National Cancer Medicines Advisory Group (NCMAG) Programme

NCMAG107 Dabrafenib plus trametinib | Advice Document v1.0 | October 2023

Dabrafenib and trametinib for treatment of adult patients with locally advanced or metastatic anaplastic thyroid cancer with evidence of a BRAF V600E mutation and with no satisfactory locoregional treatment options [A]

NCMAG Decision | This off-label use of dabrafenib plus trametinib is supported

This advice applies only in the context of the confidential pricing agreements in NHSScotland, upon which the decision was based, or confidential pricing agreements or list prices that are equivalent or lower.

[A] NCMAG considers proposals submitted by clinicians for use of cancer medicines outwith SMC remit. For more detail on NCMAG remit please see our website.

Decision rationale

After consideration of all the available evidence regarding the clinical benefits and harms, the Council were satisfied with the clinical effectiveness case for dabrafenib and trametinib in the proposed population. After consideration of all relevant information under the Decision-making framework for value judgements the Council made a decision to support this use.

Governance Arrangements

Each NHS board must ensure all internal governance arrangements are completed before medicines are prescribed. The benefits and risks of the use of a medicine should be clearly stated and discussed with the patient to allow informed consent.

Proposal Details	
Proposers	Scottish Clinical Thyroid Cancer Network
Medicine Name(s)	Dabrafenib and trametinib
Cancer type	Anaplastic thyroid cancer

Proposed off-label use[B]	The treatment of adult patients with locally advanced or metastatic anaplastic thyroid cancer with evidence of a BRAF V600E mutation and with no satisfactory locoregional treatment options.
Medicine Details	Form: Dabrafenib hard capsules and trametinib film-coated tablets Dose: Dabrafenib 150mg twice daily orally and trametinib 2mg once daily orally Treatment should continue until disease progression or unacceptable toxicity
Advice eligibility criteria	• Inclusion Criteria: Evidence of a BRAF V600E mutation, Performance status 0 – 2, adequate renal and hepatic function, radiologically evident disease. • Exclusion criteria: Active bleeding and/or radiotherapy within 7 days.

[B] Dabrafenib plus trametinib have marketing authorisation for the following indications[1]:

- for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation.
- for the adjuvant treatment of adult patients with Stage III melanoma with a BRAF V600 mutation, following complete resection.
- for the treatment of adult patients with advanced non-small cell lung cancer with a BRAF V600 mutation

1. Current Management Context

Anaplastic thyroid cancer incidence, symptoms and prognosis

Anaplastic thyroid cancer (ATC) is a rare form of thyroid cancer accounting for approximately one per cent of thyroid cancers and an annual incidence of 1-2 cases per million[2]. It is a highly aggressive cancer with patients usually presenting with locally advanced or metastatic disease. Most patients diagnosed with ATC are 65 years of age or older[2]. Symptoms of ATC include pain, difficulty breathing and swallowing, hoarse voice and a persistent cough. Most patients die from airway compromise from compression of the trachea. Less than five patients are diagnosed every year with ATC in Scotland. To ensure that treatment goals and patient counselling reflect ATC's dismal prognosis, it is staged as a minimum of stage 4 disease, regardless of the size and location of the tumour [3].

ATC has a median overall survival (OS) of approximately 4-5 months with only 20% surviving one year from diagnosis[4, 5].

Treatment options for the different stages of ATC

ATC confined to the thyroid (stage 4A disease) is treated with surgery followed by adjuvant chemotherapy and radiotherapy, to improve disease control. Some (resectable) tumours that extend outside the thyroid or involve the regional lymph nodes (stage 4B disease) are treated with surgery then adjuvant chemotherapy and radiotherapy. For unresectable 4B disease, neoadjuvant treatment may be used to reduce the tumour size, and to improve suitability for surgery. For ATC with distant metastases (4C disease), surgery is not recommended, and treatment options include palliative chemotherapy and radiotherapy.

Standard chemotherapy regimens include carboplatin and paclitaxel or cisplatin and doxorubicin, however objective response rates (ORR) to chemotherapy are low and have been reported at 16%[6].

BRAF V600E genetic mutation and targeted treatment

Approximately 40-50% of ATCs harbour the driver BRAF V600E genetic mutation. This mutation leads to activation of RAS/RAF/MEK/ERK pathway causing cell proliferation and growth and may be associated with a worse prognosis[7]. Dabrafenib and trametinib cause cancer cell death by inhibiting BRAF and MEK cancer cell signalling, respectively. Side effects of dabrafenib and trametinib include pyrexia, rash, arthralgia, headache, fatigue, diarrhoea, cardiac dysfunction and increased risk of bleeding[1].

International context for the proposed off-label use

The USA Food and Drug Authority[8], the Australian Therapeutics Good Authority[9], Singapore Agency for Care Effectiveness[10] and the New Zealand Medicines and Medical Devices Safety Authority[11] have licensed dabrafenib and trametinib as a treatment option for BRAF V600E mutant ATC. NHS England Clinical Commissioning has approved dabrafenib and trametinib for routine use in BRAF V600E mutant ATC[12]. The American Thyroid Association, National Comprehensive Cancer

Network and European Society for Medical Oncology support the use of dabrafenib and trametinib in BRAF V600E mutant ATC[4, 5, 13].

2. Evidence Review Approach

A literature search to identify clinical and economic evidence was conducted on key electronic databases including MEDLINE, Embase, the Cochrane Database of Systematic Reviews, major international health technology agencies, as well as a focused internet search. The search strategy comprised both Medical Subject Headings and keywords. The main search concepts were dabrafenib, trametinib, 'anaplastic thyroid cancer', advanced, unresectable, and 'BRAF V600E'. No filters were applied to limit the retrieval by study type. Titles and abstracts were screened by one reviewer with decisions crossed-checked (~10% of titles) with another reviewer. The included publications were critically appraised.

3. Clinical Evidence Review Summary

Clinical Efficacy Evidence

The key evidence to support the use of dabrafenib and trametinib in the proposed populations includes one single arm phase II study and three retrospective cohorts[14-17]. Additional studies were identified in the search but were excluded due to multiple confounding variables[18-20]. Across the evidence 65 patients were included; four patients were classified as either stage 4A or 4B, 59 patients had stage 4C disease, and 2 were treated with neoadjuvant intent (all stages). Across the evidence, the majority of the results were presented in mixed populations making interpretation of the results for each sub-population difficult (Table 1). The median age of patients ranged from 67 to 71 years and around 45% of patients were female.

Table 1 | Evidence matrix

	Stage 4A or 4B (n = 4) (residual disease following surgery)	Stage 4C (n = 59) (metastatic and/or relapsed)	Stage 4A, 4B or 4C (n = 2) (neoadjuvant treatment before potential surgery)
Phase III study	X	X	X
Phase II study	X	✓ 1 study 36 patients	X
Real world data[a]	✓ 1 study 4 patients	✓ 3 studies 23 patients	✓ 2 studies 2 patients
Indirect evidence	X	X	X

[a]real word data included patients at all stages

Phase II clinical trial

The key evidence comes from the final analysis of the ROAR basket study[16]. ROAR is an open label, non-randomised, phase II basket study evaluating the effectiveness of dabrafenib (150mg twice

daily orally) plus trametinib (2mg once daily orally) in patients with rare BRAF V600E mutant cancers including ATC (n=36). Patients were included if they had unresectable or metastatic ATC with BRAF V600E mutation and with no alternative treatment options. Patients were also required to have an Eastern Cooperative Oncology Group performance score of ≤2.

Patients were monitored throughout with local disease assessments every 8-weeks and within 28-days of discontinuation. The primary outcome was objective response rate defined as the percentage of participants with a confirmed overall response by investigator assessment as per the RECIST version 1.1 criteria and independent radiological review. Secondary endpoints include duration of response (DOR), progression free survival (PFS), overall survival (OS), and safety.

At the final data cut, 27 events of progression or death had been reported. The primary outcome of overall response rate was 56% when investigator-assessed and 53% following independent assessment (see Table 2 for details). After a median follow up of 11 months (range 0.9 to 77 months), investigator and independently assessed PFS was 6.7 months and 5.5 months respectively (Table 2). Median OS was 14.5 months (95% CI 6.8 to 23) with 12-month and 24-month survival rates of 52% (95% CI 34 to 67) and 31% (95% CI 16 to 48) respectively.

Table 2 | Response rates from the non-comparative phase II ROAR study[16]

	ITT ATC cohort (n=36)		BRAF V600E assessable[A] (n=33)	
	Investigator assessed	**Independent assessment**	**Investigator assessed**	**Independent assessment**
ORR (95% CI)	56% (38 to 72)	53% (36 to 70)	61% (42 to 77)	58% (39 to74)
CR n (%)	3 (8)	2 (6)	3 (9)	2 (6)
DOR Months (95% CI)	14.4 (7.4 to 44)	13.6 (3.8 to NE)	NR	NR
PFS Months (95% CI)	6.7 (4.7 to 14)	5.5 (3.7 to 13)	NR	NR

Key: ORR = objective response rate, CR = complete response, PR = partial response, DOR = duration of response, CI = confidence interval, NE = not estimated, NR = Not reported. [A]Three patients did not have centrally confirmed BRAF mutation

Real World Evidence

Real world, non-comparative, retrospective data makes up the remainder of the evidence supporting the use of dabrafenib and trametinib across patients with stage 4A, 4B and 4C disease. There is currently no head-to-head or indirect comparison evidence to support this proposal. Lorimer and colleagues evaluated the effectiveness of dabrafenib and trametinib in patients with radiologically confirmed BRAF V600E mutated, advanced ATC[15]. The cohort included 17 patients (four treated in Scotland) from eight UK centres, 65% of patients presented with disease stage 4C. Outcomes measured included OS, PFS, response and safety. Iyer and colleagues collected real world data from a single institution in the US to estimate the efficacy and safety of targeted therapies in ATC patients who are not eligible for participation within a clinical trial[14]. Six patients with confirmed BRAF V600E mutation status received dabrafenib and trametinib. Outcomes measured included best overall response, defined as the proportion of patients with either a

complete or a partial response. Finally, Bueno and colleagues present the results of a case series from five patients in Argentina with locally advanced or metastatic ATC with confirmed BRAF V600E mutation status[17]. Outcomes measured include the best overall response, defined as either complete or partial response or stable disease. Results from all three cohorts are presented in Tables 3 and 4.

Table 3 | Response rates from real world cohorts[14, 15, 17]

	Participants	Treatment cycles median (range)	ORR	CR	PR	DOR
Lorimer et al n = 17	Median age 68 Male 53% UK multicentre PS 0-2 NR	4.5 (1-22)	88%	12%	70%	NR
Iyer et al n = 6	Median age 67 Male 63% US single centre PS 0-2 73%	NR	50%	0	50%	8.3 weeks (range 1.5 to 34.5)
Bueno et al n = 5	Median age 70 Male 60% Argentinian single centre PS 0-2 100%	NR	80%	40%	40%	20 weeks (range 16 to 92)

Key: ORR = objective response rate, CR = complete response, PR = partial response, DOR = duration of response, CI = confidence interval, NR = not reported.

Table 4 | Survival outcomes from real world cohorts[14, 15, 17]

	Median follow-up	PFS	OS
Lorimer et al N=17	12 months (range 3-34)	4.7 months (95% CI 1.4 to 7.8)	6.9 (95% CI 2.5 to NE)
Iyer et al N=6	11.8 months	5.2 Months (95% CI 3.7 to NE)	9.3 Months (95% CI 5.7 to NE)
Bueno et al N=5	NR	NR	NR

Key: PFS = progression free survival, OS = overall survival, CI = confidence interval, NR = not reported, NE= not estimated

Patient reported outcomes

No patient reported outcome data were reported across the included studies.

Safety evidence

All patients in the ROAR study experienced an adverse event (AE), 27 (75%) were thought to be treatment related[16]. Treatment discontinuation or dose reduction was documented in 6 (17%) and 17 (47%) of patients respectively. Serious AEs were experienced in 20 (56%) of patients, 7 (19%) were thought to be treatment related. Grade three or four AEs were reported for 21 (58%) patients: the most common were anaemia (7, 19%), pneumonia (7, 19%), hyponatremia (6, 17%),

fatigue (3, 8%), and hypoalbuminemia (2, 6%), hypotension (2, 6%) and increased blood alkaline phosphatase (2, 6%). Three patients were reported to have had fatal adverse events, none were thought to be treatment related.

In the real-world evidence similar levels of grade 3 or greater AE were reported across the studies. Lorimer et al only reported one grade 3 or higher AE, which was neutropenia. In Iyer et al there were five grade 3 or greater AEs reported including fatigue, hyponatraemia, anaemia and hypercalcaemia. For all grades of AEs 4 (67%) patients experienced nausea and fatigue, while 3 (50%) patients experienced hyponatremia, anaemia and weight loss[14]. Two patients in the Iyer et al study had to reduce dose due to lower extremity oedema[14]. In Bueno et al all patients experienced at least one AE, with two grade ≥3 AE reported (upper gastrointestinal bleeding and subclavian vein thrombosis)[17].

Quality assessment of clinical evidence

The evidence to support this proposal came from a phase II single arm trial, two retrospective cohorts and one case series; this type of evidence is inherently poor in quality, this is mainly due to the lack of comparative data. The evidence included multiple disease stage subgroups, although patient numbers were small, the authors combined them in single analyses which makes interpretation of the findings difficult. The single arm trial tried to overcome reporting errors by including independent assessment of outcomes reducing the bias associated with investigator assessment.

Clinical effectiveness considerations

ROAR demonstrated efficacy in a metastatic and/or relapsed population, however the lack of comparative data make interpretation very uncertain

ORR in the intention-to-treat population was 56%, and median independently-assessed PFS was 5.5 months (95% CI 3.7 to 12.9 months). Median overall survival was 14.5 months (95% CI, 6.8-23.2 months), and the 12- and 24-month OS rates were 52% and 32%, respectively. ORR were slightly higher in patients with centrally assessed BRAF V600E mutant disease. ATC's rarity and highly aggressive nature hampers recruitment to trials. The small sample size in ROAR is likely to have contributed to the wide confidence intervals for PFS and OS and reduces the certainty in the estimate of the treatment effect. Additionally, ROAR is a phase II basket trial without an active control group[16]. The methodological limitations of this evidence means there is high uncertainty regarding the relative effectiveness of dabrafenib and trametinib in ATC with BRAF V600E mutation.

The dabrafenib plus trametinib safety profile in the proposed population is uncertain but there were no unexpected toxicities

As the patient population was small, there is uncertainty about the rates of both common and uncommon serious adverse events for dabrafenib and trametinib. Nevertheless, there were no unexpected side effects when compared to the extensively used on-label indications.

Current treatment options for ATC have low efficacy and significant adverse events

Standard chemotherapy options include carboplatin and paclitaxel, as well as cisplatin and doxorubicin. However, supporting evidence for these regimens is limited, with some based on trial data from the 1980s with little improvement in systemic anticancer therapy since then. A recently conducted phase 3 trial of 80 patients with ATC, for a medicine that has not been licensed, was stopped early due to difficulties in recruiting patients. The patient population was similar to ROAR with over 90% of patients having metastatic disease and all patients had prior therapy for ATC. The study included a paclitaxel plus carboplatin control arm which was reported to show an ORR of 16%, median PFS of 3.1 months, and median OS of 4.0 months. Grade 3 or higher adverse events were reported for 46% of patients in the carboplatin and paclitaxel arm, these included anaemia (17%), neutropenia (12%), and fatigue (12%)[6].

The ROAR study's ORR of 56%, median PFS of 5.5 months, median overall survival of 14 months and the 12- and 24-month overall survival rates of 52% and 32%, respectively, in conjunction with supporting real-world evidence (ORR ranging 50% to 80% and median OS ranging 6.9 to 9.4 months), suggests that targeted treatment with dabrafenib and trametinib may provide greater benefit than current chemotherapy options in this patient group with a BRAF V600E driver mutation[7-10]. Naïve unanchored comparisons of data do not account for clinical and methodological differences between studies and need to be interpreted with caution as the comparisons are very uncertain. The rates of Grade 3 adverse events were similar to those reported with paclitaxel and carboplatin. However, dabrafenib and trametinib had a different side effect profile, showing less neutropenia but more pneumonia. Additionally, duration of exposure to dabrafenib and trametinib was longer than with chemotherapy.

ROAR may have included patients with less aggressive disease and results may not be generalisable to the proposed population

The ROAR study provides the principal evidence for dabrafenib and trametinib in relapsed and metastatic disease[16]. All patients had received prior treatment with either surgery, radiotherapy, chemotherapy or a combination of the three. The median age was 71 years, and 91% of patients were performance status 1 or 2; this is likely to be reflective of patients treated in clinical practice. ROAR only included patients with a performance status of 2 or less, however, the proposal requests treatment for select patients with a performance status of 3. It is uncertain whether the findings of the ROAR study can be applied to patients with a performance status of 3.

The median duration from diagnosis to starting dabrafenib and trametinib was 4.1 months; as median overall survival for ATC is 4 to 5 months it may be that patients with less aggressive disease were recruited[16]. Patients who could not swallow dabrafenib and trametinib were excluded from the study. Given that dysphagia is a common complication of ATC, ROAR may have included patients with less advanced disease, potentially reducing the generalisability of the study results.

RWE suggests efficacy in patient populations with a mix of ATC stage 4A, B and C

Real world evidence can be especially valuable in gathering evidence on rare cancers, as these studies can include higher-risk groups. Supporting RWE showed similar efficacy to the ROAR study, although with lower overall survival. However, there are some limitations to the RWE supporting this proposal, including:

- There is uncertainty regarding the treatment effects due to retrospective reporting and small number of patients, which may contribute to wide confidence interval estimates (see Tables 3 and 4).
- The studies had different eligibility criteria, methodology and missing data. Differences include: disease stage (locally advanced or metastatic), differences in terms of prior surgery and radiation therapy, time to starting treatment, performance status and study design (measuring and reporting). These may contribute confounding variables and make interpretation of the results uncertain.
- There is no comparative RWE, which further limits the ability to draw conclusions about the treatment.

Neoadjuvant Treatment

In stage 4B ATC (extension beyond the thyroid and/or lymph node involvement), surgery may be an option if macroscopic clearance can be obtained. One case series of neoadjuvant dabrafenib plus trametinib reported complete surgical resection in all six patients who were previously inoperable, and similar results have been described in other RWE[15, 17, 20]. However, the strength of evidence is highly uncertain due to significant confounders, including the use of immunotherapy in some patients, mixed disease stages, and bridging chemotherapy.

4. Patient Group Statements Summary

Two patient group partner (PGP) statements were received from the British Thyroid Foundation and the Butterfly Thyroid Cancer Trust, the key points are summarised below:

- Anaplastic thyroid cancer is a rare and extremely aggressive cancer placing a significant burden on a patient's quality of life.
- Symptoms include significant pain, and difficulties with breathing, swallowing and speech, leading to poor nutrition, weight loss and severe fatigue. The condition has low survival rates with most patients dying from compression of the windpipe.
- One PGP comments that this treatment may not only be able to shrink the tumour making it operable but it could give patients and their families hope and quality time together. It represents hope for a small group of people who until now have had none.

In summary | anaplastic thyroid cancer is a rare and extremely aggressive cancer, therefore it is important to have effective treatments available, and the patient groups feel that dabrafenib and

trametinib may provide an alternative option to current therapy and improve patient outcomes and quality of life, as well as it being well tolerated by patients.

5. Benefit-Risk Balance

Patients with ATC who have the BRAF V600E mutation may benefit from targeted treatment with dabrafenib and trametinib including case reports of complete or durable responses and of neoadjuvant treatment allowing curative surgery. Oral treatment may also offer advantages over intravenous chemotherapy from a patient perspective.

However, there are limitations with the quality of the evidence and the outcome effect estimates are very uncertain. The clinical evidence for dabrafenib and trametinib in the proposed population is limited to data from a non-comparative phase II trial and real-world evidence.

There is no comparative evidence on the safety of dabrafenib and trametinib in ATC. One prospective study reported a serious adverse event rate of 56% and a treatment-related adverse event rate of 19%, while real-world retrospective evidence reported serious adverse events ranging from 50% or higher.

6. Council Review |Clinical Evaluation

After consideration of all the evidence regarding the clinical benefits and harms, the Council were satisfied with the clinical effectiveness case for this off-label use of dabrafenib and trametinib. Under the decision-making framework for value judgements, Council considered the clinical case to be compelling.

7. Economic Evidence Review Summary

Economic Overview

Type of economic evaluation

No relevant published cost-utility analysis was identified in the literature search. Therefore, a de-novo cost-comparison was performed.

Population, intervention, comparator and outcomes

The population was patients with a histological diagnosis of ATC with BRAF V600E mutation. This included patients with locally advanced or metastatic ATC with BRAF V600E mutation and with no satisfactory locoregional treatment options. The intervention was oral dabrafenib and trametinib. The comparator, based on it being the preferred option across the Scottish Networks, was intravenous chemotherapy with carboplatin and paclitaxel. As a cost-comparison was performed, only costs were included.

Costs

Medicine acquisition, administration and monitoring costs were included. Dabrafenib was costed as 150mg orally twice daily with trametinib as 2mg orally once daily. A 6-month treatment

duration was applied based on the upper estimate of treatment duration from the proposal. Additional monitoring costs for dabrafenib and trametinib were included. Carboplatin was costed with a 600mg dose and paclitaxel 175mg/m^2 costed with a 315mg dose (assuming 1.8m^2 body surface area) every 21 days for 4 cycles. Intravenous administration costs for the comparator were included.

Key Results

These figures exclude VAT.

The medicine acquisition cost of dabrafenib and trametinib for 6 months per patient was £65,745 (BNF list prices). When including monitoring costs this figure was £65,995 (BNF list prices).

Compared with carboplatin and paclitaxel, dabrafenib and trametinib increased medicine acquisition costs by £63,904 (BNF list prices) per patient per 6 months. When including administration and monitoring costs this figure was £61,010 (BNF list prices).

Cost-effectiveness considerations

Generalisability of the cost comparison

The dosing schedule of dabrafenib and trametinib reflects the ROAR study, consistent with the proposed dosing in NHSScotland. Carboplatin and paclitaxel dosing reflect practice in NHSScotland.

NHSScotland PAS and national framework contract prices were used to obtain results of greater relevance.

Limitations of the cost comparison

Due to an absence of a published cost-utility analysis, the cost comparison only compares costs. Dabrafenib and trametinib is a cost-increasing intervention. Given the evidence supporting the clinical benefit of this intervention, it is likely to offer an increased quality-adjusted life year (QALY) gain compared to its comparator. However, given the absence of a QALY estimate, an incremental cost-effectiveness ratio (ICER) is not available, and the cost-effectiveness remains unknown.

As the base case results used the upper estimate of 6-months of treatment duration from the proposal, the cost-comparison results may be subject to overestimation. Lorimer et al reported a median of 4.5 28-day treatment cycles. Applying this treatment duration reduces the results of the cost comparison to £43,519 (BNF list prices) (dabrafenib and trametinib compared to carboplatin plus paclitaxel, including administration and monitoring costs).

Dosing reductions and discontinuation were not considered in the cost-comparison. Including these aspects would reduce the dose or duration of treatment, reducing the treatment cost.

Treatment related adverse events were not included in the cost comparison. However, their exclusion is unlikely to significantly increase the cost-comparison results given that most of the dabrafenib and trametinib adverse events are unlikely to result in an intervention, being managed with a temporary stopping of treatment and dose reduction. In addition, as carboplatin and

paclitaxel adverse events costs were also excluded, the cost-comparison results may be subject to a small reduction if these were included.

Summary

The cost-comparison indicated that dabrafenib and trametinib is a cost increasing intervention compared to the current standard of care. However, in the absence of an appropriately robust analysis to quantify treatment benefits in relation to costs, an ICER was not available, and the cost-effectiveness remains unknown.

A detailed budget impact analysis, exploring the financial impact of medicine cost in the anticipated population is presented in Section 10.

8. Council Review | Cost-Effectiveness Evaluation

After consideration of the available evidence, the Council accepted that the proposed intervention was cost-increasing, and that in the absence of a cost-effectiveness analysis, the cost-effectiveness remained unknown. In this situation Council was able to consider other relevant information including service impact and estimated net medicines budget impact under the decision-making framework for value judgements.

9. Service Impact

Diagnostic testing for BRAF V600E mutation is required to determine eligibility for dabrafenib and trametinib, and this is routinely available across Scotland. Dabrafenib and trametinib is an oral regimen and will likely replace intravenous chemotherapy regimens in eligible patients. Switching to an oral regimen is estimated to save 4-8 hours of chair time per patient per cycle compared to the intravenous regimen, which is administered for up to 4 cycles. It is estimated that the number of patients in NHSScotland who will receive this treatment is less than five per year. Dabrafenib and trametinib may cause cardiac dysfunction, and therefore, an echocardiogram and cardiovascular assessment at baseline and throughout treatment are required.

The service impact of the proposed use is unlikely to be significant.

10.Budget Impact

In the absence of an appropriately robust cost-effectiveness analysis, a detailed budget impact analysis was conducted.

Patient uptake

The number of patients expected to be treated with dabrafenib and trametinib was less than 5 patients per year in Scotland. The figure was based on WOSCAN practice and extrapolated to provide a national estimate (WOSCAN treats approximately 50% of Scottish population). The budget impact base case assumed 4 patients per year receiving dabrafenib and trametinib.

Considering the estimated annual incidence of ATC of 1-2 cases per million[21], with approximately 40-50% of ATCs harbouring the driver BRAF V600E genetic mutation[7], applying these to the estimated population of Scotland of 5.5 million results in estimated patients numbers of 1 to 3 per year. A budget impact scenario considers the median of this, that is 2 patients per year receiving treatment.

Per patient medicine cost and treatment duration

These prices include VAT.

Dabrafenib and trametinib: Dabrafenib was costed as 150mg orally twice daily (using 75mg tablets, pack size 28, BNF list price £1,680, August 2023) with trametinib as 2mg orally once daily (using 2mg tablets, BNF list price £5,760, August 2023). A 6-month treatment duration was applied based on the upper estimate of treatment duration from the proposal (the lower bound was 3 months).

Carboplatin plus paclitaxel: Carboplatin area under the curve (AUC)5 was costed with a 600mg dose (using 600mg/60ml, 1 vial, £279.17 BNF list prices, August 2023). Paclitaxel 175mg/m^2 was costed with a 315mg dose (assuming 1.8m^2 body surface area) (using 300mg/50ml, 1 vial, £231 BNF list prices and 30mg/5ml, 1 vial, £42 BNF list prices, August 2023). These costs were applied every 21 days for 4 cycles. This treatment duration was taken from NHS Scotland protocols.

Comparator displacement

The introduction of dabrafenib and trametinib was assumed to displace 100% of carboplatin plus paclitaxel treatment.

Results

These results include VAT. The results are presented for Year 1 only, as it was assumed that patients would not continue to subsequent years, and that year 1 would represent subsequent years. The net medicines budget impact was estimated at £306,740 (BNF list prices).

Table 5 | Budget impact analysis base case results

	List price
	Year 1+
Dabrafenib and trametinib acquisition cost	
Acquisition cost	£78,894*
Carboplatin plus paclitaxel acquisition cost	
Acquisition cost	£2209**
Displacement	
Percentage of carboplatin plus paclitaxel displaced by dabrafenib and trametinib	100%
Number of patients treated	4

Budget Impact	
Budget Impact (new medicine and supportive medicine costs only)	£315,576
Budget impact – Net medicine costs	£306,740

*Based on 6 months of treatment. Dabrafenib 150md BD PO (2x daily) + Trametinib 2mg OD PO (1x daily)

**Palliative chemotherapy consisted of Carboplatin AUC5 + Paclitaxel 175mg/m^2 q21 days for 4 cycles. Assumed a dose of 600mg for carboplatin. For paclitaxel a 1.8 m^2 BSA was assumed. Therefore, a 315 mg dose was used comprising of 1x300mg and 1x30mg vials.

VAT is included in these figures.

Scenario considerations

The following tables present budget impact (PAS and net medicines cost) scenarios, exploring the reduction in treatment time, and annual patient numbers.

Table 6 | Scenario analyses (List prices)

	Base	Scenario	Dabrafenib and trametinib acquisition cost per patient	Carboplatin and Paclitaxel acquisition cost per patient	Number of patients treated	Budget impact – Net medicine costs
-	Base	-	£78,894	£2,209	4	£306,741
1	6 months of dabrafenib and trametinib (proposal upper bound)	3 months of dabrafenib and trametinib (proposal lower bound)	£39,447	£2,209	4	£148,943
2	4 patients treated per year (WOSCAN extrapolation)	2 patients treated per year (ATC Incidence and BRAF V600E estimates)	£78,894	£2,209	2	£153,371

VAT is included in these figures.

Limitations

Treatment costs for dabrafenib and trametinib assumed a duration of treatment of 6 months. This was potentially conservative, being the upper bound from the proposal. Real world data from Lorimer et al 2022 noted the median number of treatment cycles was 4.5 with a range of 1 to 22 (approximately 4 months with a range of 1 to 20)[15]. The median of this study is therefore captured in budget impact scenario 1; however, the range extends outside these results. Furthermore, if

patients continue to receive dabrafenib and trametinib, after a complete surgical resection, this will increase the budget impact accordingly.

Patient numbers were extrapolated based on limited data and used the upper bound in the base case. Therefore, they may be subject to uncertainty, with alternate patient numbers used in budget impact scenario 2.

Summary

The change in treatment to dabrafenib and trametinib will increase the budget impact for this patient group. For 6 months of dabrafenib and trametinib, the medicine acquisition cost was expected to be £78,894 (BNF list prices), compared to £2,209 (BNF list prices) for four 21-day cycles of carboplatin and paclitaxel. Based on an estimated uptake of 4 patients, the estimated net medicines budget impact was £306,741 (BNF list prices). VAT is included in these figures.

The Council considered the net medicines budget impact using confidential NHSScotland medicine pricing agreements in decision making. NCMAG is unable to publish the budget impact using confidential pricing 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 and national framework contract pricing.

Separate information will be supplied by the boards to facilitate budget impact assessment.

11. Council review | Overall proposal evaluation

After consideration of all relevant information under the Decision-making framework for value judgements the Council made a decision to support this use.

12. Acknowledgements

NCMAG would like to acknowledge the patient group partners, the British Thyroid Foundation and The Butterfly Thyroid Cancer trust for their valuable input.

13. References

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Minor document amendments

Date	Previous version	Amendment	Updated version	Approved by