BAHNO
BRITISH ASSOCIATION OF HEAD & NECK ONCOLOGISTS

Clinical Guidance

Delivery of Perioperative Pembrolizumab for Resectable Locally Advanced Head and Neck Squamous Cell Carcinoma

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1. Purpose

This guidance outlines the practical requirements for the safe and timely implementation of perioperative pembrolizumab in patients with newly diagnosed, resectable, locally advanced head and neck squamous cell carcinoma (HNSCC), based on data from the KEYNOTE-689 protocol that resulted in FDA, EMA and NICE approval of this approach.

Particular emphasis is placed on actions required of the diagnosing surgeon and wider multidisciplinary team (MDT) as outlined in Figure 1.

The objective is to ensure:

- Appropriate patient selection.
- Early completion of eligibility tests, including PD-L1 combined positive score (CPS) on diagnostic biopsies and staging investigations.
- Timely commencement of neoadjuvant pembrolizumab.
- Extent and timing of surgery.
- Seamless transition to adjuvant therapy.

These guidelines have been endorsed by the British Association of Oral and Maxillofacial Surgeons and the ENT UK Head and Neck Society.

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2. Eligible Patient Population

Patients should have newly diagnosed, non-metastatic, resectable, locally advanced HNSCC suitable for primary surgery. This approach is not designed to down-stage tumours or render borderline-resectable disease operable.

Eligible patients should have:

Oral cavity SCC, Laryngeal SCC or Hypopharyngeal SCC

- Stage III or IVA

Oropharyngeal SCC

- p16-negative Stage III or IVA
- p16-positive Stage III disease with T4 primary tumours (rare indication for surgery)
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PD-L1 positivity

- PD-L1 CPS score ≥1

Patients should:

- Have resectable tumours
- Be fit for major surgery with ECOG performance status 0–1.
- Have no evidence of distant metastatic disease.
- Be considered suitable for postoperative radiotherapy with or without chemotherapy.

3. Responsibilities of the Diagnosing ENT or Maxillofacial Surgeon

The surgeon has a central role in determining whether a patient can enter the perioperative immunotherapy pathway. While details of medical eligibility will ultimately be assessed at the MDT, pre-existing conditions and co-morbidities that are likely to contra-indicate peri-operative immunotherapy should be considered to avoid inappropriate work-up of patients for whom this approach will be judged unsuitable (Appendix 1 lists the exclusion criteria).

At first presentation the surgeon should:

3.1 Confirm Resectability

The surgeon should determine:

- Technical resectability.
- Anticipated surgical margins.

- Feasibility of reconstruction.
- Fitness for major surgery.
- Requirement for free tissue transfer.

Patients with borderline-resectable or unresectable disease **should not** enter this pathway.

Tumour mapping and surgical planning **should be documented** for future surgical reference.

3.2 Obtain Adequate Tissue

The diagnostic biopsy must provide sufficient tissue for:

- Histological confirmation of SCC.
- PD-L1 CPS assessment (this must be performed on a tissue biopsy and cannot be performed on cytology specimens).
- p16 testing where appropriate.

Inadequate biopsies may delay treatment initiation; therefore, efforts should be made to obtain biopsies of adequate size.

3.3 Request Full Staging

At diagnosis the surgeon should ensure timely completion of:

- Contrast-enhanced MRI or CT of head and neck.
- CT thorax.
- PET-CT when required by local pathways.
- Baseline blood investigations.

3.4 Early Referral to Oncology

Patients should be referred to the head and neck oncology team immediately after diagnostic confirmation.

This allows:

- Immunotherapy screening (for exclusion criteria see Appendix 1).
- Baseline assessment (multidisciplinary as indicated).
- Scheduling of neoadjuvant treatment.

4. MDT Requirements

Implementation of peri-operative immunotherapy requires a coordinated MDT pathway and a fully constituted MDT team.

Cases should be discussed at the first available MDT following completion of staging.

5. Pathology Requirements

Pathology departments should provide rapid turnaround of the diagnostic biopsy and the PD-L1 immunohistochemistry with reporting of CPS, to avoid delays in treatment initiation.

Required reports include:

Histological diagnosis

Confirmation of squamous cell carcinoma.

PD-L1 CPS

PD-L1 testing should be requested on the diagnostic biopsy specimen and reported before treatment planning. This should be locally performed or outsourced.

6. Neoadjuvant Treatment Pathway

6.1 Eligible patients should receive:

Pembrolizumab

Intravenous: 200 mg every 3 weeks or 400 mg 6-weekly

Or Subcutaneous: 395mg every 3 weeks or 790mg 6-weekly

6.2 Duration

6 weeks prior to surgery.

The surgeon must maintain careful oversight of surgical scheduling during this period, and surgical review after 3 weeks of treatment is recommended. Re-imaging preoperatively should be performed.

Surgery should be performed around the end of the six-week period following initiation of neoadjuvant treatment.

6.3 Surgical Booking

Flexibility in operating theatre scheduling and case reorganisation may be necessary to support timely surgery.

This is essential to prevent:

- Theatre delays.
- Reconstruction scheduling problems.

7. Surgery Following Pembrolizumab

Neoadjuvant pembrolizumab should not compromise delivery of definitive surgery.

The surgical procedure should follow standard oncological principles.

Surgical Objectives

- Complete tumour excision.
- Clear margins.
- Appropriate neck dissection.
- Reconstruction where indicated.

Surgeons should not reduce the extent of surgery solely because neoadjuvant therapy has been administered. Significant tumour shrinkage is rare, occurring in around 5% of patients. Clinical progression of disease can occur (approximately 10-15% of patients), in which case surgery should be adapted to take account of that. Radiological response is a poor predictor of pathological response.

8. Postoperative Pathology

The pathology report should adhere to RCP guidelines for minimum dataset for reporting of respective tumour sites. Definitive pathology must specifically document:

- Margin status
- Extranodal extension
- Pathological response to neo-adjuvant therapy (estimated % of viable tumour)

These factors determine postoperative risk stratification and adjuvant treatment selection. The choice between post-operative radiotherapy and chemoradiotherapy is based only on margin status and presence or absence of extranodal extension.

9. Adjuvant Therapy Coordination

The MDT should determine postoperative treatment following pathology review.

Low-Risk Disease

No positive margins or extranodal extension.

Treatment:

- Adjuvant radiotherapy.

High-Risk Disease

Positive margins and/or extranodal extension.

Treatment:

- Concurrent platinum based chemoradiotherapy.

Pembrolizumab Continuation

Patients continue pembrolizumab:

- During postoperative radiotherapy or chemoradiotherapy.
- Followed by maintenance pembrolizumab.

The treatment schedule consists of:

- Pembrolizumab given concurrently with postoperative radiation treatment.
- 36 weeks of additional adjuvant pembrolizumab.

10. Safety Monitoring

The MDT should establish clear immunotherapy toxicity pathways.

Potential common immune-related toxicities include:

- Pneumonitis.
- Hepatitis.
- Thyroid dysfunction.
- Colitis.
- Dermatological toxicity.
- Renal impairment.

However, many other toxicities are possible, and the treating team should have well-established pathways for referral for appropriate medical management.

Specialist nurses and oncology teams should provide rapid-access assessment pathways for toxicity management. AHPs/ CNS teams/ non-medical prescribers will require appropriate, ongoing training to safely recognise and manage treatment related toxicities.

11. Key Implementation Messages

- The MDT is responsible for early identification of eligible patients and preservation of surgical timelines.
- PD-L1 CPS testing must be requested at diagnosis on a tissue (not FNA) sample.
- Patients should enter a coordinated immunotherapy-surgery-radiotherapy pathway immediately after MDT approval.
- Treatment of patients with critical airways, borderline operable cancers or rapid tumour growth should not enter this pathway.
- Operating time should be undertaken at the end of the completion of six weeks of neoadjuvant treatment.
- Postoperative pathology reporting must be expedited to support timely adjuvant therapy.
- Radiotherapy or chemoradiotherapy should commence within six weeks of surgery.
- Close collaboration between surgeons, oncologists, pathologists and radiotherapy teams is essential to safely reproduce the benefits observed in the KEYNOTE-689 study.

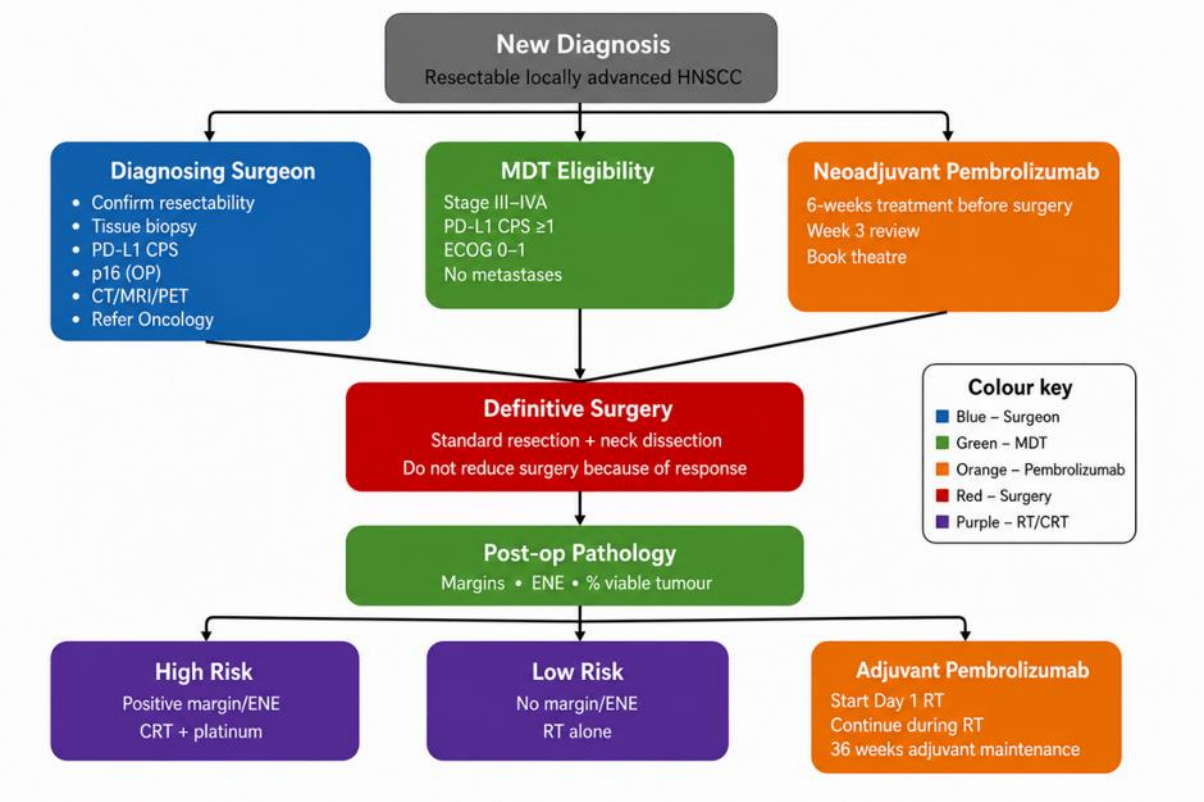

Figure 1. BAHNO Clinical Pathway for Delivery of Perioperative Pembrolizumab in Resectable Locally Advanced Head and Neck Squamous Cell Carcinoma

APPENDIX 1 Exclusion Criteria

In the trial protocol Participants were excluded from the KN-689 study if any of the following criteria applied:

1. Stage T4B and/or N3 HNSCC and/or distant metastases.

2. Cancer outside of the oropharynx, larynx, and hypopharynx or oral cavity, such as nasopharyngeal, sinus, other para-nasal, or other unknown primary HNC.

3. Pregnancy or breast feeding

4. Prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent in last 6 months

5. Prior radiotherapy treatment or systemic anti-cancer therapy for HNSCC

6. Received a live vaccine within 30 days.

7. Immunodeficiency, HIV, or receiving systemic steroid therapy (equivalent to dose >10 mg/day of prednisone) or any other form of immunosuppressive therapy.

8. Previous allogeneic tissue/solid organ transplant.

9. Active autoimmune disease or pneumonitis that has required systemic treatment in past 2 years.

10. Known history of Hepatitis B or C

11. Critical airway given risk of progression