Indication	Neoadjuvant treatment of previously untreated stage IIA or IIB or IIIA or N2 only IIIB non-small cell lung cancer that is suitable for potentially curative surgery. NB: The patient either has been documented as NOT having a NSCLC which harbours an EGFR 19 or 21 mutation or an ALK gene fusion or the patient has a squamous cell carcinoma and a decision to not test for an EGFR 19 or 21 mutation or an ALK gene fusion and proceed with nivolumab has been made following discussion at the Lung Cancer MDT and consideration of the relevant patient characteristics (including age and smoking status).
Treatment Intent	Neo-adjuvant
Frequency and number of cycles	Repeat every 21 days for 3 cycles or until disease progression or unacceptable toxicity or patient choice. A formal medical review should take place before the end of the 2nd cycle of treatment. NB: • If the patient has a resection, adjuvant immunotherapy is not allowed in patients treated with neoadjuvant nivolumab plus chemotherapy. • If there is disease progression during neoadjuvant nivolumab plus chemotherapy, no further anti-PD1 or anti-PDL1 immunotherapy is funded in any indication. • Where patients do not go on to have a resection, see Blueteq form for eligibility for subsequent 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. • EDTA/DTPA should be used to measure GFR prior to cycle 1. C+G may be used to estimate CrCl if there is a delay in obtaining EDTA result. • Monitor FBC, U&Es, LFTs, random blood glucose at each cycle. If CrCl falls by >25% repeat EDTA and d/w consultant. • If neuts >/=1.5 and PLT >/=100 proceed with treatment. • If blood parameters not met defer treatment 1 week and see dose reductions below. • 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 24hours of the last steroid dose. • **Renal impairment:** o Nivolumab - No specific dose adjustment is necessary in patients with mild to moderate renal impairment. Severe renal impairment d/w consultant. o Carboplatin: stop if CrCl<30ml/min o Paclitaxel: no dose reduction necessary. • **Hepatic impairment:** o Nivolumab - No dose adjustment in mild hepatic impairment. Use with caution in patients with moderate (total bilirubin > 1.5xULN to 3xULN and any AST) or severe (total bilirubin >3xULN and any AST) hepatic impairment. o Carboplatin: no dose adjustment required. o 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. • **Dose Modifications:** o 1st dose reduction: paclitaxel 150mg/m^2, Carboplatin AUC 4.

- 2nd dose reduction: paclitaxel 100mg/m^2, Carboplatin AUC 3.
- **Nivolumab:** Dose escalation or reduction is not appropriate. Dosing delay or discontinuation may be required based on individual safety and tolerability.
- **Paclitaxel:** Dose reduce Paclitaxel by 1 dose level 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.
- If neuts <0.5 and/or PLT <50 dose reduce paclitaxel and carboplatin.
- Febrile neutropenia >/= grade 3 (Neuts <1 and temp >38.3^{0}C or a sustained temperature of >/=38^{0}C for more than one hour) reduce paclitaxel and carboplatin.
- For adverse events (other than immune-related adverse events, N&V and alopecia, and those stated above), dose reduction of paclitaxel and/or carboplatin should be considered if grade 3 or 4 non-haematological toxicity or repeat appearance of grade 2. Delay until resolution of toxicity to </=grade 1.

- **Infusion-related reactions:** If the infusion related reaction can be attributed to a particular agent, treat as follows:
  - **Nivolumab:** In the event of severe infusion-related reactions, discontinue nivolumab and administer appropriate treatment. In the event of a mild or moderate reaction, treatment may be continued with close monitoring. Pre-medication with paracetamol and chlorphenamine should be considered for subsequent treatment.
  - **Paclitaxel**: Patients developing hypersensitivity reactions to paclitaxel may be rechallenged 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).
  - **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 rechallenged 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.
- Use with caution in patients with any history of active autoimmune disease, or medical conditions requiring systemic immunosuppression, after careful consideration of the potential risk-benefit.
- **Immune- related reactions:**
- **Cytomegalovirus (CMV) infection/reactivation** has been reported in patients with corticosteroid-refractory immune-related colitis. Patients on nivolumab who present with diarrhoea or other symptoms of colitis, and those who do not respond to steroid treatment for immune-related colitis, should be fully investigated.
  For further guidance see https://www.gov.uk/drug-safety-update/nivolumab-opdivo-reports-of-cytomegalovirus-cmv-gastrointestinal-infection-or-reactivation.
- Most common reactions are pneumonitis, colitis, nephritis, hepatitis, hyperthyroidism, hypothyroidism, hypophysitis, diabetes, diabetic ketoacidosis, immune-related rash, hypopituitarism, confusion, peripheral neuropathy, blurred vision, eye pain, hypotension, flushing, arthralgia, and myalgia.
- 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, nivolumab should be withheld

	and the patient should be referred to a specialised unit for assessment and treatment. If SJS or TEN is confirmed, nivolumab should be permanently discontinued. • Cases of myocarditis have been reported, if a patient develops signs and symptoms of myotoxicity, close monitoring should be implemented, and the patient referred to a specialist for assessment. Once a diagnosis of myocarditis is established, nivolumab should be withheld or permanently discontinued. • Treatment must be permanently discontinued for any grade 4, recurrent grade 3 (or first occurrence of grade 3 if specified in guidance) or Grade 2 or 3 immune related adverse reactions that persist despite treatment modifications and any severe or life-threatening immune-related adverse reactions. Treatment must also be permanently discontinued if corticosteroid dosing cannot be reduced to < 10mg prednisolone or equivalent per day. • If corticosteroids are used to treat an immune related reaction they should be tapered over at least 1 month. Treatment should not be resumed while the patient is receiving immunosuppressive doses of corticosteroids or other immunosuppressive therapy. Prophylactic antibiotics should be used to prevent opportunistic infections in patients receiving immunosuppressive therapy. • For guidance on managing immune-related adverse reactions, refer to SPC and guidelines available on KMCC website: https://www.kmcc.nhs.uk/medicines-and-prescribing-incorporating-sact-pathways/immunotherapy/ • Haemophagocytic lymphohistiocytosis (HLH) has been observed with nivolumab. Caution should be taken when nivolumab is administered as monotherapy or in combination with ipilimumab. If HLH is confirmed, administration of nivolumab should be discontinued and treatment for HLH initiated. • **Drug Interactions:** ○ The use of systemic corticosteroids and other immunosuppressants at baseline, before starting treatment, should be avoided, however, systemic corticosteroids and other immunosuppressants can be used after starting treatment to treat immune-related adverse reactions. ○ 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. ○ Carboplatin: Caution with other nephrotoxic drugs. • **Driving:** Nivolumab can potentially cause fatigue in some patients and therefore use caution when driving or using machines. • Each ml of nivolumab contains 0.1 mmol (or 2.5mg) sodium. To be taken into consideration when treating patients on a controlled sodium diet. • The patient should be provided with the OPDIVO® Patient Alert card with each prescription (to be carried until at least 5 months after the last dose of treatment). • Patients must be advised to contact the oncology team or the 24 hour hot-line immediately they experience any side effect, as some side effects worsen rapidly. Prompt management of side effects can ensure that the patient continues with treatment. • Patients should be monitored (for at least up to 5 months after the last dose) for immune related adverse reactions as these can occur any time during or after stopping treatment.
References	KMCC protocol V2

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

Cycles 1-3 Repeat every 21 days

Day	Drug	Dose	Route	Infusion Duration	Administration
1	Metoclopramide	20mg	PO		
	NIVOLUMAB	**360mg**	IV	30 min	Can be given undiluted or diluted. If diluted, give in 100ml Sodium Chloride 0.9% via in-line low- protein binding 0.2 micrometre filter. The diluted solution should have a final concentration ranging from 1 to 10mg/ml. **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	16mg	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	In 50ml sodium chloride 0.9%
	PACLITAXEL	**175mg/m²**	IV	Over 3 hours	Diluted in 500ml sodium chloride 0.9% (Use non-PVC bag and non-PVC administration set) Via in-line 0.22micron filter Doses <150mg in 250ml 0.9% sodium chloride Flush with sodium chloride 0.9%
	CARBOPLATIN	**AUC 5** **Dose = AUC X (GFR + 25)** **Maximum dose 700mg**	IV	30min	500ml glucose 5%
TTO	Drug	Dose	Route	Directions	
	Dexamethasone	6mg	PO	OD for 3 days starting on day 2.	
	Metoclopramide	10mg	PO	TDS for 3 days 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.	
	Filgrastim	300 micrograms or consider dose of 480 micrograms if patient > 80kg	Sub cut	OD for 5 days starting on day 5	