Clinical Priorities Advisory Group Summary Report

Agenda item	3.5
Date of Meeting	11/05/2026-13/05/2026
Title of the Proposition	Pembrolizumab in combination with dabrafenib and trametinib for patients with BRAF-mutated anaplastic thyroid cancer (all ages)
Unique Reference Number	2418
Programme of Care	Cancer
Clinical Reference Group	Chemotherapy
Service/treatment status	delegated

Action requested

Support the adoption of the policy proposition

Recommended its relative prioritisation.

Summary of the proposition:

Pembrolizumab in combination with dabrafenib and trametinib is recommended to be available as a routine commissioning treatment option for patients with BRAF-mutated anaplastic thyroid cancer (all ages) within the criteria set out in this document.

Anaplastic thyroid cancer (ATC) is a rare and aggressive form of thyroid cancer. ATC usually presents at an advanced stage and it predominately affects older patients. Therefore, patients are usually unfit for curative, surgical treatment. A small number of patients may be suitable for palliative chemotherapy or radiotherapy, however the

benefit of undergoing these treatments is marginal for patients. Subsequently, ATC has a poor prognosis with median survival being 3.16 months.

For ATCs that carry a BRAF mutation, target therapies can be used. The introduction of dual therapy with dabrafenib (a BRAF inhibitor) and trametinib (a MEK inhibitor) have significantly improved prognosis. However, patients eventually develop resistance to this treatment combination leading to disease progression. The proposed intervention is pembrolizumab, which is a monoclonal antibody (a type of biological medicine). It is an immune checkpoint inhibitor and works by deactivating ATC's ability to evade its host's immune system. This slows uncontrolled cell division and tumour growth. Eligible patients are those that have a BRAF mutation, their tumour is inoperable at the time treatment is started and have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. In the independent evidence review, pembrolizumab was shown to improve progression-free survival and overall survival.

Clinical Panel recommendation:

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

Assurances

The committee is asked to receive the following assurance:		
1.	The Deputy Director of Clinical Effectiveness confirms the proposition has completed the appropriate sequence of developmental and governance steps.	
2.	The Deputy Director of Cancer Programme confirms the proposition is supported by the following documentation (please tick the box where applicable)	
	Draft Clinical Commissioning policy proposition	☒
	Evidence Review	☒
	Public Health Evidence Report	☐
	Evidence to Decision Making (EtD) Summary	☒
	Equalities and Heath Inequalities Assessment (EHIA)	☒
	Prior Approval Form	☒
	Engagement Report	☒
	13Q Assessment and Patient & Public Voice Assurance	☒
	Clinical Panel Report	☒

	Policy Working Group membership	☒
	Other (please state if required)	☐
3.	The Deputy 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 Director of Clinical Commissioning (Specialised Commissioning) confirms that the Service and Operational Impact Assessments have been completed.	
5.	The Deputy Director of Quality and Nursing (Specialised Commissioning) confirms that the proposed quality indicators have been adequately defined (where applicable).	

Evidence Review Summary

Outcome	Evidence statement
Clinical Effectiveness	
Critical outcomes	
Progression free survival **Certainty of evidence:** Very low	This outcome is important to patients because it represents the time for which their disease is not progressing. Stable disease may represent longer survival and disease stability may result in patients experiencing fewer symptoms from the disease itself. It can be determined sooner than overall survival outcome measures. One retrospective cohort study provided evidence on progression free survival in patients with inoperable[1] BRAF-mutated ATC receiving DTP compared to DT. **At a median follow-up of 28 months (range 3 to 63 months) for DTP group and 102 months (range 0.6 to 102 months) for DT alone group[2]:** *Upfront DTP vs upfront DT*[3] • One retrospective cohort study (Hamidi et al 2024) reported a *statistically significant* increase (p=0.049) in median progression free survival in adults with inoperable BRAF-mutated ATC receiving upfront DTP (n=30, 11.0 months (95% CI 7.0 to 15.0)) compared to patients receiving upfront DT (n=31, 4.0 months (95% CI 0.7 to 7.3)). **(VERY LOW)** **One retrospective cohort study of patients with inoperable BRAF-mutated ATC provided very low certainty evidence of a *statistically significant* increase in median progression**

[1] Although not explicitly stated, it was assumed that patients included in the main analysis (n=71) of the paper

had inoperable ATC. Operable patients were included in an exploratory neoadjuvant DTP group and these patients were not included in the main analysis of the paper or in this review. Any patients who received surgery in the DT and DTP groups in the main analysis, received surgery prior to pembrolizumab and therefore could be deemed inoperable at time of pembrolizumab. Any patients who were treated with neoadjuvant-intent DT or DTP who did not ultimately undergo surgery due to either an inadequate response or patient declining surgery were included in the main analysis DT and DTP groups.

[2] Median follow-up only reported for DTP group (pembrolizumab given upfront and at progression) and DT alone group. Median follow-up not reported for upfront DTP and upfront DT groups.

[3] DT upfront group includes patients given pembrolizumab at progression. Fourteen patients who had DT upfront were given pembrolizumab at progression but the number of these patients who were evaluable for response, and hence included in the PFS results, was not reported.

Outcome	Evidence statement
	free survival in 30 patients receiving upfront DTP (11.0 months (95% CI 7.0 to 15.0)) compared to 31 patients receiving upfront DT (4.0 months (95% CI 0.7 to 7.3)) at a median follow-up of 28 months for the DTP group and 102 months for the DT alone group.
Response to treatment **Certainty of evidence:** Very low	Response rate is important to patients as it represents whether the treatment can improve disease burden and improve symptoms. Improving disease burden is important as patients may have sufficient response that their tumour is rendered operable. Operable cancers are amenable to potentially curative resection which significantly improves prognosis. One retrospective cohort study and one subgroup of a retrospective case series provided evidence relating to response to treatment in patients with inoperable BRAF-mutated ATC. One study compared DTP to DT and one study reported non-comparative results for patients receiving DTP for a subgroup of BRAF-mutated ATC patients. **At a median follow-up of 28 months (range 3 to 63 months) for DTP group and 102 months (range 0.6 to 102 months) for DT group:** *Upfront DTP vs upfront DT*[4] • One retrospective cohort study (Hamidi et al 2024) reported *no statistically significant* difference (p=0.205) in the overall response rate[5] in adults with inoperable BRAF-mutated ATC receiving upfront DTP (n=30, ORR: 73.3%; stable disease: 6 (20%), partial response: 14 (47%), complete response: 8 (27%), progressive disease: 0 (0%), non-evaluable: 2 (7%)) compared to patients receiving upfront DT (n=31, ORR: 64.5%; stable disease: 5 (16%), partial response: 16 (52%), complete response: 4 (13%), progressive disease: 3 (10%), non-evaluable: 3 (10%)). **(VERY LOW)** **Up to 20 months follow-up[6]:** *DTP* • One subgroup of patients with BRAF-mutated ATC receiving DTP (with pembrolizumab either upfront or on disease progression, n=7) from a retrospective case series of adults with locally advanced or metastatic unresectable ATC receiving immune checkpoint

[4] DT upfront group includes patients given pembrolizumab at progression. Fourteen patients who had DT upfront were given pembrolizumab at progression but the number of these patients who were evaluable for response and hence included in the response results was not reported.
[5] Response was assessed by percentage change in target lesion size between initial and serial post-treatment computed tomography (CT) scans and/or 18F-fluorodeoxyglucose positron emission tomography combined with CTs, using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.
[6] Taken from Swimmer plot of responses (Figure 3 in paper). Median length of follow-up was not reported for in-scope patients or total sample.

Outcome	Evidence statement
	inhibitors (n=13),[7] reported on response to DTP for individual patients. These were as follows: ○ Patient #2: progressive disease at nine weeks after initiation of therapy, pembrolizumab discontinued and chemo-radiation followed by chemotherapy initiated, alive with stable disease at 20 months after initiation of pembrolizumab ○ Patient #4: stable disease at 0.5 to 8.5 months after initiation of therapy, progressive disease at 8.5 months, death at 15.5 months ○ Patient #5: stable disease at start of therapy, oligoprogression at six months which was also treated with local radiotherapy ○ Patient #7: stable disease at one to four months after initiation of therapy (ongoing) ○ Patient #8: progressive disease at one month after initiation of therapy, death at 1.5 months ○ Patient #10: progressive disease and death at one month after initiation of therapy ○ Patient #12: death at 0.5 months after initiation of therapy **(VERY LOW)** **One retrospective cohort study and one subgroup of a retrospective case series provided very low certainty evidence relating to response to treatment in patients with inoperable BRAF-mutated ATC. The retrospective cohort study reported *no statistically significant* difference in the overall response rate for 30 patients receiving upfront DTP (ORR: 73.3%) compared to 31 patients receiving upfront DT (ORR: 64.5%) at a median follow-up of 28 months for the DTP group and 102 months for the DT group. The subgroup of a retrospective case series reported that six out of seven patients receiving DTP had progressive disease or death at up to 20 months follow-up.**
Overall survival **Certainty of evidence:** Very low	Overall survival is important to patients as ATC has a high mortality rate due to advanced disease and limited treatment options. Improved survival is an important marker of effective treatment. Overall survival does not, however, give indication to a patient's quality of life during this time. One retrospective cohort study and one subgroup of a retrospective case series provided evidence on overall survival in patients with inoperable BRAF-mutated ATC. One study compared DTP to DT and one study reported non-comparative results for patients receiving DTP for a subgroup of BRAF-mutated ATC patients. <u>Median overall survival</u>

[7] Patients received either pembrolizumab (n=12) or nivolumab (n=1). The seven patients with $BRAF^{V600E}$ mutations, in scope for this review, all received pembrolizumab.

Outcome	Evidence statement
	At a median follow-up of 28 months (range 3 to 63 months) for DTP group and 102 months (range 0.6 to 102 months) for DT group: *DTP vs DT alone*[8] • One retrospective cohort study (Hamidi et al 2024) reported a *statistically significant* increase (p=0.037) in median overall survival[9] in 48 adults with inoperable BRAF-mutated ATC receiving DTP (with pembrolizumab either upfront or on disease progression) (17.0 months (95% CI 11.9 to 22.1)) compared to 23 patients receiving DT alone (9.0 months (95% CI 4.5 to 13.5)). **(VERY LOW)** **Up to 20 months follow-up:** • One subgroup of patients with BRAF-mutated ATC receiving DTP (with pembrolizumab either upfront or on disease progression, n=7) from a retrospective case series of adults with locally advanced or metastatic unresectable ATC receiving immune checkpoint inhibitors (n=13), reported that the median overall survival[10] from diagnosis was 15.6 months for all patients in the case series and this remained unchanged regardless of BRAF status. **(VERY LOW)** <u>12-months overall survival</u> **At a median follow-up of 28 months (range 3 to 63 months) for DTP group and 102 months (range 0.6 to 102 months) for DT group:** *DTP vs DT alone* • One retrospective cohort study (Hamidi et al 2024) reported a higher 12-month overall survival in 48 adults with inoperable BRAF-mutated ATC receiving DTP (with pembrolizumab either upfront or on progression) (60.2%) compared to 23 patients receiving DT alone (36.7%). No statistical tests were reported. **(VERY LOW)** <u>24-months overall survival</u> **At a median follow-up of 28 months (range 3 to 63 months) for DTP group and 102 months (range 0.6 to 102 months) for DT group:** *DTP vs DT alone* • One retrospective cohort study (Hamidi et al 2024) reported a higher 24-month overall survival in 48 adults

[8] DTP group included patients receiving DT plus pembrolizumab upfront or at progression. DT alone group included patients receiving DT.
[9] Defined as time between the first dose of pembrolizumab and death from any cause.
[10] Overall survival from diagnosis was defined as the time from collection of the first sample that reported pathology/cytology consistent with ATC to death from any cause or censoring.

Outcome	Evidence statement
	with inoperable BRAF-mutated ATC receiving DTP (with pembrolizumab either upfront or on progression) (36.5%) compared to 23 patients receiving DT alone (31.5%). No statistical tests were reported. **(VERY LOW)** Number of deaths[11] **Up to 20 months follow-up:** • One subgroup of patients with BRAF-mutated ATC receiving DTP (with pembrolizumab either upfront or on disease progression, n=7) from a retrospective case series of adults with locally advanced or metastatic unresectable ATC receiving immune checkpoint inhibitors (n=13), reported that four (57%) patients died. No further details given. **(VERY LOW)** **One retrospective cohort study (n=71) and one subgroup (n=7) of a retrospective case series (n=13) provided very low certainty evidence on overall survival in patients with inoperable BRAF-mutated ATC. The retrospective cohort study reported a *statistically significant increase* in median overall survival in patients with inoperable BRAF-mutated ATC receiving DTP with pembrolizumab either upfront or on progression (17.0 months) compared to patients receiving DT alone (9.0 months) at a median follow-up of 28 months for the DTP group and 102 months for the DT group. An increase in 12-months and 24-months overall survival was also reported with DTP; data were not statistically compared. The retrospective case series of adults with locally advanced or metastatic unresectable ATC receiving immune checkpoint inhibitors reported that the median overall survival from diagnosis was 15.6 months for all patients in the case series and this remained unchanged regardless of BRAF status at up to 20 months follow-up.** **Four out of the seven patients with BRAF-mutated ATC receiving DTP died at up to 20 months follow-up.**
Important outcomes	
Quality of life **Certainty of evidence:** Not applicable	Quality of life is important to patients as it provides an indication of an individual's general health, their self-perceived well-being and their ability to participate in activities of daily living. Measurement of quality of life can help inform patient-centred decision making and inform health policy. **No evidence was identified for this outcome.**
Performance status/Activities of daily living (ADLs)	ADLs are important outcomes to patients as they facilitate enablement and independence, allowing individuals to function in education, work, home, and recreational settings. They

[11] Taken from Swimmer plot of responses (Figure 3 in paper). Median length of follow-up was not reported for in-scope patients or total sample.

Outcome	Evidence statement
Certainty of evidence: Not applicable	encompass patients' individual needs and facilitate inclusion and participation. **No evidence was identified for this outcome.**
Time to treatment failure **Certainty of evidence:** Very low	This is important because it reflects overall treatment failure due to disease progression, adverse events or death. One subgroup of a retrospective case series provided evidence relating to time to treatment failure in patients with inoperable BRAF-mutated ATC receiving DTP. **Up to 20 months follow-up:** *DTP* • One subgroup of patients with BRAF-mutated ATC receiving DTP (with pembrolizumab either upfront or on disease progression, n=7) from a retrospective case series of adults with locally advanced or metastatic unresectable ATC receiving immune checkpoint inhibitors (n=13), reported that one patient had progressive disease and pembrolizumab was discontinued at nine weeks after initiation of pembrolizumab. Chemo-radiation followed by chemotherapy was initiated and the patient was reported to be alive with stable disease at 20 months after initiation of pembrolizumab. **One subgroup (n=7) of a retrospective case series (n=13) provided very low certainty evidence on time to treatment failure in patients with locally advanced or metastatic unresectable BRAF-mutated ATC up to 20 months follow-up. The study reported that one patient had progressive disease and pembrolizumab was discontinued at nine weeks after initiation of pembrolizumab.**
Symptom control **Certainty of evidence:** Not applicable	Symptom control is an important outcome as it is a marker for the ability of the treatment to improve functional capacity and quality of life. **No evidence was identified for this outcome.**
Safety	
Adverse events **Certainty of evidence:** Very low	These outcomes are important to patients because they will an impact on their treatment choices, recovery and could have long term sequelae if they are irreversible. They reflect the tolerability and adverse effects (AEs) of the treatment. From a service delivery perspective, they reflect the additional demands placed on the health system to manage the adverse consequences of the treatment. One retrospective cohort study and one subgroup of a retrospective case series provided evidence on AEs in patients with inoperable BRAF-mutated ATC. Both studies reported non-comparative results for patients receiving DTP.

Outcome	Evidence statement
	At a median follow-up of 28 months (range 3 to 63 months): *DTP* • One retrospective cohort study (Hamidi et al 2024) reported that 13 (27%) out of 48 adults with inoperable BRAF-mutated ATC receiving DTP (with pembrolizumab either upfront or on progression) experienced immune related AEs. These were, n (%): colitis: 4 (8), nephritis: 3 (6), hepatitis: 2 (4), encephalopathy: 1 (2), DRESS: 1 (2), elevation in creatine kinase: 1 (2), pneumonitis: 1 (2), polyneuropathy: 1 (2), Sjogren: 1 (2), STEMI: 1 (2%), and thrombocytopenia: 1 (2). None of the patients experienced Grade 5 adverse events. **Up to 20 months follow-up:** *DTP* • One subgroup of patients with BRAF-mutated ATC receiving DTP (with pembrolizumab either upfront or on disease progression, n=7) from a retrospective case series of adults with locally advanced or metastatic unresectable ATC receiving immune checkpoint inhibitors (n=13), reported that one patient experienced Grade 2 joint pain, myalgias, and neuropathy, which were responsive to steroids and another patient developed diplopia and Bell's palsy which the authors reported was not likely to be treatment related, but causation could not be completely ruled out. **One retrospective cohort study and one subgroup of a retrospective case series provided very low certainty evidence on adverse events in patients with inoperable BRAF-mutated ATC. The retrospective cohort study reported that 13 (27%) patients with inoperable BRAF-mutated ATC receiving DTP with pembrolizumab (either upfront or on progression) experienced immune related adverse events and no patients experienced Grade 5 adverse events at a median follow-up of 28 months. One subgroup of seven patients with BRAF-mutated ATC from a retrospective case series of locally advanced or metastatic unresectable ATC patients receiving DTP (with pembrolizumab either upfront or on progression) reported that one patient experienced Grade 2 joint pain, myalgias, and neuropathy and another patient developed diplopia and Bell's palsy at up to 20 months follow-up. No comparative evidence was identified.**

Abbreviations

ADL: activities of daily living; AE: adverse event; ATC: anaplastic thyroid carcinoma; BRAF: B-type Raf kinase; CI: confidence interval; CT: computed tomography; DRESS: drug reaction with eosinophilia and systemic symptoms; DT: dabrafenib and trametinib; DTP: dabrafenib and trametinib plus pembrolizumab; n: number; ORR: overall response rate; PFS: progression free survival; RECIST: Response Evaluation Criteria in Solid Tumors; STEMI: ST elevation myocardial infarction

Patient Impact assessment

The condition has the following impacts on the patient's everyday life:

- **mobility: Select appropriate response:** Patients have severe problems in walking about or are unable to walk about
- **ability to provide self-care:** Patients have severe problems in washing or dressing or are unable to wash or dress
- **undertaking usual activities:** Patients severe problems in doing their usual activities or are unable to do their daily activities
- **experience of pain/discomfort:** Patients have severe pain or discomfort
- **experience of anxiety/depression:** Patients are severely anxious or depressed

Further details of impact upon patients:

Patients with ATC usually present late and suffer from debilitating symptoms resulting from local invasion, including pain, difficulty breathing and difficulty swallowing. This has a large impact on a patient's everyday life leading to difficulties with mobilising, self-care, poor nutrition and severe fatigue. The deterioration in quality of life from inability to carry out normal daily life and the increased reliance on carers, can lead to severe feelings of anxiety or depression. Moreover, patients feel hopeless as ATC has limited treatment options, with patients often having to seek treatment through private healthcare as treatment options considered standard elsewhere in the world are not currently available in the NHS, and survival is low.

Further details of impact upon carers:

In patients with ATC, families and/or carers need to assist with daily tasks such as self-care, household maintenance, mobilising and preparing meals that the patient can tolerate. The caring role can affect their relationship with their loved one as well as put significant emotional and financial strain on the carer.

Considerations

Equality and Health Inequalities Impact Assessment (EHIA)	
Summary of any potential impacts of the proposal	This policy proposition is for pembrolizumab in combination with dabrafenib and trametinib for BRAF mutated anaplastic thyroid cancer. There is not thought to be any adverse impact on patient groups with protected characteristics or that face health inequalities. In particular, as the length between pembrolizumab infusions can be increased from every

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	three to every 6 weeks once patients are stable, and pembrolizumab can be given in local chemotherapy day units, this proposition may have a particularly positive impact on those that face travel difficulties (e.g. patients who live in remote areas, low income).

13Q Assessment

PPVAG outcome	No consultation required
Were PPVAG assured of the level of stakeholder testing?	Yes

Rare Disease Advisory Group

Not Applicable

Pharmaceutical

Yes

The Clinical Commissioning Policy Proposition recommends the use of pembrolizumab, in combination with dabrafenib and trametinib, as a treatment option for BRAF mutated anaplastic thyroid cancer. This recommendation is outside pembrolizumab's marketing authorisation, so use is off-label. Post-pubescent children will be able to access this therapy under the NHS England Commissioning Medicines for Children policy. 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, using separate prior approval forms for registration of adults and post-pubescent children.

Pembrolizumab, dabrafenib and trametinib are included on the NHS Payment Scheme Annex A, so are high-cost drugs.

National Programme of Care

The proposal received the full support of the Cancer National Programme of Care Assurance Group.

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