CLINICAL PRIORITIES ADVISORY GROUP
18 07 2022

Agenda Item No	6.1
National Programme	Cancer
Clinical Reference Group	Chemotherapy
URN	2110

Title
Dabrafenib and trametinib in the treatment of patients with BRAF-mutated anaplastic thyroid cancer (All ages)

Actions Requested	1. Support the adoption of the policy proposition
	2. Support its relative prioritisation

Proposition
For routine commissioning This is a new policy proposition for a small subset of patients with anaplastic thyroid cancer (ATC) for whom there is no specific treatment for ATC currently available. ATC usually presents at a late stage and in ≤5% of patients, curative surgical resection may be feasible. Most patients are offered supportive treatment and radiotherapy to help manage their symptoms. Unfortunately, chemotherapy cannot cure ATC and it only causes a shrinkage of the tumour in fewer than 15 patients in 100 (15%). It is sometimes considered in patients who are fit enough to tolerate the side effects to try to reduce the volume of the tumour in the absence of more effective treatments. The proposed treatment is a combination of two drugs, dabrafenib and trametinib. This is a targeted treatment, which means the drugs act against specific cancer cells, such as those with the BRAF mutation. This combination is currently approved in the USA for the treatment of melanoma, certain lung cancers and ATC that carry a BRAF mutation. In the UK, the combination is approved for use in BRAF-mutated melanoma and certain lung cancers with a BRAF mutation. There is some evidence which shows that using dabrafenib and trametinib to treat locally advanced ATC with the BRAF mutation can reduce the size of the tumour such that the down staged tumour may be suitable for curative surgical resection.

Clinical Panel recommendation
The Clinical Panel recommended that the policy progress as a routine commissioning policy.

The committee is asked to receive the following assurance:	
1.	The Head of Clinical Effectiveness confirms the proposal has completed the appropriate sequence of governance steps and includes an: Evidence Review; Clinical Panel Report.
2.	The Head of Cancer confirms the proposition is supported by an: Impact Assessment; Engagement Report; Equality and Health Inequalities Impact Assessment; Clinical Policy Proposition. The relevant National Programme of Care has approved these reports.
3.	The Director of Finance (Specialised Commissioning) confirms that the impact assessment has reasonably estimated a) the incremental cost and b) the budget impact of the proposal.
4.	The Clinical Programmes Director (Specialised Commissioning) confirms that the service and operational impacts have been completed.

The following documents are included (others available on request):	
1.	Clinical Policy Proposition
2.	Engagement Report
3.	Evidence Summary
4.	Clinical Panel Report
5.	Equality and Health Inequalities Impact Assessment

In the Population what is the clinical effectiveness and safety of the Intervention compared with Comparator?

Outcome	Evidence statement
Clinical effectiveness	
Critical outcomes	

Outcome 1 **Certainty of evidence:** Insert range	Overall survival Very low certainty These studies provided very low certainty non-comparative evidence that dabrafenib and trametinib increase overall survival in patients with BRAF-mutated ATC. Median overall survival results reported exceed the minimal important clinical difference of 3 months
Outcome 2 **Certainty of evidence:** Insert range	Progression free survival Very low certainty These studies provided very low certainty non-comparative evidence that dabrafenib and trametinib increase progression free survival in patients with BRAF-mutated ATC.
Outcome 3 **Certainty of evidence:** **Insert range**	Proportion of down staged patients Very low certainty This study provides very low certainty non-comparative evidence that dabrafenib and trametinib increase the proportion of down staged patients with BRAF-mutated ATC.
Important outcomes	
Outcome 4 **Certainty of evidence:** Insert range	Time to treatment failure No evidence was identified for this outcome.
Outcome 5 **Certainty of evidence:** Insert range	Symptom control Very low certainty One study provides very low certainty non-comparative evidence that dabrafenib and trametinib improve symptom control in patients with BRAF-mutated ATC.
Outcome 6 **Certainty of evidence:** Insert range	Performance status No evidence was identified for this outcome.
Outcome 7 **Certainty of evidence:** Insert range	Quality of life No evidence was identified for this outcome.
Safety	
Outcome 1 **Certainty of evidence:**	Adverse events Very low

Insert range	The four studies provided very low certainty non-comparative evidence on the safety of dabrafenib and trametinib. One study reported serious adverse effects in 3 of 16 patients and two report grade 3 or 4 adverse effects, the remainder reporting on either no treatment discontinuations or treatment discontinuations due to surgery rather than the drugs themselves.
Outcome 2 **Certainty of evidence:** Insert range	

In the Population what is the cost effectiveness of the Intervention compared with Comparator?

Outcome	**Evidence statement** No evidence was identified for cost effectiveness
Certainty of evidence:	No evidence was identified

From the evidence selected, are there any subgroups of patients that may benefit from the intervention more than the wider population of interest?

Outcome (or Subgroup or Indicator as relevant)	**Evidence statement** No evidence was identified regarding any subgroups of patients that would benefit from treatment with dabrafenib and trametinib more than the wider population of interest.
Certainty of evidence:	No evidence was identified

Patient Impact Summary
The condition has the following impacts on the patient's everyday life: • **mobility:** patients can have severe problems in walking about or are unable to walk about • **ability to provide self-care:** patients can have severe problems in washing or dressing or are unable to wash or dress • **undertaking usual activities:** patients can have severe problems in doing their usual activities or are unable to do their daily activities • **experience of pain/discomfort:** patients can have severe pain or discomfort • **experience of anxiety/depression:** patients can be severely anxious or depressed
Further details of impact upon patients:

Patients with anaplastic thyroid cancer (ATC) typically present at a late stage, when the tumour has invaded surrounding structures. Patients often suffer from debilitating symptoms resulting from local invasion; such as pain, stridor, difficulty breathing and difficulty swallowing. These symptoms can impair a patient's ability to oxygenate and sustain oral nutrition. As a result, these factors tend to have a large impact on a patient's everyday life. Impaired breathing can affect a patient's ability to mobilise, provide self-care and carry out daily activities. It can also lead to severe fatigue, which further exacerbates existing impediments with these activities. Poor nutrition can lead to severe weight loss and loss of lean body mass, which affects strength and further contributes to difficulties with mobilisation, self-care and undertaking usual activities. Patients may need to be fed artificially through the vein or directly into the stomach or small intestine through a feeding tube. All symptoms, combined with pain from the tumour, and the impact of deterioration in quality of life from inability to carry out normal activities of daily living can lead to severe feelings of anxiety or depression.

Further details of impact upon carers:
Anaplastic thyroid cancer can lead to a high burden on the carer to help with many self-care tasks, which may be difficult or impossible for the affected individual. In patients with advanced disease, families and/or carers may have to help with daily tasks such as self-care, household maintenance, getting out and about or help using mobility aids. Carers may need to spend more time cooking and preparing meals that the patient is able to tolerate/swallow. Carers may also experience additional financial burden from the increased care required by the patient and from potential loss of household income from the inability of either the patient (where applicable) or their carer to carry on working. The loss of independence and ability to perform self-care and activities of daily living may result in depression and expressions of challenging behaviour, which may add further strain on carers or family.

Considerations from review by Rare Disease Advisory Group
Not applicable

Pharmaceutical considerations
This clinical commissioning policy proposition supports the use of dabrafenib and trametinib in the treatment of patients with BRAF-mutated anaplastic thyroid cancer. These are oral therapies with a confidential PAS currently categorised as high cost drugs to be reimbursed under the cost and volume process. The recommendation of this policy is outside their respective marketing authorisations which are for melanoma and non-small cell lung cancer patients with BRAF V600 mutations. These medicines are not licensed for use in children, so separate treatment criteria (blueteq from) will be needed for children in addition to the adult treatment criteria which will need to include age specific dosing recommendations for children.

Considerations from review by National Programme of Care
The proposal received the full support of the cancer POC on the 9th June 2022