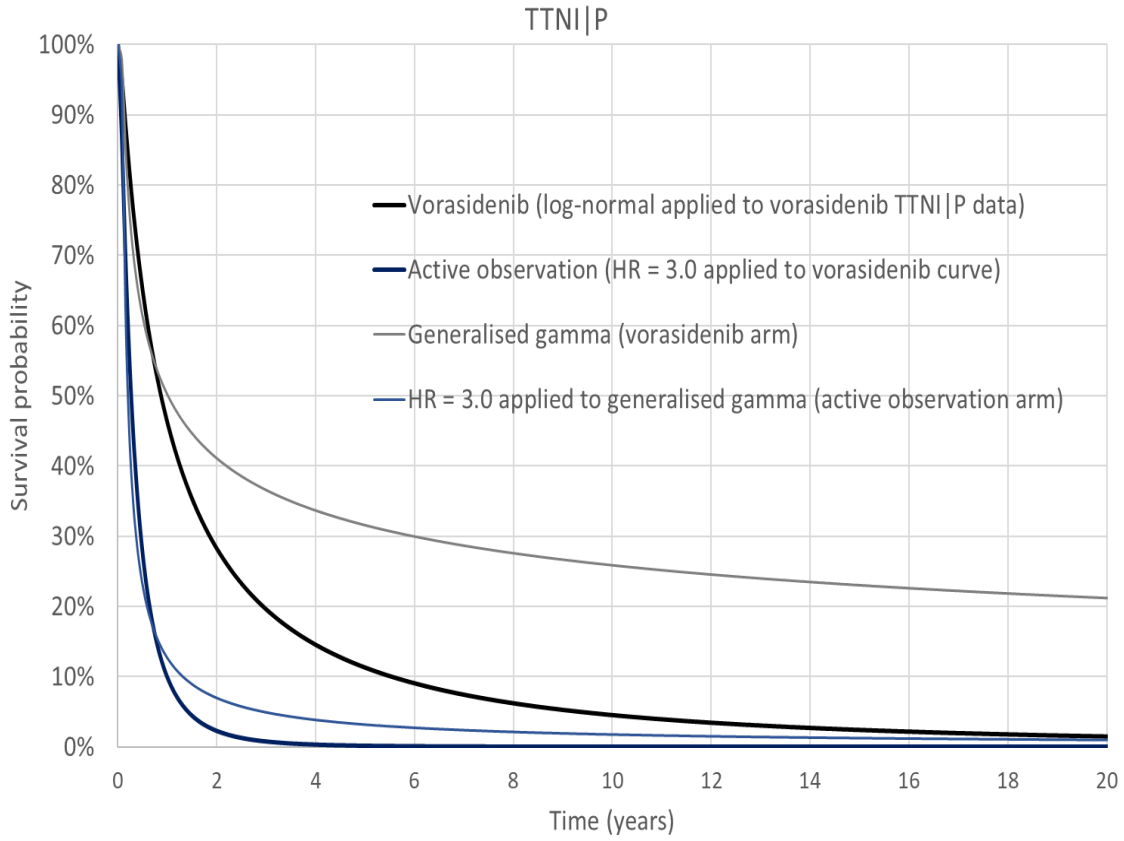
TTNI | P: Exploring alternative extrapolations for vorasidenib

Alternative parametric distribution fits to extrapolated vorasidenib TTNI | P data

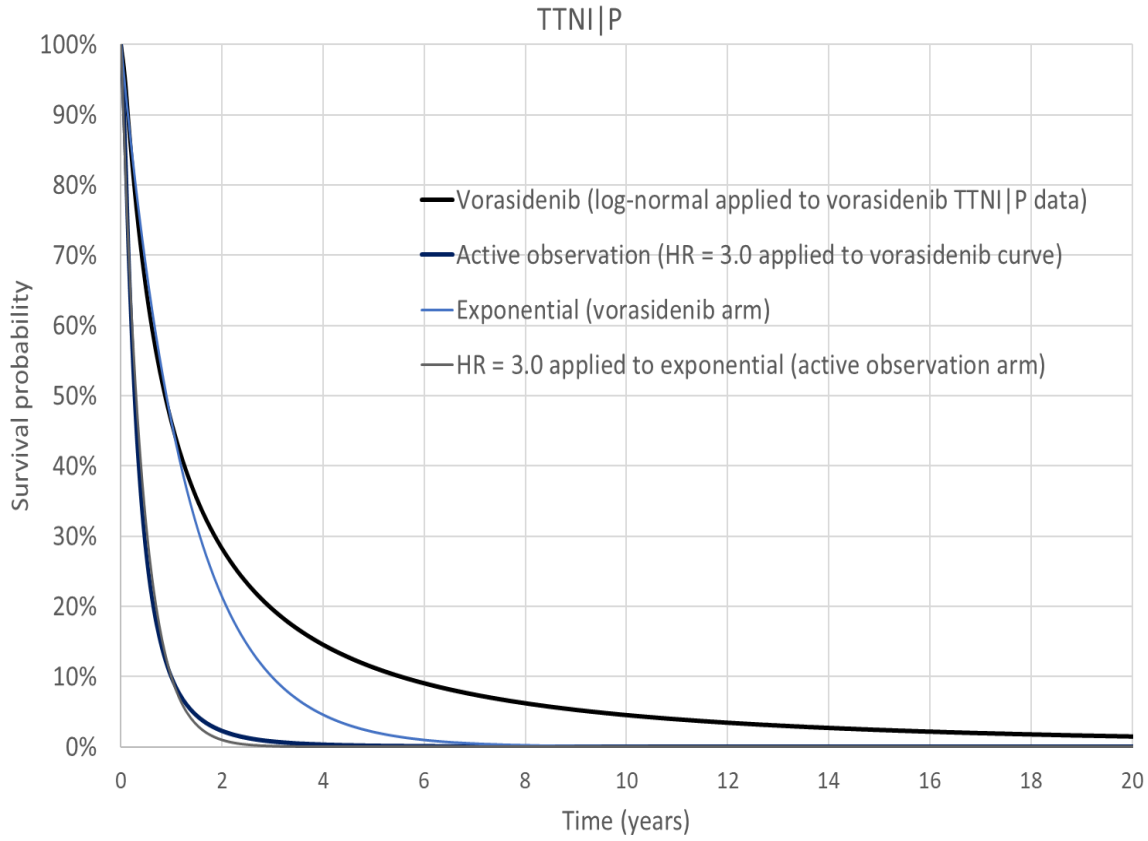


TTNI | P: Exploring alternative extrapolations for vorasidenib

Company's revised base case with generalised gamma model for vorasidenib TTNI-P



Company's revised base case with exponential model for vorasidenib TTNI-P



Link to main deck: TTNI | P

HR, hazard ratio; TTNI | P, time to next intervention given progression

EAG scenarios (full)

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Link to main deck: EAG scenarios

EAG's deterministic scenario analysis varying the HR for active observation, PAS price for vorasidenib

HR active observation	Distribution for vorasidenib	Inc. Costs	Inc. QALYs	ICER (£/QALY)
HR of 1.0	Log normal (EAG base case)	[redacted]	1.67	[redacted]
	Generalised gamma	[redacted]	1.39	[redacted]
	Exponential	[redacted]	1.75	[redacted]
HR of 1.5	Log-normal	[redacted]	2.20	[redacted]
	Generalised gamma	[redacted]	2.67	[redacted]
	Exponential	[redacted]	1.98	[redacted]
HR of 2.0	Log-normal	[redacted]	2.42	[redacted]
	Generalised gamma	[redacted]	3.40	[redacted]
	Exponential	[redacted]	2.10	[redacted]
HR of 2.5	Log-normal	[redacted]	2.54	[redacted]
	Generalised gamma	[redacted]	3.81	[redacted]
	Exponential	[redacted]	2.17	[redacted]
HR of 3.0	Log normal (company base case)	[redacted]	2.60	[redacted]
	Generalised gamma	[redacted]	4.03	[redacted]
	Exponential	[redacted]	2.22	[redacted]

HR, hazard ratio; PAS, patient access scheme; QALY, quality adjusted life-year; ICER, incremental cost-effectiveness ratio

Link to main deck: Managed Access

Criteria for managed access

The committee can make a recommendation with managed access if:

- the technology cannot be recommended for use because the evidence is too uncertain
- the technology has the **plausible potential** to be cost effective at the **currently agreed price**
- new evidence that could **sufficiently support the case for recommendation** expected from ongoing or planned clinical trials, or could be collected from people having the technology in clinical practice
- data could feasibly be collected within a reasonable timeframe (up to a **maximum of 5 years**) without **undue burden**.

RECAP: Insights from managed Access Team, ACM1

1. INDIGO trial is ongoing and may help resolve some uncertainties but:
    - Limitations to data: populations unblinded, high crossover in placebo arm
2. May be value in collecting SACT and RTDS data:
    - Could help resolve uncertainties related to TTNI and time spent off treatment following progression and provide useful information about vorasidenib within an NHS context
    - Will need to link SACT and RTDS data sets to obtain useful RWE.
    - Limitations to data: may have limited usefulness in 5-year period of a MAA

ACM, appraisal committee meeting; MAA, managed access arrangement; RTDS, Radiotherapy Data Set; RWE, real world evidence; SACT, Systemic Anti-Cancer Therapy; TTNI, time to next intervention