Indication	Metastatic or unresectable Melanoma
Treatment Intent	Induction therapy
Frequency and number of cycles	Repeat every 21 days 4 cycles NB Patients should receive the entire induction regimen (4 doses) as tolerated, regardless of the appearance of new lesions or growth of existing lesions. Assessments of tumour response should be conducted only after completion of induction therapy.

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 and LDH at each cycle.
	• Thyroid function must be assessed at baseline, before cycle 2 and cycle 4.
	• 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 specific dose adjustment is necessary in patients with mild hepatic impairment. If ALT/AST >/= 5 x ULN or bilirubin >/= 3 x ULN at baseline, use ipilimumab only with caution, as there is no data on this population.
	• **Renal impairment:** No specific dose adjustment is necessary in patients with mild to moderate renal impairment. Severe renal impairment d/w consultant.
	• **Dose modification:** Dose escalation or reduction is not recommended, only omission, therefore patients may not receive all 4 doses. Dosing delay or discontinuation may be required based on individual safety and tolerability, see table 1 and table 2.
	• **Infusion-related reactions:** In the event of severe infusion-related reactions, discontinue Ipilimumab 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:**
	  ○ Immune-related reactions may appear during the treatment course, or after the course has completed.
	  ○ The most common immune-related reactions are: diarrhoea, rash, pruritis, abdominal pain, abnormal hepatic function, hypothyroidism, hypopituitarism, confusion, peripheral neuropathy, blurred vision, eye pain, hypotension, flushing, arthralgia, myalgia.
	  ○ Any diarrhoea, increased stool frequency, bloody stool, LFT elevations, rash and endocrinopathy must be considered ipilimumab-related and managed appropriately to minimise life-threatening complications.
	  ○ 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/

	• **Gastrointestinal disorders:** 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. • **Common drug interactions (for comprehensive list refer to BNF/SPC):** The use of systemic corticosteroids before starting treatment should be avoided. • Immunosuppressants should not be used during treatment (unless to treat immune-related adverse reactions). • The use of anticoagulants is known to increase the risk of gastrointestinal haemorrhage. Since gastrointestinal haemorrhage is an adverse reaction with ipilimumab, patients who require concomitant anticoagulant therapy should be monitored closely. • **Driving:** Ipilimumab can potentially cause fatigue in some patients and therefore use caution when driving or using machines. • Each patient should be given a copy of the Yervoy® patient brochure and alert card (to be carried until 1 year after completion 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. • Each ml of this medicinal product contains 0.1 mmol (or 2.30 mg) sodium. To be taken into consideration when treating patients on a controlled sodium diet.
References	SPC accessed online 12.10.2023 KMCC proforma SKI-004 V3

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

Table 1 SPC guidance on **withholding** ipilimumab dose[a] in patients with the following immune-related adverse reactions.	
Adverse reactions	**Action**
Gastrointestinal: Moderate diarrhoea or colitis that either is not controlled with medical management or that persists (5-7 days) or recurs	1. Withhold dose until an adverse reaction resolves to Grade 1 or Grade 0 (or returns to baseline). 2. If resolution occurs, resume therapy.[d] 3. If resolution has not occurred, continue to withhold doses until resolution then resume treatment.[d] 4. Discontinue if resolution to Grade 1 or Grade 0 or return to baseline does not occur.
Hepatic: Grade 2 elevation in AST, ALT, or total bilirubin	
Skin: Moderate to severe (Grade 3)[b] skin rash or (Grade 2) widespread/intense pruritus regardless of etiology	
Endocrine: Severe adverse reactions in the endocrine glands, such as hypophysitis and thyroiditis that are not adequately controlled with hormone replacement therapy or high-dose immunosuppressive therapy Grade 3 diabetes	
Neurological: Moderate (Grade 2)[b] unexplained motor neuropathy, muscle weakness, or sensory neuropathy (lasting more than 4 days)	
Other moderate adverse reactions[c]	

[a] No dose reduction of ipilimumab is recommended.
[b] Toxicity grades are in accordance with National Cancer Institute Common Terminology Criteria for Adverse Events. Version 4.0 (NCI-CTCAE v4).
[c] Any other organ system adverse reactions that are considered immune-related should be graded according to CTCAE. Decision whether to withhold a dose should be based on severity.
[d] Until administration of all 4 doses or 16 weeks from first dose, whichever occurs earlier.

Table 2 SPC guidance on **permanently discontinuing** ipilimumab in patients with the following adverse reactions. Management of these adverse reactions may also require systemic high-dose corticosteroid therapy if demonstrated or suspected to be immune-related	
Adverse reactions	**NCI-CTCAE v4 Grade[a]**
Gastrointestinal: Severe symptoms (abdominal pain, severe diarrhoea or significant change in the number of stools, blood in stool, gastrointestinal haemorrhage, gastrointestinal perforation)	▪ Grade 3 or 4 diarrhoea or colitis
Hepatic: Severe elevations in aspartate aminotransferase (AST), alanine aminotransferase (ALT), or total bilirubin or symptoms of hepatotoxicity	▪ Grade 3 or 4 elevation in AST, ALT, or total bilirubin
Skin: Life threatening skin rash (including Stevens-Johnson syndrome or toxic epidermal necrolysis) or severe widespread pruritus interfering with activities of daily living or requiring medical intervention	▪ Grade 4 rash or Grade 3 pruritus
Neurologic: New onset or worsening severe motor or sensory neuropathy	▪ Grade 3 or 4 motor or sensory neuropathy
Other organ systems[b]: (e.g. nephritis, pneumonitis, pancreatitis, non-infectious myocarditis, diabetes)	▪ ≥ Grade 3 immune-related reactions[c] ▪ ≥ Grade 2 for immune-related eye disorders NOT responding to topical immunosuppressive therapy ▪ Grade 4 diabetes

[a] Toxicity grades are in accordance with National Cancer Institute Common Terminology Criteria for Adverse Events. Version 4.0 (NCI-CTCAE v4).
[b] Any other adverse reactions that are demonstrated or suspected to be immune-related should be graded according to CTCAE. Decision whether to discontinue ipilimumab should be based on severity.
[c] Patients with severe (Grade 3 or 4) endocrinopathy controlled with hormone replacement therapy may remain on therapy.

Repeat every 21 days.

Day	Drug	Dose	Route	Infusion Duration	Administration
1	Metoclopramide	20mg	PO		
	IPILIMUMAB	**3mg/kg**	IV	30min	Administer undiluted or diluted with 0.9% sodium chloride to a concentration of 1-4mg/ml via in-line 0.22 microns filter. Usually diluted in 100ml Sodium Chloride 0.9%. **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	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.	