Scope – This guidance refers to **management of immune-related adverse events caused directly by immunotherapy**. Immune-related adverse events can affect any organ system, however, the most common adverse reactions include:

- Immune-related pulmonary toxicities
- Immune-related colitis
- Immune-related hepatitis
- Immune-related nephritis or renal dysfunction
- Immune-related endocrinopathies
- Immune-related skin toxicities
- Immune-related fatigue (new)
- Immune-related cardiovascular toxicities
- Immune-related rheumatic events
- Immune-related neurological complications
- Immune-related ophthalmological complications (new)

The aim of this guidance is to help ensure that all those involved in the delivery of immunotherapy within the West of Scotland Cancer Network (WoSCAN) have the appropriate knowledge and resources to deliver these treatments safely through the provision of treatment algorithms for toxicity management.

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Immune-related Adverse Events (IrAEs)

Immune checkpoint inhibition is associated with a unique spectrum of side effects termed “Immune-related Adverse Events”. Appropriate management of irAEs is essential to minimise the risk of severe toxicity and enable treatment to be continued, where appropriate, maximising the potential benefits of therapy.

Patients receiving immunotherapy (e.g. ipilimumab, pembrolizumab, nivolumab, avelumab, atezolizumab, cemiplimab, durvalumab and dostarlimab) must be made aware of the potentially severe and fatal immune-mediated adverse reactions that can occur during treatment or weeks to months after the last dose of drug has been administered. Early identification of adverse events and timely intervention are critical to effective management. The majority of irAEs improve or resolve with appropriate management, including interruptions of treatment and administration of corticosteroids and/or supportive care. Long-term hormone replacement therapy may be necessary in cases of irreversible immune-related endocrinopathies. Regular communication between patients, carers and the clinical team is pivotal in the successful management of irAEs.

Patients receiving immunotherapy must be monitored continuously and if an irAE is suspected, adequate evaluation must be performed to confirm aetiology or exclude other causes. Vigilance, prompt recognition and early intervention can quickly reverse the majority of irAEs. The incidence of irAEs has been observed to be higher in patients receiving combination immunotherapy compared with single agent treatment. There has also been a substantial growth in the use of immunotherapy as part of cancer treatment in combination with chemotherapy and other agents.

Combination Treatments

Combination treatments with immunotherapies and other systemic anticancer treatments, such as chemotherapy, targeted therapies or other immunostimulatory drugs is an emerging treatment option for some cancers. This approach aims to achieve maximum therapeutic benefit by combining treatments that work by different mechanisms. This in turn may lead to more or different side effects. It is essential that clinicians keep up-to-date about the side effects associated with these regimens and how best to recognise early symptoms of toxicity.

The approach to the management of specific toxicities is discussed in the individual sections.

Please note: these guidelines have been developed by members of the BWoSCC Immunotherapy subgroup and in conjunction with non-cancer specialists (gastroenterologist, respiratory physician, dermatologist, nephrologist, endocrinologist, cardiologist, neurologist and ophthalmologist) from across NHSGGC.
Due to the evolving understanding of these drugs, the algorithms will be reviewed regularly and will be updated at relatively short intervals; particularly if / when new information arises. Therefore, the online version should always be consulted as this will be the most up-to-date version.

Immune-related Pulmonary Toxicities

- Severe pneumonitis or interstitial lung disease, including fatalities, have been observed with immunotherapy treatment.
- Patients should be monitored for signs and symptoms of pneumonitis including:

- breathing difficulties
- cough
- dyspnoea
- hypoxia
- radiographic changes (e.g. focal ground glass opacities, patchy infiltrates).

- HRCT should be performed if pneumonitis suspected. If other causes thought more likely, standard CT or CTPA to exclude disease progression or PE. Ensure clear information is entered on the CT request. Discuss with radiology where possible.
- Alternative aetiologies should be ruled out e.g. infection, disease progression. Discuss with respiratory physician if appropriate (for out-patients, respiratory team in patient's local hospital; for Beatson in-patients, initial point of contact is respiratory registrar at BWoSCC or on-call respiratory team at QEUH).
- The incidence of immune mediated sarcoidosis appears to be low, however, it is important that clinicians recognise the possibility of sarcoidosis, as the formation of granulomas may resemble disease progression or recurrence. As sarcoidosis is usually asymptomatic, and can mimic progressive disease, a biopsy may be necessary to differentiate.
- For detailed information regarding steroid administration please see "other information" section at the end of document. For suggested steroid taper schedules see appendix 1 or 2.

Pneumonitis: A term which refers to a variety of disease states characterised by inflammation of lung tissue

Baseline investigations in all patients with suspected pneumonitis:

- FBC, U+E, LFT, CRP, clinical evaluation, monitoring of oxygenation, sputum sample for M, C + S
- Request chest x-ray / consider CT scan (see notes above)

Grade	Management	Additional Investigations
<u>Grade 1 (radiographic changes only)</u> Asymptomatic; clinical or diagnostic observations only; intervention not indicated	• Monitor patient for worsening of symptoms, ensure patient and clinical team in regular contact • Consider withholding immunotherapy treatment as clinically appropriate during diagnostic process	
<u>Grade 2 (mild to moderate new symptoms)</u> Symptomatic; medical intervention indicated; limiting instrumental ADL	• Withhold immunotherapy treatment until symptoms resolve, radiographic abnormalities improve and management with corticosteroids is complete • Discuss with respiratory physician and consider hospitalisation for close monitoring • If no evidence of infection, promptly administer corticosteroids – prednisolone 1-2mg/kg/day or equivalent for a minimum of 5 days then taper over no less than 1 month • If worsening or no improvement occurs within 72 hours, despite initiation of corticosteroids treat as a grade 3/4 pneumonitis • Permanently discontinue immunotherapy for recurrent grade 2 pneumonitis	• Re-image as clinically indicated • Consider bronchoscopy +/- lavage

Grade	Management	Additional Investigations
Grade 3 Severe symptoms; limiting self-care ADL; oxygen indicated	• Permanently discontinue immunotherapy treatment • Admit patient to hospital and inform treating oncologist • Exclude atypical infections • Promptly administer high dose intravenous corticosteroids – methylprednisolone 2-4mg/kg/day or equivalent • Consider empirical antibiotics and antifungal therapy • Seek urgent respiratory consultation +/- transfer to a “hot site” where daily respiratory review and HDU available • Maintain initial corticosteroid dose for a minimum of 5 days prior to commencing reduction schedule • When symptoms improve to grade 0-1 switch to oral prednisolone 1 - 2 mg/kg/day or equivalent • A prolonged taper over 45 – 60 days is essential	• Regular nursing observations • Initiate supportive care (e.g. oxygen) • Re-image as clinically indicated
Grade 4 Life-threatening respiratory compromise; urgent intervention indicated (e.g. tracheotomy or intubation)	• Admit / transfer to a “hot site” where daily respiratory review and ITU available • Exclude atypical infections • Promptly administer high dose intravenous corticosteroids – methylprednisolone 1000 mg/day • After 3 - 5 days of IV methylprednisolone 1000 mg/day with response, switch to oral methylprednisolone 1 mg/kg/day reducing every 5 days • If patient not responding or deteriorating consider 2nd line immunosuppressant (in no particular order) e.g. high dose IV immunoglobulin, mycophenolate mofetil, infliximab, tociluzumab or cyclophosphamide. Please note : the use of these drugs is unlicensed and would be subject to the ULM approval	• Regular nursing observations • Initiate supportive care (e.g. oxygen) Re-image as clinically indicated

Immune-related Diarrhoea and Colitis

- Severe diarrhoea and colitis have been observed with immunotherapy treatment.
- As immune-related diarrhoea is a manifestation of inflammatory colitis, separate classification of diarrhoea and colitis is somewhat artificial.
- Patients should be monitored for diarrhoea and additional symptoms of colitis including:
- watery, loose or soft stools
- abdominal pain
- blood or mucous in stool.

- **Red flag** symptoms:

- nocturnal diarrhoea
- new incontinence
- fever
- weakness
- blood or mucous in stool
- abdominal pain.

- Alternative aetiologies should be ruled out e.g. infection, sub-acute obstruction, peritonitis, perforation, constipation with overflow.
- For detailed information regarding steroid administration please see “other information” section at the end of document. For suggested steroid taper schedules see appendix 1 or 2.

Diarrhoea: a disorder characterised by frequent and watery bowel movements
Colitis: a disorder characterised by inflammation of the colon

Baseline investigations in all patients with suspected colitis:

- FBC, U+E, LFT, CRP, TFTs, stool cultures x 3 including clostridium difficile

Grade	Management	Additional Investigations
Grade 1 (mild): <u>Diarrhoea</u> - increase of <4 stools per day over baseline	• Continue immunotherapy treatment, unless on combination anti PD1/CTLA4 then consider withholding • Symptomatic management with oral fluids and loperamide (max 16mg/24h – use with caution as may mask symptoms of worsening colitis), avoiding high fibre diet • Corticosteroids are not indicated unless diarrhoea persists for >14 days (if so treat as grade 2)	• Patient and clinical team should be in regular contact to assess symptoms
Grade 2 (moderate): <u>Diarrhoea</u> - increase of 4-6 stools per day over baseline <u>Colitis</u> - abdominal pain; mucus or blood in stool, nocturnal diarrhoea	• Withhold immunotherapy treatment • Symptomatic management with oral fluids, avoiding high fibre diet**, <u>do not</u>** administer loperamide. • Administer prednisolone 40-60 mg for a minimum of 5 days then taper • Manage in out-patient setting if appropriate, ensuring patient and clinical team in regular contact • If worsening or no improvement occurs within 72 hours despite initiation of corticosteroids, the patient should be admitted to hospital and switched to IV methylprednisolone 1 mg/kg/day or equivalent and further investigations performed as per grade 3 colitis • Permanently discontinue immunotherapy for recurrent grade 2 colitis	• Issue patient with Bristol stool chart • Consider AXR if signs/ symptoms of colitis • Urgent flexible sigmoidoscopy or colonoscopy and biopsy is strongly recommended in patients with grade 2 diarrhoea

Grade	Management	Additional Investigations
Grade 3 / 4 (severe / life threatening): Diarrhoea - increase of >=7 stools per day over baseline; incontinence; hospitalisation indicated; limiting self-care ADL Colitis - Severe abdominal pain; change in bowel habits; medical intervention indicated; peritoneal signs	• Discontinue immunotherapy treatment. Reintroduction may be considered, by clinical team, in patients with a resolved grade 3 toxicity • Inform treating oncologist and make arrangements for admission to hospital • Seek urgent gastroenterology consultation and consider direct admission to a "hot site" with access to HDU/ITU, inpatient gastroenterology services, emergency endoscopy, emergency surgery and daily review by surgeons • **Do not** administer loperamide • IV fluid replacement should be initiated whilst aetiology is investigated. Ensure patient remains in isolation until infection excluded • Administer IV methylprednisolone 1 mg/kg/day or equivalent (It is increasingly recognised that there is a microscopic colitis-phenotype which may respond to budesonide rather than prednisolone. The diagnosis is established by biopsy of the colonic mucosa demonstrating characteristic histologic changes). • Maintain initial corticosteroid dose for a minimum of 5 days prior to commencing reduction schedule • If worsening or no improvement occurs despite 72 hours of IV corticosteroids consider alternative immunosuppressive therapy e.g. infliximab 5 mg/kg (*see information below) or subsequently vedolizumab (**see information below).	• Recheck bloods daily • Request urgent sigmoidoscopy and biopsy. This should be done prior to starting treatment with biologics as the results may help decision making in the earlier use of these agents. • Screen for Tuberculosis (Quanti-FERON TB Gold), HIV, Hepatitis B and C (required as work-up for potential infliximab therapy). Inform microbiology of request • Regular nursing observations: Bristol stool chart, fluid balance, twice weekly weight, 4 hourly NEWS assessment • Dietician review

Caution: use of analgesia/opioids for abdominal pain in the setting of suspected immune-related diarrhoea/colitis may mask symptoms of perforation or peritonitis.

***Infliximab**

- Patients with severe colitis who have persistent symptoms, despite treatment with corticosteroids, may benefit from treatment with Infliximab (unlicensed indication), a monoclonal antibody against TNFα.

- Infliximab should **not** be given to patients with:
  - bowel perforation
  - tuberculosis or other active / severe infections
  - moderate or severe heart failure (NYHA class III/IV)

- Infliximab 5 mg/kg is administered by a 2 hour IV infusion, refer to local prescribing guidance.

- The dose should be repeated after 2 and 6 weeks after the first infusion, to a minimum of 3 doses.

- If there is a failure to respond after 2 doses seek gastroenterology advice. Consideration should be given to switching to vedolizumab / surgery.

- Patients should be given a verbal explanation of the potential side effects. Key counselling points:
- increased risk of infection – including TB and HBV/HBC reactivation
- hepatitis
- hypersensitivity reaction
- small increased risk of malignancy (lymphoma).

- For infliximab ordering procedure discuss with local pharmacy team. If required urgently i.e. out of hours please liaise with the on-call pharmacist.

****Vedolizumab**

- Patients who have had an inadequate response to treatment with infliximab may be eligible to receive vedolizumab (unlicensed indication), a monoclonal antibody which targets $\alpha_4\beta_7$ integrin, which is expressed in white blood cells that are found in the gut.

- Vedolizumab must only be prescribed following collaboration with a senior member of the gastroenterology team and the treating oncologist, with consideration given to disease stage, symptom burden and prognosis.

- Vedolizumab must **not** be given to patients with:
- sepsis
- tuberculosis or other active / severe infections

- Vedolizumab 300mg is administered by a 30 minute infusion.

- The dose is repeated at weeks 2, 6, 10, 14 then 8 weekly maintenance if required. This decision must be made based upon clinical assessment by the gastroenterology consultant / speciality doctor.

- For vedolizumab ordering procedure discuss with local pharmacy team. If required urgently i.e. out of hours please liaise with the on-call pharmacist.

Immune-related Hepatitis

- Severe hepatitis has been observed with immunotherapy.
- Patients should be monitored for signs and symptoms of hepatotoxicity including:

- elevations in total bilirubin or transaminases (early laboratory changes may be indicative of emerging immune-related hepatitis)
- right upper quadrant abdominal pain
- jaundice
- nausea and vomiting
- tiredness / drowsiness
- dark urine
- bleeding or bruising.

- Alternative aetiologies should be ruled out e.g. liver metastases, biliary obstruction, drug related cause (medication other than immunotherapy e.g. antibiotics).
- For detailed information regarding steroid administration please see "other information" section at the end of document. For suggested steroid taper schedules see appendix 1 or 2.

Hepatitis: A disorder characterised by inflammation of the liver. Often there are no initial symptoms and the disease is detected by abnormal liver function tests.

Baseline investigations in all patients with suspected hepatitis:

- FBC, U+E, LFT, CRP, Coagulation screen, Albumin, Liver screen
- Physical examination

Grade	Management	Additional Investigations
Grade 1 AST **or** ALT >ULN - 3 x ULN if baseline was normal; 1.5 – 3 x baseline if baseline was abnormal **or** Bilirubin >ULN - 1.5 x ULN if baseline was normal; > 1.0 - 1.5 x baseline if baseline was abnormal	• Continue immunotherapy treatment as per individual drug protocol • Monitor blood parameters weekly and assess symptoms • Corticosteroids are not indicated	• Patient should be advised to contact clinical team if symptoms change or worsen
Grade 2 AST **or** ALT >3 – 5 x ULN if baseline was normal; >3 - 5 x baseline if baseline was abnormal **or** Bilirubin >1.5 - 3.0 x ULN if baseline was normal; >1.5 - 3.0 x baseline if baseline was abnormal	• Withhold immunotherapy treatment until LFTs return to baseline • Review patient twice weekly – monitor blood parameters and assess symptoms • Manage in out-patient setting, if appropriate, ensuring patient and clinical team in regular contact --- • Persistent elevations (>7 days) in LFTs should be managed with prednisolone 0.5 - 1 mg/kg/day or equivalent for a minimum of 5 days, taper over 1 month • If worsening or no improvement occurs within 72 hours, despite initiation of corticosteroids, the patient should be admitted to hospital and switched to IV methylprednisolone 1 mg/kg/day or equivalent and further investigations performed as per grade 3 hepatitis	• Recheck LFTs twice weekly • Consider liver ultrasound --- • If corticosteroids initiated bloods should be rechecked every 3 days until stable or improving

Grade	Management	Additional Investigations
Grade 3 AST **or** ALT >5 - 20 x ULN if baseline was normal; >5 – 20 x baseline if baseline was abnormal **or** Bilirubin >3.0 - 10.0 x ULN if baseline was normal; >3.0 - 10.0 x baseline if baseline was abnormal --- Grade 4 AST **or** ALT >20 x ULN if baseline was normal; >20 x baseline if baseline was abnormal **or** Bilirubin >10.0 x ULN if baseline was normal; >10.0 x baseline if baseline was abnormal --- Liver metastasis with baseline grade 2 elevation of AST or ALT and hepatitis with AST or ALT increases of ≥ 50% and lasting longer than 1 week	• Discontinue immunotherapy treatment. Reintroduction may be considered, by clinical team, in patients with a resolved grade 3 toxicity • Admit patient to hospital for evaluation and close monitoring and discuss with hepatologist • Administer corticosteroids: IV methylprednisolone 1 mg/kg/day or equivalent for a minimum of 5 days and taper over 4 – 6 weeks • If no decrease in LFTs after 3 days or rebound hepatitis occurs despite corticosteroids, consider addition of **mycophenolate mofetil** (see below**) with supportive treatment – co-trimoxazole - for prophylaxis for opportunistic infections	• Recheck LFTs, INR and albumin daily until stable or showing signs of improvement for at least 3 consecutive days • Request liver ultrasound +/- doppler of hepatic veins • Regular nursing observations • Monitor daily for signs and symptoms of liver failure: encephalopathy/hypoglycaemia/ coagulopathy, if they develop consider transferring to specialist site for intensive monitoring and escalation of care

****Mycophenolate Mofetil (MMF)**

- Patients with severe hepatitis who have no improvement in LFTs, despite treatment with corticosteroids, are likely to benefit from treatment with MMF (unlicensed indication), an immunosuppressive agent usually used to prevent organ rejection in patients who have undergone transplants.
- MMF should **not** be given to:

- women of child bearing potential who are not using a highly effective method of contraception (please refer to 'Educational Risk Minimisation Materials' available by searching 'mycophenolate mofetil' on http://www.medicines.org.uk
- women who are breastfeeding.

- MMF is available in capsule or tablet form and is usually taken twice a day, swallowed whole with a glass of water, and can be ordered as per standard ward ordering procedure.
- The recommended dose is 1000 mg twice daily. It may be necessary to start some patients on 500 mg twice daily and increase the dose if no side effects occur.
- MMF should be continued for 6 weeks after LFTs back within normal range and corticosteroids stopped.
- Patients should be given a verbal explanation of the potential side effects. Key counselling points:

- GI disturbance
- increased risk of lymphomas and other malignancies
- infection risk (opportunistic infections)

- risk of haematological toxicity and requirement for regular blood monitoring (please refer to SmPC available via http://www.medicines.org.uk)
- teratogenic effects.

- If inadequate response with MMF, seek Hepatologist review and consider other drug options e.g. tacrolimus.

Immune-related Nephritis and Renal Dysfunction

- Severe nephritis and renal dysfunction has been observed with immunotherapy.
- Patients should be monitored for signs and symptoms of nephritis and renal dysfunction including:

- asymptomatic increases in creatinine
- decreased volume of urine.

- Alternative aetiologies should be ruled out e.g. AKI, UTI, drug related cause (medication other than immunotherapy e.g. NSAIDS, recent IV contrast administration) or urinary obstruction.
- For detailed information regarding steroid administration please see “other information” section at the end of document. For suggested steroid taper schedules see appendix 1 or 2.

Nephritis: A disorder characterised by inflammation of the kidneys		
Baseline investigations in all patients with suspected nephritis: - FBC, blood film, U+E, LFT, urinalysis, bone profile		
Grade	**Management**	**Additional Investigations**
Grade 1 Creatinine >ULN – 1.5 x ULN	• Continue immunotherapy treatment as per individual drug protocol	• Recheck creatinine weekly
Grade 2 Creatinine >1.5 – 3 x baseline; >1.5 - 3 x ULN **OR** Grade 3 Creatinine >3 x baseline; 3 - 6 x ULN	• Withhold immunotherapy treatment • Administer prednisolone 1 mg/kg/day or equivalent for a minimum of 5 days then taper over at least 6 weeks • If worsening or no improvement occurs within 72 hours despite initiation of corticosteroids, the dose may require to be increased and / or further investigations performed • Discuss with the renal team • Review concomitant medication and withhold nephrotoxic drugs / dose adjust to creatinine clearance	• Dip urine. If positive for protein send urine protein:creatinine ratio • Monitor creatinine every 48 hours • Consider renal ultrasound +/- renal biopsy
Grade 4 Creatinine >6 x ULN	• Permanently discontinue immunotherapy treatment • Discuss with renal team • Manage as grade 2 / 3 nephritis	• Investigate as grade 2 / 3 nephritis • Daily creatinine, weight and fluid balance

Immune-related Endocrinopathies

- Several endocrine effects have been observed with immunotherapy.
- The mean onset of endocrine effects is 9 weeks after initiation (range 5 - 36 weeks) of therapy.
- Patients should be monitored for signs and symptoms of endocrine dysfunction, in the majority of patients symptoms are usually non-specific and vague and may include:

- headache
- visual changes
- severe fatigue
- hyperglycaemia
- changes in thyroid function.

- Alternative aetiologies should be ruled out e.g. brain metastasis, sepsis, or progression of disease. Unless an alternate aetiology has been identified, signs and symptoms of endocrinopathies should be considered immune related.

Endocrinopathies	Management Pathway	Additional Investigations
Baseline investigations in all patients with suspected endocrinopathy: - TSH, T4, anti-TPO antibodies, cortisol, IGF-1, prolactin, LH , FSH, Testosterone (males only), Oestradiol (females only) - Assess for clinical features of endocrine dysfunction (fatigue, tiredness, nausea, **headache**, visual disturbance, diarrhoea, tachycardia, tremors, hypotension, hypoglycaemia, hyponatraemia) prior to each cycle		
<u>Hypophysitis (inflammation of the pituitary gland) with or without hypopituitarism</u> – A high index of suspicion is needed in patients with hyponatraemia, hypoglycaemia, hypotension and hypogonadism	• Withhold immunotherapy treatment for ≥ grade 2 symptomatic hypophysitis until event is controlled with hormone replacement • The management of hypophysitis primarily involves replacement of pituitary deficient hormones, consideration of drug discontinuation and/or high dose corticosteroid therapy. (If patient is showing signs of raised intracranial pressure (ICP) administer dexamethasone 4 mg qds). This should be carried out in accordance with standard endocrine practice. • If the patient is currently or very recently on corticosteroids then serum cortisol will likely be suppressed. Discuss with endocrinology prior to commencing replacement therapy	• Request MRI pituitary to assess extent of hypophysitis • If baseline cortisol is less than 300 nmol/L, consider short synacthen test and endocrine review • If morning cortisol is less than 240 nmol/L, refer to endocrinology. Start hydrocortisone replacement (the usual dose is 20 mg to 30 mg a day, split into 2 doses) pending review • The presence of visual disturbance may indicate pituitary mass effect; admit patient, seek urgent endocrinology advice
<u>Adrenalitis with or without hypoadrenalism</u> – there are occasional reports of primary adrenal failure	• Withhold immunotherapy treatment • Due to the potentially fatal nature of untreated hypoadrenalism, immediate hospitalisation and prompt investigation is essential in patients with suspected adrenal insufficiency	• Manage according to routine practice • Refer to endocrinology

Endocrinopathies	Management Pathway	Additional Investigations
Thyroid dysfunction - manifestations include transient thyrotoxicosis, transient or long lasting hypothyroidism, thyroiditis, thyroid disease and rarely thyroid storm	• For management of hypothyroidism** see below, it is not always necessary to interrupt immunotherapy treatment – discuss with responsible consultant • Immunotherapy treatment must be withheld for grade ≥2 hyperthyroidism. Anti-thyroid medication is rarely required, management should be symptomatic e.g. beta-blockers • Patients with grade 3 /4 hyperthyroidism should be referred to specialist endocrinology services	• Monitor TFTs every treatment cycle. The majority of patients with hyperthyroidism as an irAE will become hypothyroid within a few weeks
Diabetes Mellitus – may present as new-onset insulin-dependent diabetes or worsening pre-existing type 2 diabetes, however the underlying mechanism is considered similar to that of type 1 diabetes	• Withhold immunotherapy treatment for grade 3 hyperglycaemia (fasting glucose > 13.9mmol/L) or other signs and symptoms of diabetes e.g. diabetic ketoacidosis (DKA) • Check for signs of DKA: - ketonaemia ≥3 mmol/L or significant ketonuria (more than 2+ on standard urine sticks) - blood glucose >11 mmol/L or known diabetes - Bicarbonate (HCO3-) ≤ 15 mmol/L and/or venous pH<7.3 • Urgent management of hyperglycaemia / hospital admission in patients with DKA is essential • If DKA excluded - check pancreatic antibodies (e.g. GAD65, Zn transporter 8 or anti-islet cell) and C-peptide • Commencement of insulin therapy is almost always required, and therefore early/prompt referral to the specialist diabetes team is necessary • Immunotherapy can be restarted when glycaemic control is achieved	• Manage according to routine practice and always refer to specialist diabetes team. It should be noted that immune mediated diabetes is a very rare side effect, however, it is often irreversible and will require life-long treatment

- Do not restart immunotherapy treatment for any grade 4 hypothyroidism, hyperthyroidism, hypophysitis, adrenal insufficiency or diabetes (see table 1 below for CTCAE grading of endocrine disorders) without discussing with responsible consultant.

****Hypothyroidism**

Hypothyroidism is a well documented adverse effect of immunotherapy. Patients should have thyroid function tests performed by means of a blood test at baseline and every 4 - 6 weeks thereafter.

Diagnosis and management of **hypothyroidism** should be as follows:

- Start thyroid replacement in those with TSH>10 or if T4 below reference range.
- Check cortisol prior to starting thyroid replacement (if thyroid function is compromised within a hypopituitary picture cortisol must be replaced for 24-48 hours prior to commencing thyroid replacement).
- Consider replacement if TSH 5-10. Check anti-TPO antibodies if symptomatic and borderline. These patients should be discussed with the responsible consultant.
- Start all patients with hypothyroidism on levothyroxine. The usual starting dose is 50 -100 micrograms daily. Patients who are very lean or are elderly or male may require starting doses at the lower end of this range. Patients who are very frail or with ischaemic heart disease should start at 25 micrograms daily.
- Re-check levels after 6 weeks of treatment and titrate doses as necessary. The target is to achieve TSH within the reference range.
- Patients with continuing symptoms after appropriate levothyroxine treatment should be referred for further investigation.
- Corticosteroids are not indicated for the treatment of hypothyroidism.

Table 1: CTCAE grading of endocrine disorders

Endocrine disorders	Grade1	Grade 2	Grade 3	Grade 4	Grade 5
Pituitary	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or Non-invasive intervention indicated; limiting age appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening hospitalisation or prolongation of existing hospitalisation indicated; disabling; limiting self-care	Life-threatening consequences; urgent intervention indicated	Death
Thyroid	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self-care ADL; hospitalisation indicated	Life-threatening consequences; urgent intervention indicated	Death
Adrenal	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; medical intervention indicated	Severe symptoms; hospitalisation indicated	Life-threatening consequences; urgent intervention indicated	Death

Immune-related Skin Toxicities

- Skin adverse events occur frequently (30-40%) and usually occur within 3-11 weeks after initiation of immunotherapy.
- Severe rash (including cases of fatal toxic epidermal necrolysis) has been observed with immunotherapy.
- Patients should be monitored for signs and symptoms of skin toxicity including:
- pruritus
- maculopapular (morbilliform) drug rash consisting of erythema, flat macules and elevated papules
- peeling, blisters, erosions and ulcers
- acneiform or pustular eruptions
- blisters, erosions, ulcers, skin peeling or sloughing associated with erythema (erythroderma if >90% BSA) and/or purpura are indicative of severe rash
- other features may be observed e.g. vitiligo, lichenoid eruptions.

- The skin should be evaluated to determine the extent and severity of rash.
- Mucosal skin (eyes, mouth and anogenital) must also be examined particularly when considering bullous or necrotizing skin rashes.
- Consider other causes of rash e.g. skin infection, alternative drug rash or flare of pre-existing skin condition
- Systemic symptoms e.g. flu like symptoms and fever may be associated with severe skin toxicities such as Stevens - Johnson syndrome (SJS) or Toxic Epidermal necrolysis (TEN) and DRESS (Drug Rash with Eosinophilia and Systemic Symptoms).
- If symptoms or signs of SJS or TEN appear, immunotherapy treatment should be discontinued permanently and the patient referred to a specialist unit for assessment and treatment.
- If DRESS is suspected, immunotherapy should be discontinued and the patient discussed urgently with Dermatology for assessment and management.
- For detailed information regarding steroid administration please see “other information” section at the end of document. For steroid taper schedules see appendix 1.

Cutaneous Toxicities
All grades:
- prescribe soap substitute to wash e.g. Dermol 500®
- prescribe greasy emollient e.g. Zerobase® or Hydromol® ointment to be applied twice daily

Grade	Management	Additional Investigations
Grade 1 Mild rash (macules/papules/pustules) covering <10% BSA with or without symptoms (e.g., pruritus, burning, tightness)	• Symptomatic treatment with oral antihistamine e.g. cetirizine 10 mg once daily if indicated • Topical steroid **mild – moderate** potency e.g. 1% hydrocortisone ointment (mild) or 0.05% clobetasone butyrate ointment (moderate) to apply twice daily	• Patient should be advised to contact clinical team if symptoms change or worsen
Grade 2 Moderate rash -covering 10 - 30% BSA with or without symptoms and limiting instrumental ADL	• Symptomatic treatment with oral antihistamine e.g. cetirizine 10 mg once daily if indicated • Topical steroid **potent or super potent** e.g. 0.1% betamethasone valerate ointment (potent) or 0.05% clobetasol propionate ointment (super potent) to apply twice daily (not to face where mild- moderate potency only should be used)	• Patient should be advised to contact clinical team if symptoms change or worsen • Consider Dermatology referral

Grade	Management	Additional Investigations
Grade 3 Severe rash includes blisters and erythema/erythroderma >30% BSA (or <30% if associated with significant symptoms)	• Withhold immunotherapy treatment • Topical therapy as per grade 2 rash • Administer prednisolone 1 - 2 mg/kg/day or equivalent for a minimum of 5 days then taper over 1 month	• Discuss with Dermatologist and arrange urgent outpatient appointment
Grade 4 Severe rash >30% BSA with skin sloughing, peeling, erythroderma, blisters, purpura, epidermal detachment and associated symptoms including pain	• Discontinue immunotherapy • Topical therapy as per grade 2 rash • Administer IV methylprednisolone 1-2 mg/kg/day or equivalent	• Emergency referral to Dermatology required
Suspected Stevens-Johnson syndrome / toxic epidermal necrolysis • **Clinical features of SJS / TEN:** - **abrupt onset of fever, systemic toxicity and typical skin features, rapidly progressive** - **atypical presentations are observed in patients on immunotherapy with TEN-like rashes** - **epidermal apoptosis causes a generalised dusky erythematous rash with target lesions and blisters Skin friable with epidermal loss and is associated with significant pain. Nikolsky sign is present (shearing of skin on lateral pressure)** - **mucosae can be affected, particularly of the eyes, mouth and genital tract. Less commonly the respiratory and GI tract can be affected leading to GI haemorrhage and bronchial obstruction secondary to mucosal debris, or ARDS.**		
SJS / TEN	• Permanently discontinue immunotherapy treatment • Admit to hospital: HDU / ITU • Initiate a primary management plan • Administer IV methylprednisolone 2 mg/kg/day or equivalent, if worsening or no improvement occurs despite 72 hours of IV corticosteroids consider alternative immunosuppressive therapy e.g. addition of **mycophenolate mofetil** with supportive treatment – co-trimoxazole - for prophylaxis for opportunistic infections or immunoglobulin • Emergency referral to dermatology (same day) required • Arrange to transfer patient to specialist centre with experience of treating patients with SJS / TEN and facilities to manage the logistics of extensive skin loss wound care	Refer to: UK guidelines for management of Stevens-Johnson syndrome/toxic epidermal necrolysis 2016

Immune-related Fatigue

- Fatigue is a very common and disruptive effect of immunotherapy treatment, but difficult to manage.
- The aetiology of immunotherapy induced fatigue is often multifactorial and not fully understood.
- Fatigue may be a manifestation of other known adverse effects of immunotherapy such as cardiac, pulmonary or endocrine toxicity.
- Fatigue can also be an effect of comorbidities or cancer itself (e.g. cancer cachexia) or it can result from concomitant systemic therapies such as cytotoxic chemotherapy, targeted agents, and radiation.
- There are a number of important reversible causes of fatigue including endocrinopathies, anaemia and cardiac toxicity. The aetiology has important implications on treatment and prognosis as immune mediated myocarditis has an approximate 50% mortality rate.

Baseline investigations in all patients with suspected immune-related fatigue:

- Perform physical exam including vital signs: weight, temperature, heart rate, RR, BP, O2 saturation (rest and walking)
- **Check routine immunotherapy bloods**
- **Hormone screen - cortisol, IGF-1, prolactin, LH , FSH, Testosterone (males only), Oestradiol (females only)**
- **Check troponin, CK, NT-pro-BNP, B12, folate, iron, vitamin D**
- If no treatable cause found monitor for new or worsening symptoms
- Continue immunotherapy if no major impact on ADL
- If severe, withhold immunotherapy. Exclude disease progression, other medical conditions or other irAE. Follow up based on diagnosis

Immune-related Cardiovascular Toxicities

- The World Health Organisation's (WHO) global database (VigiBase) of individual drug case safety reports confirmed that myocarditis is strongly associated with immunotherapy as reports of this adverse effect were 11 fold higher for immunotherapies than for all drugs.
- The prevalence/recognition of myocarditis has also been increasing over the years. This may reflect the increased use of immunotherapy in larger patient populations and also the use of immunotherapies in combination.
- Immunotherapy treatment is also associated with other inflammatory cardiovascular adverse effects, including pericardial disease, vasculitis and coronary artery disease.
- Signs and symptoms, such as new-onset or worsening fatigue, chest pain, dyspnoea, palpitations, peripheral oedema, or hypotension should prompt an immediate clinical evaluation.
- The range of presentations can be broad, therefore any relevant alerting symptoms should prompt immediate investigations as detailed below.
- **Early initiation of high-dose steroids is crucial to reduce mortality from myocarditis.**

Myocarditis: A disorder characterised by inflammation of the heart muscle (myocardium)		
Baseline investigations in all patients with suspected myocarditis: - ECG, troponin (preferably troponin I), BNP/NT-proBNP and echocardiogram (including global longitudinal strain [GLS])		
	Immediate Management	**Additional Information**
Stable patient	• Withhold immunotherapy treatment. • Admit to hospital for baseline investigations. • If troponin elevated and/or ECG abnormal without alternative explanation, administer IV methylprednisolone 1000 mg/day or equivalent for 3 - 5 days before commencing reduction schedule, if effective. • Consider alternate aetiologies (e.g. acute coronary syndrome) but do not delay administration of high dose steroids. • Discuss with cardiology and commence continuous cardiac rhythm monitoring. Consider transfer to CCU depending on balance of competing oncologic vs cardiovascular risk / prognosis. • Monitor troponin daily. If worsening or no improvement occurs within 72 hours despite initiation of corticosteroids, consider addition of **mycophenolate mofetil** with supportive treatment (co-trimoxazole for prophylaxis for opportunistic infections) or immunoglobulin (IVIG)	• The majority of patients with ICI-associated myocarditis will have elevated troponin and abnormal ECG. • A normal echo does not rule out myocarditis (preserved left ventricular function may be more common in immunotherapy-related myocarditis than in other cases of myocarditis). • Brady- and tachy-arrhythmia are common. • Consider Cardiac magnetic resonance (CMR) imaging after discussion with cardiology. • Consider Endomyocardial biopsy (EMB) if ongoing clinical suspicion but other investigations negative after discussion with cardiology. • Skeletal myositis is observed in 25% of patients with immunotherapy myocarditis. There is an association between immunotherapy myocarditis and immunotherapy-induced myasthenia gravis.

	Immediate Management	Additional Information
Unstable patient (e.g. presenting with cardiogenic shock, cardiac arrest, or unstable arrhythmias)	• Withhold immunotherapy treatment. • Seek urgent cardiology consultation and potential transfer to a “hot site” for admission to CCU depending on balance of competing oncologic vs cardiovascular risk / prognosis • Administer IV methylprednisolone 1000 mg/day with second immunosuppressant (mycophenolate, mofetil, abatacept, ATG, IVIG or alemtuzumab). Consider plasmapheresis. • Once patient stabilised and improving, transition to oral prednisolone and commence reduction schedule.	• Consider mechanical circulatory support if appropriate • Consider CMR imaging and EMB as above after discussion with cardiology.

Recommended steroid reduction schedule:

- After 3 - 5 days of IV methylprednisolone 1000 mg/day, switch to oral prednisolone 1 mg/kg/day reducing if clinical improvement in symptoms, LV systolic function, conduction abnormalities **and** significant troponin reduction (troponin reduced by > 50% from peak)
- Taper prednisolone dose by 10mg per week with close monitoring of troponin.

Immune-related Rheumatic Events

- Rheumatic events have been described rarely in clinical trials; however, they appear more prevalent in clinical practice. As a result, a European League Against Rheumatism (EULAR) task force was convened to provide guidance on this.
- Rheumatic and musculoskeletal irAEs are observed in about 10% of patients receiving immunotherapy.
- Patients may report symptoms of arthralgia, arthritis, myalgia, myositis, dry mouth, musculoskeletal and back pain.
- Patients with pre-existing autoimmune rheumatic and/or systemic disease may receive immunotherapy; however, baseline immunosuppressive regimen should be kept at the lowest dose possible (for glucocorticoids, <10 mg/day prednisolone, if possible).
- Oncologists should be encouraged to promptly consult with rheumatologists when rheumatic symptoms are suspected because of immunotherapy. Consider checking autoimmune bloods including ANA, RF, anti-CCP and inflammatory markers (ESR and CRP)
- Early referral is recommended in order to alleviate patient symptoms, maintain a good quality of life and allow for ongoing immunotherapy treatment

- EULAR has issued a warning for severe myositis, a spectrum of potentially fatal toxicity associated with bulbar symptoms (dysphagia, dysarthia, dysphonia), dyspnoea and myocarditis:

    - generally occurs very early after initiation of immunotherapy treatment
    - proximal weakness and myalgia are the major symptoms (can mimic a polymyalgia rheumatica – like condition)
    - if suspected, creatinine kinase (CK) level should be measured as increased CKs are seen in the majority of patients with myositis
    - cardiac evaluation (troponin, ECG) must be carried out for any patient with suspected myositis due to high risk of myocarditis
    - Also associated with myasthenic symptoms – patient should be assessed for fatigable weakness.

- Alternative aetiologies should be ruled out e.g. tumour progression, non-rheumatic events (i.e. viral infection, thrombosis, endocrine abnormality)

- In the absence of contraindications, symptomatic treatment with NSAIDS +/- analgesics should be the initial treatment for mild-moderate symptoms.

- The decision to withhold or withdraw immunotherapy treatment should be based on the severity of rheumatic irAE (number of joints involved and functional assessment), the required treatment and discussion with the responsible consultant.

The European League Against Rheumatism (EULAR) details 3 treatment escalations to consider as described in the table below:

Grade	Management
1 (mild – moderate)	• In the absence of contraindications, symptomatic treatment with paracetamol and / or NSAIDs • Consider intra-articular steroids into affected joint(s), depending on joint location and number involved
2 (no improvement/ uncontrolled symptoms	• Consider withholding immunotherapy • Systemic corticosteroids if symptoms are not controlled by symptomatic treatment (prednisolone 0.5 mg/kg/day), subsequently tapered to the lowest effective dose • Rheumatology referral for conventional synthetic DMARDs in the event of an inadequate response to glucocorticoids or for steroid-sparing
3 – 4 (severe / refractory)	• Withhold immunotherapy and make urgent referral to rheumatology • Biological DMARDs

Immune-related Neurological Complications

- Neurological complications from immunotherapy are rare but diverse, with significant potential to cause morbidity and mortality.
- Patients may present with an overlap in syndromes, for example myositis overlapping with a myasthenia-like presentation. Furthermore, they may present with both CNS and PNS involvement (such as CNS demyelination in combination with a demyelinating neuropathy).
- In patients presenting with possible neurotoxicity, have a low threshold to withdraw treatment even if symptoms are mild (grade 1).

- Neuro-inflammatory complications include:

    - myositis (many will also have cardiac involvement – myocarditis)
    - myasthenia gravis (MG)
    - Guillain Barre syndrome (be aware of potential autonomic dysfunction including cardiac, bowel and bladder involvement)
    - chronic inflammatory demyelinating polyradiculoneuropathy (CIDP).
    - vasculitic neuropathy or cranial neuropathies
    - brain and/or spinal cord demyelination – exacerbation of multiple sclerosis or de novo CNS demyelinating disease manifesting as acute tumefactive brain lesions or transverse myelitis or optic neuritis
    - autoimmune encephalitis.

- Patients should be monitored for symptoms and signs, including the following:

    - progressive muscle weakness (proximal >distal), which may be fatigable and variable; especially in the context of MG development. There may be neck muscle weakness and a head drop as a result of neck extensor muscle weakness. The head drop, if severe, may cause mechanical swallowing difficulties, or expose and exacerbate any mild dysphagia if in the background.
    - ptosis (may be symmetrical) with or without associated facial muscle weakness
    - blurring of vision or diplopia (usually in context of MG) with evidence of ocular motility disturbance or asymmetry (however, please note this can also be seen in brainstem disorders such as internuclear ophthalmoplegia occurring in the context of brainstem demyelination).
    - bulbar weakness – can present as dysarthria with or without fatigability, dysphonia, dysphagia and chewing disturbance with weakness and/or fatigability (this is also usually in the context of MG or occasionally myositis, however note some of these symptoms can also represent brainstem disorders).
    - ascending sensory disturbances in a length-dependent manner (from the tips of the toes extending proximally, and involving the hands when at the level of the patient's knees), indicating a peripheral neuropathy. Reflexes will either be diminished or absent. However, if there is sensory disturbance without upper limb involvement, this would be more in keeping with transverse myelitis. There will be hyper-reflexia and there may be an extensor plantar response or associated sphincter disturbance.
    - neuropathic pain
    - limb weakness (distal>proximal); +/- ataxia, or +/- sensory disturbance, in which case peripheral nerve aetiology must be considered.
    - headaches, fever, altered cognition or conscious level or acute confusional state, psychotic behaviour, involuntary movements, autonomic dysfunction
    - breathlessness, orthopnea.

- Investigations and management should be directed in accordance with symptom presentation, guidance for which has been outlined below.
- Four main categories have been developed; however, the clinician must be aware of the potential for overlap between presentations.
- **<u>Discussion with neurology is paramount in all cases.</u>**

Presentation	Investigations	Management
Myositis: gradually progressive muscle weakness with discomfort **Myasthenia Gravis**: -As above, but with an element of fatigability or variation -Involvement of ocular or bulbar muscles Please be aware that there may potentially be a degree of overlap	• Check CK, myositis specific antibody panel, acetylcholine receptor (AChR) antibodies, MuSK antibodies. • If the patient is taking statin, withhold this and check HMG CoA reductase antibodies (N.B. co-existent statin-induced myositis would be unusual). • If AChR antibodies negative → consider EMG studies with repetitive nerve stimulation and/or single fibre EMG studies (following discussion with neurology). • Check bedside FVCs (both sitting and supine to assess for diaphragmatic involvement). If abnormal perform ABGs.	• Discuss with neurology for further advice. • SALT assessment if swallow deemed unsafe • If at risk of aspiration, consider NGT insertion • Myositis: commence high dose PO prednisolone 40mg once daily. • If more in keeping with myasthenia gravis commence steroids, however these should be introduced at a more gradual rate (**high dose steroids may precipitate myasthenic crisis- as above, please consult neurology /myasthenia team for further guidance regarding tailoring of regimens**)
Guillain-Barre Syndrome (GBS) or CIDP -Ascending sensory disturbance (length-dependent manner) -Hypo-/areflexia Patients may also present with cranial mononeuropathies or develop these in the context of meningoradiculoneuritis	• Check anti-ganglioside antibodies, hepatitis and virology screen, campylobacter serology and conventional neurology screen. • Consider paranodal antibody testing (consult with neurology team). • Lumbar Puncture: CSF would typically illustrate an elevated protein level and would be acellular (if cellular in nature, this would not be classical for GBS). • Nerve conduction studies to confirm nature of neuropathy (axonal or demyelinating, +/- evidence of conduction block). • For vasculitic neuropathies, carry out a vasculitis blood panel and consider nerve biopsy if conduction studies fail to demonstrate evidence of multifocal nerve involvement.	• Discuss with neurology team • GBS: Consider IV Immunoglobulin (0.4 g/kg/day) for a total of five days. If no response/evolving symptoms consider plasma exchange. High dose steroids have a role in a subgroup of patients however steroids would usually exacerbate GBS; please discuss with neurology in the first instance. • If presenting with cranial mononeuropathies (facial diplegia, abducent nerve palsies, optic neuropathy), initial brain imaging will be required; these patients are likely to respond to high-dose steroids

Presentation	Investigations	Management
Symptoms suggestive of Brain/Spinal Cord Involvement (exacerbation of pre-existing Multiple sclerosis, de novo CNS demyelinating disease, optic neuritis, transverse myelitis or acute tumefactive demyelinating brain/spinal cord lesions)	• MRI brain and MRI whole spine should be performed (consider the addition of gadolinium for identification of actively enhancing lesions). • Following imaging, perform a lumbar puncture and send samples for biochemistry, cytology, microbiology and oligoclonal bands. Viral PCR should also be sent if there is suspicion of an infective/encephalitis aetiology. Remember to send a paired serum glucose and also a CSF sample to test oligoclonal bands. • Send serum for anti-aquaporin-4 and anti-MOG antibodies.	• Initial treatment would normally consist of high-dose intravenous steroids: Methylprednisolone 1g daily for a total of three doses, often followed by oral prednisolone. • Depending on the rate of symptom evolution and neurological impairment, some patients may require plasma exchange
Autoimmune Encephalitis: -Acute confusional state, altered cognition, agitation or psychosis -Fever, headache or movement disorder -Autonomic Instability	• Serology for NMDA, LGl1, CASPR2, GAD, GABA, AMPA, glycine receptor and anti-neuronal antibodies • Brain Imaging • Lumbar puncture with additional investigations for CSF NMDAR • *Please note: sedation may be required for the above investigations depending on the patient's presentation*	• Discuss with neurology team • High-dose steroids are usually implemented in the management of autoimmune encephalitis however IV Immunoglobulin or plasma exchange may be implemented for immediate stabilisation of the patient. High-dose steroids may worsen agitation- as above, please consult your local neurology team for further advice. • Psychiatric input may be required.
Aseptic meningitis **-**headache commonly, neck pain and stiffness, fever, nausea and vomiting and sometimes altered conscious level	• MRI brain scan with gadolinium • Lumbar puncture • Septic screen is crucial, including on CSF	• Patients often respond to high dose steroids
Hypophysitis **-**headache, fatigue, and manifestations reflecting deficiency of anterior pituitary function (see endocrine section)	• MRI brain scan with gadolinium and including dedicated imaging of hypothalamopituitary axis • Testing of pituitary function (discuss with endocrinology)	• Patients often respond to high dose steroids and will require hormonal replacement (discuss with endocrinology)

Immune-related Ophthalmological Complications

- Ophthalmic issues with immunotherapy are quite rare, usually only affecting a small number of patients, however, they are becoming more relevant as indications increase and demand for treatment grows.
- Ocular adverse effects can be serious and sight threatening.
- Clinicians should have an awareness of the possible signs and symptoms (described below).
- Concerning symptoms should be discussed with ophthalmology (for out-patients, ophthalmology team in patient's local hospital)
- The patient may be directed to their optician, depending on context.

Ocular Effect	Management
Uveitis Signs and symptoms may include: photophobia (pain when looking at lights) redness in eye (particularly around the edge of the cornea), watering, visual problems, pain in eye, blurred vision	• Patients should be advised on and monitored for signs and symptoms of uveitis. It can have an insidious onset in this patient population and can bilateral. (Note: symptoms of photophobia and increased pain when attempting to focus on close objects are useful indicators for distinguishing uveitis from conjunctivitis) • If uveitis is suspected, urgent referral (within 1 week) to ophthalmology is indicated. Treatment with steroid drops should not be initiated until ophthalmic input • Patients previously diagnosed with uveitis who recognise a recurrence of symptoms should contact ophthalmology for confirmation of diagnosis. They will usually reviewed within 24-48 hours. • Ocular surface disturbance (symptoms of dryness resulting in over production of tears, photophobia, blurred vision) appears to be a relatively common side effect of immunotherapy and can present similarly to uveitis. Patients should be advised to ask their local pharmacy for lubricant eye drops. In most instances ophthalmological input is not required. • In the context of immunotherapy, ocular surface disease (with significant, unrelenting pain and photophobia) does sometimes progress rapidly to the formation of corneal ulcers. These do require very urgent specialist ophthalmic attention.
Retinitis Symptoms of rapidly progressive visual impairment. Some patients may present with photopsia (flashing lights), nyctalopia (difficulty in seeing dim light), photophobia (pain when looking at lights) and visual field constriction. These symptoms are generally bilaterally symmetrical; and there is usually no visible abnormality in the eyes.	• Electroretinography (ERG) may be helpful in the diagnosis: in cancer-associated retinopathy it is unrecordable. • The electrodiagnostic team at the department of ophthalmology at Gartnavel General Hospital should be contacted for advice. A hand-held ERG machine ("Reteval") is available in some hospitals' ophthalmology clinics. • Contact Dr John Goodfellow, consultant Neuro-immunologist at GRI, for advice about testing for anti-retinal antibodies. • No form of treatment has been found to be consistently beneficial. • Considerable support may be needed for patients who lose their eyesight in the context of cancer treatment, whether or not the immunotherapy could have contributed.
Other rare inflammatory-type manifestations may include vasculitis, granulomas and sub-retinal fluid	• Refer any patients with loss of vision, especially persistent features, including photopsia, photo aversion (struggling in bright lights), nyctalopia, photophobia, reduced acuity and reduced visual field.

Other Immune-related Adverse Events

- The following adverse reactions were reported in patients treated with immunotherapy in clinical trials, irrespective of tumour type:

- Pancreatitis
- Haematological toxicity

- For a suspected IrAE, adequate evaluation should be performed to confirm aetiology and exclude other causes.

- Based on the severity of the adverse reaction, immunotherapy treatment should be withheld.

Miscellaneous immune-related adverse effects	Management
Pancreatitis Signs and symptoms may include: severe pain in upper abdomen, decreased appetite, nausea, vomiting, raised amylase / lipase	• Patients should be monitored for signs and symptoms of pancreatitis; clinical features alongside elevated enzymes. The clinical significance of elevated amylase / lipase in the absence of associated symptoms remains unknown • Monitoring serum amylase and lipase in asymptomatic patients is not recommended unless pancreatitis is suspected clinically • Corticosteroid treatment is not indicated for asymptomatic elevations in serum amylase / lipase, providing there are no other signs or symptoms of pancreatitis • If pancreatitis suspected, patient should be discussed with gastroenterology and admitted to hospital, preferably a specialist unit, for full investigation • A stool sample should be tested for faecal elastase. This allows the diagnosis or exclusion of pancreatic exocrine insufficiency. Elastase 100-199 µg/g is consistent with exocrine pancreatic insufficiency. Elastase < 100 µg/g is consistent with severe exocrine pancreatic insufficiency • Patients with exocrine pancreatic insufficiency should be commenced on Creon® (pancreatin). The recommended starting dose for adults is 2 x Creon® 25,000 unit capsules per meal and 1 x Creon® 25,000 unit capsule per snack with subsequent titration depending on level of response • Prompt diagnosis and management is associated with earlier resolution and lower mortality rates
Haematological toxicities Immune related haematological toxicities can include a wide range of haematological conditions such as haemolytic or aplastic anaemia, lymphophenia, immune thrombocytopenia (ITP) and haemolytic uraemic syndrome. There is a lack of recognition of these toxicities, partly because they have been poorly described and also as they appear to be a much rarer occurrence	• Full blood counts must be monitored during treatment with immunotherapy • Depending on the grade of adverse event, treatment may require to be withheld or discontinued • The optimal treatment for haematological toxicity is unknown and treatment with high dose corticosteroids or other immunosuppressive agents must be done in collaboration with a haematologist.

Miscellaneous immune-related adverse effects	Management
Other	• On suspicion of other irAEs, patient should be fully assessed to rule out non-immune related causes • For mild / moderate (grade 1 / 2) irAEs: - increase monitoring - consider symptomatic treatments - consider withholding next dose of treatment until event resolves - if symptoms worsen or do not improve after 1-2 weeks then manage as a serious adverse event • For severe (grade 3 / 4) irAEs: - increase monitoring - withhold next dose of treatment until event resolves - strongly consider treatment with corticosteroids - consider referral to specialist

OTHER INFORMATION

Corticosteroids

General points

- All patients (including those started on oral hydrocortisone for adrenal insufficiency) should be issued with a **Steroid Treatment Card** which gives guidance on minimising risk and provides details of prescriber, drug, dosage and expected duration of treatment.

- For mild/moderate irAEs, regardless of improvement, the initial oral steroid dose should be maintained for a minimum of 5 days and tapered over 1 month. The dose should be reduced (by approximately 10%) every 3 days. Patients should be monitored regularly (at least once a week) for recurrence of symptoms as doses are reduced.

- Patients who develop a recurrence of symptoms should have their oral steroid dose increased back to the previous effective dose for a further 5 days and then return to a taper schedule.

- For severe irAEs, regardless of improvement, the initial IV steroid dose should be maintained for a minimum of 5 days.

- It is important to be aware of, and monitor patients for the potential detrimental effects of prolonged corticosteroid administration such as:

- opportunistic infections (consider PJP prophylaxis)
- diabetes
- osteoporosis and increased risk of fractures, particularly in the elderly (consider addition of an oral bisphosphonate e.g. alendronic acid 70 mg once weekly +/- calcium + vitamin D supplementation)
- muscle wasting (proximal myopathy)
- peptic ulceration and perforation (consider PPI e.g. omeprazole 20 mg once daily).

- Non-corticosteroid immunosuppressive therapy should be added if there is worsening or no improvement despite corticosteroid use.

- Immunotherapy treatment should not be resumed while the patient is receiving immunosuppressive doses of corticosteroids or other immunosuppressive therapy (>10mg prednisolone once daily or equivalent).

- Treatment should be permanently discontinued for:

- any severe immune-related adverse reaction that recurs and for any life-threatening immune related adverse reaction
- grade 2 or 3 immune-related adverse reactions that persist despite treatment modifications or if a reduction in corticosteroid dose to 10mg prednisolone or equivalent cannot be achieved.

- For suggested steroid reduction schedules please refer to Appendix 1 and 2.

Equivalent anti-inflammatory (glucocorticoid) doses of corticosteroids

Prednisolone 5mg
= betamethasone 750 micrograms
= deflazacort 6 mg
= dexamethasone 750 micrograms
= hydrocortisone 20 mg
= methylprednisolone 4mg
= prednisone 5mg
= triamcinolone 4mg

Switching from IV methylprednisolone to oral prednisolone

- Prednisolone 5mg orally is equivalent to 4mg methylprednisolone intravenously (equivalent anti-inflammatory dose)
- e.g. patient receiving 80 mg of IV methyprednisolone per day (4:5 ratio with prednisolone) = 100mg of prednisolone per day.

Infusion Related Reaction

- Infusion related reactions, which may be severe, have been reported with immunotherapy:
- patients should be monitored for signs and symptoms of infusion related reactions including pyrexia, chills, flushing, hypotension, dyspnoea, wheezing, back pain, abdominal pain and urticaria.

- For grade 1 infusion related reactions, the infusion rate should be slowed by 50% for the current infusion.

- For grade 2 infusion related reactions, the infusion should be temporarily discontinued until grade 1 or resolved, then the infusion will restart with a 50% slower infusion rate.

- For grade 3 or 4 infusion related reactions, the infusion should be stopped and immunotherapy treatment permanently discontinued.

- In cases of recurrence of grade 1 or 2 infusion related reactions, the patient may continue to receive immunotherapy treatment under close monitoring, after infusion rate modification and premedication with paracetamol and antihistamine.

Endocrinology Reference Ranges

Tests	**Adult Serum Reference Range**
Cortisol	7 - 9 am: 240 – 600 nmol/L 9pm – 12 midnight: 50 – 290 nmol/L Morning to Evening: >100 nmol/L
ACTH	7 – 9am <20 mU/L
Prolactin	Male <400 mU/L Female <630 mU/L
Free thyroxine (T4)	9 – 21 pmol/l
Triiodothyronine (T3)	0.9 – 2.5 nmol/l
Thyroid Stimulating Hormone (TSH)	0.35 – 5 mU/l
Anti-thyroid peroxidase antibody (anti-TPOAb)	<6 IU/L
Luteinising hormone (LH)	Follicular 2 – 13 U/L Luteal 1.0 -16 U/L Postmenopausal 16 – 64 U/L
Follicle stimulating hormone (FSH)	Follicular 3 – 8 U/L Luteal 1 – 5 U/L Postmenopausal 18 – 150 U/L

Synacthen Test

- 0.25mg Synacthen® (tetracosactrin, 1-24 ACTH) injected INTRAVENOUSLY between 8am and 10am. Blood sample at times 0 and 30 minutes for serum cortisol.

- Principle: a normal functioning adrenal gland will increase its production of cortisol in response to ACTH administration.

- Indications: to exclude/screen for adrenal insufficiency.

- Response:
- adequate >450 nmol/L
- inadequate <450 nmol/L

- Interpretation:
- an adequate response indicates normal function, there is no need for further investigation unless clinical concerns
- an inadequate response indicates adrenal suppression and will warrant further investigation. Follow up with additional tests and seek endocrinology opinion.

Pneumocystis Jiroveci Pneumonia (PJP) Prophylaxis

- Co-trimoxazole 960mg ONCE daily on a Monday, Wednesday and Friday.

- If patient is allergic to either trimethoprim or sulfamethoxazole please discuss alternative agent with responsible consultant.

Prophylaxis against fungal infections

- Prophylaxis against fungal infections (e.g. fluconazole 50 mg od) should be considered in patients receiving a prednisolone dose of 20 mg od or equivalent for longer than 6 – 8 weeks.

Thromboprophylaxis (for patients admitted to hospital)

- All patients must have their risk of venous thromboembolism (VTE) assessed at admission using the appropriate risk assessment tool and then regularly during their stay in hospital.

- A record of these assessments must be made and documented in the thromboprophylaxis section of the kardex.

- Do not offer pharmacological prophylaxis to patients with risk factors for bleeding unless the risk of VTE outweighs the risk of bleeding.

- Patients already receiving therapeutic anticoagulation do not need additional thromboprophylaxis.

- Patients who merit pharmacological thromboprophylaxis should receive treatment as per local guidelines.

Vaccines

- Vaccines that are inactivated or killed preparations are permissible during a course of immunotherapy

- Due to the lack of clarity regarding live vaccine use, it is not recommended during immunotherapy.

Appendix 1: Suggested prednisolone dosing schedules (1 mg/kg standard taper). NB. Some patients may require higher steroid doses and slower tapers, please adjust accordingly.

Prednisolone 1 mg/kg/day	Patient Weight (kg)						
	40-44	45-49	50-54	55-59	60-64	65-69	70-74
Days 1 - 5	45 mg	50 mg	55 mg	60 mg	65 mg	70 mg	75 mg
Days 6 – 8	35 mg	40 mg	45 mg	45 mg	50 mg	50 mg	60 mg
Days 9 – 11	30 mg	30 mg	35 mg	35 mg	40 mg	40 mg	45 mg
Days 12 – 14	25 mg	25 mg	30 mg	30 mg	30 mg	30 mg	30 mg
Days 15 – 17	20 mg	20 mg	25 mg	25 mg	25 mg	25 mg	25 mg
Days 18 – 20	15 mg	15 mg	20 mg	20 mg	20 mg	20 mg	20 mg
Days 21 - 23	10 mg	10 mg	15 mg	15 mg	15 mg	15 mg	15 mg
Days 24 – 26	5 mg	5 mg	10 mg	10 mg	10 mg	10 mg	10 mg
Days 27 – 29	**STOP**	**STOP**	5 mg	5 mg	5 mg	5 mg	5 mg
Days 30 – 32	-	-	**STOP**	**STOP**	**STOP**	**STOP**	**STOP**
Days 33 - 35	-	-	-	-			
Days 36 - 38	-	-	-	-			

Prednisolone 1 mg/kg/day	Patient Weight (kg)						
	75-79	80-84	85-89	90-94	95-99	100-104	105-109
Days 1 - 5	80 mg	85 mg	90 mg	95 mg	100 mg	105 mg	110 mg
Days 6 – 8	60 mg	65 mg	70 mg	75 mg	80 mg	80 mg	90 mg
Days 9 – 11	40 mg	45 mg	50 mg	55 mg	60 mg	60 mg	70 mg
Days 12 – 14	30 mg	30 mg	40 mg	40 mg	40 mg	40 mg	50 mg
Days 15 – 17	25 mg	25 mg	30 mg	30 mg	30 mg	30 mg	40 mg
Days 18 – 20	20 mg	20 mg	25 mg	25 mg	25 mg	25 mg	30 mg
Days 21 - 23	15 mg	15 mg	20 mg	20 mg	20 mg	20 mg	25 mg
Days 24 – 26	10 mg	10 mg	15 mg	15 mg	15 mg	15 mg	20 mg
Days 27 – 29	5 mg	5 mg	10 mg	10 mg	10 mg	10 mg	15 mg
Days 30 – 32	**STOP**	**STOP**	5 mg	5 mg	5 mg	5 mg	10 mg
Days 33 - 35			**STOP**	**STOP**	**STOP**	**STOP**	5 mg
Days 36 - 38							**STOP**

Appendix 2: Suggested methylprednisolone starting dose (1 mg/kg) and conversion to oral prednisolone. NB. Some patients may require higher steroid doses and slower tapers, please adjust accordingly.

Patient weight 40-44 kg	IV methyl-prednisolone 1 mg/kg/day	Oral prednisolone dose
Days 1 - 5	45 mg	-
Days 6 – 8	-	50 mg
Days 9 – 11	-	45 mg
Days 12 – 14	-	40 mg
Days 15 – 17	-	35 mg
Days 18 – 20	-	30 mg
Days 21 - 23	-	25 mg
Days 24 – 26	-	20 mg
Days 27 – 29	-	15 mg
Days 30 – 32	-	10 mg
Days 33 – 35	-	5 mg
Day 36	-	STOP

Patient weight 45-49 kg	IV methyl-prednisolone 1 mg/kg/day	Oral prednisolone dose
Days 1 - 5	50 mg	-
Days 6 – 8	-	55 mg
Days 9 – 11	-	50 mg
Days 12 – 14	-	45 mg
Days 15 – 17	-	40 mg
Days 18 – 20	-	35 mg
Days 21 - 23	-	30 mg
Days 24 – 26	-	25 mg
Days 27 – 29	-	20 mg
Days 30 – 32	-	15 mg
Days 33 – 35	-	10 mg
Days 36 - 38	-	5 mg
Day 39	-	STOP

Patient weight 50-54 kg	IV methyl-prednisolone 1 mg/kg/day	Oral prednisolone dose
Days 1 - 5	55 mg	-
Days 6 – 8	-	60mg
Days 9 – 11	-	50 mg
Days 12 – 14	-	45 mg
Days 15 – 17	-	40 mg
Days 18 – 20	-	35 mg
Days 21 - 23	-	30 mg
Days 24 – 26	-	25 mg
Days 27 – 29	-	20 mg
Days 30 – 32	-	15 mg
Days 33 – 35	-	10 mg
Days 36 - 38	-	5 mg
Day 39	-	STOP

Patient weight 55-59 kg	IV methyl-prednisolone 1 mg/kg/day	Oral prednisolone dose
Days 1 - 5	60 mg	-
Days 6 – 8	-	65mg
Days 9 – 11	-	55 mg
Days 12 – 14	-	50 mg
Days 15 – 17	-	45 mg
Days 18 – 20	-	40 mg
Days 21 - 23	-	35 mg
Days 24 – 26	-	30 mg
Days 27 – 29	-	25 mg
Days 30 – 32	-	20 mg
Days 33 – 35	-	15 mg
Days 36 – 38	-	10 mg
Days 39 – 41	-	5 mg
Day 42	-	STOP

Patient weight 60-64 kg	IV methyl-prednisolone 1 mg/kg/day	Oral prednisolone dose
Days 1 - 5	65 mg	-
Days 6 – 8	-	70 mg
Days 9 – 11	-	60 mg
Days 12 – 14	-	50 mg
Days 15 – 17	-	45 mg
Days 18 – 20	-	40 mg
Days 21 - 23	-	35 mg
Days 24 – 26	-	30 mg
Days 27 – 29	-	25 mg
Days 30 – 32	-	20 mg
Days 33 – 35	-	15 mg
Days 36 – 38	-	10 mg
Days 39 – 41	-	5 mg
Day 42	-	STOP

Patient weight 65-69 kg	IV methyl-prednisolone 1 mg/kg/day	Oral prednisolone dose
Days 1 - 5	70 mg	-
Days 6 – 8	-	75 mg
Days 9 – 11	-	65 mg
Days 12 – 14	-	55 mg
Days 15 – 17	-	50 mg
Days 18 – 20	-	45 mg
Days 21 - 23	-	40 mg
Days 24 – 26	-	35 mg
Days 27 – 29	-	30 mg
Days 30 – 32	-	25 mg
Days 33 – 35	-	20 mg
Days 36 – 38	-	15 mg
Days 39 – 41	-	10 mg
Days 42 – 44	-	5 mg
Day 45	-	STOP

Patient weight 70-74 kg	IV methyl-prednisolone 1 mg/kg/day	Oral prednisolone dose
Days 1 - 5	75 mg	-
Days 6 – 8	-	80 mg
Days 9 – 11	-	70 mg
Days 12 – 14	-	60 mg
Days 15 – 17	-	50 mg
Days 18 – 20	-	45 mg
Days 21 - 23	-	40 mg
Days 24 – 26	-	35 mg
Days 27 – 29	-	30 mg
Days 30 – 32	-	25 mg
Days 33 – 35	-	20 mg
Days 36 – 38	-	15 mg
Days 39 – 41	-	10 mg
Days 42 – 44	-	5 mg
Day 45	-	STOP

Patient weight 75-79 kg	IV methyl-prednisolone 1 mg/kg/day	Oral prednisolone dose
Days 1 - 5	80 mg	-
Days 6 – 8	-	85 mg
Days 9 – 11	-	75 mg
Days 12 – 14	-	65 mg
Days 15 – 17	-	55 mg
Days 18 – 20	-	45 mg
Days 21 - 23	-	40 mg
Days 24 – 26	-	35 mg
Days 27 – 29	-	30 mg
Days 30 – 32	-	25 mg
Days 33 – 35	-	20 mg
Days 36 – 38	-	15 mg
Days 39 – 41	-	10 mg
Days 42 – 44	-	5 mg
Day 45	-	STOP

Patient weight 80-84 kg	IV methyl-prednisolone 1 mg/kg/day	Oral prednisolone dose
Days 1 - 5	85 mg	-
Days 6 – 8	-	90 mg
Days 9 – 11	-	80 mg
Days 12 – 14	-	70 mg
Days 15 – 17	-	60 mg
Days 18 – 20	-	50 mg
Days 21 - 23	-	40 mg
Days 24 – 26	-	35 mg
Days 27 – 29	-	30 mg
Days 30 – 32	-	25 mg
Days 33 – 35	-	20 mg
Days 36 – 38	-	15 mg
Days 39 – 41	-	10 mg
Days 42 – 44	-	5 mg
Day 45	-	STOP

Patient weight 85-89 kg	IV methyl-prednisolone 1 mg/kg/day	Oral prednisolone dose
Days 1 - 5	90 mg	-
Days 6 – 8	-	95 mg
Days 9 – 11	-	85 mg
Days 12 – 14	-	75 mg
Days 15 – 17	-	65 mg
Days 18 – 20	-	55 mg
Days 21 - 23	-	45 mg
Days 24 – 26	-	35 mg
Days 27 – 29	-	30 mg
Days 30 – 32	-	25 mg
Days 33 – 35	-	20 mg
Days 36 – 38	-	15 mg
Days 39 – 41	-	10 mg
Days 42 – 44	-	5 mg
Day 45	-	STOP

Patient weight 90-94 kg	IV methyl-prednisolone 1 mg/kg/day	Oral prednisolone dose
Days 1 - 5	95 mg	-
Days 6 – 8	-	100 mg
Days 9 – 11	-	90 mg
Days 12 – 14	-	80 mg
Days 15 – 17	-	70 mg
Days 18 – 20	-	60 mg
Days 21 - 23	-	45 mg
Days 24 – 26	-	35 mg
Days 27 – 29	-	30 mg
Days 30 – 32	-	25 mg
Days 33 – 35	-	20 mg
Days 36 – 38	-	15 mg
Days 39 – 41	-	10 mg
Days 42 – 44	-	5 mg
Day 45	-	STOP

Patient weight 95-99 kg	IV methyl-prednisolone 1 mg/kg/day	Oral prednisolone dose
Days 1 - 5	100 mg	-
Days 6 – 8	-	105 mg
Days 9 – 11	-	90 mg
Days 12 – 14	-	80 mg
Days 15 – 17	-	70 mg
Days 18 – 20	-	60 mg
Days 21 - 23	-	45 mg
Days 24 – 26	-	35 mg
Days 27 – 29	-	30 mg
Days 30 – 32	-	25 mg
Days 33 – 35	-	20 mg
Days 36 – 38	-	15 mg
Days 39 – 41	-	10 mg
Days 42 – 44	-	5 mg
Day 45	-	STOP

Patient weight 100-104 kg	IV methyl-prednisolone 1 mg/kg/day	Oral prednisolone dose
Days 1 - 5	105 mg	-
Days 6 – 8	-	110 mg
Days 9 – 11	-	95 mg
Days 12 – 14	-	85 mg
Days 15 – 17	-	75 mg
Days 18 – 20	-	60 mg
Days 21 - 23	-	45 mg
Days 24 – 26	-	35 mg
Days 27 – 29	-	30 mg
Days 30 – 32	-	25 mg
Days 33 – 35	-	20 mg
Days 36 – 38	-	15 mg
Days 39 – 41	-	10 mg
Days 42 – 44	-	5 mg
Day 45	-	STOP

Patient weight 105-109 kg	IV methyl-prednisolone 1 mg/kg/day	Oral prednisolone dose
Days 1 - 5	110 mg	-
Days 6 – 8	-	115 mg
Days 9 – 11	-	100 mg
Days 12 – 14	-	85 mg
Days 15 – 17	-	75 mg
Days 18 – 20	-	60 mg
Days 21 - 23	-	45 mg
Days 24 – 26	-	35 mg
Days 27 – 29	-	30 mg
Days 30 – 32	-	25 mg
Days 33 – 35	-	20 mg
Days 36 – 38	-	15 mg
Days 39 – 41	-	10 mg
Days 42 – 44	-	5 mg
Day 45	-	STOP

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Document control

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Pulmonary Toxicities – Dr Steve Bicknell, Dr Chris Wright

Gastrointestinal Toxicities – Dr John Paul Seenan, Dr Robert Boulton-Jones, Dr Jonathan MacDonald

Renal Toxicities – Dr Emily McQuarrie

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Rheumatic Events – Dr Neil Basu

Neurological Complications – Dr Maria-Elena Farrugia

Ophthalmological Toxicity – Dr Rosie Irvine

Updates in Version 4.2023 of the WoSCAN Guideline for Management of Immune-related Adverse Events

Scope – as use of IO expands and experience in managing side effects changes, guideline has been updated to reflect current practice within WoSCAN.

Background – non cancer specialists from across NHSGGC, who previously advised on the guidelines, contacted by email and asked to review current guidance and update on any changes to management of toxicity.

- Addition of index
- Introduction section updated to highlight increase use of combination treatments

Pulmonary Toxicities

- No changes have been recommended by respiratory team

Diarrhoea and colitis

- Grade 2 – prednisolone dose changed to lower dose of 40 – 60 mg (not weight based)
- Grade 2 – addition of recommendation that patients should have urgent flexible sigmoidoscopy or colonoscopy and biopsy
- Grade 3 – seek urgent gastroenterology consultation and consider direct admission to "hot" site
- Grade 3 – removal of recommendation for CT as no role in diagnosing enterocolitis, endoscopic evaluation much more useful

Hepatitis

- Signs and symptoms of hepatotoxicity updated
- Gradings updated to reflect abnormal baseline parameters
- Grade 1 – advised to monitor blood parameters and symptoms weekly
- Grade 2 – advised to monitor blood parameters and symptoms twice weekly
- Grade 2 – steroid dose changed to 0.5 - 1 mg/kg/day (previously suggested 1 mg)
- Grade 3 / 4 – corticosteroid taper over 4 – 6 weeks (previously 1 month)

Nephritis and renal dysfunction

- Dr Emily McQuarrie advised no changes required

Endocrinopathies

- No changes have been recommended by endocrinology team

Skin

- Dr Lorna Mackintosh advised no changes required

Fatigue

- New section

Cardiovascular Toxicity

- Guideline now advises to consider transferring a stable/unstable patient to CCU, depending on balance of oncologic vs cardiovascular risk/prognosis
- MMF added to option for 2nd immunosuppressant
- Oral prednisolone switch dose after methylprednisolone changed to 1 mg/kg/day (from 1-2 mg) reducing if clinical improvement and significant troponin reduction

Rheumatic Events

- No changes have been recommended by rheumatology team

Neurological complications

- Autoimmune encephalitis – investigations updated to include CASPR2, GAD and anti-neuronal antibodies

Ophthalmological complications

- New Section under guidance of Dr Rosie Irvine

Other immune-related adverse events

- Fatigue, uveitis and retinitis removed from table and independent section created