PEMBROLIZUMAB (Keytruda)

INDICATION (ICD10) C18, C20, C34, C43, C49

Check the most recent Blueteq eligibility criteria before prescribing. Blueteq registration required. (www.england.nhs.uk/publication/national-cancer-drugs-fund-list/) (PEMB1) (PEMB2) (PEM7) (PEM9Ba) (PEMB9b) (PEMB9c) (PEMB12) (PEMB14) (PEMB19) (PEMB20) (PEMB28) (PEMB31)

1. Pembrolizumab monotherapy for the treatment of PD-L1 positive locally advanced or metastatic non-small cell lung cancer after chemotherapy. The treatment of PD-L1-positive (TPS ≥1%) non small-cell lung (squamous or non-squamous) cancer without active brain metastases or leptomeningeal metastases that recurred after previous potentially curative local management of NSCLC with surgery/chemoradiotherapy/radiotherapy which has progressed after treatment with at least two cycles of platinum-containing doublet chemotherapy for stage IIIB, IIIC or IV or recurrent NSCLC after previous potentially curative local management or has progressed within 6 months of completing platinum-based adjuvant or neoadjuvant therapy or chemoradiation and if appropriate that the patient has had all appropriate targeted treatments if the patient has a tumour which 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, has not received prior treatment with an anti PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-Cytotoxic T-lymphocyte associated antigen-4 (CTLA-4) antibody unless the patient discontinued or completed checkpoint inhibitor immunotherapy 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. PS 0 or 1. (TA428)
2. Pembrolizumab monotherapy for the first line treatment of untreated (not received previous systemic therapy for locally advanced or metastatic non-small cell lung cancer (squamous or non-squamous) which expresses PD-L1 with a tumour proportion score of at least 50% w. Stage IIIB, IIIC or IV NSCLC or has disease that has recurred after previous potentially curative local management of NSCLC with surgery/chemoradiotherapy/radiotherapy, has not received any previous systemic therapy for NSCLC or the patient completed the last treatment with chemotherapy or chemoradiotherapy or checkpoint inhibitor immunotherapy as part of adjuvant/neoadjuvant/maintenance therapy at least 6 months prior to the first diagnosis of locally recurrent or metastatic disease, not received prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-Cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4)) antibody unless the patient discontinued/completed treatment with checkpoint inhibitor immunotherapy as part of adjuvant/neoadjuvant/maintenance therapy without disease progression and at least 6 months elapsed between the date of last immunotherapy treatment and the date of first diagnosis of relapse with recurrent or metastatic disease, without active brain metastases or leptomeningeal metastases. PS 0 or 1. (TA531)
3. Pembrolizumab monotherapy for previously untreated metastatic or unresectable, head and neck squamous cell carcinoma (HNSCC), without symptomatically active brain metastases or leptomeningeal metastases, that is not amenable to curative intent with local therapy (surgery and/or radiation therapy with or without chemotherapy), recurrent PD-L1 positive (Combined Positive Score (CPS) is ≥1)The patient has not received prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-Cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody. PS 0 or 1 and would otherwise be potentially fit for 1st line combination chemotherapy. (TA661)
4. Pembrolizumab for adjuvant treatment of melanoma with high risk of recurrence treatment naïve to systemic therapy for malignant melanoma and in particular has not previously received any BRAF V600 inhibitors or MEK inhibitors or immunotherapy with any check point inhibitors. Complete resection has taken place for stage III disease and this has been done with either a sentinel lymph node biopsy ('sentinel lymphadenectomy') or when indicated with a completion lymph node dissection and Adjuvant pembrolizumab will commence no more than 3 months after the date of surgery which documented the complete resection of stage III melanoma.
   PS 0 or 1. (TA766)

5. Pembrolizumab for the adjuvant treatment of newly diagnosed and completely resected stage IIB or stage IIC malignant melanoma. Treatment naïve to any systemic therapy for malignant melanoma and in particular has not previously received any immunotherapy with any check point inhibitors or BRAF V600 inhibitors or MEK inhibitors. (NHS England does not commission any adjuvant immunotherapy with checkpoint inhibitors for stage III disease in patients who have previously received adjuvant immunotherapy for stage IIB or IIC disease). PS 0 or 1. (TA837)
6. Pembrolizumab monotherapy for treating unresectable or advanced malignant melanoma, at the time of starting pembrolizumab, the patient is/was treatment-naïve to systemic therapy or has/had previously only received BRAF/MEK-targeted therapy or ipilimumab monotherapy or both BRAF/MEK-targeted treatment and ipilimumab monotherapy and has/had not received prior treatment with any of the following: anti-PD-1, anti-PD-L1, anti-PD-L2 and anti-CD137 treatments unless the patient has received adjuvant immunotherapy with nivolumab or pembrolizumab in which case the patient must have relapsed after the discontinuation of such adjuvant immunotherapy. PS to be fit to receive treatment with immunotherapy. (TA366)
   There is the future opportunity for patients continuing in a stable disease or a response disease state after 2 or more years of planned treatment to choose to discontinue pembrolizumab and then to re-start pembrolizumab on disease progression as the next systemic therapy and should this option be chosen that both the date of discontinuation must be registered on the second part of form and the application to re-start pembrolizumab be made on the third part of form.
7. Pembrolizumab for the 1st line treatment of patients with metastatic colorectal cancer exhibiting microsatellite instability-high (MSI-H) or mismatch repair deficiency (dMMR), wild type or mutant RAS status, wild type or mutant BRAF status has been determined on the patient's tumour. Has not received previous systemic therapy for metastatic colorectal cancer unless this was given with neoadjuvant intent (may have previously received neoadjuvant systemic therapy for non-metastatic disease and/or adjuvant chemotherapy after surgery.) but not received prior treatment with an anti-PD-1, anti-PD-L2, anti-CD137, or anti-Cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody. No symptomatic brain or leptomeningeal metastases. PS 0 or 1. (TA709)
8. Pembrolizumab monotherapy for adjuvant treatment after complete tumour resection of renal cell carcinoma in adult patients at increased risk of recurrence following nephrectomy or following nephrectomy and resection of all metastatic disease. At first presentation with RCC, the patient had either loco-regional disease only or had both loco-regional and distant metastatic (M1) disease) has undergone a partial nephro-protective or radical nephrectomy and complete resection of all known metastatic disease if present with all surgical excision margins being negative i.e. a R0 resection(s) has/have taken place, and radiologically re-staged after completion of surgery and has no evidence of residual or metastatic disease, has an increased risk of recurrence of RCC after surgery as defined in the 3 categories of 'intermediate-high' risk, 'high' risk and 'M1 with no evidence of disease'. No more than 12 weeks have elapsed since the date of nephrectomy or metastasectomy. Has not received prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-Cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody or with any other systemic therapy for RCC. PS 0 or 1. (TA830)
9. Pembrolizumab monotherapy for adjuvant treatment after complete tumour resection in adult patients with UICC/AJCC 8th edition stage IIA or IIB or IIIA or N2 only IIIB non-small cell lung cancer, had M0 disease prior to surgery and has undergone a complete resection of the primary NSCLC with all surgical margins negative for tumour i.e. a R0 resection has taken place, and whose disease has not progressed on recently completed adjuvant platinum based (maximum 4 cycles) chemotherapy, which started within 12 weeks of resection, and continues to have no evidence of residual metastatic disease. The patient has not received any neoadjuvant chemotherapy for this NSCLC or any prior planned radiotherapy. (TA1037)
10. Pembrolizumab monotherapy for the subsequent treatment of patients with previously treated unresectable or metastatic biliary tract cancer exhibiting microsatellite instability-high (MSI-H) or mismatch repair deficiency (dMMR). Has progressive disease during or following the most recent

chemotherapy, but has NOT received prior treatment with an anti-PD-1, anti-PD-L2, anti-CD137, or anti-Cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody. PS 0 or 1 (TA914)

REGIMEN (42 day) SC – recommended regimen
Day 1 PEMBROLIZUMAB 790mg subcutaneous* (4.8ml) over 2 minutes

*Into the thigh or abdomen, avoiding the 5cm area around the navel

REGIMEN (42 day) IV
Day 1 PEMBROLIZUMAB 400mg in 100ml sodium chloride IV infusion over 30 minutes

CYCLE FREQUENCY AND NUMBER OF CYCLES
Formal medical review as to whether pembrolizumab treatment should continue will occur at least:
Lung adjuvant - – by the end of the 2nd month of treatment
Lung metastatic- by the end of the first 6 weeks of treatment
Melanoma - by the end of the first 9 weeks of treatment,
Colorectal – by the end of the 2nd month of treatment
Renal – by the end of the 3rd month of treatment
Biliary tract - by the end of the 2nd month of treatment

Colorectal - every 42 days until disease progression up to 17 cycles (maximum 2 years)
Head and neck - every 42 days until disease progression up to 17 cycles (maximum 2 years)
Lung adjuvant - every 42 days up to 9 cycles (12 months)
Lung metastatic- every 42 days until disease progression up to 17 cycles (maximum 2 years)
Melanoma adjuvant – every 42 days up to 9 cycles (12 months)
Melanoma metastatic - every 42 days until disease progression or intolerance
Renal adjuvant – every 42 days up to 9 cycles (12 months)
Biliary tract - every 42 days until disease progression up to 17 cycles (maximum 2 years)

REGIMEN (21 day then 42 day) IV
Cycles 1 and 2
Days 1 and 22 PEMBROLIZUMAB 200mg in 100ml sodium chloride IV infusion over 30 minutes

Cycles 3 onwards (number of cycles depends on indication)
Day 1 PEMBROLIZUMAB 400mg in 100ml sodium chloride IV infusion over 30 minutes

CYCLE FREQUENCY AND NUMBER OF CYCLES
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Lung adjuvant - – by the end of the 2nd month of treatment
Lung metastatic - by the end of the first 6 weeks of treatment
Melanoma - by the end of the first 9 weeks of treatment,
Colorectal – by the end of the 2nd month of treatment
Renal – by the end of the 3rd month of treatment

Colorectal - until disease progression up to total maximum 2 years ie 4 doses 3 weekly then 15 doses 6 weekly
Head and neck - until disease progression up to total maximum 2 years ie 4 doses 3 weekly then 15 doses 6 weekly
Lung adjuvant - every 42 days up to 9 cycles (12 months)
Lung metastatic - until disease progression up to total maximum 2 years ie 4 cycles 3 doses then 15 doses 6 weekly
Melanoma adjuvant – 4 doses 3 weekly then 7 doses 6 weekly (12 months)

Melanoma metastatic - until disease progression or intolerance ie 4 doses 3 weekly then 6 weekly dosing
Renal adjuvant – 4 doses 3 weekly then 7 doses 6 weekly (12 months)
Biliary tract - until disease progression up to total maximum 2 years ie 4 doses 3 weekly then 15 doses 6 weekly
Can be given 3 weekly SC or IV if necessary (see SPC for details including 3 weekly dose)

ADMINISTRATION
Pembrolizumab SC - withdraw the required volume using a transfer needle (18-21G recommended). To avoid needle clogging, change the needle to a 25-30G, 13 mm hypodermic injection needle immediately prior to SC injection.
Do not administer other medicinal products for injection at the same site as the pembrolizumab.

ANTI-EMETICS
Minimal risk

CONCURRENT MEDICATION REQUIRED

Pembrolizumab	None required

EXTRAVASATION AND TYPE OF LINE / FILTERS
Pembrolizumab – neutral
Use low protein binding 0.2 to 5micron in-line or add-on filter
Peripheral line

INVESTIGATIONS
Blood results required before SACT administration
FBC, U&E and LFTs every cycle
Neutrophils x 10^9/L ≥1.5
Platelets x 10^9/L ≥100
Thyroid function* baseline, then every cycle
Random cortisol baseline, then every cycle (or as specified in Trust guideline)
Random glucose every cycle
Hba1c baseline
Baseline weight every cycle

MAIN TOXICITES AND ADVERSE REACTIONS

Pembrolizumab	Immune related toxicities - pneumonitis, colitis or hepatitis etc Pembrolizumab SC skin reactions at site of administration route

INTERACTIONS WHICH MAY REQUIRE DOSE MODIFICATIONS
(not exhaustive list check SPC/BNF/Stockleys)

Pembrolizumab	-

DOSE MODIFICATIONS
Non-haematological
Pembrolizumab
Immune-related adverse reactions - refer to TV immune-oncology agent immune related adverse event clinical guideline.
If the drug-related toxicity does not resolve to grade 0-1 within 12 weeks after onset of toxicity, discontinuation is recommended.

Hepatic impairment
Pembrolizumab
No dose adjustment is needed

Renal impairment
Pembrolizumab
No dose adjustment is needed

REFERENCES
1. Herbst, R et al; Lancet 2016; 387 (10027): 1540–1550 (NSCLC)
2. Reck, M et al; NEJM 2016; 375: 1823–1833 (NSCLC)
3. Burtness, B et al ; Lancet 2019; 394 (10212): 1915–1928 (H&N)
4. Ribas, A et al; Lancet 2015;16 (8): 908–918 (melanoma)
5. Robert, C et al ; NEJM 2015; 372: 2521–2532 (melanoma)
6. Eggermont, A et al ; NEJM 2018; 378: 1789–1801 (melanoma, adjuvant)