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

Technology appraisal committee HST [18th September 2025]

Single Technology Appraisal: First 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]

- ✓ **Background and key issues**
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ❑ Other considerations
- ❑ Summary

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Background: IDH1/IDH2-mutant astrocytoma & oligodendroglioma [3]

- 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

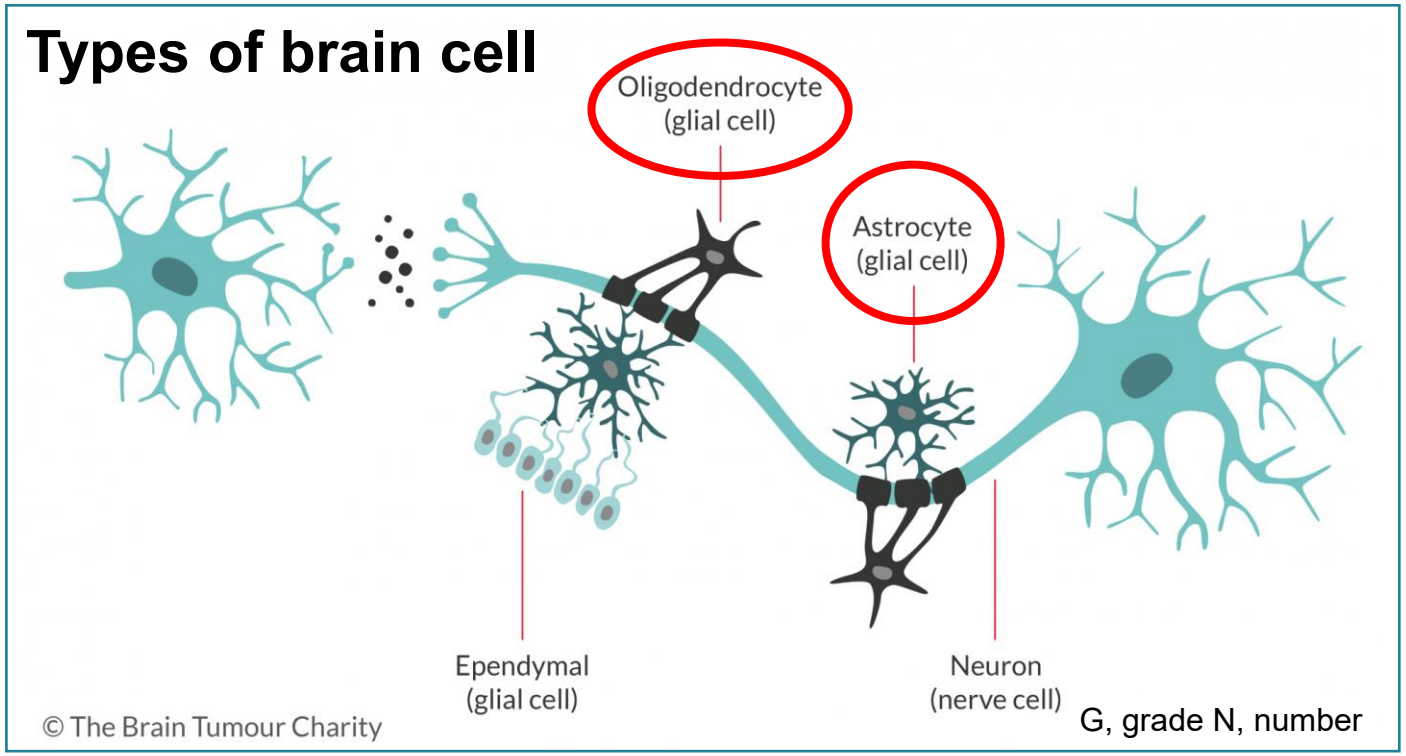
Epidemiology:

	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

Patient perspectives (1)

Submissions from Astro Brain Tumour Fund (ABTF), The International Brain Tumour Alliance (IBTA), The Brain Tumour Charity and patient experts

Large psychological and physical impact of living with LGG

- Rare condition commonly affecting young people → impacts all aspects of life, especially family, social, finance, education and work
- Physical symptoms (e.g. mobility issues, neuro-cognitive and fatigue) challenging, especially seizures which impact mental health and independence
- Being diagnosed with unpredictable, incurable and slowly progressive condition can cause anxiety, personality changes and depression

Significantly impacts carers and families:

- 78% carers report LGG moderately to severely impacts their lives:
  - ❖ Exhaustion from practical challenges in providing support
  - ❖ Financial burden as may be sole provider for whole family
  - ❖ Constant anxiety about future and loved one's wellbeing
- Many people with LGG have young families who can be severely affected → traumatic for children to see loved one suffering

"Living with the condition is a constant state of anxiety…"

"patients face physical and cognitive challenges, including fatigue, seizures, and memory issues, often struggling with mobility, speech, and sensory impairments …"

"Carers … often face profound emotional and practical challenges. They share the emotional burden of uncertainty and fear…"

LGG, low-grade glioma

Patient perspectives (2)

Unmet need for more effective, less invasive treatments

1. Watch and wait: can lead to growing tumours (and seizures) and anxiety for patients and families → no active treatment to delay or stop inevitable tumour growth post surgery
2. Chemotherapy and radiotherapy harsh and disruptive:
   - ❖ "devastating side effects", e.g. cognitive decline, fatigue
   - ❖ not a cure
   - ❖ need regular hospital visits → daily life and work impacted
   - ❖ can negatively affect fertility

"The watch and waiting is the hardest part. Like I've got a bomb in my head that could go off at any time."

"Chemotherapy was brutal."

"Vorasidenib allows me to live a nearer 'normal' life"

"Vorasidenib has given our son hope"

Vorasidenib is first in class, innovative new treatment for LGG:

- Increased PFS without life changing negative impacts of RT/CT → crosses blood brain barrier, unlike other chemotherapies
- Reduces physical symptoms (e.g. seizures) → easier to work
- Improves QoL as actively delays progression
- Oral treatment requiring less frequent hospital visits
  - ❖ Benefits: for young people, those working or living in rural areas
  - ❖ Cons: extra monitoring, may reduce axillary healthcare support

CT, chemotherapy; LGG, low-grade glioma; PFS, progression-free survival; RT, radiotherapy; QoL, quality of life

Clinical perspectives

Submissions from Association of British Neurologists Special Interest Group (ABN SIG) Neuro-oncology, The British Neuro Oncology Society (BNOS), The Royal College of pathologists and The Society of British Neurological Surgeons (SBNS) and clinical experts

Need for targeted treatments that delay disease progression:

- LGG unpredictable but ultimately progresses to HGG despite multiple RT/CT lines
- Growing tendency to delay RT/CT after surgery in slow growing tumours → avoid debilitating side effects (cognitive impairment, cerebral oedema, thrombosis)
- LGG pathway established but some regional variation (chemotherapy choice, surgery timing)
- Key aims of treatment: increase progression free survival and time to next intervention

Vorasidenib is first targeted treatment for IDH mutation:

- INDIGO trial suggests clinically meaningful benefits in PFS, with potential seizure control
- Increases treatment options and could delay need for RT/CT, maintaining QoL and time in employment
- Easier to administer than current treatments → administrated by clinical neurooncologists in specialist secondary care clinics where any complications can be managed
- Low toxicity but requires closer monitoring (clinical review, MRI, frequent bloods) vs. watch and wait
- No additional testing requirements → IDH mutation tests standard care in NHS
- Vorasidenib would be stopped if evidence of progression
- People can maintain active lifestyle with limited disruption to work/study on treatment (unlike RT/CT)

CT, chemotherapy; HGG, high-grade glioma; IDH, isocitrate dehydrogenase; LGG, low-grade glioma; PFS, progression-free survival; RT, radiotherapy; QoL, quality of life

Equality considerations

Stakeholders raised equalities issues related to age, pregnancy and travel

ABTF, patient experts: gliomas disproportionately impact a younger age group who generally have young families to support

The Brain Tumour Charity:

- Treatment costs related to vorasidenib including travel or time away from work could disproportionately affect those from lower-income backgrounds if additional monitoring needed for vorasidenib
- Vorasidenib not licenced for use in pregnancy → treatment is life long or until progression which impacts ability to have children

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

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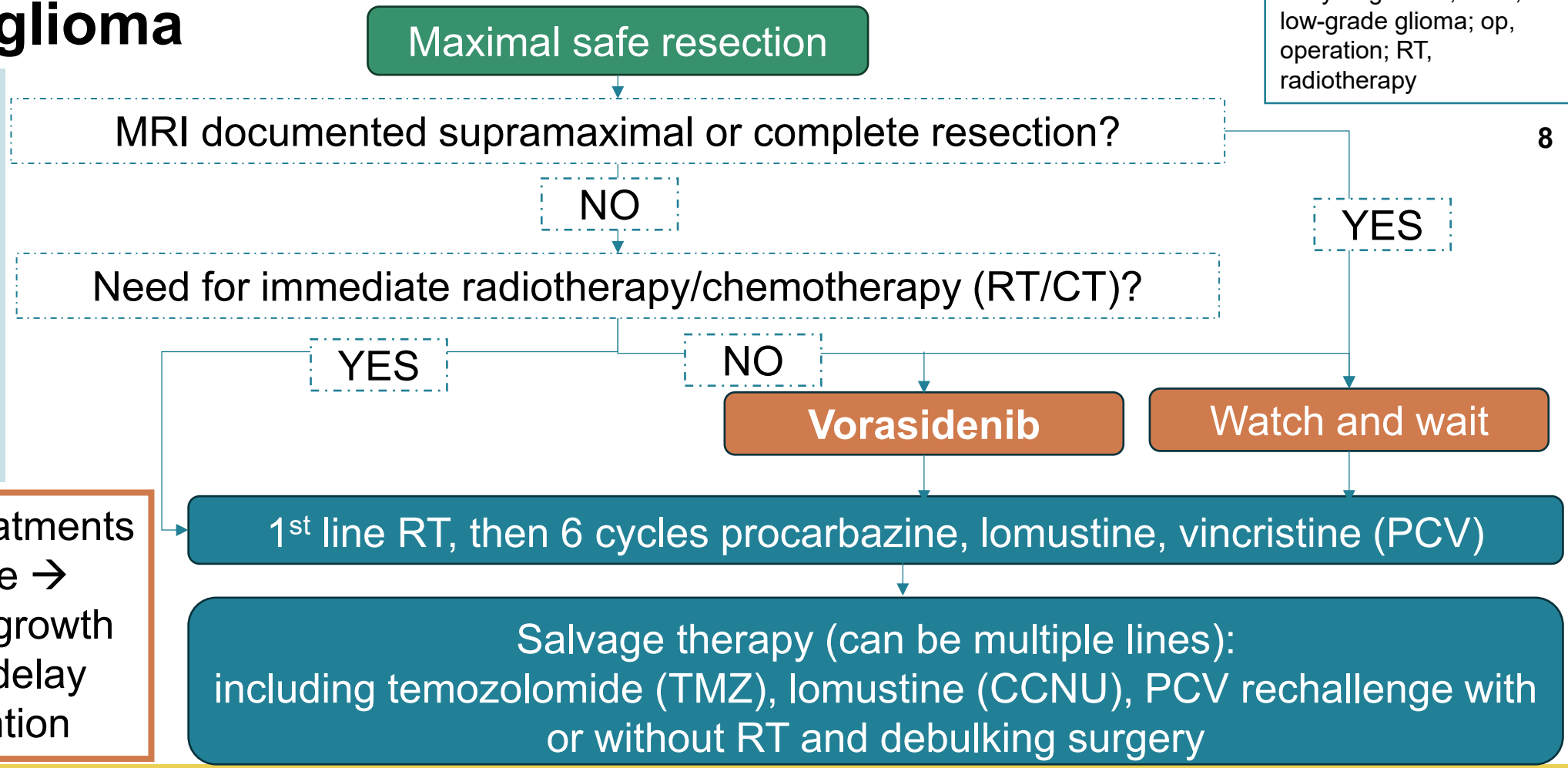
ABTF, Astro Brain Tumour Fund

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

Does the proposed pathway reflect clinical practice for LGG? Would this be the same for astrocytoma and oligodendroglioma? Is the pathway the same for adults and children?

- How is the need for immediate RT/CT determined?
- Are the salvage therapies correct? What determines which salvage therapies are used at each line?
- Is the proposed positioning for vorasidenib appropriate? Would it always be stopped on progression?

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

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

Key issues

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

Issue	Resolved?	Impact
Restricted trial population compared to NHS LGG population	No: for discussion	Unknown
Generalisability of outcomes from INDIGO	No: for discussion	Unknown
Immaturity of INDIGO data	No: for discussion	Unknown
Surrogacy relationship for OS benefit	No: for discussion	Unknown
Interpretation of TTNI I P outcome and resulting duration of time off treatment with progressed disease	No: for discussion	Large
Evidence for subsequent treatment lines and excess mortality for BSC	See supplementary appendix	Unknown
Use of French market share data for subsequent chemotherapies	No: for discussion	Small
Bevacizumab as subsequent treatment	Yes	Small
Plausibility of health state utility values from vignette	No: for discussion	Large
Include costs of monitoring CT scans	Yes	Small
Non-reference case discount rate for costs and health effects	No: for discussion	Large
Appropriate severity weighting	No: for discussion	Large

BSC, best supportive care; CT, computed tomography; LGG, low-grade glioma; ICER, incremental cost-effectiveness ratio; OS, overall survival; TTNI I P, time to next intervention given progression

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NICE National Institute for Health and Care Excellence

Link to supplementary slides: analyses sets in INDIGO, baseline characteristics INDIGO

Key clinical trials

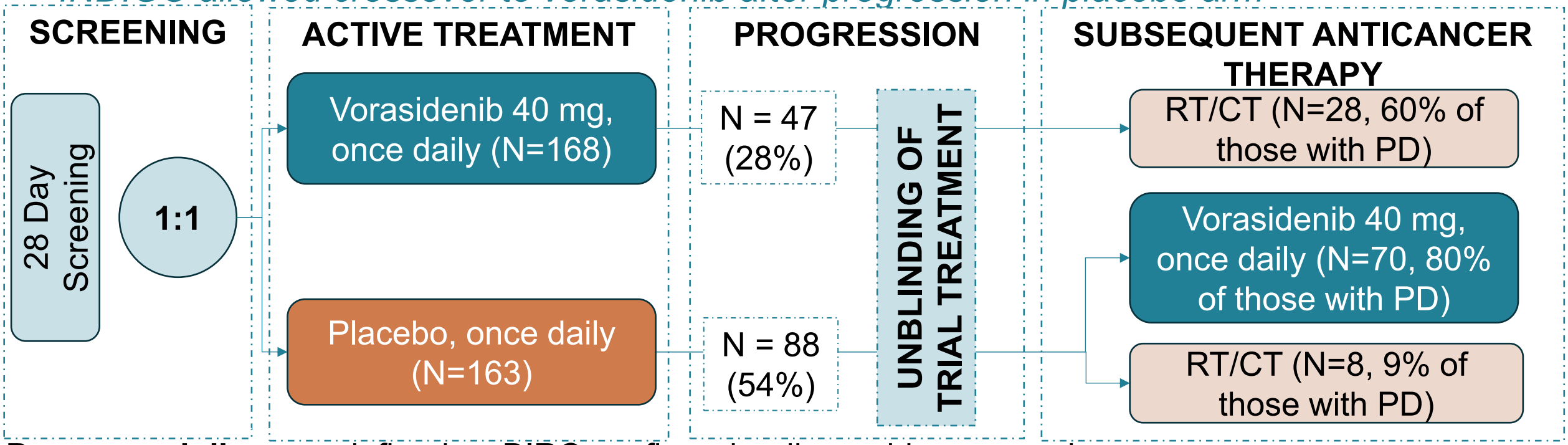
Clinical effectiveness evidence for vorasidenib from INDIGO: double blind RCT vs. placebo

	INDIGO (NCT04164901)
Design	International, double-blind, randomised, placebo-controlled trial
Population	Residual / recurrent non-enhancing Grade 2 oligodendroglioma or astrocytoma, with IDH1 or IDH2 mutation, who have undergone surgical intervention as only treatment, not in immediate need of CT or RT
Intervention	Vorasidenib 40mg once daily
Comparator(s)	Placebo
1° outcome	Progression-free survival
Key 2° outcomes	Time to next intervention, tumour growth rate, response rates, overall survival, HRQoL, AEs
Locations	International study, USA, Europe, including sites in the UK
Used in model?	Yes

AE, adverse event; CT, chemotherapy; IDH, isocitrate dehydrogenase; LGG, low-grade glioma; RCT, randomised controlled trial; RT, radiotherapy; HRQoL, health related quality of life

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

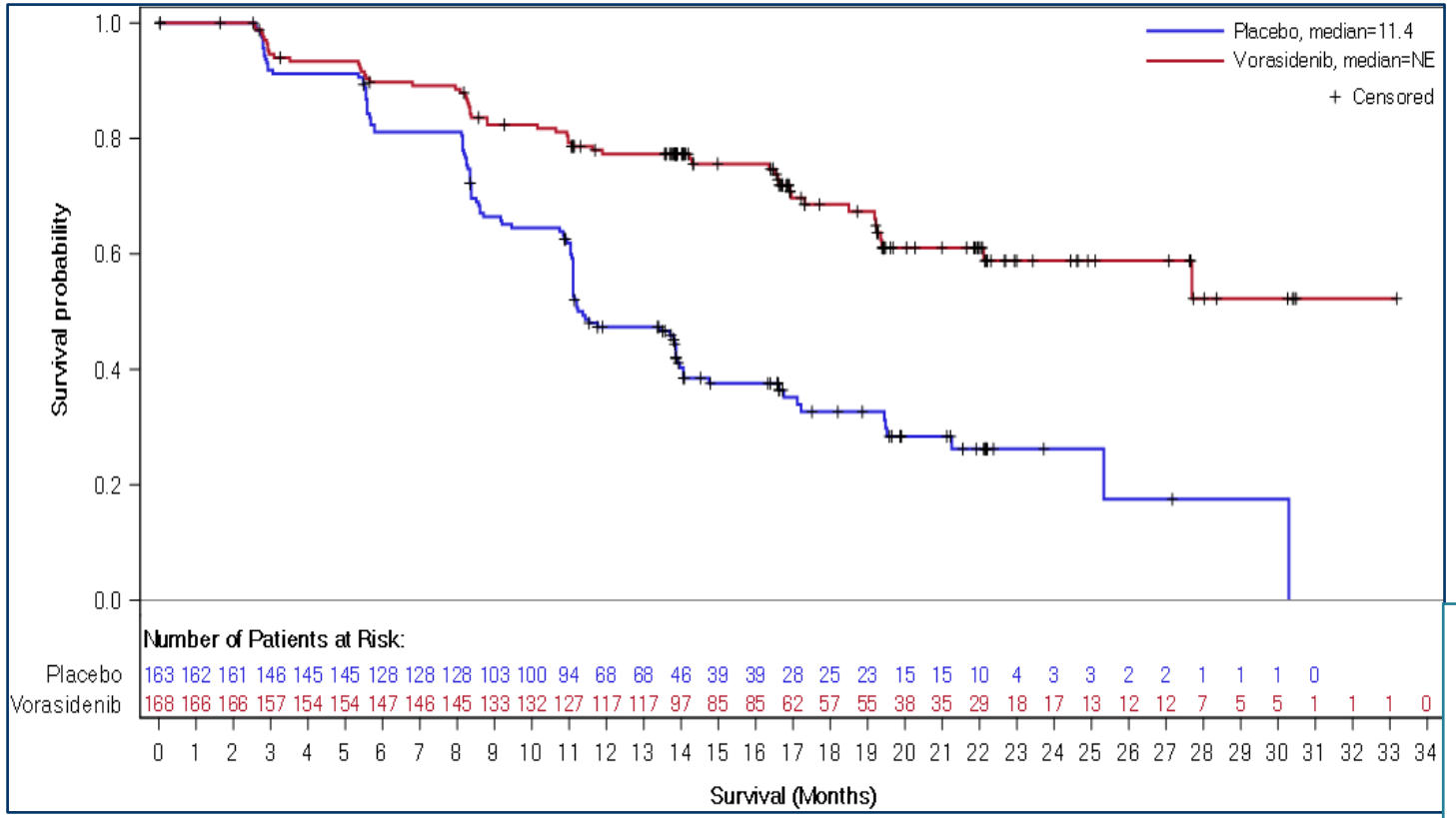
- Inclusion criteria: ≥12 years old, no high-risk features, ≥1 surgery for glioma (last surgery 1 to 5 years from randomisation) no other anti-cancer therapy, measurable, non-enhancing disease on MRI (≥1 target lesion measuring ≥1 cm x ≥1 cm) confirmed by blinded review
- Stratified by: 1p/19q status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

INDIGO trial: Progression Free Survival, March 2023 data-cut

Results suggest vorasidenib improves progression-free survival compared to placebo

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



- PFS statistically significant: favours vorasidenib
- All events were PD, no deaths
- Median follow up for March 2023 DCO: ~20 months

BIRC assessed PFS: data cut-off March 2023 (ad-hoc analysis)

PFS	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	

Subgroup analysis: improved PFS across all prespecified subgroups vs. placebo

- Potential subgroup effect for tumour volume at baseline (see supplementary appendix)

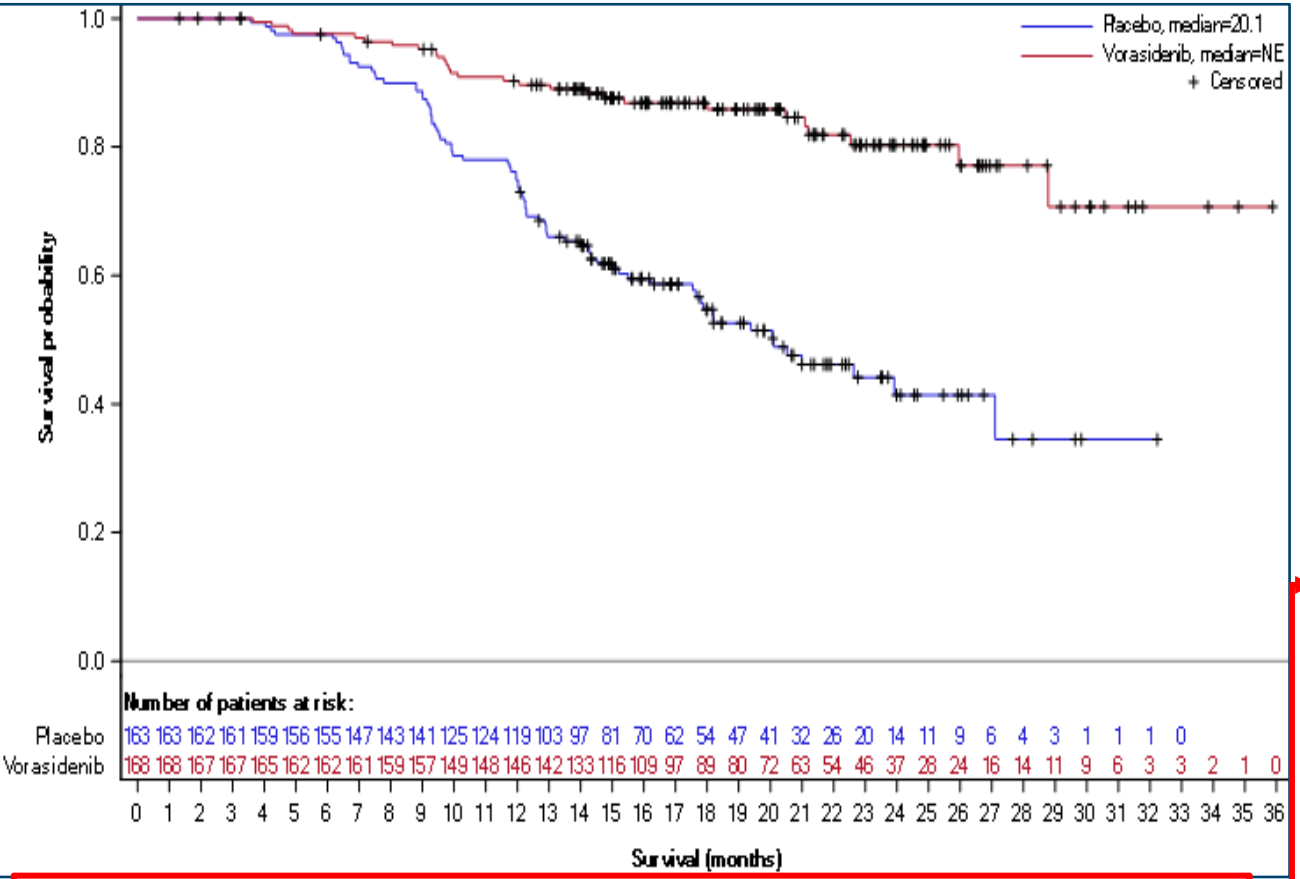
BIRC, blinded independent review committee; CI, confidence interval; DCO, data cut off; FAS, full analysis set; N, number; NE, not evaluable; HR, hazard ratio; PFS, progression free survival; PD, progressed disease

INDIGO trial: Time to next intervention (TTNI)

See supplementary slides: other key clinical results, safety outcomes

Results suggest longer time to next intervention with vorasidenib vs placebo

Kaplan-Meier plot for TTNI (FAS), March 2023 data cut



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

CI, confidence interval; DCO, data cut off; N, number; NE, not evaluable; FAS, full analysis set; HR, hazard ratio; PD, progressed disease; TTNI, time to next intervention

Key TTNI results from INDIGO

Results	Vorasidenib N = 168	Placebo N = 163
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%)
"Other" anticancer therapies (unknown DCO)		
Antineoplastic therapy	13 (8%)	3 (2%)
Radiotherapy	11 (7%)	5 (3%)
Surgery	10 (6%)	3 (2%)

Key issue: 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 (see supplementary appendix)

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

- Are the results from INDIGO generalisable to the population with LGG in the NHS?
- What population should be included in any potential positive recommendation?

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

Key issue: 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

In clinical practice: a) how is PD assessed? b) what factors determine when to start NI? Are INDIGO outcomes generalisable to NHS? If not, how does this impact results?

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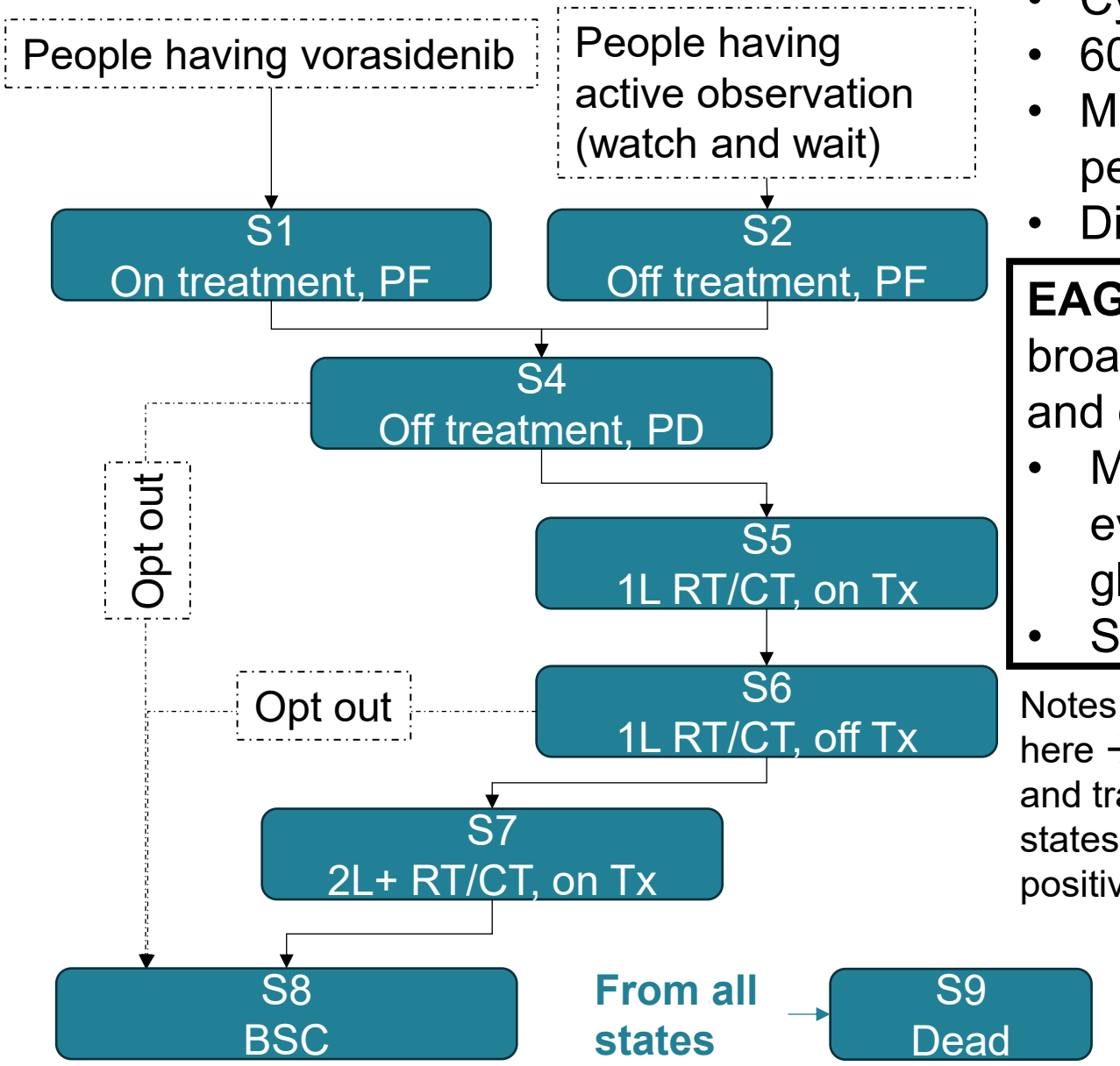
Company's base case model overview

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
- Discount rate: 1.5% (see key issue: discount rate)

EAG comments: model conceptually acceptable and broadly appropriate as treatment aim is to reduce PD risk and delay TTNI.

- May be more appropriate to model progression events over time (e.g. transition to HGG or malignant glioma) as in TA997 but hard with limited data
- See supplementary appendix for full EAG comments

Notes: a) state S3 (on treatment, PD) not in base case so not shown here → see supplementary appendix for non-base case health states and transitions. b) General population mortality applies to all health states but S8 (BSC). TA997: Dabrafenib for BRAF V600E mutation-positive glioma

Is the company's model appropriate for decision making?

BRAF, B-Raf proto-oncogene, serine/threonine kinase; BSC, best supportive care; CT, chemotherapy; HGG, high-grade glioma; PD, progressed disease; PF, progression free; RT, radiotherapy; TA, technology appraisal; TTNI, time to next intervention, Tx, treatment;

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 • (see subsequent treatments) • 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

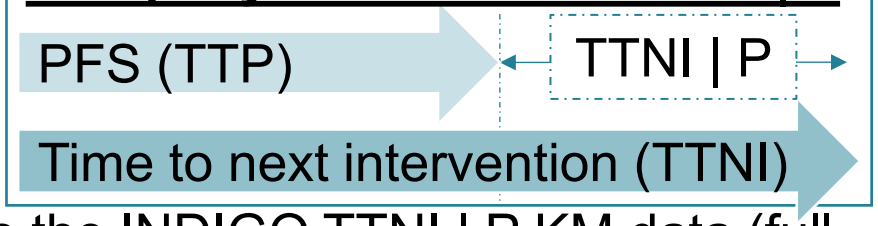
Key issue: TTNI | P, time with progression before NI (1)

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

Company: long TTNI | P for vorasidenib plausible: people have more favourable features on progression vs placebo → choose to delay RT/CT (avoid side effects). Supported by:

- INDIGO results (supplementary appendix):
  - ❖ Higher % with tumour shrinkage on progression after vorasidenib than placebo (~50% vorasidenib arm had tumour shrinkage)
  - ❖ Smaller change in mean tumour volume at PD vs baseline with vorasidenib: difference in mean tumour volume change [redacted]

CI, confidence interval; CT, chemotherapy; NI, next intervention; KM, Kaplan-Meier; PD, progressed disease; PF, progression free; PFS, progression free survival; RT, radiotherapy

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

Company cont.:

- ❖ Mathematical modelling of tumour growth rate: vorasidenib fundamentally alters growth trajectory of mIDH1/2 gliomas, leading to gradual tumour shrinkage vs. continuous growth on placebo
- ❖ Longer TTNI |P for vorasidenib with smaller change in baseline tumour volume (see appendix).
- Perioperative study: vorasidenib impacts tumour biology via 2HG suppression
- [redacted] in mouse model of IDH-mutant astrocytoma

EAG: Company's assumed benefit in TTNI | P for vorasidenib applies on top of PFS benefit → concerned implausibly high rates off treatment with PD with company's chosen curves

- Separately fitted curves inappropriate → prefer same curve for each arm because:
  - ❖ No evidence in INDIGO that management / outcomes differs by arm after PD
  - ❖ PD EQ-5D lower with vorasidenib than placebo and did not improve malignant transformation rates
- Difference in tumour growth cannot account for the following in company's base case:
  - ❖ people staying longer in PD, off treatment state than in PFS state → lacks face validity
  - ❖ a % in vorasidenib arm never having NI → implausible as LGG progressive condition
- Benefits from reduced tumour volume likely already captured by extended PFS vs placebo

Patient expert: people with LGG can live comparably long vs. other cancers → delay long-term effects of RT/CT if possible

See supplementary slides: INDIGO tumour growth results, TTNI|P by tumour growth

2HG, 2-hydroxyglutarate; CT, chemotherapy; mIDH, mutant isocitrate dehydrogenase; NI, next intervention; KM, Kaplan-Meier; LGG, low-grade glioma; OS, overall survival; PD, progressed disease; PFS, progression free survival; RT, radiotherapy; TMZ. temozolomide; TTNI | P, time to next intervention given progression

Key issue: TTNI | P, impact of crossover in placebo arm (3)

Bias in results as 90% of people having NI with PD in placebo arm had vorasidenib

Background: 90% having NI for progressed diseases in placebo arm had vorasidenib as NI (March 2023 DCO).

Company: completed multiple imputation (MI) adjustment for cross-over in placebo arm (see supplementary appendix)

- Curves visually similar to unadjusted data so not in base case

EAG: TTNI | P confounded by crossover (see supplementary appendix for full EAG critique):

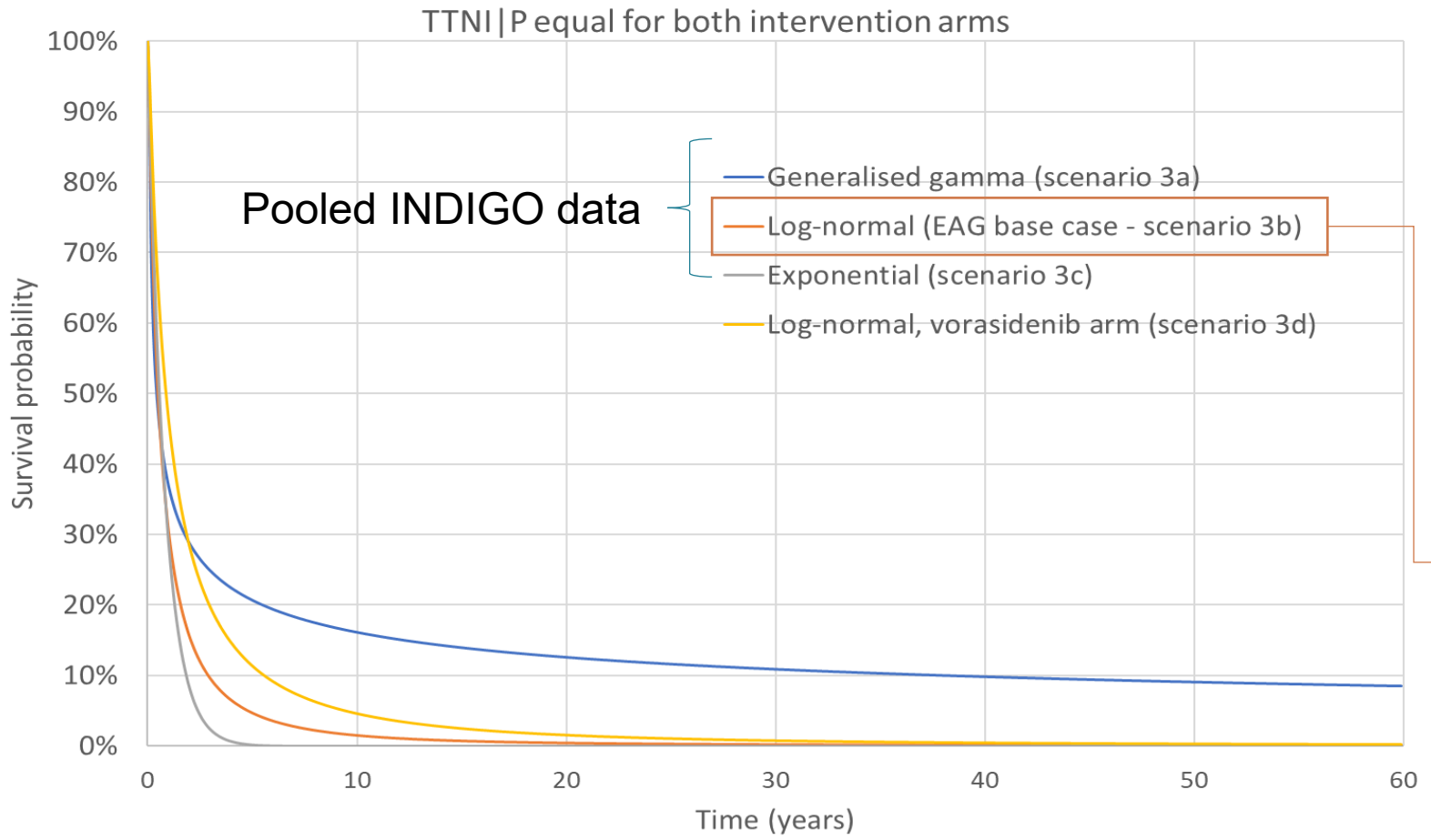
- Inappropriate to include vorasidenib as NI → unavailable on NHS
- Small N informing TTNI | P for vorasidenib at data cut off due to increased PFS vs placebo (more censoring in vorasidenib arm)
- MI adjusted curve less favourable for vorasidenib but concerns with method: a) IPCW, not MI, is standard cross-over adjustment in HTAs, b) imputed data comes from vorasidenib arm instead of placebo, c) company only adjusted TTNI, not TTNI | P

DCO, data cut off; HTA, health technology assessment; IPCW, inverse-probability-of-censoring weighting; N, next intervention; NI, next intervention; KM, Kaplan-Meier; PFS, progression free survival; TTNI, time to next intervention; TTNI | P, time to next intervention given progression

TTNI | P curves in EAG scenarios

EAG prefers log normal extrapolation using pooled TTNI | P KM data from INDIGO

EAG (cont.): TTNI | P curves highly uncertain: confounded by crossover, company curve lacks face validity. EAG explore alternative distributions using pooled INDIGO data + vorasidenib curve in both arms



EAG base case: log normal curve fitted to pooled INDIGO data → 2nd best fitting curve and more plausible time in PD, off tx (less than in PFS):

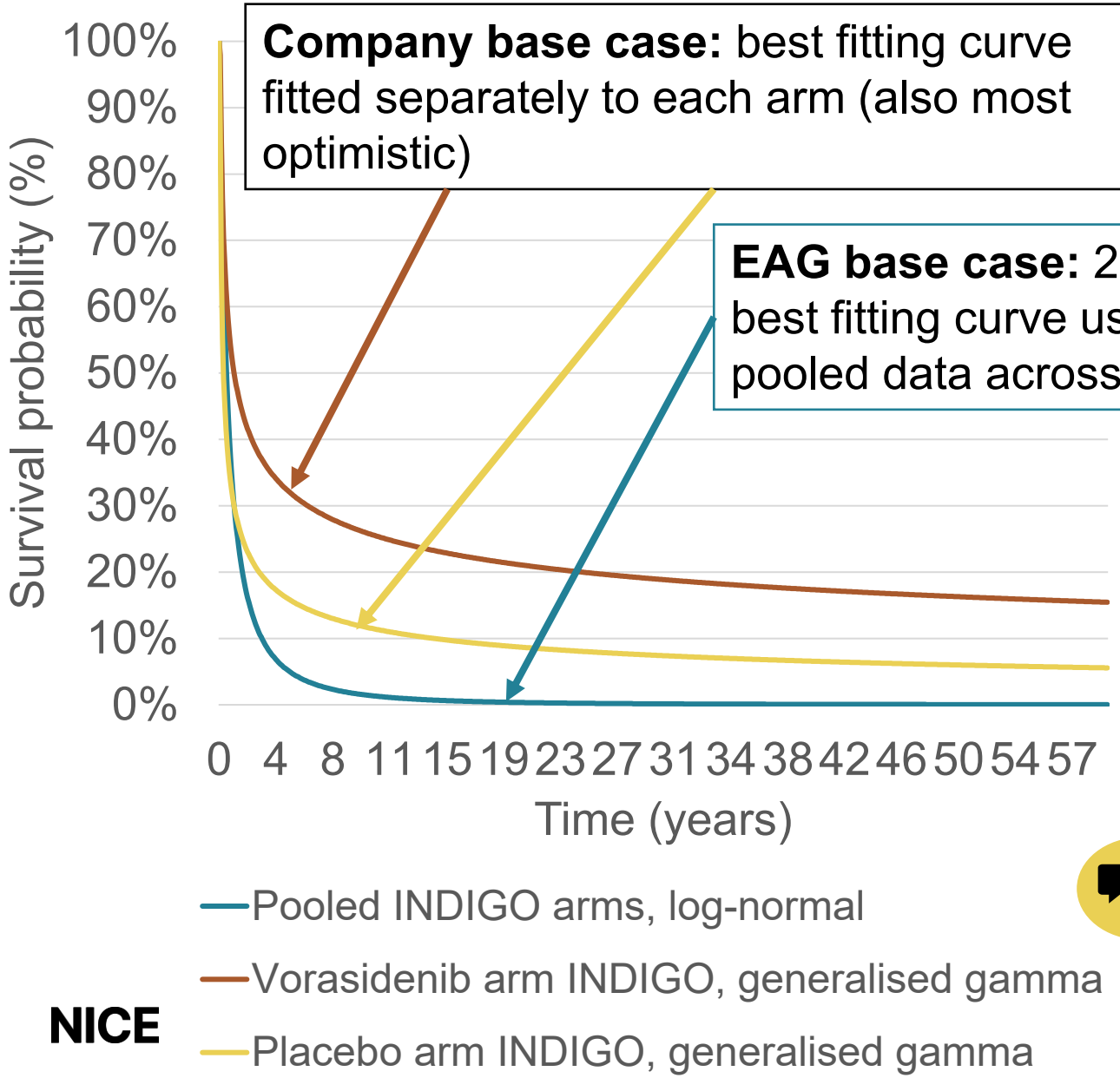
Total life years accrued in model (undiscounted)

	Total LY	
	PFS	PD, off-tx
Company base case		
Vorasidenib	5.22	8.58
Active observation	1.42	4.44
EAG base case		
Vorasidenib	5.22	1.21
Active observation	1.42	1.25

KM, Kaplan-Meier; LY, life years; PD, progressed disease; PFS, progression free survival; TTNI | P, time to next intervention given progression; tx, treatment

TTNI | P curves used in company and EAG base cases

Company and EAG choose different base case extrapolations of INDIGO TTNI|P data



Number at risk for TTNI|P extrapolations

Arm	Months			
	0	6	12	18
Vorasidenib	54	29	11	0
Placebo	104	36	8	1

Proportion off treatment with PD in company and EAG base cases

Base case	Arm	Time (years)			
		5	10	20	30
Company	Vorasidenib	32%	26%	21%	19%
	Placebo	16%	12%	9%	7%
EAG	Pooled arms	5%	2%	0%	0%

Which parametric curve best represents expected TTNI|P for people with LGG in the NHS?

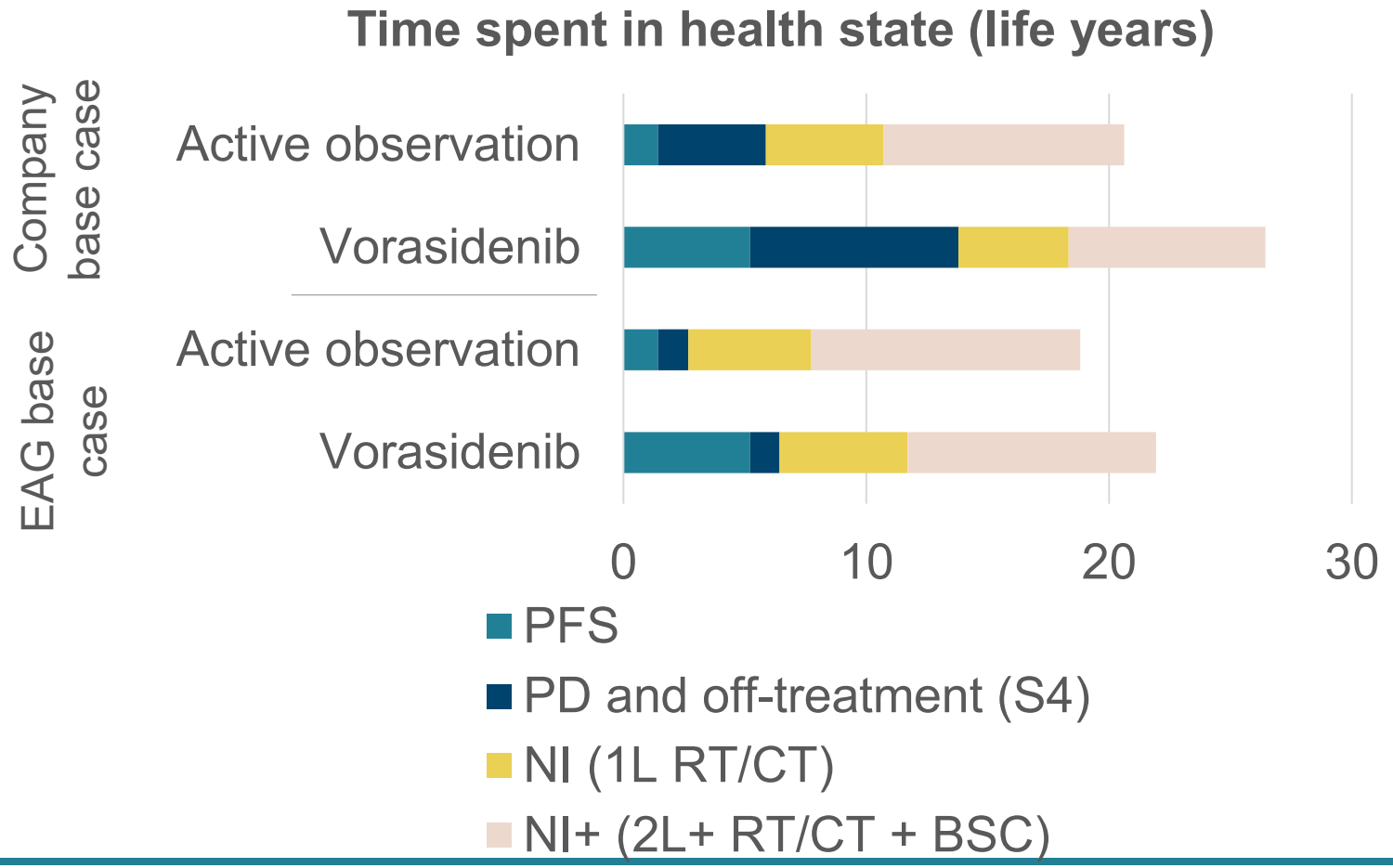
PD, progressed disease; TTNI | P, time to next intervention given progression

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)

- OS benefit for vorasidenib comes from delaying time to BSC through better PFS/TTP and TTNI | P vs active observation



Total LY spent in the company and EAG's base case models

	Company base case	EAG base case
Vorasidenib	26.45	21.93
Active observation	20.63	18.81
Difference	5.81	3.12

Difference between EAG and company base case driven by differences in TTNI|P

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; TTP, time to progression

Key issue: Modelling overall survival (2)

EAG: Lack of evidence from INDIGO makes overall survival highly uncertain

Company: Miller et al. (2016): Retrospective analysis of 275 with IDH-mutant glioma treated in US 1991 -2017

- Shorter time to PFS2 and OS after 1st progression

PFS and OS from Miller et al

	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 following PFS1

EAG: Lack of INDIGO OS data → hard to judge effect on OS for vorasidenib

- Miller et al. suggests PFS2 likely a surrogate prognostic marker for poorer OS but:
  - ❖ Includes 51% G3 glioma and doesn't adjust OS for grade, treatment and glioma type
  - ❖ 100% had salvage treatment on progressing (high % with PD had no NI in INDIGO)
- TTNI | P outcome not validated as OS surrogate and likely confounded: see key issues
- No data showing vorasidenib delays HGG or malignant gliomas (both have mortality risk)

More recent data cut would reduce uncertainty in PFS and TTNI outcomes but any OS data hard to interpret because of crossover and unknown impact of subsequent therapies

- No OS data identified from literature in people with LGG not in need of immediate RT/CT post surgery

Clinical experts: expect vorasidenib improves life expectancy in people with LGG by delaying need for 2nd surgery, CT and RT and their associated toxic effects

- Is it appropriate to use PFS and TTNI | P as a proxy for OS?
- Would more mature OS data from INDIGO reduce the uncertainty?

CT, chemotherapy; HGG, high-grade glioma; 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: Modelling overall survival (3)

Company assumes excess mortality only applies to people having BSC

Background: Excess mortality for LGG extrapolated from Ma et al. (2021) only applies to people having BSC (see supplementary appendix for survival curves)

Company: scenarios: a) SMR of 1.2 to background mortality rates, b) varying rate of opt out to BSC (0%, 10%)

EAG: applying excess mortality to only BSC state may be appropriate as:

- Avoids double counting of deaths in NI states caused by use of different sources at each line
- Clinical expert advice suggests most people die at end of pathway, not on active treatment lines

But, concerned that:

- Data source for excess mortality in BSC not representative of UK population (see key issue: subsequent treatments)
- Some people never progress to subsequent treatments in company model, so never have excess mortality risk (see key issue: TTNI | P)

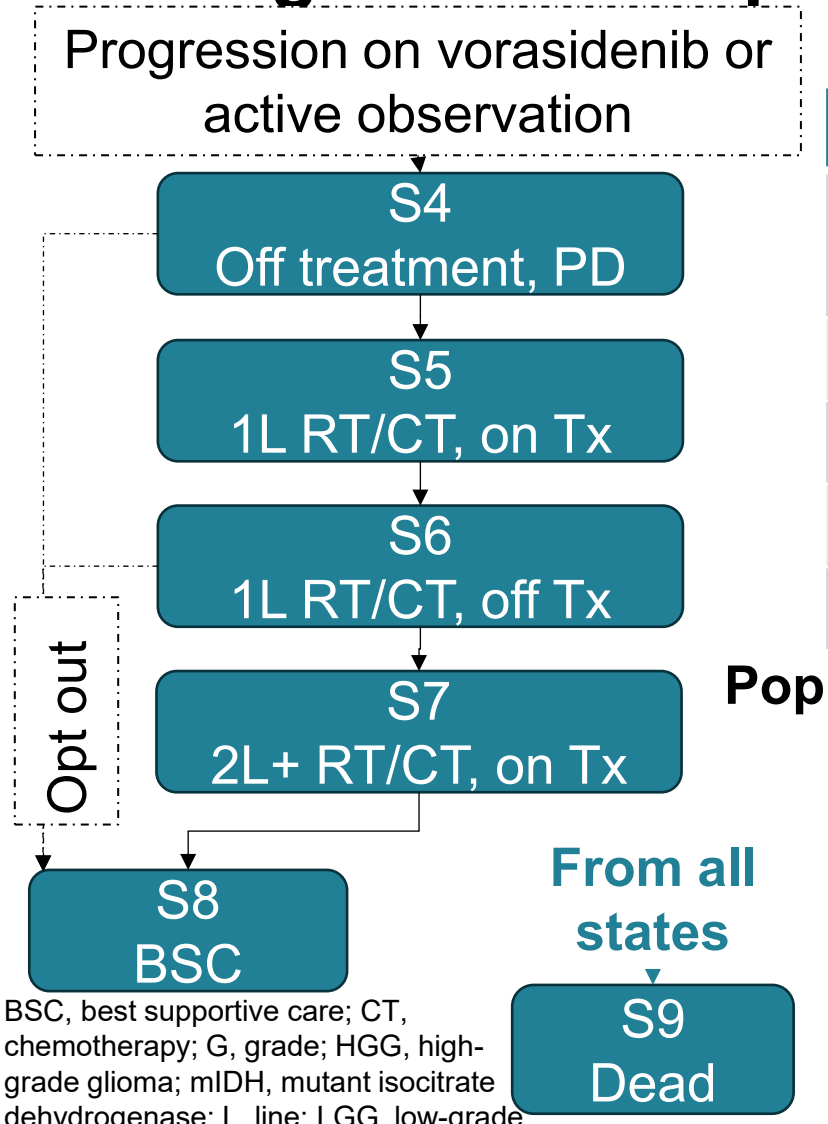
Alternative OS approach: survival hazards based on progression events over time (e.g time to HGG)

Technical team: Company assumption informs % opting out of treatment for BSC before each NI (5%)

- Is it appropriate to apply excess mortality for LGG in only the BSC health state?
- What proportion of people would choose BSC instead of RT/CT at NI each line?

BSC, best supportive care; HGG, high-grade glioma; LGG, low-grade glioma; NI, next intervention; OS, overall survival; SMR, Standardised Mortality Ratio; TTNI | P, time to next intervention given progression

Background: company's modelling of subsequent therapies



BSC, best supportive care; CT, chemotherapy; G, grade; HGG, high-grade glioma; mIDH, mutant isocitrate dehydrogenase; L, line; LGG, low-grade glioma; OS, overall survival; PFS, progression free survival; RT, radiotherapy; TTNI | P, time to next intervention given progression; TTP, time to progression

See supplementary slides: Subsequent treatments

Sources: company's modelling of subsequent treatments

N	Source
S4→ S5	INDIGO TTNI | P weighted by subtype (Baumert et. al. 2016) and % HGG (Hervey-Jumper et al. 2023)
S5 → S6	PFS (weighted by subtype) from Baumert et al. 2016, weighted by % HGG (Juratli et al. 2012)
S6 → S7	
S7 → S8	TTP: Ma et al. (2021)
S8 → S9	OS (weighted by subtype): Ma et al. (2021)

Population included in company's sources for subsequent treatment

Study	Population
Baumert et al. (2016)	G2 glioma for mIDH co-deleted and non-co-deleted having 1L RT or temozolomide (TMZ)
Hervey-Jumper et al. (2023)	Newly diagnosed G2 mIDH astrocytoma and mIDH 1p19q codeleted oligodendroglioma
Juratli et al. (2012)	Secondary mIDH HGG
Ma et al. (2021)	Recurrent mIDH astrocytoma and 1p/19q codeleted oligodendroglioma after RT

Key issue: Distribution of subsequent treatments

Company bases subsequent treatment distribution on French report, EAG uses proxy data

Background: % on subsequent treatments varies by treatment line (supplementary appendix):

- Distribution of CT treatments from French periodic synthesis report for ivosidenib (mIDH1 LGG ineligible for surgery and progressing after / ineligible to RT/CT)
- No data to inform % RT with CT: company assume 64% at 1st NI (rates in INDIGO) with 50% reduction for each successive line

EAG: Clinical advisers: differences in subsequent treatments used in Europe vs. UK.

- French review doesn't reflect NICE guideline 99 (brain cancers), includes small N and:
  - ❖ Less PCV and more TMZ as 1st NI than in UK
  - ❖ Bevacizumab as subsequent treatment (see other key issues)
- % having RT uncertain but higher at 1st line and lower at later lines in NHS than company model → RT only used twice in NHS
- Distribution of subsequent treatments in company model not histology specific, unlike PFS, TTD and OS

EAG base case: proxy for NHS practice based on NG99 and clinical advice to EAG

Subsequent treatments in EAG base case

Line	Treatment
NI 1	100% PCV + RT
NI 2	100% TMZ, 50% RT
NI 3	33% each PCV, TMZ, CCNU, no RT

Professional organisation: risk of long-term toxicity (stroke, secondary tumours, radio necrosis) often precludes use of RT in >1 line of therapy.

Do company or EAG's assumptions better reflect subsequent treatments used in the NHS?

CCNU, lomustine; CT, chemotherapy; mIDH, mutant isocitrate dehydrogenase; N, number; NG, nice guideline; NI, next intervention; OS, overall survival; LGG, low-grade glioma; PCV, procarbazine, lomustine, vincristine; PFS, progression free survival; RT, radiotherapy; TMZ. temozolomide; TTD, time to discontinuation

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

Company uses INDIGO utilities for PF and PD states and vignette utilities for NI states

Background: Company used:

a) INDIGO EQ-5D-5L mapped to EQ-5D-3L for health states associated with initial treatment

b) Company vignette in general public using EQ-5D and time trade off methods (TTO) for next intervention health states

- Health state utilities age adjusted

Company: lack of utility data from SLR required vignette for health states NI onwards

- Vignette HRQoL higher off tx than on RT/CT → considered implausible so used average between on and off tx in model

Patient experts/organisations: large impact on carers of people with LGG (see patient perspectives)

Potential sources of utility values

Health state	Utility value		
Regression model fitted to INDIGO EQ-5D-5L:			
S1: PF, on tx	0.737		
S2: PF, off tx	0.737		
S4: PD, off tx	0.728		
Vignette:	EQ-5D adjusted (company base case)	EQ-5D unadjusted (EAG base case)	TTO (EAG scenario)
S5: On NI	0.48	0.40	0.55
S6: Off NI	0.48	0.56	0.70
S7: On NI+	0.34	0.26	0.33
S8: BSC	0.34	0.42	0.54

BSC, best supportive care; CT, chemotherapy; HRQoL, health related quality of life; LGG, low-grade glioma; ; NI, next intervention; PD, progressed disease; PF, progression free; RT, radiotherapy; SLR, systematic literature review; Tx, treatment

EAG: 1. INDIGO EQ-5D appropriate but highly uncertain as:

- High baseline utility → INDIGO population more stable LGG than in NHS?
- Small HRQoL decrement moving from PF, off tx to PD, off tx (0.009) and utilities for PD lower for vorasidenib than placebo → plausible?

See supplementary slides: calculating INDIGO utilities

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

EAG: pairing vignette and INDIGO utilities may be inappropriate

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

EAG: 2. Vignette for NI states onwards: Considerable concerns about vignette:

- Lowest quality of evidence for utility values and did not separate by glioma type or grade
- EQ-5D from vignette considerably lower than a) TTO vignette utilities, b) INDIGO utilities
- Inappropriate to average on- and off-tx utilities based on:
  - ❖ Clinical advice: HRQoL increases when off-tx with RT/CT (S6) as toxicities stop
  - ❖ Different outcomes described in vignette for NI, on-tx (S5 and S7) and NI, off-tx (S6) states
- Use of different sources for utilities may be misleading as:
  - ❖ Large drop in utility when progress to NI uncertain:
    - PF (S1, S2) and PD (S4) states not included in vignette for comparison with INDIGO utilities
  - ❖ Large difference between PD, off tx (S4) and unadjusted NI, off tx (S6)
- Explored using TA977 utilities (mean utility decrements for progression lines and malignant transformation from US retrospective cohort study of N=336 (Vera et al (2023)) but:
  - ❖ Cannot translate decrements to model based on line of treatment not progression status
  - ❖ Different populations (subsequent lines in Vera et al = mix of LGG, HGG and malignant HGG).

EAG base case: unadjusted EQ-5D vignette values for NI health states onwards

EAG scenario: TTO vignette values for NI health states onwards

- Is the company's vignette appropriate for utility values for NI onwards?
- If yes, should the model use a) adjusted ED-5D (company base case), b) unadjusted EQ-5D (EAG base case) or c) TTO values?

BSC, best supportive care; HGG, high grade glioma; HRQoL, health related quality of life; LGG, low-grade glioma; N, number; NI, next intervention; PD, progressed disease; PF, progression free; TA, technology appraisal; TTO, time trade off; Tx, treatment

Other key issues highlighted by the EAG

	Description	EAG comment	Impact
Monitoring costs	Monitoring costs for CT and MRI scans included in company submission • Company assumes 3 monthly CT scans before NI, then ~1.5 monthly until BSC stated	Clinical advisers: CTs not routinely used for LGG (avoid radiation) → only used for seizure management ***EAG base case:*** no CT costs	Small 
Bevacizumab as subsequent therapy	Company base case assumes off-label bevacizumab used 35% at third line and 33% at fifth line → associated with higher cost compared to RT/CT	Bevacizumab not licenced in UK and clinical advisers confirmed not routinely used off licence to treat gliomas ***EAG base case:*** removed bevacizumab as subsequent treatment	Small 

- Are the EAG's changes appropriate for decision making?

BSC, best supportive care; CT scan, computed tomography scan; CT, chemotherapy; LGG, low-grade glioma MRI, magnetic resonance imaging; NI, next intervention; RT, radiotherapy; Tx, treatment

Key issue: non-reference case discount rate

Company uses 1.5% discount rate for costs and effects; EAG prefer 3.5%

Criterion for applying a 1.5% discount rate for costs and effects

	1. People would otherwise die / QoL severely impaired	2. Likely restores full health
Company	• Active observation arm: rapid negative effect with current care, especially with RT/CT • Large QoL impact from RT/CT side effects of → productivity loss, inability to work, premature mortality	INDIGO trial: vorasidenib prolongs time spent in good heath prior to progression
EAG	**Population would not otherwise die:** • Early stable LGG with no immediate need of RT/CT → evidenced by active observation as comparator • Model predicts 15-year median OS for active observation and only 1 death in INDIGO **No evidence to support that QoL severely impaired:** • INDIGO EQ-5D: small HRQoL decrement vs age and sex matched general population utilities • Utility values for progressed disease highly uncertain and do not support large QoL impact from RT/CT → low vignette utilities for both on/off tx.	**No supportive evidence:** • IDH-mutant glioma incurable after resection • Relative rate of delayed progression to RT/CT uncertain due to issues with TTNI outcome • Higher HRQoL in INDIGO in placebo arm vs. vorasidenib arm after progression

CT, chemotherapy; HRQoL, health related quality of life; IDH, isocitrate dehydrogenase; LGG, low-grade glioma; OS, overall survival; QoL, quality of life; RT, radiotherapy; TTNI, time to next intervention; tx, treatment

Key issue: non-reference case discount rate

Company uses 1.5% discount rate for costs and effects; EAG prefer 3.5%

3. Benefits sustained for long period of time

Company	Lifetime benefits → median PFS not reached in INDIGO for vorasidenib arm
EAG	**Insufficient evidence to confirm** → not supported by INDIGO results: • No OS data, PFS benefit at 30 months based on small N, TTNI outcome uncertain → unproven that these outcomes translate to OS gains • No difference in rate of malignant transformation between arms

NICE technical team: NICE health technology evaluations: the manual states that to accept a 1.5% discount rate committee need to be:

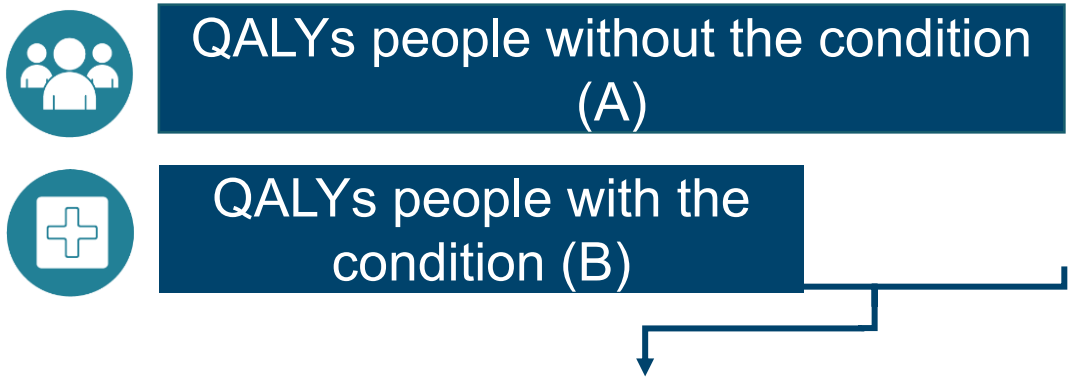
- *"confident that there is a highly plausible case for the maintenance of benefits over time"*
- *"satisfied that any irrecoverable costs associated with the technology … have been appropriately captured in the economic model or mitigated through commercial arrangements"*

N, number; OS, overall survival; PFS, progression free survival; TTNI, time to next intervention

Have the criteria for applying a 1.5% discount rate been met?

QALY weightings for severity (1/2)

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 (2/2)

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

Background: EAG and company agree that severity weighting applies for this topic

- EAG base case applies lower severity weighting of x1.2 vs company base case of x1.7 → driven by use of 3.5% discount rate (see key issue: discount rate)
- All EAG scenarios using 3.5% discount rate meet x1.2 weighting criteria except scenario 3a (generalised gamma for TTNI | P, pooled INDIGO data) and 8 (TTO utility values) where no severity weight applies

Baseline characteristics used in company's calculation of QALY shortfall

Factor	Value
% female	44%
Starting age	40 years

	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**
Company base case (3.5% discount rate)	18.65	6.26	12.39	0.66	**x1.2**
EAG base case	18.65	5.69	12.96	0.69	**x1.2**

Is it appropriate to apply a QALY weighting for severity? If yes, x1.2 or x1.7 weighting?

Other considerations

CT, chemotherapy; RT, radiotherapy

Uncaptured benefits

Company: following benefits of vorasidenib from delaying disease progression or effects of RT/CT are not captured in the modelling:

1. Beneficial health effects to family members or caregivers including:
   - Ability to perform daily activities
   - Productivity loss resulting care requirements
2. Wider societal benefits including:
   - Lack of neurological deficit: continued ability to work and reduced nursing home care
   - Continued ability to drive

Rarity

Technical team: condition is rare (oligodendroglioma = ~0.5 per 10,000, astrocytoma = ~1.12 per 10,000 in England).

NICE health technology evaluations: the manual: *"the committee will be mindful that there are certain technologies or populations for which evidence generation is particularly difficult because they are…rare diseases… In these specific circumstances, the committee may be able to make recommendations accepting a higher degree of uncertainty. The committee will consider how the nature of the condition or technology(s) affects the ability to generate high-quality evidence before applying greater flexibility."*

Are there uncaptured benefits or rarity considerations relevant for decision making?

Summary of company and EAG base case assumptions

Assumptionc	Company base case	EAG base case
TTNI | P curves	Separate curves by treatment arm, generalised gamma	Same curve for vorasidenib and active observation → pooled arms of INDIGO, log-normal
Bevacizumab as subsequent treatment	Include	Exclude
% RT/CT at subsequent lines	Market share data from France	Proxy for NHS practice
Monitoring costs for CT scans	Included	Excluded
EQ-5D utilities values for subsequent treatment lines	Adjusted vignette values - do not differentiate on- and off-treatment	Unadjusted vignette values
Discount rate	1.5% per annum	3.5% per annum
Severity weighting	X1.7	X1.2

CT, chemotherapy; CT scan, computed tomography scan; RT, radiotherapy; TTNI | P, time to next intervention given progression

See supplementary slides: Company scenarios, EAG scenarios

ICER, incremental cost-effectiveness ratio;
QALY, quality-adjusted life year

Cost-effectiveness results

All ICERs are reported in PART 2 slides

because they include confidential

Patient Access Scheme discounts

- There are confidential discounts in place for vorasidenib and for other medicines used in the model
- The company's base case is between £20,000 and £30,000 per QALY gained
- The EAG's base case is above the range NICE normally considers acceptable

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

- ❑ Background and key issues
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ✓ **Other considerations**
- ❑ Summary

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Managed access

Criteria for a managed access recommendation

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**.

Company: propose vorasidenib as candidate for Cancer Drugs Fund (CDF):

- 2028 INDIGO data cut could resolve uncertainty on OS, PFS and TTNI benefit with vorasidenib and duration of treatment with vorasidenib
- SACT, RTDS and Blueteq data could help resolve outstanding uncertainties.

EAG comments: value of CDF data likely limited as:

- Limited clinical value of TTNI outcome due to high crossover in placebo arm
- Max CDF follow up 5 years: unlikely median OS (and plausibly TTNI) calculable for vorasidenib
- Next planned data cuts are May 2025 (safety data only) and May 2028.

OS, overall survival; PFS, progression free survival; RTDS, radiotherapy data set; SACT, systemic anti-cancer therapy; TTNI, time to next intervention

Insights from the NICE managed access team

May be further value in collecting data through managed access scheme

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 managed access agreement.

Questions from the MAA team:

- Would data on surgery pre-intervention aid in decision making at managed access exit?
- Would it be helpful to collect data on surgery and/or RT post-treatment through SACT? Is this data currently available for people having active observation?
- Is the interval between stopping vorasidenib and starting next treatment a suitable proxy for time off treatment?
- Is there is enough time to collect data on subsequent treatments considering the length of time people are likely to stay on vorasidenib for?

MAA, managed access arrangement; RTDS, radiotherapy data set; RWE, real world evidence; SACT, systemic anti-cancer therapy; TTNI, time to next intervention

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

- ❑ Background and key issues
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ❑ Other considerations
- ✓ **Summary**

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Key issues

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

Issue	Resolved?	Impact
Restricted trial population compared to NHS LGG population	No: for discussion	Unknown
Generalisability of outcomes from INDIGO	No: for discussion	Unknown
Immaturity of INDIGO data	No: for discussion	Unknown
Surrogacy relationship for OS benefit	No: for discussion	Unknown
Interpretation of TTNI I P outcome and resulting duration of time off treatment with progressed disease	No: for discussion	Large
Evidence for subsequent treatment lines and excess mortality for BSC	See supplementary appendix	Unknown
Use of French market share data for subsequent chemotherapies	No: for discussion	Small
Bevacizumab as subsequent treatment	Yes	Small
Plausibility of health state utility values from vignette	No: for discussion	Large
Include costs of monitoring CT scans	Yes	Small
Non-reference case discount rate for costs and health effects	No: for discussion	Large
Appropriate severity weighting	No: for discussion	Large

BSC, best supportive care; CT, computed tomography; LGG, low-grade glioma; 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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INDIGO trial data analysis sets

See main deck: INDIGO trial design

Analysis set	Description	Endpoints
Full Analysis Set (FAS)	All randomised subjects (according to ITT principle)	Baseline characteristics, disposition, major protocol deviations, subsequent therapies, efficacy
Per Protocol Set (PPS)	Subset of FAS → excluded people who had: • No dose of randomised treatment • No measurable lesions at baseline assessed by BIRC using mRANO-LGG • No histopathologically diagnosed G2 oligodendroglioma or astrocytoma per WHO 2016 criteria • Prior anticancer therapy apart from surgery for glioma	PFS and TTNI
Safety Analysis Set (SAS)	Had 1 or more dose of study treatment → classed according to randomised treatment	Exposure, concomitant treatment

BIRC, blinded independent review committee; G, grade; ITT, intention to treat; mRANO-LGG, modified Response Assessment in Neuro-Oncology for LGG; PFS, progression free survival; TTNI, time to next intervention; WHO, world health organisation

Baseline characteristics INDIGO

Link to, main slides: key clinical trials

Baseline characteristics of the INDIGO trial (Full analysis set)

	Vorasidenib (n=168)	Placebo (n=163)
Median age, years (range)	41 (21-71)	39 (16-65)
Male sex, %	60	53
Recruited in Western Europe, %	34	25
Time from last surgery for glioma to randomisation, mean, years	2 (1)	3 (1)
Location of tumour at initial diagnosis %		
Frontal	64	71
Non-frontal	36	29
Number of previous surgeries for glioma, n (%)		
1	126 (75)	134 (82)
≥2	42 (25)	29 (18)
Longest diameter of tumour, n (%)		
≥2 cm	139 (83)	137 (84)
<2 cm	29 (17)	26 (16)

BNOS, British Neuro Oncology Society; cm, centimetre; n, number

EAG comments

- Clinical advice suggests % with longest diameter ≥2 cm likely lower in NHS (max 60-70% people) than INDIGO
- Tumour diameter may be effect modifier → reduced treatment effect (and cost effectiveness) in NHS vs INDIGO?

Stakeholders: BNOS:

- Only 1 patient (in placebo arm) under 18 and only 3 over 65 years.
- Unclear how extent of resection, tumour size and site, time of treatment, recurrent disease, affect effectiveness

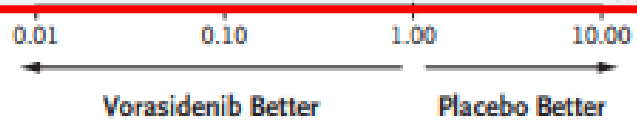
See main deck: generalisability of INDIGO

INDIGO trial: Subgroup analyses

Potential subgroup effect by tumour diameter at baseline for PFS and TTNI

Subgroup analyses of a) PFS and b) TTNI, September 2022 data cut

Subgroup	No. of Events/ Total No. of Patients (%)	Hazard Ratio for Disease Progression or Death (95% CI)	No. of Events/ Total No. of Patients (%)	Hazard Ratio for Next Anticancer Treatment or Death (95% CI)
Overall	135/331 (40.8)	0.39 (0.27–0.56)	77/331 (23.3)	0.26 (0.15–0.43)
Age				
<18 yr	0/1	NE (NE–NE)	0/1	NE (NE–NE)
18 to 39 yr	80/163 (49.1)	0.47 (0.29–0.75)	49/163 (30.1)	0.30 (0.16–0.59)
40 to 64 yr	53/164 (32.3)	0.32 (0.18–0.58)	28/164 (17.1)	0.23 (0.10–0.53)
≥65 yr	2/3 (67)	NE (NE–NE)	0/3	NE (NE–NE)
Sex				
Male	72/187 (38.5)	0.39 (0.24–0.64)	43/187 (23.0)	0.25 (0.13–0.49)
Female	63/144 (43.8)	0.41 (0.24–0.70)	34/144 (23.6)	0.27 (0.12–0.63)
Geographic region				
North America	89/193 (46.1)	0.34 (0.21–0.54)	48/193 (24.9)	0.18 (0.09–0.39)
Western Europe	31/97 (32)	0.54 (0.27–1.10)	14/97 (14)	0.37 (0.12–1.11)
Israel	15/41 (37)	0.45 (0.16–1.31)	15/41 (37)	0.30 (0.10–0.84)
Location of tumor at initial diagnosis				
Frontal lobe	92/222 (41.4)	0.47 (0.30–0.73)	52/222 (23.4)	0.29 (0.16–0.55)
Nonfrontal lobe	43/109 (39.4)	0.26 (0.14–0.50)	25/109 (22.9)	0.20 (0.08–0.50)
Time from last surgery to randomization				
<2 yr	51/130 (39.2)	0.44 (0.24–0.82)	34/130 (26.2)	0.28 (0.12–0.64)
2 to 3 yr	59/145 (40.7)	0.39 (0.23–0.66)	34/145 (23.4)	
≥4 yr	25/56 (45)	0.28 (0.10–0.76)	9/56 (16)	
No. of previous surgeries				
1	106/260 (40.8)	0.41 (0.27–0.61)	58/260 (22.3)	
≥2	29/71 (41)	0.31 (0.14–0.68)	19/71 (27)	
Chromosome 1p/19q codeletion status				
Codeleted	59/172 (34.3)	0.32 (0.18–0.57)	27/172 (15.7)	
Non-codeleted	76/159 (47.8)	0.47 (0.29–0.75)	50/159 (31.4)	
Longest diameter of tumor at baseline				
≥2 cm	109/269 (40.5)	0.32 (0.21–0.48)	65/269 (24.2)	0.21 (0.12–0.38)
<2 cm	26/62 (42)	0.81 (0.37–1.77)	12/62 (19)	0.64 (0.20–2.03)



Potential subgroup effect?

CI, confidence interval; cm, centimetre; NE, non evaluable; no, number; PFS, progression free survival; TTNI, time to next intervention; yr, year

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 Neuro-Oncology for LGG; MR, minor response; PD, progressed disease; PR, partial response

See main deck: TTNI results

INDIGO trial: safety outcomes

Higher treatment emergent AEs in vorasidenib vs placebo arm, especially grade 3 and over

Most common TEAEs (any Grade in ≥10% of patients or Grade ≥3 in ≥5% of patients) (SAS), DCO September 2022

Event, N (%)	Vorasidenib (N=167)		Placebo (N=163)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Any AE	**158 (95)**	**38 (23)**	**152 (93)**	**22 (14)**
Increased ALT	65 (39)	16 (10)	24 (15)	0
Increased AST	48 (29)	7 (4)	13 (8)	0
Increased GTT	26 (16)	5 (3)	8 (5)	2 (1)
COVID 2019	47 (29)	0	55 (33)	0
Fatigue	54 (32)	1 (1)	52 (32)	2 (1)
Headache	45 (27)	0	44 (27)	1 (1)
Diarrhoea	41 (25)	1 (1)	27 (17)	1 (1)
Nausea	36 (22)	0	37 (23)	0
Dizziness	25 (15)	0	26 (16)	0
Seizure	23 (14)	7 (4)	19 (12)	4 (3)
Constipation	21 (13)	0	20 (12)	0

- Treatment related TEAEs higher in vorasidenib arm (109, 65%) than placebo (95, 58%) of which:
  - 22 (13%) in vorasidenib arm and 6 (4%) in placebo arm were grade ≥3
- No AEs led to death

TEAEs leading to discontinuations, interruption, or reduction, DCO March 2023

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

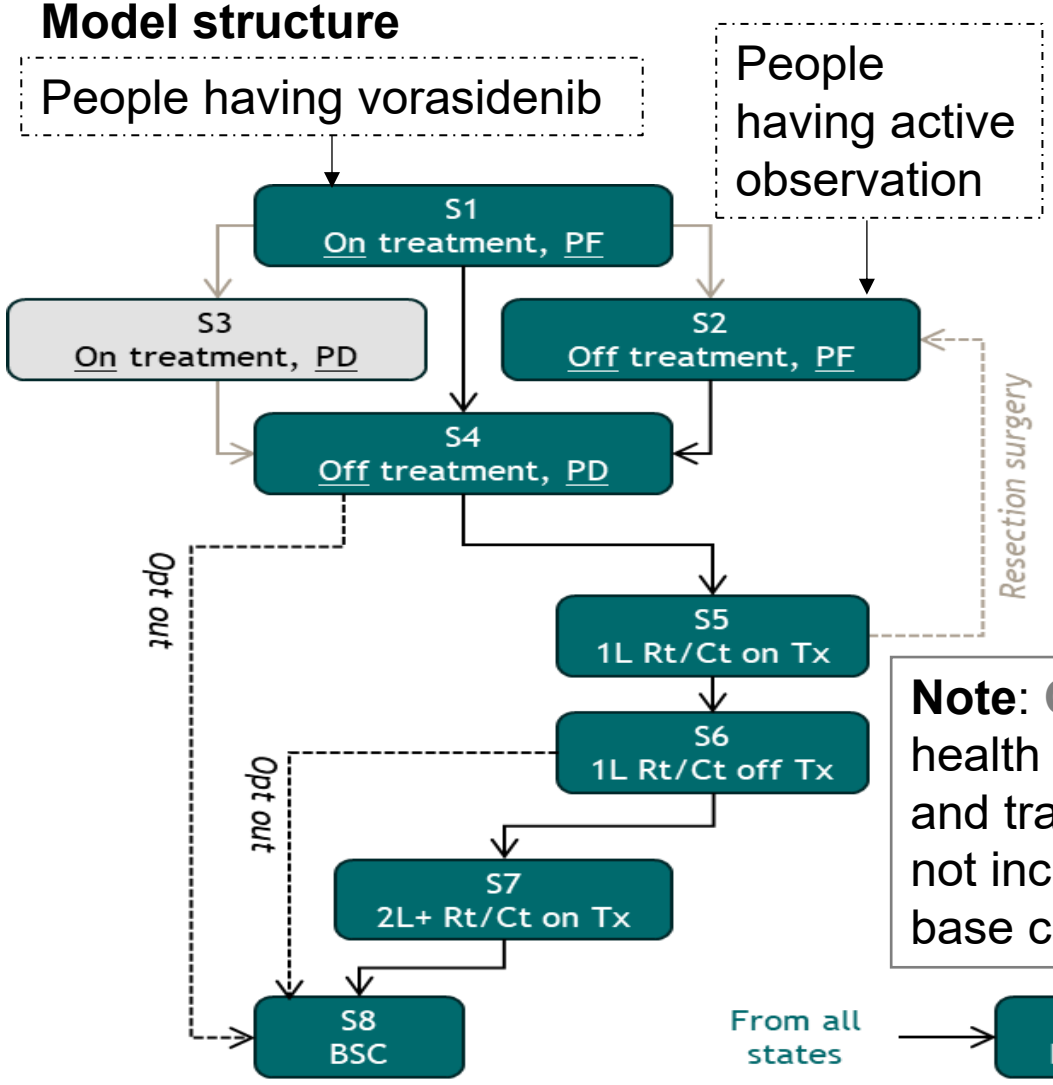
AE, adverse event; ALT, Alanine Aminotransferase; AST, aspartate aminotransferase; DCO, data cut off; GGT, γ-glutamyltransferase; N, number; TEAE, treatment emergent adverse events; SAS, safety analysis set

Company's model overview

See main deck: Company base case model

INDIGO informs initial treatment health states, literature sources inform later treatment lines

Model structure



Note: Grey health states and transitions not included in base case

BSC, best supportive care; CT, chemotherapy; HGG, high-grade glioma; ICER, incremental cost-effectiveness ratio; PD, progressed disease; PF, progression free; PFS, progression free survival; RT, radiotherapy; sPFS, secondary progression-free survival; TTNI, time to next intervention; TTNI | P, time to next intervention given progression; TTP, time to progression; QALY, quality adjusted life year

Vorasidenib affects costs vs active observation by:

- Accruing treatment costs in PF states
- Avoiding costs for subsequent treatments (delays time to next intervention after PD)

Vorasidenib affects QALYs vs active observation by:

- Increasing time in PF states and delaying TTNI and RT/CT

Assumptions with greatest effect on the ICER:

- Extrapolation of TTNI (curve chosen, separate vs pooled arms)
- Health state utility values for subsequent treatments

Sources informing transitions in company's base case model

State	Source
S1 or S2 → S4	INDIGO PFS (as proxy for TTP)
S4→ S5	INDIGO TTNI | P with histological mix from Baumert et. al. (2016) and % with HGG from Hervey-Jumper et. al. (2023)
S5 → S6	Baumert 2016 PFS, weighted, combined with HGG sPFS median from Juratli 2012
S6 → S7	
S7 → S8	Ma 2021 TTP
S1 to S7 → S9	General population life tables
S8 → S9	Ma 2021

See main deck: Company base case model

Detailed efficacy inputs in the company's model

Parameter	Intervention	Source selected	Extrapolation
PFS/TTP	Vorasidenib	PFS vorasidenib arm of INDIGO	Log-normal
	Active observation	PFS placebo arm of INDIGO	Log-normal
TTNI | P	Vorasidenib	TTNI | P for INDIGO vorasidenib arm	Gen. gamma
	Active observation	TTNI | P for INDIGO placebo arm	Gen. gamma
NI	1L RT/CT	PFS 1L RT/CT (Baumert et al. 2016), weighted by glioma subtype + combined with HGG median sPFS from Juratli et al. (2012)	IDH codeleted: Log-normal IDH non-codeleted: Gamma
NI+	2L+ RT/CT	TTP for salvage therapy (Ma et al., 2021) as time to BSC proxy, weighted by glioma subtype	Astro: Gen. gamma Oligo: Gompertz
	BSC	OS for salvage therapy from Ma et al (2021) , weighted by glioma subtype	Astro: Log-normal Oligo: Log-normal
OS	NA	General population lifetables: excess mortality assumed only for BSC (S8 health state)	N/A

BSC, best supportive care; CT, chemotherapy; HGG, high-grade glioma; IDH, isocitrate dehydrogenase; L, line; NA, not applicable; NI, next intervention; OS, overall survival; PFS, progression free survival; RT, radiotherapy; sPFS, secondary progression-free survival; TTNI | P, time to next intervention given progression; TTP, time to progression; tx, treatment

EAG comments on company model

See main deck: Company base case model

EAG comments:

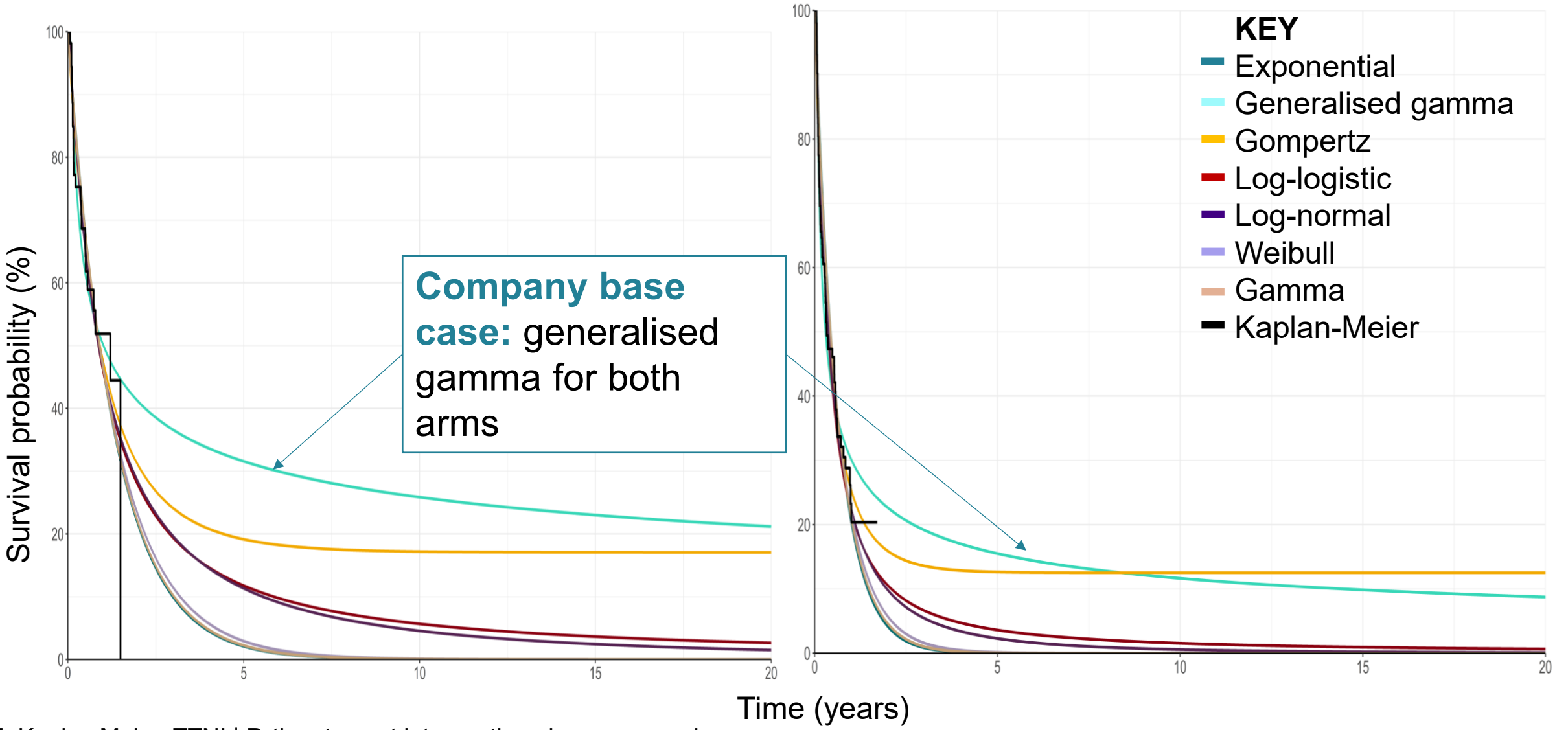
- May be more appropriate to model progression events over time (e.g. transition from LGG to HGG or malignant glioma) → key milestones in context of prognosis, HRQoL and survival
- TA977 used treatment-based milestones but also modelled transformation to malignant glioma and HGG and limited LGG to 25 years
- Company's model requires clear link between treatments required and progression events (transition to HGG, malignant transformation)
- Company was unable to adopt partitioned survival model due to lack of mature OS data
- Model assumes that delaying progression to subsequent treatments is surrogate for OS but time to subsequent treatments uncertain as based on multiple sources (see key issue: subsequent treatments)

HRQoL, health related quality of life; HGG, high-grade glioma; LGG, low-grade glioma; OS, overall survival; TA, technology appraisal

Background: company's use of conditional outcome TTNI | P

Company independently fitted parametric curves to extrapolate the INDIGO TTNI | P KM data

a) vorasidenib **b) placebo**

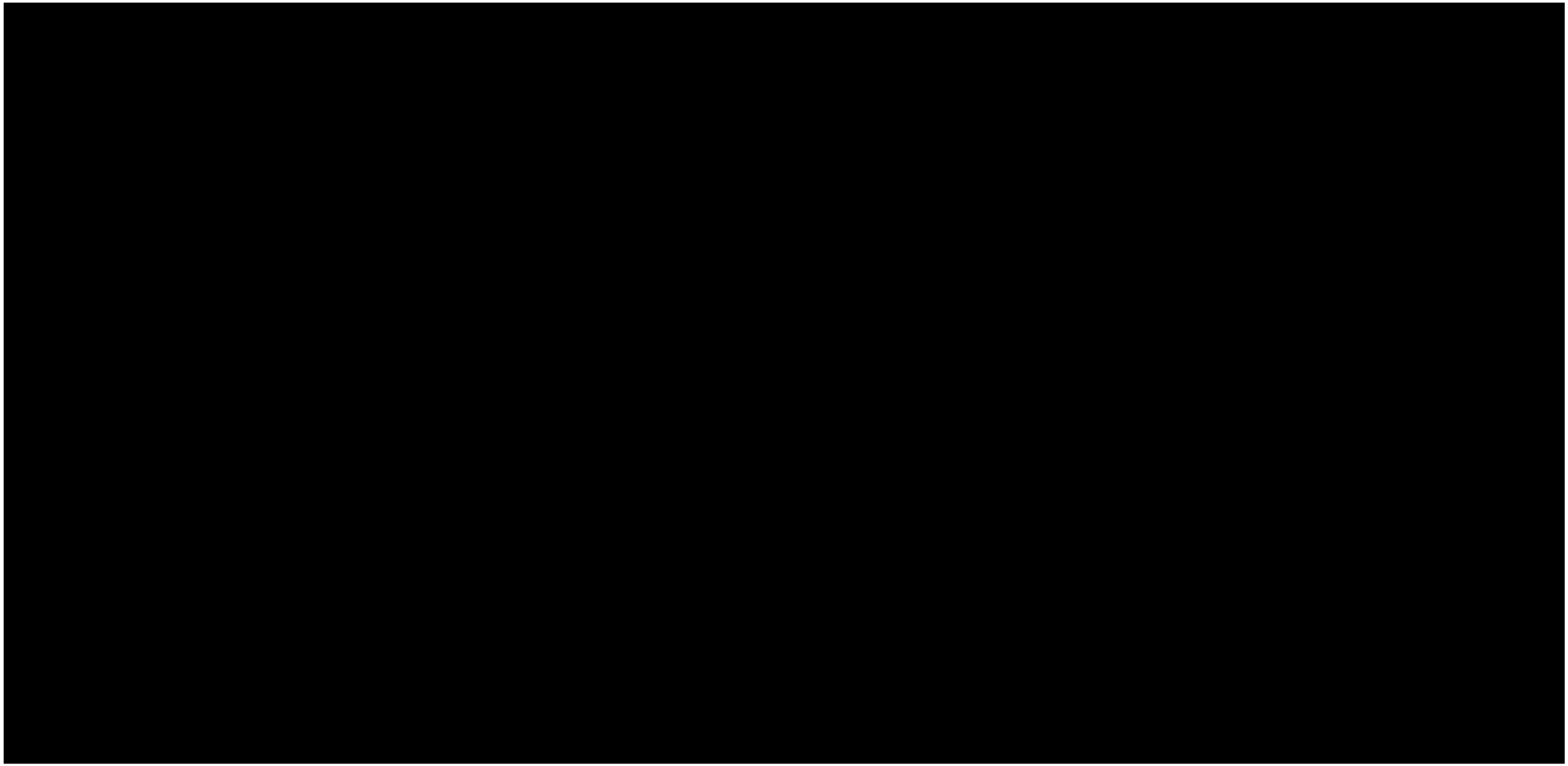


KM, Kaplan Meier; TTNI | P, time to next intervention given progression

See main deck: Key issue: TTNI|P

See main deck: Key issue: TTNI|P

INDIGO trial: TTNI | P by change in tumour volume



BIRC, blinded independent review committee; CI, confidence interval; DCO, data cut off; NE, not evaluable; PD, progressed disease; TTNI, time to next intervention; TTNI | P, time to next intervention given progression; TV, tumour volume

See main deck: Key issue: TTNI|P

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%).

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

[redacted]

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

- [redacted]
- [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

Company's multiple imputation (MI) method

See main deck: Key issue: TTNI|P: impact of crossover

Exploratory analysis adjusting INDIGO TTNI data for crossover using MI method

Company: used MI instead of IPCW as missing data required estimation, not just reweighting

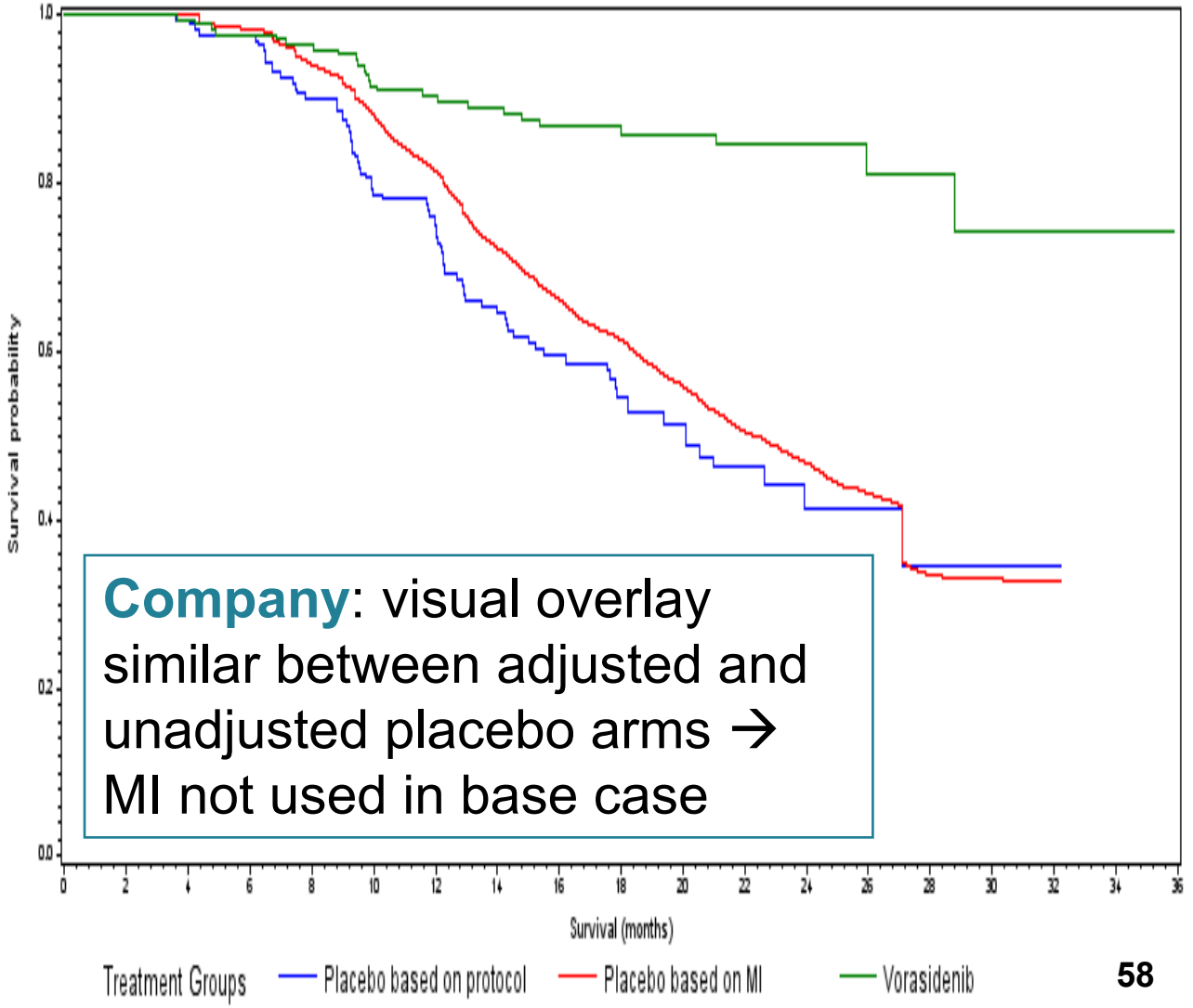
- MI method assumes vorasidenib unavailable in trial so TTNI for people who crossed over could not be used in analysis → TTNI imputed for these people

Source of TTNI in the placebo arm of company's MI analysis

Cross over to vorasidenib?	N	Source of TTNI data
No	93	TTNI in non-crossover group
Yes	70	TTNI for people who discontinued treatment for any reason in the vorasidenib arm

DCO, data cut off; IPCW, inverse-probability-of-censoring weighting; N, next intervention; TTNI, time to next intervention

Exploratory analysis of TTNI based on MI and protocol definition Mar 2023 DCO



Company: visual overlay similar between adjusted and unadjusted placebo arms → MI not used in base case

Key issue: TTNI | P a) Impact of crossover in placebo arm

EAG comments: TTNI | P confounded by cross-over in 43% placebo arm (see key issue: trial outcomes)

- Limited relevance of placebo arm results to NHS practice → vorasidenib used as subsequent treatment
  - May not be best available treatment after PD → delayed access to life-prolonging therapies
  - TTNI | P measured time to any NI, not just RT/CT as in model
- Timing of progression differs between INDIGO arms → number of patients at risk informing TTNI | P in vorasidenib arm extremely low (most people's follow up ended before had NI)
- Concerns with MI method:

1. Not standard cross-over adjustment → IPCW preferred in HTAs for censored crossover data
2. Imputed data from vorasidenib, not placebo arm → assumes similar reasons and timings for NI between arms, contradicts company's preference for individually fitted curves
3. Company have not adjusted TTNI | P → cannot address impact of crossover on ICER

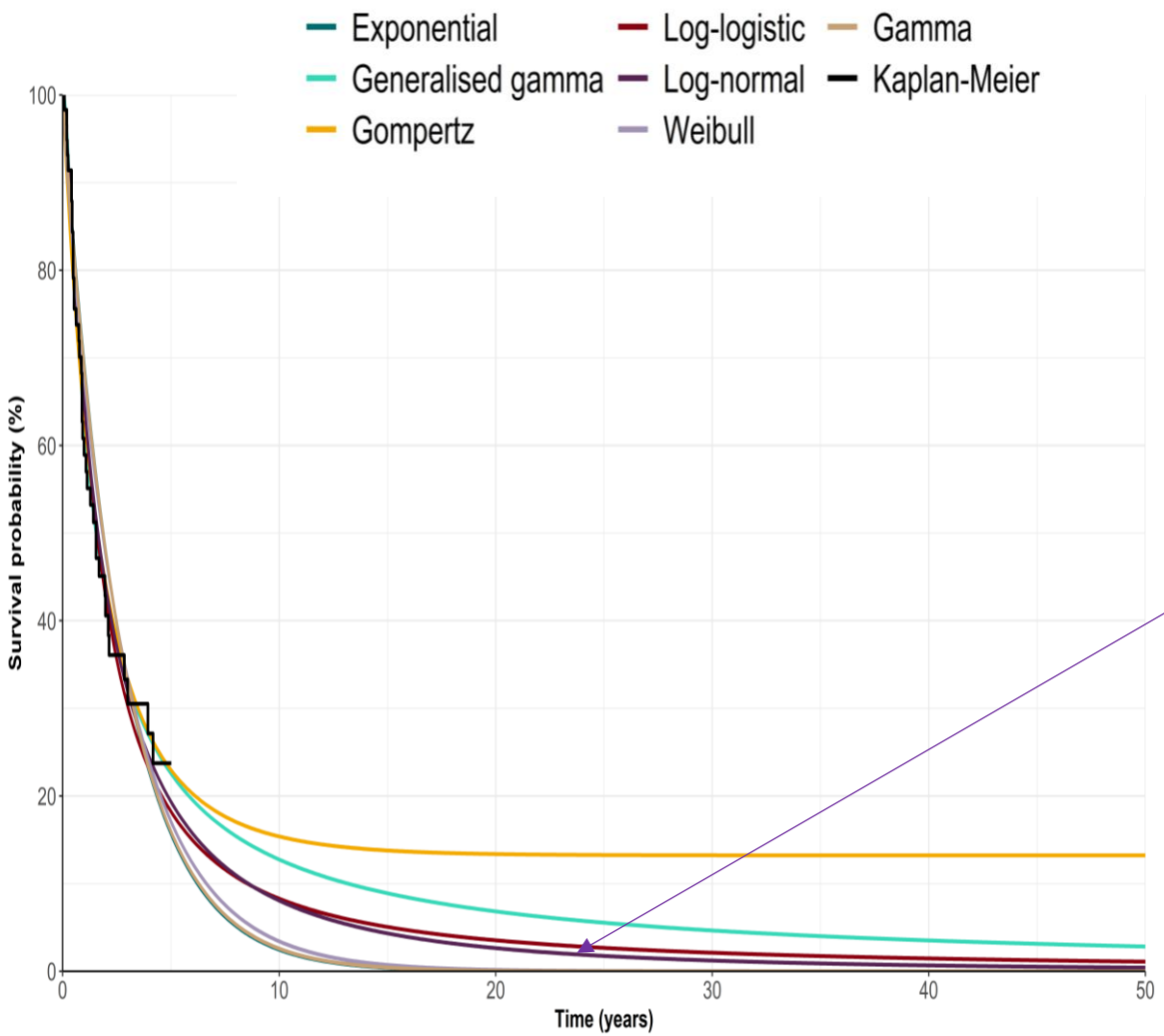
Company chose less conservative approach for base case → TTNI longer for placebo arm in adjusted vs unadjusted analysis

DCO, data cut off; HTA, health technology assessment; ICER, Incremental Cost-Effectiveness Ratio; IPCW, inverse-probability-of-censoring weighting; MI, multiple imputation; NI, next intervention; PD, progressed disease; TTNI, time to next intervention; TTNI | P, time to next intervention given progression

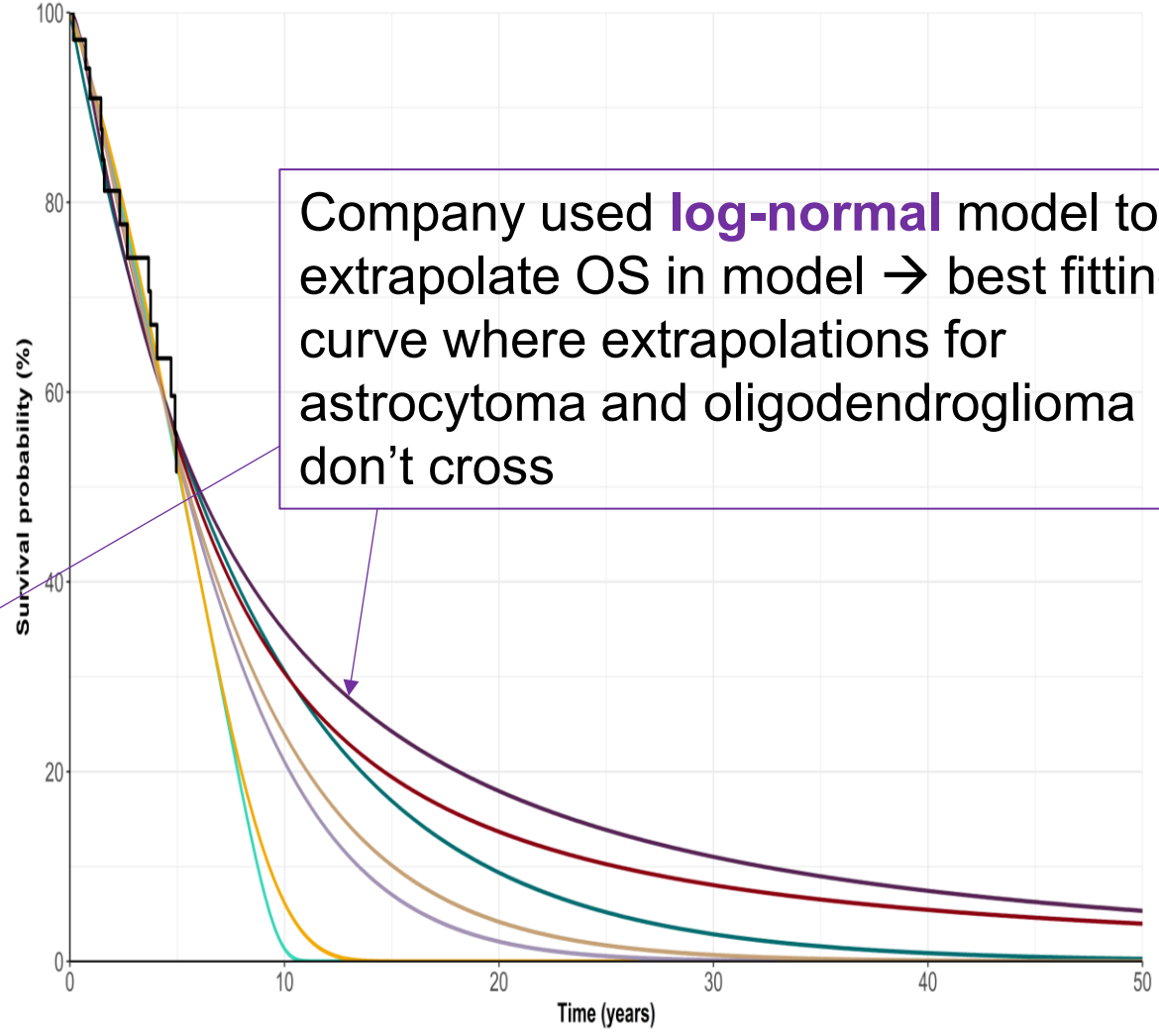
See main deck: Key issue: overall survival

Key issue: Modelling overall survival (3)

Extrapolations of OS in IDHmt astrocytoma in people having BSC, Ma *et al.*, (2021)



Extrapolations of OS in 1p/19q co-deleted oligodendrogliomas in people having BSC, Ma *et al.*, (2021)



Company used **log-normal** model to extrapolate OS in model → best fitting curve where extrapolations for astrocytoma and oligodendroglioma don't cross

BSC, best supportive care; IDHmt, mutant isocitrate dehydrogenase; OS, overall survival

Subsequent treatments in the company's base case model

Subsequent treatments used in the company's model

Line	Treatment	Percentage of cohort within treatment line		
		With RT	Without RT	Total CT/RT
NI: 1L	PCV	4.28%	2.41%	6.69%
	TMZ	22.38%	12.59%	34.97%
	CCNU	37.33%	21.00%	58.33%
NI+: 2L	PCV	8.61%	39.25%	47.86%
	TMZ	7.14%	32.52%	39.66%
	CCNU	1.88%	8.55%	10.43%
	Bevacizumab	0.37%	1.68%	2.05%
NI+: 3L	PCV	2.34%	23.64%	25.98%
	TMZ	1.19%	11.98%	13.17%
	CCNU	2.34%	23.64%	25.98%
	Bevacizumab	3.14%	31.74%	34.88%
NI+: 4L	PCV	0.71%	13.41%	14.12%
	TMZ	1.41%	26.83%	28.24%
	CCNU	2.88%	54.77%	57.65%
NI+: 5L	PCV	0.67%	32.66%	33.33%
	TMZ	0.33%	16.34%	16.67%
	CCNU	0.33%	16.34%	16.67%
	Bevacizumab	0.67%	32.66%	33.33%

Company assumes:

- RT used with TMZ and bevacizumab and before PCV and CCNU
- CT reported as 'other'= CCNU

See main deck: Key issue: distribution of subsequent treatments

CT, chemotherapy; CCNU, lomustine; L, line; NI, next intervention; PSV, procarbazine, CCNU and vincristine; RT, radiotherapy; TMZ, temozolomide

Key issue: Subsequent treatments

EAG concerned that sources informing efficacy for NI onwards not comparable

Company: sources for subsequent treatment lines based on targeted pragmatic searches informed by clinical experts → did not do SLR

EAG: concerns about reliance on multiple sources for non-comparable populations:

1. Limited justification for sources/relevance to UK and INDIGO populations → no UK studies or studies for people who don't need immediate treatment after surgery
2. Simplifying PFS assumptions: PFS assumed equal to TTP in Baumert et al, despite deaths in study; rate of malignant transformation not specifically modelled; PFS estimates based on mix of populations, settings and treatments
3. Ma et al. (used for progression to BSC and excess mortality in BSC state) includes:

- treatments not reflective of NHS → included bevacizumab (not licenced in UK)
- Small cohort, includes pre-progression deaths for people having 2L+ RT/CT→ not reflective of model where excess mortality only applies to BSC

Prefer company to do full SLR to inform post progression data sources.

BSC, best supportive care; CT, chemotherapy; L, line; PFS, progression free survival; TTP, time to progression; SLR, systematic literature review; RT, radiotherapy

See main deck: Key issue: distribution of subsequent treatments

Background: calculating utility values from INDIGO

See main deck: Key issue: health state utilities

1. Company took EQ-5D-5L collected before and after progression in the INDIGO trial:

	Vorasidenib, PF	Vorasidenib, PD	Placebo, PF	Placebo, PD
N observations	716	81	549	170
Mean utility (95% CI)	0.744 (0.731, 0.621)	0.678 (0.621, 0.735)	0.745 (0.732, 0.758)	0.730 (0.707, 0.753)
SD	0.179	0.258	0.152	0.151
Median	0.777	0.742	0.777	0.774

EAG: note PD utilities higher in placebo than vorasidenib arm

2. Calculated utility values by progression and treatment status (not treatment specific):

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

3. Mapped utility values from EQ-5D-5L to 3L and fitted regression models:

Status	Base case (Progression flag and baseline utility)	Sensitivity analysis (progression flag only)
S1 and S2 – PF, on and off tx	0.737	0.747
S3 and S4 – PD, on and off tx	0.728	0.729

CI, confidence interval; LQ, lower quartile; N, number; PD, progressed disease; PF, progression free; SD, standard deviation; tx, treatment; UQ, upper quartile

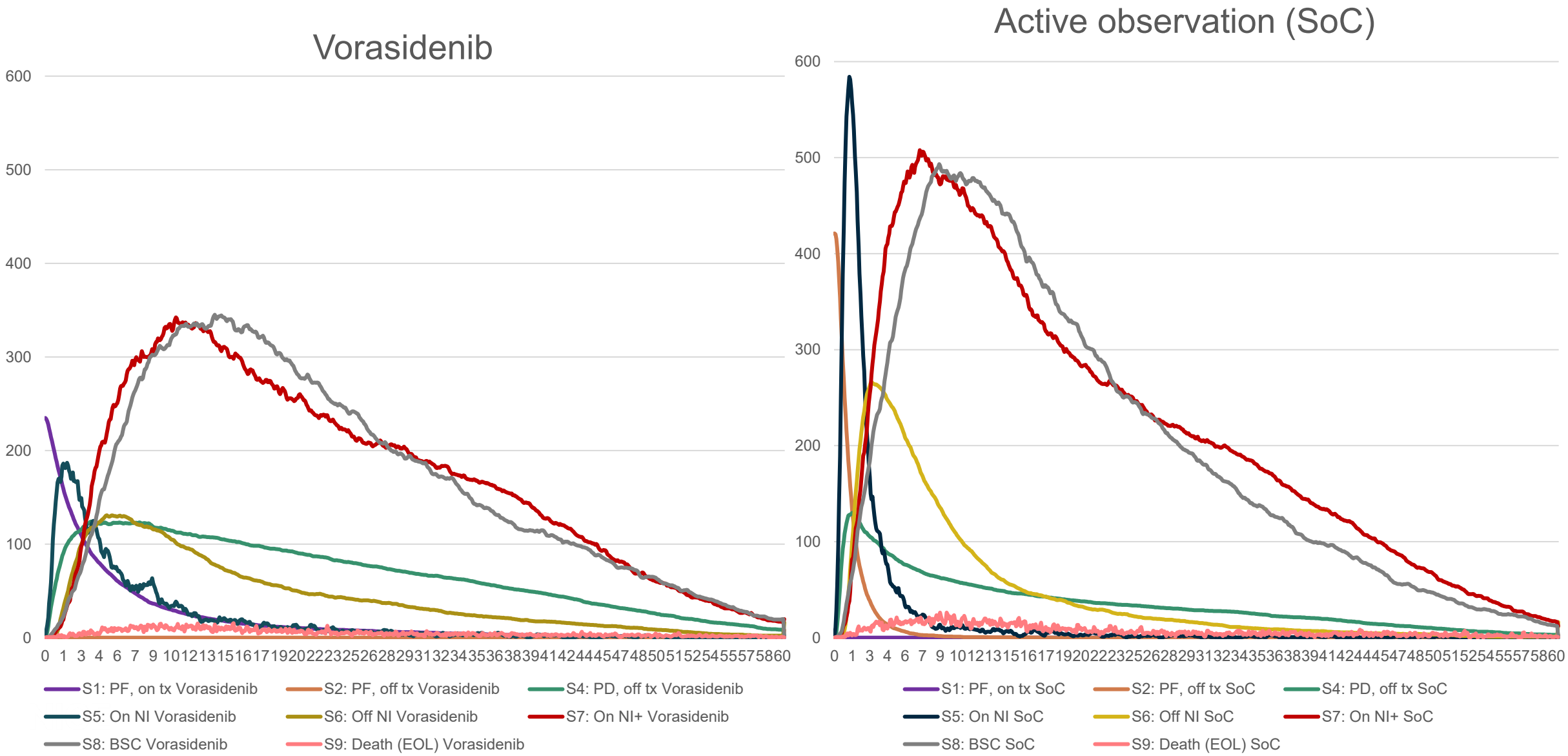
Health state resource use and costs in company and EAG base case models

Resource/ state	Cost per use	Health state (state 3 not in base case)							
		PF		PD	NI		NI +		Death
		On tx	Off tx	Off tx	On tx	Off tx	On tx	Off tx	
		Expected frequency per 28 days							
CT scan	£117	0.33	0.33	0.33	0.67	0.67	0.67	0.00	0.00
MRI scan	£197	0.17	0.17	0.17	0.33	0.33	0.33	0.00	0.00
Hospital visit (unscheduled)	£873	0.01	0.01	0.01	2.00	0.01	2.00	2.00	0.00
Consultant visit	£231	0.17	0.17	0.33	0.33	0.33	0.33	0.33	0.00
Seizure management	£203	0.52	1.43	1.43	1.79	1.79	2.24	2.80	0.00
GP appointment	£49	0.16	0.16	0.31	0.31	0.31	0.31	0.31	0.00
Home visitor	£28	0.08	0.08	0.08	0.08	0.08	0.08	0.08	0.00
		One off resource use when entering health state							
Debulking surgery	£15,877	0.00	0.00	0.00	0.30	0.00	0.30	0.00	0.00
Total costs per health state (undiscounted) in base case for:									
Company	Vorasidenib	15,995	0	52,314	16,075	32,932	131,165	129,812	5,351
	Active observation	0	7,806	27,054	18,620	34,877	166,491	155,501	5,446
EAG	Vorasidenib	13,327	0	6,751	22,184	32,511	164,371	157,733	5,444
	Active observation	0	7,080	6,977	22,853	31,001	183,307	165,132	5,480

Note that the EAG base case does not include resource use and costs for CT scans

CT, computed tomography; GP, general practitioner; MRI, magnetic resonance imaging; NI, next intervention; PD, progressed disease; PF, progression free; tx, treatment

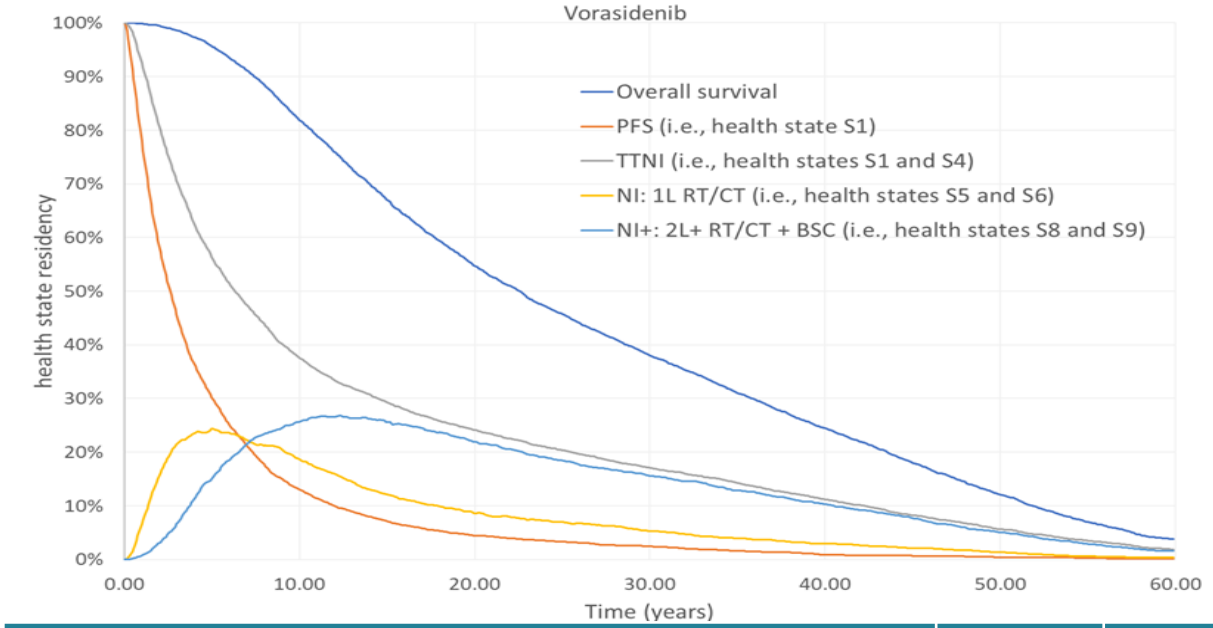
Accrual of MRU costs in the company's model after clarification

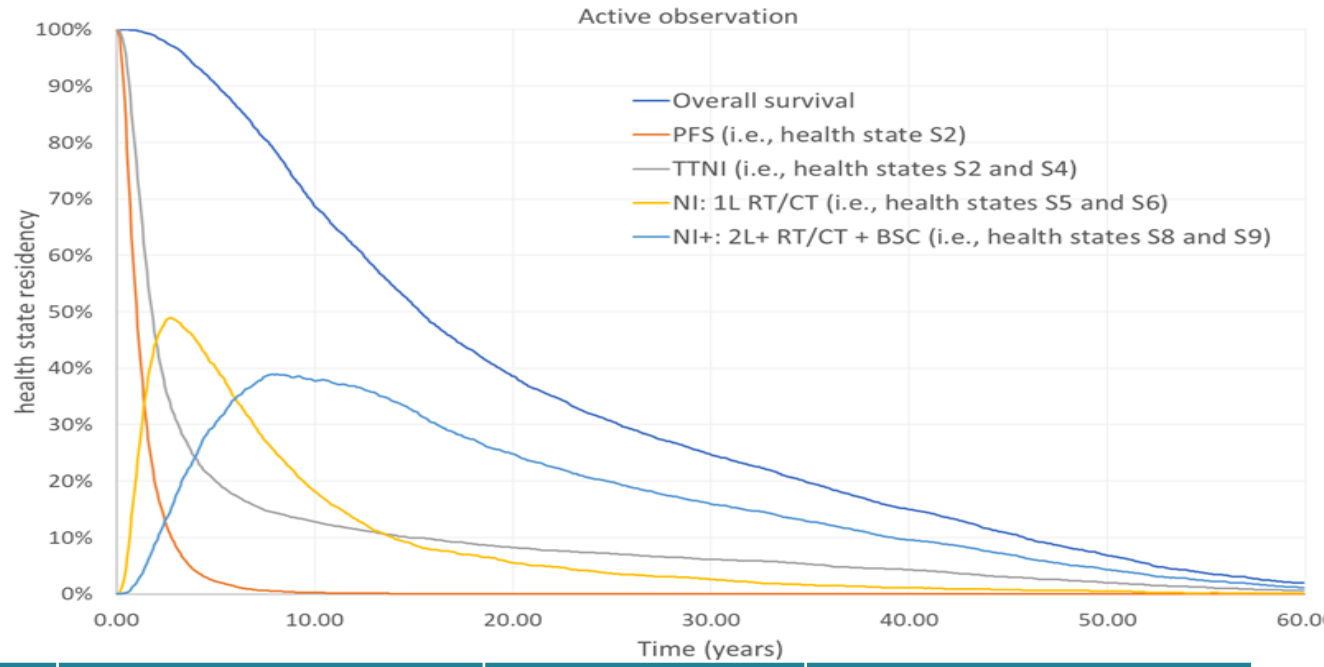


BSC, best supportive care; MRU, medical resource use; NI, next intervention; PD, progressed disease; PF, progression free; SoC, standard of care; tx, treatment

Health state occupancy in company's base case model

Time-dependent health state residency for vorasidenib and active observation in company's base case analysis



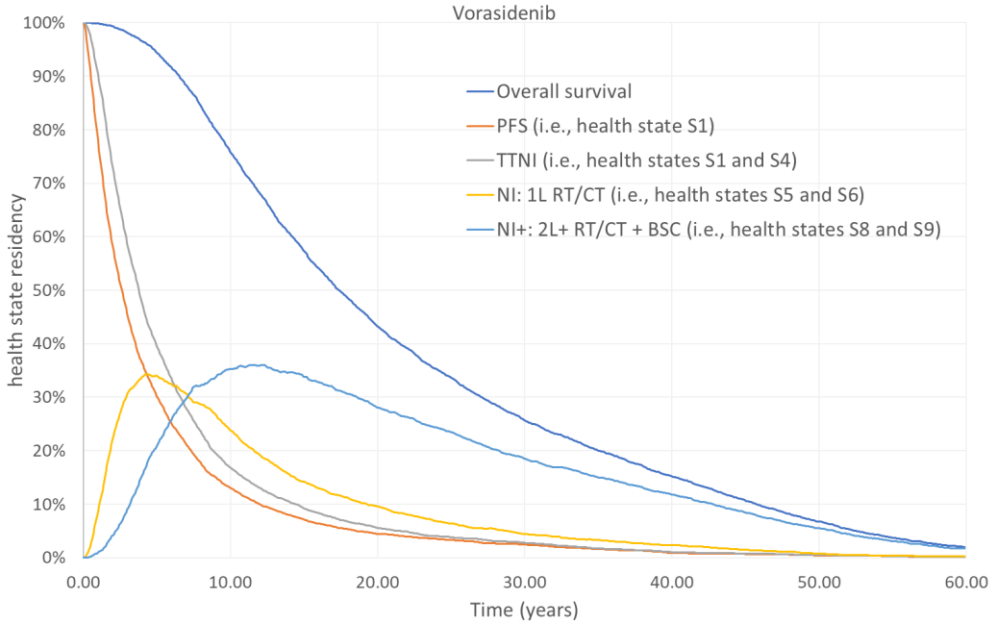


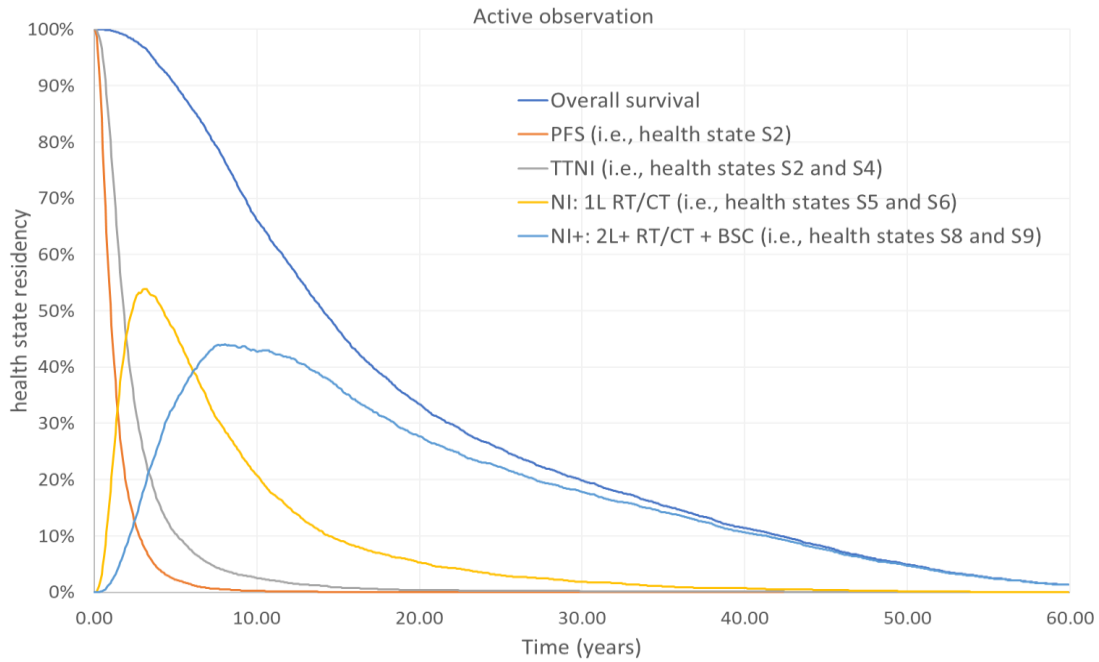
	OS	PFS	PD and off-treatment (S4)	NI (1L RT/CT)	NI+ (2L+ RT/CT + BSC)
Vorasidenib	26.45	5.22	8.58	4.53	8.11
Active observation	20.63	1.42	4.44	4.84	9.93
Difference (vorasidenib - active observation)	5.81	3.80	4.14	-0.31	-1.82

BSC, best supportive care; CT, chemotherapy; L, line; NI, next intervention; OS, overall survival; PD, progressed disease; PF, progression free; RT, radiotherapy; TTNI, time to next intervention; tx, treatment

Health state occupancy in EAG's base case model

Time-dependent health state residency for vorasidenib and active observation in EAG's base case analysis





	OS	PFS	PD and off-treatment (S4)	NI (1L RT/CT)	NI+ (2L+ RT/CT + BSC)
Vorasidenib	21.93	5.22	1.21	5.27	10.23
Active observation	18.81	1.42	1.25	5.07	11.07
Difference (vorasidenib - active observation)	3.12	3.80	-0.04	0.20	-0.84

BSC, best supportive care; CT, chemotherapy; L, line; NI, next intervention; OS, overall survival; PD, progressed disease; PF, progression free; RT, randiotherapy; TTNI, time to next intervention; tx, treatment

See main deck: Company and EAG base case assumptions

Company's scenario analyses

#	Scenario name	Company base-case	Scenario
1	INDIGO extrapolations: PFS	Log-normal	Log-logistic
2			Gamma
3	INDIGO extrapolations: TTNI | PS	Generalised gamma	Log-logistic
4			Gompertz
5	Annual discount rates for cost and outcomes	1.5%	6.0%
6			0.0%
7			3.5%
8	INDIGO utility regression	Progression and baseline	Progression only
9	Time horizon	60 years	30 years
10			40 years
11			50 years
12	SMR applied to background mortality rates	1.0	1.2
13	% opt out of treatment at S4 and S6	5%	10%
14			0%
15	Increase in seizures at subsequent treatment lines	25%	50%
16	S5/6 to S7 PFS non-co deleted from Baumert	Gamma	Weibull
17	S7 to S8 TTP oligo from Ma et al	Gompertz	Exponential
18	S7 to S9 OS astro and oligo from Ma et al	Log-normal	Exponential

OS, overall survival; PFS, progression free survival; SMR, standardised mortality ratio; TTNI | P, time to next intervention given progression; TTP, time to progression

EAG's scenario analyses

#	Company base case assumption	EAG scenario
1	Discount rate	3.5% per annum
2a	Separate TTNI | P curves by treatment arm	Log-normal for both arms
2b		Exponential for both arms
3a	Equal TTNI | P curves for both treatments	Pooled INDIGO arms: Generalized gamma
3b		Pooled INDIGO arms: Log-normal model
3c		Pooled INDIGO arms: Exponential model
3d		INDIGO vorasidenib curve for both arms: Log normal
4	Subsequent treatments	Excluding bevacizumab
5		Using proportion of treatments at subsequent lines a proxy for NHS practice
6	Costs	No monitoring costs for CT scans
7	Health state utilities at subsequent treatment lines	Unadjusted
8		TTO responses to vignette study

CT, computerized tomography; TTNI | P, time to next intervention given progression; TTO, time trade off; TTP, time to progression

See main deck: Company and EAG base case assumptions