PROTOCOL

The Clatterbridge Cancer Centre NHS Foundation Trust

Systemic Anti Cancer Therapy Protocol

Pembrolizumab
Head and Neck and Lung Cancer

PROTOCOL REF: MPHAPECOVHN
(Version No.: 1.2)

Approved for use:

Head and Neck Cancer

- FIRST-LINE treatment of metastatic or recurrent unresectable PD-L1 positive (1% or greater) squamous cell carcinoma of the head and neck.
- ECOG performance status of 0 or 1.

Non-Small Cell Lung Cancer (NSCLC)

First line indication

Locally advanced (Stage IIIB or IIIC) or metastatic NSCLC which expresses PD-L1 with a tumour proportion score (TPS) of 50% or greater and satisfies the following criteria:

- Non-squamous NSCLC which is negative for EGFR 19 or 21 mutation or ALK gene fusion **OR** squamous NSCLC (testing for EGFR 19 or 21 mutation or ALK gene fusion NOT a requirement).
- Prior treatment with checkpoint inhibitor immunotherapy is PERMITTED if discontinued or completed as part of adjuvant/neoadjuvant/maintenance therapy without disease progression AND at least 6 months elapsed between the date of the last immunotherapy treatment and the date of first diagnosis of relapse with recurrent or metastatic disease.
- ECOG performance status of 0 or 1.

Second line indication

NSCLC after **at least 2 cycles of platinum-based chemotherapy** for advanced/metastatic disease OR adjuvant therapy/neoadjuvant therapy/chemoradiotherapy that has progressed within 6 months of treatment. Eligibility is subject to the following criteria:

- All appropriate targeted treatments have been tried if the tumour is positive for an actionable genomic change in relation to EGFR or ALK or ROS1 or MET exon 14 or KRAS G12C or RET or BRAF V600 status.
- Prior treatment with checkpoint inhibitor immunotherapy is PERMITTED if discontinued or completed as part of adjuvant/neoadjuvant/maintenance therapy without disease progression AND at least 6 months elapsed between the date of the last immunotherapy treatment and the date of first diagnosis of relapse with recurrent or metastatic disease.
- ECOG performance status of 0 or 1.

******Blueteq registration is required for ALL indications******

Dosage:

Drug	Dosage	Route	Frequency	Duration of Treatment
Pembrolizumab	400mg (Flat dose)	IV Infusion	6 weekly	Disease progression or unacceptable toxicity or **on completion of 2 years in total duration,** whichever is first
OR				
Pembrolizumab	200mg* (Flat dose)	IV Infusion	3 weekly	Disease progression or unacceptable toxicity or **on completion of 2 years (35 cycles) in total duration,** whichever is first

* Where risk factors for toxicity are present e.g. pre-existing autoimmune disease or previous toxicity, the 3 weekly regimen may be used.*

Exclusions

- History of pneumonitis, organ transplantation, autoimmune disorders, HIV infection, myocarditis, active hepatitis B or C infection
- Active infection requiring systemic treatment
- Less than 4 weeks from major surgery
- History of clinically severe autoimmune disease (can proceed with immunotherapy if
- Well controlled autoimmune disease at the discretion of the clinical team, this needs to be documented on Meditech)

Extravasation risk:

Pembrolizumab is a monoclonal antibody- considered to be neutral.

Refer to the CCC policy for the '[Prevention and Management of Extravasation Injuries]'.

Dosing in renal and hepatic impairment (Prior to start of treatment ONLY/Baseline):

Renal	Pembrolizumab	GFR ≥ 10ml/min- proceed with treatment GFR < 10ml/min- limited data use with caution

Hepatic	Pembrolizumab	Administered with caution in patients with: Moderate (total bilirubin > 1.5 -3 × ULN and any AST) or Severe (total bilirubin > 3 × ULN and any AST*) hepatic impairment. * Within normal limits or high

Patient Counselling Points

Women of childbearing potential should use effective contraception throughout treatment and for at least 5 months following the last dose of pembrolizumab.

Contact the triage team for the following:

- New or worsening cough, chest pain or shortness of breath
- Diarrhoea or severe abdominal pain (with or without blood/mucous)
- Jaundice, severe nausea or vomiting, or easy bruising or bleeding
- Persistent or unusual headache, extreme weakness, dizziness or fainting, or vision changes
- Monitor for signs of infection / sepsis

Interactions:

No formal pharmacokinetic drug interaction studies have been conducted with pembrolizumab. Since pembrolizumab is cleared from the circulation through catabolism, no metabolic drug-drug interactions are expected.

The use of systemic corticosteroids or immunosuppressants before starting pembrolizumab should be avoided because of their potential interference with the pharmacodynamic activity and efficacy of pembrolizumab. However, systemic corticosteroids or other immunosuppressants can be used after starting pembrolizumab to treat immune-related adverse reactions.

Please consult SmPC for full information on interactions.

Administration:

Day	Drug	Dose	Route	Frequency	Diluent and rate
1	Sodium chloride 0.9%	250mL	IV	Prior to each Atezolizumab infusion.	Flush
1	**Pembrolizumab**	**400mg**	**IV**	6 weekly	100mL sodium chloride 0.9%. Infused over 30 minutes in a non-

					pyrogenic line with a 0.2 micron filter
OR					
1	**Pembrolizumab**	**200mg***	**IV**	3 weekly	100mL sodium chloride 0.9%. Infused over 30 minutes in a non-pyrogenic line with a 0.2 micron filter

Disease progression or unacceptable toxicity or **on completion of 2 years in total duration,** whichever is first

* Where risk factors for toxicity are present e.g. pre-existing autoimmune disease or previous toxicity, the 3 weekly regimen may be used.*

Routine prophylaxis against infusion related reactions is not required. However, monitor during the infusion and treatment given if necessary (antihistamines, steroids etc.). Please refer to the CCC Hypersensitivity; Management Prevention Policy

Main Toxicities:

For full details on assessment and management of immune-related toxicities refer to CCC Immuno-Oncology toxicity specific guidance for adverse event management.

Immune related toxicities	
Immune-Mediated Pneumonitis Pneumonitis occurred in 3% of melanoma patients (including G3 in 0.2%).	Monitor patients for signs and symptoms and evaluate with radiographic imaging and administer corticosteroids for toxicities of grade 2 or above.
Immune-Mediated Colitis	Monitor patients for signs and symptoms and administer corticosteroids for grade 2 or greater.
Other Immune-Mediated Toxicities: Hepatitis Hypophysitis Nephritis Hyperthyroidism or Hypothyroidism Less frequently: Exfoliative dermatitis, uveitis, arthritis, myositis, pancreatitis, haemolytic anaemia, Guillain-Barré syndrome	Monitor LFTs, biochemistry, cortisol, TFTs and blood glucose, consider corticosteroids for grade 2 or greater.
Other non-immune adverse events: Fatigue, anaemia Cough, dyspnoea Nausea, decreased appetite Pruritis, rash Constipation, diarrhoea Arthralgia	Symptomatic management for grade 1 with close monitoring
Laboratory abnormalities: Hyponatraemia, hypocalcaemia, hyperglycaemia, hypertriglyceridaemia	Monitor at each cycle and rule out immune-medicated reaction

Investigations and treatment plan:

If suspicion of endocrinopathies: request TSH, T4, T3, ACTH, cortisol, LH, FSH, testosterone (men) and prolactin (women)

	Pre	Cycle 1	Cycle 2	Home treatment if eligible	Cycle 3	Ongoing
Informed Consent	x					
Clinical Assessment	x		x			Then every 12 weeks or as clinically indicated
SACT Assessment (to include PS and toxicities)	x	x	x		x	Every cycle
OTR/ Go-ahead	x		x		x	Every cycle
Immunotherapy bloods as per Meditech order set: FBC, U&E/renal profile, Magnesium, LFTs (ALT, AST and Bilirubin), TFTs, cortisol, blood glucose, LDH, CRP	x	x	x		x	Every cycle

Lipid profile (cholesterol)	x					At baseline then if clinically indicated
Fatigue profile as per Meditech order set: B12, folate, Iron profile, vitamin D, Zinc, Testosterone (men only), ESR	x					At baseline then if clinically indicated
Full set of observations (*BP, heart rate, temperature, respiratory rate and O_2 sats*)		x				At baseline then if clinically indicated
Creatinine Clearance (Cockcroft and Gault)	x					Every cycle only if baseline CrCL <40ml/min or creatinine increases above 1.5x upper limit of normal or baseline
CT scan	x					Every 12 weeks or as clinically indicated
Trop-T, CK, pro-BNP	x					At baseline (refer to 'Pre-assessment Baseline Cardiac Pathway' guidance) and thereafter as clinically indicated (ECG to be reviewed by ANP or ECG clinic or clinical team)
ECG	x					

Weight recorded	x	x	x		x	Every cycle
Height recorded	x					

Pregnancy test if applicable.

Dose Modifications and Toxicity Management:

- Dosing delay or discontinuation may be required based on individual safety and tolerability.
- Guidelines for permanent discontinuation or withholding of doses are contained in dose modifications.
- Detailed guidelines for the management of immune-related adverse reactions are provided in the CCC Immuno-Oncology toxicity specific guidance for adverse event management.

Treatment Threshold

Administer treatment on day 1 if:

Platelets	Neutrophils	Serum Creatinine	Bilirubin	AST/ALT	Alkaline Phosphatase	TSH and Free T4
≥ 75 x 10^9/L	≥ 1.0 x 10^9/L	≤ 1.5 ULN or baseline	<3 x ULN	<5 x ULN	<5 x ULN	Within range or no change from base line

ULN = upper limit of normal

Platelets must be within normal range prior to Cycle 1.

Toxicity management:

Detailed guidelines are provided in the CCC clinical network immunotherapy acute oncology guidelines. Systemic high-dose corticosteroid with or without additional immunosuppressive therapy may be required for management of severe immune-related adverse reactions.

Toxicity Grade	Action
Grade 1 Mild	Continue treatment increase monitoring and provide symptomatic treatment.
Grade 2 Moderate	Withhold treatment until resolved to ≤ grade 1. Refer to Immuno-Oncology toxicity specific guidance for adverse event management.
Grade 3 and Grade 4 Severe	Withhold treatment. Treatment will be permanently discontinued for any unresolving grade 3-4, severe or life-threatening adverse reaction at the treating clinician's discretion. Refer to Immuno-Oncology toxicity specific guidance for adverse event management.

References:

1. Burtness, B., Harrington, K.J., Greil, R., Soulières, D., Tahara, M., De Castro, G., Psyrri, A., Rotllan, N.B., Neupane, P.C., Bratland, Å. and Fuereder, T. (2018). KEYNOTE-048: Phase III study of first-line pembrolizumab (P) for recurrent/metastatic head and neck squamous cell carcinoma (R/M HNSCC). *Annals of Oncology*, 29, p.viii729.
2. Herbst, R.S., Baas, P., Kim, D.W., Felip, E., Pérez-Gracia, J.L., Han, J.Y., Molina, J., Kim, J.H., Arvis, C.D., Ahn, M.J. and Majem, M., (2016). Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. *The Lancet*, 387(10027), pp.1540-1550.
3. Leighl, N.B., Hellmann, M.D., Hui, R., Carcereny Costa, E., Felip, E., Ahn, M.J., Eder, J.P., Balmanoukian, A.S., Aggarwal, C., Horn, L. and Patnaik, A. (2017). KEYNOTE-001: 3-year overall survival for patients with advanced NSCLC treated with pembrolizumab. pp 9011-9011
4. NICE TA (TA428): Pembrolizumab for treating PD-L1-positive non-small-cell lung cancer after chemotherapy. Published: 11 January 2017.
5. NICE TA (TA531): Pembrolizumab for untreated PD-L1-positive non-small-cell lung cancer. Published: 18th July 2018.
6. NICE TA (TA661): Pembrolizumab for untreated metastatic or unresectable recurrent head and neck squamous cell carcinoma. Published: 25 November 2020.
7. Keytruda® 25 mg/mL concentrate for solution for infusion, Summary of Product Characteristics, Merck Sharp and Dohme (UK) Limited. Available from www.medicines.org.uk/emc/medicine. Last updated 1st February 2022.

Circulation/Dissemination

Date added into Q-Pulse	2nd February 2023
Date document posted on the Intranet	N/A

Version History

Date	Version	Author name and designation	Summary of main changes
December 2020	1.1	**Lisa Dobson** **H&N SRG Pharmacist**	Routine Protocol update
June 2023	1.2	**Hala Ghoz** **Lung SRG Pharmacist**	**Palliative lung cancer indications added to H&N protocol**