AWTTC
All Wales Therapeutics & Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

Evidence Status Report: dabrafenib (Taflinar®) and trametinib (Mekinist®) for the treatment of inoperable BRAF V600E variant anaplastic thyroid cancer **(OW27)**

Report prepared by the All Wales Therapeutics and Toxicology Centre
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Key findings

Licence status
Dabrafenib (Taflinar®) in combination with trametinib (Mekinist®) is not licensed in the UK to treat BRAF V600E variant anaplastic thyroid cancer (ATC); their use for this indication is off-label.

Clinical evidence
One open-label phase II study (ROAR) assessed the use of dabrafenib plus trametinib to treat BRAF V600E variant ATC in 36 patients. An updated analysis of results after 4 years showed an investigator-assessed overall response rate of 56% (95% CI 38.1% to 72.1%), which included 3 complete responses and 17 partial responses; an additional 11 patients had stable disease. The investigator-assessed median progression-free survival was 6.7 months and median overall survival was 14.5 months (95% CI 6.8 to 23.2 months).

Results of 4 retrospective studies reported outcomes including complete and partial responses to treatment, in some cases allowing for resection of the tumour. However, these studies were of small numbers of patients and had different criteria for including patients.

Safety
No new safety signals have been observed for the use of dabrafenib and trametinib to treat ATC.

Patient factors
Dabrafenib and trametinib are oral treatments continued until disease progression or toxicity occurs. Current alternative treatments include chemotherapy and radiotherapy requiring more visits to hospital. In studies, treatment increased patients' survival when compared to current treatments, which would give them more time with their families and friends, and improve their quality of life.

Cost effectiveness
There are no studies on the cost effectiveness of dabrafenib and trametinib for this indication.

Budget impact
The addition of the combination of dabrafenib and trametinib is estimated to increase the spend associated with this patient group in Wales by between

[commercial in confidence data removed] per year. This is based on an estimated uptake of between 2 and 5 patients receiving treatment for 7 months and takes into account both full displacement and no displacement of comparator palliative chemotherapy.

Impact on health and social care services
The presence of the BRAF variant in a biopsy sample from the tumour needs to be confirmed by genetic testing before treatment with dabrafenib and trametinib can be started. NHS Wales already has a standard molecular test and has developed a fast-track pathway for test results; the All Wales Genomics Service plans to publish this by mid-2024.

Innovation and/or advantages
Patients with inoperable BRAF variant ATC have limited treatment options and usually receive supportive care. Treatment with dabrafenib and trametinib offers them increased survival, with the possibility of tumour reduction sufficient for it to be surgically resected.

Background

Anaplastic thyroid cancer (ATC) is a very rare form of thyroid cancer that progresses quickly. For those patients with inoperable disease there are few treatment options. Clinicians in Wales submitted dabrafenib and trametinib as a treatment option for ATC with BRAF V600E variant for consideration through the One Wales process. They consider there is an unmet need in Wales and have identified a cohort of patients who could benefit from this treatment. Therefore, dabrafenib and trametinib was considered suitable for assessment though the One Wales Medicines process.

Dabrafenib and trametinib are inhibitors of enzymes called protein kinases. Dabrafenib inhibits BRAF kinases with activating codon 600 variants (BRAF V600E)[1,2]. Trametinib inhibits MEK-1 and MEK-2 kinases. In the UK, dabrafenib and trametinib are each licensed to treat cancers with BRAF V600 variants: as monotherapy for melanoma, and for use in combination to treat melanoma and non-small cell lung cancer (NSCLC)[1,2].

Combination treatment with dabrafenib and trametinib is routinely commissioned in NHS England and NHS Scotland to treat inoperable ATC[3,4]. In Wales, the current route of access for treating ATC with dabrafenib plus trametinib is through the individual patient funding request (IPFR) process.

Target group

The indication under consideration is inoperable anaplastic thyroid cancer (ATC) with a biopsy-proven BRAF V600E variant.

Clinicians said that the combination of dabrafenib and trametinib is likely to be used first-line, but could be used second-line if another treatment failed.

Marketing authorisation date: Not applicable, off-label

[commercial in confidence data removed]

Dosing information

The recommended total daily dose of dabrafenib is 300 mg (two 75 mg capsules twice a day), and the recommended dose of trametinib is 2 mg once daily[5,6]. Treatment is continued until disease progression or unacceptable toxicity occurs.

Clinical background

Anaplastic thyroid cancer is the rarest type of thyroid cancer[7]. It is more common in women, and mostly affects people aged over 60 years. About 1–2% of thyroid cancers are anaplastic. Patients commonly present with a fast-growing lump in the neck with symptoms of difficulty in breathing and swallowing, hoarseness and persistent cough. There is a high risk of loss of life from asphyxiation due to the lump pressing on the trachea.

Due to the aggressive nature of this disease metastatic spread is usually present, with only 10–15 % of patients having disease confined to the thyroid gland at time of presentation[8]. Therefore, treatment aims to try to slow the growth of the cancer, and to improve symptoms and people's quality of life[7]. Treatments include radiotherapy, surgery, chemotherapy and immunotherapy, as well as supportive care to manage symptoms. Surgery to resect the cancer is only suitable for a small number of people, and might be recommended if the cancer has not spread outside the thyroid gland[7].

A recent review noted that despite treatment strategies including surgery and chemotherapy, the median overall survival (OS) for ATC is still between 3 months and 6 months[8]. Patients with unresectable ATC have a median OS of around 2 months. The BRAF V600E variant is present in 25–45% of ATCs. This variant leads to activation of RAS/RAF/MEK/ERK pathway causing cell proliferation and growth and may be associated with a worse prognosis. Therefore, based on these mechanisms of action, patients may benefit from treatment with a combination of the BRAF inhibitor (dabrafenib) and the MEK inhibitor (trametinib)[8].

Incidence/prevalence

Based on All Wales pathology data, clinicians in Wales estimate between 5 and 10 people are diagnosed with ATC in Wales each year with approximately 50% having the BRAF V600E variant. Therefore, they estimate that between 2 and 5 patients per year would be eligible for treatment with dabrafenib and trametinib. This is similar to the predicted annual incidence of 1–2 ATC cases per million[9], which results in an estimated 3–6 patients diagnosed annually with ATC in Wales. Of those diagnosed with ATC, published data indicates that approximately 25-45% will have the BRAF V600E variant. The proportion of patients that are likely to be inoperable has not been reported but, using a measure of the incidence of metastatic disease (for whom a reasonable proportion would be inoperable), the All Wales Therapeutics and Toxicology Centre (AWTTC) estimates that around 1 to 3 patients would be eligible for treatment with dabrafenib plus trametinib each year.

Current treatment options and relevant guidance

There is no cure for ATC, and no standard treatment for inoperable ATC[8]. Surgery then adjuvant chemotherapy and radiotherapy are used to treat Stage IVA ATC that is confined to the thyroid. Some tumours extending outside the thyroid, or involving the nearby lymph nodes, may be treated by surgery, adjuvant chemotherapy and

radiotherapy. Unresectable Stage IVB and Stage IVC disease may be treated with targeted treatment, dependent upon the variants present. Neoadjuvant treatment to reduce the size of the tumour might allow surgical removal where there has been significant response to treatment. For disease not responding to targeted therapy or without presence of targeted variants, treatment options include palliative chemotherapy and radiotherapy. The OS for treatment modalities such as chemotherapy with or without radiotherapy is poor at around 2 months[8].

The European Society of Medical Oncology (ESMO) and American Thyroid Association (ATA) both recommend using the combination of dabrafenib and trametinib to treat locally advanced or metastatic unresectable ATC if the BRAF V600E variant is present[10,11]. If the tumour responds well to the combination treatment, it might then be possible to resect the tumour and start radiation therapy or chemotherapy[11]. In May 2018 the US FDA approved the combination of dabrafenib and trametinib to treat unresectable ATC that has the BRAF V600E variant[11].

In the UK, combination treatment with dabrafenib and trametinib is routinely commissioned in NHS England to treat inoperable ATC with a biopsy-proven BRAF variant and if patients have an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2[3]. In October 2023 NHS Scotland supported the use of dabrafenib plus trametinib to treat locally advanced or metastatic ATC with evidence of a BRAF V600E variant in adults with no satisfactory locoregional treatment option[4].

The genetic testing of biopsy samples for the BRAF variant is a prerequisite for treatment of ATC with dabrafenib plus trametinib. There is a standard molecular test for this, and a “fast-track” pathway is being put in place for the results, as patients can quickly become critically unwell due to breathing difficulties. The All Wales Genomics Service plans to publish the genomics testing pathway by mid-2024.

Summary of evidence on clinical effectiveness and safety

A literature search was conducted in December 2023 by the AWTTC relating to dabrafenib plus trametinib to treat locally advanced or metastatic ATC with BRAF variant. Searches were performed using MEDLINE, EMBASE and the Cochrane Library. The search terms used were dabrafenib, trametinib, ‘anaplastic thyroid cancer’, advanced, unresectable, and ‘BRAF V600E’. The primary outcomes intended were OS, progression-free survival (PFS), adverse events, health-related quality of life, resource use, surgical rates (where tumour is downgraded resulting in ability to operate), response rates and/or symptom control. Conference abstracts, reviews, non-systematic reviews, letters and editorials were excluded. We also excluded studies if they did not clearly identify outcomes for the group of patients with inoperable ATC treated with dabrafenib and trametinib in combination.

A total of 201 clinical papers were retrieved during the literature search, from which 14 duplicates were removed. 177 papers were excluded by inspecting titles and abstracts, and the full texts of 10 papers were reviewed for suitability in this report. Central Register of Controlled Trials and the TRIP database were also searched and did not provide any additional relevant references to those already found.

The literature search identified one single-arm phase II study, and four retrospective studies (included below). Additional studies were identified in the search but were

excluded due to multiple confounding variables[12-14]. We identified one case study and one case series on adverse effects relating to the effects of treatment with dabrafenib plus trametinib (included in the safety section below). No studies were found for dabrafenib plus trametinib compared with best supportive care or palliative treatment for ATC.

Efficacy

Phase II clinical study (ROAR)

The main evidence comes from the cohort of ATC patients included in the rare oncology agnostic research (ROAR) study[15]. This was an open-label, non-randomised, phase II basket study of dabrafenib (150 mg twice daily) plus trametinib (2 mg once daily) continued until disease progression, unacceptable toxicity, or death. Patients were included if they had BRAF V600E-variant unresectable or metastatic ATC for which no standard treatments were available. Thirty-six patients (20 women; median age 71 years) with an ECOG performance status of <2 were included in the study. A total of 30 patients had undergone prior surgery and/or radiotherapy to the primary tumour; the other patients had metastatic disease without surgery or radiotherapy. A total of 33 patients had BRAF V600E variant confirmed by central assessment[15].

The primary endpoint was investigator-assessed (using Response Evaluation Criteria in Solid Tumours [RECIST] v1.1 criteria) overall response rate (ORR) and secondary endpoints were: duration of response (DOR), PFS, OS and safety[15]. Response rates are provided after a median follow-up of 11.1 months (range 0.9 to 76.6 months)[15]. Results are given in Table 1.

Table 1: Primary and secondary endpoints from the ROAR study

	ITT ATC cohort (n=36)		BRAF V600E assessable (n=33)	
	Investigator assessed	**Independent assessment**	**Investigator assessed**	**Independent assessment**
ORR (95% CI)	56% (38.1% to 72.1%)	53% (35.5% to 69.6%)	61% (42.1% to 77.1%)	58% (39.2% to 74.5%)
CR (patients)	8% (3)	6% (2)	9% (3)	6% (2)
PR (patients)	47% (17)	47% (17)	52% (17)	52% (17)
Median DOR (95% CI)	14.4 months (7.4 to 43.6 months)	13.6 months (3.8 to not reached)	NR	NR
Median PFS (95% CI)	6.7 months (4.7 to 13.8 months)	5.5 months (3.7 to 12.9 months)	NR	NR
Overall survival	14.5 months (95% CI 6.8 to 23.2 months)	NR	NR	NR

ATC: anaplastic thyroid cancer; CI: confidence interval; CR: complete response; PR: partial response; DOR: duration of response; ITT: intention to treat; NR: not reported; ORR: overall response rate; PFS: progression-free survival

The 12-month and 24-month investigator-assessed PFS rates for the ITT ATC group

were 43.2% (95% CI 26.6% to 58.8%) and 27.0% (95% CI 13.2% to 42.9%) respectively; 12-month and 24-month OS rates were 51.7% (95% CI 33.6% to 67.1%) and 31.5% (95% CI 16.3% to 47.9%) respectively. These rates were not reported for the BRAF V600E assessable group nor after independent assessment[15].

Real world evidence
Four retrospective reviews or case series evaluated the outcomes of treating BRAF-V600E-variant ATC with dabrafenib plus trametinib (see Table 2).

Lorimer et al. (2023) retrospectively evaluated the outcomes of treating 17 patients (mean age 68 years) with locally advanced or metastatic radiologically confirmed BRAF-V600E-variant ATC with dabrafenib plus trametinib at 8 centres in the UK[16]. Patients had no locoregional radical treatment options.

Two patients had a complete response. One patient proceeded to surgery after an excellent response to dabrafenib plus trametinib, and maintained a complete response on dabrafenib plus trametinib post-surgery. One patient had a hemi-thyroidectomy and neck dissection after 12 cycles of dabrafenib plus trametinib and also maintained a complete response post-surgery on continuation of treatment[16].

Iyer et al. (2018) reported a retrospective review of targeted therapy in ATC, which included 6 patients with BRAF V600E-variant tumours treated with dabrafenib plus trametinib[17]. Best overall response was assessed using RECIST v1.1. Three patients had a partial response to treatment; two achieved stable disease (and tumour regression) and one patient had progressive disease[17].

In a case series reported by **Wang et al. (2019)**, 6 patients with initially unresectable BRAF V600E-variant ATC were treated with dabrafenib plus trametinib and all later achieved complete surgical resection of the tumour[18]. All (n=6) patients were alive at 6 months and 83% (n=5) at 1 year[18].

In a retrospective, observational study **Bueno et al. (2023)** reported the outcomes of 5 patients (median age 70 years; 60% male) with BRAF V600E-variant ATC treated with dabrafenib plus trametinib in Argentina[19]. ECOG performance status at diagnosis of ATC was ≤2.Overall mortality was 60% (3 patients) at 20 weeks of follow-up; in 2 patients death was due to non-related underlying disease. One patient received dabrafenib plus trametinib in the neoadjuvant setting allowing surgical resection. OS and PFS were not reached because of a lack of events[19].

Table 2. Outcomes of four real-world studies of dabrafenib (150 mg twice daily) plus trametinib (2 mg daily) to treat ATC

	Median follow up	Treatment cycles (range)	ORR (CR + PR)	CR	PR	DOR	PFS	OS
Lorimer et al. 2023 n=17 (9 men; mean age 68 years; UK	12 months (range 3–43)	4.5 (range 1–22)	82%	12%	70%	NR	4.7 months (95% CI 1.4 to 7.8 months)	6.9 months (95% CI 2.46 to ULNR)
Iyer et al. 2019 n=6 (USA)	11.8 months	NR	50%	0%	50%	8.3 weeks (range 1.5 to 34.5)	5.2 months (95% CI 3.7 months to ULNR)	9.3 months (95% CI 5.7 to ULNR)
Wang et al. 2019 n=6 (2 men, median age 59 years; USA)	15 months (range 6.4 to 25.2)	NR	100%	0%	100%	NR	NR	NR
Bueno et al. 2023 n=5 (3 men; median age 70 years; Argentina)	5 months (range 1.5 to 23)	NR	80%	40%	40%	20 weeks (range 16 to 92 weeks; 95% CI 15.7 to 24.3).	NR	NR

ATC: anaplastic thyroid cancer; CI: confidence interval; CR: complete response; DOR: duration of response (or clinical benefit); NR: not reported; ORR: objective response rate; PFS: progression-free survival; PR: partial response; OS: overall survival; ULNR: upper limit not reached

Safety
The Summaries of Product Characteristics for dabrafenib and trametinib list the most common adverse reactions (an incidence of ≥20%), when the medicines are given in combination, as: pyrexia, fatigue, nausea, chills, headache, diarrhoea, vomiting, arthralgia and rash[5,6].

Data from the ROAR study showed that adverse events were consistent with the established tolerability of dabrafenib plus trametinib[15]. After additional follow-up, no new safety signals were identified. A total of 27 patients experienced more than one adverse event related to dabrafenib and trametinib. The most common adverse events were pyrexia (47%), anaemia (36%), decreased appetite (33%), fatigue (33%) and nausea (33%). Twenty patients had serious adverse events, including 7 with serious treatment-related adverse events[15].

Adverse events reported in the retrospective studies included: nausea (n = 7 cases), fatigue (5), anaemia (4), fevers (4), anorexia (4), hand-foot skin reaction (3), hyponatraemia (3), weight loss (3), hypothyroidism (2) pneumonitis (1), muscle cramps (1), hypocalcaemia (1) and uveitis (1)[16,17,19].

In the Lorimer et al. study, 7 patients stopped treatment due to medicine-related toxicities[16]. In one case, dabrafenib plus trametinib treatment was permanently stopped due to recurrent uveitis. The only other reason for discontinuing treatment was disease progression[16]. Bueno et al. reported that all patients had at least one adverse event: 2 patients had Grade 3 or higher adverse events (upper gastrointestinal bleeding and subclavian vein thrombosis) for which treatment was temporarily suspended[19]. Iyer et al. reported one patient with grade 3 anaemia requiring a blood transfusion and two patients developed lower limb oedema that needed a dose reduction; one of them had chronic heart failure at baseline[17].

Batra et al. (2023) reported a case of Guillain-Barre syndrome secondary to treatment with dabrafenib plus trametinib for inoperable ATC in a 75-year-old man [20]. Dabrafenib and trametinib were stopped; intravenous immunoglobulin was started and his weakness started improving. After 1 month the patient was restarted on dabrafenib plus trametinib[20]. One case of Guillain-Barre syndrome has been reported with the use of dabrafenib plus trametinib to treat melanoma[21] and one case has been reported with the use of dabrafenib for melanoma[22].

Cabanillas et al. (2020) reported that 4 patients with ATC who were treated with dabrafenib plus trametinib had acquired a RAS variant at the time of disease progression, in addition to the BRAF V600E variant[23]. The emergence of RAS variants, also reported in patients with melanoma treated with dabrafenib plus trametinib, may act as a mechanism of resistance to BRAF inhibitors[23].

Patient factors
Patients with dysphagia may have difficulty in taking dabrafenib and trametinib, which are oral preparations. Whilst the ROAR study excluded patients who could not swallow tablets, some real world studies have reported on patients with dysphagia responding to dabrafenib plus trametinib treatment given either as a modified oral

form, by crushing (trametinib) or dissolving in a suspension (dabrafenib), or via a gastronomy tube until they are able to swallow[17,18].

Submissions giving the patient perspective were received from the British Thyroid Foundation and the Thyroid Cancer Support Group Wales, with very similar views expressed by both. The fast-growing and aggressive nature of ATC is highlighted and that, on average, most patients live only for 3 months after diagnosis. Symptoms, which include problems with breathing, swallowing and speaking, are physically challenging, painful and distressing and significantly affect quality of life. There is a significant burden on carers and family members who may have to help the patient with daily self-care. Some patients report on the additional psychological burden of knowing that there are almost no treatment options and those that are offered are unlikely to be successful.

Most patients are offered palliative treatment with radiation and/or chemotherapy but the side effects of chemotherapy are very unpleasant and many patients are not well enough to tolerate them. Both organisations highlight the positive trial results demonstrating that the combination of dabrafenib and trametinib could increase survival by reducing tumour size and, in some cases, could allow surgery to remove it, which was not possible before. Treatment could improve patients' quality of life and give them more time to spend with their family and friends.

Discussion

The main evidence is from a phase II open-label study, in a small number of patients. The ROAR study demonstrated clinical benefit of dabrafenib and trametinib treatment in the advanced/metastatic ATC population although the lack of a comparator study makes interpretation difficult, and it is therefore hard to assess the relative effectiveness of dabrafenib plus trametinib compared with current treatments. The data have wide confidence intervals due to the small data set, which increases the level of uncertainty in the results. There is also a lack of data about patients' quality of life given that this treatment is potentially life-extending.

However, it is acknowledged that ATC is a rare cancer and conducting large-scale studies would be difficult. The real-world evidence suggests efficacy in ATC patient populations but comes from retrospective studies involving small numbers of patients, with differences between the studies in the criteria for including patients, such as prior treatments or stages of disease, and also differences in what outcomes were measured. The strength of the evidence is uncertain because of these differences. Responses varied within studies and the confidence intervals around treatment effects were again wide.

Wang et al. (2019) reports on the clinical efficacy of this treatment combination in 6 patients with initially unresectable BRAF V600E-variant ATC who all later achieved complete surgical resection of the tumour[18]. Two further cases of surgical resection following dabrafenib plus trametinib are described in case series[16,19]. However, the clinical effectiveness of dabrafenib plus trametinib in the neoadjuvant setting is limited and uncertain due to differences in prior exposure to treatment modalities and stage of disease at presentation.

Patients with advanced inoperable ATC have an extremely poor prognosis with a median survival of around 2 months and current treatment options have low efficacy and significant adverse events[8]. Clinicians in Wales indicate that most patients are managed with best supportive care with only a few fit enough for palliative

chemotherapy, most commonly carboplatin and paclitaxel. Palliative radiotherapy may be offered although this is now less favoured as high doses are required to provide any response, and toxicity is high. There is little supporting evidence that standard chemotherapy regimens (including carboplatin and paclitaxel or cisplatin and doxorubicin) are effective, with one study demonstrating a 16% overall response rate and a median PFS of 3.1 months with carboplatin plus paclitaxel treatment[24].

The safety profile of both medicines is known and no new safety signals were reported in the studies. We report on one case of Guillain-Barre syndrome developing during treatment with dabrafenib plus trametinib for ATC[20]. This adverse effect is not mentioned in the Summary of Product Characteristics for these medicines but there are case reports of this occurring in the literature when this combination has been used to treat melanoma.

The rate of all treatment-related adverse events is comparable between chemotherapy (18 of 24 patients; 75%) and treatment with dabrafenib plus trametinib (27 of 36 patients; 75%), although treatment-related serious (grade 3/4) adverse events were less common for dabrafenib plus trametinib (7/36; 19%) than for carboplatin plus paclitaxel chemotherapy (11/24; 46%)[15,24]. The side effect profiles are also different.

Dabrafenib plus trametinib is an oral treatment taken at home and so may also offer additional benefits from a patient perspective over weekly intravenous chemotherapy given in a clinical setting.

Cost-effectiveness evidence

No cost-effectiveness analyses were identified for the use of dabrafenib plus trametinib to treat BRAF V200E-variant ATC. However, comparison with other treatment strategies and consideration of quality of life (QoL) factors on the benefits that dabrafenib plus trametinib may offer this patient cohort, may allow some value judgements to be made. Please also refer to the clinical evidence section and discussion above.

A literature search has identified several publications looking at QoL in people with thyroid cancer[25-27]. These mainly focus on patients with the more common type: differentiated thyroid cancer (DTC). There is a paucity of published QoL data relating to ATC. Due to the favourable prognosis of DTC and that surgery is curative in the majority of cases, the main factors identified as reducing QoL in these patients include post-operative effects (such as scarring and loss of neck sensation), the effects of thyroid hormone withdrawal, thyroid stimulating hormone suppression or radioactive iodine treatment, and fear of reoccurrence. But it is likely that these are not the predominant factors for patients with inoperable ATC. For ATC, growth of the primary tumour in the neck necessitates the management of local complications, such as airway obstruction, haemorrhaging, dysphagia, or severe pain, until the end of life[28]. AWTTC's two submissions from patient organisations refer to pain, fatigue and the detrimental impact of the tumour on breathing, swallowing and speech, as having a significant impact on day-to-day quality of life. One retrospective study of 14 operable patients with ATC investigated the role of surgical resection in improving their QoL and states that factors detrimentally affecting QoL are caused by the rapidly enlarging primary neck tumour. Tracheostomy is usually necessary to prevent

asphyxia but which hinders speech and the tumour often causes serious conditions such as complete oesophageal obstruction, large amounts of exudate, or bleeding from the tumour eroding from the tracheostomy site[28,29]. These conditions decrease the QoL of patients and may even impair their dignity for the rest of their lives. The study demonstrated that surgical resection can improve the QoL in patients with ATC by delaying or reducing the need for tracheostomy, and that tumour resection should be favoured as much as possible. In this small study, the mean survival period for patients with ATC who underwent surgical resection was significantly longer than for those who did not, 15.4 ± 18.2 months vs. 4.3 ± 4.6 months, respectively ($p < 0.0024$)[29].

Some real-world studies have reported on patients with previously unresectable tumours who, after treatment with neoadjuvant dabrafenib plus trametinib, have responded sufficiently to allow full or partial resection. The authors report that the QoL of the patients was preserved until the end of life by resection of the primary tumour. These patients were able to maintain their ability to breathe, eat, and communicate[18]. Therefore, the reduction in tumour size in response to treatment with dabrafenib plus trametinib, which may enable resection in some cases, may offer health gains to this patient cohort although it is not possible to estimate if these gains could be considered cost effective.

Budget impact

The proposed total daily dosing regimen is 300 mg dabrafenib (taken as two 75 mg capsules twice daily) and 2 mg trametinib taken orally once daily. The list price for 75 mg dabrafenib (pack size 28 tablets) is £1,400 and there is a commercial arrangement in place which reduces the pack cost to [commercial in confidence data removed] (excluding VAT). The list price for 2 mg trametinib (pack size 30 tablets) is £4,800**;** again, there is a commercial arrangement reducing the pack cost to [commercial in confidence data removed] (excluding VAT).

Treatment with dabrafenib and trametinib would continue until disease progression or unacceptable toxicity. The budget impact was calculated using a treatment duration of seven months; this was the median as reported in the ROAR study[15].

The medicine acquisition cost for 7 months treatment per patient is [commercial in confidence data removed] which includes VAT. According to clinical experts in Wales, between 2 and 5 patients per year would to eligible for treatment, with an estimated associated cost of between [commercial in confidence data removed] in Year 1. This does not include costs of monitoring or adverse events.

Currently, patients with unresectable BRAF-variant ATC are offered best supportive care which may include palliative chemotherapy, or, much less frequently, radiotherapy. The chemotherapy regimen can vary but clinicians in Wales indicate that three-weekly carboplatin (AUC 5 – 600 mg dose) and weekly paclitaxel (80 mg/m^2 body surface area) for a maximum of 6 cycles is usual; they also indicate that radiotherapy treatment for this cohort would be typically between 20 Gy in five fractions to 60 Gy in 30 fractions. Table 3 shows the costs associated with these treatment options.

Table 3. Total costs of palliative treatment options per patient

Treatment	Cost	
Chemotherapy	**1 cycle**	**6 cycles**
Carboplatin 3 weekly (AUC5) at 600 mg plus paclitaxel weekly at 80 mg/m^2*	[commercial in confidence data removed]	[commercial in confidence data removed]
Radiotherapy		
20 Gy in 5 fractions†	£2,060	
60 Gy in 30 fractions†	£6,546	
* Calculated using a body surface area of 1.8m^2. List price used for carboplatin, confidential NHS Wales contract price used for paclitaxel. Costs include VAT and administration costs; 2020-2021 National Schedule of Reference Costs: assumes 'Deliver Simple Parenteral Chemotherapy at first attendance' (HRG code SB12Z) for the first cycle, followed by 'Deliver Subsequent Elements of a Chemotherapy Cycle' for each subsequent cycle (HRG code SB15Z) † Calculated from 2020-21 National Schedule of Reference Costs: Preparation for Simple Radiotherapy with Imaging and Dosimetry (SC45Z); Deliver a Fraction of Treatment on a Megavoltage Machine (HGR code SC22Z)		

According to clinical expert opinion, treatment with dabrafenib plus trametinib would displace either palliative chemotherapy or, much less commonly, radiotherapy. As chemotherapy is the preferred option in Wales, a net budget impact has been calculated assuming that all 2 to 5 eligible patients would have received 6 cycles of palliative chemotherapy as specified in Table 3. This results in a net annual budget impact of between [commercial in confidence data removed] to [commercial in confidence data removed].

Therefore, the introduction of dabrafenib plus trametinib will increase the spend for this patient group. Based on an estimated uptake of between 2–5 patients receiving treatment for 7 months, the budget impact is expected to be between [commercial in confidence data removed] to [commercial in confidence data removed] per year; this range considers both full displacement and no displacement of comparator palliative chemotherapy.

Budget impact issues

- The budget impact assumed a treatment duration with dabrafenib plus trametinib for seven months which was based on the median treatment duration reported in the ROAR study. However, a wide range of treatment duration was reported of between 1 and 63 months. Additionally, some real-world studies report surgical resection in patients previously deemed inoperable after treatment with adjuvant dabrafenib plus trametinib[16,18,19]. Treatment with dabrafenib plus trametinib is usually continued post-surgery until disease-progression or unacceptable toxicity. Whilst the strength of this real-world evidence is uncertain due to significant confounders, there remains a possibility that some eligible patients may respond sufficiently to treatment for their disease to stabilise for a considerable time or to become operable; thus, the cost of treatment for these patients will increase the budget impact accordingly.

- Budget impact estimates are sensitive to small changes in patient numbers. The budget impact uses clinical expert estimates of between 2-5 eligible patients per year. However, based on published incidence data, AWTTC estimate between 1–3 eligible patients; therefore, budget impact may be lower than that presented.

- A net budget impact range has been calculated accounting for displacement of the most common comparator treatment given in Wales which is palliative chemotherapy. However, clinicians in Wales state that, in practice, many patients with unresectable ATC are not fit enough or opt not to have palliative treatment and, of those that do, most can only tolerate 1–2 cycles of chemotherapy. Therefore, the estimated annual medicine acquisition costs of dabrafenib plus trametinib are likely to be a better reflection of budget impact.

- Additional screening and monitoring and adverse event costs are excluded from the budget impact.

- Genetic testing for BRAF variant status is a prerequisite for treatment with dabrafenib plus trametinib. The molecular testing is standard in NHS Wales and so not considered an extra cost; therefore, this has been excluded from the budget impact calculations.

Care has been taken to ensure the information is accurate and complete at the time of publication. However, the All Wales Therapeutics and Toxicology Centre (AWTTC) do not make any guarantees to that effect. The information in this document is subject to review and may be updated or withdrawn at any time. AWTTC accept no liability in association with the use of its content. An Equality and Health Impact Assessment (EHIA) has been completed in relation to the One Wales policy and this found there to be a positive impact. Key actions have been identified and these can be found in the One Wales Policy EHIA document.

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