Indication	Nivolumab in combination with ipilimumab for the first line treatment of adult patients with unresectable malignant pleural mesothelioma. NB Patients are eligible for treatment with nivolumab and ipilimumab if prior treatment via EAMS scheme has been received.
Treatment Intent	Palliative
Frequency and number of cycles	Repeat every 42 days. Continue until progressive disease or unacceptable toxicity or patient choice to discontinue treatment or completion of 2 years of treatment (a maximum of 35 doses of nivolumab and a maximum of 17 doses of ipilimumab), whichever is the sooner. Formal medical review as to whether treatment with nivolumab in combination with ipilimumab should continue or not will be scheduled to occur at least by the end of the first 6 weeks of treatment. NB: Atypical responses (i.e., an initial transient increase in tumour size or small new lesions within the first few months followed by tumour shrinkage) have been observed. It is recommended to continue treatment for clinically stable patients with initial evidence of disease progression until disease progression is confirmed.
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 and LFTs on day 1 and 22 of each cycle. • Random blood glucose on day 1 each cycle. • Prior to treatment neuts must be >/=1.5 and PLT>/=100 otherwise d/w consultant. During treatment, if neuts <1.0 and/or PLT <50 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. • **Hepatic impairment:** No dose adjustment of either agent in mild hepatic impairment. Data from patients with moderate or severe hepatic impairment are too limited to draw conclusions on these populations. Nivolumab must be administered with caution in patients with moderate (total bilirubin > 1.5 × to 3 × ULN and any AST) or severe (total bilirubin > 3 × ULN and any AST) hepatic impairment. Ipilimumab must be administered with caution in patients with transaminase levels >/= 5 x ULN or bilirubin levels > 3 x ULN at baseline. • **Renal impairment**: No specific dose adjustment of either agent is necessary in patients with mild to moderate renal impairment. Severe renal impairment d/w consultant. • The patient should have no known brain metastases or if the patient has brain metastases, the patient should be symptomatically stable prior to starting nivolumab in combination with ipilimumab. • 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.
	• **Dose Modification:**
	  ○ Dose escalation or reduction is not appropriate. Dosing delay or discontinuation may be required based on individual safety and tolerability.
	  ○ If either agent is withheld, the other agent should also be withheld. If dosing is resumed after a delay, either the combination treatment or nivolumab monotherapy could be resumed based on the evaluation of the individual patient.
	  ○ If nivolumab has to be discontinued as a consequence of toxicity, ipilimumab must also be stopped.
	  ○ If ipilimumab has to be discontinued as a consequence of toxicity, nivolumab can be continued as monotherapy (in which case consult the nivolumab SmPC for guidelines on the management of immune-related adverse reactions).
	• **Infusion-related reactions**: In the event of severe infusion-related reactions, discontinue Ipilimumab or nivolumab and administer appropriate treatment. In the event of a mild or moderate reaction, treatment may be continued with close monitoring. Pre-medication should be considered for subsequent treatment.
	• **Immune- related reactions:**
	  ○ Most common reactions are pneumonitis, colitis, hepatitis, nephritis hyperthyroidism, hypothyroidism, hypophysitis, diabetes, diabetic ketoacidosis, immune-related rash, hypopituitarism, confusion, peripheral neuropathy, blurred vision, eye pain, hypotension, flushing, arthralgia, and myalgia.
	  ○ 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/
	• **Cardiac adverse events** and pulmonary embolism have also been reported with combination therapy. Nivolumab in combination with ipilimumab should be discontinued for life-threatening or recurrent severe cardiac and pulmonary adverse reactions.
	• **Gastrointestinal disorder:** These post-marketing reports have included fatalities. Patients on ipilimumab who present with diarrhoea/other colitis symptoms, and those who do not respond to steroids for immune-related colitis, should be investigated to exclude other causes, including infections such as CMV.
	• **Solid organ transplant rejection** has been reported in the post-marketing setting in patients treated with PD-1 inhibitors.
	• **Haemophagocytic lymphohistiocytosis** (HLH) has been observed with nivolumab in combination with ipilimumab. If HLH is confirmed, administration of nivolumab in combination with ipilimumab should be discontinued and treatment for HLH initiated.
	• **Common drug interactions (for comprehensive list refer to BNF/SPC):** The use of anticoagulants is known to increase the risk of gastrointestinal haemorrhage. Since gastrointestinal haemorrhage is an adverse reaction with ipilimumab, patients on anticoagulation therapy should be closely monitored.
	• Each ml of nivolumab contains 0.1mmol (or 2.5mg) sodium and each ml of ipilimumab contains 0.1mmol (or 2.3mg) sodium. To be taken into consideration when treating patients on a controlled sodium diet.

	• **Driving:** Nivolumab and ipilimumab can potentially cause fatigue in some patients and therefore use caution when driving or using machines. • Patients treated with nivolumab in combination with ipilimumab must be given the patient alert cards, (to be carried until at least 5 months after the last dose of treatment), the ipilimumab patient information guide, and be informed about the risks of nivolumab and ipilimumab which may occur during or after discontinuation 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.
References	KMCC protocol LUN-045 V2 SPC accessed online 07.11.2023

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

Repeat every 42 days

Day	Drug	Dose	Route	Infusion Duration	Administration
1	Metoclopramide	20mg	PO		stat
	NIVOLUMAB	**360mg**	IV	30 min	Can be given undiluted or diluted in sodium chloride 0.9%. The diluted solution should have a final concentration of 1 to 10mg/ml. The total volume of infusion must not exceed 160 ml. Give via in-line low protein binding 0.22 micrometre filter. Flush the line with sodium chloride 0.9% for injection at the end of the infusion. **Use separate filters for each infusion.**
	IPILIMUMAB	**1mg/kg**	IV	30 min	Administer undiluted or diluted with 0.9% sodium chloride to a concentration of 1-4mg/ml (usually diluted in 50ml) Give via in-line low protein binding 0.22 micrometre filter. Flush the line with sodium chloride 0.9% for injection at the end of the infusion. **Use separate filters for each infusion.**
22	Metoclopramide	20mg	PO		stat
	NIVOLUMAB	**360mg**	IV	30 min	Can be given undiluted or diluted in sodium chloride 0.9%. The diluted solution should have a final concentration of 1 to 10mg/ml. The total volume of infusion must not exceed 160 ml. Give via in-line low protein binding 0.22 micrometre 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 3 times a day as required (max. 30mg per day including 20mg pre-chemo dose). Do not take for more than 5 days continuously.	