Guideline for the Management of Immunotherapy Toxicities in Adult Haematology and Oncology patients

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1.0 Introduction

Immunotherapy is increasingly being used in treating cancer, both as standard therapy and within the context of clinical trials. Examples of drugs include but are not limited to Ipilimumab, Pembrolizumab, Nivolumab, Avelumab, Durvalumab and Atezolizumab (see Appendix 1 for current immunotherapy treatment). These drugs are associated with inflammatory adverse reactions resulting from increased or excessive immune activity.

Immune-related reactions may be life-threatening and appear during the treatment course and up to 12 months after the treatment has been completed. Early recognition that these are side effects of the immunotherapy is KEY.

The most common toxicities are: fatigue, diarrhoea, rash, pruritis, abdominal pain, abnormal hepatic function, hypothyroidism, hypopituitarism, confusion, peripheral neuropathy, blurred vision, eye pain, hypotension, flushing, arthralgia, myalgia, and infusion reactions.

Some patients will receive treatment with both ipilimumab and nivolumab (other PD-1/PDL-1 inhibitors and CTLA-4 inhibitors may also be given in combination on a clinical trial). These patients are at an increased risk of toxicity, with grade 3-4 toxicities occurring in approximately 50% of patients.

Prompt management of toxicity is essential; patients should be given written information and an alert card on initiation of treatment. In addition patients, must be educated on what signs or symptoms to look out for and encouraged to report persistent or worsening symptoms to their own cancer team or the Cancer Treatment Helpline **immediately.**

If patients do not respond to IV Methylprednisolone within 3 days, they should be treated with immunosuppressant drugs e.g. mycophenolate mofetil or infliximab. Specialist medicines such as mycophenolate mofetil or infliximab should only be initiated after review by the appropriate specialist team (e.g. gastroenterology, respiratory, dermatology) and with their advice.

Permanently discontinue immunotherapy for any persistent Grade 2 adverse reactions (excluding endocrinopathies controlled with hormone replacement therapy) that do not recover to Grade 0-1 within 6 weeks of last dose of Ipilimumab, or 12 weeks of last dose of other immunotherapy. Treatment should only be re-initiated once toxicity is ≤ Grade 1 (except endocrinopathies). Refer to individual SACT protocol or Summary of Product Characteristics (SmPC) for specific recommendations.

Unless stated otherwise under treatment of the specific condition, oral Prednisolone dose should be tapered over at least 1 month reducing by 10% every 3-5 days (round to nearest 5mg), where tolerated and ensuring that symptoms do not worsen during this time. Any worsening symptoms, signs or investigations (e.g. LFTs) should be treated by increasing the steroid dose and tapering slower.

1.1 Skin Toxicity

If there is **any** bullous formation, the treating consultant should be contacted regardless of percentage body surface area affected and the planned immunotherapy should be withheld.

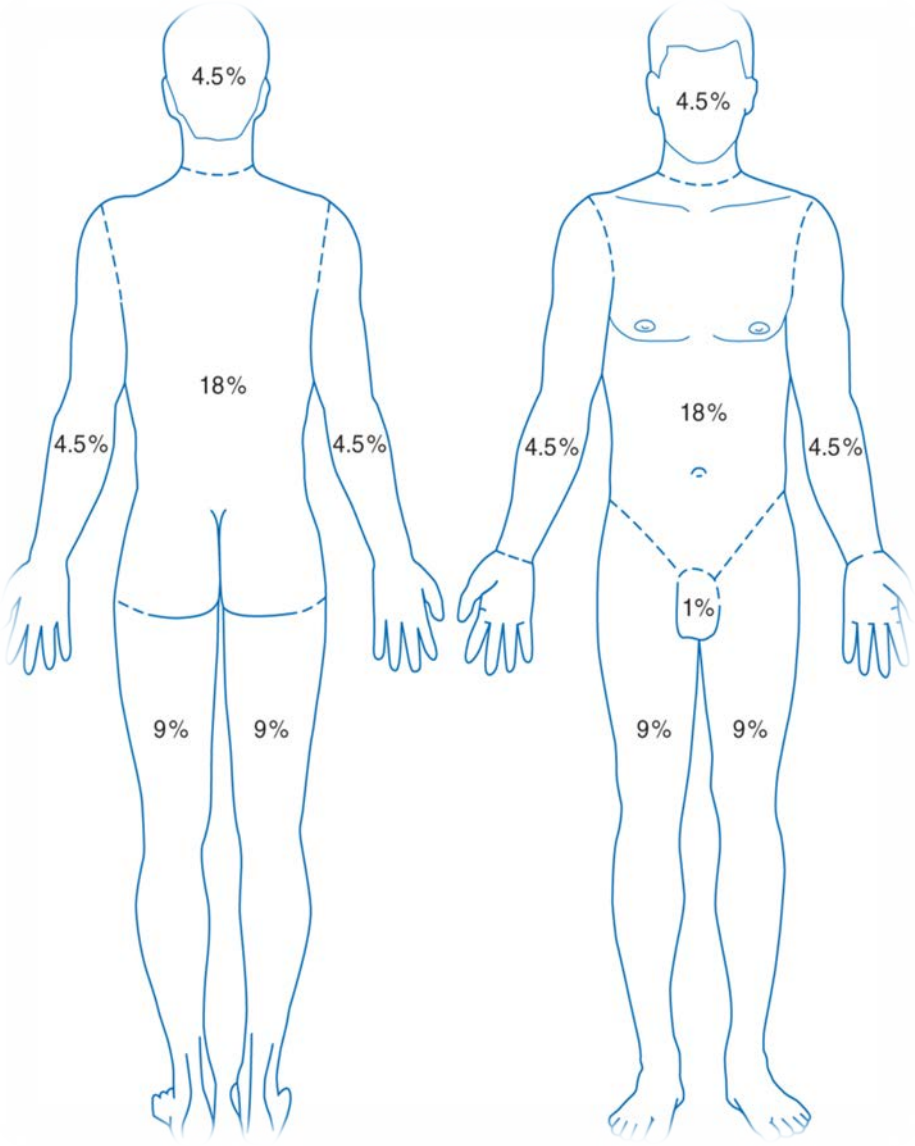
Grade 1 Skin rash (with or without symptoms) < 10% BSA	**Continue with scheduled dose of immunotherapy** • Exclude other causes of skin toxicity such as viral illness, infection, rash induced by other medication, or drug-induced photosensitivity • Avoid skin irritants and sun exposure • Treat symptomatically with oral antihistamine, regular topical emollients and topical steroid of mild to moderate potency e.g. 1% Hydrocortisone (mild) applied sparingly twice daily • Advise patient to contact Cancer Treatment Helpline or treating team if rash/symptoms are worsening
Grade 2 Rash covers 10-30% of BSA. May be limiting instrumental ADL* **BUT** without substantial symptoms	**Continue with scheduled dose of immunotherapy** • Senior review by medical team • Exclude other causes of skin toxicity such as viral illness, infection, rash induced by other medication, or drug-induced photosensitivity • Avoid skin irritants and sun exposure • Treat symptomatically with oral antihistamine, regular topical emollients and topical steroid of mild to moderate potency e.g. 1% Hydrocortisone (mild) or 0.05% clobetasone butyrate ointment (moderate) applied sparingly twice daily • Review patient once weekly until Grade 1 and escalate treatment if worsening or unresolving rash/symptoms
Grade 2 with substantial or unresolving symptoms **or** **Grade 3** >30% of BSA Widespread skin rash or intense pruritis May be limiting self-care	**Withhold any scheduled dose of immunotherapy** • Senior review by medical team • Exclude other causes of skin toxicity such as viral illness, infection, rash induced by other medication, drug-induced photosensitivity • Avoid skin irritants and sun exposure • Consider dermatology referral • Consider medical photography of rash • Treat symptomatically with oral antihistamine and regular topical emollients and potent topical corticosteroid cream e.g. 0.1% betamethasone valerate ointment applied sparingly twice daily, or alternative, as advised by the dermatology team. • Initiate oral Prednisolone 1mg/kg/day (or IV equivalent) once daily • When rash is controlled, taper the dose over at least one month • If symptoms resolve to Grade 0-1, on a dose of Prednisolone ≤ 10mg/day, immunotherapy treatment may be resumed if appropriate (for Ipilimumab administration of all 4 doses should be completed within 16 weeks from first dose) - Consultant decision

Grade 4 Skin sloughing > 30% of BSA Life-threatening rash (including Stevens-Johnson syndrome, or toxic epidermal necrolysis), severe widespread pruritis interfering with activities of daily living or DRESS**	**Permanently discontinue immunotherapy** • Initiate IV Methylprednisolone 2mg/kg/day • Urgent dermatology review • When rash is controlled, switch to oral Prednisolone and taper the dose over at least one month

*ADL, i.e. activities of daily living

**DRESS (Drug Reaction with Eosinophilia and Systemic Symptoms) which presents as rash with eosinophilia with one or more of the following: fever, lymphadenopathy, facial oedema and internal organ involvement (hepatic, renal or pulmonary)

Schematic of Body Surface Area



1.2 Gastro-intestinal toxicity (including colitis)

Any diarrhoea, increased stool frequency, or bloody stools should be considered to be related to immunotherapy and managed accordingly until proven otherwise. Ensure a stool sample is sent off at same time as initiating treatment. Patients should be re-assessed every 72 hours. For management of Grade 1 and 2, see table 1 and for management of Grade 3 and 4, see table 2.

Table 1: Grade 1 and 2 GI toxicity

Grade 1 Increase of ≤3 bowel movements a day over pre-treatment baseline or mild increase in stoma output	**Continue with scheduled dose of immunotherapy** • Treat symptomatically with Loperamide (2 capsules (4 mg) initially followed by 1 capsule (2 mg) after every loose stool. The maximum daily dose is 8 capsules (16mg) daily • Fluid replacement • Avoid high fibre diet • Assess frequently – if symptoms persist, Grade 1 for 5 days or worsening to Grade ≥2 follow guidance for Grade 2 otherwise continue with scheduled immunotherapy • Patient should be advised to contact the Cancer Treatment Helpline or treating team earlier if symptoms worsen
Grade 2 Increase of 4-6 bowel movements a day over pre-treatment baseline or moderate increase in stoma output. Moderate cramping, nocturnal stools	**Withhold any scheduled immunotherapy** • Assess stool frequently • FBC, U&Es, LFTs, bone profile, Mg, cortisol and TFTs • Stool cultures including clostridium difficile toxin • Fluid replacement • Abdominal X-ray if abdominal pain • Consider if inpatient admission is appropriate • If being managed as an outpatient then review every 3 days • Manage as per Grade 1 • If diarrhoea persists for more than 3 days then initiate Prednisolone at a dose of 1mg/kg/day for patients • If no improvement within 72 hours or worsening then consider switch to 2mg/kg IV Methylprednisolone. If no improvement or worsening despite this, discuss with GI consultant regarding endoscopy and discuss escalating treatment (options including Infliximab 5mg/kg) • Upon improvement, taper steroids over at least one month • If symptoms resolve to Grade 0-1, on a dose of ≤10mg Prednisolone daily then immunotherapy treatment may be resumed if appropriate (for Ipilimumab administration of all 4 doses should be completed within 16 weeks from first dose) - Consultant decision

Table 2. Grade 3 and 4 GI toxicity

Grade 3 Increase of 7-9 bowel movements a day over pre-treatment baseline or incontinence; severe increase in stoma output; severe cramping; nocturnal stools; interfering with ADL	**Permanently discontinue immunotherapy** • Admit patient and after ruling out bowel perforation immediately start IV Methylprednisolone 2mg/kg/day – do not start steroids if bowel perforation is present. Urgent specialist advice should be sought in these patients • Assess stool frequency • FBC, U&Es, LFTs, Bone profile, Mg, Cortisol, TFTs, and lactate • Stool cultures including clostridium difficile toxin • Fluid replacement • CT Scan of abdomen / pelvis • Discuss with GI consultant regarding endoscopy and discuss escalating treatment options (including Infliximab 5mg/kg) • Switch to oral Prednisolone once symptoms have resolved to Grade 2 or less • Once symptoms have resolved to Grade 0-1, the dose of steroids can be gradually tapered over a period of at least one month • If symptoms resolve to Grade 0-1, on a dose of ≤10mg Prednisolone daily then treatment may be resumed if appropriate.
Grade 4 Increase to > 10 bowel movements a day over pre-treatment baseline and/or grossly bloody diarrhoea and/or need for parenteral support	**Permanently discontinue immunotherapy** • Management as per Grade 3

1.3 Hepatotoxicity

Any rise in liver function tests should be investigated for alternative causes but should be considered immunotherapy related and treated accordingly until proven otherwise. Hepatitis B screening should have been undertaken before treatment was commenced but if not then check for reactivation. **Screen** for hepatitis E if abnormal LFTs develop in an immunosuppressed patient. In patients with hepatic metastases who presented with LFT abnormalities prior to the cycle, treatment limits may differ - refer to individual SACT protocol or SmPC.

Grade 1 AST/ALT ULN to < 3 x ULN **or** Bilirubin ULN to <1.5	**Continue with scheduled dose of immunotherapy** • Exclude other causes e.g. worsening disease, concomitant drugs (including alcohol), infectious causes or disease progression • Monitor LFTs in 1 week
Grade 2 AST / ALT ≥ 3 to <5 times ULN **or** Bilirubin >1.5 to < 3 times ULN	• **Withhold any scheduled dose of immunotherapy** • Exclude other causes e.g. worsening disease, concomitant drugs (including alcohol), infectious causes or disease progression • Re-check LFTs, INR, clotting and albumin twice weekly • If no improvement over 5 days or worsening LFTs then discuss with treating consultant and initiate Prednisolone at a dose of 1mg/kg/day orally or IV equivalent. • If worsening or no improvement despite initiation of initial steroids consider switch to IV Methylprednisolone 2mg/kg/day • Monitor LFTs regularly until recovery to ≤ grade 1 (AST < 3 x ULN and/or Bilirubin <1.5 x ULN) then taper Prednisolone over a period of at least one month • Once Prednisolone dose ≤ 10mg/day and LFTs ≤ grade 1, immunotherapy treatment may be resumed if appropriate (for Ipilimumab administration of all 4 doses should be completed within 16 weeks from first dose) - Consultant decision
Grade 3 or 4 AST / ALT ≥ 5 ULN **or** Bilirubin ≥3 ULN	**Permanently discontinue treatment** • Exclude other causes e.g. worsening disease, concomitant drugs (including alcohol), infectious causes • Admit patient • Immediately initiate IV Methylprednisolone 2mg/kg/day. Discuss with treating Consultant • Re-check LFTs, INR, clotting albumin daily • Perform liver ultrasound • If no response within 2-3 days, discuss with Hepatologist/GI Physician for consideration of liver biopsy and advise as to whether treatment with additional immunosuppressant is required (e.g. treatment with mycophenolate mofetil). • Switch to oral Prednisolone once AST < 3 x ULN • Monitor LFTs regularly until recovery to ≤ Grade 1 (AST < 1.5 x ULN) then taper Prednisolone over a period of at least one month. Any elevations in LFTs during taper may be managed with an increase in the steroid dose and a slower taper

1.4 Pulmonary Toxicity

Consider non-inflammatory causes and disease progression. Suspected pneumonitis should be confirmed with radiographic imaging.

Grade 1 Radiographic changes only. Ground glass changes, non-specific, interstitial pneumonia	**Consider delay in immunotherapy treatment** • Infection screen • Observations e.g. pulse oximetry • Assess for development of clinical symptoms every 3 days • Consider referral to respiratory service for advice • Once improves, re-image every 3 weeks initially • If deteriorates – treat as Grade 2
Grade 2 Mild to moderate new symptoms	**Withhold any scheduled immunotherapy** • Review as above • Consider In-Patient Admission • Outpatients should be monitored every 3 days and advised to Contact Cancer Treatment helpline if symptoms worsen prior to review. • Initiate oral Prednisolone 2mg/kg/day or IV equivalent • Consider high resolution CT scan • If worsening or no improvement of symptoms after initiation of steroids, treat as Grade 3–4 • If symptoms improve – taper steroids over at least one month. • Once Prednisolone dose ≤ 10mg/day, immunotherapy treatment may be resumed if appropriate (for Ipilimumab administration of all 4 doses should be completed within 16 weeks from first dose) - Consultant decision.
Grade 3 – 4 Severe new symptoms, new/worsening hypoxia, life threatening	**Permanently discontinue immunotherapy** • Admit patient • Supportive therapy including oxygen • Respiratory consultation • Start IV Methylprednisolone 2 mg/kg/day • Monitor for signs of infection • Respiratory review for consideration of high resolution CT scan, bronchoscopy, lung biopsy • Once symptoms have resolved to Grade 0-1, the dose of steroid should be gradually tapered over a period of at least one month • If deteriorated then consider additional immunosuppression on the advice of the respiratory consultant, e.g. Cyclophosphamide, Infliximab, IV immunoglobulins (i.e. gG)

1.5 Endocrine toxicity

Several endocrinopathies have been observed, many requiring prompt recognition and treatment -

- **Hypophysitis:** swelling of the pituitary gland that can result in pressure effects and hypopituitarism including secondary adrenal insufficiency
- **Adrenalitis:** resulting in primary adrenal insufficiency
- **Thyroiditis**: resulting in thyroid dysfunction (either hypothyroidism or hyperthyroidism)
- **Diabetes Mellitus**: most often seen with high-dose steroid therapy

Incidence is difficult to determine (~9% hypophysitis, ~15% thyroiditis, ~1% adrenalitis) and is likely to vary with the particular immunotherapy and cancer being treated.

As hypophysitis and adrenalitis may be life threatening and present with non-specific symptoms such as fatigue and headache, **patient awareness of warning symptoms is essential.**

It is recommended that, due to the complexities of interpreting cortisol and thyroid function tests, these patients are discussed with the Endocrine team. In patients with suspected adrenal insufficiency, treatment with replacement hydrocortisone should not be delayed.

Evidence for high dose steroid treatment is limited. A decision to use steroids is likely to be based on multiple factors including the endocrine organ affected. A discussion is recommended between the Oncology / Haematology and Endocrine teams.

1.5.1 Adrenal Insufficiency and Hypopituitarism

9am cortisol <250 or Random cortisol <150	**Withhold any scheduled immunotherapy** • Check if patient is taking any corticosteroids • Discuss urgently with local Endocrine team • Perform short Synacthen® test • Pituitary axis bloods (ACTH, TSH, FT4, LH, FSH, oestradiol (if pre-menopausal women), testosterone (male), IGF-1, prolactin • Replacement hydrocortisone may be necessary
Increasing fatigue, mood alteration or worsening anorexia, but haemodynamically stable, no electrolyte disturbances	• Check 9am or random cortisol • If 9am cortisol <250 or random cortisol <150 **withhold any scheduled immunotherapy.** • Check if patient is taking any corticosteroids • Pituitary axis bloods (ACTH, TSH, FT4, LH, FSH, oestradiol (if pre-menopausal women), testosterone (male), IGF-1, prolactin • Refer to Endocrinologist urgently
Signs of adrenal crisis (Severe dehydration, shock, hypovolemic shock, hypotension SBP <90mmHg, postural hypotension >20mmHg drop, dizziness/collapse, nausea and vomiting, abdominal pain, fever, confusion, delirium, coma, electrolyte disturbances, pre-renal failure)	**Withhold any scheduled immunotherapy** • Random cortisol & ACTH (blood tests ideally taken before hydrocortisone replacement but shouldn't delay this) • Aggressive fluid replacement • **Treat immediately with IV Hydrocortisone 100mg and then 50mg every 6 hours** • Review for infection or sepsis • Discuss urgently with local endocrine team • Pituitary axis bloods (TSH, FT4, LH, FSH, oestradiol (if pre-menopausal women), testosterone (male), IGF-1, prolactin
Pituitary insufficiency (fatigue, headache, visual field defects, electrolyte disturbances, changes in mental state, hypotension, abnormal thyroid function tests)	**Withhold any scheduled dose of immunotherapy** • Discuss urgently with local endocrine team • Pituitary axis bloods (ACTH, TSH, FT4, LH, FSH, oestradiol (if pre-menopausal women), testosterone (male), IGF-1, prolactin • Consider MRI pituitary • Consider MRI /CT head to exclude brain metastases

1.5.2 Thyroid dysfunction

- Subclinical hyperthyroidism (low TSH and normal FT4 often precedes overt hypothyroidism)
- If patient is unwell with symptomatic hyperthyroidism immunotherapy should be withheld and patient should be referred for urgent Endocrinologist review. Treatment may be restarted once symptoms are under control.
- A falling TSH across two measurements, with normal or lowered FT4, may also suggest pituitary dysfunction - weekly cortisol measurements are advised.
- Levothyroxine should be initiated with caution in elderly patients and those with a cardiac history
- Iodine from CT scans may impact TFTs.

Elevated TSH >10 and FT4 normal / Low T4 Symptoms include: fatigue, weakness, sensitivity to cold, weight gain, coarse dry hair, muscle cramps/aches, constipation, depression, irritability, memory loss, abnormal menstrual cycles, decreased libido and in severe cases slow speech, jaundice and increase tongue size.	Initiate levothyroxine 50micrograms once daily and titrate according to response/endocrine advice. For high risk patients (history of or co-existing cardiac conditions and elderly patients) consider starting at 25micrograms once daily.
Normal TSH and elevated FT4	Monitor and review at next cycle - if ongoing abnormality discuss with endocrinologist
Normal TSH and Low FT4	Check 9am cortisol and discuss with endocrinologist
Low TSH and elevated FT4 Symptoms include: fatigue or muscle weakness, hand tremor, mood swings, nervousness or anxiety, tachycardia, insomnia, anorexia/cachexia, increase frequency or bowel movements and menstrual disturbances.	If no symptoms, check next cycle and if ongoing abnormality discuss with Endocrinologist. **If symptomatic withhold immunotherapy and discuss with endocrinologist**
Low TSH and Low FT4	Check 9am cortisol and discuss with Endocrinologist

1.5.3 Diabetes

- New diabetes occurs in <1% of patients
- Patients should have regular glucose monitoring
- Role of steroids is unclear and likely to have a negative impact on diabetic control
- Refer urgently to diabetic team for review and treatment and consider admission
- Withhold any scheduled immunotherapy until diabetes is controlled

1.6 Ocular toxicity

- Patients presenting with symptoms of immune related eye disorders (uveitis, iritis, episcleritis) should be referred urgently to ophthalmology
- Topical corticosteroid eye drops should be considered
- Consider systemic corticosteroids in cases of severe ocular or orbital inflammation
- Withhold any scheduled immunotherapy if Grade ≥2
- Permanently discontinue immunotherapy if any Grade 2 immune-related eye disorders do not respond to topical corticosteroid eye drops or any Grade 3 or 4 reactions

1.7 Renal toxicity

Grade 1 Serum creatinine ≤ 1.5 x baseline or ≤ 1.5 x ULN	**Continue immunotherapy** • Repeat creatinine weekly • Review hydration, concurrent medication, any urinary symptoms, dipstick urine for proteinuria. • If proteinuria then perform 24h urine collection • Patients should be advised to contact Cancer Treatment helpline earlier than planned review if they develop any symptoms e.g. reduced urine output despite adequate intake, worsening oedema
Grade 2 Increase in serum creatinine >1.5 - <3.0 ULN	**Withhold any scheduled immunotherapy** • Review hydration, concurrent medication, any urinary symptoms, dipstick urine for proteinuria. If proteinuria then perform 24h urine collection • If no improvement in 48 hours then initiate Prednisolone 1mg/kg/day until creatinine reduces • Consider renal review to discuss renal USS +/- renal biopsy • If no improvement in symptoms switch to IV Methylprednisolone 2mg/kg/day and permanently discontinue all future immunotherapy • Once creatinine improves to baseline, the dose of steroids should be tapered over a period of at least one month (for Ipilimumab administration of all 4 doses should be completed within 16 weeks from first dose) • Once Prednisolone dose ≤ 10mg/day – treatment may be resumed if appropriate (for Ipilimumab administration of all 4 doses should be completed within 16 weeks from first dose) - Consultant decision
Grade 3 Increase in serum creatinine ≥3.0 – 6.0 x ULN	**Withhold any scheduled immunotherapy.** • Admit for daily creatinine monitoring and fluid balance • Refer to renal team • Initiate Prednisolone 1mg/kg/day until creatinine reduces • If no improvement consider switch to IV Methylprednisolone 2mg/kg/day and permanently discontinue all future immunotherapy • If creatinine improves to baseline, the dose of steroids should be tapered over a period of at least one month • Once Prednisolone dose ≤ 10mg/day – treatment may be resumed (for Ipilimumab administration of all 4 doses should be completed within 16 weeks from first dose) - Consultant decision
Grade 4 Increase in serum creatinine >6.0 x ULN	**Discontinue immunotherapy** • Admit and initiate IV Methylprednisolone 2mg/kg/day • Refer to Renal team

1.8 Neurological toxicity

A range of neurological symptoms have been described - please consult individual drug Summary of Product Characteristics for more information www.medicines.org.uk

Grade 1	**Withhold any scheduled treatment until nature of adverse event is determined** • Important to rule out disease progression, seizure activity, infection or any other drug-induced causes • Early consultation with Neurology is advised • Initiate prednisolone 1mg/kg/day orally if worsening symptoms • Refer to patient's consultant for further management
Grade 2 Motor neuropathy, muscle weakness or sensory neuropathy lasting > 4 days but with no impact on activities of daily living	**Withhold any scheduled immunotherapy treatment** • If symptoms worsen – manage as per Grade 3-4 • Start Prednisolone 1mg/kg/day and escalate if needed or give IV Methylprednislone 2mg/kg/day • Refer to patient's consultant for further management • If neurological symptoms resolve to baseline, treatment may be resumed if appropriate (for Ipilimumab administration of all 4 doses should be completed within 16 weeks from first dose) - Consultant decision
Grade 3-4 Motor neuropathy, muscle weakness or sensory neuropathy lasting > 4 days but with an impact on activities daily living	**Permanently discontinue immunotherapy** • Immediately start IV Methylprednisolone 2mg/kg/day • Consider referral to Consultant neurologist for management of sensory neuropathy • Both an atypical Guillain-Barré and myasthenic conditions have been reported. In some cases, ITU support may be required for motor neuropathy affecting respiratory muscles • Once symptoms have resolved, the dose of steroids should be gradually tapered over a period of at least one month

If myasthenia gravis-like toxicity is present, patients may be candidates for plasmapheresis or immunoglobulins if unable to tolerate steroids, decisions should be made in conjunction with the neurology team.

If Guillain-Barré is suspected it is important to consider that steroids may not typically be effective and treatment with plasmapheresis or immunoglobulins should be considered.

1.9 Myocarditis

Symptoms may be similar to pneumonitis. Signs and symptoms may include chest pain, arrhythmia, palpitations, peripheral/pulmonary oedema, progressive or acute dyspnoea, pleural effusion, fatigue.

Grade 1 Asymptomatic with laboratory (e.g. BNP) or cardiac imagining abnormalities	**Continue immunotherapy.** • Monitor for worsening clinical symptoms • Patient should be advised to contact the Cancer Treatment Helpline if they develop any new or worsening symptoms e.g. new onset or worsening shortness of breath, new or worsening chest pain, arrhythmia, peripheral oedema
Grade 2 Symptoms with mild to moderate activity/exertion	**Withhold any scheduled immunotherapy** • Review by a member of senior medical team • Refer to cardiology team • Consider admission if appropriate • If outpatient, review daily • Cardiac enzyme, ECG, ECHO, pulse oximetry • Exclude other causes e.g. disease progression, other medication • Start Methylprednisolone 2mg/kg/day • Once toxicity has resolved, the dose of steroids should be tapered over a period of at least one month • Once steroid dose is equivalent to Prednisolone dose ≤ 10mg/day – treatment may be resumed if appropriate (for Ipilimumab administration of all 4 doses should be completed within 16 weeks from first dose) - Consultant decision
Grade 3-4 Severe symptoms, symptoms at rest or with minimal activity/exertion. Life threatening consequences	**Permanently discontinue immunotherapy** • Review by a member of senior medical team • Admit to hospital • Urgent referral to cardiology team • Cardiac enzyme, ECG, ECHO, pulse oximetry • Exclude other causes e.g. disease progression, other medication • Start Methylprednisolone 2mg/kg/day

1.10 Other toxicities

Refer to SmPC (www.medicines.org.uk) for details of how to manage other toxicities.

All Grade 2 toxicities not listed should be discussed with the treating Consultant (refer to SmPC). Treatment will depend on the site of toxicity and the severity of symptoms and may require treatment with oral Prednisolone 1mg/kg/day - discuss with consultant. Scheduled immunotherapy should be withheld until symptoms resolve to Grade 1 or less and should only be restarted under the treating Consultant's direction.

Other toxicities reported include eosinophilia, lipase elevation, haemolytic anaemia.

For any Grade 3-4 suspected reactions IV Methylprednisolone 2mg/kg/day should be initiated and should be discussed with the treating Consultant. Scheduled treatment should be withheld and treatment may need to be permanently discontinued discuss with treating Consultant.

Permanently discontinue immunotherapy for any persistent Grade 2 adverse reactions (excluding endocrinopathies controlled with hormone replacement therapy) that do not recover to Grade 0-1 within 6 weeks of last dose of Ipilimumab, or 12 weeks of last dose of PD-1/PDL-1 inhibitors.

2.0 Conversion IV Methylprednisolone to oral Prednisolone

- IV Methylprednisolone can be converted to oral Prednisolone when symptoms start to resolve
- Methylprednisolone IV 4mg is equivalent to Prednisolone oral 5mg
- Consider prophylactic antibiotics against pneumocystis pneumonia (PCP), random blood glucose monitoring, bone protection if on steroids > 4 weeks
- Consider initiation of proton-pump inhibitor if on long term steroids and other medication which increase the risk of GI bleed e.g. Non-Steroidal Anti-inflammatory Drugs (NSAIDs), SSRIs

2.1 Prednisolone Dosing Tables

These tables are for guidance only since some patients may need slower reduction or re-escalation. Doses should only be reduced once the toxicity has returned to Grade 1 or baseline. Doses should be reduced by approximately 10% every 3-5 days, tapering over at least one month, rounding to the nearest 5mg. Patients >100kg should receive the appropriate mg/kg/day dosing and tapered accordingly.

Patient Weight 40-45Kg	Prednisolone 1mg/Kg/Day	Prednisolone 2mg/Kg/Day
Days 1-5	45mg	90mg
Days 6-8	35mg	70mg
Days 9-11	30mg	55mg
Days 12-14	25mg	40mg
Days 15-17	20mg	30mg
Days 18-20	15mg	25mg
Days 21-23	10mg	20mg
Days 24-26	5mg	15mg
Days 27-29	STOP	10mg
Days 30-32	-	5mg
Day 33	-	STOP

Patient Weight 46-50Kg	Prednisolone 1mg/Kg/Day	Prednisolone 2mg/Kg/Day
Days 1-5	50mg	100mg
Days 6-8	40mg	80mg
Days 9-11	35mg	60mg
Days 12-14	30mg	50mg
Days 15-17	20mg	40mg
Days 18-20	15mg	30mg
Days 21-23	10mg	25mg
Days 24-26	5mg	20mg
Days 27-29	STOP	15mg
Days 30-32	-	10mg
Day 33-35	-	5mg
Day 36	-	STOP

Patient Weight 51-55Kg	Prednisolone 1mg/Kg/Day	Prednisolone 2mg/Kg/Day
Days 1-5	55mg	110mg
Days 6-8	45mg	90mg
Days 9-11	35mg	70mg
Days 12-14	30mg	55mg
Days 15-17	25mg	40mg
Days 18-20	20mg	30mg
Days 21-23	15mg	25mg
Days 24-26	10mg	20mg
Days 27-29	5mg	15mg
Days 30-32	STOP	10mg
Day 33-35	-	5mg
Day 36	-	STOP

Patient Weight 56-60Kg	Prednisolone 1mg/Kg/Day	Prednisolone 2mg/Kg/Day
Days 1-5	60mg	120mg
Days 6-8	45mg	100mg
Days 9-11	35mg	80mg
Days 12-14	30mg	60mg
Days 15-17	25mg	45mg
Days 18-20	20mg	30mg
Days 21-23	15mg	25mg
Days 24-26	10mg	20mg
Days 27-29	5mg	15mg
Days 30-32	STOP	10mg
Day 33-35		5mg
Day 36		STOP

Patient Weight 61-65Kg	Prednisolone 1mg/Kg/Day	Prednisolone 2mg/Kg/Day
Days 1-5	65mg	130mg
Days 6-8	50mg	110mg
Days 9-11	40mg	90mg
Days 12-14	30mg	70mg
Days 15-17	25mg	50mg
Days 18-20	20mg	40mg
Days 21-23	15mg	30mg
Days 24-26	10mg	25mg
Days 27-29	5mg	15mg
Days 30-32	STOP	10mg
Day 33-35	-	5mg
Day 36	-	STOP

Patient Weight 66-70Kg	Prednisolone 1mg/Kg/Day	Prednisolone 2mg/Kg/Day
Days 1-5	70mg	140mg
Days 6-8	50mg	120mg
Days 9-11	40mg	100mg
Days 12-14	30mg	80mg
Days 15-17	25mg	60mg
Days 18-20	20mg	50mg
Days 21-23	15mg	40mg
Days 24-26	10mg	30mg
Days 27-29	5mg	25mg
Days 30-32	STOP	10mg
Day 33-35	-	10mg
Day 36-38	-	5mg
Day 39	-	STOP

Patient Weight 71-75Kg	Prednisolone 1mg/Kg/Day	Prednisolone 2mg/Kg/Day
Days 1-5	75mg	150mg
Days 6-8	60mg	125mg
Days 9-11	45mg	100mg
Days 12-14	30mg	80mg
Days 15-17	25mg	60mg
Days 18-20	20mg	50mg
Days 21-23	15mg	40mg
Days 24-26	10mg	30mg
Days 27-29	5mg	25mg
Days 30-32	STOP	15mg
Days 33-35	-	10mg
Day 36-38	-	5mg
Days 39	-	STOP

Patient Weight 76-80Kg	Prednisolone 1mg/Kg/Day	Prednisolone 2mg/Kg/Day
Days 1-5	80mg	160mg
Days 6-8	60mg	130mg
Days 9-11	45mg	100mg
Days 12-14	30mg	80mg
Days 15-17	25mg	60mg
Days 18-20	20mg	50mg
Days 21-23	15mg	40mg
Days 24-26	10mg	30mg
Days 27-29	5mg	25mg
Days 30-32	STOP	15mg
Days 33-35	-	10mg
Day 36-38	-	5mg
Days 39	-	STOP

Patient Weight 81-85Kg	Prednisolone 1mg/Kg/Day	Prednisolone 2mg/Kg/Day
Days 1-5	85mg	170mg
Days 6-8	65mg	140mg
Days 9-11	45mg	110mg
Days 12-14	30mg	80mg
Days 15-17	25mg	60mg
Days 18-20	20mg	45mg
Days 21-23	15mg	30mg
Days 24-26	10mg	25mg
Days 27-29	5mg	20mg
Days 30-32	STOP	15mg
Days 33-35	-	10mg
Day 36-38	-	5mg
Days 39	-	STOP

Patient Weight 86-90Kg	Prednisolone 1mg/Kg/Day	Prednisolone 2mg/Kg/Day
Days 1-5	90mg	180mg
Days 6-8	70mg	150mg
Days 9-11	50mg	120mg
Days 12-14	40mg	90mg
Days 15-17	30mg	60mg
Days 18-20	25mg	40mg
Days 21-23	20mg	30mg
Days 24-26	15mg	25mg
Days 27-29	10mg	20mg
Days 30-32	5mg	15mg
Days 33-35	STOP	10mg
Day 36-38	-	5mg
Days 39	-	STOP

Patient Weight 91-95Kg	Prednisolone 1mg/Kg/Day	Prednisolone 2mg/Kg/Day
Days 1-5	95mg	190mg
Days 6-8	75mg	160mg
Days 9-11	55mg	130mg
Days 12-14	40mg	100mg
Days 15-17	30mg	70mg
Days 18-20	25mg	50mg
Days 21-23	20mg	40mg
Days 24-26	15mg	30mg
Days 27-29	10mg	25mg
Days 30-32	5mg	20mg
Days 33-35	STOP	15mg
Day 36-38	-	10mg
Days 39-41	-	5mg
Day 42	-	STOP

Patient Weight 96-100Kg	Prednisolone 1mg/Kg/Day	Prednisolone 2mg/Kg/Day
Days 1-5	100mg	200mg
Days 6-8	90mg	180mg
Days 9-11	80mg	160mg
Days 12-14	70mg	140mg
Days 15-17	60mg	120mg
Days 18-20	50mg	100mg
Days 21-23	40mg	80mg
Days 24-26	30mg	60mg
Days 27-29	25mg	40mg
Days 30-32	20mg	20mg
Days 33-35	15mg	15mg
Day 36-38	10mg	10mg
Days 39-41	5mg	5mg
Day 42	-	STOP

3.0 References

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2. NHS Highland Guidelines for Management of Immunotherapy Toxicity: Ipilimumab, Nivolumab and Pembrolizumab, August 2016

3. Ipilimumab Summary of Product Characteristics. Accessed online at http://www.medicines.org.uk/emc/medicine/24779

4. Nivolumab Summary of Product Characteristics. Accessed online at http://www.medicines.org.uk/emc/medicine/30476

5. Pembrolizumab Summary of Product Characteristics. Accessed online at http://www.medicines.org.uk/emc/medicine/30602

6. ESMO Clinical Practice Guidelines: Management of toxicities from immunotherapy: ESMO Clinical Practice guidelines for diagnosis and follow up

Appendix 1 Licensed immunotherapies

Atezolizumab	https://www.medicines.org.uk/emc/product/8442
Avelumab	https://www.medicines.org.uk/emc/product/8453
Durvalumab	https://www.medicines.org.uk/emc/product/9495
Ipilimumab	https://www.medicines.org.uk/emc/product/4683
Nivolumab	https://www.medicines.org.uk/emc/product/6888
Pembrolizumab	https://www.medicines.org.uk/emc/product/6947/smpc

Replaces:	Not applicable
Lead Author(s):	Dr Gillian Price Consultant Medical Oncologist NHS Grampian Leanne Miller Oncology Pharmacist NHS Highland Louise McKee SACT Lead Pharmacist NHS Grampian
Responsibilities of the Lead Author(s):	• Retain master copy of this document (will also be available on regional website) • Review document in advance of review date
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Purpose/description:	To provide guidance for recognising and managing immunotherapy toxicities
Policy statement:	It is the responsibility of all staff to ensure that they are working to the most up to date and relevant clinical process documents.
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Revision History

Revision Date	Previous Revision Date	Summary of Changes (Descriptive summary of the changes made)	Changes Marked (Identify page numbers and section heading)
Not applicable	Not applicable	Not applicable	Not applicable

* Changes marked should detail the section(s) of the document that have been amended i.e. page number and section heading (If there is no previous document, insert N/A into the boxes in the top row of the table below)