Indication	Pembrolizumab in combination with paclitaxel is indicated for the treatment of previously untreated locally advanced unresectable or metastatic triple negative breast cancer in patients with PD-L1 expression test results of immune cell staining (IC) <1% and a combined positive score (CPS) of 10 or more. No previous anti-PD-1/PD-L1 treatment can have been received, unless it was for neoadjuvant or adjuvant therapy, as long as there was no disease progression during such treatment and for at least 12 months after completion of anti-PD-1/PD-L1 therapy. Note: if the PD-L1 immune cell staining (IC) result is >/=1%, the patient must not be treated with pembrolizumab.
Treatment Intent	Palliative
Frequency and number of cycles	Paclitaxel on days 1, 8 and 15 of a 28-day treatment cycle Given with Pembrolizumab* 200mg every 3 weeks or 400mg every 6 weeks. Continue until disease progression or unmanageable toxicity or patient choice, however Pembrolizumab must be stopped after 2 years of treatment (or after 35 x 3-weekly cycles or its equivalent if 6-weekly pembrolizumab is used) (paclitaxel may continue). NB: Pembrolizumab may be continued as a single agent if paclitaxel has to be discontinued due to toxicity. A formal medical review must be scheduled to occur by the end of the first 8 weeks of treatment to assess tolerance and whether to continue with treatment or not. *When pembrolizumab and paclitaxel are administered on the same day, give pembrolizumab first.
Monitoring Parameters pre-treatment	• **Virology screening:** All new patients referred for systemic anti-cancer treatment should be screened for hepatitis B and C and the result reviewed prior to the start of treatment. Patients not previously tested who are starting a new line of treatment, should also be screened for hepatitis B and C. Further virology screening will be performed following individual risk assessment and clinician discretion. • Monitor FBC, U&Es, LFTs prior to each dose of paclitaxel. • Monitor FBC, U&Es, LFTs, LDH, Ca++ and glucose prior to each dose of pembrolizumab. • **Day 1 Paclitaxel:** If neutrophils >/=1.5 and PLT >/=100 continue with paclitaxel. Otherwise delay paclitaxel one week. • **DAY 8 and 15 Paclitaxel**: If neutrophils >/=1 and PLT >/=100 continue with paclitaxel. Otherwise omit paclitaxel. • On the day of pembrolizumab treatment, if neutrophils >/=1.0 and PLT >/=75 continue with pembrolizumab, otherwise d/w consultant. • Thyroid function must be assessed at baseline then every 6-8 weeks or as clinically indicated. • Cortisol monitoring should be undertaken in line with ESMO immunotherapy toxicity guidance available on KMCC website (see link below). Cortisol level should not be taken within 24 hours of the last steroid dose. • The patient must have no symptomatically active brain metastases or leptomeningeal metastases. • **Hepatic impairment:** **Pembrolizumab** – Prior to treatment: No dose adjustment is needed for patients with mild or moderate hepatic impairment. Pembrolizumab has not been studied in patients with severe hepatic impairment (bilirubin > 1.5 x ULN, ALT, AST > 2.5 x ULN in the absence of liver metastases at baseline). During treatment: For immune related hepatitis see immune related toxicity guidance below.

Paclitaxel - If bilirubin < 1.25 x ULN and transaminase < 10 x ULN, dose at full dose. Otherwise consider dose reduction, not recommended in severe hepatic impairment.

- **Renal impairment:**
  Pembrolizumab - No specific dose adjustment is necessary in patients with mild to moderate renal impairment. Severe renal impairment d/w consultant.
  Paclitaxel – no dose reduction necessary.
- **Immune-related adverse reactions** may appear during or after treatment. The most common immune-related reactions are: pneumonitis, colitis, nephritis, hepatitis, symptomatic hypophysitis, hyperthyroidism, hypothyroidism and type 1 diabetes. The following additional, immune related adverse reactions have been reported in patients receiving pembrolizumab: uveitis, arthritis, myositis, pancreatitis, severe skin reactions, myasthenic syndrome, encephalitis, Guillian-Barre syndrome, optic neuritis, rhabdomyolysis, sarcoidosis, myocarditis, haemolytic anaemia and partial seizures arising in a patient with inflammatory foci in brain parenchyma.
  See guidelines for management of immune-related adverse reactions following immunotherapy: https://www.kmcc.nhs.uk/medicines-and-prescribing-incorporating-sact-pathways/immunotherapy/
  Cases of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), some with fatal outcome, have been reported. For signs or symptoms of SJS or TEN, pembrolizumab should be withheld and the patient should be referred to a specialised unit for assessment and treatment. If SJS or TEN is confirmed, pembrolizumab should be permanently discontinued.
- **Infusion-related reactions:**
  If the infusion related reaction can be attributed to a particular agent, treat as follows:
  Pembrolizumab: Severe infusion-related reactions have been reported in patients receiving pembrolizumab. For severe infusion reactions (grade 3-4), infusion should be stopped and pembrolizumab permanently discontinued. Patients with mild or moderate infusion reaction may continue to receive pembrolizumab with close monitoring; premedication with antipy-retic and antihistamine may be considered.
  Paclitaxel: Patients developing hypersensitivity reactions may be re-challenged with full dose Paclitaxel following prophylactic medication (e.g. famotidine 40mg po given 4 hours prior to treatment plus hydrocortisone 100mg iv and chlorphenamine 10mg iv 30 minutes prior to treatment), then give paclitaxel over 3-6 hours (i.e. starting at over 6 hours and gradually increase rate if possible). If patients experience no hypersensitivity reactions after the first two doses of paclitaxel, remove pre-medication with dexamethasone (unless needed as anti-emetic) and chlorphenamine from dose 3 onwards.
- **Management of adverse reactions and dose adjustments:**
  Dose Modification:
  Pembrolizumab - dose reductions are not recommended. Dosing delay or discontinuation may be required based on individual safety and tolerability.
  Pembrolizumab may be restarted within 12 weeks after last dose of pembrolizumab if the adverse reaction recovers to Grade ≤ 1 and corticosteroid dose has been reduced to ≤ 10 mg prednisone or equivalent per day
  Paclitaxel - Dose reduce by 20% in the event of grade >/= 2 neuropathy and consider delay until recovery to </= grade 1. Consider omitting Paclitaxel in event of recurrent grade >/=3 neuropathy OR recurrent or persistent grade >/= 2 neuropathy following a dose reduction. Dose reduction of paclitaxel should be considered if any other grade 3 or 4 non-haematological toxicity or repeat appearance of grade 2 (except N&V and alopecia). Delay until resolution of toxicity to </= grade 1.
  Pembrolizumab may be continued as a single agent if paclitaxel has to be discontinued due to toxicity.

	• **Common drug interactions (for comprehensive list refer to BNF/SPC):** **Pembrolizumab**: The use of systemic corticosteroids or immunosuppressants before starting pembrolizumab should be avoided; dexamethasone is permitted as prescribed within this protocol. Systemic corticosteroids or other immunosuppressants can be used after starting pembrolizumab to treat immune-related adverse reactions Vaccines should only be given where the benefit outweighs the risk and after discussion between consultant and patient. **Paclitaxel**: Caution should be exercised when administering paclitaxel concomitantly with medicines known to inhibit either CYP2C8 or CYP3A4 (e.g. ketoconazole, erythromycin, fluoxetine, clopidogrel, cimetidine, ritonavir and nelfinavir); toxicity may be increased. CYP2C8 or CYP3A4 inducers (e.g. rifampicin, carbamazepine, phenytoin, efavirenz, nevirapine) may reduce efficacy. • **Driving & using machines:** Pembrolizumab may have a minor influence on the ability to drive and use machines. Fatigue has been reported following administration of pembrolizumab. • Each patient should be given a copy of the **Keytruda ® patient alert card** at each cycle. Patients must be advised to contact the oncology team or the 24-hour hot-line immediately if they experience any side effect, as some side effects worsen rapidly. Prompt management of side effects can ensure that the patient continues with treatment. • **Missed dose:** If a planned dose of pembrolizumab is missed, it should be administered as soon as possible. The schedule of administration must be adjusted to maintain the appropriate interval between doses.
References	SPC accessed online 31.10.2023 KMCC protocol BRE-087 V2

NB For funding information, refer to CDF and NICE Drugs Funding List

Pembrolizumab
Repeat every 21 days

Day	Drug**	Dose	Route	Infusion Duration	Administration
1	Metoclopramide	20mg	PO		Stat Omit if given with paclitaxel (antiemetics already included in paclitaxel regimen)
	PEMBROLIZUMAB	**200mg**	IV	30min	In 100ml Sodium Chloride 0.9% via in-line low- protein binding 0.22 microns filter. Flush the line with sodium chloride 0.9% for injection at the end of the infusion.
TTO	Drug	Dose	Route	Directions	
Day 1	Metoclopramide	10mg	PO	Up to TDS PRN (max. 30mg per day including 20mg pre-chemo dose). Do not take for more than 5 days continuously. Omit if dispensed as TTO with paclitaxel (antiemetics already included in paclitaxel regimen)	

***NB see eprescribing system for order of administration of drugs when given in combination*

Alternative dosing schedule of Pembrolizumab
Repeat every 42 days

Day	Drug**	Dose	Route	Infusion Duration	Administration
1	Metoclopramide	20mg	PO		Stat Omit if given with paclitaxel (antiemetics already included in paclitaxel regimen)
	PEMBROLIZUMAB	**400mg**	IV	30min	In 100ml Sodium Chloride 0.9% via in-line low- protein binding 0.22 microns filter. Flush the line with sodium chloride 0.9% for injection at the end of the infusion.
TTO	Drug	Dose	Route	Directions	
Day 1	Metoclopramide	10mg	PO	Up to TDS PRN (max. 30mg per day including 20mg pre-chemo dose). Do not take for more than 5 days continuously. Omit if dispensed as TTO with paclitaxel (antiemetics already included in paclitaxel regimen)	

***NB see eprescribing system for order of administration of drugs when given in combination*

Paclitaxel
Repeat every 28 days

Day	Drug**	Dose	Route	Infusion Duration	Administration
1,8 and 15	**Give pre-meds 30 minutes prior to paclitaxel** NB: If patients experience no hypersensitivity reactions after the first two doses of paclitaxel, remove pre-medication with dexamethasone (unless needed as anti-emetic) and chlorphenamine from dose 3 onwards.				
	Dexamethasone	8mg	IV	bolus	
	Chlorphenamine	10mg	IV	bolus	Over 3 min through a fast running Sodium chloride 0.9% intravenous infusion
	Metoclopramide	20mg	IV	bolus	
	PACLITAXEL	**90mg/m²**	IV	Over 1 hour	Diluted in 250ml sodium chloride 0.9% (non-PVC bag and non PVC administration set) Via in-line 0.22micron filter Flush with sodium chloride 0.9%
TTO	Drug	Dose	Route	Directions	
1,8 and 15	Metoclopramide	10mg	PO	3 times a day for 3 days after paclitaxel, then 10mg up to 3 times a day as required. (max. 30mg per day including 20mg pre-chemo dose) Do not take for more than 5 days continuously.	
	Dexamethasone	4mg	PO	OM for 2 days starting the day after paclitaxel dose. Take with or just after food, or a meal.	

***NB see eprescribing system for order of administration of drugs when given in combination*