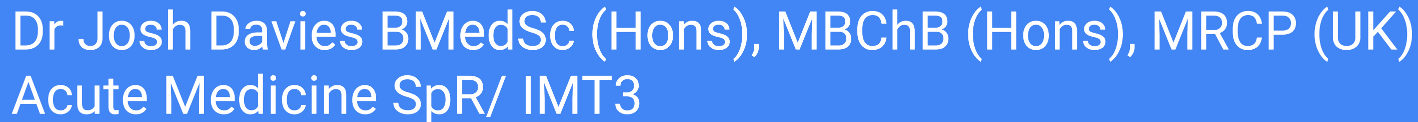
Front Door Oncological Emergencies: Focus on Immunotherapy

Acute Medicine Lunchtime Teaching - October 2023



Overview

- Quick fire oncological emergencies
- Immunotherapy overview
- Toxicities
- Case study
- Resources

Quick Fire Oncological Emergencies

Cord Compression

- Watch out for spinal shock
- MRI whole spine (makes it difficult for oncology to arrange treatment without whole spine imaging)
- High dose dexamethasone (8mg BD) + PPI cover (monitor BMs)
- Physio review and good analgesia
- Prompt and early liaison with neurosurgeons
- Bed rest

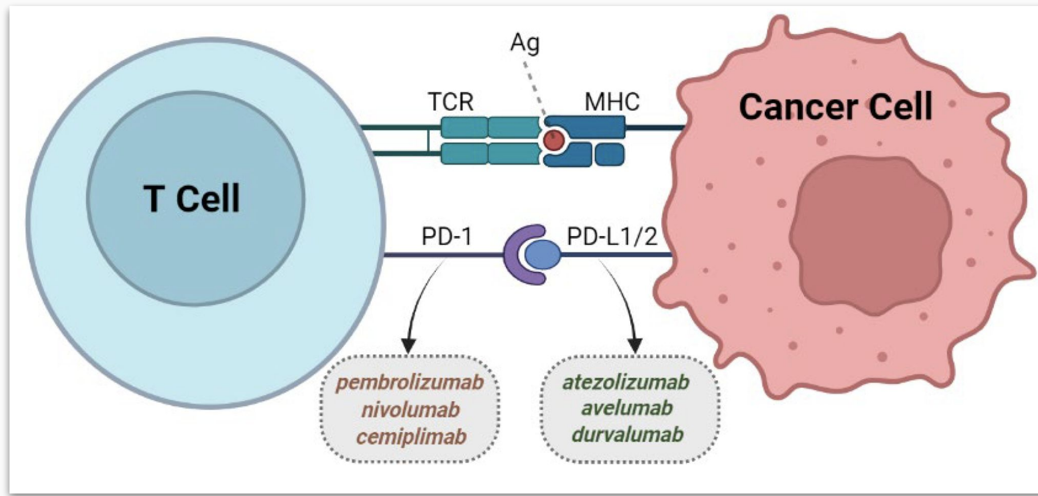
Febrile Neutropenia

- Sepsis 6 before results back (use the bundle!)
- Robust infection screen (sputum, urine, CXR) - check for lines
- Tazosin 4.5g QDS if neutropenic (meropenem or cipro if pencillin allergic) plus aminoglycoside
- Are they adjuvant? - implies that cancer has already been cleared and therefore patients should be for full escalation based on other comorbidities
- Early AOS review

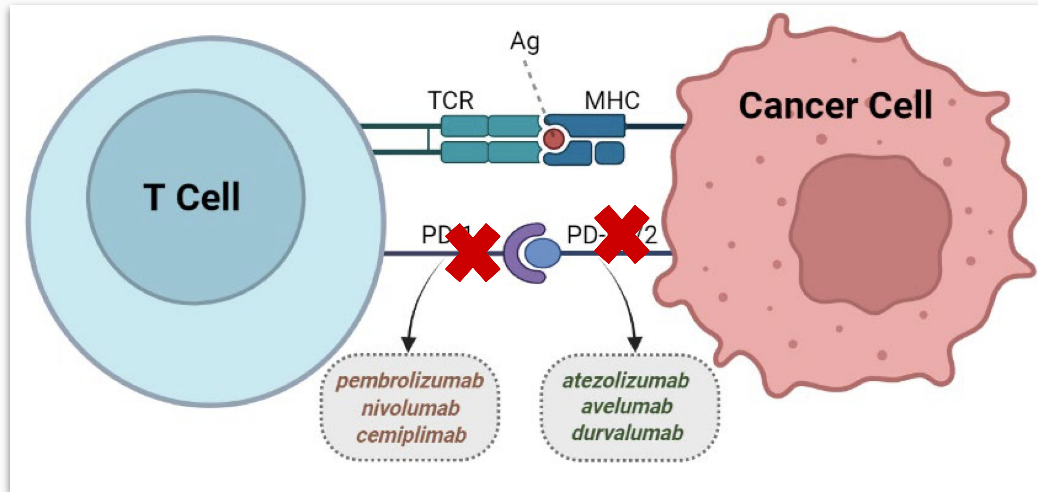
Superior Vena Cava Obstruction

- Plethoric torso and facial vessels, Pemberton’s sign
- Usually with proximal lung cancers/ mediastinal lymphoma
- Role for steroids
- D/w oncologist on call - biopsy often needed and treatment of SVCO is often of the underlying cancer
- Interventional radiology - stenting vs. radiotherapy

What is Immunotherapy?



T cell activity inhibited



T cell “brake” released and can kill tumour cell

Common Types of Immunotherapy

- Watch out for “L’s” and “Mabs”
- Toxicities are more pronounced with immune checkpoint inhibitors
  - **CTLA-4 inhibitors = ipilimumab**
  - **PD-1 inhibitors = Pembrolizumab, Nivolumab**
  - **PD-L1 inhibitors = Avelumab, Durvalumab**
- Dendritic cell vaccines
- DNA and peptide vaccines
- Immune activating cytokines
- And more….

Q1 Q3 Q4 Q1 Q2 Q3 Q4 Q1 Q2 Q3 Q4 Q1 Q2 Q3 Q4 Q1 Q2 Q3 Q4 Q1 Q2 Q3 Q4 Q1 Q2 Q3 Q4 Q1 Q2 Q3 Q4

2011 2012-13 2014 2015 2016 2017 2018 2019 2020 2021

IPI Late stage Melanoma

PEMBRO Advanced Melanoma

NIVO Advanced Melanoma

NIVO Squamous NSCLC

IPI + NIVO Braf V600 wt melanoma

PEMBRO mNSCLC

NIVO mNSCLC

IPI Adjuvant Melanoma

NIVO RCC

IPI + NIVO BRAF V600 melanoma

PEMBRO HNSCC

NIVO cHL

ATEZO UC

NIVO HNSCC

ATEZO mNSCLC

PEMBRO mNSCLC 1L

NIVO UC

PEMBRO cHL

AVE MCC

NIVO MSI-H/dMMR mCRC

ATEZO Bladder cancer

NIVO HCC

PEMBRO Gastric or GEJ cancer

DURVA Bladder cancer

AVE UC

PEMBRO mNSCLC 1L all PD-1

PEMBRO UC

PEMBRO AnyMSI-H or dMMR solid tumor

NIVO Adjuvant Lymphoma

DURVA Stage III NSCLC

IPI + NIVO RCC 1L

IPI + NIVO MSI-H/dMMR mCRC

NIVO SCLC

PEMBRO Cervical cancer

PEMBRO PMBCL

CEMI Cutaneous SCC

PEMBRO mNSCLC 1L

PEMBRO HCC

ATEZO mNSCLC 1L

PEMBRO MCC

PEMBRO Adjuvant Melanoma

PEMBRO mNSCLC 1L mono

PEMBRO RCC 1L

PEMBRO HNSCC 1L

PEMBRO SCLC

ATEZO PD-L1+ TNBC

ATEZO SCLC 1L

PEMBRO Esophageal cancer

AVE RCC

PEMBRO Endometrial cancer

ATEZO mNSCLC 1L

PEMBRO NMIBC

IPI + NIVO HCC

DURVA Extensive-Stage SCLC

IPI + NIVO mNSCLC 1L

ATEZO mNSCLC 1L mono

ATEZO HCC

NIVO Advanced ESCC

PEMBRO Cutaneous SCC

PEMBRO MSI-H/dMMR mCRC 1L

AVE UC 1L maintenance

ATEZO Advanced Melanoma

IPI + NIVO Mesothelioma

PEMBRO cHL

PEMBRO TNBC

NIVO RCC 1L

CEMI Advanced BCC

CEMI mNSCLC 1L mono

PEMBRO Gastric, GEJ HER2+ Adenocarcinoma

NIVO Adjuvant Esophageal or GEJ cancer

NIVO Gastric, GEJ, Esophageal adenocarcinoma

PEMBRO Esophageal, GEJ Carcinoma

PEMBRO Cutaneous SCC

PEMBRO Endometrial carcinoma

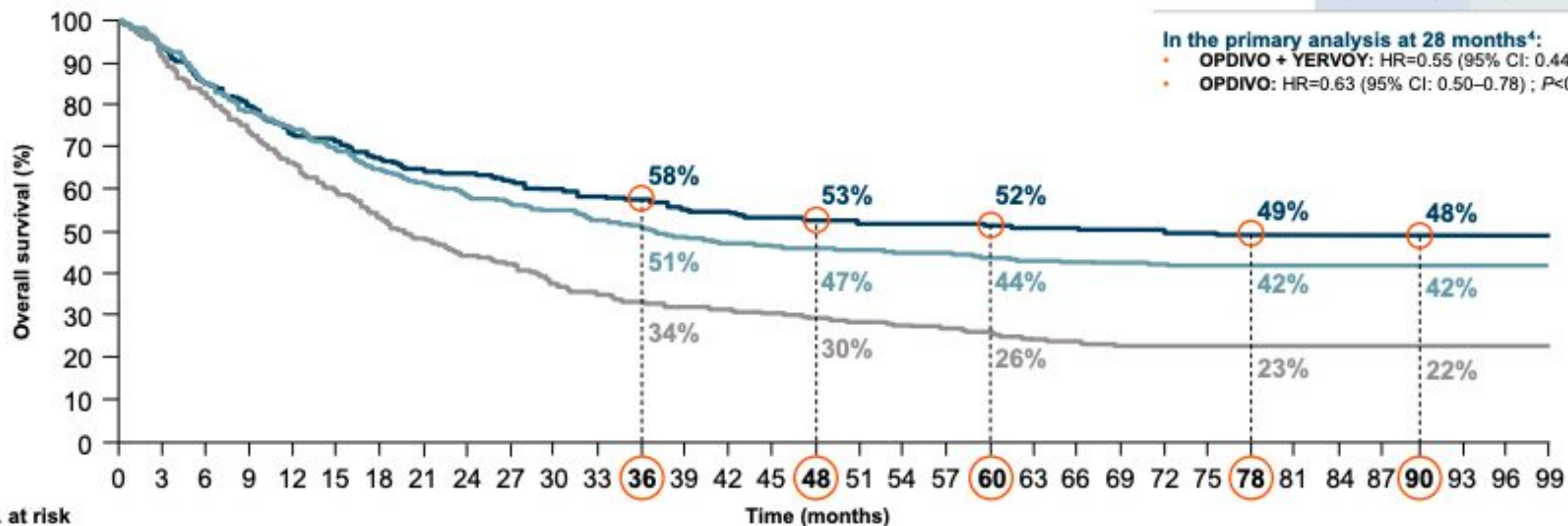
PEMBRO Adjuvant TNBC

Maritaz C, Broutin S, Chaput N, Marabelle A, Paci A. Immune checkpoint-targeted antibodies: a room for dose and schedule optimization? J Hematol Oncol. 2022 Jan 15;15(1):6. doi: 10.1186/s13045-021-01182-3. PMID: 35033167; PMCID: PMC8760805.

OS analysis in the ITT population through 7.5 years[1-3]

	OPDIVO + YERVOY (n=314)	OPDIVO (n=316)	YERVOY (n=315)
Median OS, mos (95% CI)[2]	72.1 (38.2–NR)	36.9 (28.2–58.7)	19.9 (16.9–24.6)
HR (95% CI) vs YERVOY[2]	0.53 (0.44–0.65)	0.63 (0.52–0.77)	–

In the primary analysis at 28 months[4]:
- **OPDIVO + YERVOY:** HR=0.55 (95% CI: 0.44–0.69); *P*<0.0001
- **OPDIVO:** HR=0.63 (95% CI: 0.50–0.78) ; *P*<0.0001



	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54	57	60	63	66	69	72	75	78	81	84	87	90	93	96	99
OPDIVO + YERVOY	314	292	265	248	227	222	210	201	199	193	187	181	179	172	169	164	163	159	158	157	156	154	153	150	147	145	144	143	141	138	129	58	7	0
OPDIVO	316	292	265	245	231	214	201	191	181	175	171	164	158	150	145	142	141	139	137	137	134	132	130	128	126	124	123	121	120	118	107	54	4	0
YERVOY	315	285	253	227	203	181	163	148	135	128	113	107	100	95	94	91	87	84	81	77	75	70	68	64	64	63	63	63	63	62	57	24	5	0

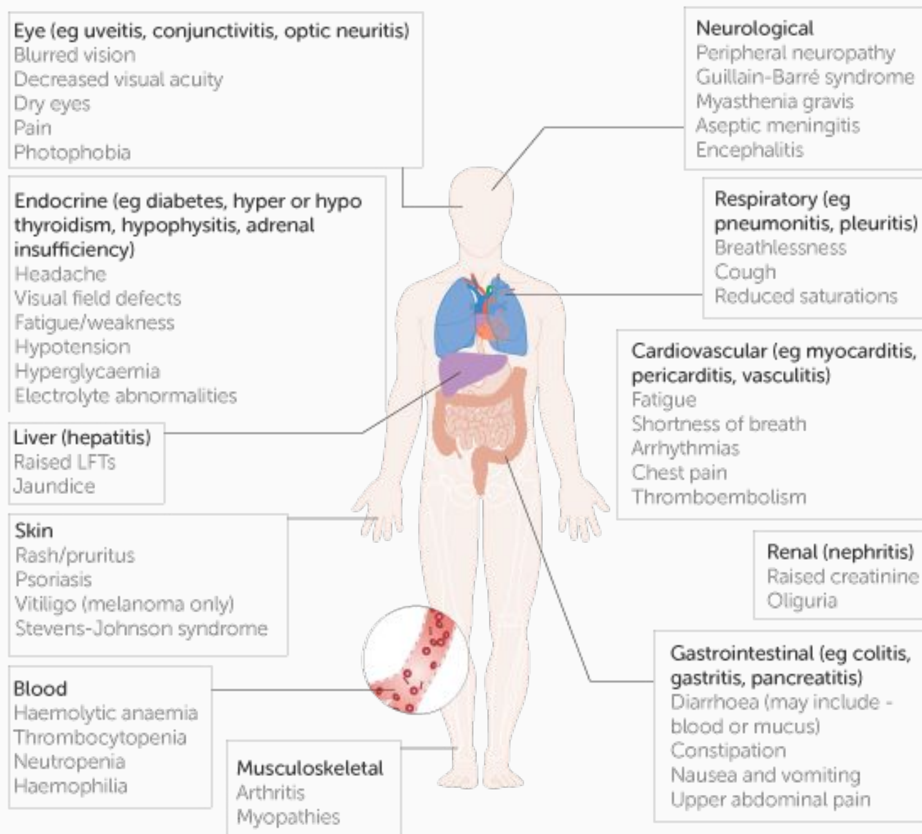
Wolchok JD, Chiarion-Sileni V, Gonzalez R, Grob JJ, Rutkowski P, Lao CD, Cowey CL, Schadendorf D, Wagstaff J, Dummer R, Ferrucci PF, Smylie M, Butler MO, Hill A, Márquez-Rodas I, Haanen JBAG, Guidoboni M, Maio M, Schöffski P, Carlino MS, Lebbé C, McArthur G, Ascierto PA, Daniels GA, Long GV, Bas T, Ritchings C, Larkin J, Hodi FS. Long-Term Outcomes With Nivolumab Plus Ipilimumab or Nivolumab Alone Versus Ipilimumab in Patients With Advanced Melanoma. J Clin Oncol. 2022 Jan 10;40(2):127-137. doi: 10.1200/JCO.21.02229. Epub 2021 Nov 24. PMID: 34818112; PMCID: PMC8718224.

Toxicities

Toxicities

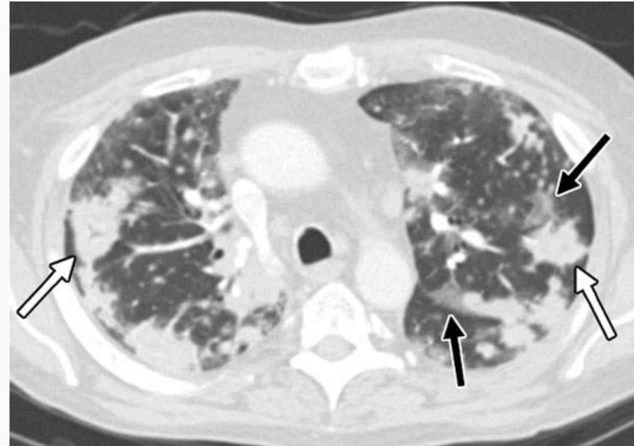
- Majority of patients tolerate immunotherapy very well, but immune related adverse events (irAEs) are more likely to occur depending on the agent:
  - Up to 90% patients receiving CTLA-4 inhibitors
  - Up to 70% patients receiving PD-1 and PD-1L inhibitors
- Activated T cells mis-read the bodies proteins bound to MHC molecules → immune mediated attack of native tissue
- Immunotherapy can therefore trigger autoimmune disease (this is different from chemotherapy related complications, e.g. neutropenic sepsis)

Name and organ…

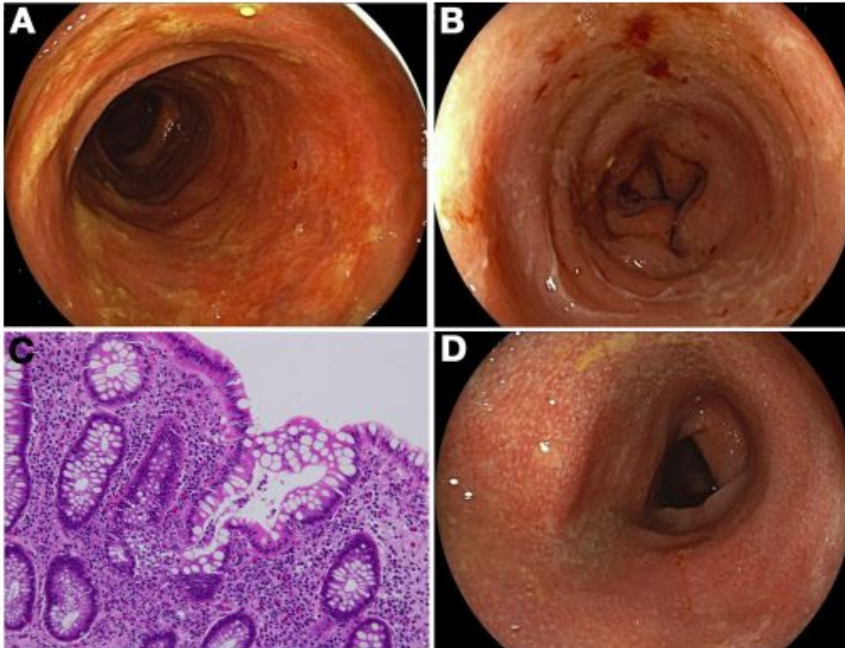


Pneumonitis

- Signs and symptoms
  - SOB (40-50%)
  - Cough (35%)
  - Pyrexia
  - Chest pain
  - Hypoxaemia
- Rapidly progressive
- HRCT: Ground glass changes, mostly in upper lobes
- DDx: atypical pneumonia, ARDS
- Treat with steroids (1mg/kg methypred)



Colitis



- Severe and potentially fatal
- 10% grade ¾ with combination treatment
- Signs and symptoms:
  - Diarrhoea
  - Blood/ mucus in stools
  - Abdominal pain
  - Fever
- Take it seriously!
- NBM, IVI, steroids → Flexi-sigmoidoscopy +/- infliximab if not improving
- Early referral to gastro/ AOS

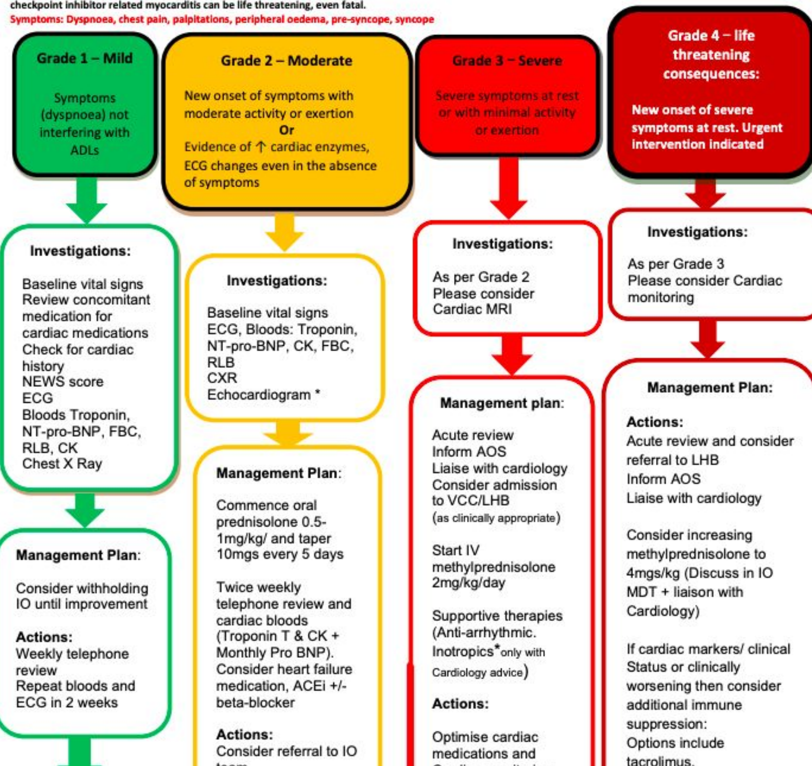
Neurological & Cardiac Toxicity

- Varied - affect ~ 1-5% of patients on immunotherapy
  - Myasthenia
  - GBS
  - Mononeuropathies
  - Limbic encephalitis
  - PRES (seizures, headache, hypertension)
- Cardiac toxicity - echo is often normal, cardiac MR is better imaging modality
  - Myo/pericarditis
  - Arrhythmias
  - Pericardial effusion
- Need increased doses of methylprednisolone (i.e. 500mg)

Endocrinopathies

- >10% affected
- Thyroid disturbance and hypophysitis most commonly affected
- Hypophysitis often needs basal and dynamic pituitary function tests + MRI pituitary
- Adrenal insufficiency can be a diagnostic challenge
  - A tired patient on immunotherapy needs a 9am cortisol and thyroid function checking
  - Weight loss
  - Decreased appetite
  - Postural instability

Guidelines



Immune Related Adverse Event: Cardiac/Myocarditis

Myocarditis is a recognised complication of checkpoint inhibitors. Approximately 1% of patients treated with checkpoint inhibitors develop cardio toxicity. Myocarditis is associated with a high mortality rate if not treated. It is common for patients to be asymptomatic or to have minimal symptoms and abnormal cardiac tests are significant. In practice, if a patient has unremitting respiratory symptoms, despite intervention, then need to exclude cardiac toxicity. Although rare, immune checkpoint inhibitor related myocarditis can be life threatening, even fatal.

Symptoms: Dyspnoea, chest pain, palpitations, peripheral oedema, pre-syncope, syncope

Grade 1 – Mild

Symptoms (dyspnoea) not interfering with ADLs

Investigations:

Baseline vital signs
Review concomitant medication for cardiac medications
Check for cardiac history
NEWS score
ECG
Bloods Troponin, NT-pro-BNP, FBC, RLB, CK
Chest X Ray

Management Plan:

Consider withholding IO until improvement

Actions:
Weekly telephone review
Repeat bloods and ECG in 2 weeks

Grade 2 – Moderate

New onset of symptoms with moderate activity or exertion
Or
Evidence of ↑ cardiac enzymes, ECG changes even in the absence of symptoms

Investigations:

Baseline vital signs
ECG, Bloods: Troponin, NT-pro-BNP, CK, FBC, RLB
CXR
Echocardiogram *

Management Plan:

Commence oral prednisolone 0.5-1mg/kg/ and taper 10mgs every 5 days

Twice weekly telephone review and cardiac bloods (Troponin T & CK + Monthly Pro BNP).
Consider heart failure medication, ACEi +/- beta-blocker

Actions:
Consider referral to IO team

Grade 3 – Severe

Severe symptoms at rest or with minimal activity or exertion

Investigations:

As per Grade 2
Please consider Cardiac MRI

Management plan:

Acute review
Inform AOS
Liaise with cardiology
Consider admission to VCC/LHB
(as clinically appropriate)

Start IV methylprednisolone 2mg/kg/day

Supportive therapies (Anti-arrhythmic. Inotropics* only with Cardiology advice)

Actions:

Optimise cardiac medications and

Grade 4 – life threatening consequences:

New onset of severe symptoms at rest. Urgent intervention indicated

Investigations:

As per Grade 3
Please consider Cardiac monitoring

Management Plan:

Actions:
Acute review and consider referral to LHB
Inform AOS
Liaise with cardiology

Consider increasing methylprednisolone to 4mgs/kg (Discuss in IO MDT + liaison with Cardiology)

If cardiac markers/ clinical Status or clinically worsening then consider additional immune suppression:
Options include tacrolimus,

IV PICC and HICK
Immunotherapy Guidelines
Chemotherapy guidance
COVID-19 Staff Information

Immunotherapy Guidelines

Velindre Immunotherapy Guidelines

Information for GP's/Doctors and allied healthcare professionals

The following documents provide advice for healthcare professionals. If you have reached this page in error, please look through our patient information files.

Immunotherapy Guidelines (pdf)

Take Home Messages

- Immunotherapy is changing the way certain cancers are treated
- Potentially curing stage 4 cancers
- Immunotherapies are increasing and we need to be aware of potential toxicities as front door medics
- Toxicities can present at the start, middle or end of treatment
- Mainstay of toxicity treatment is....Steroids!

Resources

- Local and national guidelines
- Regional immunotherapy networkds

Thank You - Any Questions