Indication	Pembrolizumab in combination with chemotherapy for untreated locally advanced or early stage **triple negative breast cancer** at high risk of recurrence (T1cN1-2 OR T2-4N0-2) as **neoadjuvant** treatment and then continued as **adjuvant** pembrolizumab monotherapy after definitive surgery and in the absence of disease progression. The patient cannot have received prior treatment with an anti-PD-1, anti-PD-L2, anti-CD137, or anti-Cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody unless the patient has received neoadjuvant/adjuvant pembrolizumab in a company early access scheme for this same indication.
Treatment Intent	Neo adjuvant: Pembrolizumab in combination with chemotherapy. Adjuvant: Pembrolizumab monotherapy.
Frequency and number of cycles	**Neo-Adjuvant:** Pembrolizumab with weekly paclitaxel and weekly carboplatin repeated every 21 days for 4 cycles. Followed by Pembrolizumab with EC repeated every 21 days for 4 cycles. **Adjuvant:** (treatment to commence within 2 months of surgery) Pembrolizumab 400mg repeated every 42 days* for 5 cycles. *pembrolizumab can be given at a dose of 200mg every 21 days (for 9 cycles) if there is a clinical requirement. NB in the event of disease progression during or at the end of neo-adjuvant therapy treatment should be discontinued. In the event of unacceptable toxicity or patient choice treatment should be stopped. A formal medical review must be scheduled to take place by the end of the first 6 weeks of treatment to review tolerance and whether to continue treatment.
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. • Consider using actual BSA. • **CYCLES 1-4** • ECG should be checked prior to cycle 1 and undertake ECHO/MUGA at baseline if clinically indicated. • Monitor FBC, U&Es, LFTs, LDH, Ca++ and glucose prior to day 1 of each cycle. • Monitor FBC, U&E and LFTs on **day 8 and 15**. • EDTA/DPTA or estimated CrCl using C+G should be used to measure GFR prior to cycle 1. CrCl must be >/=30ml/min for carboplatin. Repeat EDTA if CrCl drops by 25% during carboplatin treatment. • If neuts <1 or PLT <100, delay D1 by 1 week or omit day 8 or 15. Consider dose reduction for subsequent cycles. If neuts >/=1 and PLT>/=100 continue with treatment. • Thyroid function must be assessed at baseline then every 6 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. • **CYCLES 5-8** • Monitor FBC, LFT, U&E, LDH, Ca++ and glucose at each cycle. • If neuts <1 or PLT <100 delay by 1 week. If neuts >/= 1 and PLT>/= 100 continue with treatment.

- Thyroid function must be assessed every 6 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.
- **Cycles 9-13**
- Monitor FBC, U&Es, LFTs, LDH, Ca++ and glucose at each cycle.
- If PLT <75 or neuts <1.0 d/w consultant
- Thyroid function must be assessed every 6 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.
- **Dose reductions:**
  - **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.
  - Dose reduce **paclitaxel** by 20% in the event of >/= grade 2 neuropathy and consider delay until recovery to </= grade 1.
  - Consider omitting paclitaxel in the event of recurrent >/= grade 3 neuropathy OR recurrent or persistent >/= grade 2 neuropathy following dose reduction.
  - Dose reduction of chemotherapy 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.
- **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.
  - During treatment: For immune related hepatitis see immune related toxicity guidance below.
  - **Carboplatin**: No dose adjustment required.
  - **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.
  - **Epirubicin:** if bilirubin is 24-51 µmol /L give 50%, if bilirubin is 52-85µmol/L give 25%, if bilirubin is >85µmol/L omit.
  - **Cyclophosphamide:** No dose adjustment for mild or moderate impairment. Severe d/w consultant.
- **Renal impairment:**
  - **Pembrolizumab:** No specific dose adjustment is necessary in patients with mild to moderate renal impairment. Severe renal impairment d/w consultant, pembrolizumab has not been studied in patients with CrCl < 30ml/min.
  - **Carboplatin:** stop if CrCl<30ml/min
  - **Paclitaxel:** no dose reduction necessary.
  - **Cyclophosphamide:** No dose adjustment for mild or moderate impairment. Severe d/w consultant.
  - **Epirubicin:** If CrCl>10ml/min no dose adjustment needed.
- **Infusion related reactions:**
  - **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, chlorphenamine (and H2 antagonist) from dose 3 onwards.

- **Carboplatin:** Mild/moderate reactions (grade 1-2): If symptoms resolve after treatment with hydrocortisone and chlorphenamine, the infusion may be restarted at 50% rate for 30 mins, then, if no further reaction, increase to 100% rate.
  If symptoms do not resolve after treatment with hydrocortisone and chlorphenamine, do not restart the infusion. At consultant's discretion, patients may be re-challenged at a later date with additional prophylaxis.
  In the event of further reaction (grade 1-3), stop infusion and consider alternative treatment.
  Severe (grade 3): Do not restart infusion. Consider alternative treatment.
  Anaphylaxis (grade 4): Follow anaphylaxis protocol. Discontinue permanently and consider alternative treatment.
- **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 antipyretic and antihistamine may be considered.

- **Pembrolizumab specific information:**
- The use of systemic corticosteroids (with the exception of those used as part of the chemotherapy pre-medication) or immunosuppressants before starting pembrolizumab should be avoided. Systemic corticosteroids or other immunosuppressants can be used after starting pembrolizumab to treat immune-related adverse reactions.
- **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 with pembrolizumab. 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.
- **Common drug interactions (for comprehensive list refer to BNF/SPC):**
  - **Paclitaxel:** Avoid concomitant use of paclitaxel with CYP2C8 or CYP3A4 inducers (e.g. rifampicin, carbamazepine, phenytoin) and inhibitors (e.g. ketoconazole erythromycin, fluoxetine, gemfibrozil, clopidogrel, cimetidine, ritonavir, nelfinavir).
  - **Carboplatin:** Caution with other nephrotoxic drugs.
  - **Epirubicin:** Caution, ciclosporin increases concentration of epirubicin.
  - **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. • **Driving and 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.
References	https://www.nejm.org/doi/suppl/10.1056/NEJMoa1910549/suppl_file/nejmoa1910549_protocol.pdf KMCC protocol BRE-092 V2

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

Cycles 1-4
Repeat every 21 days

Day	Drug	Dose	Route	Infusion Duration	Administration
1	Ondansetron	<75yrs 16mg >/=75yrs 8mg	IV	15 min	Sodium chloride 0.9% 50ml
	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**
	Give pre-meds 30 minutes prior to paclitaxel				
	Dexamethasone	8mg (may be reduced to 4mg on subsequent doses)	IV	Bolus	
	Chlorphenamine	10mg	IV	Slow bolus	Through the side of a fast running Sodium Chloride 0.9% intravenous infusion.
	PACLITAXEL	**80mg/m²**	IV	1 hr	In 250ml Sodium Chloride 0.9% (non-PVC bag and non-PVC administration set) via in-line 0.22 microns filter. Flush with sodium chloride 0.9%
	CARBOPLATIN Dose = (GFR + 25) x AUC	**AUC 1.5 (maximum dose 225mg)**	IV	30 mins	In 250ml - 500ml 5% glucose
8 and 15	**Give pre-meds 30 minutes prior to paclitaxel**				
	Dexamethasone	8mg (may be reduced to 4mg on subsequent doses)	IV	Bolus	
	Chlorphenamine	10mg	IV	Slow bolus	Through the side of a fast running Sodium Chloride 0.9% intravenous infusion.
	Ondansetron	<75yrs 16mg >/=75yrs 8mg	IV	15 min	Sodium chloride 0.9% 50ml
	PACLITAXEL	**80mg/m²**	IV	1 hr	In 250ml Sodium Chloride 0.9% (non-PVC bag and non-PVC administration set) via in-line 0.22 microns filter. Flush with sodium chloride 0.9%
	CARBOPLATIN Dose = (GFR + 25) x AUC	**AUC 1.5 (maximum dose 225mg)**	IV	30 mins	In 250ml - 500ml 5% glucose

TTO Cycle 1-4

TTO	Drug	Dose	Route	Directions
Day 1	Dexamethasone	4mg	PO	OM for 2 days after day 1, 8 and 15. Take with or just after food, or a meal.
	Metoclopramide	10mg	PO	3 times a day for 3 days after day 1,8 and 15, then 10mg up to 3 times a day as required. Do not take for more than 5 days continuously.

Neo-adjuvant treatment: Cycles 5-8 repeat every 21 days

Day	Drug	Dose	Route	Infusion Duration	Administration Details
1	Ondansetron	<75yrs 16mg >/=75yrs 8mg	IV	15 min	In 50ml Sodium chloride 0.9%
	PEMBROLIZUMAB	**200mg**	IV	30 min	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**
	Dexamethasone	8mg	PO		
	EPIRUBICIN	**90mg/m²**	IV	Slow bolus	Through the side of a fast running Sodium Chloride 0.9% intravenous infusion.
	CYCLOPHOSPHAMIDE	**600mg/m²**	IV	Slow bolus	Through the side of a fast running Sodium Chloride 0.9% intravenous infusion.

TTO cycle 5-8

TTO	Drug	Dose	Route	Directions
Day 1	Dexamethasone	6mg	PO	Every AM for 3 days. Take with or just after food, or a meal.
	Metoclopramide	10mg	PO	10mg TDS for 3 days then 10mg up to TDS when required. Do not take for more than 5 days continuously.
	Ondansetron	8mg	PO	BD for 3 days
	Fligrastim	5micrograms/ kg	Sub-cutaneous	Starting on day 5 for 5 days

Adjuvant treatment: Cycle 9-13 repeat every 42 days.

NB: Pembrolizumab can be given at a dose of 200mg every 21 days (for 9 cycles) if there is a clinical requirement.

Day	Drug	Dose	Route	Infusion Duration	Administration
1	Metoclopramide	20mg	PO		stat
	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.	