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	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).

[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

Certainty of evidence: Not assessed for 3 paper summaries

Table 1: Events in patients with advanced melanoma treated with neoadjuvant-adjuvant pembrolizumab or adjuvant-only pembrolizumab reported by Patel et al 2023

Event type	Neoadjuvant-adjuvant group (n=154)[3]	Adjuvant-only group (n=159)[4]
Failure to receive surgery due to:		
Toxicity	1	0
Progression	12	0
Co-morbidities	1	0
Non-COVID scheduling issue	0	1
Received surgery but did not receive adjuvant treatment due to:		
Patient refusal	1[5]	2
Neo-adjuvant toxicity	3 (colitis, pneumonitis, and polymyalgia rheumatica in 1 patient each)	0
Metastatic disease/disease progression	9	16
Residual disease	1	2
Extended radiation	0	1
Recurrence after starting adjuvant treatment	9	41
Death	1	4
Total events	**38**	**67**

At the time of analysis, 10 of the 313 randomised patients were still receiving neoadjuvant pembrolizumab. Of the remaining patients, 127 of 144 (88%) patients in the neoadjuvant–adjuvant group and 151 of 159 (95%) patients in the adjuvant-only group had undergone definitive surgery.

At two years, event-free survival was greater in patients with advanced melanoma in the neoadjuvant-adjuvant group (72%; 95% confidence interval [CI] 64.0 to 80.0) compared to patients in the adjuvant-only group (49%; 95% CI 41.0 to 59.0); the difference was 23% (95% CI 11.0 to 35.0), but no other statistical measures were reported. The authors reported similar between-treatment group results for two-year event-free survival according to subgroups (including age, sex, Zubrod's performance-

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).

	status score[6], lactate dehydrogenase (LDH) level, disease stage, ulceration, and BRAF mutation status). **The included paper (n=313) reported that at a median follow-up of 14.7 months, event-free survival was statistically significantly greater in patients with advanced melanoma treated with neoadjuvant-adjuvant pembrolizumab (38 events in 154 patients) compared to patients treated with adjuvant-only pembrolizumab (67 events in 159 patients).**
Disease recurrence **Certainty of evidence:** Not assessed for 3 paper summaries	Patel et al (2023) reported that at the time of data cut-off, nine patients with advanced melanoma in the neoadjuvant-adjuvant group and 41 patients in the adjuvant-only group had disease recurrence during or after the adjuvant pembrolizumab treatment phase (see Table 1). Of the patients in the neoadjuvant-adjuvant group, 50 completed all adjuvant treatment cycles and none had subsequent disease recurrence. Of the patients in the adjuvant-only group, 38 patients completed all adjuvant cycles and four (11%) had subsequent disease recurrence; no statistical measures were reported. **The included paper (n=313) reported no subsequent disease recurrence in the 50 patients with advanced melanoma who completed all adjuvant treatment cycles in the neoadjuvant-adjuvant group, while 11% of patients who completed all adjuvant treatment cycles in the adjuvant-only group had subsequent disease recurrence; no statistical measures were reported.**
Overall response to treatment[7] **Certainty of evidence:** Not assessed for 3 paper summaries	Patel et al (2023) reported that after completion of neoadjuvant treatment in the neoadjuvant-adjuvant group, nine of 142 (6%) evaluable patients[8] with advanced melanoma had a complete imaging-based response and 58 (41%) evaluable patients had a partial response. The authors reported that a review of the institutional pathology reports indicated that 28 of 132 (21%) patients had a complete pathological response (i.e. no viable tumour) after neoadjuvant treatment. **The included paper (n=142 evaluable patients) reported that after completion of neoadjuvant pembrolizumab treatment in the neoadjuvant-adjuvant group, 6% of evaluable patients with advanced melanoma had a complete imaging-based response and 41% of evaluable patients had a partial response.**
Safety	
Safety **Certainty of evidence:** Not assessed	Patel et al (2023) reported that in patients with advanced melanoma who received neoadjuvant-adjuvant treatment, 11 of 152 (7%) evaluable patients had at least one grade 3 or 4 adverse event (e.g. fever, diarrhoea, sepsis) that was considered to be related to pembrolizumab, nine of 127 (7%) evaluable patients who completed surgery in the neoadjuvant-adjuvant group had at least one grade 3 or 4 adverse event (e.g. increase in alanine aminotransferase level, infections or infestations, wound infection)

[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 2 that the patient is unable to work but is ambulatory and capable of self-care and up and about more than 50% of waking hours.

[7] Overall response was defined as the percentage change in tumour measurement from baseline using objective response (≥30% decrease) and disease progression (>20% increase) according to Response Evaluation Criteria in Solid Tumours.

[8] N=142 evaluable patients excludes the 10 patients still receiving neoadjuvant treatment and the two patients who withdrew consent after randomisation.

for 3 paper summaries	considered to be related to surgery. In patients with advanced melanoma in the adjuvant-only group, five of 141 (4%) evaluable patients had at least one grade 3 adverse event (e.g. chest-wall pain, seroma, skin infection) that was considered to be related to surgery (no grade 4 adverse events were noted). The authors reported that the number of adverse events of grade 3 or higher were similar in both treatment groups during adjuvant pembrolizumab treatment (12% in the neoadjuvant-adjuvant group and 14% in the adjuvant-only group). No deaths due to pembrolizumab were reported. **The included paper (n=313) reported that during neoadjuvant pembrolizumab treatment in the neoadjuvant-adjuvant group, 7% of evaluable patients (n=152) with non-advanced melanoma experienced at least one pembrolizumab-related grade 3 or 4 adverse event and 7% of evaluable patients (n=127) experienced a grade 3 or 4 adverse event related to surgery. Of the evaluable patients in the adjuvant-only group (n=141), 4% had at least one grade 3 adverse event related to surgery (no grade 4 adverse events were noted). Adverse events of grade 3 or higher were reported to be similar during adjuvant pembrolizumab treatment in both treatment groups. No deaths due to pembrolizumab were reported.**

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.