Clinical Commissioning Policy

Neo-adjuvant followed by adjuvant pembrolizumab for stage III macroscopic resectable melanoma (≥ 12 years) [2426]

Summary

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. As pembrolizumab is only licensed for adjuvant use in advanced melanoma, the use of neoadjuvant followed by adjuvant pembrolizumab as outlined in this policy is off-label.

The policy is restricted to 12 years and older only as there is insufficient evidence to confirm safety in patients < 12 years.

Committee discussion

Panel members agreed that the evidence base supported the policy and recommended that this progresses as a routine commissioning policy. Please see Clinical Panel reports for full details of Clinical Panel's discussion.

The Clinical Priorities Advisory Group committee papers can be accessed here: NHS England » Clinical commissioning policy: Neo-adjuvant followed by adjuvant pembrolizumab for stage III macroscopic resectable melanoma (12 years and older)

What we have decided

NHS England has carefully reviewed the evidence to treat stage III macroscopic resectable melanoma with neoadjuvant followed by adjuvant pembrolizumab. We have concluded that there is enough evidence to make the treatment available at this time.

The single paper evidence summary which informs this commissioning position can be accessed here: NHS England » Clinical commissioning policy: Neo-adjuvant followed by adjuvant pembrolizumab for stage III macroscopic resectable melanoma (12 years and older)

Links and updates to other policies

There are no updates to other NHS England Clinical Commissioning policies. This policy is linked to:

- Overview | Pembrolizumab for advanced melanoma not previously treated with ipilimumab | Guidance | NICE
- Overview | Pembrolizumab for adjuvant treatment of completely resected stage 3 melanoma | Guidance | NICE

- Overview | Pembrolizumab for adjuvant treatment of resected stage 2B or 2C melanoma | Guidance | NICE
- Overview | Pembrolizumab for treating advanced melanoma after disease progression with ipilimumab | Guidance | NICE

Plain language summary

About melanoma

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.

About current treatment

Patients presenting with macroscopic (visible or palpable) stage III melanoma are referred to a multidisciplinary meeting where a decision about whether the cancer and lymph node disease can be removed surgically is made. Following surgery, patients are referred to oncology to consider the option of adjuvant therapy to reduce the risk of future relapse.

The adjuvant treatments used routinely in the UK include pembrolizumab or nivolumab, which are immune checkpoint inhibitors, and dabrafenib in combination with trametinib (TA544), which is a targeted therapy against the BRAF mutation that is present in 40% of melanomas. Adjuvant immune checkpoint inhibitors and targeted therapies are thought to be equally efficacious. Currently, approximately a year's worth (54 weeks) of pembrolizumab is given following surgery. This is usually given every 3 weeks (18 cycles) or every 6 weeks (9 cycles).

About neoadjuvant followed by adjuvant pembrolizumab

This clinical commissioning policy recommends that the 54 weeks of pembrolizumab treatment is started 9 weeks before surgery (neoadjuvant). Patients will then have surgery to remove the melanoma and lymph node disease and then complete the remaining pembrolizumab as adjuvant therapy. Neoadjuvant therapy generates more anti-tumour T cells (cancer fighting cells) and has been shown to improve clinical outcomes, not only for pembrolizumab but for the wider class of immune checkpoint inhibitors as well (Blank et al

2024; Patel et al, 2023). Under this new regime, patients would continue to complete the same number of total cycles of pembrolizumab equating to 54 weeks treatment and would continue to have the same number of scans and appointments.

Currently, pembrolizumab is licensed in melanoma for patients aged 12 years and older with advanced (unresectable or metastatic) melanoma or for **adjuvant** treatment for stage IIB, IIC or III melanoma who have undergone complete resection (EMC, 2024). The licensing recommends up to one year's treatment with adjuvant pembrolizumab for advanced melanoma. The use of pembrolizumab as **neoadjuvant followed by adjuvant** therapy for macroscopic, resectable stage IIIB-D melanoma as outlined by this policy is therefore off-label. Neoadjuvant pembrolizumab is now a standard of care in several other countries including Australia, Ireland, Canada, Italy and Sweden.

There are four NICE technology appraisals (TA) for the use of pembrolizumab for melanoma which recommend the use of pembrolizumab as:

1. Adjuvant therapy for stage IIB and C melanoma: Overview | Pembrolizumab for adjuvant treatment of resected stage 2B or 2C melanoma | Guidance | NICE

2. Adjuvant therapy for stage III melanoma (in line with its marketing authorisation): Overview | Pembrolizumab for adjuvant treatment of completely resected stage 3 melanoma | Guidance | NICE

3. Advanced melanoma that has not been previously treated with another monoclonal antibody, ipilimumab: Overview | Pembrolizumab for advanced melanoma not previously treated with ipilimumab | Guidance | NICE

4. Advanced melanoma where there has been disease progression following ipilimumab: Overview | Pembrolizumab for treating advanced melanoma after disease progression with ipilimumab | Guidance | NICE

The only change in this application to the licensed indication for stage III melanoma and the NICE TA recommending its use for stage III melanoma is the timing of when pembrolizumab is started (pre-surgery rather than post-surgery).

Epidemiology and needs assessment

Melanoma is the 5th most common cancer in the UK, accounting for 5% of all new cancer cases. There are approximately 17,500 new melanoma cases in the UK every year and the incidence is expected to continue to rise (Cancer Research UK, n.d.). In 2023-2024, prior approval software data shows that approximately 900 patients with resected stage III melanoma received adjuvant pembrolizumab and 400 adjuvant dabrafenib and trametinib. This policy is only for macroscopic, resectable stage IIIB-D melanoma, and it is estimated that this represents 40% of all stage III melanomas currently receiving treatment in the adjuvant setting. This means there were approximately 360 patients who were treated with adjuvant pembrolizumab or 160 treated with adjuvant dabrafenib and trametinib who would be eligible for neoadjuvant pembrolizumab.

It is estimated that all patients who would have previously been treated with adjuvant pembrolizumab would switch to neoadjuvant pembrolizumab, and approximately half of those who would have had adjuvant dabrafenib and trametinib would switch to neoadjuvant

pembrolizumab[1]. This equates to approximately 440 patients. There will not be a significant pool of existing patients, as patients would have already undergone surgery and started or planned to be started on adjuvant therapy. The intended age group for this policy is patients aged 12 years and older, in line with the licensed age range for adjuvant pembrolizumab.

Implementation

Inclusion criteria

Patients aged 12 years and older with melanoma will be eligible for treatment with neoadjuvant followed by adjuvant pembrolizumab if they fulfil **all** of the following criteria:

- Histologically confirmed cutaneous, acral or mucosal melanoma

AND

- Macroscopic, resectable stage IIIB, C or D melanoma[2]

AND

- No previous treatment with any of the following treatments: anti-programmed death (PD-1), anti-programmed death ligand-1 (PD-L1), anti-programmed death ligand-2 (PD-L2), or anti-cytotoxic T lymphocyte associated antigen-4 (anti-CTLA-4) antibodies

AND

- Complete surgical resection of the tumour and therapeutic lymph node dissection is planned within 3 to 5 weeks of the last dose of neoadjuvant pembrolizumab and adjuvant pembrolizumab is expected to start within 3 months of surgery

AND

- An Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1

Exclusion criteria

Patients are ineligible for treatment if they meet **at least one** of the following exclusion criteria:

- Uveal melanoma

[1] Patients who would have otherwise had adjuvant dabrafenib and trametinib may switch to neoadjuvant pembrolizumab due to its side effect profile. However, some patients may still continue with adjuvant dabrafenib and trametinib, even if neoadjuvant followed by adjuvant pembrolizumab was an option, due to improved clinical outcomes. Once patients have started immunotherapy, they cannot switch between the different immunotherapy regimes unless clinically indicated.
[2] Patients are eligible for treatment if they initially had stage I-IIIA, and their disease has now progressed to stage IIIB-D. This includes patients who stage IIIA disease that was observed only and then progressed to stage IIB-D disease.

- Microscopic disease[3]
- Previous immunotherapy for melanoma
- Surgical resection is not planned at the time of initial diagnosis or first detected nodal disease[4]
- Product-specific contraindications as listed in the Summary of Product Characteristics for pembrolizumab: KEYTRUDA 25 mg/mL concentrate for solution for infusion - Summary of Product Characteristics (SmPC) - (emc)

Starting criteria

Pembrolizumab should be initiated and managed by an oncologist specifically trained and accredited in the use of systemic anti-cancer therapy and with experience in the treatment of melanoma and immunotherapy. Patients should have at least a baseline full blood count (FBC), urea and electrolytes (U&E), liver function tests (LFT), thyroid function tests (TFTs), blood glucose and electrocardiogram (ECG).

Stopping criteria

Pembrolizumab should be continued until the patient has completed 54 weeks of treatment, unless they meet **ANY** of

[3] Patients are not eligible for treatment if they have stage IIIB or IIIC with microscopic nodal disease.
[4] Surgical resection may not be possible due to the tumour or nodal disease size, location or characteristics OR due to the patient's comorbidities

the following

- Distant disease progression
- Unacceptable toxicity
- Withdrawal of patient consent

Dosing:

Adults:

The recommended dose of pembrolizumab is 200mg as an intravenous infusion over 30 minutes every 3 weeks or 400mg every 6 weeks. The total treatment time with pembrolizumab is 54 weeks. Neoadjuvant pembrolizumab is where the first 3 treatments (or cycles) are given every 3 weeks before surgery. Patients should then have surgery (resection of melanoma and lymph node disease) within 3 weeks of the last dose of neoadjuvant pembrolizumab. Adjuvant therapy should be resumed as soon as safely possible after surgery, however this should not exceed 3 months. Following this, patients would continue with adjuvant pembrolizumab usually given every 6 weeks for 7 treatments **OR** every 3 weeks for 15 treatments. If clinically indicated, subcutaneous pembrolizumab

can be considered. The recommended dose of subcutaneous pembrolizumab in adults is either:

- 395 mg every 3 weeks administered as a subcutaneous injection over 1 minute or;
- 790 mg every 6 weeks administered as a subcutaneous injection over 2 minutes.

Children (12 years and older):

The recommended dose in children aged 12 years and over is 2mg/kg as an intravenous infusion (up to a maximum of 200mg). The total treatment time with pembrolizumab is 54 weeks (1 year).

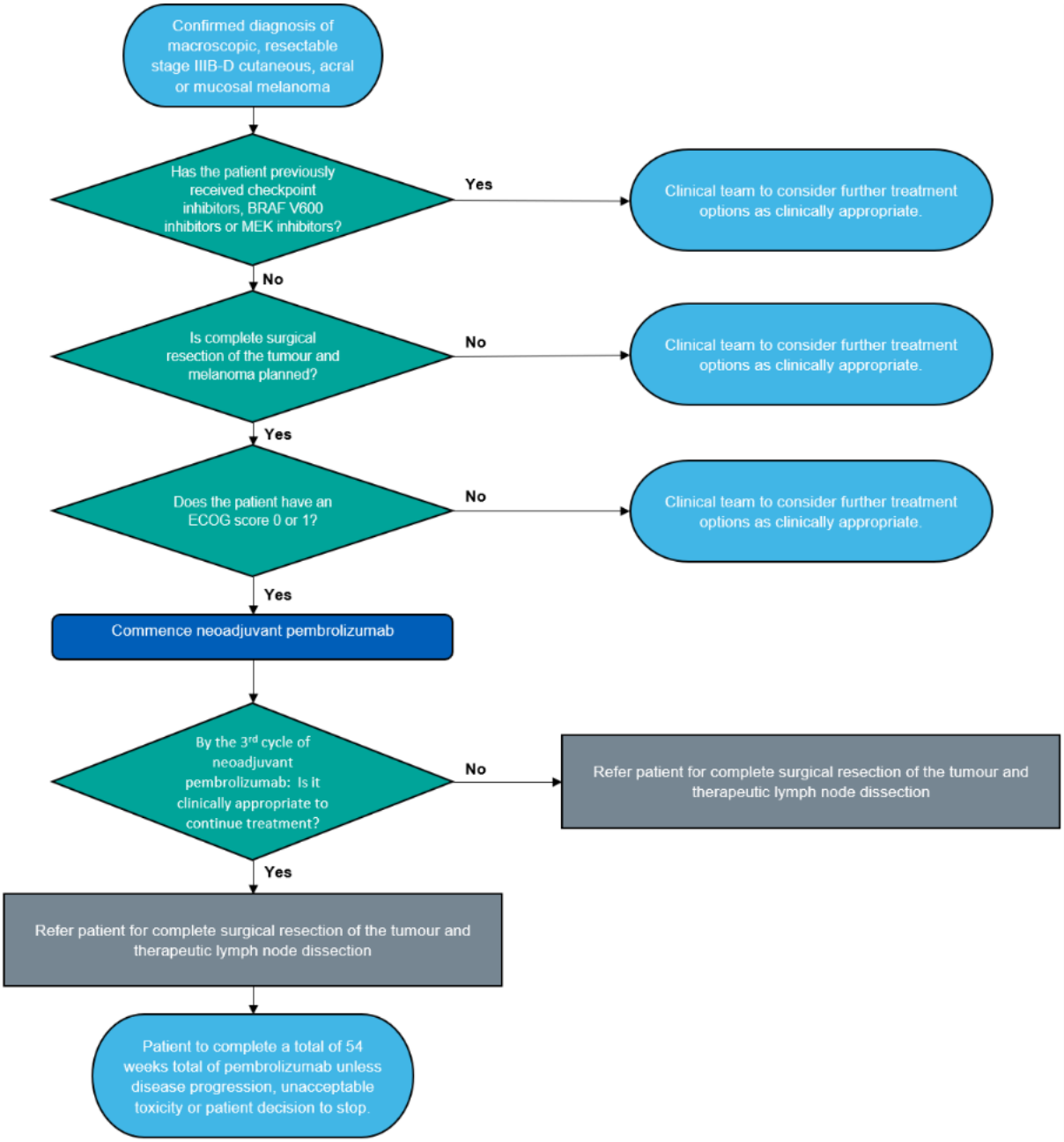
Neoadjuvant pembrolizumab is where the first 3 treatments (or cycles) are given every 3 weeks before surgery. Patients should then have surgery (resection of melanoma and lymph node disease) within 3 weeks of the last dose of neoadjuvant pembrolizumab. Adjuvant therapy should be resumed as soon as safely possible after surgery, however this should not exceed 3 months. Following this, children should complete their adjuvant treatment with 1 year of treatment.

In line with the Summary of Product Characteristics, NHS England does not commission subcutaneous pembrolizumab in patients less than 18 years old as it is not licensed in this population.

Monitoring:

A formal medical review by an oncologist to assess the tolerability of treatment should initially take place by the start of the 3rd 3-weekly treatment cycle of neoadjuvant pembrolizumab. Specific monitoring requirements for pembrolizumab can be found in its Summary of Product Characteristics.

Patient pathway



Governance arrangements

This policy should be used in conjunction with the following service specifications:

- Cancer: Chemotherapy (Adult)
- Specialist cancer services for children and young people: Teenage and Young Adults Principal Treatment Centre Services
- Children's Cancer Network - Principal Treatment Centres

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. Pembrolizumab must only be used for treatment in specialised centres or in collaboration with specialised centres under the supervision of a multi-disciplinary team.

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.

Mechanism for funding

Initiation and maintenance of neoadjuvant followed by pembrolizumab within the criteria set out in this document will be commissioned and funded by NHS England under existing arrangements for the provision of specialised services.

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. This information is collected to inform future policy revisions.

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.

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.

Definitions

Adjuvant	Treatments that are used after the primary treatment (usually surgery) to reduce the risk of cancer recurrence.
Cancer	Abnormal cells that divide in an uncontrolled way.
Immune checkpoint inhibitor	A treatment that blocks proteins involved with regulating the immune system. Immune checkpoint inhibitors are commonly used in treating cancer.
Melanocytes	The cells in the body that produce the dark pigment (melanin) that leads to tanned skin.
Mutation	A change or alternation to genetic material. Mutations can result in altered function of the gene which can be harmful or beneficial. In cancer the mutations are usually harmful
Neoadjuvant	Treatments that are used before the primary treatment (usually surgery) to reduce the risk of cancer recurrence.
Ultraviolet (UV) radiation	The transmission of light energy.

References

Blank, C.U. et al. (2024) 'Neoadjuvant nivolumab and ipilimumab in resectable stage III melanoma,' New England Journal of Medicine, 391(18), pp. 1696–1708. https://doi.org/10.1056/nejmoa2402604.

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Patel, S.P. et al. (2023) 'Neoadjuvant–Adjuvant or Adjuvant-Only pembrolizumab in advanced melanoma,' New England Journal of Medicine, 388(9), pp. 813–823. https://doi.org/10.1056/nejmoa2211437.