Clinical Priorities Advisory Group summary report

Agenda item	2.1
Date of Meeting	01/04/2026
Title of the Proposition	Neo-adjuvant followed by adjuvant pembrolizumab for stage III macroscopic resectable melanoma (> 12 years)
Unique Reference Number	2426
Programme of Care	Cancer
Clinical Reference Group	Chemotherapy
Service/treatment status	delegated

Action requested

Support the adoption of the policy proposition

Recommended its approval as an in year service development.

Summary of the proposition

Neoadjuvant followed by adjuvant pembrolizumab is recommended to be available as a routine commissioning treatment option for stage III macroscopic resectable melanoma within the criteria set out in this document.

Melanoma is a cancer of melanocytes, the pigment (melanin) producing cells of the body. Most melanoma originates from the skin. Melanoma is more common in older populations, with more than a quarter of melanoma cases being in patients aged 75 years and older. However, there are a significant number of younger patients. Other risk factors include exposure to ultraviolet radiation (e.g. sun, tanning beds) and gene mutations (e.g. BRAF mutation). It is estimated that 86% of melanoma cases in the UK are preventable (Cancer Research UK, n.d.).

Stage III melanoma, where the cancer cells have spread to regional lymph nodes has a 5-year survival of 75% however stage IV melanoma has a 5-year survival of approximately 20% (Cancer Research UK, n.d.). It is therefore important to minimise the likelihood of patients with stage III disease progressing to stage IV disease.

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 Summary	☒
	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

One paper included in the summary **Paper 1:** Patel, S.P. et al. (2023) Neoadjuvant-adjuvant or adjuvant-only pembrolizumab in advanced melanoma, The New England Journal of Medicine, 388(9), pp. 813-823. • A phase II, open-label randomised trial of 313 adults with clinically detected, resectable stage III or IV melanoma treated with either intravenous pembrolizumab before surgery, followed by additional pembrolizumab as adjuvant treatment (neoadjuvant–adjuvant group; n=154), or surgery followed by adjuvant intravenous pembrolizumab (adjuvant-only group; n=159). The median follow-up duration was 14.7 months.	
Outcome	**Evidence statement**
Clinical effectiveness	
Overall survival **Certainty of evidence:** Not assessed for 3 paper summaries	Patel et al (2023) reported that at the time of data cut-off, 36 patients with advanced melanoma had died: 14 of 154 patients in the neoadjuvant-adjuvant group and 22 of 159 patients in the adjuvant-only group. No statistical measures were reported as the authors stated that the small number of deaths prevented definitive comparison between the two treatment groups. **The included paper (n=313) reported 14 deaths in patients with advanced melanoma treated with neoadjuvant-adjuvant pembrolizumab (n=154) and 22 deaths in patients treated with adjuvant-only pembrolizumab (n=159); no statistical measures were reported.**
Event-free survival **Certainty of evidence:**	Patel et al (2023) reported that at a median follow-up of 14.7 months, event-free survival[1] (ITT analysis) was statistically significantly greater in patients with advanced melanoma in the neoadjuvant-adjuvant group (38 events in 154 patients) compared to the adjuvant-only group (67 events in 159 patients); p=0.004[2] (see Table 1).

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

[1] Events included disease progression or adverse effects of treatment that prevented surgery; the inability to resect all gross disease; disease progression, surgical complications, or toxic effects of treatment that prevented the initiation of adjuvant treatment within 84 days after surgery; recurrence of melanoma after surgery; or death from any cause.

[2] Data on patients last known to be alive without an event were censored at the date of last contact. To account for differences in time to administration of treatment in the two groups, any events that occurred before adjuvant treatment were assigned the event time of day 84. Patients in the neoadjuvant–adjuvant group who declined surgery due to complete radiographic response were not counted as having had an event and were followed up for

recurrence. Data on patients whose surgery or adjuvant treatment was cancelled due to coronavirus disease 2019 (Covid-19)–related trial limitations were censored at the time of withdrawal without an event.

[3] N=154 patients includes the two patients who withdrew consent after randomisation.
[4] N=159 includes the seven patients who withdrew consent after randomisation.
[5] The authors stated that four additional patients did not receive adjuvant treatment due to clinical trial closure because of COVID-19 (n=1), concerns regarding exposure to COVID-19 (n=1), and disease other than melanoma identified at surgery (n=2). There is therefore a discrepancy in the number of patients reported by the authors not to have received adjuvant treatment (i.e. 18 patients and not the stated 14 patients).
[6] Zubrod's performance-status scores range from 0 to 5, with higher scores indicating greater disability; a score of 0 indicates that the patient is fully active, 1 that the patient is restricted in strenuous activity but is ambulatory, and

[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 range of impacts on the patient's everyday life:

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

Further details of impact upon patients:

Melanoma is cancer that affects young people and is a highly curable when it is diagnosed at an early stage. However, if it progresses to stage IV, with usual spread to the lungs, liver, bone or brain, patients may experience distressing symptoms such as intractable pain, breathing difficulties and seizures. The fear of progression, particularly to the brain, can cause significant anxiety, however neoadjuvant pembrolizumab can maximise the chance of survival for stage III patients.

Further details of impact upon carers:

Caring for a loved one with melanoma is emotionally draining, with carers often having fears about their relative/friend's cancer spreading or recurring. There is also often a considerable financial burden as many melanoma patients are young and economically active. Additionally, carers often accompany patients to medical appointments, and if the disease progresses, assist patients with day-to-day activities whilst they undergo intensive treatments or as the disease affects more body systems.

Considerations

Equality and Health Inequalities Impact Assessment (EHIA)	
Summary of any potential impacts of the proposal	This policy proposition allows adults with melanoma to be treated with neoadjuvant followed by adjuvant pembrolizumab. The current standard of care is adjuvant pembrolizumab, and therefore patients will continue to have the same number of immunotherapy cycles, scans and appointments however the treatment will start earlier. The treatment setting will also be the same. As the only change is moving the start date of pembrolizumab before surgery, there will be no change in the impact of the policy proposition on patient groups with protected characteristics and the

	proposition is not thought to adversely impact any groups. The policy proposition is informed by the evidence base and clinical expertise of the policy working group. A national commissioned policy proposition will reduce variation in clinical practice promoting equity of care nationally for those in which this intervention is indicated.

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 neoadjuvant followed by adjuvant pembrolizumab as a treatment option for stage III macroscopic resectable melanoma. This recommendation is outside pembrolizumab's marketing authorisation, so use is off-label. Clinical Panel agreed that the age range for use of pembrolizumab should be 12 years and above (in line with the licensing for adjuvant pembrolizumab).

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.

Pembrolizumab is included on the NHS Payment Scheme Annex A, so is a high-cost drug.

National Programme of Care

Cancer Programme of Care

The proposal received the full support of the Cancer PoC.