Treatment Guideline: Basic Principles for Management of Immune-related Adverse Events (IrAEs) Caused by immunotherapy

Introduction: Immunotherapy agents or **Immune Checkpoint Inhibitors (ICPi),** block key immune system pathways (Checkpoints) and enhance activation of the T cell mediated immune response. This compares to "releasing the brakes" of the immune system which in turn can lead to **immune-related adverse events (IrAEs).**

This treatment guideline includes the following:

Immunotherapy drugs list	**TABLE 1**
Immunotherapy organ system toxicities	**TABLE 2**
IrAEs-Onset, who is at risk, general recommendations, grading of toxicity	**TEXT**
Algorithm-Interruption of ICPi, steroid use, rechallenge	**TABLE 3**
General principles of management once toxicity identified and graded	**TABLE 4**
ALERT: Cardiovascular toxicities recently identified **ALERT: Fatal toxicities with ICPi (fatality rates by regimen and toxicity)**	**TABLE 5a** **TABLE 5b**
Corticosteroid dosing and dose tapering	**TABLE 6**
References (#): Includes ASCO (1) ESMO (2) and Thames Valley (3) guidelines, time to onset of IrAEs (4,5), cardiovascular toxicities (6), fatal toxicities by regimen/ toxicity (7), overview on practical aspects of management (8)	**TEXT**
APPENDIX A-Common toxicities that are at least grade 2	**TABLE 7**
APPENDIX B-Schematic for estimation of BSA and grade of skin toxicity	**FIG 1**
APPENDIX C-Onset of gr3-4 AEs after Ipilimumab AND Nivolumab	**FIG 2**
APPENDIX D-Time to occurrence of IrAEs after Ipilimumab alone	**FIG 3**
APPENDIX E-Links to risk minimization information by manufacturers	**TEXT**
APPENDIX F-South West clinical network regimen-specific information	**TEXT**

Scope: This treatment guideline covers the **basic principles of management of IrAEs caused by immunotherapy** including when to interrupt/ resume treatment. IrAEs can affect any organ system; the most common organs affected include **the skin, bowel, liver, endocrine system and lungs**. Local organ system-specific guidelines are currently in development and once available will complement this treatment guideline.

- ICPi commonly (>10%) cause diarrhoea/ rash/ pruritus/ nausea/ fatigue
- **ICPi infrequently (<10-15%) cause life-threatening toxicities (IrAEs).**
- The incidence of treatment-related grade 3-4 toxicities (include. IrAEs) with combination immunotherapy (Ipilimumab + Nivolumab) in advanced melanoma is substantially higher (59% in the Checkmate-067 study)

This treatment guideline focuses on the identification, grading, treatment of these life-threatening IrAEs where early recognition, investigation, treatment is paramount.

TABLE 1. Immunotherapy drugs currently in use in the NHS (excludes clinical trial agents)	
PD-1 inhibitors	**Nivolumab, Pembrolizumab**
PD-L1 inhibitors	**Atezolizumab, Durvalumab, Avelumab**
CTLA-4 inhibitors	**Ipilimumab, usually in combination with nivolumab (melanoma only)**
Administration	2-4 weekly by ivi
Treatment duration	Until progression/ unacceptable toxicity/ maximum 2years (lung) Ipilimumab is given for 4 cycles only

TABLE 2. Immunotherapy organ system toxicities (IrAEs; Refs 1-3)		
Skin	**Bowel (colitis)**	**Liver (hepatitis)**
Itching/ Rash Blistering Vitiligo (melanoma only) Increased sensitivity to RT	Diarrhoea/ blood/ mucous Constipation Nausea/ vomiting Upper abdo pain	Raised LFTs (AST/ALT) Jaundice
Endocrine (Pituitary/ Thyroid/ Adrenal/ Pancreas)		**Lung (pneumonitis)**
Headache Visual field defects Fatigue/ weakness Hypotension	Electrolyte abnormalities Polyuria/ polydipsia Hyperglycaemia	Breathlessness Cough Wheezing Reduced saturations
Neurological	**Eye (uveitis)**	**Renal (nephritis)**
Symptoms/ signs of: Myasthenia gravis Guillain-Barre Peripheral neuropathy Autonomic neuropathy Aseptic meningitis Encephalitis Transverse myelitis	Blurred vision Altered colour vision Photophobia Field defects Tenderness Painful eye movement Eyelid swelling Proptosis	Raised Creatinine Oliguria
Cardiac	**Musculoskeletal**	**Haem**
Myocarditis/ Pericarditis Arrhythmias Reduced LVEF with Heart failure* Vasculitis Thromboembolism *Overt heart failure with LVEF <50% or significantly below baseline	Arthritis Myositis Polymyalgia-like syndrome	Symptoms/ signs of: Autoimmune Haemolytic anaemia Immune thrombocytopenia Haemolytic Uraemic Syndrome Acquired TTP Aplastic anaemia Acquired haemophilia
Conditions underlined: Immunotherapy to be STOPPED irrespective of toxicity grade		

IrAEs: Immune-related adverse events
Onset: Most develop weeks to 3 months after initiation of treatment **Late onset:** Up to 1 year after cessation of treatment
At risk patients: • All patients treated with checkpoint inhibitors but risk of IrAEs is significantly increased with combination therapy (Ipilimumab + Nivolumab) • Patients with history of autoimmune disease (may experience flare of pre-existing condition)
For organ specific management refer to respective Organ-specific treatment guidelines (In development) or American Society of Clinical Oncology Guidelines (ref 1)

The following GENERAL RECOMMENDATIONS should be followed for ALL immune checkpoint inhibitors (ICPi) irrespective of affected organs
HIGH LEVEL OF SUSPICION For new symptoms/ signs or worsening of existing symptoms/ signs ⬇
GRADE THE TOXICITY USING **COMMON TERMINOLOGY CRITERIA OF ADVERSE EVENTS (CTCAE) v5** (Use either of the links below) ⬇ https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf https://www.eortc.be/services/doc/ctc/CTCAE_v5_Quick_Reference_5x7.pdf **NB.** Top link takes you to the NCI website, bottom link is a back-up link through EORTC website ⬇
FOLLOW THE ALGORITHM IN TABLE 3

TABLE 3. ALGORITHM	
Toxicity Grade (NCI CTCAE v5)	**When to interrupt ICPi, when to commence steroids, when to rechallenge**
1	**Continue ICPi with close monitoring EXCEPT for:** **Underlined Neurologic, Cardiac, Haematological toxicities (see table 2)**
2	**HOLD ICPi for NEARLY ALL toxicities AND CONSIDER STEROIDS** (For Lymphopenia, Haemolytic uraemic syndrome may continue) **Prednisolone 0.5-1mg/kg/day or equivalent** **Rechallenge when toxicity (incl. labs) reverts to grade 1**
3	**HOLD ICPi for ALL toxicities AND START STEROIDS** **Methylpred iv 1-2mg/kg/day or Prednisolone 1-2mg/kg/day or equivalent** **If no improvement after 48 to 72 hours:** Consider additional immunosuppressive treatment in some toxicities (see note below) **Steroid taper:** Over at least 4-6weeks **Rechallenge:** Consider if reverts to grade 1 (cautious in early-onset irAE)
4	**DISCONTINUE ICPi for ALL toxicities AND START STEROIDS** **Methylprednisolone iv 1-2mg/kg/day** **If no improvement after 48 to 72 hours:** Consider additional immunosuppressive treatment in some toxicities (see note below) **Steroid taper:** Over at least 4-6weeks **Rechallenge:** Only endocrinopathies if controlled with hormone replacement

SUPPLEMENTARY NOTES

1. Recommended steroid doses vary between different international guidelines (ASCO, ESMO)

2. CONSIDER IF PATIENT IS ON INTERACTING DRUGS; e.g. P450 inducers/ P450 inhibitors which enhance/ inhibit steroid metabolism thus reducing/ increasing respectively desired effect of same dose and titrate prednisolone/ methylprednisolone dose accordingly
   Drug Interactions Checker Link: https://www.drugs.com/drug_interactions.html

3. CONSIDER INCREASING STEROID DOSE if gr.3-4 AND no improvement after 48-72hrs of steroids- e.g. from 1mg/kg to 2mg/kg (ESMO guidance recommends 2-4mg/kg methylprednisolone for gr.3-4 pneumonitis)

4. CONSIDER ADDITIONAL IMMUNOSUPPRESSION if gr.3-4 AND worsening after 48-72hrs of steroids
   Examples:
   For colitis, Infliximab
   For pneumonitis, Infliximab
   For hepatitis, Mycophenolate / azathioprine/ tacrolimus
   For musculoskeletal, Methotrexate/ azathioprine/ mycophenolate/ tocilizumab
   For Myasthenia/ Guillain-Barre syndrome, iv immunoglobulin / plasmaphaeresis

5. CONSIDER STEROID DOSE ESCALATION if symptoms/ labs worsen after initial improvement which was followed by steroid dose reduction (i.e. go back to the previous steroid dose level)

TABLE 4. General Principles of Management once toxicity identified and graded
1. **NOTIFY CONSULTANT ON-CALL**+/- patient's TREATING ONCOLOGIST/ HAEMATOLOGIST of reported/ observed toxicity that is potentially an immune-related adverse event.
2. **ADMIT patients with grade 3 - 4 toxicity** and investigate (see reference 1, ASCO Guidelines) Consider admission for grade 2 toxicity if this is persisting and/ or hospitalization deemed safer.
3. **REFER TO ORGAN-SPECIFIC GUIDELINES** (ASCO, ESMO as referenced below- *Oncology/ Haematology Treatment Guidelines for organ-specific IR-AEs in progress)*. Depending on individual toxicity consider CT imaging (for colitis/ pneumonitis), endoscopy (for colitis), cultures (stool, c. diff, septic screen), viral serology (for hepatitis), full endocrine profile +/- MRI pituitary (for endocrinopathies), ECG/ troponin/ Echo (for cardiac)
4. **LIAISE with relevant specialty** (e.g. dermatology, gastroenterology, endocrinology, etc.) about patients with grade 3 - 4 toxicity and consider also liaising about patients with persistent grade 2 toxicity.
5. **COMMENCE high-dose corticosteroids when necessary (as per Algorithm in TABLE 3)** with oral prednisolone or iv methylprednisolone; latter preferred if rapid symptom control warranted in a decompensated patient or oral intake/ absorption compromised. Convert to oral prednisolone after 2-3 days of iv methylprednisolone; then reduce by 10mg/ week (TABLE 6b).
6. **MONITORING while on steroids:** • Capillary blood glucose and BP • Avoid proton pump inhibitors unless gastric symptoms develop • Consider PCP prophylaxis if on prolonged steroids (e.g. >20mg for >4weeks) • If diabetic use bd dosing for oral prednisolone • If diabetic treat hyperglycaemia with oral hypoglycaemics/ insulin
7. ALERT ON CARDIOVASCULAR TOXICITIES AND ALL FATALITIES by regimen/ toxicity: see TABLES 5a and 5b

TABLE 5a: Cardiovascular toxicities associated with ICPi therapy recently identified (Ref 6)		
	Fatality rate	**Median time to onset (range) from 1st dose**
Myocarditis (n=122)	**50%**	30d (1-240)
Pericardial diseases (n=95) • Pericarditis/ effusion/ tamponade	21%	30d (0-330)
Vasculitis-related disorders (n=116) • Temporal arteritis (n=18) • Polymyalgia rheumatica (n=16) • Vasculitis (n=82)	 0% 0% 6%	 21d (21-131) 77d (20-168) 55d (1-542)
Early recognition (symptoms, ECG changes, troponin elevation), echo, cardiology referral		

Table 5b: Fatal toxicities associated with ICPi therapy (Ref 7)			
Fatalities by regimen (N=613)	**Commonest fatal IrAE**	**% of deaths**	**Median time to death from onset of Rx**
Anti-PD1/PDL1 monotherapy	**Pneumonitis** Hepatitis Neurotoxicity	**35%** 22% 15%	40 days
Anti-CTLA4 (Ipilimumab)	**Colitis**	**70%**	40 days
Combination (Anti-PD1/PDL1 & Anti-CTLA4)	**Colitis** Myocarditis	**37%** 25%	15 days

Fatalities by toxicity	**% of deaths**	**Median time to death from onset of symptoms**
Myocarditis Other organ systems Colitis/ Endocrine	**40%** 10-17% 5%/ 2%	32 days

Toxicity-related fatality rates by ICPi used:	
Anti-PD-1 0.36%,	**Anti-CTLA-4 1.08%**
Anti PD-L1 0.38%	**Anti-PD-1/PD-L1 plus Anti-CTLA-4 1.23%**
Data from meta-analysis of 19,217 patients treated in 112 trials of ICPi	

TABLE 6a. Equivalent anti-inflammatory doses of corticosteroids

PREDNISOLONE	METHYLPREDNISOLONE
5mg	4mg
60mg	48mg
80mg	64mg
100mg	80mg
120mg	96mg
140mg	112mg
160mg	128mg

Prednisolone SPC: https://www.medicines.org.uk/emc/product/5887/smpc

Methylprednisolone SPC: https://www.medicines.org.uk/emc/product/757/smpc

TABLE 6b. Oral prednisolone tapering dose for 70kg patient

Dose	Duration (days)	Total (days)
70mg	5-7	5-7
60mg	5-7	10-14
50mg	5-7	15-21
40mg	5-7	20-28
30mg	5-7	25-35
20mg	5-7	30-42
15mg	5-7	35-49
10mg	Until clinic review. If ICPi is to be restarted the prednisolone dose must not exceed 10mg/day (=dexamethasone 1.5mg/d)	40-56 (~6weeks)
Notes: 1. In accordance with ASCO guidance steroids should be tapered over at least 4-6 weeks. 2. Escalate dose to previous dose level if symptoms/ labs indicate worsening toxicity after initial improvement		

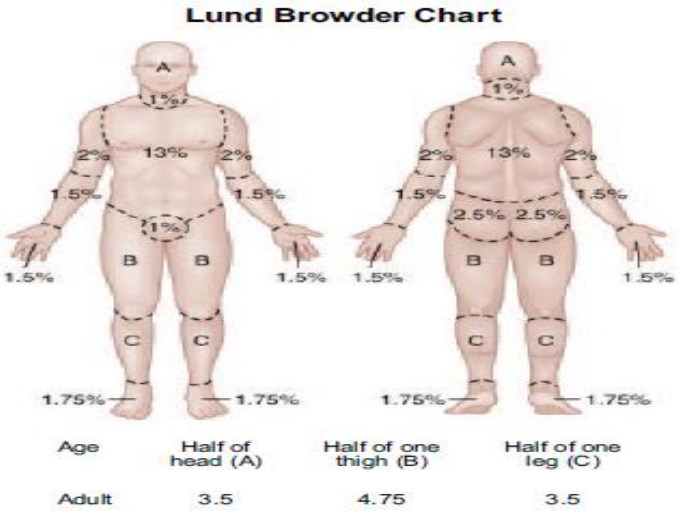
REFERENCES

1. Brahmer JR et al., Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: **American Society of Clinical Oncology Clinical practice Guideline**. J Clin Oncol, 36; 2018
http://ascopubs.org/doi/pdfdirect/10.1200/JCO.2017.77.6385
2. Haanen JBAG et al. Management of toxicities from immunotherapy: **ESMO Clinical Practice Guidelines** for diagnosis, treatment and follow-up. Ann Oncol 28 (S4); iv119-142, 2017
https://www.esmo.org/Guidelines/Supportive-and-Palliative-Care/Management-of-Toxicities-from-Immunotherapy
3. **Thames Valley** Immuno-oncology agent immune-related adverse event clinical guideline, v1.0-April 2017
http://tvscn.nhs.uk/networks/cancer/cancer-topics/chemotherapy/
4. Sznol M et al. Pooled analysis safety profile of **nivolumab and ipilimumab combination therapy** in patients with advanced melanoma. J Clin Oncol 35; 3815-22, 2017
5. Weber JS et al. Management of **immune-related adverse events and kinetics of response** with ipilimumab. J Clin Oncol 30; 2691-7, 2012
6. Salem JE et al. **Cardiovascular toxicities** associated with immune checkpoint inhibitors: an observational, retrospective, pharmacovigilance study. Lancet Oncol 19; 1579-89, 2018
7. Wang DY et al. **Fatal effects associated with immune checkpoint inhibitors:** A systematic review and meta-analysis. JAMA 4; 1721-28, 2018
8. Champiat S et al. **Management of immune checkpoint blockade dysimmune toxicities**: a collaborative paper. Ann Oncol 27; 559-74, 2016

APPENDIX A: TABLE 7

SOME COMMON TOXICITIES THAT ARE *AT LEAST GRADE 2* (refer to CTC 5.0 for complete list)	
Arthritis	At least moderate pain with signs of inflammation, limiting instrumental ADL
Diarrhoea	At least 4-6 liquid stools/ day over baseline
Endocrine	At least moderate symptoms (still able to perform ADL)
Eye	At least symptomatic, anterior uveitis, vision 20/40 (or better)
Myositis	At least moderate weakness +/- pain, limiting age-appropriate instrumental ADL
Neurologic	At least moderate symptoms, some interference with ADL
Polymyalgia	At least moderate stiffness and pain, limiting age-appropriate instrumental ADL
Pulmonary	At least mild-moderate symptoms (e.g. dyspnoea, cough)
Rash	At least 10% of BSA affected (see Lund Browder Chart below)
ADL: Activities of daily living; **Instrumental ADL:** Not necessary for fundamental functioning but enable an individual to live independently in community (e.g. taking medication, preparing meals)	
Bloods • **LFTs** • **Creatinine** • **Glucose**	 ALT/ AST more than 3x ULN and/ or Bilirubin more than 1.5x ULN More than 1.5x ULN or 1.5x baseline At least moderate symptoms (still able to perform ADL), fasting glucose >8.9, ketosis or evidence of Type 1 DM at any glucose level

APPENDIX B: FIG 1. Schematic for estimation of BSA to help grade skin toxicity



GRADE	DEFINITION BY %BSA (body surface area) INVOLVEMENT
1	<10% BSA, e.g. half of [thigh + lower leg +foot]
2	10-30% BSA, e.g. front of [chest + abdo] OR whole of lower limb
3	>30% BSA or Gr. 2 + substantial symptoms, e.g. most of [chest + abdo + one limb]
4	>30% BSA with symptoms (erythema/ purpura/ epidermal detachment)

APPENDIX C: FIG 2. Onset of gr.3-4 treatment-related AEs after Ipilimumab AND Nivolumab

TIME IN WEEKS TO ONSET OF SELECT GRADE 3-4 ADVERSE EVENTS For combination immunotherapy: APPLIES TO IPILIMUMAB & NIVOLUMAB Used in advanced MELANOMA patients				
Organ system	**Median**	**Interquartile range**	**Earliest**	**Latest**
Skin (n=33)	**3**	1-8	0.1	**55**
GI (n=73)	**7**	4-11	0.6	**49**
Liver (n=76)	**8**	5-12	2	**48**
Lungs (n=6)	**9**	4-20	4	**21**
Endocrine (n=21)	**11**	7-14	3	**19**
Renal (n=7)	**16**	4-24	3	**29**

Adapted and modified from Sznol et al., JCO 2017 (Ref 4)

APPENDIX D: FIG 3. Time of onset of ir-AEs after Ipilimumab in advanced melanoma

Organ system	Peak	Onset	End
Skin (rash, itching)	**6**	3	10
GI (diarrhoea/ colitis)	**8-9**	5	10
Liver (raised LFTs)	**10-12**	7	14
Pituitary (hypophysitis)	**12-14**	7	Ongoing

Adapted and modified from Weber et al., JCO 2012 (Ref 5)

APPENDIX E: Links to risk minimization information provided by manufacturers

Ipilimumab alone
https://www.medicines.org.uk/emc/rmm/93/Document

Nivolumab or Nivolumab and Ipilimumab
https://www.medicines.org.uk/emc/rmm/212/Document

Pembrolizumab
https://www.medicines.org.uk/emc/rmm/243/Document

Atezolizumab
https://www.medicines.org.uk/emc/rmm/1053/Document

APPENDIX F: Links to South West Clinical network regimen-specific information

Ipilimumab for melanoma
http://www.swscn.org.uk/wp/wp-content/uploads/2015/01/Ipilimumab.pdf

Nivolumab for melanoma
http://www.swscn.org.uk/wp/wp-content/uploads/2018/09/Nivolumab-melanoma-v2.pdf

Nivolumab and Ipilimumab for melanoma
http://www.swscn.org.uk/wp/wp-content/uploads/2018/09/Ipilimumab-and-Nivolumab-v2.pdf

Pembrolizumab for melanoma
http://www.swscn.org.uk/wp/wp-content/uploads/2014/12/Pembrolizumab.pdf

Pembrolizumab for lung
http://www.swscn.org.uk/wp/wp-content/uploads/2014/12/Pembrolizumab-lungv2.pdf

Pembrolizumab for urothelial
http://www.swscn.org.uk/wp/wp-content/uploads/2018/07/Pembrolizumab-urothelial.pdf
Atezolizumab for urothelial
http://www.swscn.org.uk/wp/wp-content/uploads/2018/05/Atezolizumab.pdf

Nivolumab for Head and Neck
http://www.swscn.org.uk/wp/wp-content/uploads/2018/09/Nivolumab-HN-v2.pdf