Dabrafenib with trametinib for treating BRAF V600E mutation-positive glioma in children and young people aged 1 to 17

For projector – confidential information redacted

Technology appraisal committee A [12 March 2024]

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Company: Novartis

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Dabrafenib with trametinib for treating BRAF V600E mutation-positive glioma in children and young people aged 1 to 17

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

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Background on BRAF V600E mutation-positive glioma

- Gliomas are a type of brain tumour that originate in glial cells
- Gliomas are differentiated into low grade and high grade based on how quickly they grow
- BRAF is a protein kinase that mediates an important cell signalling pathway, promoting cell proliferation

Low-grade glioma (LGG)

Classification

- Grade 1 and 2, do not grow or grow slowly

Epidemiology

- Approximately 150 cases of LGG in children and young people per year
- Estimated 15 to 20% of LGGs have BRAF V600 mutation (most commonly V600E)

Prognosis

- 5-year survival of grade 1 LGG is around 95%
- BRAF V600E mutated LGG is associated with poorer outcomes and higher risk of transformation to HGG

High-grade glioma (HGG)

Classification

- Grade 3 and 4, malignant and grow rapidly

Epidemiology

- Approximately 30 cases of HGG in children and young people per year
- Estimated 5 to 7% of HGGs have BRAF V600 mutation (most commonly V600E)

Prognosis

- 5-year survival of grade 4 HGG is <10%

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Abbreviations: HGG: high-grade glioma, LGG, low-grade glioma.

Patient and clinical perspectives

See appendix – Patient and clinical perspectives

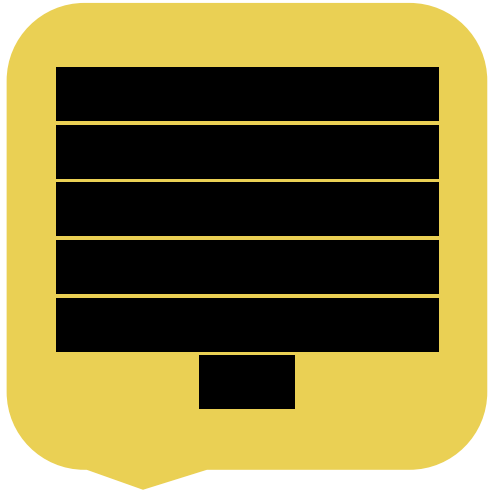
Substantial unmet need for children with glioma and their caregivers

Submission from The Brain Tumour Charity

Brain tumour diagnosis is extremely traumatic for patients and caregivers

Current treatment for glioma delays education, restricts socialising and can cause lasting emotional impact. In addition, caregivers report significant financial burden and a substantial time commitment associated with having to travel to hospital for treatment

Patients and caregivers would welcome treatment that improves QoL and is easy to take



Submissions from Prof Kilday (CCLG) and Dr Marshall

The aims of treatment are to stop progression, improve neuro function, and improve QoL

Overall tumour response is defined as complete (disappearance of target lesion) or partial response (50% or more reduction in the product of the longest perpendicular tumour diameters), in combination with clinically stable or improved disease

In LGG, patients experience poor responses to conventional treatment and significant health issues; in HGG, response and survival rates are low, and there is no recognised standard care after relapse

"D+T represents a step-change in the management of BRAF V600E gliomas, providing significant health benefits compared to current treatment"

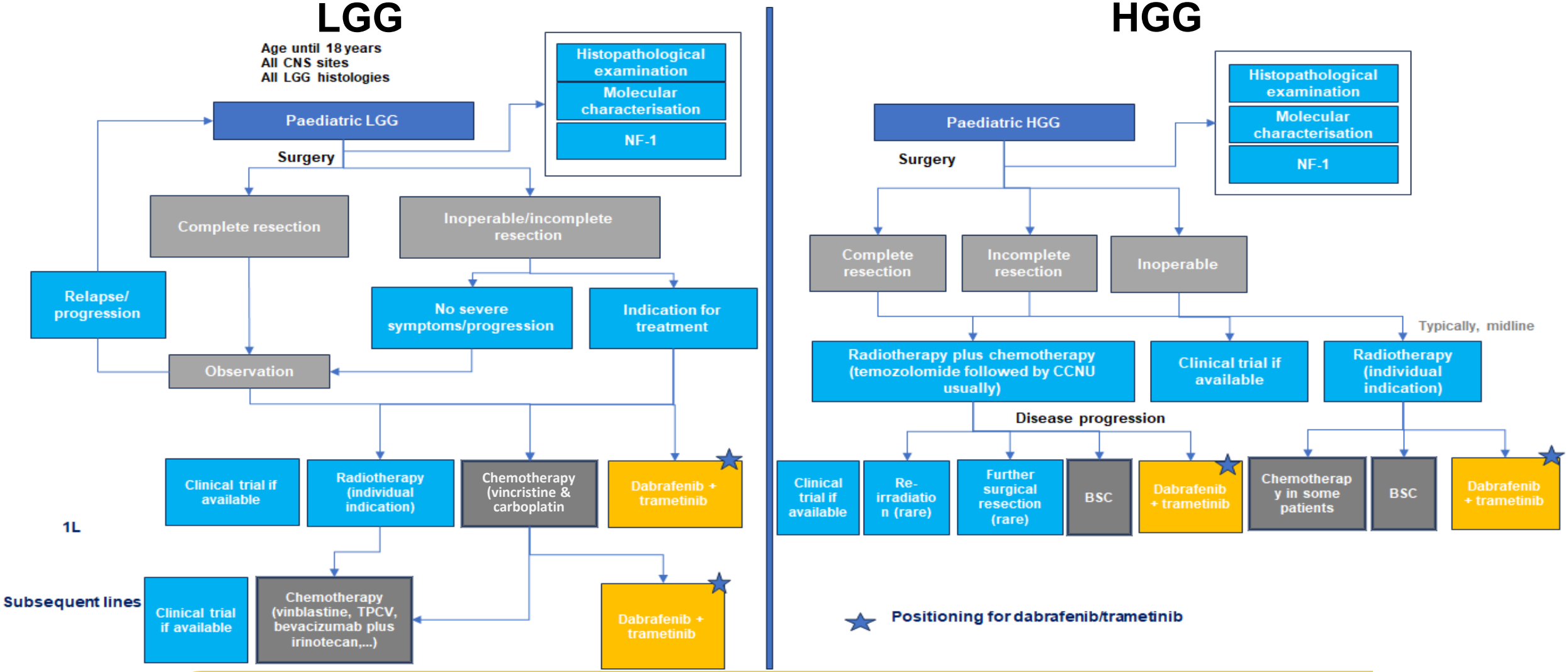
Abbreviations: CCLG, Children's Cancer and Leukaemia Group; D+T, dabrafenib and trametinib; HGG, high-grade glioma, LGG, low-grade glioma; OS, overall survival; QoL, quality of life; RANO, Response Assessment in Neuro-Oncology criteria.

Equality considerations

At scoping consultation, stakeholders highlighted that the remit and population in the scope is restricted to people aged 1 to 17 years and suggested that this contributes to inequality based on age.

However, the remit and population in the scope reflects the population in the key clinical trial population and therefore the marketing authorisation for this indication. The committee is only able to make recommendations within the marketing authorisation.

Treatment pathway – company submission



Does the company's description of the treatment pathway represent NHS practice?

Abbreviations: 1L, first-line; BSC: best supportive care; CCNU, lomustine; CNS, central nervous system; HGG, high-grade glioma; LGG, low-grade glioma; NF: neurofibromatosis; TPCV: tioguanine, procarbazine, lomustine, vincristine.

Dabrafenib (Finlee®) plus trametinib (Spexotras®), Novartis

Marketing authorisation (Spexotras)	• LGG: Trametinib in combination with dabrafenib is indicated for the treatment of paediatric patients aged 1 year and older with low-grade glioma (LGG) with a BRAF V600E mutation who require systemic therapy • HGG: Trametinib in combination with dabrafenib is indicated for the treatment of paediatric patients aged 1 year and older with high-grade glioma (HGG) with a BRAF V600E mutation who have received at least one prior radiation and/or chemotherapy treatment. • GBMA issued: Trametinib,13 February 2024; Dabrafenib, 20 March 2024
Mechanism of action	• Dabrafenib is an inhibitor specific to the ATP binding site of BRAF V600 mutant enzymes • Trametinib is an inhibitor specific to the allosteric site of the MEK1+2 enzymes • Together they function to disrupt a cell growth pathway and reduce uncontrolled cell division
Administra-tion	Both administered as an oral solution, dosing is based on weight: • Dabrafenib: from 20 mg twice daily (8 to 9 kg) to 150 mg twice daily (51 kg or higher) • Trametinib: ranges from 0.3 mg once daily (8 to 9 kg) to 2 mg once daily (51 kg or weight)

Price	• List price for this indication:
	  • Dabrafenib: £2,800 per pack of 420 10 mg dispersible tablets
	  • Trametinib: £376 per bottle containing 4.7 mg trametinib
	  • The expected average cost of a course of treatment for dabrafenib and trametinib at list price is [redacted] for LGG, [redacted] for HGG not previously treated with TMZ and [redacted] for HGG previously treated with TMZ
	• There is a confidential simple patient access scheme for dabrafenib with trametinib

Abbreviations: ATP, adenosine triphosphate; HGG, high-grade glioma; LGG, low-grade glioma; MA, marketing authorisation; TMZ, temozolomide.

Key issues for discussion

Issues	ICER impact
Decision problem issues	
Missing comparator in the LGG population	Unknown
In the LGG population, the evidence for dabrafenib and trametinib is limited to use as a first line systemic therapy	Unknown
Clinical effectiveness issues	
Use of a prospective cohort study and ITC methods to estimate effects in the HGG population	Unknown
Cost-effectiveness issues	
Choice of data assumptions for progression in the company submission	**Large**
Use of adult utilities in children	Unknown
Treatment duration	Medium

! Key issues 'The populations included' and 'Small population size' are unresolvable and are therefore not presented in the main slides

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Abbreviations: HGG, high-grade glioma; ITC, indirect treatment comparison; LGG, low-grade glioma.

Key issue: Missing comparator in the LGG population

Background

- For the LGG population, the final scope lists 'chemotherapy (including but not limited to vincristine with carboplatin)' as the comparator

Company

- Consider vincristine with carboplatin as most appropriate comparator as it is the recommended first-line chemotherapy for LGG as per the UK CCLG guideline

EAG

- Advice to the EAG suggests that vinblastine alone would be considered for 1L systemic therapy in LGG, as this is used interchangeably with vincristine and carboplatin in their practice
- The company's restriction of the comparator to only vincristine with carboplatin is against the final scope that specifically requests that chemotherapies other than vincristine with carboplatin are considered
- Recognise that as both regimens are used interchangeably, they are likely to have similar efficacy at similar cost

Clinical expert statements

Current management follows CCLG guidelines:

Non-NF1 LGG:

- 1L: vincristine with carboplatin
  - Alternative (in case of carboplatin hypersensitivity): vincristine/cisplatin and vincristine/cyclophosphamide
- 2L: vinblastine

NF1 LGG:

- 1L: vincristine with carboplatin, or vinblastine

Is vinblastine a relevant comparator in LGG? Are vinblastine monotherapy and vincristine with carboplatin interchangeable?

Abbreviations: 1L, first-line; 2L, second-line; CCLG, Children's Cancer and Leukaemia Group; LGG, low-grade glioma; NF1, Neurofibromatosis Type 1.

See appendix – Decision problem

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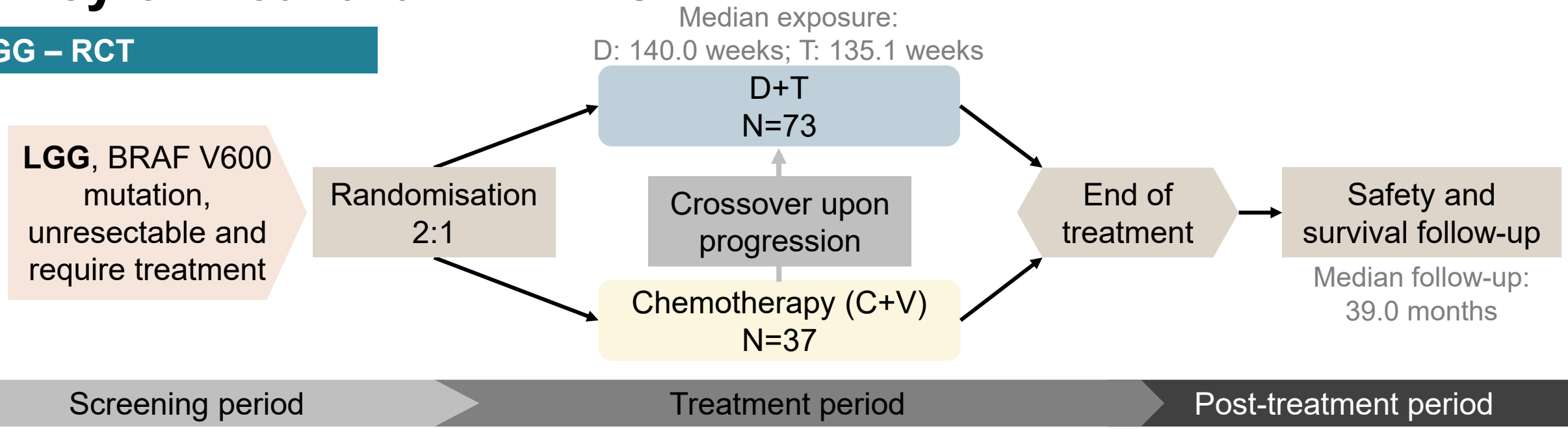
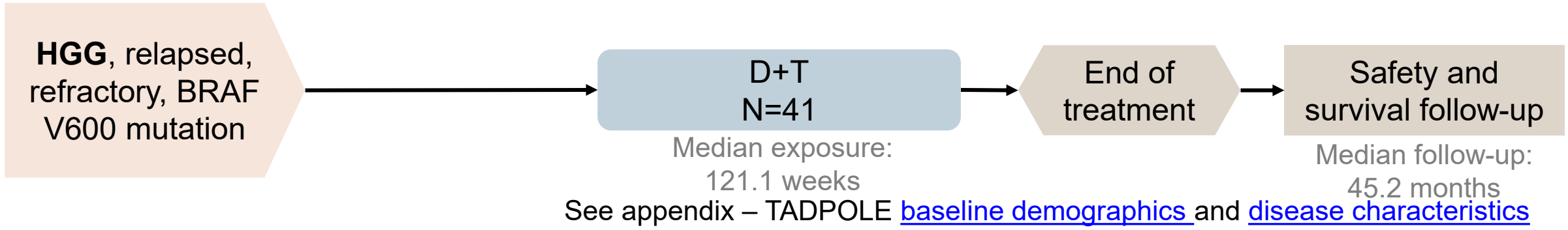
Key clinical trial: TADPOLE

LGG – RCT



HGG – prospective cohort



See appendix – TADPOLE baseline demographics and disease characteristics

Abbreviations: C+V, carboplatin and vincristine; D+T, dabrafenib and trametinib; HGG, high-grade glioma; LGG, low-grade glioma.

Key issue: In the LGG population, the evidence for D+T is limited to use as a 1L systemic therapy

Company

- For LGG, the final scope lists 'Low-grade glioma that requires systemic treatment' as the population
- TADPOLE LGG eligibility criteria:
  - Inclusion: Progressive disease following surgical excision, or non-surgical candidates with necessity to begin first systemic treatment because of a risk of neurological impairment with progression
  - Exclusion: Any systemic anti-cancer therapy (chemotherapy, immunotherapy, biologic therapy, or vaccine therapy) or investigational drugs prior to enrolment

EAG

- Notes that the key inclusion criteria in TADPOLE for the LGG population was that they were eligible to receive their 1st systemic therapy
- Economic analysis for LGG was conducted on evidence from 1L use of D+T only

Clinical expert statements

CCLG has created a national MAPK glioma group, recommending:

- D+T can be administered as 3L or later treatment for progressive or recurrent BRAF V600E LGG, after discussion with the national MAPK glioma group
- D+T is only to be considered for progression after 2L of systemic chemotherapy as per UK CCLG LGG guidance and patient must have risk of severe or significant neurological decline or death

Is the evidence from TADPOLE sufficient to appraise D+T at the point in the treatment pathway at which it will likely be used for LGG?

Abbreviations: 1L, first-line; 2L, second-line; 3L, third-line; CCLG, Children's Cancer and Leukaemia Group; D+T, dabrafenib and trametinib; LGG, low-grade glioma; MAPK, mitogen-activated protein kinase; NF1, Neurofibromatosis Type 1.

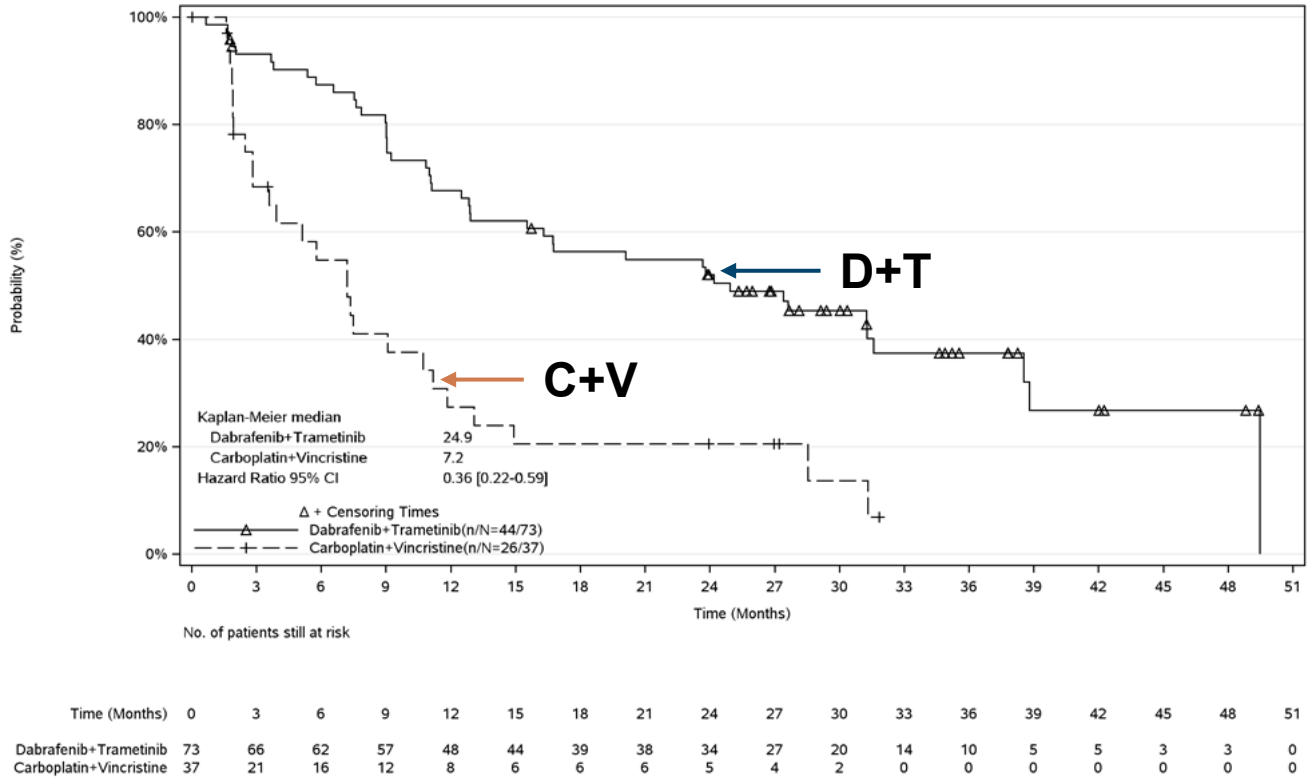
Link to Treatment pathway

Clinical trial results – LGG

Summary of outcomes

	D+T (N=73)	C+V (N=37)	
Primary outcome			OR (95% CI)
ORR*, n (%)	40 (54.8)	6 (16.2)	6.26 (2.3, 16.8)
95% CI	42.7, 66.5	6.2, 32.0	
Secondary outcomes			OR (95% CI)
CBR**, n (%)	63 (86.3)	16 (43.2)	8.27 (3.3, 21.0)
95% CI	76.2, 93.2	27.1, 60.5	
PFS, n (%)			HR (95% CI)
Independent	44 (60.3)	26 (70.3)	0.36 (0.22, 0.59)
Median, m	24.9	7.2	
95% CI	12.9, 31.6	2.8, 11.2	HR (95% CI)
Investigator	23 (31.5)	15 (40.5)	0.46 (0.24, 0.88)
Median, m	46.0	30.8	
95% CI	38.6, NE	7.0, NE	
OS, n (%)	0 (0)	1 (2.7)	-

PFS (independent review)



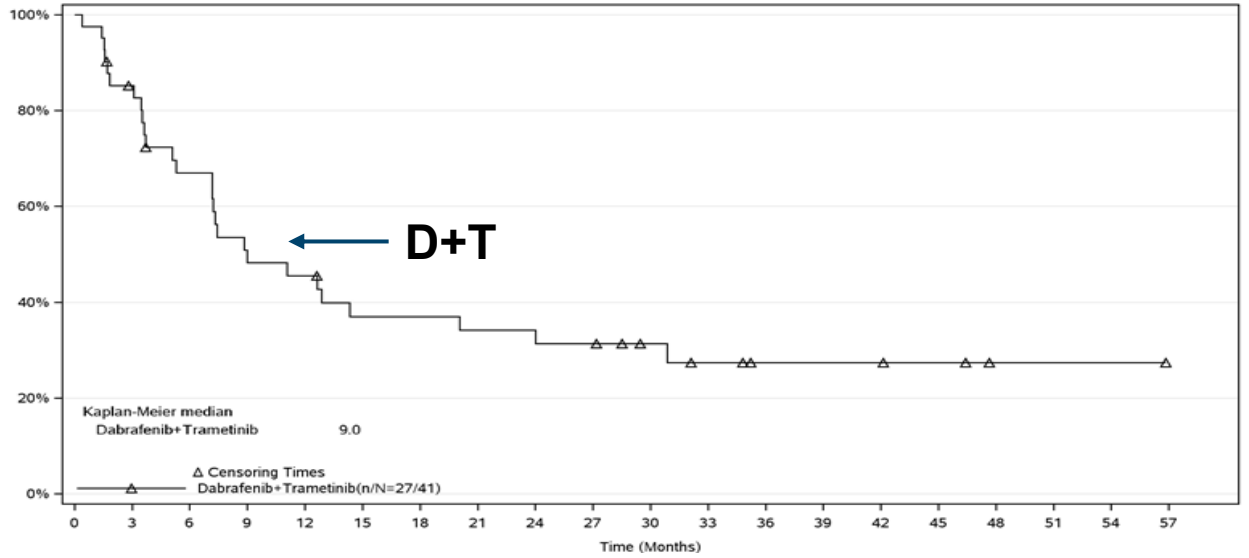
*ORR calculated as addition of complete response (CR) and partial response (PR).
**CBR calculated as addition of CR, PR, and stable disease (SD).
Abbreviations: CBR, clinical benefit rate; CI, confidence interval; C+V, carboplatin and vincristine; D+T, dabrafenib and trametinib; HR, hazard ratio; LGG, low-grade glioma; m, months; NE, not estimable; OR, odds ratio; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.

Clinical trial results – HGG

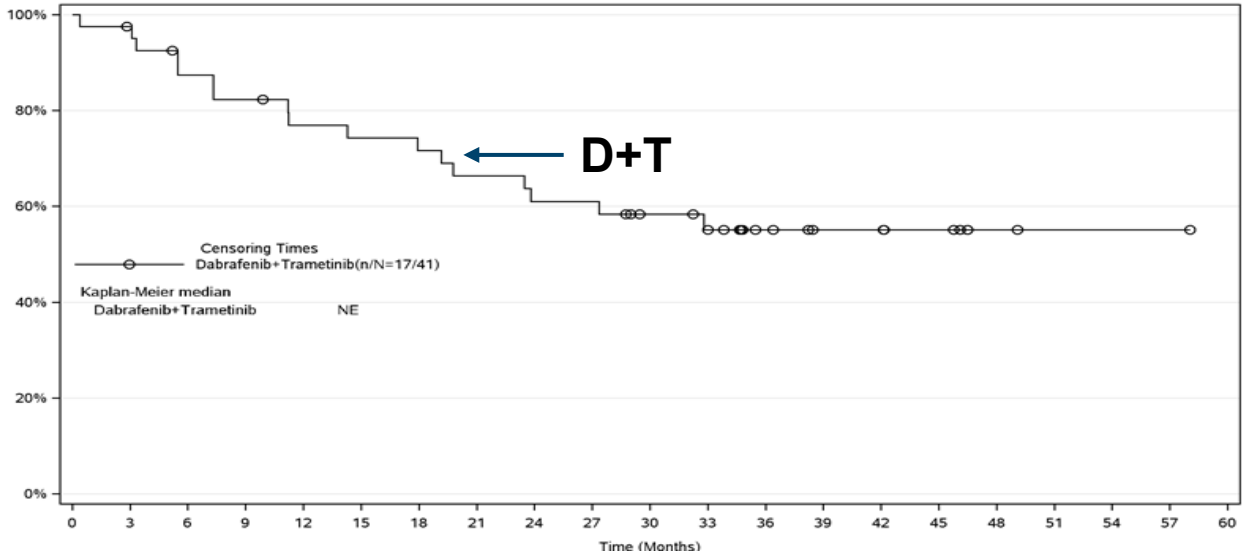
Summary of outcomes

	D+T (N=41)
Primary outcome	
ORR*, n (%)	23 (56.1)
95% CI	39.7, 71.5
Secondary outcomes	
CBR**, n (%)	27 (65.9)
95% CI	49.4, 79.9
PFS, n (%)	
Independent	27 (65.9)
Median, m	9.0
95% CI	5.3, 20.1
Investigator	24 (58.5)
Median, m	24.0
95% CI	12.5, NE
OS, n (%)	17 (41.5)
Median, m	NE
95% CI	19.8, NE

PFS (independent review)



OS



*ORR calculated as addition of complete response (CR) and partial response (PR).
**CBR calculated as addition of CR, PR, and stable disease (SD).
Abbreviations: CBR, clinical benefit rate; CI, confidence interval; D+T, dabrafenib and trametinib; HGG, high-grade glioma; m, months; NE, not estimable; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.

Key issue: Indirect treatment comparison (ITC) – HGG

Company

- HGG cohort of TADPOLE was single arm, so company used ITCs to estimate comparative effectiveness
- The company conducted a systematic review to identify studies of comparators in the HGG subgroups:
  - No prior TMZ subgroup – 2 studies selected: Lashford *et al*. and Verschuur *et al*., both using TMZ
  - Prior TMZ subgroup:
    - No studies identified with the preferred comparator (BSC)
    - Clinical advice to company: 'following TMZ failure, chemotherapy tends to be ineffective, and therefore using chemotherapy studies in patients previously treated with TMZ is a reasonable proxy'
    - 2 proxy studies selected: MacDonald *et al*. (cilengitide) and Narayana *et al*. (bevacizumab)
- ITCs using either matching-adjusted indirect comparison (MAIC; when only aggregate data available for the comparator) or inverse probability of treatment weighting (IPTW) methods were performed
- For both subgroups, ITCs show D+T significantly improves OS and PFS vs. comparator (HRs less than 1 and 95% CIs do not contain 1) – exact results cannot be shown since they are confidential

EAG: Agrees with the ITC methods used by the company

- Highlights ITCs are associated with uncertainty: limited covariates adjusted; small sample sizes; unknown BRAF V600E mutation status for comparator studies; comparator studies were conducted about 20 years ago (no prior TMZ subgroup), and comparator studies are only proxies for BSC (prior TMZ subgroup).

Are the ITCs appropriate for estimating comparative effectiveness in the HGG population?

See appendix – ITC results

Abbreviations: BSC, best supportive care; D+T, dabrafenib and trametinib; HGG, high-grade glioma; HR, hazard ratio; IPTW, inverse probability of treatment weighting; ITC, indirect treatment comparison; MAIC, matching-adjusted indirect comparison; OS, overall survival; PFS, progression-free survival; TMZ, temozolomide.

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Key issue: Assumptions for progression (1)

Background

- The company and EAG used different assumptions for progression
- For LGG, this had a large impact on the ICER
- For HGG, this had a medium-sized impact on the ICER in the prior-TMZ subgroup, and a small impact on the ICER in the no prior-TMZ subgroup

Assumption	Company preference	EAG preference
Progression assessment	Investigator-assessed PFS • Clinical advice suggested 'investigator-assessed PFS is a more accurate reflection of when a patient would be deemed to have progressive disease in clinical practice, and is a more accurate reflection of the decision for when to stop treatment'	Independent-review PFS for health state occupancy; investigator-assessed PFS for time on treatment • Could not implement due to model inflexibility, so: Independent-review PFS for both
Curve fitting	Piecewise hybrid approach using KM data followed by parametric extrapolation at a fixed time point • For HGG no prior TMZ, a HR was applied to the D+T curve to model TMZ • For HGG prior TMZ, all patients on BSC started the model in the progressed disease state	Independently fitted parametric models for the entire time horizon • For HGG no prior TMZ, using IPTW adjusted KM • For HGG prior TMZ, PFS based on D+T PFS KM

Abbreviations: BSC, best supportive care; D+T, dabrafenib and trametinib; HGG, high-grade glioma; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; IPTW, inverse probability of treatment weighting; KM, Kaplan-Meier; LGG, low-grade glioma; PFS, progression-free survival; TMZ, temozolomide.

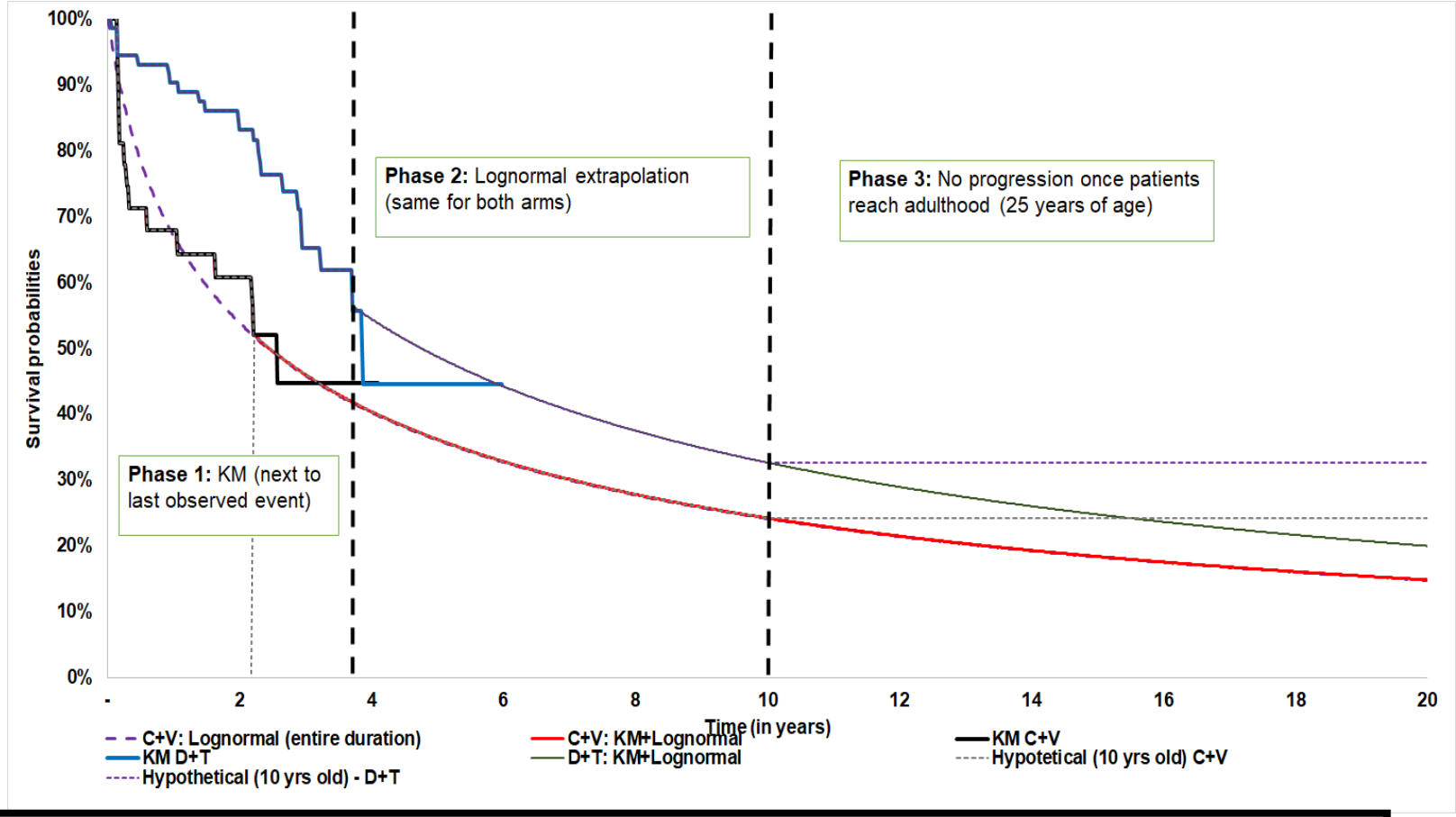
See appendix – LGG and HGG investigator and independent PFS curves

Key issue: Assumptions for progression – LGG (2)

Company approach to LGG extrapolation

Company

- Piecewise hybrid approach using investigator KM data until next to last observed event followed by Lognormal extrapolation
- Justifications:
  - Parametric extrapolations did not fit KM well
  - Cut-off point chosen due to low number of patients at risk after 2 years and aligned to duration
  - No progression in adults reflects clinical advice
- After KM, same progression rate assumed for both arms



EAG: Investigator assessed PFS is not used routinely in practice; piecewise approach is arbitrary, disagree with using the same rate of progression for both arms beyond the observed KM

➢ Preferred approach is to independently fit parametric models to independent review assessed PFS data

Abbreviations: C+V, carboplatin and vincristine; D+T, dabrafenib and trametinib; KM, Kaplan-Meier; LGG, low-grade glioma; PFS, progression-free survival.

See appendix – Company survival extrapolation predictions

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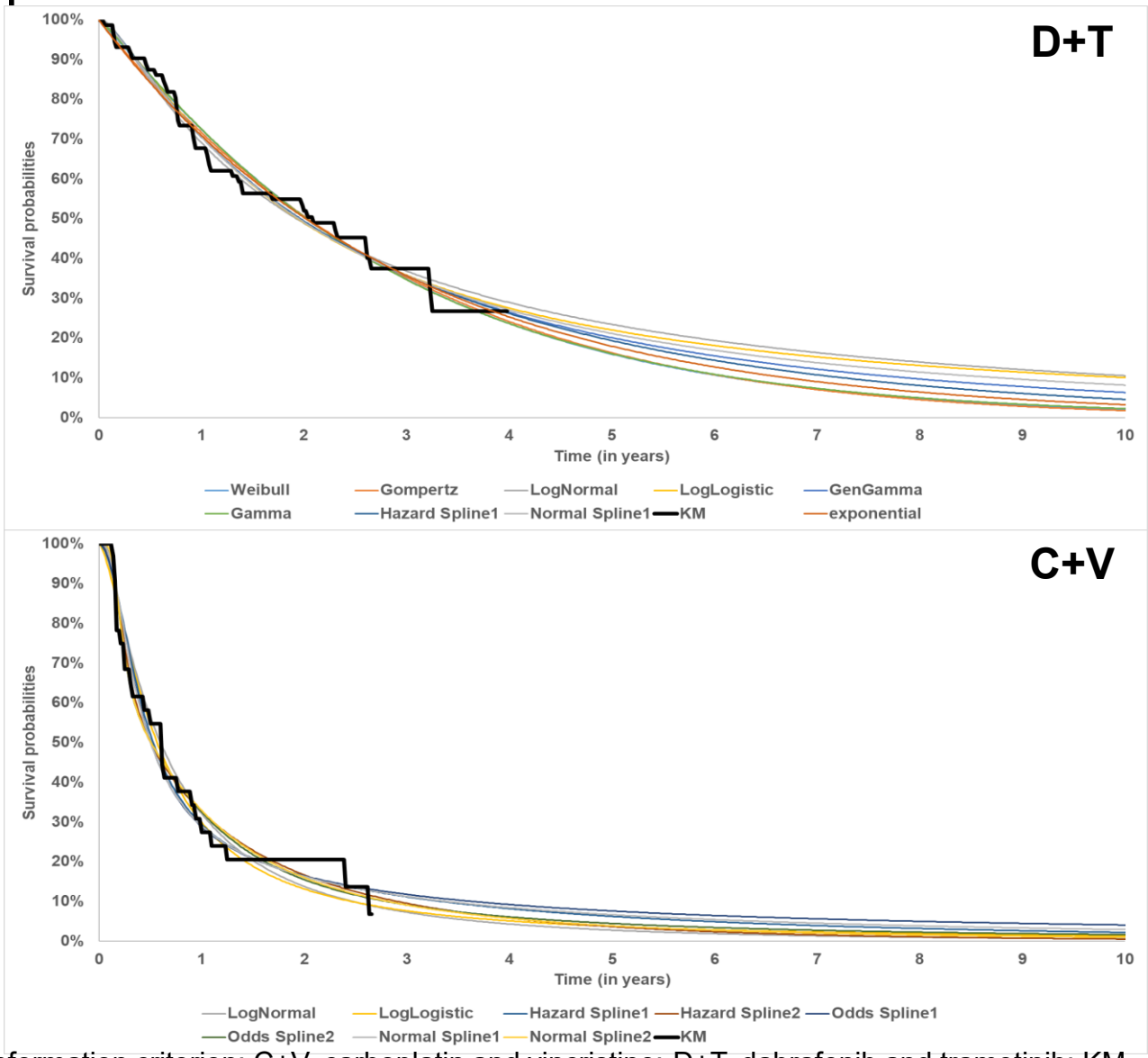
Key issue: Assumptions for progression – LGG (3)

EAG approach to LGG extrapolation

EAG

- Fit independent curves to the D+T and C+V independent review KM data, extrapolated over entire time horizon
- Models selected based on AIC/BIC goodness-of-fit criteria, and
- On clinical advice relating to estimated PFS:
  - D+T: 15 to 20% at 7 years
  - C+V: less than 10% at 5 years

Arm (model)	PFS prediction		
	5-year	7-year	10-year
D+T (Log-logistic)	22%	15%	10%
C+V (Lognormal)	3%	-	1%



Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; C+V, carboplatin and vincristine; D+T, dabrafenib and trametinib; KM, Kaplan-Meier; LGG, low-grade glioma; PFS, progression-free survival.

Key issue: Assumptions for progression – HGG (4)

Company approach to HGG extrapolation

See appendix – Company survival extrapolation predictions

Company

- Piecewise hybrid approach using investigator KM data until next to last observed event followed by exponential extrapolation
- Justifications:
  - Parametric extrapolations did not fit KM well
  - All extrapolations except exponential plateau, which the company considers implausible

Comparator extrapolation:

- No prior TMZ – HR applied from IPTW ITC
- Prior TMZ – all patients assumed progressed from model start

[redacted]

EAG: Piecewise approach is arbitrary, disagree with constant HR (for no prior TMZ subgroup). Prefer to independently fit curves to independent review PFS data, using IPTW adjustment (for no prior TMZ) and D+T curve (for prior TMZ)

Abbreviations: D+T, dabrafenib and trametinib; HGG, high-grade glioma; HR, hazard ratio; IPTW, inverse probability of treatment weighting; KM, Kaplan-Meier; PFS, progression-free survival; TMZ, temozolomide.

Key issue: Assumptions for progression – HGG (5)

EAG approach to HGG extrapolation – no prior TMZ

EAG

- Fit independent curves to the IPTW-adjusted D+T and TMZ KM, extrapolated over entire time horizon
- Models selected based on AIC/BIC goodness-of-fit criteria
- On clinical advice relating to estimated PFS:
  - D+T: 10% at 7 years
  - TMZ: 10% at 1 year – all extrapolations predicted far lower PFS

[redacted]

Arm (model)	PFS			
	1-year	5-year	7-year	10-year
D+T (Lognormal)	-	[redacted]	[redacted]	[redacted]
TMZ (Log-logistic)	[redacted]	[redacted]	-	-

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; D+T, dabrafenib and trametinib; HGG, high-grade glioma; IPTW, inverse probability of treatment weighting; KM, Kaplan-Meier; PFS, progression-free survival; TMZ, temozolomide.

Key issue: Assumptions for progression – HGG (6)

EAG approach to HGG extrapolation – prior TMZ

EAG

- Fit independent curves to D+T PFS KM, extrapolated over entire time horizon
- Models selected based on AIC/BIC goodness-of-fit criteria, and
- On clinical advice relating to estimated PFS:
  - D+T: 15 to 20% at 10 years
- Similar to company base case, all BSC patients start in the progressed health state

[redacted]

Arm (model)	PFS	
	5-year	10-year
D+T (Lognormal)	[redacted]	[redacted]

What is committee's preferred approach to progression?

- Investigator PFS, piecewise with HR (Company)
- Independent PFS, extrapolation throughout (EAG prag.)
- Independent PFS for health state occupancy, investigator PFS for ToT, extrapolation throughout (EAG preferred; not presented in slides; would require model rework)

Are the PFS predictions clinically plausible?

- See appendix for side-by-side comparison

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; BSC, best supportive care; D+T, dabrafenib and trametinib; HGG, high-grade glioma; KM, Kaplan-Meier; LGG, low-grade glioma; PFS, progression-free survival; prag., pragmatic; ToT, time on treatment; TMZ, temozolomide.

Key issue: Adult utilities used for children

Company

- Systematic review was unable to identify utility studies in children
- All decrements were sourced from studies in adults

EAG

- Acknowledge lack of evidence in children
- Could not source decrements from clinical experts
- Caution that adult utilities may be invalid for children

Are the adult utility values acceptable for decision-making in children?

Abbreviations: CI, confidence interval; EQ-5D, Euroqol 5-dimensions; HGG, high-grade glioma; HRQoL, health-related quality of life; LGG, low-grade glioma.

Utility values used in company model

State	Utility value: mean	Justification
Main health states – LGG analysis		
Decrements relative to patients without the condition		
LGG – model entry	-0.155	Drewes 2018 and Vera 2023
Decrements relative to the previous health states		
Any progression (1st to 5th) Malignant transformation (1L)	-0.06 (95% CI -0.1; -0.02)	EQ-5D decrement associated with progression in Vera 2023
QALY loss – one off at model entry for C+V		
Mode of admin (IV chemo)	-0.187	Hadi 2018
Main health states – HGG analysis		
Decrements relative to patients without the condition		
HGG relapsed/refractory	-0.155	Vera 2023
Weekly reduction in EQ-5D while in progressed disease health state		
Weekly reduction in HRQoL	1.10%	Drewes 2018

Key issue: Treatment duration

See appendix – D+T SmPC summary

Company

- In TADPOLE, patients on D+T were treated until progression

LGG

- Clinical advice indicated that chemotherapy is usually given for less than 2 years due to cumulative toxicity
- Similarly, in the absence of progression, D+T would likely be stopped at between 2 to 5 years
- In the base case, the KM was used up to Week 193 (≈3.7 years) – therefore the base case assumes a maximum treatment duration of 193 weeks
- Scenario analyses conducted varying maximum treatment duration from 2 to 6 years

HGG

- Clinical advice: unlikely to stop D+T because of poor prognosis and limited other treatment options, though a minority may stop if they respond well
- Base case assumes informal stopping rule at 12.5 years
- Scenario analyses conducted varying maximum treatment duration between 5 years to lifetime

EAG

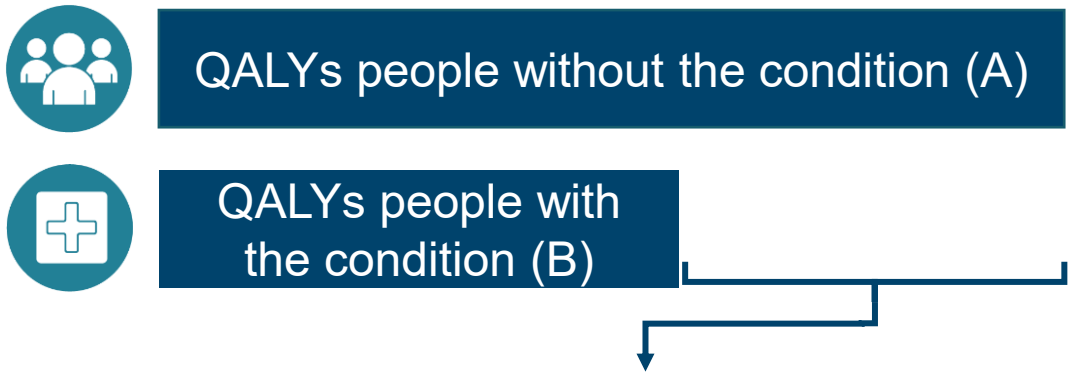
- SmPC states that treatment should be continued until disease progression or unacceptable toxicity
- Clinical advice mixed as to whether treatment would continue indefinitely or stop around the base case
- Removal of stopping rules increases the ICERs – conducted scenario analyses with indefinite duration

Should a stopping rule be applied?

Abbreviations: D+T, dabrafenib and trametinib; ICER, incremental cost-effectiveness ratio; KM, Kaplan-Meier; SmPC, summary of product characteristics.

QALY weightings for severity

Severity modifier calculations and components:



Health lost by people with the condition:

- Absolute shortfall: total = A – B
- Proportional shortfall: fraction = (A – B) / A

! Both company and EAG agree on:

- **1.2** severity weighting for **LGG**
- **1.7** severity weighting for **HGG**

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

- 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

See appendix – Severity calculations

 Abbreviations: HGG, high-grade glioma, LGG, low-grade glioma; QALY, quality-adjusted life year

Company base case results – LGG

ICERs in these slides do not include confidential discounts for subsequent treatments

Deterministic incremental base case results

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	ICER (£/QALY) with modifier
C+V	£88,450	11.39	–	–	–	1.2x
D+T	[redacted]	[redacted]	[redacted]	[redacted]	£31,102	£25,918

Probabilistic incremental base case results

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	ICER (£/QALY) with modifier
C+V	£86,779	10.99	–	–	–	1.2x
D+T	[redacted]	[redacted]	[redacted]	[redacted]	£31,952	£26,630

Abbreviations: C+V, carboplatin and vincristine; D+T, dabrafenib and trametinib; ICER, incremental cost-effectiveness ratio; LGG, low-grade glioma; QALY, quality-adjusted life year

Company deterministic scenario analysis – LGG*

No.	Scenario (applied to company base case)	Company base case assumption	ICER (£/QALY) versus C+V (1.2x severity modifier applied)
1	**Company base case**	-	£25,918
2	PFS defined by independent review	Investigator review	£14,396
3	PPS from literature source (Gnekow et al. 2017)	Kandels et al. 2020	£18,103
4	Max treatment duration – 2 years	3.71 years	£11,518
5	Max treatment duration – 3 years	3.71 years	£21,008
6	Max treatment duration – 4 years	3.71 years	£27,154
7	Max treatment duration – 5 years	3.71 years	£30,887
8	Max treatment duration – 6 years	3.71 years	£33,769
9	KM cut off point – 2.5 years	Next to last event	£19,746
10	Dose by weight	Dose as per TADPOLE	£20,539

*ICERs do not include confidential discounts for subsequent treatments

Abbreviations: C+V, carboplatin and vincristine; ICER, incremental cost-effectiveness ratio; KM, Kaplan-Meier; LGG, low-grade glioma; PFS, progression-free survival; PPS, post-progression survival.

EAG base case results – LGG*

! The EAG believes the model is linear, so all EAG analyses are deterministic

No.	Scenario (applied to company base case)	Incremental QALYs (1.2x modifier)	Incremental costs	ICER (£/QALY) versus C+V (1.2x modifier)
	Company base case (EAG corrected)	[redacted]	[redacted]	£25,776
1	Change PFS to EAG's base case: independent assessment of disease progression; independent curve fitting; extrapolation for whole time period; log logistic distribution for D+T, lognormal of C+V	[redacted]	[redacted]	£13,111
2	Change distribution for time to progressed malignant transformation to a two knot odds spline model	[redacted]	[redacted]	£25,773
3	Change distribution for time to death after developing a progressed malignant transformation to log logistic	[redacted]	[redacted]	£25,769
4	Change the progressed HGG utility decrement to 0.5% per week	[redacted]	[redacted]	£25,760
5	Use Hernandez *et al*. to calculate the utility decrement for having LGG	[redacted]	[redacted]	£26,734
6	Implement wastage for comparator treatments	[redacted]	[redacted]	£25,557
	EAG base case: 1+2+3+4+5+6	[redacted]	[redacted]	£13,604

*ICERs do not include confidential discounts for subsequent treatments

Abbreviations: C+V, carboplatin and vincristine; D+T, dabrafenib and trametinib; HGG, high-grade glioma; ICER, incremental cost-effectiveness ratio; KM, Kaplan-Meier; LGG, low-grade glioma; PFS, progression-free survival; QALY, quality-adjusted life year.

EAG deterministic scenario analysis – LGG*

No.	Scenario (applied to company base case)	Base case assumption	ICER (£/QALY) versus C+V (1.2x modifier)
	Company base case (EAG corrected)	-	£25,776
	EAG base case	-	£13,604
1	Patients can remain on D+T for 100 years	3.71 years	£20,636

*ICERs do not include confidential discounts for subsequent treatments
Abbreviations: C+V, carboplatin and vincristine; D+T, dabrafenib and trametinib; ICER, incremental cost-effectiveness ratio; LGG, low-grade glioma; QALY, quality-adjusted life year.

Company base case results – HGG*

Deterministic incremental base case results

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	ICER (£/QALY) with modifier
HGG – no prior TMZ						
SoC (TMZ)	£27,339	0.73	–	–	–	1.7x
D+T	[redacted]	[redacted]	[redacted]	[redacted]	£48,660	£28,624
HGG – prior TMZ						
SoC (BSC)	£20,873	0.45	–	–	–	1.7x
D+T	[redacted]	[redacted]	[redacted]	[redacted]	£49,423	£29,072

Probabilistic incremental base case results

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	ICER (£/QALY) with modifier
HGG – no prior TMZ						
SoC (TMZ)	£27,720	0.82	–	–	–	–
D+T	[redacted]	[redacted]	[redacted]	[redacted]	£47,916	£28,186
HGG – prior TMZ						
SoC (BSC)	£21,375	0.45	–	–	–	–
D+T	[redacted]	[redacted]	[redacted]	[redacted]	£48,578	£28,575

*ICERs do not include confidential discounts for subsequent treatments

Company deterministic scenario analysis – HGG*

No.	Scenario (applied to company base case)	Company base case assumption	ICER (£/QALY) versus SoC (1.7x modifier)
	HGG – no prior TMZ		
1	**Company base case**	**-**	£28,624
2	PFS – Gompertz	Exponential	£13,670
3	PFS – Log-logistic	Exponential	£20,794
4	PFS – Spline	Exponential	£21,129
5	Max treatment duration – 7.5 years	12.5 years	£20,445
6	Max treatment duration – 27.5 years	12.5 years	£30,195
	HGG – prior TMZ		
1	**Company base case**	**-**	£29,072
2	PFS – Gompertz	Exponential	£13,732
3	PFS – Log-logistic	Exponential	£21,518
4	PFS – Spline	Exponential	£23,654
5	Max treatment duration – 7.5 years	12.5 years	£26,581
6	Max treatment duration – 27.5 years	12.5 years	£29,192

*ICERs do not include confidential discounts for subsequent treatments

Abbreviations: ICER, incremental cost-effectiveness ratio; HGG, high-grade glioma; ICER, incremental cost-effectiveness ratio; PFS, progression-free survival; QALY, quality-adjusted life year; SoC, standard of care; TMZ, temozolomide.

EAG base case results – HGG*

! The EAG believes the model is linear, so all EAG analyses are deterministic

No.	Scenario (applied to company base case)	Incremental QALYs (1.7x modifier)	Incremental costs	ICER (£/QALY) versus SoC (1.7x modifier)
	HGG – no prior TMZ			
	Company base case (EAG corrected)	[redacted]	[redacted]	£28,785
1	PFS, independent review, IPTW adjusted, extrapolation for the entire period, D+T uses log normal distribution, TMZ uses log logistic distribution	[redacted]	[redacted]	£27,419
2	Change distribution for time to death after developing a progressed malignant transformation to log-logistic	[redacted]	[redacted]	£28,665
3	Progressed HGG utility decrement 0.5% per week	[redacted]	[redacted]	£28,945
	EAG base case: 1+2+3	[redacted]	[redacted]	£27,500
	HGG – prior TMZ			
	Company's base case (EAG corrected)	[redacted]	[redacted]	£29,214
1	PFS, independent review, log normal parametric model, extrapolation the entire period	[redacted]	[redacted]	£21,568
2	Change distribution for time to death after developing a progressed malignant transformation to log-logistic	[redacted]	[redacted]	£29,044
3	Progressed HGG utility decrement 0.5% per week	[redacted]	[redacted]	£29,422
	EAG base case: 1+2+3	[redacted]	[redacted]	£21,512

*ICERs do not include confidential discounts for subsequent treatments

Abbreviations: D+T, dabrafenib and trametinib; ICER, incremental cost-effectiveness ratio; IPTW, inverse probability of treatment weighting; HGG, high-grade glioma; ICER, incremental cost-effectiveness ratio; PFS, progression-free survival; QALY, quality-adjusted life year; SoC, standard of care; TMZ, temozolomide.

EAG deterministic scenario analysis – HGG*

No.	Scenario (applied to company base case)	Base case assumption	ICER (£/QALY) versus SoC (1.7x modifier)
	HGG (no prior TMZ)		
	Company base case (EAG corrected)	-	£28,785
	EAG base case	-	£27,500
1	Patients can remain on D+T for 100 years	12.5 years	£29,592
	HGG (prior TMZ)		
	Company base case (EAG corrected)	-	£29,214
	EAG base case	-	£21,512
1	Patients can remain on D+T for 100 years	12.5 years	£28,109

*ICERs do not include confidential discounts for subsequent treatments

Abbreviations: D+T, dabrafenib and trametinib; ICER, incremental cost-effectiveness ratio; HGG, high-grade glioma; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; SoC, standard of care; TMZ, temozolomide.

Dabrafenib with trametinib for treating BRAF V600E mutation-positive glioma in children and young people aged 1 to 17

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

NICE National Institute for Health and Care Excellence

Key issues for discussion

Issues	ICER impact
Decision problem issues	
Missing comparator in the LGG population	Unknown
In the LGG population, the evidence for dabrafenib and trametinib is limited to use as a first line systemic therapy	Unknown
Clinical effectiveness issues	
Use of a prospective cohort study and ITC methods to estimate effects in the HGG population	Unknown
Cost-effectiveness issues	
Choice of data assumptions for progression in the company submission	**Large**
Use of adult utilities in children	Unknown
Treatment duration	Medium

! Key issues 'The populations included' and 'Small population size' are unresolvable and are therefore not presented in the main slides

NICE

Abbreviations: HGG, high-grade glioma; ITC, indirect treatment comparison; LGG, low-grade glioma.

Committee decision making slide

Assumption	Question for committee
Decision problem	Does the company's description of the treatment pathway represent NHS practice? Is vinblastine monotherapy a relevant comparator in LGG? Are vinblastine monotherapy and vincristine with carboplatin interchangeable?
Clinical evidence	Is the evidence from TADPOLE sufficient to appraise D+T at the point in the treatment pathway at which it will likely be used for LGG?
	Are the ITCs appropriate for estimating comparative effectiveness in the HGG population?
Cost-effectiveness	What is committee's preferred approach to progression? Company, EAG pragmatic, or EAG preferred? Are the PFS predictions clinically plausible?
	Are the adult utility values acceptable for decision-making in children?
	Should a stopping rule be applied?
Severity/threshold modifiers	Does the committee agree with the 1.2 modifier for LGG and the 1.7 modifier for HGG? Are there any benefits of D+T which are not captured in the QALY calculations?
ICER threshold	What is the committee's preferred ICER threshold?
Preferred ICER	What is the committee's preferred ICER?

NICE

Abbreviations: D+T, dabrafenib and trametinib; HGG, high-grade glioma; ICER, incremental cost-effectiveness ratio; ITC, indirect treatment comparison; LGG, low-grade glioma; QALY, quality-adjusted life year.

Supplementary appendix

NICE National Institute for Health and Care Excellence

Patient perspectives

Link back to Patient and clinical perspectives

Substantial unmet need for children and young people with glioma and their caregivers

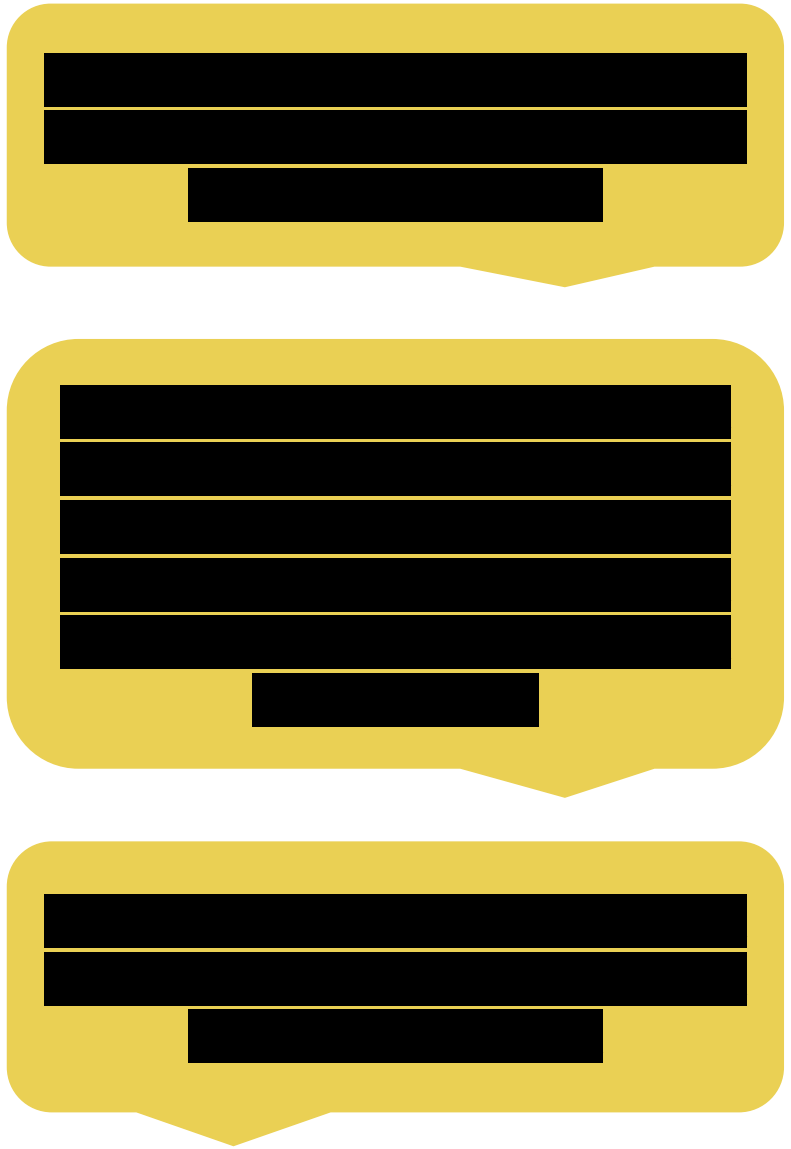
Submission from The Brain Tumour Charity

Brain tumour diagnosis is extremely traumatic for patients and caregivers

Caregivers report a difficult route to diagnosis requiring multiple GP visits

Current treatment for glioma delays education, restricts socialising and can cause lasting emotional impact. In addition, caregivers report significant financial burden and a substantial time commitment associated with having to travel to hospital for treatment

Patients and caregivers would welcome a treatment that improves quality of life, allows patients to spend more time playing with their family, and is easy to take



Abbreviations: GP, general practitioner; PTSD, post-traumatic stress disorder.

Clinical perspectives

Link back to Patient and clinical perspectives

Substantial unmet need for children and young people with glioma and their caregivers

Submissions from Prof. John-Paul Kilday (CCLG) and Dr Lynley Marshall

The aims of treatment for LGG and HGG are to stop subsequent tumour progression, improve neurological function, achieve tumour response, and improve quality of life

Overall tumour response, as per RANO criteria, is defined radiologically as complete (disappearance of target lesion) or partial response (50% or more reduction in the product of the longest perpendicular tumour diameters), in combination with clinically stable or improved disease

There is an unmet need for new treatment:

- In BRAF V600E LGG, patients experience suboptimal responses to conventional treatment, multiple relapses, and significant health and wellbeing issues
- In BRAF V600E HGG, response rates are low, there is no recognised standard care after relapse, and OS can be lower than 20% at 2 years

D+T would be attractive to patients due to oral administration and the need for fewer hospital visits

Abbreviations: CCLG, Children's Cancer and Leukaemia Group; D+T, dabrafenib and trametinib; HGG, high-grade glioma, LGG, low-grade glioma; OS, overall survival; RANO, Response Assessment in Neuro-Oncology criteria.

Decision problem

	Final scope	Decision problem addressed	Rationale if different from the final NICE scope
Population	Children and young people with BRAF V600E mutation-positive glioma: • Low-grade glioma that requires systemic treatment • High-grade glioma that has relapsed, progressed or failed to respond to previous systemic treatment	As per final scope	N/A – in line with the NICE final scope
Intervention	Dabrafenib with trametinib	As per final scope	N/A – in line with the NICE final scope
Comparator	For children and young people with low-grade glioma: • Chemotherapy (including but not limited to vincristine with carboplatin) For children and young people with high-grade glioma: • Chemotherapy • Best supportive care	*LGG cohort:* • Carboplatin with vincristine (C+V) *HGG cohort:* • Temozolomide (TMZ) (in patients not previously treated to TMZ) • Best supportive care (in patients previously treated with TMZ)	*LGG cohort:* C+V is the recommended 1L chemotherapy for LGG as per the UK CCLG guideline *HGG cohort:* • TMZ is the only chemotherapy with marketing authorisation in children and young adults with relapsed or refractory malignant glioma. • Many patients receive TMZ in the adjuvant setting. • No other chemotherapy is effective in the recurrent setting – patients would typically have BSC/palliative care
Subgroups	LGG that requires systemic treatment HGG that has relapsed, progressed or failed to respond to previous systemic treatment	As per final scope	N/A – in line with the NICE final scope

Abbreviations: BSC, best supportive care; C+V, carboplatin and vincristine; CCLG, Children's Cancer and Leukaemia Group; HGG, high-grade glioma; LGG, low-grade glioma; TMZ, temozolomide.

Key issue: The populations included in the appraisal

EAG

- Think this appraisal has 2 separate populations rather than 1 population with 2 subgroups, because:
  - The key clinical trial, the TADPOLE study, consists of 2 separate parts:
    - The first part is an RCT in the LGG population
    - The second part is a prospective cohort study in the HGG population
  - LGG and HGG have very different disease course and treatment pathway
  - Position of D+T in the treatment pathways was different and matched the populations recruited into the 2 parts of the TADPOLE study
- The EAG caution the committee that same evidence or assumptions may be viewed favourably in one population but not the other

NICE comments

- NICE considers that this is compliant with the final scope due to the differences in comparator treatments described in the final scope

Abbreviations: D+T, dabrafenib and trametinib; HGG, high-grade glioma; LGG, low-grade glioma; RCT, randomised controlled trial.

TADPOLE – demographics

Link back to TADPOLE design

	LGG		HGG
	D+T (N=73)	C+V (N=37)	D+T (N=41)
Age, mean (SD)	9.3 (4.97)	8.8 (5.01)	12.12 (4.451)
Age, median (range)	10.0 (1.0 to 17.0)	8.0 (1.0 to 17.0)	13.00 (10.00 to 16.00)
Female, n (%)	44 (60.3)	22 (59.5)	23 (56.1)
Race, n (%)			
White	55 (75.3)	25 (67.6)	25 (61.0)
Asian	5 (6.8)	3 (8.1)	11 (26.8)
Black or African American	2 (2.7)	3 (8.1)	1 (2.4)
Unknown/Other/NR	11 (15.1)	6 (16.2)	4 (9.7)
Weight (kg), mean (SD)	43.02 (26.364)	43.81 (26.527)	49.82 (27.381)
Performance status*, n (%)	N=73	N=33	
100	44 (60.3)	17 (51.5)	15 (36.6)
90	20 (27.4)	12 (36.4)	13 (31.7)
80	7 (9.6)	2 (6.1)	7 (17.1)
70	2 (2.7)	2 (6.1)	1 (2.4)
<70	0	0	5 (12.2)

*Lansky and Karnofsky criteria

Abbreviations: C+V, carboplatin and vincristine; D+T, dabrafenib and trametinib; HGG, high-grade glioma; LGG, low-grade glioma; NR, not reported; SD, standard deviation.

TADPOLE – disease characteristics

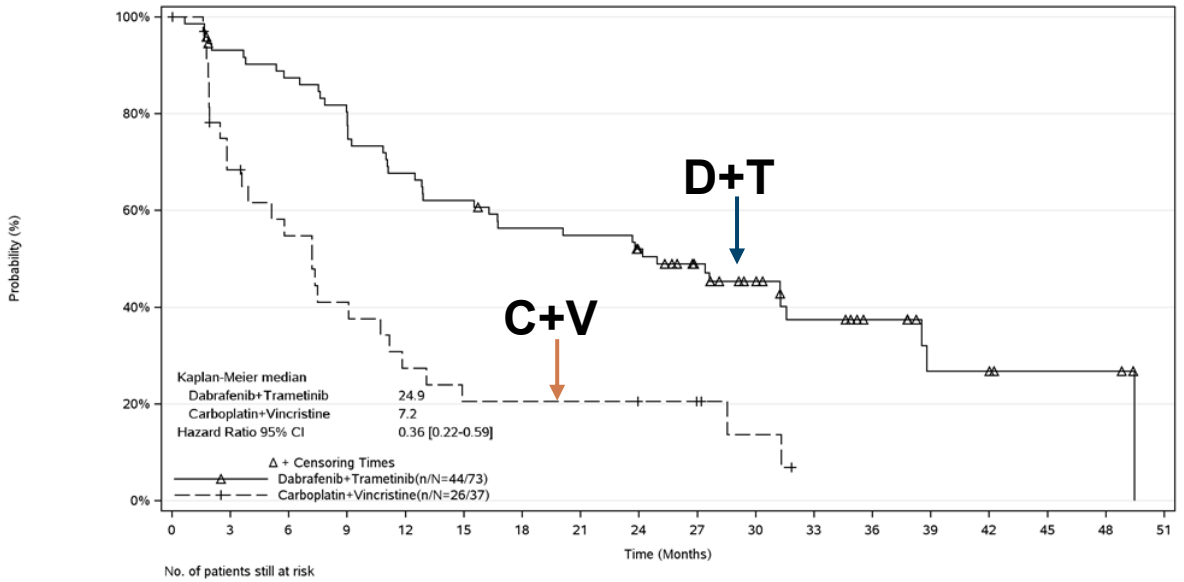
Link back to TADPOLE design

	LGG		HGG
	D+T (N=73)	C+V (N=37)	D+T (N=41)
Pathology at diagnosis, n (%) (top 3)			
Pilocytic astrocytoma	22 (30.1)	12 (32.4)	0
Ganglioglioma	21 (28.8)	9 (24.3)	1 (2.4)
LGG, NOS	14 (19.2)	6 (16.2)	1 (2.4)
Glioblastoma multiforme	0	0	13 (31.7)
Anaplastic pleomorphic xanthoastrocytoma	0	0	6 (14.6)
Pleomorphic xanthoastrocytoma	6 (8.2)	5 (13.5)	4 (9.8)
Grade at initial diagnosis, n (%)			
Grade I	60 (82.2)	28 (75.7)	3 (7.3)
Grade II	12 (16.4)	8 (21.6)	4 (9.8)
Grade III	0	0	13 (31.7)
Grade IV	0	0	20 (48.8)
Missing	1 (1.4)	1 (2.7)	1 (2.4)
Time since initial diagnosis of primary site to study entry (months), mean (SD)	N=73 15.4 (31.69)	N=33 6.5 (11.57)	30.5 (38.89)
BRAF mutation status			
V600E	72 (98.6)	35 (94.6)	41 (100)
Non-mutant	0	1 (2.7)	0
Other/Missing	1 (1.4)	1 (2.7)	0
Metastatic sites, n (%)	7 (9.6)	2 (5.4)	NR

Abbreviations: C+V, carboplatin and vincristine; D+T, dabrafenib and trametinib; HGG, high-grade glioma; LGG, low-grade glioma; NOS, not otherwise specified; NR, not reported; SD, standard deviation.

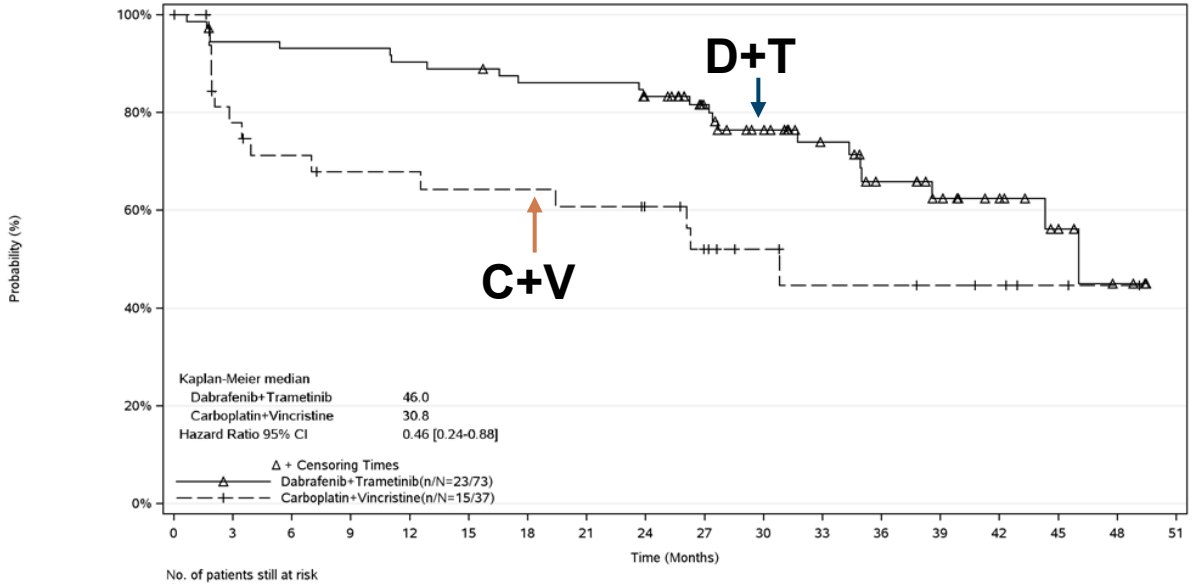
LGG: investigator and independent review TADPOLE PFS KM curves

Independent review



Time (Months)	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51
Dabrafenib+Trametinib	73	66	62	57	48	44	39	38	34	27	20	14	10	5	5	3	3	0
Carboplatin+Vincristine	37	21	16	12	8	6	6	6	5	4	2	0	0	0	0	0	0	0

Investigator



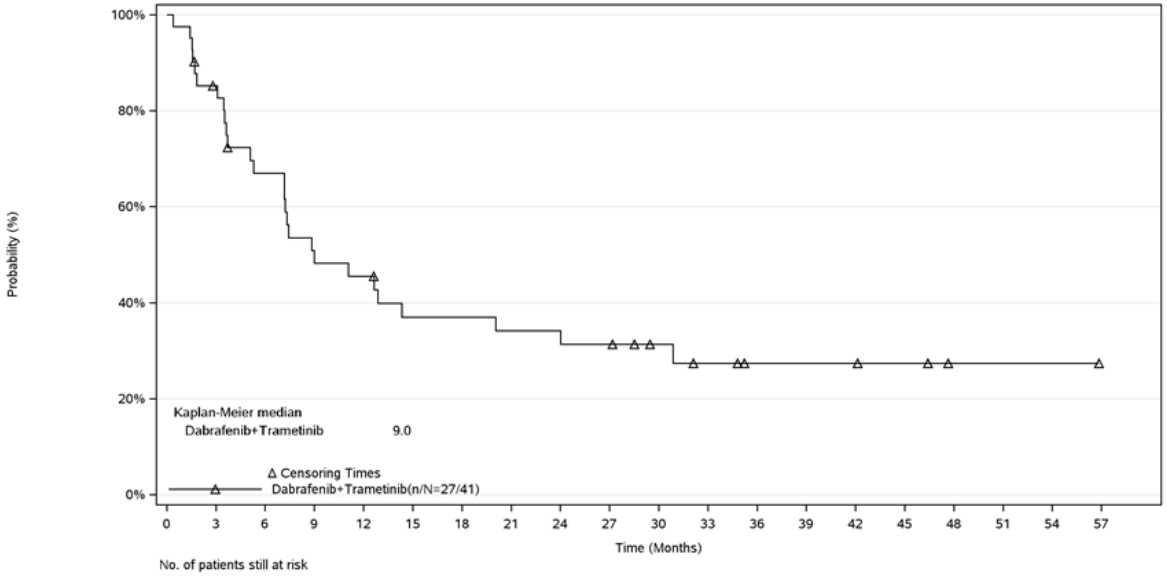
Time (Months)	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51
Dabrafenib+Trametinib	73	68	67	67	65	64	61	61	57	47	39	29	22	17	13	8	3	0
Carboplatin+Vincristine	37	24	21	19	19	18	18	17	15	11	8	6	6	5	4	2	1	0

Link back to Assumptions for progression

Abbreviations: KM, Kaplan-Meier; LGG, low-grade glioma; PFS, progression-free survival.

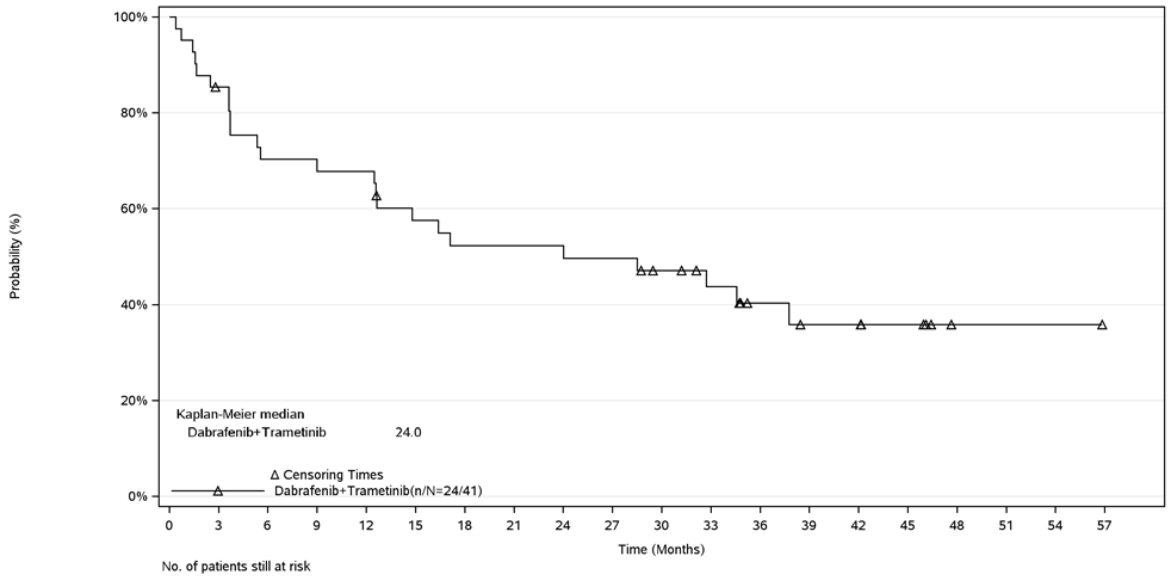
HGG: investigator and independent review TADPOLE PFS KM curves

Independent review



Time (Months)	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54	57
Dabrafenib+Trametinib	41	33	25	19	17	13	13	12	12	11	8	6	4	4	4	3	1	1	1	0

Investigator



Time (Months)	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54	57
Dabrafenib+Trametinib	41	34	28	28	27	22	20	20	20	19	16	13	9	7	7	5	1	1	1	0

Link back to Assumptions for progression

Abbreviations: HGG, high-grade glioma; KM, Kaplan-Meier; PFS, progression-free survival.

Key issue: Indirect treatment comparison (ITC) – HGG

Summary of results – no prior TMZ subgroup

Treatment (vs Verschuur et al.)	N/ESS	Events	D+T vs TMZ HR (95% CI)
OS (MAIC)			
D+T naïve	[redacted]	[redacted]	[redacted]
D+T weighted	[redacted]	[redacted]	[redacted]
TMZ	20	16	Comparator
PFS independent review (IPTW)			
D+T naïve	[redacted]	[redacted]	[redacted]
TMZ unweighted	11	11	Comparator
D+T weighted	[redacted]	[redacted]	[redacted]
TMZ weighted	[redacted]	[redacted]	[redacted]

KM curves for OS (Verschuur et al. MAIC) – no prior TMZ subgroup

[redacted]

Company: ITCs show D+T significantly improves OS and PFS vs. TMZ in patients who have not previously had TMZ (HRs less than 1 and 95% CIs do not contain 1)

Abbreviations: CI, confidence interval; D+T, dabrafenib and trametinib; ESS, effective sample size; HGG, high-grade glioma; HR, hazard ratio; IPTW, inverse probability of treatment weighting; ITC, indirect treatment comparison; KM, Kaplan-Meier; MAIC, matching-adjusted indirect comparison; OS, overall survival; PFS, progression-free survival; SE, standard error; TMZ, temozolomide.

Key issue: Indirect treatment comparison (ITC) – HGG

Summary of results – prior TMZ subgroup

Treatment (vs MacDonald et al)	N/ESS	Events	D+T vs cilengitide HR (95% CI)
OS (MAIC)			
D+T naïve	[redacted]	[redacted]	[redacted]
D+T weighted	[redacted]	[redacted]	[redacted]
Cilengitide	24	23	Comparator
PFS independent review (MAIC)			
D+T naïve	[redacted]	[redacted]	[redacted]
D+T weighted	[redacted]	[redacted]	[redacted]
Cilengitide	24	23	Comparator

KM curves for OS (MacDonald et al. MAIC) – prior TMZ subgroup

Company: ITCs show D+T significantly improves OS and PFS vs. chemotherapy (proxy for BSC) in patients who have previously had TMZ (HRs less than 1 and 95% CIs do not contain 1)

Abbreviations: BSC, best supportive care; CI, confidence interval; D+T, dabrafenib and trametinib; ESS, effective sample size; HGG, high-grade glioma; HR, hazard ratio; ITC, indirect treatment comparison; KM, Kaplan-Meier; MAIC, matching-adjusted indirect comparison; OS, overall survival; PFS, progression-free survival; TMZ, temozolomide.

HGG PFS ITCs

KM curves for PFS (Verschuur et al. IPTW) – no prior TMZ subgroup

KM curves for PFS (MacDonald et al. MAIC) – prior TMZ subgroup

Link back to ITCs for HGG

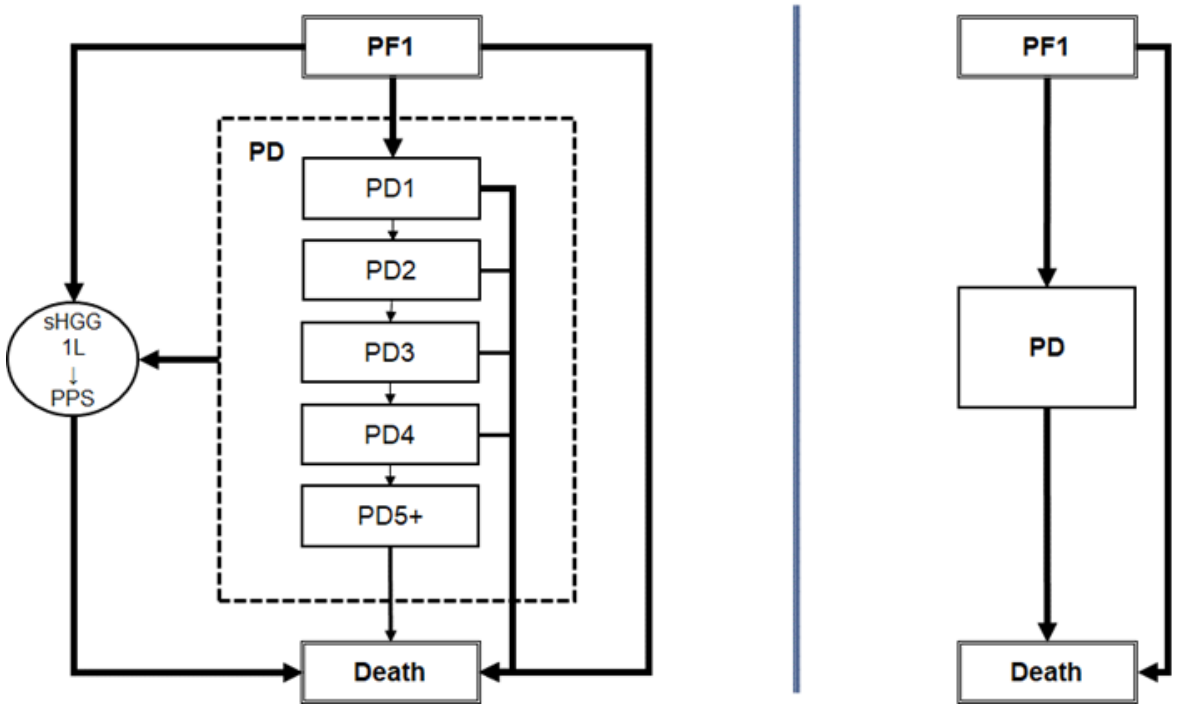
Abbreviations: D+T, dabrafenib and trametinib; HGG, high-grade glioma; IPTW, inverse probability of treatment weighting; ITC, indirect treatment comparison; KM, Kaplan-Meier; PFS, progression-free survival; TMZ, temozolomide.

Company's model overview

Model structure

- Individual-based state-transition model
- 3 health states common to both models: progression-free following 1st treatment, progressed, and death
- LGG has an additional health state: secondary HGG

LGG



HGG

Technology affects **costs** by:

- Increasing costs of treatment
- Decreasing costs associated with drug administration and hospital acquisition
- Different monitoring costs for patients treated
- Marginally changing AE costs

Technology affects **QALYs** by:

- Increasing progression-free survival
- Marginally changing utility at the start of the model in the 2 arms, due to differences in AEs

Assumptions with **greatest ICER effect**:

- Modelling PFS: the definition of progression and selection of models fitted to the data*†
- The time spent by patients on D+T treatment*†‡
- The time spent by patients on BSC in the post-progression survival health state†‡

*LGG
†HGG no prior TMZ
‡HGG prior TMZ

Abbreviations: 1L, first-line; AE, adverse event; BSC, best supportive care; D+T, dabrafenib and trametinib; HGG, high-grade glioma; ICER, incremental cost-effectiveness ratio; LGG, low-grade glioma; PD, progressed disease; PF, progression-free; PPS, post-progression survival; QALY, quality-adjusted life year; sHGG, secondary HGG; TMZ, temozolomide.

Company survival extrapolation predictions

	LGG cohort				HGG cohort - No prior TMZ				HGG cohort - Prior TMZ			
	C+V		D+T		TMZ		D+T		BSC		D+T	
Years	PFS	OS	PFS	OS	PFS	OS	PFS	OS	PFS	OS	PFS	OS
0.5	70%	99%	93%	100%	15%	81%	83%	97%	–	58%	58%	89%
1	66%	98%	90%	99%	7%	50%	77%	90%	–	32%	58%	75%
2	59%	96%	82%	99%	2%	17%	65%	73%	–	10%	39%	53%
3	45%	94%	63%	98%	0%	6%	55%	65%	–	3%	22%	35%
4	38%	91%	52%	97%	0%	2%	46%	55%	–	1%	14%	23%
5	35%	89%	47%	96%	0%	1%	37%	45%	–	1%	9%	15%
10	23%	82%	31%	91%	0%	0%	13%	16%	–	0%	1%	2%
15	19%	75%	26%	87%	0%	0%	6%	6%	–	0%	0%	0%
20	18%	71%	23%	84%	0%	0%	2%	2%	–	0%	0%	0%
30	17%	64%	23%	79%	0%	0%	0%	0%	–	0%	0%	0%
40	17%	58%	22%	74%	0%	0%	0%	0%	–	0%	0%	0%
50	16%	52%	21%	68%	0%	0%	0%	0%	–	0%	0%	0%

Link back to company assumptions for progression – LGG and HGG

NICE

Abbreviations: BSC, best supportive care; C+V, carboplatin and vincristine; D+T, dabrafenib and trametinib; HGG, high-grade glioma; LGG, low-grade glioma; OS, overall survival; PFS, progression-free survival; TMZ, temozolomide.

Side-by-side PFS extrapolation predictions

LGG

	Company		EAG	
Years	C+V	D+T	C+V	D+T
5	35%	47%	3%	22%
10	23%	31%	1%	10%

HGG

No prior TMZ

	Company		EAG	
Years	TMZ	D+T	TMZ	D+T
1	7%	77%	1%	-
5	0%	37%	[redacted]	[redacted]
10	0%	13%	-	[redacted]

Prior TMZ

	Company		EAG	
Years	BSC	D+T	BSC	D+T
5	-	9%	-	[redacted]
10	-	1%	-	[redacted]

Link back to assumptions for progression – final slide

Abbreviations: BSC, best supportive care; C+V, carboplatin and vincristine; D+T, dabrafenib and trametinib; HGG, high-grade glioma; LGG, low-grade glioma; PFS, progression-free survival; TMZ, temozolomide.

D+T SmPC wording on duration

Dabrafenib (Finlee; link to SmPC)

Treatment with Finlee should continue until disease progression or until the development of unacceptable toxicity. There are limited data in patients older than 18 years of age with glioma, therefore continued treatment into adulthood should be based on benefits and risks to the individual patient as assessed by the physician.

Trametinib (Spexotras; link to SmPC)

Treatment with Spexotras should continue until disease progression or until the development of unacceptable toxicity. There are limited data in patients older than 18 years of age with glioma, therefore continued treatment into adulthood should be based on benefits and risks to the individual patient as assessed by the physician.

Link back to Treatment duration

Abbreviations: D+T, dabrafenib and trametinib; SmPC, summary of product characteristics.

QALY weightings for severity

Background

- Company calculated the QALY shortfall using the following assumptions:
  - Sex and age distribution: TADPOLE
  - Total life expectancy: ONS population mortality data (2018 to 2020), quality-adjusted using UK population norm values for EQ-5D by age and sex as reported by Hernández Alava 2023

	QALYs of people without the condition	QALYs with the condition on current treatment	Absolute QALY shortfall (has to be >12)	Proportional QALY shortfall (has to be >0.85)	Severity modifier
Company					
LGG	24.12	11.39	12.73	52.8%	1.2
HGG – no prior TMZ	23.81	0.73	23.08	96.9%	1.7
HGG – prior TMZ	23.81	0.43	23.38	98.2%	1.7
EAG					
LGG	24.12	6.33	17.79	73.8%	1.2
HGG – no prior TMZ	23.81	1.36	22.45	94.3%	1.7
HGG – prior TMZ	23.81	1.21	22.60	94.9%	1.7

Link back to QALY weightings

 Abbreviations: EQ-5D, Euroqol 5-dimensions; ONS, Office for National Statistics; QALY, quality-adjusted life year