dabrafenib dispersible tablets (Finlee®)

Novartis Pharmaceuticals UK Ltd

09 August 2024

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

ADVICE: following a full submission assessed under the end of life and orphan medicine process

dabrafenib (Finlee®) is accepted for use within NHSScotland.

Indication under review: in combination with trametinib (Spexotras®) for:

- the treatment of paediatric patients aged 1 year and older with low-grade glioma with a BRAF V600E mutation who require systemic therapy.
- the treatment of paediatric patients aged 1 year and older with high-grade glioma with a BRAF V600E mutation who have received at least one prior radiation and / or chemotherapy treatment.

In an open-label, phase II study, dabrafenib plus trametinib significantly improved overall response rate compared with standard chemotherapy in the first-line treatment of unresectable low-grade glioma and resulted in an overall response rate of 56% in patients with relapsed or refractory high-grade glioma.

This advice applies only in the context of approved NHSScotland Patient Access Scheme (PAS) arrangements delivering the cost-effectiveness results upon which the decision was based, or PAS/ list prices that are equivalent or lower.

This advice takes account of the views from a Patient and Clinician Engagement (PACE) meeting.

Chair
Scottish Medicines Consortium

1. Clinical Context

1.1. Medicine background

This is a new oral dispersible tablet formulation of the rapidly accelerated fibrosarcoma (RAF) kinases inhibitor, dabrafenib. It is licensed for use with a new powder for oral solution formulation of the mitrogen-activated extracellular signal regulated kinase 1 (MEK1) and MEK2 inhibitor, trametinib. When used in combination, dabrafenib plus trametinib inhibit two kinases in the mitogen-activated protein kinase pathway, RAF and MEK, resulting in enhanced inhibition. Dabrafenib is dosed twice daily and trametinib once daily; recommended doses for both are based on the bodyweight of the child.[1, 2]

1.2. Disease background

Gliomas are a heterogeneous group of primary central nervous system (CNS) tumours arising from glial cells. They are categorised by the World Health Organisation (WHO) from grade I to grade IV depending on histopathological and molecular features. Low-grade gliomas (WHO grade I and II) are slow growing and high-grade gliomas (WHO grade III and IV) grow rapidly.[2]

Low-grade gliomas include a varied group of tumours of different histological subtypes, locations, age at presentation and symptoms. They are the most commonly diagnosed brain tumours in children and young adults and account for approximately 40% of cases; about 150 cases of childhood low-grade gliomas are diagnosed in the UK each year. They are generally slow growing and survival outcomes can be very good but are affected by the level of resection, histological and molecular tumour subtype, presence of disseminated disease and concurrent diencephalic syndrome. In patients with low-grade gliomas, approximately 17% have been found to have BRAF V600E mutations, which are associated with poorer outcomes for progression-free survival (PFS) and overall survival (OS).[2, 3]

High-grade gliomas also include a heterogeneous group of tumours with differing histologies; WHO grade III anaplastic astrocytoma and grade IV glioblastoma multiforme are the most common. Patients with high-grade gliomas have a poor prognosis with a median duration of survival of 9 to 15 months from diagnosis and 5-year survival rates of 10 to 35%. BRAF V600E mutations have been identified in approximately 6% of patients with high-grade gliomas, more often in those with a favourable prognosis, and has been associated with improved OS compared with patients with wildtype BRAF V600.[2]

1.3. Treatment pathway and relevant comparators

Surgery is the primary treatment of most low- and high-grade gliomas. Further management depends on whether resection was complete or incomplete and may include observation, chemotherapy and radiotherapy (which may be limited because of neurocognitive toxicity). Current guidelines for low-grade glioma (excluding Neurofibromatosis Type 1 [(NF1], a syndrome in 10 to 20% of low-grade gliomas) recommend vincristine plus carboplatin as first-line chemotherapy, with vinblastine as second-line, irinotecan plus bevacizumab as third-line and tioguanine, procarbazine, lomustine plus vincristine (TPCV) as fourth-line. These medicines are all used off-label.[3]

Following surgery with or without radiotherapy in patients with high-grade gliomas, there is no accepted standard of care for patients with recurrent disease. There are limited chemotherapy options and response rates are low. Temozolomide is the only medicine licensed for children with high-grade gliomas; specifically for children from 3 years, adolescents and adult patients with malignant glioma, such as glioblastoma multiforme or anaplastic astrocytoma, showing recurrence or progression after standard therapy.[4] However the submitting company notes that since some patients receive temozolomide in the adjuvant setting, best supportive care may be used on disease recurrence.

1.4. Category for decision-making process

Eligibility for a PACE meeting
Dabrafenib (Finlee®) meets SMC orphan and end of life (high-grade glioma only) criteria.

2. Summary of Clinical Evidence

2.1. Evidence for the licensed indication under review

Evidence to support the use of dabrafenib with trametinib in paediatric patients with glioma comes from the open-label, phase II study, TADPOLE.

Table 2.1. Overview of relevant study[2, 5, 6]

Criteria	TADPOLE study
Study design	An international, open-label, phase II study comprising two cohorts (one randomised, active-controlled cohort in unresectable low-grade glioma and one single-arm cohort in relapsed or refractory high-grade glioma).
Eligible patients	• Patients aged ≥12 months to < 18 years; patients aged <6 years weighed ≥7kg; patients ≥6 years weighed ≥10kg. • Low-grade or high-grade glioma according to WHO classification • In the low-grade cohort, patients were eligible for first-line systemic therapy; progressive disease following surgical excision, or were unresectable patients with a risk of neurological impairment with progression • In the high-grade cohort, patients had relapsed, progressed or failed to respond to first-line therapy. • BRAF V600 mutation-positive tumour assessed locally or at a designated reference laboratory. • Centrally confirmed measurable disease according to RANO criteria • Performance status of ≥50% on either the Karnofsky or Lansky scale
Treatments	Low-grade cohort: • dabrafenib (orally in two equally divided doses: 5.25 mg/kg/day for patients <12 years and 4.5 mg/kg/day for patients ≥12 years; capped at 150 mg twice daily) plus trametinib (orally once daily: 0.032 mg/kg for patients <6 years and 0.025mg/kg for patients ≥6 years; capped at 2 mg once daily); treatment continued until disease progression by RANO criteria or loss of clinical benefit, unacceptable toxicity, new anticancer treatment, discontinuation, loss to follow-up or death. • Or carboplatin (175 mg/m^2 BSA) and vincristine (1.5 mg/m^2 BSA) for a 10-week induction course (weekly infusions on weeks 1 to 4 and week 7 to 10) followed by eight 6-week cycles of maintenance (four weekly doses of carboplatin, and three weekly doses of vincristine given concomitantly with the first 3 weeks of carboplatin, followed by 2 weeks of rest). On confirmed progression, patients could cross over to dabrafenib plus trametinib.

	High-grade glioma cohort: •dabrafenib plus trametinib at doses above.
Randomisation	In the low-grade cohort, patients were randomised 2:1 to receive dabrafenib plus trametinib (n=73) or carboplatin plus vincristine (n=37) without stratification. There was no randomisation in the high-grade cohort; all patients received dabrafenib plus trametinib (n=41).
Primary outcome	ORR, defined as the proportion of patients with a best overall confirmed complete or partial response. This was assessed by BICR according to RANO criteria in the low-grade cohort and independently according to RANO criteria in the high-grade cohort.
Selected secondary outcomes	•PFS by BICR (defined as the time from first dose of study treatment to the first progression or death due to any cause) •PFS by investigator •OS (defined as the time from first dose of study treatment to death due to any cause) •DOR (defined as the time from response to the first progression or death due to any cause) •CBR (defined as complete or partial response or stable disease for ≥24 weeks) • PROMIS questionnaire.
Statistical analysis	A hierarchical statistical testing strategy was applied in the low-grade glioma cohort for the primary (ORR) and secondary outcomes (PFS and OS) with no formal testing of outcomes after the first non-significant outcome in the hierarchy. Therefore, the results reported for these outcomes are descriptive only and not inferential (no p-values reported). There was no hierarchical testing strategy in the high-grade glioma cohort.

BICR = blinded independent central review; BSA = body surface area; CBR = clinical benefit rate; DOR = duration of response; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PROMIS = Patient-Reported Outcomes Measurement Information System; RANO = Response Assessment in Neuro-Oncology

The primary analysis (data cut-off 23 August 2021) of TADPOLE was performed 32 weeks after the last patient was enrolled and the final analysis (data cut-off 28 April 2023) after all patients had been followed for survival for ≥2 years. At the primary analysis, there were significant improvements in overall response rate (ORR) and PFS assessed by blinded independent central review (BICR) in patients treated with dabrafenib plus trametinib compared with vincristine plus carboplatin in the low-grade glioma cohort and an independently assessed ORR of 56% in the high-grade glioma cohort. Results were similar at the final analysis. At both analyses, there were too few deaths to estimate the median OS in any treatment group, with the exception of a median OS of 32.8 months in the high-grade glioma cohort at the primary analysis.[2, 5-7] Details of results are presented in Table 2.2.

Table 2.2 Results for the primary and selected secondary outcomes of the TADPOLE study[2, 5-8]

	Low-grade glioma cohort		**High-grade glioma cohort**
	dabrafenib plus trametinib (n=73)	**carboplatin plus vincristine (n=37)**	**dabrafenib plus trametinib (n=41)**
Primary analysis (data cut-off 23 August 2021)			
Median duration of follow up, months	18.9		25.1
ORR assessed independently, %	47%	11%	56%
Odds ratio (95% CI), p-value	7.19 (2.3 to 22.4) p<0.001		-

Median duration of response assessed independently, months	20.3	NE	22.2
Number of PFS events assessed independently	30	22	24
Median PFS assessed independently, months	20.1	7.4	9.0
Hazard ratio (95% CI)	0.31 (0.17 to 0.55) p<0.001		-
PFS free at 6 months	87%	58%	67%
PFS free at 12 months	67%	26%	44%
Number of deaths	0	1	14
Median OS, months	NE	NE	32.8
Final analysis (data cut-off 28 April 2023)			
ORR assessed independently, %	55%	16%	56%
Median PFS assessed independently, months	24.9	7.2	9.0
Number of deaths	0	1	17
Median OS, months	NE	NE	NE

CI = confidence interval; DOR = duration of response; NE = not estimable; ORR = overall response rate; OS = overall survival; PFS = progression-free survival

In the low-grade glioma cohort, patients randomised to vincristine plus carboplatin were allowed to cross over to dabrafenib plus trametinib on centrally confirmed Response Assessment in Neuro-Oncology (RANO)-defined disease progression. Twenty-four percent (9/37) of patients in the carboplatin plus vincristine group had crossed over at the time of the primary analysis and 32% at the time of the final analysis. At the final analysis, an ORR by BICR was reported in 42% of the 12 patients who had crossed over.[5, 7]

2.2. Health-related quality of life outcomes

Health Related Quality of Life was only assessed in the low-grade glioma cohort using the generic Patient-Reported Outcomes Measurement Information System (PROMIS) Parent Proxy Global Health 7+2. The 7+2 item parent proxy paediatric global health measure include a one global health score plus a single score for pain and a single score from fatigue interference item; a higher score for global health indicates better overall health and a higher score for pain and fatigue indicates worse pain and fatigue. Results over the study period found numerically improved scores for global health and fatigue with dabrafenib plus trametinib compared with vincristine plus carboplatin but little difference between the treatment groups in terms of the pain score. The numbers of patients included in later assessments were small, particularly in the vincristine plus carboplatin group.[5, 7]

2.3. Indirect evidence to support clinical and cost-effectiveness comparisons

In the absence of direct evidence comparing dabrafenib plus trametinib with temozolomide in patients with relapsed or refractory high-grade glioma, the submitting company conducted indirect comparisons using unanchored matched-adjusted indirect comparison (MAIC) and inverse of probability of treatment weighting (IPTW) methods, depending on the availability of individual patient data (IPD) for the comparator study. Comparison was conducted in two populations: all patients regardless of previous use of temozolomide and temozolomide-naïve patient subgroup.

The temozolomide-naïve subgroup was considered the most relevant population and these results were used in the economic analysis. Overall, the results suggested that dabrafenib plus trametinib was superior to temozolomide for OS, PFS and ORR.

Table 2.3: Summary of indirect treatment comparisons

Criteria	Overview
Design	Unanchored MAIC and IPTW (only for PFS and ORR versus Verschuur IPD data)
Population	Paediatric patients with high-grade glioma who had received at least one prior radiation and/or chemotherapy treatment
Comparators	Temozolomide
Studies included	High-grade glioma cohort of TADPOLE for dabrafenib plus trametinib (temozolomide-naïve subgroup and all patients) [6, 8] and two uncontrolled studies for temozolomide (Lashford 2002 and Verschuur 2004).[9, 10]
Outcomes	OS and independently assessed PFS and ORR
Results	The company acknowledged that due to the limited available data, there was uncertainty in the results, however concluded that dabrafenib plus trametinib was superior to temozolomide for OS and independently assessed PFS and ORR in the temozolomide-naïve subgroup

CI = confidence interval HR = hazard ratio; MAIC = matched-adjusted indirect treatment comparison; IPTW = inverse of probability of treatment weighting; ORR = overall response rate; OS= overall survival; PFS = progression-free survival.

*Other data were also assessed but remain confidential.**

3. Summary of Safety Evidence

In the safety population of the low-grade glioma cohort (n=106), at the time of the primary analysis (cut-off date 23 August 2021), the median duration of treatment in the dabrafenib plus trametinib group was 75.7 weeks and in the carboplatin plus vincristine group was 34.0 weeks and 35.3 weeks respectively. In the dabrafenib plus trametinib (n=73) and vincristine plus carboplatin (n=33) groups, all patients reported a treatment-emergent adverse event (AE) and these were considered treatment-related in 92% and 97% respectively. A grade 3 or higher AE was reported by 47% versus 94%, patients with a reported serious AE were 40% versus 39%, and patients discontinuing therapy due to an AE was 4.1% versus 18%.[2, 5, 7, 8]

There was an increased incidence of grade ≥3 AEs of pyrexia (8.2% versus 3.0%) and increased weight (6.8% versus 0) in the dabrafenib plus trametinib group compared with the vincristine plus carboplatin group. Grade ≥3 haematological AEs of neutropenia, anaemia and decreased white blood cells were more frequent in the vincristine plus carboplatin group. [2, 5]

In the safety population of the high-grade glioma cohort (n=41), at the time of the primary analysis, the median duration of treatment in the dabrafenib plus trametinib group was 72.7 weeks. Any treatment-emergent AE was reported by all 41 patients, and these were considered treatment-related in 83%. In 68% of patients, a grade 3 or higher AE was reported, patients with a reported serious AE were 61%, and patients discontinuing therapy due to an AE were 4.9%. The most frequently reported grade ≥3 AEs were headache (9.8%), vomiting (4.9%), pyrexia (2.4%), neutropenia (2.4%), diarrhoea (2.4%) and rash (2.4%). [2, 6]

The safety profile of dabrafenib plus trametinib in this paediatric population was considered manageable and was generally similar to the adult population, with the exception of increased

weight, which was reported in 16% of patients treated with dabrafenib and trametinib and was considered a new AE.[2, 7]

The SPC recommends that patients have regular skin examinations, are monitored for visual signs and symptoms of ophthalmic reactions and have serum creatinine, liver function and blood pressure monitored during treatment with dabrafenib plus trametinib.[1]

4. Summary of Clinical Effectiveness Considerations

4.1. Key strengths

- In the low-grade glioma cohort of the TADPOLE study, first-line treatment with dabrafenib plus trametinib significantly improved ORR and PFS when assessed by BICR compared with the most relevant comparator of vincristine plus carboplatin. At the time of the primary analysis, there was a 36% improvement in ORR and a 12.7-month improvement in PFS; at the final analysis 39% and 17.7 months respectively. These improvements were considered clinically relevant by regulators. [2, 5-7]
- In the relapsed or refractory high-grade glioma cohort, the ORR of 56% at the primary and final analyses was higher than the 20% rate based on historical controls who were unselected in terms of BRAF mutations status. This ORR was considered clinically relevant and the duration of response clinically meaningful by regulators. Regulators noted that although the impact of treatment on PFS and OS in the high-grade cohort cannot be isolated it looks promising for patient who otherwise have a poor prognosis [2, 6]
- The dispersible tablet formulation of dabrafenib and powder for oral solution formulation of trametinib would ease oral administration in children who may have difficulty swallowing tablets.

4.2. Key uncertainties

- The TADPOLE study enrolled a small number of study patients. The data for young patients with high-grade glioma are particularly limited with only five patients aged 1 to 6 years and two patients aged 1 to 2 years in this cohort. Since gliomas are heterogeneous in nature, the results from a small study may not be generalisable to the wider population in clinical practice. However, this is not unexpected given that this is an orphan condition affecting a small number of patients in Scotland.[2, 5, 6]
- The high-grade cohort was single-arm and lacks a control to determine the size of the treatment effect.[2, 6]
- At the time of the final analysis of TADPOLE, there had been too few deaths in both study cohorts to estimate median OS survival. In the high-grade glioma cohort, who have a poorer prognosis, 17 of 41 patients had died but median OS was not estimable. Therefore, the size of the treatment effect on survival remains unclear.[7]
- There were discrepancies in PFS results when assessed independently and by investigator. PFS was notably longer when assessed by investigator compared with independent assessment. This may have been the result of more rigorous use of the progression definition (25% increase in the sum of the products of the biperpendicular diameters over

nadir measurements) by independent than investigator assessment.[2, 7] Results for PFS assessed by the investigator were used in the base case economic analysis, with independently-assessed PFS used in scenario analyses.

- Patients with low-grade glioma in TADPOLE were receiving first-line systemic treatment and the study results may not be generalisable to patients receiving second or subsequent systemic treatment. There are no comparative data against treatments that may be used as second or subsequent lines in practice.[2, 5] The ORR of 42% in the 12 patients who crossed over to dabrafenib plus trametinib provide some limited uncontrolled efficacy data in the second-line.[2, 7]
- There are no direct comparative data versus temozolomide which the company considered was the most relevant comparator in the temozolomide-naïve high-grade glioma population. There are several limitations that affect the robustness of the results of the indirect treatment comparisons versus temozolomide. Unanchored methods may be prone to bias. Only three small, single-arm studies were included (numbers reduced further by using temozolomide subgroup and by matching), populations were heterogeneous (unable to match all prognostic factors), BRAF mutation status was unknown in temozolomide patients, OS data are immature for dabrafenib plus trametinib patients, and temozolomide studies were 20 years old. Due to these limitations, the results of the indirect comparisons are highly uncertain.
- There are no comparative data available for patients with high-grade glioma who have previously received temozolomide and who may be managed with best supportive care in clinical practice.

4.3. Clinical expert input

Clinical experts consulted by SMC considered that dabrafenib, in combination with trametinib, fills an unmet need in this therapeutic area, namely offering a suitable, oral formulation for children who are unable to swallow tablets. They considered that this is a therapeutic advancement which provides an effective, targeted treatment for paediatric patients with low-grade or high-grade glioma.

4.4. Service implications

Diagnostic test required to identify patients eligible for treatment: contact local laboratory for information**.**

Clinical experts consulted by SMC considered that dabrafenib, in combination with trametinib, had no service implications as an orally administered, outpatient treatment.

5. Patient and Clinician Engagement

A patient and clinician engagement (PACE) meeting with patient group representatives and clinical specialists was held to consider the added value of **dabrafenib**, as an **orphan and end of life (high-grade glioma only)** medicine, in the context of treatments currently available in NHSScotland.

The key points expressed by the group were:

- Low-grade gliomas are the most common group of central nervous system tumours in children

and young adults and, when not amenable to complete surgical resection, they can have a substantial impact on neurological and endocrine function depending on location. High-grade gliomas represent a significant treatment challenge as they are unlikely to be completely resectable, resulting in very poor prognosis. The symptoms of glioma vary depending on the location and extent of the tumour but may include nausea, vomiting, headaches, lethargy, irritability, clumsiness, seizures, changes in personality and behaviour. The diagnosis of a childhood brain tumour is incredibly traumatic for patients, families and carers with stress and anxiety around delays in diagnosis, hospital visits for treatment and post-treatment challenges including the worry over future therapy. In addition, active treatment can leave long-term cognitive and neurological symptoms which affect all aspects of a child's life.

- PACE participants highlighted that there is a clear need for additional treatment options for patients with gliomas. There are several chemotherapy options for patients with low-grade glioma who require systemic therapy but multiple lines of treatment may be needed, thus increasing the risk of adverse side effects. Patients with high-grade glioma have very limited treatment options to which responses are poor and further therapies are needed. The availability of dabrafenib for use in combination with trametinib would address an unmet need by offering an additional, effective treatment option, targeted for patients with low-grade and high-grade glioma with a BRAF V600 mutation.
- Evidence suggests that low-grade and high-grade glioma with a BRAF V600 mutation may respond better to dabrafenib in combination with trametinib compared with current conventional treatments. Improvements in response rates may reduce morbidity, such as visual impairment, neurological outcomes and mortality.
- Dabrafenib with trametinib is an oral therapy which can be taken at home and the new formulations would allow accurate dosing and easy administration to this young patient population. This could offer a huge benefit to patients and their parents by reducing the burden of treatment, reducing the number of hospital visits and stays and would better fit into normal family life. These benefits may improve quality of life by freeing patients to lead as normal a life as possible, including education, playing with siblings, mixing with others, participating in recreational activities and living life, feeling like they are not on treatment.
- Compared with conventional chemotherapy in low-grade glioma, dabrafenib in combination with trametinib, as an oral treatment, avoids the need for central venous access (with its management and associated risks) and prolonged hospital attendance. Available data suggests these targeted medicines have a more favourable short-term side effect profile and are associated with less immunosuppression, nephrotoxicity and ototoxicity compared with the most frequently used conventional chemotherapy agents. These factors may allow families to live more normal lives, including socialising and travelling away from home.
- PACE clinicians noted that the optimal duration of treatment with dabrafenib and trametinib is currently uncertain as are the longer-term side effects in this paediatric and young adult population. Although the safety profile appears favourable, there is less clinical experience in using these medicines in this young population and an awareness of potentially differing and unexpected side effects would be needed.

Additional Patient and Carer Involvement

We received a patient group submission from The Brain Tumour Charity, which is a registered charity. The Brain Tumour Charity has not received any pharmaceutical company funding in the past two years. A representative from The Brain Tumour Chairty participated in the PACE meeting. The key points of their submission have been included in the full PACE statement considered by SMC.

6. Summary of Comparative Health Economic Evidence

6.1. Economic case

The submitting company provided an economic case as described in Table 6.1.

Table 6.1 Description of economic analysis

Criteria	Overview
Analysis type	Cost-utility analysis
Time horizon	Lifetime
Population	The analysis was split into two paediatric populations defined as: (1) Low-grade glioma: patients aged 1 year and older with low-grade glioma with a *BRAF* V600 mutation who require systemic therapy. (2) High-grade glioma: patients aged 1 year and older with high-grade glioma with a *BRAF* V600 mutation who have received at least one prior radiation and/or chemotherapy treatment. The high-grade population was further split into two separate analyses depending on prior or no-prior treatment with temozolomide.
Comparators	Low-grade: Carboplatin plus vincristine. High-grade**:** (i) Temozolomide in patients not previously treated with temozolomide; (ii) Best supportive care (BSC) in patients previously treated with temozolomide.
Model description	An individual-based simulation utilising three key health states common to both low-grade and high-grade analyses: progression-free, progressive disease and death. In the low-grade model an additional health state was included to allow transformation into malignant glioma (secondary high-grade glioma), and the progressive disease state was divided into five sub-health states to capture the impact of subsequent progressions on costs and quality of life. Patients in the low-grade analysis, as well as patients receiving either dabrafenib plus trametinib or temozolomide in the high-grade analysis were assumed to start the model in the pre-progression state. High-grade patients in the BSC arm were assumed to start the model in the progressive disease state.
Clinical data	The main clinical data source was the final data-cut (28th April 2023) of the TADPOLE study.[2, 5, 6] In the low-grade group, this informed baseline patient characteristics, PFS and incidence of AEs across both treatment arms. For low-grade analysis, given immature OS data from the TADPOLE study, external data were used to inform time to death following progression, and event free survival following malignant transformation.[11,12] In the high-grade group the final data-cut of the TADPOLE study informed baseline patient characteristics and time to death across all treatment arms as well as incidence of AEs and PFS for dabrafenib plus trametinib patients. The TADPOLE study was uncontrolled for the high-grade group, and so the relative treatment effect on PFS for patients receiving temozolomide was derived from the ITC (described in Table 2.3). Incidence of AEs for high-grade patients receiving dabrafenib plus trametinib and temozolomide came from the TADPOLE study and Verschuur (2004) respectively. [10] In the base case analysis PFS was defined by investigator assessment.
Extrapolation	Predicting the long term PFS adopted a piecewise extrapolation approach. For the low-grade analysis, the Kaplan Meier (KM) data from the TADPOLE study were used up to the next to last observed event (week 115 for carboplatin plus vincristine patients, week 193 for dabrafenib plus trametinib patients) followed by log-normal extrapolation for both arms. This

	extrapolation was applied up to age 25 years, after which point it assumed no further progression would take place. Time to death following progression for the low-grade analysis was assumed to be different between those with early (<18 months) and late (≥18 months) progression, using data from Kendels et al. 2020,[11] which reported survival at 5 and 10 yrs. The company adopted a piecewise exponential approach assuming a constant rate between years 0–5 and then between years 5–10, with the latter extrapolated over the lifetime of the patient. For the high-grade analysis the KM data for dabrafenib plus trametinib were used up to the next to last observed event followed by exponential extrapolation. For the comparison against temozolomide (no prior temozolomide) the treatment effect was estimated from the results of the ITC analysis, applying a hazard ratio to the dabrafenib plus trametinib PFS curve. Time to death in the pre-progressed state was taken from TADPOLE and Scottish lifetables. For the high-grade analyses survival following progression was estimated from the TADPOLE study KM data and assumed to be the same for all treatment arms, an exponential curve was selected for base case and the entire curve fitted.
Quality of life	Health related quality of life in the TADPOLE study was collected using the PROMIS Parent Proxy instrument. The company noted they were unable to map from this instrument to a generic health measure, like the EQ-5D. Therefore, utilities were derived from literature. Utility evidence was lacking in paediatric populations, so the values are taken from adult populations as proxy. The model applied utility decrements to background general population utility values by age and gender for experiencing the various model states: low-grade glioma, progression (1st through to 5th), malignant transformation, high-grade glioma, high-grade progression. A utility decrement was also applied for intravenous chemotherapy administration, allowing dabrafenib patients a utility benefit from oral administration. The impact of Grade 3 /4 AEs on HRQoL is included as a one off quality adjusted life year (QALY) loss applied at model entry for each treatment arm, based on the frequency and grade of AEs reported in TADPOLE for each arm.
Costs and resource use	Costs included medicine acquisition and administration, management of glioma/monitoring of treatments, adverse events, subsequent treatment costs, management at the end of life. Where possible Scotland specific unit costs were applied, standard NHS reference costs were used. The cost of diagnostic testing for BRAF mutations was not included in the analyses, which is acceptable given that patients in Scotland are already currently tested for BRAF mutations.
PAS	A Patient Access Scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHS Scotland. Under the PAS, a discount was offered on list price of dabrafenib. A confidential PAS discount is also in place on trametinib.

6.2. Results

The base case analysis, inclusive of the PAS discount on dabrafenib and trametinib, estimated incremental cost-effectives ratio (ICER) of £30,994, £48,071 and £49,235 for the low-grade population, the high-grade population who have never received temozolomide and the high-grade population who have previously received temozolomide respectively.

6.3. Sensitivity analyses

The company conducted deterministic sensitivity analysis, probabilistic sensitivity analysis and scenario analysis to explore areas of uncertainty. Selected scenario analyses are summarised in Tables 6.3a, 6.3b and 6.3c for the low-grade population, the high-grade population versus temozolomide and the high-grade population versus BSC analyses respectively.

Table 6.3a Selected scenario analyses (PAS price) for low-grade analysis

	Parameter	Base case	Scenario	ICER (£/QALY)
	Base case			£30,994
1a	PFS assessment	Investigator assessed	Independent Review	£17,158
2a	PFS extrapolation Piecewise cut-off	second last point	last point	£36,926
3a	PFS extrapolation Piecewise cut-off	second last point	2 years	£24,382
4a	PFS extrapolation	Piecewise + lognormal	Piecewise + exponential	£35,925
5a	PFS extrapolation - entire curve	Piecewise + lognormal	spline (C+V) and exponential (D+T)	£21,117
	Combined scenarios			
6a	PFS assessment & extrapolation	Investigator, Piecewise + lognormal	Independent review plus spline (C+V) and exponential (D+T)	£15,257
7a	PFS assessment & extrapolation	Investigator, Piecewise + lognormal, 2nd last cut-off	Independent review piecewise last cut-off point	£17,188

PFS=progression free survival ; C+V=carboplatin plus vincristine D+T= dabrafenib plus trametinib

Table 6.3b Selected scenario analyses (PAS price) for high-grade analysis vs temozolomide

	Parameter	Base case	Scenario	ICER (£/QALY)
	Base case			£48,071
1b	ITC PFS hazard ratio	Mean [value academic in confidence]	95% CI lower	£46,086
2b			95% CI upper	£67,943
3b	PFS assessment	Investigator assessed	Independent Review	£49,713
4b	PFS extrapolation Piecewise cut-off	second last point	last point	£48,284
5b	PFS extrapolation Piecewise cut-off	second last point	2 years	£48,046
6b	PFS extrapolation	Piecewise + exponential	Piecewise + Weibull	£44,524
7b	PFS extrapolation	Piecewise + exponential	Entire curve exponential	£49,075
	Combined scenarios			
8b	PFS assessment & extrapolation	Investigator, 2nd last point	Independent, last cut-off point	£49,682

PFS=progression free survival; ITC = indirect treatment comparison

Table 6.3c Selected scenario analyses (PAS price) for high-grade analysis vs BSC

	Parameter	Base case	Scenario	ICER (£/QALY)
	Base case			£49,235
1c	PFS assessment	Investigator assessed	Independent Review	£48,891
2c	PFS extrapolation Piecewise cut-off	second last point	last point	£49,222
3c	PFS extrapolation Piecewise cut-off	second last point	2 years	£49,187
4c	PFS extrapolation	Piecewise + exponential	Piecewise + Weibull	£46,327
5c	PFS extrapolation	Piecewise + exponential	Entire curve exponential	£49,316
6c	PFS assessment & extrapolation	Investigator, 2nd last point	Independent, last cut-off point	£48,823

PFS=progression free survival; ITC = indirect treatment comparison

6.4. Key strengths

- The model structure was appropriate and best available data from the final data cut of the TADPOLE study (with over 2 years follow-up) were used where possible.
- For the low-grade glioma analysis treatment with dabrafenib plus trametinib significantly improved PFS when assessed by BICR compared with the most relevant comparator of vincristine plus carboplatin.

6.5. Key uncertainties

- For the high-grade analyses an ITC was used to compare dabrafenib plus trametinib against temozolomide, given lack of comparator arm in the TADPOLE study. The results from the ITC were assessed as being highly uncertain and varying the relative efficacy of the comparator arm is led to large changes in the estimated cost-effectiveness (see Scenarios 1b and 2b, Table 6.3b).
- There is considerable uncertainty regarding the extrapolation of the PFS data in both the low-grade and high-grade analyses, despite the company following good practice in selecting their base case. The company preferred to adopt a piecewise extrapolation approach given the parametric curves lack of good fit to KM data, and the second to last point on the KM curve is chosen as cut-off point in the base case. Scenario analyses exploring extrapolations using single piece curves, alternative cut-off points, and differing functional forms lead to changes in the ICER, particularly in the low-grade population (Scenarios 2a to 5a, Table 6.3a).
- There are two alternative definitions of PFS in TADPOLE (i) assessed by independent review and (ii) assessed by investigator review. The base case analyses used PFS as per investigator review, and the company argued that was more reflective of decision making in clinical practice. However, the statistical analysis plan for hierarchical testing in TADPOLE noted that PFS would be assessed by independent review, and typically this would be considered more robust than investigator assessed. Scenario analysis using independent review substantially reduced the ICER in the low-grade group (Scenario 1a, Table 6.3a) highlighting uncertainty in how PFS was assessed, although this analysis suggested that the company's approach could be considered conservative in regards to the economics. The impact on high-grade patients from the assessment approach was much smaller (Scenario 3b, Table 6.3b and Scenario 1c, Table 6.3c).

7. Conclusion

The Committee considered the benefits of dabrafenib in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that as dabrafenib is an orphan medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence and the output from the PACE process, the Committee accepted dabrafenib for use in NHSScotland.

8. Guidelines and Protocols

The Children's Cancer and Leukaemia Group in the UK published "guidelines for the diagnosis and management of paediatric and adolescent low-grade glioma" in 2020.[3]

The International Society of Paediatric Oncology Europe Brain tumour group (SIOP-E-BTG) and the Society of Paediatric Oncology and Haematology (GPOH) published "guidelines for the diagnosis and treatment of children and adolescents with low-grade glioma" in 2019.[13]

9. Additional Information

9.1. Product availability date

04 June 2024

Table 9.1 List price of medicine under review

Medicine	Dose regimen	Cost per year (£)
Dabrafenib dispersible tablets **Trametinib oral solution**	**For 10 kg patient:** **30 mg orally twice daily** **0.35 mg orally daily** **For patient ≥51 kg (max. dose)** **150 mg orally twice daily** **2 mg orally once daily**	For 10 kg patient 14,560 +10,192 For patient ≥51 kg (max. dose) 72,800 +58,240

Costs from company submission and NICE website. Costs calculated for 10 kg child and ≥51 kg child. Costs do not take any patient access schemes into consideration.

10. Company Estimate of Eligible Population and Estimated Budget Impact

For low-grade glioma, the submitting company estimated that there would be 1 patient treated with dabrafenib plus trametinib in years 1 and 5. For high-grade glioma the company estimated that fewer than 1 patient would be treated with dabrafenib plus trametinib in years 1 and 5.

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS. This template does not incorporate any PAS discounts associated with comparator medicines or PAS associated with medicines used in a combination regimen.

*Other data were also assessed but remain confidential.**

References

1. Novartis Pharmaceuticals UK Ltd. Dabrafenib dispersible tablets (Finlee®) summary of product characteristics. www.products.mhra.gov.uk Last updated 20 March 2024.
2. European Medicines Agency (EMA). European Public Assessment Report. Finlee. 14/09/2023, EMEA/H/C/005885/0000. www.ema.europa.eu
3. Picton S, Kilday J, Hargrave D, Bailey S, O'Hare P, Ajithkumar T, *et al.* Guidelines for the diagnosis and management of paediatric and adolescent Low-Grade Glioma. Children's Cancer and Leukaemia Group. 2020.
4. Merck Sharp & Dohme (UK) Ltd. Temozolomide capsules (Temodal®) summary of product characteristics. www.medicines.ork.uk/emc Last updated 3 August 2023.
5. Bouffet E, Hansford JR, Garre ML, Hara J, Plant-Fox A, Aerts I, *et al.* Dabrafenib plus Trametinib in Pediatric Glioma with BRAF V600 Mutations. New England Journal of Medicine. 2023;389(12):1108-20. https://dx.doi.org/10.1056/NEJMoa2303815
6. Hargrave DR, Hara J, Kordes UR, Upadhyaya SA, Sahm F, Bouffet E, *et al.* Phase II Trial of Dabrafenib Plus Trametinib in Relapsed/Refractory BRAF V600 Mutant Pediatric High-Grade Glioma. Journal of Clinical Oncology. 2023;41(33):5174-83. https://dx.doi.org/10.1200/JCO.23.00558
7. ClinicalTrials.gov Identifier NCT02684058. Study of efficacy and safety of dabrafenib in combination with trametinib in pediatric patients with BRAF V600 mutation positive LGG or relapsed or refractory HGG tumors www.clinicaltrials.gov. Last updated 13 December 2023.
8. Novartis data on file. Phase II open-label global study to evaluate the effect of dabrafenib in combination with trametinib in children and adolescent patients with BRAF V600 mutation positive Low Grade Glioma (LGG) or relapsed or refractory High Grade Glioma (HGG). Final clinical study report, 13 October 2023.
9. Lashford LS, Thiesse P, Jouvet A, Jaspan T, Couanet D, Griffiths PD, *et al.* Temozolomide in malignant gliomas of childhood: a United Kingdom Children's Cancer Study Group and French Society for Pediatric Oncology Intergroup Study. J Clin Oncol. 2002;20(24):4684-91. 10.1200/JCO.2002.08.141
10. Verschuur AC, Grill J, Lelouch-Tubiana A, Couanet D, Kalifa C, Vassal G. Temozolomide in paediatric high-grade glioma: a key for combination therapy? Br J Cancer. 2004;91(3):425-9. 10.1038/sj.bjc.6601997
11. Kandels D, Pietsch T, Bison B, Warmuth-Metz M, Thomale UW, Kortmann RD, *et al.* Loss of efficacy of subsequent nonsurgical therapy after primary treatment failure in pediatric low-grade glioma patients-Report from the German SIOP-LGG 2004 cohort. Int J Cancer. 2020;147(12):3471-89. 10.1002/ijc.33170
12. Jakacki RI, Cohen KJ, Buxton A, Krailo MD, Burger PC, Rosenblum MK, *et al.* Phase 2 study of concurrent radiotherapy and temozolomide followed by temozolomide and lomustine in the treatment of children with high-grade glioma: a report of the Children's Oncology Group ACNS0423 study. Neuro Oncol. 2016;18(10):1442-50. 10.1093/neuonc/now038
13. Gnekow AK, Kandels D, Tilburg CV, Azizi AA, Opocher E, Stokland T, *et al.* SIOP-E-BTG and GPOH Guidelines for Diagnosis and Treatment of Children and Adolescents with Low Grade Glioma. Klin Padiatr. 2019;231(3):107-35. 10.1055/a-0889-8256

This assessment is based on data submitted by the applicant company up to and including 14 June 2024.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:*https://www.scottishmedicines.org.uk/about-us/policies-publications/

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHSScotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.