Kent and Medway Cancer Collaborative

Systemic Anti-cancer Therapy Care Pathway – Management of Immune Related Toxicities with immunotherapy treatments

Pathway of Care

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1.0 Introduction

- Immune-related adverse reactions may appear during or after treatment and patients should be monitored for at least 5 months after the last dose.
- The most common immune-related reactions are listed in the table.
- The following immune related adverse reactions have been reported in patients receiving immunotherapy: arthritis, myositis, pancreatitis, iritis, polymyalgia rheumatica, myocarditis, vasculitis, DRESS syndrome (drug reaction with eosinophilia and systemic symptoms), myasthenic syndrome, optic neuritis, rhabdomyolysis, haemolytic anaemia, gastritis, duodenitis, sarcoidosis and partial seizures arising in a patient with inflammatory foci in brain parenchyma.
- Based on the severity of the adverse reaction, immunotherapy should be withheld and corticosteroids administered. Upon improvement to Grade < 1, corticosteroid taper should be initiated and continued over at least 1 month. If immune-related adverse events cannot be controlled with corticosteroids, administration of other systemic immunosuppressants can be considered.

2.0 When to permanently discontinue treatment

2.1 Pembrolizumab

- Grade 4 toxicity affecting any organ system except for endocrinopathies that are controlled with replacement hormones
- Recurrent grade 3 immune-related adverse reactions.
- After first occurrence of selected grade 3 immune related toxicities – pneumonitis, nephritis, hepatitis, myocarditis and infusion reactions.
- If corticosteroid dosing cannot be reduced to ≤ 10mg prednisolone or equivalent per day within 12 weeks or if a treatment-related toxicity does not resolve to Grade 0-1 within 12 weeks after the last dose of Pembrolizumab.

2.2 Ipilimumab

- Grade 3/4 toxicity affecting any organ system excluding;
    i. G3/4 endocrine toxicity controlled by hormonal therapy.
    ii. G3 rash i.e discontinue **only** for Grade 4. However, discontinue for Grade 3 pruritus

- Any toxicity that fails to resolve to G0/1 with treatment
- >Grade 2 ophthalmological toxicity not responding to topical therapy
- Severe infusion reactions

2.3 Nivolumab

- Grade 4 toxicity affecting any organ system
- Recurrent grade 3 toxicity
- After first occurrence of selected grade 3 immune related toxicities – pneumonitis, hepatitis, adrenal insufficiency and myocarditis, uveitis and neurological toxicity
- Grade 2/3 adverse reactions that persist despite management.

2.4 Ipilimumab / Nivolumab

- Grade 4 toxicity affecting any organ system
- Recurrent grade 3 toxicity
- After first occurrence of selected grade 3 immune related toxicities – pneumonitis, colitis, hepatitis, uveitis, pruritis, adrenal insufficiency and myocarditis, and neurological toxicity.
- >Grade 2 ophthalmological toxicity not responding to topical therapy

Note – if either agent is withheld the other agent should also be withheld.

3.0 Restarting Guidelines:

- **Pembrolizumab**: Immunotherapy may be restarted within 12 weeks after last dose if the adverse reaction remains at Grade ≤1 and corticosteroid dose has been reduced to ≤ 10mg prednisolone or equivalent per day.
- **Nivolumab**: Immunotherapy may be restarted if the adverse reaction remains at Grade ≤1 and corticosteroid treatment is complete.
- **Ipilimumab:** Immunotherapy may be restarted if the adverse reaction remains at Grade ≤1until all 4 doses are administered or 16 weeks from the first dose, whichever occurs first.
- **Ipilimumab/Nivolumab** treatment may be restarted if the adverse reaction remains at Grade ≤1 and corticosteroid treatment is complete. Treatment may be restarted as combination therapy or with single agent nivolumab only based on clinical evaluation of the individual patient

4.0 Guidance for treatment with Nivolumab, Nivolumab & Ipilimumab or Pembrolizumab

Immune-related adverse reactions	Severity	Management and treatment modification
Colitis	**Grade 2** (4-6 motions/day, abdominal pain)	Withhold until recovery to Grade 0-1 (delayed dose may then be given) Treatment with loperamide/fluids may be considered if mild Administer 1-2 mg/kg/day prednisolone or equivalent followed by a taper Stool culture and C.Diff toxin Consider endoscopy Consider gastroenterology input
	Grade 3 colitis (>7 motions/day hospitalisation, severe abdominal pain)	Withhold treatment until recovery to Grade 0-1 or permanently discontinue for ipilimumab/ nivolumab combination treatment and manage as per Grade 4 colitis below. Administer 1-2 mg/kg/day prednisolone or equivalent followed by a taper Stool culture and C.Diff toxin Consider endoscopy Consider gastroenterology input Consider methylprednisolone 1-2mg/kg IV if no improvement on oral prednisolone.
	Grade 4 colitis (life threatening)	Permanently discontinue Admit patient for clinical and laboratory assessments. The potential risk of gastrointestinal perforation should be taken into consideration Start IV methylprednisolone 1-2mg/kg/day Gastroenterology input If no improvement, consider Infliximab 5mg/kg single dose (consultant decision only, retrospective IFR required, contra-indicated if perforation or sepsis) Once symptoms resolved, the dose of steroid may be gradually tapered over a period of at least one month. Too rapid de-escalation is known to risk incomplete treatment of colitis.
Hepatitis	**Grade 2** aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 3 to 5 times ULN or total bilirubin > 1.5 to 3 times ULN (Grade 2)	Withhold until recovery to Grade 0-1 (AST / ALT ≤ 3 x ULN and bilirubin ≤ 1.5 x ULN, the delayed dose may then be given). Initiate prednisolone 0.5-1mg/kg/day (or equivalent). Once symptoms resolve and LFT elevations normalise, the dose of steroid may be gradually tapered.
	Grade 3/4 AST or ALT > 5 times ULN or total bilirubin > 3 times ULN (Grade ≥ 3)	Grade 3/4 Permanently discontinue pembrolizumab/nivolumab/ipilimumab Initiate prednisolone 1 - 2mg/kg/day (or equivalent). Needs specialist input. If symptoms fail to improve after 5 days consider

		non-corticosteroid based immunosuppressive medication e.g. mycophenolate mofetil Once symptoms resolve and LFT elevations normalise taper the dose of steroids over one month
	In case of liver metastasis with baseline Grade 2 elevation of AST or ALT, hepatitis with AST or ALT increases ≥ 50% and lasts ≥ 1 week	Permanently discontinue Initiate prednisolone 1 - 2mg/kg/day (or equivalent). Consider specialist input Once symptoms resolve and LFT elevations normalise, the dose of steroid may be gradually tapered.
Skin Toxicities/Rash	**Grade 1-2** <30% BSA	Treat symptomatically with topical emollients, steroid cream and/or oral antihistamines, treatment can continue with on-going monitoring. If Grade 2 rash/pruritus persists for 1-2 weeks, consider withholding treatment. Consider skin biopsy
	Grade 3 >30% BSA	Withhold treatment; treat symptomatically as above and consider adding oral steroids; prednisolone 1mg/kg. Dermatology input Consider skin biopsy Once symptoms have resolved steroids should be tapered over 1 month
	Grade 4 TENS, erythroderma, Stevens-Johnson syndrome	Permanently discontinue treatment, start PO or IV steroids at 2 mg/kg of methylprednisolone equivalent, seek dermatology opinion. Once symptoms have resolved steroids should be tapered over 1 month
Pneumonitis	**Grade 2** pneumonitis (symptomatic/affecting ADLs)	Withhold until recovery to Grade 0-1 (delayed dose may then be given) Administer 1-2 mg/kg/day prednisolone or equivalent followed by a taper over at least one month. Consider early respiratory referral and bronchoscopy
	Grade 3 (severe symptoms, oxygen required) or **Grade 4** (life-threatening symptoms), or **recurrent Grade 2** pneumonitis	Permanently discontinue Administer 1-2 mg/kg/day prednisolone or equivalent. Escalate to IV methylprednisolone 2-4mg/kg/day if required and obtain early specialist input. If symptoms fail to improve after 2 days consider non-corticosteroid based immunosuppressive medication – mycophenolate/cyclophosphamide Once symptoms and radiological changes resolve, steroids may be gradually tapered.
Endocrinopathies		
Hypophysitis	**Grade 2** moderate symptoms limiting instrumental ADLs **Grade 3** severe symptoms hospitalisation, limiting self care **Grade 4** life threatening consequences	Grade 2-3 Withhold until recovery to Grade 0-1 Grade 4 permanently discontinue Hormone replacement should be administered as clinically indicated. Endocrine review Consider pituitary MRI Grade 3-4 1-2mg/kg/day predinisolone
Adrenal Insufficiency	**Grade 2** moderate symptoms limiting instrumental ADLs **Grade 3** severe symptoms	Grade 2 withhold treatment Grade 3-4 permanently discontinue

	hospitalisation, limiting self care **Grade 4** life threatening consequences	Hormone replacement should be administered as clinically indicated. Grade 3-4 1-2mg/kg/day predinisolone Endocrine review Rule out sepsis
Type 1 Diabetes	**Grade > 3** hyperglycemia (glucose > 13.9 mmol/L) or associated with ketoacidosis	Patients should be monitored for <u>hyperglycaemia</u> or other signs and symptoms of diabetes. Grade 3 hyperglycaemia – withhold treatment Grade 4 permanently discontinue Insulin should be administered for type 1 diabetes.
Hyperthyroidism/ Hypothyroidism	**Grade 2** symptomatic, thyroid suppression/replacement therapy indicated **Grade 3** severe symptoms hospitalisation, limiting self care **Grade 4** life threatening consequences	<u>Hyperthyroidism</u> may be managed symptomatically Grade 3/4 Withhold treatment until recovered to </=Grade 2 <u>Hypothyroidism</u> may be managed with replacement therapy **without** treatment interruption. Consider endocrine input Discontinue nivolumab or nivolumab & ipilimumab combination in the event of Grade 4 hyperthyroidism or hypothyroidism.
Uveitis	**Grade 2** Anterior Uveitis medical intervention indicated	Withhold treatment until recovery to Grade 0-1 Opthalmology review Topical corticosteroid eye drops
	Grade 3/4 posterior or panuveitis	Permanently discontinue Opthalmology review Commence oral predisolone
Nephritis	**Grade 2** nephritis with creatinine > 1.5 to 3 times upper limit of normal (ULN)	Withhold until recovery to Grade 0-1 (delayed dose may then be given) Initiate prednisolone 1-2mg/kg/day (or equivalent), followed by a taper over at least 4 weeks
	Grade 3 nephritis with creatinine ≥ 3-6 times ULN	**Pembrolizumab:** Permanently discontinue Initiate prednisolone 1 - 2mg/kg/day (or equivalent), and consider further escalation to IV methylprednisolone 2mg/kg/day, followed by a taper over at least 4 weeks Consider renal review **Nivolumab / Nivolumab & Ipilimumab:** Initiate prednisolone 1 - 2mg/kg/day (or equivalent), and consider further escalation to IV methylprednisolone 2mg/kg/day, followed by a taper over at least 4 weeks. Withhold until creatinine returns to baseline and management with corticosteroids is complete. Consider renal review Outrule alternative causes Discontinue if no improvement on prednisolone.
	Grade 4 creatinine >6x ULN	Permanently discontinue treatment Initiate prednisolone 1 - 2mg/kg/day (or equivalent), and consider further escalation to IV methylprednisolone 2mg/kg/day, followed by a taper over at least 4 weeks Consider renal review Outrule alternative causes

Neurological toxicity	**Grade 2** (moderate symptoms limiting ADLs)	Withhold treatment Consider neurology input 1mg/kg/day prednisolone Once symptoms have resolved steroids should be tapered over 1 month
	Grade 3-4	Permanently discontinue treatment Neurology review 1-2mg/kg/day IV methylprednisolone If symptoms worsen/fail to resolve consider non-steroid immunosuppressive therapy e.g IVIg Once symptoms have resolved steroids should be tapered over 1 month

For additional documents for Guidance on the Management of Ipilimumab- related toxicities, please use the link below to the KMCC website (n.b. these documents are in the process of being updated- October 2017): http://www.kentmedwaycancerguide.nhs.uk/medicines-and-prescribing-incorporating-sact-pathways/sact-pathways-guidelines-for-the-management-of-sact-induced-adverse-reactions-and-nursing/

5.0 Personnel and Contact Information

A comprehensive, up to date list of MDM contact details can be found on the KMCN website via the following link: http://www.kentmedwaycancernetwork.nhs.uk/home-page/for-professionals/

6.0 Glossary

Acronyms in common usage throughout KMCN documentation

CNB	Cancer Network Board
CYP	Children & Young People (in relation to the IOG)
DCCAG	Diagnostic Cross Cutting Advisory Group
DOG	Disease Orientated Group (NSSG/TSSG/TWG)
DVH	Darent Valley Hospital
EK	East Kent
EKHUFT	East Kent Hospitals University Foundation Trust
HoP	High Level Operational Policy
IOSC	Improving Outcomes: A Strategy for Cancer
K&C	Kent & Canterbury Hospital, Canterbury, (EKHUFT)
KMCN	Kent & Medway Cancer Network
KMCRN	Kent & Medway Cancer Research Network
LSESN	London & South East Sarcoma Network
MFT	Medway Foundation Trust
MTW	Maidstone & Tunbridge Wells NHS Trust
NOG	Non Surgical Oncology Group *(Permanent oncologist sub group of the DOGs with a specific responsibility for chemo/rad pathways and advice to the DOG, Network and GEOGRAPHICAL LOCATIONs on new drugs)*
PoC	Pathway of Care *(Network agreed disease site specific clinical guidelines)*
QEQM	Queen Elizabeth the Queen Mother Hospital, Margate (EKHUFT)
QoL	Quality of life
RAT	Research and Trial Group *(Permanent sub-group of the DOGs with a specific responsibility for taking forward the clinical trials agenda)*
RMH	Royal Marsden Hospital
RNOH	Royal National Orthopaedic Hospital
QVH	Queen Victoria Foundation Trust Hospital East Grinstead
UCLH	University College Hospital London
WHH	William Harvey Hospital, Ashford (EKHUFT)
WK	West Kent

7.0 Document Administration

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