Lancashire & South Cumbria Cancer Network
Systemic Anticancer Treatment Protocol

Drug regimen
Ipilimumab

Indications for use
Stage III (unresectable) or stage IV malignant melanoma

Regimen

DAY	DRUG	FLUID	TIME
1	Ipilimumab 3mg/kg	100ml N/saline	IV over 30 mins

Then repeat every 3 weeks for 4 doses

If the treatment is tolerated tumour response should be assessed at week 12.

Investigations prior to initiating treatment
FBC, U&Es inc bicarbonate, LFTs, LDH, Ca, glucose, TFTs
Serum samples for HIV, hep C antibody and HBs Ag if risk factors.
Pregnancy test (if applicable)
Weight and vital signs
For melanoma patients LDH is required at baseline and on each treatment as a prognostic marker. Treatment can be given irrespective of LDH levels and can go ahead if LDTH is not available or haemolysed

Requirements
ECOG performance status 0, 1, 2
Women of child bearing potential must be using adequate method of contraception throughout treatment and up to 26 weeks after last dose.

Contra-indication
Patients on high dose immunosuppression

Cautions
Autoimmune disease: history of active inflammatory bowel disease, history of symptomatic autoimmune disease e.g. rheumatoid arthritis, SLE< autoimmune vasculitis, history of autoimmune neuropathy e.g. Guillan-Barre
Presence of HIV, hepatitis B or C
Patients should be on the lowest clinically effective dose of systemic steroids.

Investigations and consultations prior to each cycle
ECOG performance status
FBC, U&Es, LFTs, LDH
TFTs before 2nd and 4th doses

Acceptable levels for treatment to proceed
WBC>2
ANC>1
Platelets>75
Hb>9
Creat<2xULN
AST/ALT <2.5xULN if no liver mets, <5xULN if liver mets
Bilirubin <2 xULN

Check with consultant prior to any deferrals.

Administration Guidelines
Administer the drug solution using a volumetric pump through an in-line 0.2 µm or 1.2 µm polyethersulfone or 0.2 µm positively charged nylon filter

DOSE MODIFICATIONS
Dose de-escalation and/or escalation of ipilimumab from 3 mg/kg is not allowed

Side effects and side effect Management:
Refer to Immunotherapy Toxicity Guidance for Further Information. Most toxicities should be treated with high does oral or Iv steroids with slow tapering.

Table 1A When to permanently discontinue Ipilimumab	
Permanently discontinue 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	
Severe or life-threatening adverse reactions	**NCI-CTCAE v3 Grade[a]**
Gastrointestinal: Severe symptoms (abdominal pain, severe diarrhoea or significant change in the number of stools, blood in stool, gastrointestinal haemorrhage, gastrointestinal perforation). Evaluate for evidence of gastrointestinal perforation or peritonitis.	• Grade 3 or 4 diarrhoea or colitis
Hepatic: Severe elevations in aspartate aminotransferase (AST), alanine aminotransferase (ALT), or total bilirubin or symptoms of hepatotoxicity.	• AST or ALT > 8 x ULN or • Total bilirubin > 5 x ULN
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) Consider immediate high-dose corticosteroid therapy as per local treatment guidelines.	• Grade 3 immune-related events[c] • Grade 2 for immune-related eye disorders NOT responding to topical immunosuppressive therapy

[a] Toxicity grades are in accordance with National Cancer Institute Common Terminology Criteria for Adverse Events. Version 3.0 (NCI-CTCAE v3).
[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.
ULN = upper limit of normal

Table 1B When to omit scheduled dose of Ipilimumab	
Omit Ipilimumab dose[a] in patients with the following immune-related adverse reactions.	
Mild to moderate adverse reactions	**Action**
Gastrointestinal: Moderate diarrhoea or colitis that either is not controlled with medical management (loperamide, fluid replacement) or that persists (5-7 days) or recurs (consider prednisolone 1mg/kg PO once daily)	1. Omit dose until an adverse reaction resolves to Grade 1 or Grade 0 (or returns to baseline). 2. If resolution occurs before the next scheduled dose, resume therapy at next scheduled dose. 3. If resolution has not occurred before next scheduled dose, continue to omit doses until resolution then resume treatment schedule. Do not re-place omitted doses. 4. Discontinue Ipilimumab if resolution to Grade 1 or Grade 0 or return to baseline does not occur.
Hepatic: Moderate elevations in transaminase (AST or ALT > 5 to 8 x ULN) or total bilirubin (> 3 to 5 x ULN) levels	
Skin: Moderate to severe (Grade 3)[b] skin rash or widespread/intense pruritus regardless of etiology. Add antihistamine therapy to control symptoms, treat rash with topical and oral corticosteroids (prednisolone 1mg/kg PO once daily).	
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.	
Neurological: Moderate (Grade 2)[b] unexplained motor neuropathy, muscle weakness, or sensory neuropathy (lasting more than 4 days)	
Other moderate adverse reactions[c] (uveitis, easinophilia, lipase elevation, glomerulonephritis, iritis, haemolytic anaemia, amylase elevations, multi-organ failure, pneumonitis have been reported) Treat Ipilimumab related uveitis, iritis or episcleritis with topical corticosteroid eye-drops.	

[a] No dose reduction of Ipilimumab is recommended. Doses that are omitted due to an adverse reaction must not be replaced.
[b] Toxicity grades are in accordance with National Cancer Institute Common Terminology Criteria for Adverse Events. Version 3.0 (NCI-CTCAE v3).
[c] Any other organ system adverse reactions that are considered immune-related should be graded according to CTCAE. Decision whether to omit a scheduled dose should be based on severity.
ULN = upper limit of norm

Side Effects

Gastrointestinal events include:
− Very common (≥ 1/10): diarrhoea, nausea, vomiting, abdominal pain;
− Common (≥ 1/100 to < 1/10): colitis, constipation, gastrointestinal haemorrhage;
− Uncommon (≥ 1/1,000 to < 1/100): gastroesophageal reflux disease.
Skin adverse events include:
− Very common (≥ 1/10): pruritus, rash;
− Common (≥ 1/100 to < 1/10): erythema, vitiligo, alopecia, dermatitis, night sweats;
− Uncommon (≥ 1/1,000 to < 1/100): urticaria.
Hepatic events include:
− Common (≥ 1/100 to < 1/10): abnormal hepatic function;
− Uncommon (≥ 1/1,000 to < 1/100): hepatic failure, hepatitis and hepatomegaly.
Endocrine events include:
− Common (≥ 1/100 to < 1/10): hypopituitarism, adrenal insufficiency, hyperthyroidism and hypothyroidism.
Neurological events include:
− Common (≥ 1/100 to < 1/10): headache;

− Uncommon (≥ 1/1,000 to < 1/100): dizziness, myoclonus, peripheral neuropathy and tremor.

• Low-grade (Grade 1 or 2) immune-related adverse events may be treated symptomatically without withdrawal of ipilimumab.
• Any high-grade (Grade 3 or 4) events except for skin-related toxicities should be treated with corticosteroid or other immunosuppressive therapy and ipilimumab should be discontinued.

FURTHER INFORMATION CAN BE FOUND IN FAQS FOR PATIENTS, NURSES AND DOCTORS SUPPLIED BY BMS
PLEASE REFER TO APPROPRIATE IMMUNOTHERAPY TOXICITY RELATED GUIDANCE AVAILABLE HERE

THIS PROTOCOL HAS BEEN DIRECTED BY DR BOARD, CLINICIAN FOR MELANOMA

RESPONSIBILITY FOR THIS PROTOCOL LIES WITH THE HEAD OF SERVICE

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