Clinical Commissioning Policy
Dabrafenib and trametinib in the treatment of patients with BRAF-mutated anaplastic thyroid cancer (2110) [221006P]

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Commissioning position

Summary

The combination of dabrafenib and trametinib is recommended to be available as a routine commissioning treatment option for anaplastic thyroid cancer (ATC) within the criteria set out in this document.

Equality statement

Promoting equality and addressing health inequalities are at the heart of NHS England's values. Throughout the development of the policies and processes cited in this document, we have:

- Given due regard to the need to eliminate discrimination, harassment and victimisation, to advance equality of opportunity, and to foster good relations between people who share a relevant protected characteristic (as cited under the Equality Act 2010) and those who do not share it; and
- Given regard to the need to reduce inequalities between patients in access to, and outcomes from healthcare services and to ensure services are provided in an integrated way where this might reduce health inequalities.

Plain language summary

About anaplastic thyroid cancer (ATC)

ATC is a rare, aggressive form of thyroid cancer. It is usually diagnosed at a late stage, when the cancer has spread to the surrounding area and to other parts of the body. At this stage, surgery to remove the tumour and cure the patient is usually not an option. ATC usually occurs in older people and following diagnosis, patients typically survive for an average of three months.

Most patients suffer from symptoms related to compression of surrounding structures by the cancer such as the windpipe (trachea) and gullet (oesophagus). Examples of symptoms include pain, difficulty breathing and swallowing, a hoarse voice and a persistent cough. Most patients die from difficulty breathing from compression of the windpipe.

Approximately 40-50% of ATCs have a mutation in a gene called BRAF, which is involved in signalling for the growth of cells, leading to uncontrolled growth of cancer cells. Targeted drugs (such as dabrafenib and trametinib) have been developed which can block the effects of BRAF mutations on cancer cells and in some cancers with BRAF mutations (including ATC) these drugs have been shown to result in significant shrinkage and control of the cancer.

About current treatment

There is currently no specific treatment for ATC. Very rarely, if detected/diagnosed in the early stages, surgery 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.

About the new treatment

The new 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 (a type of skin cancer), 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 (when the cancer has spread to the surrounding structures) with the BRAF mutation can reduce the size of the tumour. This means that surgery to remove the tumour and cure the cancer may be possible.

To identify suitable patients for treatment, a biopsy of the tumour needs to be taken for genetic testing to test for the BRAF mutation in line with the NHS England Genomics Test Directory for cancer.

What we have decided

NHS England has carefully reviewed the evidence to treat anaplastic thyroid cancer with dabrafenib and trametinib. We have concluded that there is enough evidence to make the treatment available at this time.

Committee discussion

Clinical Panel members agreed this treatment may improve patient prognosis and survival by rendering inoperable cancers amenable to resection that could be curative.

See the committee papers (link) for full details of the evidence.

The condition

Anaplastic thyroid cancer (ATC) is a rare subtype of thyroid cancer and is an aggressive malignancy that usually presents with locally advanced inoperable disease, and often with metastases. It is typically a disease of older adults with an incidence of 1 per million population (Lin et al, 2019). The disease is associated with an extremely poor prognosis, with a median survival of about 3 months following diagnosis (Lin et al, 2019). Anaplastic thyroid cancer is almost universally fatal within one year of diagnosis. Patients usually have a high symptom burden related to invasion of local structures by progressive disease, such as pain, stridor, dyspnoea, hoarseness and a persistent cough. These symptoms lead to a poor quality of life and patients typically die of difficulty breathing due to airway compromise.

About 40-50% of ATCs will have developed as a result of a mutation arising in the BRAF oncogene.

Current treatments

The majority of patients are managed within cancer centres with a specialist interest in thyroid cancer. There is no specific treatment for anaplastic thyroid cancer at present and most patients are managed with best supportive care and palliative radiotherapy. A small proportion of patients that are medically fitter may be candidates for palliative chemotherapy, typically with a platinum/taxane combination but response rates are poor (less than 15%) and duration of response is short.

Proposed treatments

The treatment is the combination of dabrafenib and trametinib, which are both administered orally. Dabrafenib is a BRAF-kinase inhibitor and is used as a targeted therapy against BRAF-mutated cancers. Trametinib is a protein kinase inhibitor against the enzymes MEK-1 and MEK-2 and is used in combination with dabrafenib in the treatment of BRAF-mutated cancers.

As these are targeted therapies, genetic testing of biopsy specimens for BRAF mutation status is a prerequisite for treatment. As of December 2021, genetic testing for the BRAF-mutation has been made available via the Genomic Laboratory Hubs (GLHs) and is listed in the NHS England National Genomic Test Directory for cancer.

Emerging evidence (Subbiah et al, 2018; Wang et al, 2019) suggests that treatment of locally advanced and metastatic ATC with dabrafenib and trametinib has shown response rates of 60% in reducing disease volume and symptoms and also having the potential to downstage tumours and render the disease operable. The latter situation provides patients with the option of a curative resection, which could potentially lead to a significant improvement in prognosis.

Dabrafenib and trametinib currently have FDA approval in the USA for the treatment of BRAF-mutated melanoma, non-small cell lung cancer and anaplastic thyroid cancer (US Food and Drug Administration, 2020). Based on the current body of evidence, the 2021 American Thyroid Association guidelines for the management of patients with anaplastic thyroid cancer make a conditional recommendation for neoadjuvant treatment with dabrafenib and trametinib in patients with BRAF-mutated unresectable disease and a strong recommendation that the combination is used in patients with BRAF-mutated ATC that decline radiation (Bible et al, 2021). In the UK, the combination of dabrafenib and trametinib currently has marketing authorisation for use in the treatment of BRAF-mutated melanoma and non-small cell lung cancer.

Epidemiology and needs assessment

Anaplastic thyroid cancer has an annual incidence of 1 per million population (Lin et al, 2019). It is estimated that there are roughly 50-60 patients newly diagnosed with ATC per year in England. Given that approximately 40-50% of these patients (Choi et al, 2016, Rao et al, 2017) will harbour a BRAF mutation, this equates to 20-30 new cases of BRAF-mutated ATC annually in England. As this is typically a disease of the elderly, patients may present with significant co-morbidities and be unfit for treatment. It is therefore estimated that approximately 20 patients would be eligible annually for treatment under this policy.

Evidence summary

An independent evidence review was conducted for the use of dabrafenib and trametinib in the treatment of anaplastic thyroid cancer. NHS England has concluded that there is sufficient evidence to support a policy for the routine commissioning of this treatment for the indication.

The evidence review which informs this commissioning position can be accessed here: [Link to be added at publication].

Implementation

Criteria

Inclusion criteria

Patients with anaplastic thyroid cancer will be eligible for treatment with dabrafenib and trametinib if they fulfil the following criteria:

- The cancer is deemed inoperable at the time of treatment commencement[1];

  AND

- BRAF-mutation has been confirmed;

  AND

- Have an Eastern Cooperative Oncology Group (ECOG) performance status of 0-2.

Exclusion criteria

- ECOG performance status of 3 or worse
- Absence of BRAF mutation
- Operable disease (patients who are downstaged following initial treatment with dabrafenib and trametinib and undergo surgical resection with curative intent will continue to be eligible for treatment)

Please consult the Summary of Product Characteristics for dabrafenib and trametinib for product-specific contraindications.

Starting criteria

- Confirmation of BRAF mutation

Stopping criteria

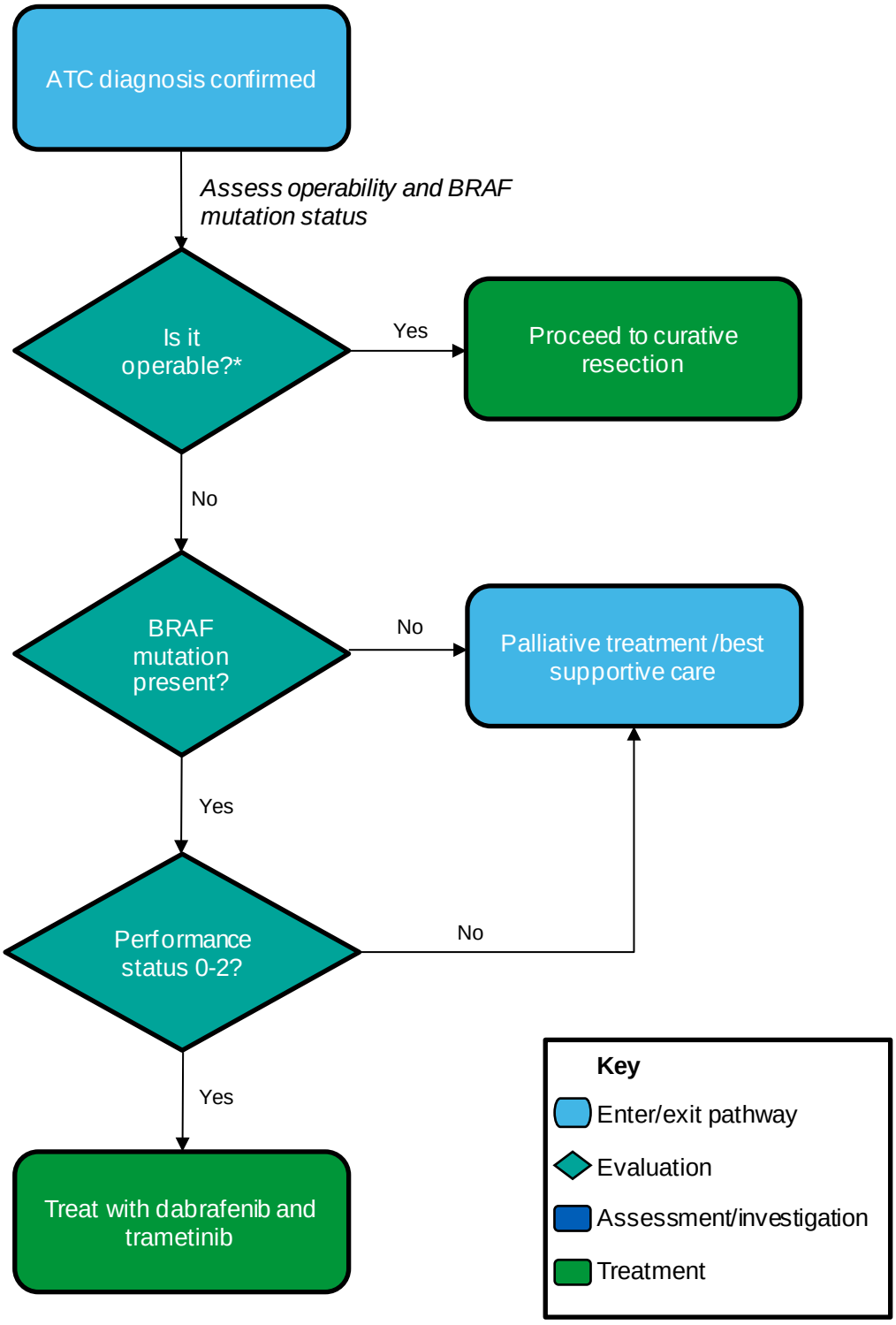
Once commenced, patients should remain on treatment until the stopping criteria are met. For the combination of dabrafenib and trametinib, the stopping criterion is as follows:

- The patient will continue treatment until disease progression or symptomatic deterioration or unacceptable toxicity or withdrawal of patient consent

Patients who have received treatment with dabrafenib and trametinib who subsequently undergo surgical intervention to improve local control are likely to need to continue treatment post-surgical resection, unless MDT discussion deems that the adequacy of resection was such that adjuvant treatment with dabrafenib and trametinib is no longer indicated.

[1] Patients with operable disease should proceed straight to curative surgery

Patient pathway



**Any patient with operable disease should be offered curative resection irrespective of BRAF mutation status*

Governance arrangements

The service specification for Cancer Chemotherapy (adult) may be found at the following link: https://www.england.nhs.uk/wp-content/uploads/2013/06/b15-cancr-chemoth.pdf

Provider organisations must ensure all patients are registered via the prior approval system and meet the clinical treatment criteria on the registration form to confirm funding before the use of dabrafenib and trametinib.

The use of dabrafenib and trametinib in the treatment of BRAF-mutated anaplastic thyroid cancer is off-label. Any provider organisation treating patients with this intervention will be required to assure itself that the internal governance arrangements have been completed before the medicine is prescribed. These arrangements may be through the Trust's Drugs and Therapeutics committee (or similar) and NHS England may ask for assurance of this process.

Mechanism for funding

The proposed mechanism for funding for dabrafenib and trametinib is categorised as a high cost drug to be reimbursed under the cost and volume process.

Audit requirements

Provider organisations must register all patients using prior approval software and ensure monitoring arrangements are in place to demonstrate compliance against the criteria as outlined.

All systemic anti-cancer treatments (SACT) must be recorded via the SACT portal as required within the NHS standard contract.

There are no specific audit requirements, however data collection using case report forms (CRF) to facilitate a multicentre service evaluation is strongly encouraged.

Policy review date

This document will be reviewed when information is received which indicates that the policy requires revision. If a review is needed due to a new evidence base then a new Preliminary Policy Proposal needs to be submitted by contacting england.CET@nhs.net.

Our policies provide access on the basis that the prices of therapies will be at or below the prices and commercial terms submitted for consideration at the time evaluated. NHS England reserves the right to review policies where the supplier of an intervention is no longer willing to supply the treatment to the NHS at or below this price and to review policies where the supplier is unable or unwilling to match price reductions in alternative therapies.

Definitions

Term	Definition
Anaplastic	A term used to describe cancer cells that divide rapidly and have little or no resemblance to normal cells.
Prognosis	The likely outcome or course of a disease; the chance of recovery or recurrence.
Metastasis (pl. metastases)	The spread of cancer cells from the place where they first formed to another part of the body.
Stridor	An abnormal, high-pitched, musical breathing sound caused by a blockage in the throat or voice box (larynx).
Dyspnoea	Difficult or laboured breathing.
Oncogene	A gene that is a mutated (changed) form of a gene involved in normal cell growth and may cause the growth of cancer cells.

Neoadjuvant	Systemic anti-cancer therapy (SACT) treatment used before the main treatment (usually surgery) as a first step to shrink a tumour size.
SACT	Systemic anti-cancer therapies is the generic term used to describe all chemotherapy and targeted agents used for the treatment of cancer. This includes Chemotherapy, Hormonal therapy, Targeted therapy Immunotherapy, and Advanced Therapy Medicinal Products (ATMPs)

References

1. Bible KC, Kebebew E, Brierley J, et al. 2021 American Thyroid Association Guidelines for Management of Patients with Anaplastic Thyroid Cancer [published correction appears in Thyroid. 2021 Oct;31(10):1606-1607]. Thyroid. 2021;31(3):337-386. doi:10.1089/thy.2020.0944
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6. Wang JR, Zafereo ME, Dadu R, et al. Complete Surgical Resection Following Neoadjuvant Dabrafenib Plus Trametinib in BRAFV600E-Mutated Anaplastic Thyroid Carcinoma. Thyroid. 2019;29(8):1036-1043. doi:10.1089/thy.2019.0133