Acute Oncology Group

Hull University Teaching Hospitals NHS Trust

Queen's Centre

HEY Guidelines for the management of Toxicities associated with immune checkpoint inhibitors.

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Version Control

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Signature Sheet

This Document has been agreed by the following				
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HEY Guidelines for the management of Toxicities associated with immune checkpoint inhibitors.

Ipilimumab (anti-CTLA4 Mab), nivolumab and pembrolizumab (anti-PD-1 Mab) are being introduced in the management of a variety of metastatic malignancies including malignant melanoma, renal cancer and lung cancer. The use of such medications are expected to become more prevalent as research identifies additional indications.

The immune checkpoint inhibitors (ICPIs) share a list of immune-mediated toxicities induced by the deregulation of the immune system which is the basis of the mode of action of these agents. Significant attention needs to be given for managing patients experiencing toxicity from ICPIs since they often resemble toxicity caused by cytotoxic chemotherapy but management needs to be very specific often quite diverse from algorithms developed for cytotoxics.

Awareness of the possible immune-mediated toxicities associated with these agents within the context of units managing patients with acute presentation of symptoms while being treated with ICPIs is crucial for their safe and appropriate managemet inorder to avert unnecessary morbidity or even mortality.

In the following sections we describe the major categories of immune-mediated toxicities caused by these agents and the principles of their management.

Specialist advice will need to be sought early in the management of severe toxicity.

The CTCAE v4 criteria are used throughout the document to grade toxicity.

Principles

The following principles have been published by the manufacturer of nivolumab and ipilimumab as part of risk minimisation material produced as part of regulatory application reflecting the products' SPC and may serve as basic guidelines for the management of toxicity of this class of agents.

"Early identification of adverse reactions and timely intervention are an important part of the appropriate use of nivolumab or nivolumab in combination with ipilimumab

Patients should be monitored continuously (including at least up to 5 months after the last dose) as an adverse reaction with nivolumab or nivolumab in combination with ipilimumab may occur at any time during or after discontinuation of therapy.

If immunosuppression with corticosteroids is used to treat an adverse reaction, a taper of at least 1 month duration should be initiated upon improvement.

Rapid tapering may lead to worsening or recurrence of the adverse reaction.

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

Prophylactic antibiotics should be used to prevent opportunistic infections in patients receiving immunosuppressive therapy.

Nivolumab or nivolumab in combination with ipilimumab should not be resumed while the patient is receiving immunosuppressive doses of corticosteroids or other immunosuppressive therapy.

When nivolumab is administered in combination with ipilimumab, if either agent is withheld, the other agent should also be withheld. If dosing is resumed after a delay, either the combination treatment or nivolumab monotherapy could be resumed based on the evaluation of the individual patient.

Nivolumab or nivolumab in combination with ipilimumab must be permanently discontinued for any severe immune-related adverse reaction that recurs and for any life threatening immune-related adverse reaction. Nivolumab or nivolumab in combination with ipilimumab should also be permanently discontinued for Grade 4 or recurrent Grade 3 immune-related adverse reactions, and for Grade 2 or 3 immune-related adverse reactions that persist despite treatment modifications or if a reduction of corticosteroid dose to 10 mg prednisone or equivalent per day cannot be achieved."

Diarrhea / Colitis

Signs and symptoms

• Watery, loose or soft stools

• Abdominal pain

• Mucus or blood in stool

Rule out infectious and disease-related aetiologies (stool cultures).

Inform Treating Oncologist

	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Life-threatening
Colitis/ diarrhoea	Asymptomatic, increase < 4 stools per day over baseline	Increase 4-6 stools/day over baseline, abdominal pain, mucous or blood in stool	Increase ≥ 7 stools/day over baseline , severe abdominal pain, change in bowel habit, peritoneal signs, medical intervention indicated	Life-threatening consequences, urgent intervention required
Medication	Loperamide Iv Fluids	Loperamide IV Fluids Prednisolone 1mg/kg/day PPI	Admit patient IV fluids High dose steroids (1-2mg/kg/day of methylprednisolone IV or oral equivalents	
Clinical management / follow-up	FBC/BCP Increase monitoring If symptoms persist or relapse treat as grade 2	FBC/BCP Increase monitoring If symptoms persist >5 days or worsen or relapse treat as	Intensive monitoring as inpatient, specialist advice. If symptoms do not improve or worsen or relapse consider infliximab 5mg/kg unless perforation, sepsis other contraindication.	

		grade 4 If symptoms resolve or improve to grade , taper steroids over 4 weeks and continue immunotherapy after that	 If symptoms resolve monotherapy could be resumed for grade 3 diarrhoea after corticosteroid tapering, combination CTLA4 and PD-1 treatment should be discontinued for both grade3 and 4 diarrhea) Taper steroids over >2 months
Immunotherapy modification		Omit/defer ICPI treatment	Discontinue immunotherapy (permanently for relapse or grade 4 or for combination CTLA4/PD1 and grade 3 diarrhea)

Endocrinopathies

Severe endocrinopathies, including hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis, diabetes mellitus, and diabetic ketoacidosis have been observed.

Monitor patients for clinical signs and symptoms of endocrinopathies (see box below) and for hyperglycaemia and for changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation)

Signs and Symptoms

- Fatigue
- Headache
- Mental status change
- Abdominal pain
- Unusual bowel habits
- Hypotension
- Visual disturbances
- Weight change
- Excessive thirst
- Passing a greatly increased amount of urine
- Increased appetite with a loss of weight
- Feeling tired, drowsy, weak, depressed, irritable and generally unwell

Other non-specific symptoms which may resemble other causes such as brain metastasis or underlying disease.

Unless an alternate aetiology has been identified, signs or symptoms of endocrinopathies should be considered immune-related

	Grade 1	Grade 2	Grade 3	Grade 4
Hyperthyroidism	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; thyroid suppression therapy indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL; hospitalization indicated	Life-threatening consequences; urgent intervention indicated
Hypothyroidism	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; thyroid replacement indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL; hospitalization indicated	Life-threatening consequences; urgent intervention indicated
Hypohysitis	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated
Adrenal insufficiency	Asymptomatic; clinical or diagnostic observations only; intervention not indicated Grade 2: Grade 3: Grade 4	Moderate symptoms; medical intervention indicated	Severe symptoms; hospitalization indicated	: Life-threatening consequences; urgent intervention indicated
Hyperglycaemia	Fasting glucose value >ULN - 8.9 mmol/L	Fasting glucose value >8.9 - 13.9 mmol/L	Glucose >13.9 - 27.8 mmol/L; hospitalization indicated	>27.8 mmol/L; life-threatening consequences
Acidosis	pH <normal, but >=7.3		: pH <7.3	Life-threatening consequences

- Assess: TSH, T4, T3, ACTH, LH, FSH & cortisol, prolactin, and testosterone. MRI of the pituitary when hypophysitis is suspected.
- Inform treating Oncologist.
- For asymptomatic grade 1, endocrinopathies early specialist endocrinology advice is recommended but immunotherapy can continue
- For symptomatic endocrinopathies: immunotherapy is withheld.
- For isolated symptomatic hyperthyreoidism propranolol and prednisolone 0.5-1mg.kg/day are indicated. Before initiating thyroxine replacement adrenal insufficiency must be ruled out with short synacten test if any features of hypoadrenalism are present.
- For symptomatic hyperthyroidism and hypophysitis corticosteroids are initiated such as methylprednisolone IV at 1-2mg/kg/day or IV/oral equivalents if acute gland inflammation is suspected.
- Hormone replacement therapy must me initiated as needed for hypothyreoidism, hypophysitis, hypoadrenalism, diabetes.
- Early referral to endocrinology is recommended in all cases.
- The Nivolumab and SPC recommends permanent discontinuation of the drug, for all grade 4 endocrinological events as well as for grade 3 adrenal insufficiency.
- The Pemblrolizumab SPC recommends withholding or discontinuing pembrolizumab for grade 3 and 4 hypophysitis and hyperthyreoidism.
- In general, for grade2-3 endocrinopathies that are under control with hormone replacement and if symptoms are resolved, treatment can continue with close monitoring of endocrine function.
- When steroids are used for physiological replacement immunotherapy can resume, but high dose steroids need to have been slowly tapered before resumption in other cases.
- Gonadotrophin and TSH can recover but ACTH insufficiency rarely does.

For severe endocrinopathy: Grade 3,4, severely unwell patient, dehydration, hypotension or shock

- Admit patient- URGENT endocrinology advice
- Immediate hydrocortisone 100 mg intravenously (IV) every 6 hours
- Commence IV hydration if indicated
- Exclude infection/sepsis
- Assess: TSH, T4, T3, ACTH, LH, FSH & cortisol, prolactin, testosterone piror to iv steroids
- ECG
- Withhold next cycle of immunotherapy
- MR imaging brain with pituitary cuts

- **SUSPECT ADRENAL CRISIS**

Defined by severe dehydration, hypotension or shock

Pneumonitis

Signs and symptoms

• Breathing difficulties or cough

• Radiographic changes (e.g. focal ground glass opacities, patchy filtrates)

• Dyspnoea

• Hypoxia

Rule out infectious and disease-related aetiologies

CXR

Inform treating Oncologist

	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Life-threatening
Pneumonitis	Radiographic changes only. Clinically asymptomatic	Mild or moderate symptoms (dyspnoea/cough/SOB limiting instrumental ADL)	Severe symptoms; limiting self care ADL; oxygen indicated	Life-threatening respiratory compromise; urgent intervention indicated (e.g., tracheotomy or intubation)
Medication		Corticosteroids (methylprednisolone IV 1mg.kg/day or oral equivalent i.e prednisolone 1mg/kg/day	Initiate corticosteroids at a dose of 2 to 4 mg/kg/day methylprednisolone IV or IV equivalent Prophylactic antibiotics for opportunistic infections	
Clinical management / Clinical management / follow-up	Close monitoring Re-image every two weeks	Monitor daily – consider admission. Consider HRCT, repeat imaging according to symptoms Of symptoms persist or worsen treat as grade 3	Admit patient CT imaging (HRCT if possible) Refer to a chest physician Consider Bronchoscopy with biopsy	
Immunotherapy modification	Consider delay	Withhold until symptoms resolve, radiographic abnormalities improve, and management with corticosteroids is complete (taper corticosteroids ove >4	Permanently discontinue	

		weeks)	

Hepatitis

Signs and symptoms

• Elevations in transaminases

• Total bilirubin elevations

• Jaundice

• Right sided abdominal pain

• Tiredness

Rule out infectious and disease-related aetiologies

Inform treating Oncologist

	Grade 2 Moderate	Grade 3,4 Severe or Life-threatening
Hepatobiliary disorders	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL, Grade 4: Life-threatening consequences; urgent intervention indicated
ALT **AST**	3-5xULN	>5xULN
Bilirubin	1.5-3xULN	>3xULN
Medication	Persistent elevations in laboratory values should be managed with corticosteroids at a dose of 0.5 to 1 mg/kg/day methylprednisolone IV or oral equivalents	Initiate corticosteroids at a dose of 1 to 2 mg/kg/day methylprednisolone IV or oral equivalents (i.e prednisolone 1mg/kg/day) Consider prophylactic antibiotics to prevent opportunistic infections
Clinical management / follow-up	Imaging of liver to rule out PD Check autoimmune panel-anti-ANA, SMA, SLA/LP, LKM-1, LCI Perform hepatitis viral serology Check LFT's every 3 days Review concomitant medication If symptoms persist or worsen or	Imaging of liver to rule out PD Consider admission depending on clinical condition and severity of liver abnormalities. •Assess: autoimmune panel-anti-ANA, SMA,

	relapse treat as grade 3	SLA/LP, LKM-1, LCI Perform hepatitis viral serology Daily LFT's Review concomitant medication Consider referal to hepatologist for further advice especially for patients who are referactory to corticosteroids- to consider mycophenolate mofetil 1G twice daily has been used (using guidelines for immunosuppression of liver transplants) with supportive treatment including prophylactic infection treatment If still no improvement after 5- days- consider adding 0.10 -0.15mg/kg/day of tacrolimus. Continue to check LFT's regularly for at least 2 weeks to monitor sustained response to treatment
Immunotherapy modification	Withhold dose until an adverse reaction resolves to Grade 1 or Grade 0 (or returns to baseline). If symptoms persist or worsen or relapse manage as grade 3	Permanently discontinue

Skin toxicity

	Grade 1	**Grade2**	**Grade 3**	**Grade4**
Rash maculopapular	Macules/papules covering <10% BSA with or without symptoms (e.g., pruritus, burning, tightness)	Macules/papules covering 10 - 30% BSA with or without symptoms (e.g., pruritus, burning, tightness); limiting instrumental ADL	Macules/papules covering >30% BSA with or without associated symptoms; limiting self care ADL	
Rash papulopustular or acneiform	Papules and/or pustules covering <10% BSA, which	Papules and/or pustules covering 10-30% BSA,	Papules and/or pustules covering >30% BSA, which	Papules and/or pustules covering any

	may or may not be associated with symptoms of pruritus or tenderness	which may or may not be associated with symptoms of pruritus or tenderness; associated with psychosocial impact; limiting instrumental ADL	may or may not be associated with symptoms of pruritus or tenderness; limiting self-care ADL; associated with local superinfection with oral antibiotics indicated	% BSA, which may or may not be associated with symptoms of pruritus or tenderness and are associated with extensive superinfection with IV antibiotics indicated; lifethreatening consequences
Allergic reaction	Transient flushing or rash, drug fever <38 degrees C (<100.4 degrees F); intervention not indicated	Intervention or infusion interruption indicated; responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics); prophylactic medications indicated for <=24 hrs	Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae (e.g., renal impairment, pulmonary infiltrates)	Life-threatening consequences; urgent intervention indicated
Toxic epidermal necrolysis (Stevens-Johnson Syndrome)				Skin sloughing covering >=30% BSA with associated symptoms (e.g.,

				erythema, purpura, or epidermal detachment)

Grade 1 rash

- Regular monitoring
- Consider anti-histamines
- Conider topical steroids
- Continue immunotherapy

Grade 2 rash

- Increase monitoring
- Anti-histamines
- Localised rash:

Topical steroidal based cream

1% Hydrocortisone (acetate) cream bd for face

Betamethasone valerate (Betnovate) 0.1% cream to other sites

- Extensive rash: prednisolone 0.5- 1mg/kg od x 3-7 days-max. 60mg/day
- Withhold treatment until ≤ Grade 1

Grade 3 rash

Withhold immunotherapy until symptoms resolve and management with steroids is complete

Sever rash should be treated with high-dose corticosteroids i.e 1-2mg.kg/day or BD of IV

methylprednisolone or equivalents.

Specialist dermatology advice

Steroids need to be tapered over >4 weeks

Grade 4 rash, >50% skin surface, generalised, exfoliative, ulcerative, bullous dermatitis

Permanently discontinue immunotherapy

Admit patient

Urgent specialist Dermatology advice

- High-dose IV corticosteroid therapy (eg, methylprednisolone 2 mg/kg once/twice or equivalent eg hydrocortisone)
- Regular ob's and fluid balance
- Anti-histamines-hydroxyzine 25mg qds max. 100mg daily

- Topical emollient cream-cetraben

Steroid tapper over >2 months

Stevens-Johnson Syndrome

Urgnet admission and early specialist referral, will require referral to specialist centre

Renal toxicity / Nephritis

Signs and symptoms

- Asymptomatic increase in serum creatinine
- Other abnormal kidney function tests
- Decreased volume of urine

Rule out disease–related aetiologies

Inform Treating Oncologist

	Grade1	Grade2/3	Grade 4
Creatinine	1-1.5xbaseline, 1-1.5 x ULN	>1.5 - 6.0 x baseline; >1.5 -6.0 x ULN,	>6.0 x ULN
Medication		Initiate corticosteroids at a dose of 0.5 to 1 mg/kg/day methylprednisolone IV or oral equivalents (i.e prednisolone 1mg/kg/day)	Initiate corticosteroids at a dose of 1 to 2 mg/kg/day methylprednisolone IV or oral equivalents
Clinical management / follow-up	Weekly creatinine monitoring Exclude other casues of renal impairment	Monitor Cratinine every 2-3 days. Exclude other causes of renal impairment If symptoms persist, worsen or relapse, treat as grade 4	Admit patient Monitor creatinine daily Exclude other causes of renal impairment Consider renal biopsy/USS Refer to renal team for further advice
Immunotherapy modification	Continue immunotherapy	Withhold until creatinine returns to baseline and management with corticosteroids is complete	Permanently discontinue

Other autoimmune adverse reactions

Infusion / allergic reactions

Allergic reaction	Transient flushing or	Intervention or infusion	Prolonged (e.g., not	Life-threatening

	rash, drug fever <38 degrees C (<100.4 degrees F); intervention not indicated	interruption indicated; responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics); prophylactic medications indicated for <=24 hrs	rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae (e.g., renal impairment, pulmonary infiltrates)	consequences; urgent intervention indicated

Aseptic meningitis /encephalitis

Autoimmune neuropathy (including facial and abducens nerve paresis)

Guillain‑Barré syndrome

Pancreatitis

Uveitis

Demyelination

Myasthenic syndrome

- For suspected immune‑related adverse reactions, adequate evaluation should be performed to confirm aetiology or exclude other causes.
- Based on the severity of the adverse reaction, immunotherapy should be withheld and corticosteroids administered.
- Early specialist advice should be sought.
- Upon improvement, immunotherapy may be resumed after corticosteroid taper (taper > 4 weeks).
- Immunotherapy should be permanently discontinued for any severe immune‑related adverse reaction that recurs and for any life‑threatening immune‑related adverse reaction.

From Pembrolizumab SPC

Withhold KEYTRUDA for any of the following:

- Grade 2 pneumonitis.
- Grade 2 or 3 colitis.
- Grade 3 or 4 endocrinopathies.
- Grade 2 nephritis.

- Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) greater than 3 and up to5 times upper limit of normal (ULN) or total bilirubin greater than 1.5 and up to 3 times ULN
- Any other severe or Grade 3 treatment-related adverse reaction
- Resume KEYTRUDA in patients whose adverse reactions recover to Grade 0-1.
  Permanently discontinue KEYTRUDA for any of the following:
- Any life-threatening adverse reaction (excluding endocrinopathies controlled with hormone
- replacement therapy)
- Grade 3 or 4 pneumonitis or recurrent pneumonitis of Grade 2 severity [see Warnings and
- Precautions
- Grade 3 or 4 nephritis [see Warnings and Precautions.
- AST or ALT greater than 5 times ULN or total bilirubin greater than 3 times ULN. For patients with liver metastasis who begin treatment with Grade 2 AST or ALT, if AST or ALT increases by greater than or equal to 50% relative to baseline and lasts for at least 1 week Grade 3 or 4 infusion-related reactions [see Warnings and Precautions.
- Inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks
- Persistent Grade 2 or 3 adverse reactions (excluding endocrinopathies controlled with hormone replacement therapy) that do not recover to Grade 0-1 within 12 weeks after last dose of KEYTRUDA.
- Any severe or Grade 3 treatment-related adverse reaction that recurs [see Warnings andPrecautions.

From Nivolumab SPC

- When nivolumab is administered in combination with ipilimumab, refer to the Summary of Product Characteristics for ipilimumab prior to initiation of treatment. Immune-related adverse reactions have occurred at higher frequencies when nivolumab was administered in combination with ipilimumab compared with nivolumab as monotherapy. Most immune-related adverse reactions improved or resolved with appropriate management, including initiation of corticosteroids and treatment modifications (see section 4.2).
- Cardiac adverse events and pulmonary embolism have also been reported with combination therapy. Patients should be monitored for cardiac and pulmonary adverse reactions continuously, as well as for clinical signs, symptoms, and laboratory abnormalities indicative of electrolyte disturbances and dehydration prior to and periodically during treatment. Nivolumab in combination with ipilimumab should be discontinued for life-threatening or recurrent severe cardiac and pulmonary adverse reactions.

- Patients should be monitored continuously (at least up to 5 months after the last dose) as an adverse reaction with nivolumab or nivolumab in combination with ipilimumab may occur at any time during or after discontinuation of therapy.

- For suspected immune-related adverse reactions, adequate evaluation should be performed to confirm aetiology or exclude other causes. Based on the severity of the adverse reaction,

nivolumab or nivolumab in combination with ipilimumab should be withheld and corticosteroids administered. If immunosuppression with corticosteroids is used to treat an adverse reaction, a taper of at least 1 month duration should be initiated upon improvement. Rapid tapering may lead to worsening or recurrence of the adverse reaction. Non-corticosteroid immunosuppressive therapy should be added if there is worsening or no improvement despite corticosteroid use.

- Nivolumab or nivolumab in combination with ipilimumab should not be resumed while the patient is receiving immunosuppressive doses of corticosteroids or other immunosuppressive therapy. Prophylactic antibiotics should be used to prevent opportunistic infections in patients receiving immunosuppressive therapy.
- Nivolumab or nivolumab in combination with ipilimumab must be permanently discontinued for any severe immune-related adverse reaction that recurs and for any life-threatening immune-related adverse reaction

References

1) Pembrolizumab - highlights of prescribing information. http://www.merck.com/product/usa/pi_circulars/k/keytruda/keytruda_pi.pdf
2) Nivolumab - Important Safety Information To Minimise The Risks Of Immune-Related Adverse Reactions For Healthcare Professionals https://www.medicines.org.uk/emc/RMM.212.pdf