National University Cancer Institute, Singapore

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Dealing with toxicities of immune checkpoint inhibitors – what needs to be done and a national IO toxicity database

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DISCLOSURE SLIDE

Research Support	Astra Zeneca, Karyopharm Therapeutics, Bayer, National Medical Research Council Singapore
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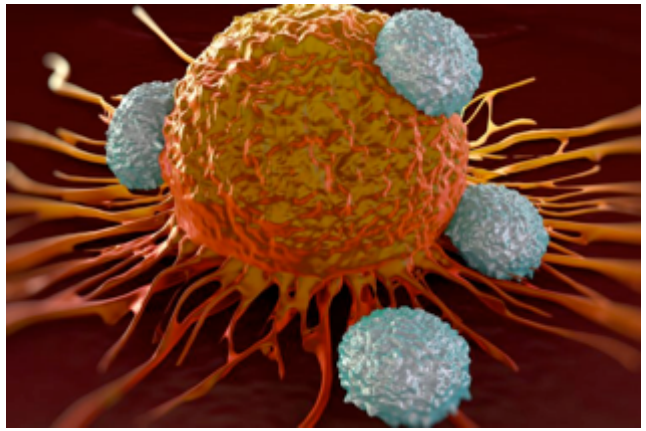
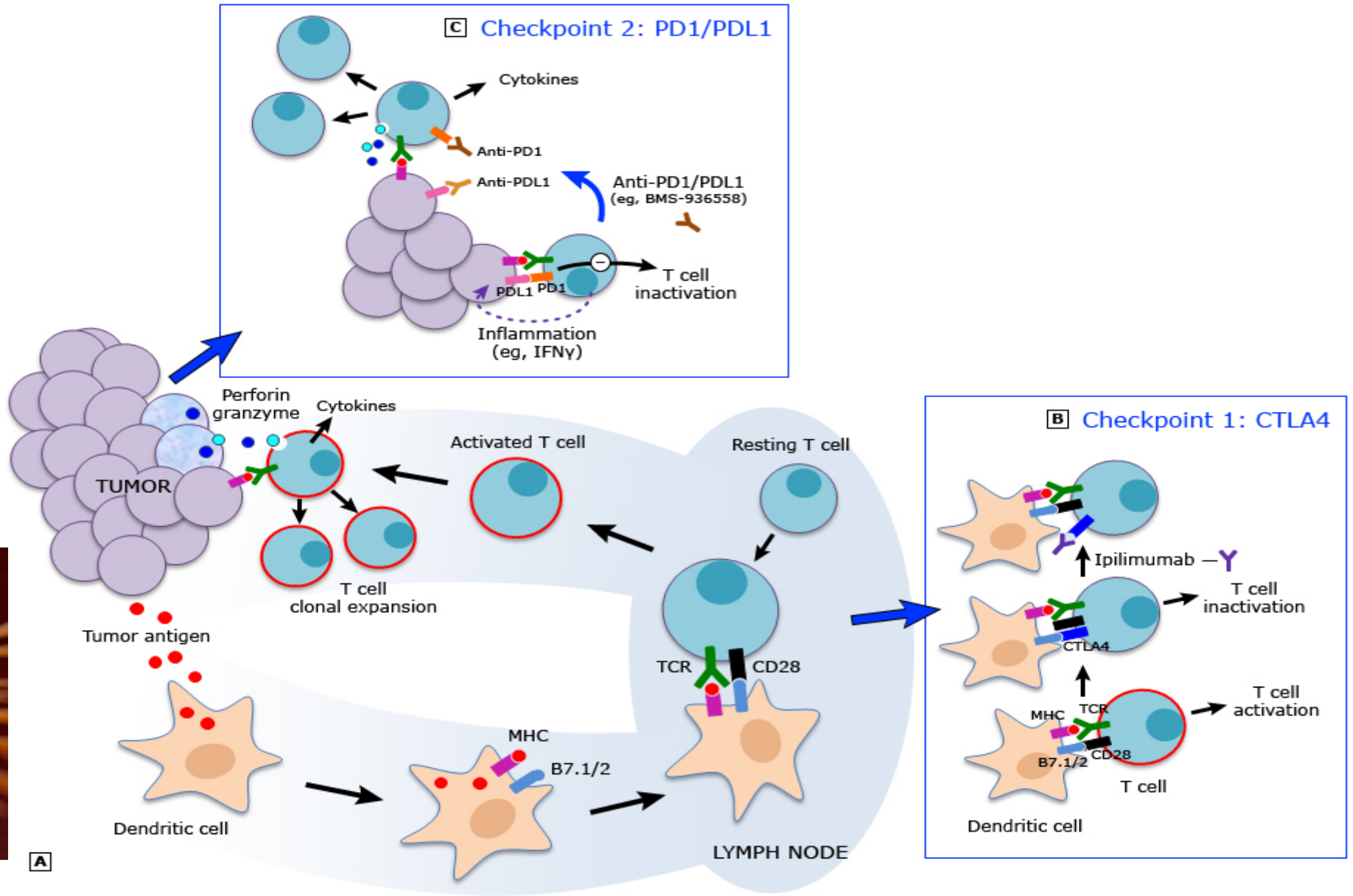
Checkpoint inhibitor toxicity is autoimmune-mediated toxicity

Gettinger et al 2016

Anti-tumour immune activation & checkpoint inhibition





Main Questions

What are the side effects of IO agents?

- Immune related adverse events - irAEs

When and how often do they happen?

What should I do about it?

Grade 3-4 irAEs are less frequent with anti-PD-1/ PD-L1 antibodies vs CTLA-4 inhibitors

CheckMate 067 Phase 3 trial

Comparison of AEs in Nivolumab vs Ipilimumab monotherapy groups

Adverse events, %	NIVO (n = 313)		IPI (n = 311)	
	All grades	CTCAE grade 3–4	All grades	CTCAE grade 3–4
Treatment-related	82.1	16.3	86.2	27.3
Treatment-related, prompting treatment discontinuation	7.7	5.1	14.8	13.2
Treatment-related deaths	0.3 (1 neutropenia)		0.3 (1 cardiac arrest)	

Larkin et al. N Engl J Med 2015; 373: 23–34.

Treatment selected irAEs from Checkmate 067: Nivolumab vs Ipilimumab monotherapy groups

Patients Reporting Event, %	NIVO (N=313)		IPI (N=311)	
	Any Grade	Grade 3–4	Any Grade	Grade 3–4
Skin	41.9	1.6	54.0	2.9
Pruritus	18.8	0	35.4	0.3
Rash	21.7	0.3	20.9	1.6
Rash maculo-papular	4.2	0.3	11.9	0.3
Gastrointestinal	19.5	2.2	36.7	11.6
Diarrhea	19.2	2.2	33.1	6.1
Colitis	1.3	0.6	11.6	8.7
Hepatic	6.4	2.6	7.1	1.6
Increase in alanine aminotransferase	3.8	1.3	3.9	1.6
Increase in aspartate aminotransferase	3.8	1.0	3.5	0.6
Endocrine	14.4	0.6	10.9	2.3
Hypothyroidism	8.6	0	4.2	0

Larkin et al. N Engl J Med 2015; 373: 23–34.

General Principles for management of immune related adverse events (irAEs)

Grade of irAE	Action
Grade 1 (mild)	• Symptomatic management • Monitor and continue therapy
Grade 2 (moderate)	• Discontinue checkpoint inhibitor → early specialist referral • Only resume when symptoms or toxicity is grade 1 or less • If symptoms do not resolve in < 1week → start Corticosteroids (prednisone 0.5 mg/kg/day or equivalent)
For grade 3 or 4 (severe or life-threatening)	• Permanently discontinue treatment → early specialist referral • High doses of corticosteroids (prednisone 1 to 2 mg/kg/day or equivalent) • Use alternative immunosuppressive therapy if symptoms persist beyond 2-3days on steroids • When symptoms subside to grade 1 or less, steroids tapered over at least one month.

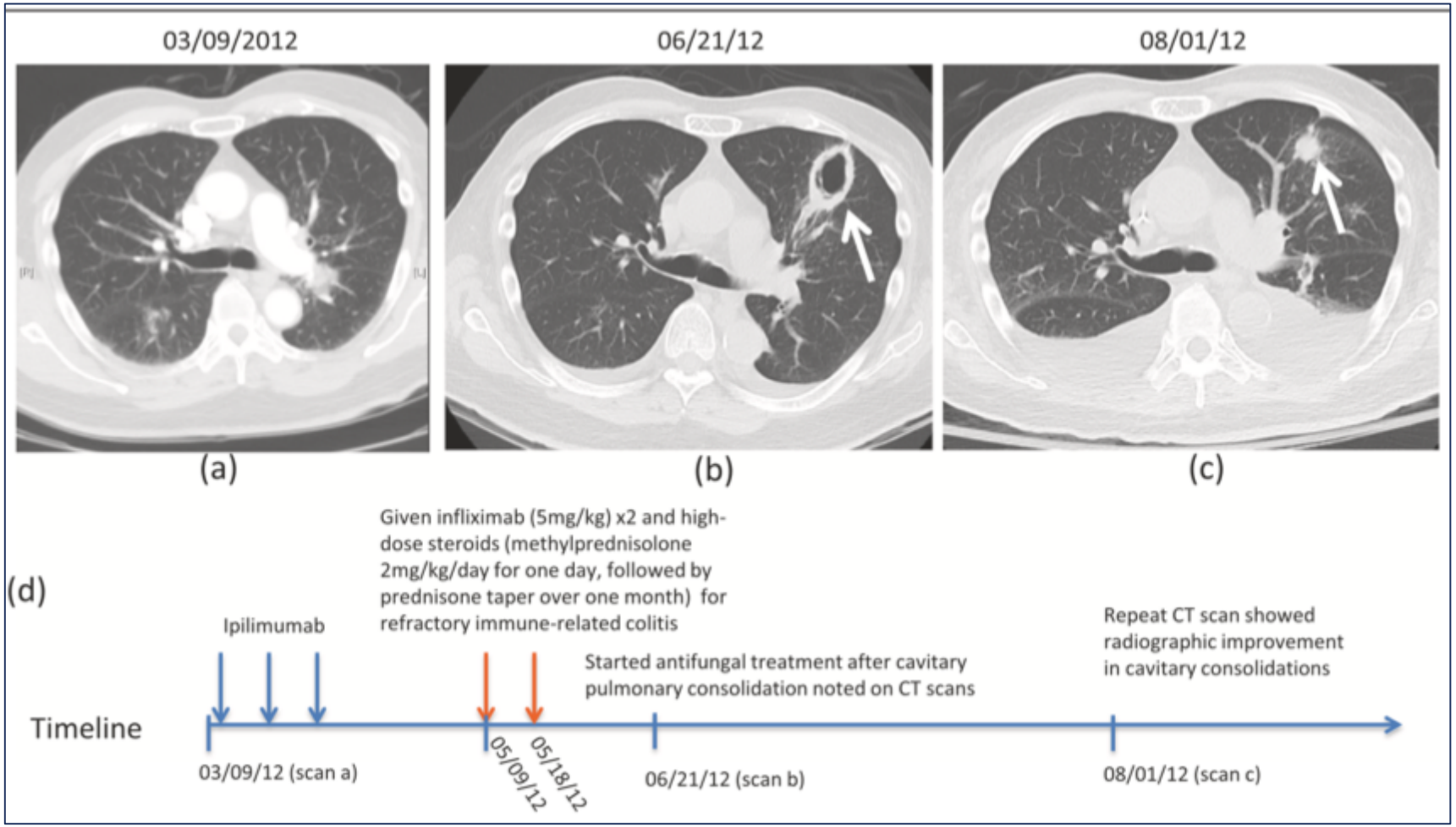
General Principles for management of immune related adverse events (irAEs)

- **Corticosteroid benefit usually in 2-3 days**

- **If no improvement after 3 days with IV steroids, consider alternative immunosuppressive treatment depending on autoimmune condition**
    - **infliximab (5 mg/kg) – Anti TNF-α (most data in autoimmune colitis)**
    - **Intravenous immunoglobulin (IVIG) - pooled polyvalent IgG antibodies**
    - **Cyclophosphamide/ MMF etc**
    - **?Plasmapheresis → removal of active drug from patient**

Opportunistic infections

- **Risk of infections after prolonged immune suppression for treatment of irAEs e.g. *Aspergillus* pneumonia and *Pneumocystis jiroveci (PCP)***
- **PCP prophylaxis with cotrimoxazole/ pentamidine if > 4weeks of 20 mg daily of prednisone**
- **Reactivation of Hepatitis B and TB**

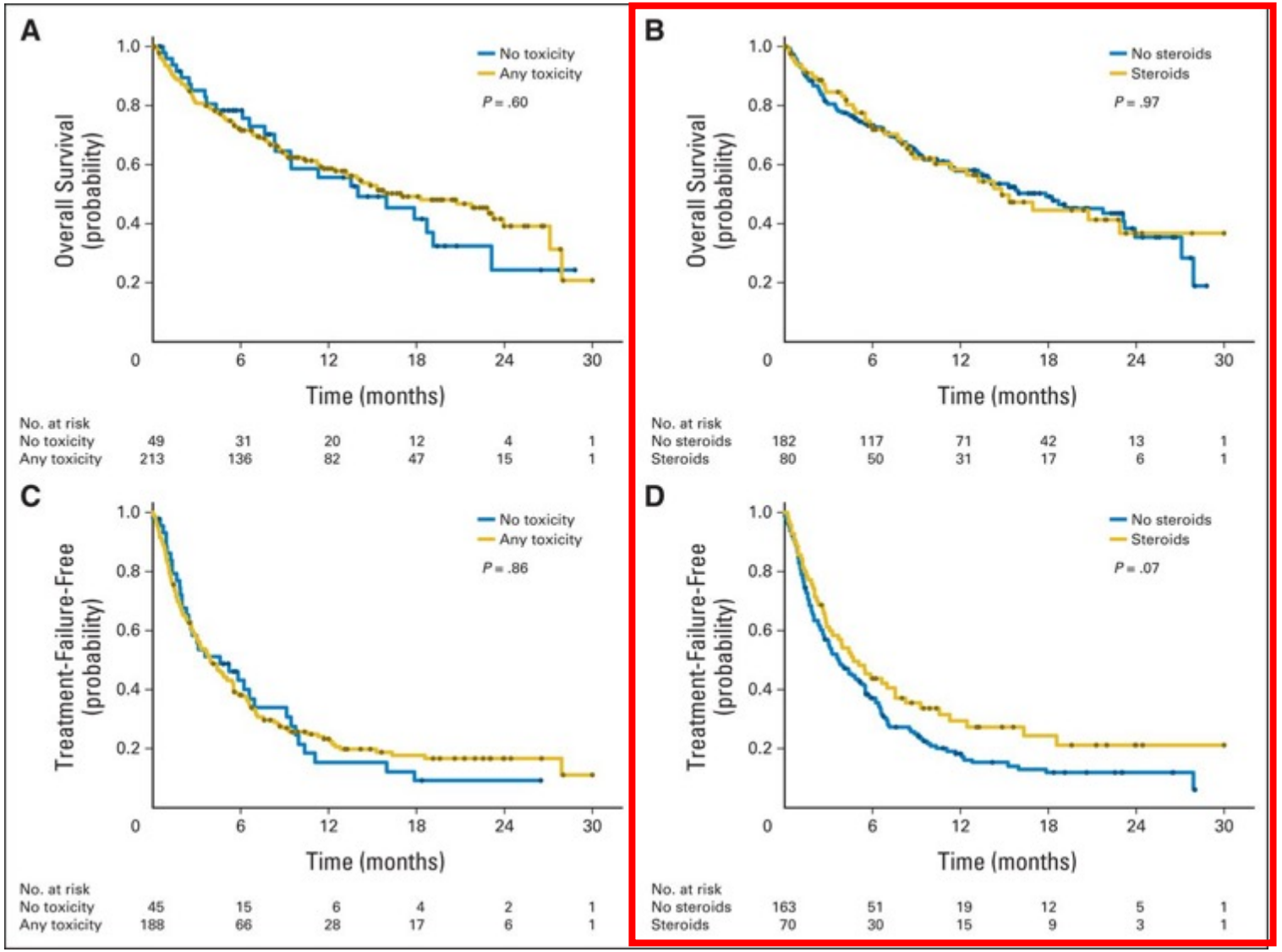


Kyi et al. Journal for ImmunoTherapy of Cancer 2014, 2:19

Does immunosuppression reduce efficacy of checkpoint inhibitors?

298 patients treated with ipilimumab (3 mg/kg) for advanced melanoma.

- 85% IrAEs → 35% required corticosteroids, 10% Anti-TNF.
- No difference in outcome for steroid vs non-steroid treated patients



Horvat et al. JCO 2015;33:3193-3198

Does immunosuppression reduce efficacy of PD1/ PD-L1 checkpoint inhibitors?

576 patients with melanoma pooled from nivolumab clinical trials

	NIVO monotherapy with IM N = 139	NIVO monotherapy without IM N = 437
ORR, n (%), [95% CI]	40 (28.8) [21.4–37.1]	141 (32.3) [27.9–36.9]
BOR, n (%)		
CR	7 (5.0)	22 (5.0)
PR	33 (23.7)	119 (27.2)
SD	31 (22.3)	102 (23.3)
PD	63 (45.3)	173 (39.6)
Not evaluable	5 (3.6)	21 (4.8)
Median duration of response, mo (95% CI)	NR (9.3–NR)	22.0 (22.0–NR)
Median time to response, mo (range)	2.1 (1.2–8.8)	2.1 (1.4–9.2)

Pts evaluable for response had a baseline tumor assessment and a confirmatory scan at least 4 weeks after the first documented response
BOR, best overall response; CR, complete response; PR, partial response; SD, stable disease

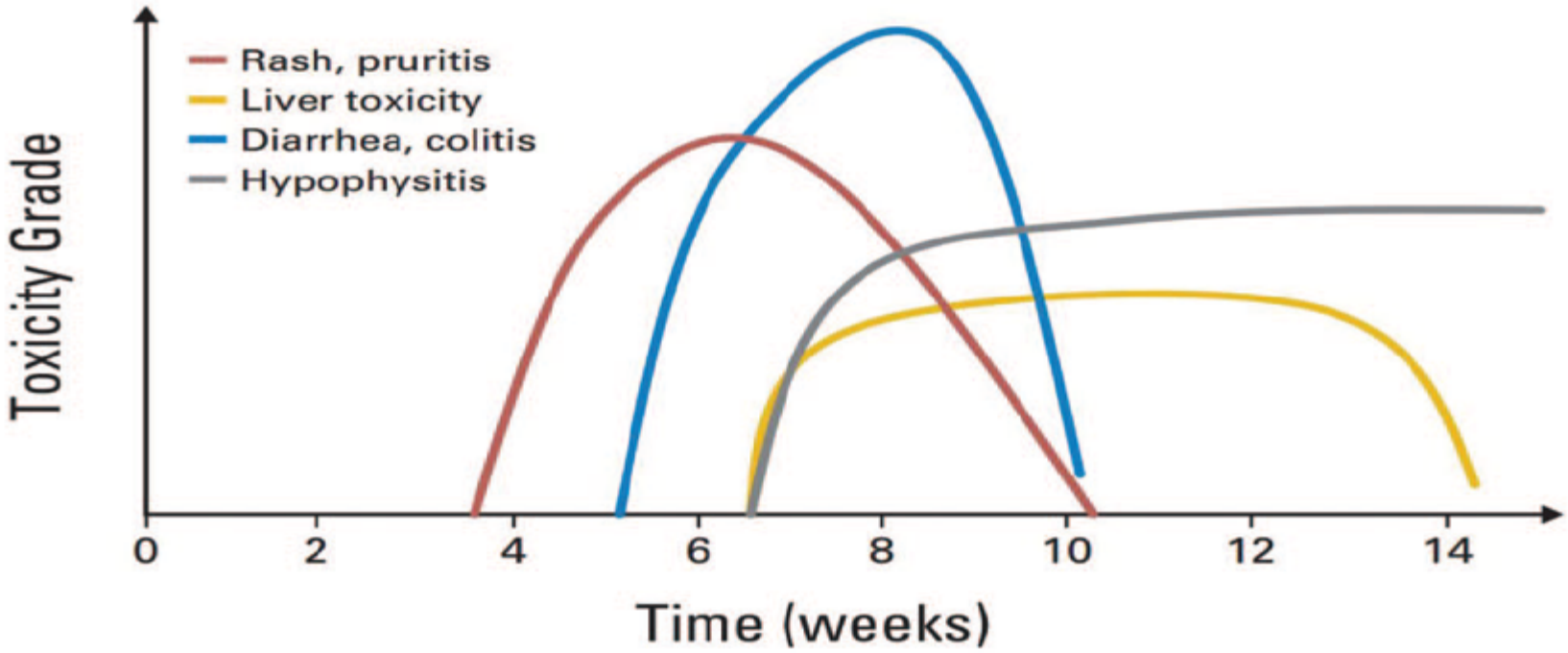
Weber et al, J Clin Oncol 33, 2015 (suppl; abstr 9018).

Onset and Kinetics of Immune-Related Adverse Events for Ipilimumab (CTLA-4 inhibitor)

Onset usually from week 3-8

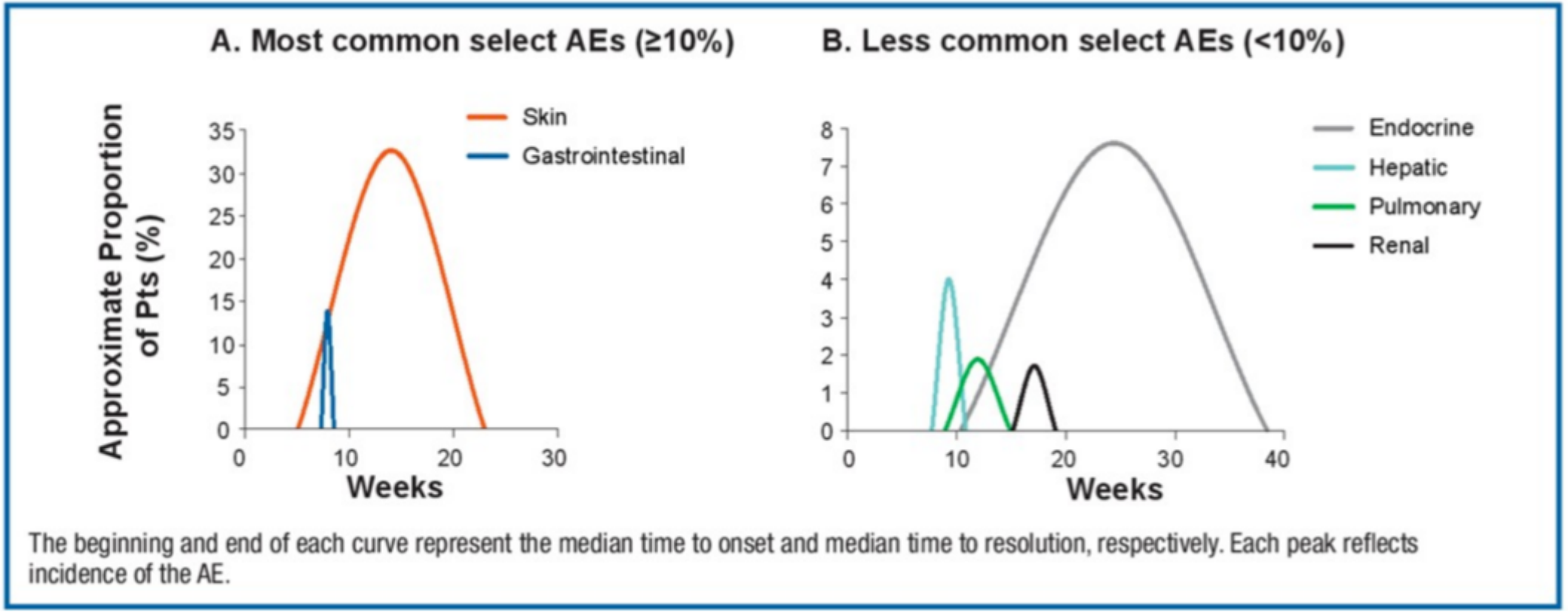
early (<2 months):
skin, gastrointestinal and hepatic AEs or

late (>2 months):
pulmonary, endocrine and renal AEs



Weber J, et al: J Clin Oncol 30(21), 2012:2691-2697

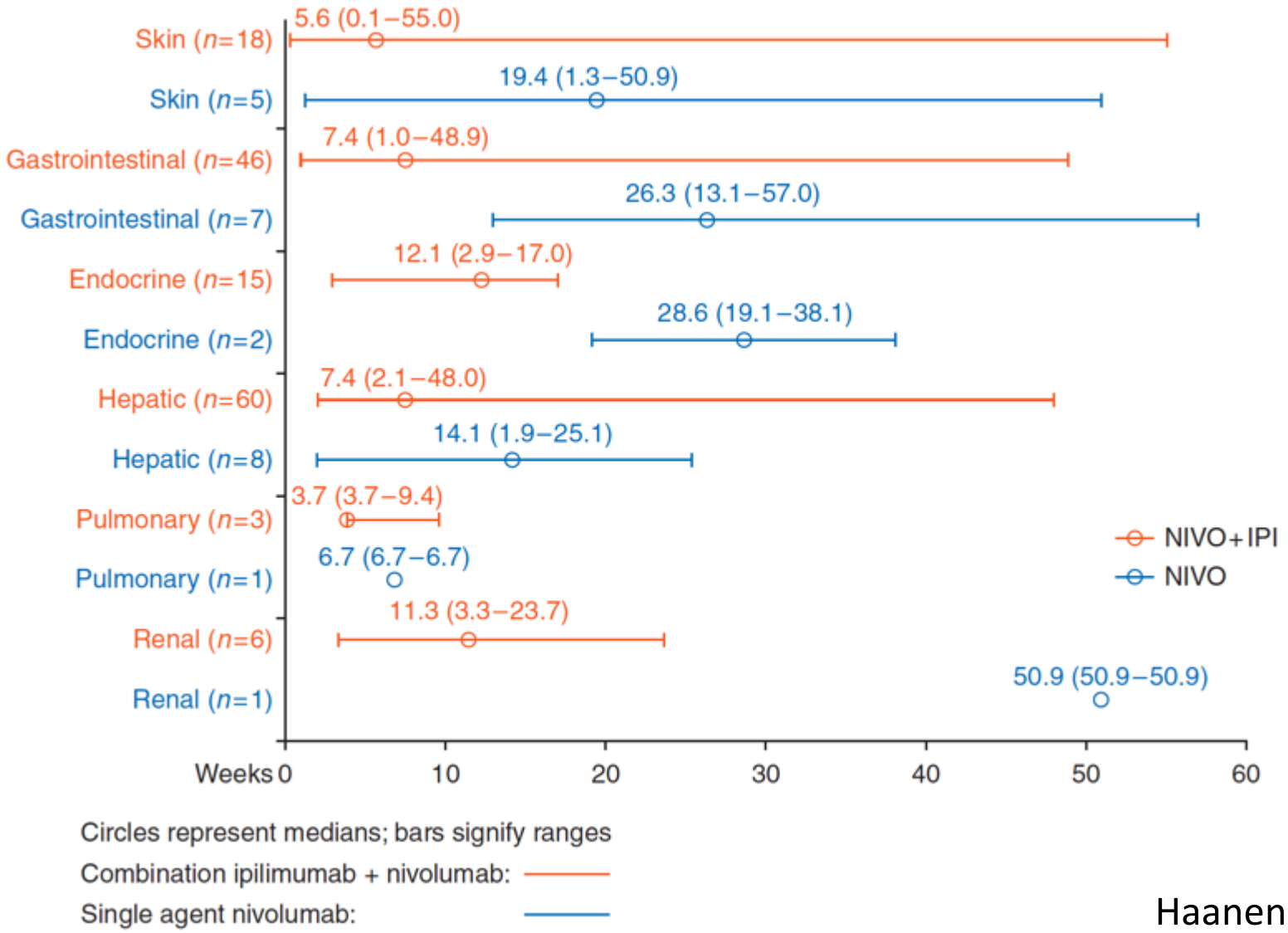
Onset and Kinetics of Immune-Related Adverse Events for Nivolumab (PD-1 inhibitor)



The beginning and end of each curve represent the median time to onset and median time to resolution, respectively. Each peak reflects incidence of the AE.

Weber et al, J Clin Oncol 33, 2015 (suppl; abstr 9018).

Time to onset of grade 3–4 treatment-related select AEs: Ipi+nivo vs nivo



Haanen et al Ann Oncol 2017

Dermatological Toxicities

The most common and typically earliest onset - 3-4 weeks

- ~50% treated with ipilimumab - rash and/or pruritus.
- 30-40% treated with PD1 inhibitor will have skin AEs

Early

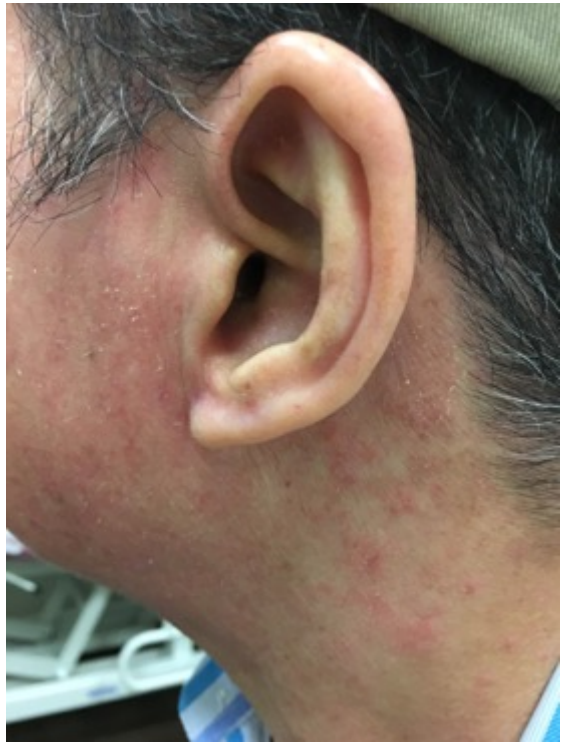
- Pruritic, erythematous, reticular, maculopapular rash - trunk and extremities
- Neutrophilic infiltration (Sweet's Syndrome) reported

Late

- Vitiligo → usually months after the initiation of checkpoint blockade.

Treatment:

- Topical corticosteroid creams and oral antipruritics
- Severe rashes (grade 3/4) – oral/ IV corticosteroids, discontinue drug and refer to dermatologist



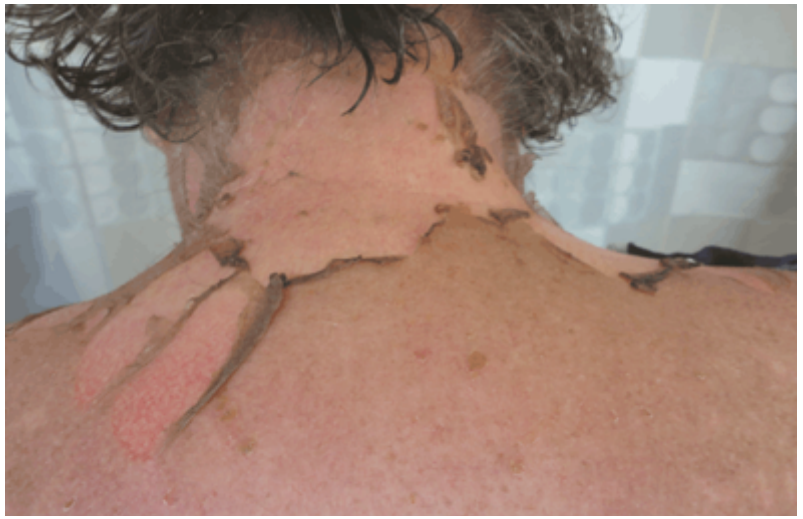
Schmerling *Chin Clin Oncol* 2014;3(3):31

Dermatological Toxicities: Steven Johnson Syndrome (SJS)

Epidermal death and separation involving:

- < 10% of the skin surface → SJS
- 10–30% of the skin surface → SJS/ toxic epidermal necrolysis (TEN) overlap
- > 30% of the skin is involved → TEN

Rx:
Refer to dermatologist - transfer to burns unit/ ICU
Biopsy of skin to confirm diagnosis
Artificial tears and Lacrilube to eyes.
Dressing/ ointments to denuded skin.
IV fluid resuscitation
No evidence for use of high dose steroids - ?IVIG



Pathria et al Int J Case Rep Imag 2016

Nikolsky Sign : Dislodging of epidermis by lateral finger pressure in the vicinity of lesions, which leads to an erosion.
Shearing stresses on normal skin can cause new erosions to form

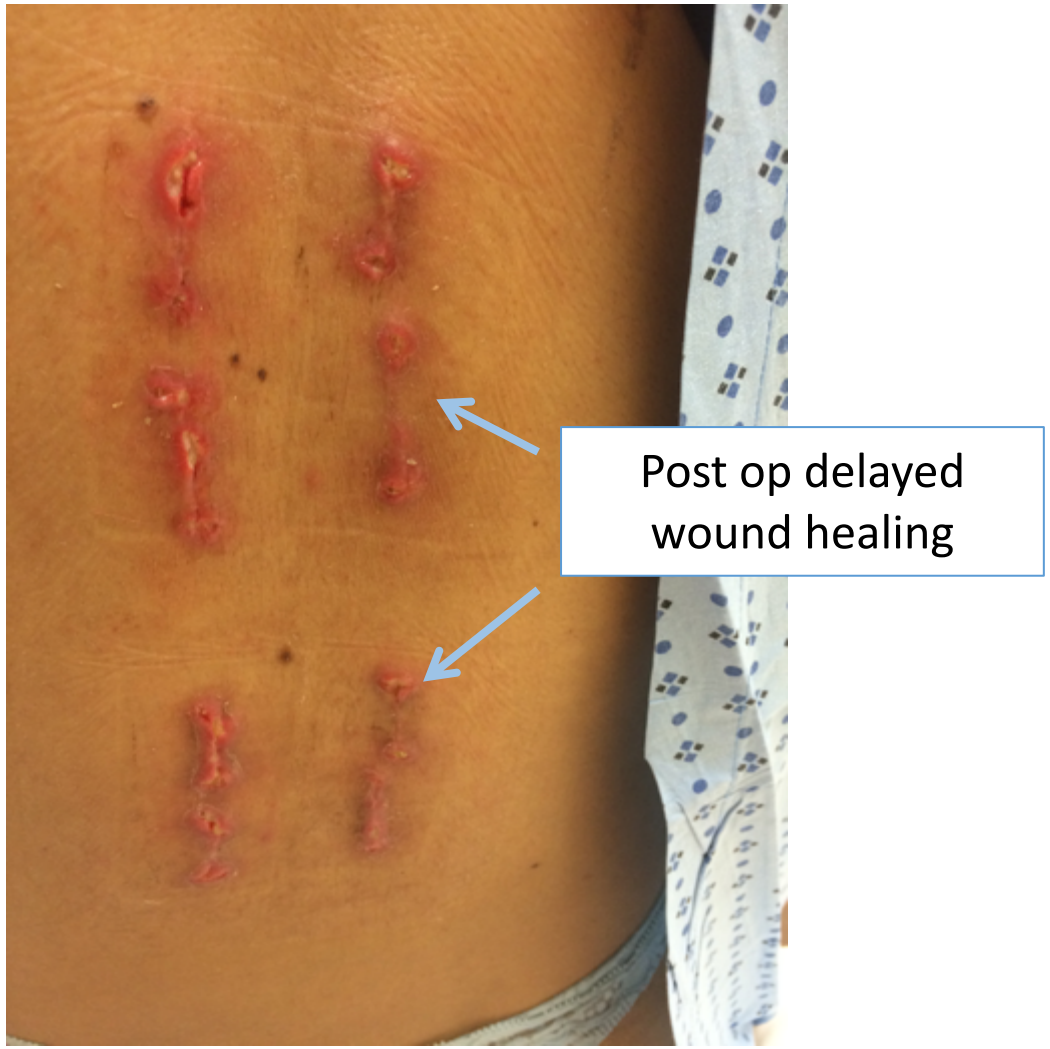
Dermatological Toxicity: Effects on wound healing following checkpoint inhibitor therapy?

Miss J - 37 year old metastatic SCC cervix

D29 post Cycle 2 pembrolizumab - decompression and spinal instrumentation for T2 vertebral metastasis

2 weeks post op → sloughy wound
Subsequent spinal RT delayed

More data required re effects of checkpoint inhibitors on wound healing post surgery
→ ?Neoadjuvant checkpoint blockade



Fatigue

Occurs in 15–35 % of patients during immune checkpoint inhibitor therapy

Severe fatigue (CTCAE grade 3 or higher) → 1-4 %

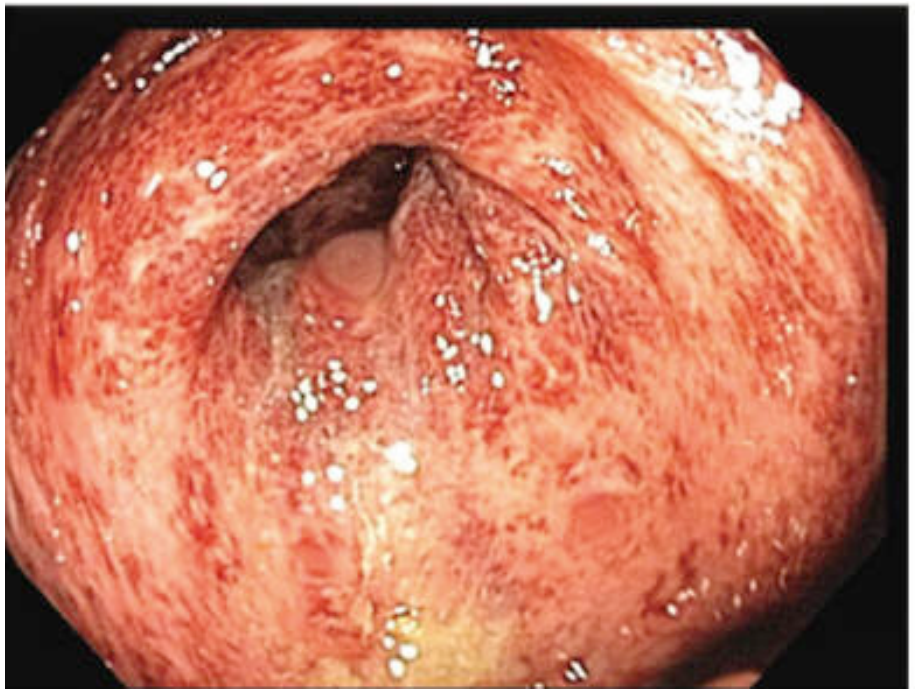
Need to exclude endocrinopathies/ myopathies/ neuropathy (e.g. Guillain Barre Syndrome)

Checkpoint inhibitor	Frequency
ipilimumab	15 %
nivolumab	35 %
pembrolizumab	19–28%
ipilimumab/nivolumab	35 %

Larkin J, et al N Engl J Med 2015; 373: 23–34.
Robert C et al. N Engl J Med 2015; 372: 2521–32.
Ribas A, et al. Lancet Oncol 2015; 16: 908–18

GI Toxicities – Diarrhoea/ Colitis

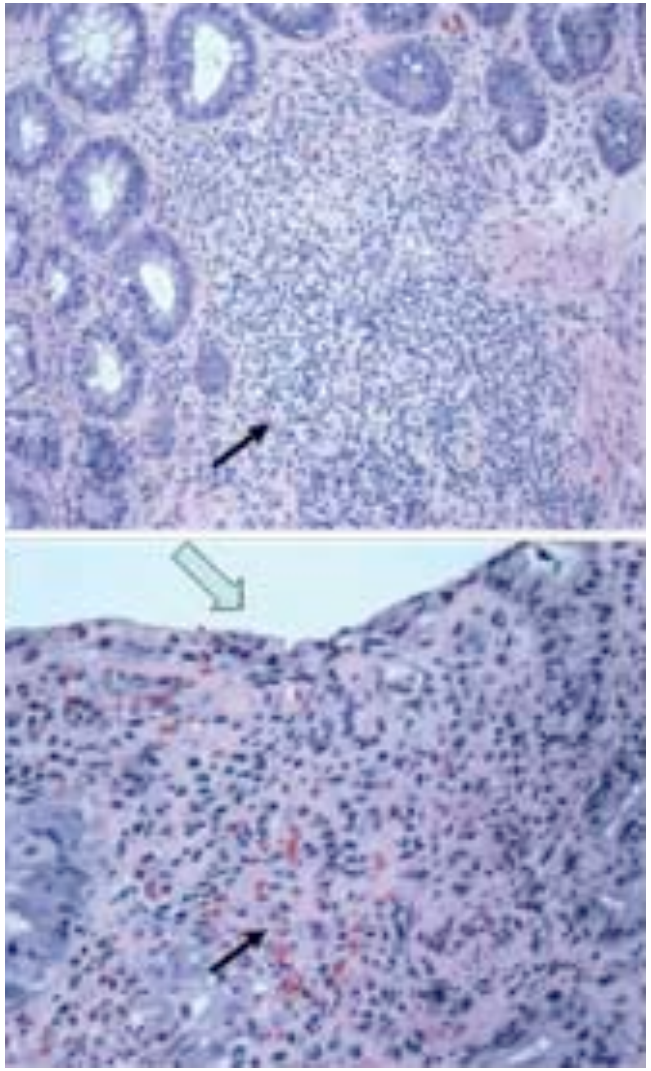
- Common AE → Need to exclude infectious cause e.g. c.difficile
- Ipilimumab → 5-10% G3/4
- PD-1/PDL1 → 1-2% G3/4
- Usually ~6 weeks into treatment
- Colonoscopy if diagnosis is unclear.



- erythematous mucosa
- loss of normal vascular pattern
- multiple ulcers

McCutcheon et al Gastroenterology Research, 2014

Inflammation & ulceration



Thumar et al Oncology Journal 2010

GI Toxicities – Diarrhoea/ Colitis Management

Grade of irAE	Action
Grade 1 (<4 stools over baseline)	• Symptomatic management • Loperamide and maintain oral hydration
Grade 2 (4-6 stools over baseline)	• Discontinue checkpoint inhibitor → early specialist referral • Add prednisolone 0.5-1mg/kg/day or budesonide with loperamide • Only resume when symptoms or toxicity is grade 1 or less
Grade 3 or 4 (>7 stools over baseline)	• Permanently discontinue drug and start high dose IV 1-2mg/kg methylprednisolone BD - taper over 1mth • If no improvement after 3 days → 2 weekly infliximab (5 mg/kg) • Rarely, perforation → colostomy

Corticosteroid prophylaxis to prevent ipilimumab diarrhoea?

Budesonide locally acting corticosteroid with low systemic bioavailability after oral administration because of extensive first-pass metabolism
→ Randomised Phase 2 study of budesonide prophylaxis vs placebo in unresectable stage III/ IV melanoma pts on ipilimumab

Rate of grade ≥ 2 diarrhea in patients given ipilimumab with or without prophylactic budesonide

Patients with grade ≥2 diarrhea*	Ipilimumab+ budesonide (group A; *n* = 58)	Ipilimumab+ placebo (group B; *n* = 57)	Total (*N* = 115)
Grade 2, *n* (%)	11 (19.0)	10 (17.5)	21 (18.3)
Grade 3, *n* (%)	6 (10.3)	10 (17.5)	16 (13.9)
Grade 4, *n* (%)	2 (3.4)	0	2 (1.7)
Grade ≥2 diarrhea rate, *n* (%)	19/58 (32.7)	20/57 (35.0)	39/115 (33.9)

No difference in frequency of Grade ≥2 diarrhoea
No evidence for Budesonide prophylaxis

Weber et al Clin Cancer Res 2009;15(17)

Endocrinopathies, ~10% of patients

Symptoms – fatigue/ lethargy/ headache (hypophysitis)/ weight loss

Monitor TSH/ T4, 8am ACTH/ cortisol - MRI pituitary gland if headache/ low ACTH/cortisol

Rx:
Early diagnosis → hormone replacement therapy (permanent in most cases)

- **Levothyroxine**
- **Hydrocortisone**

?High dose steroids in acute hypophysitis to prevent long-term pituitary dysfunction

Autoimmune adrenalitis → hypoadrenalism – may lead to adrenal crisis under stress e.g. surgery/infection

NB: Most endocrine events do not resolve

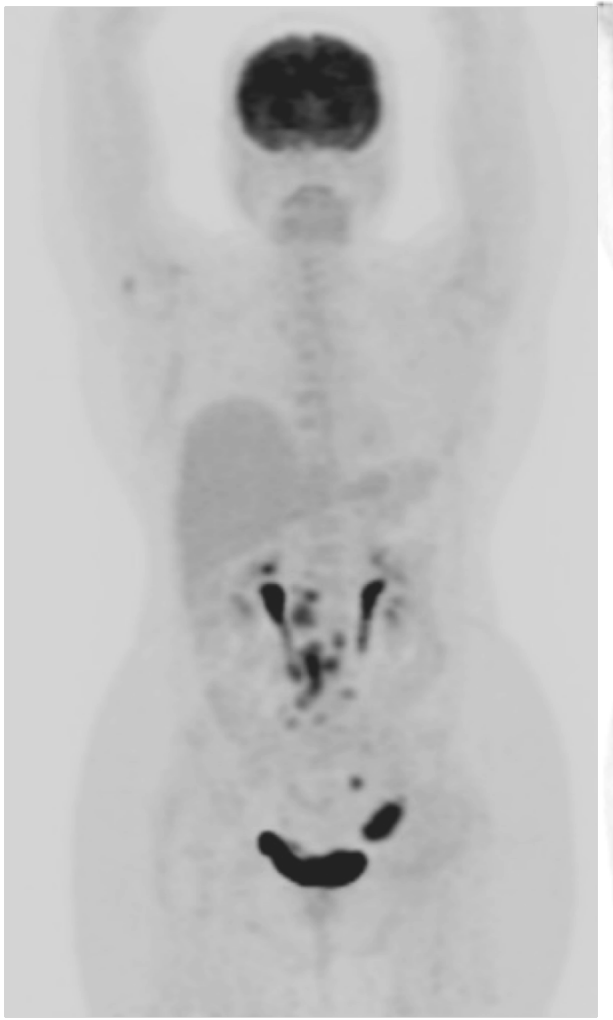
Mdm M

Stage 4 cervical carcinoma

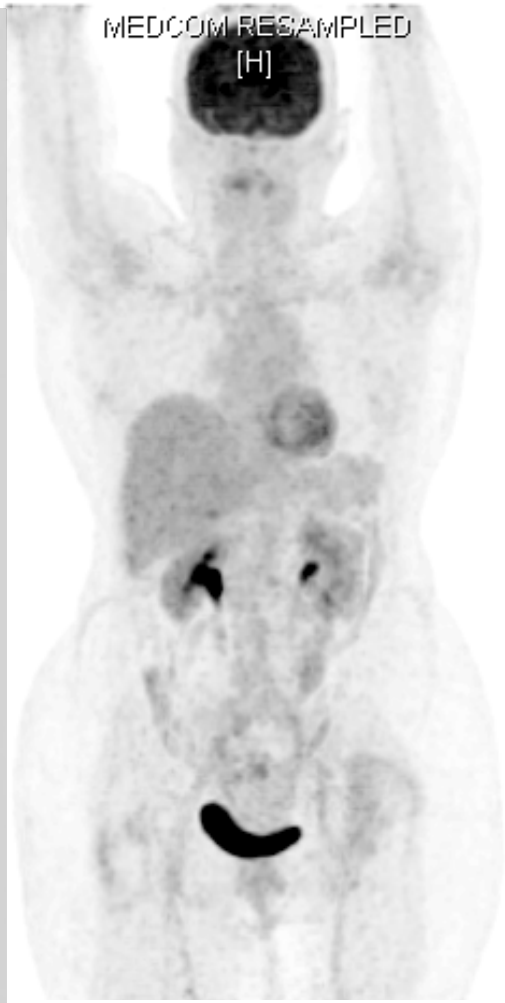
July 2015: Progressed 3mths post completion of carboplatin paclitaxel and bevacizumab

Aug 2015: Commenced Pembrolizumab

May 2016 to Sept 2016:
Reduced appetite/ fatigue
Lower limb oedema
Weight loss 12Kg
Intermittent nausea and vomiting

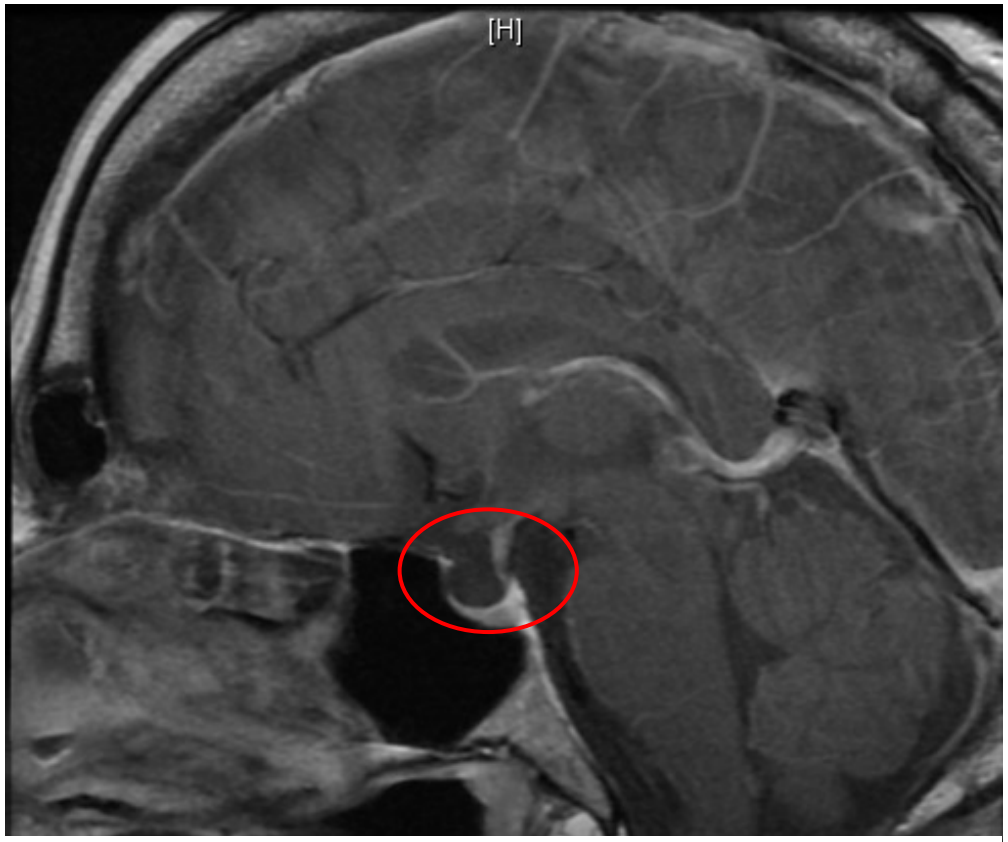


July 2015



Sep 2016

Mdm M continued….



MRI Pituitary Sept 2016: Partially empty sella appearance. Anterior pituitary gland appearing relatively small and flattened along the floor and lateral walls of the pituitary fossa

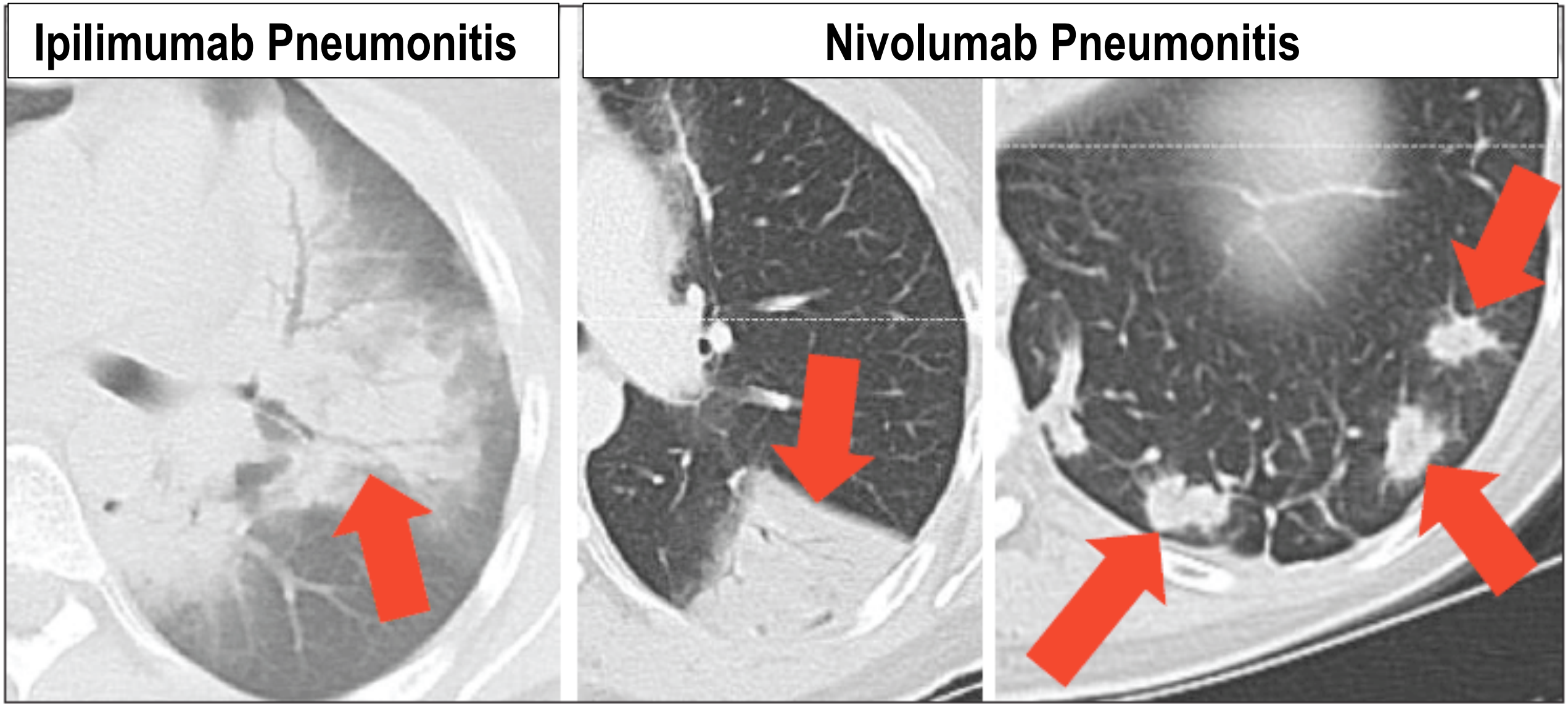
	Results	Units	Ref range
ACTH (8am)	2	pmol/L	0.0-10.2
Cortisol (8am)	<11	nmol/L	123 - 626
Insulin like GF1	75	ug/l	87 - 238
Prolactin	185	mIU/L	78 - 540
Thryoxine	11.3	pmol/L	8.0 - 20.0
TSH	1.29	mIU/L	0.45 - 4.50

Diagnosis: Pembrolizumab induced hypophysitis with partial hypopituitarism

Commenced hydrocortisone 10mg/5mg/5mg daily

Patient continued on pembrolizumab

Pneumonitis (<10%)



Teply et al Oncology Journal 2014

Pneumonitis Management

Grade 1 pneumonitis (asymptomatic radiographic changes only):

- immune checkpoint blockade therapy should be withheld
- Monitor every 2 to 3 days for symptoms.
- Repeat CT chest within 3-4 weeks
- Refer to Lung specialist

Symptomatic pneumonitis (grade ≥ 2):

- Admit, monitor daily - Bronchoscopy with bronchoalveolar lavage and biopsies.
- Start high-dose corticosteroids + empiric antibiotics
- If no improvement in 2-3days of high-dose steroid treatment → consider alternative immunosuppressive rx e.g. infliximab therapy (once infection excluded).
- Additional Rx e.g. cyclophosphamide may be required

Liver Toxicity <5% G3/4

Hepatic parenchyma inflammation → cholestasis, liver enzyme elevation, hepatitis.
Onset usually after 6 weeks of therapy → need to exclude viral hepatitis, disease-related hepatic dysfunction and other drug-induced (e.g. ETOH and TCM) transaminitis

Grade of liver toxicity	Action
Grade 1 (AST/ALT <3 x ULN and Bil <1.5xULN)	Close monitoring.
Grade 2 (AST/ALT >3 and <5 x ULN and Bil >1.5 to <3 x ULN)	Oral steroid therapy and the interrupt drug until normalization.
Grade 3/4 (AST/ALT >5 and <20 x ULN and Bil >3 x ULN)	IV steroids and permanently stop drug No improvement after 3 days → MMF/ Tacrolimus/ Antithymocyte globulin (NB infliximab can be associated with liver toxicity – avoid)

Less frequently seen <1%

Eye – episcleritis, conjunctivitis, uveitis

Renal – Interstitial nephritis

Pancreas – Pancreatitis

Muscle – Polymyositis/ Myasthenia Gravis

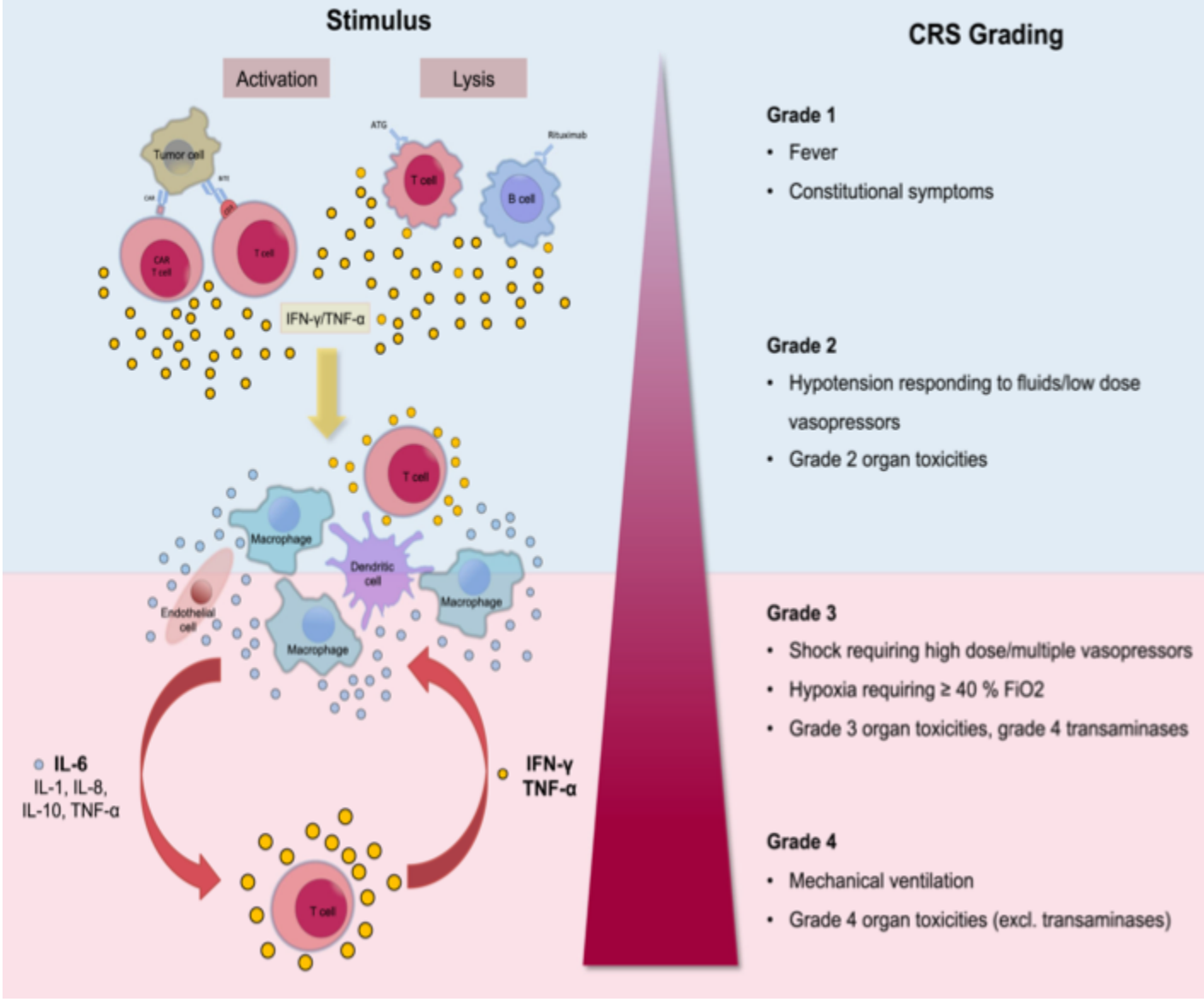
Neurological – posterior reversible encephalopathy, transverse myelitis, Guillain Barre Syndrome

Haematologic – red cell aplasia, neutropenia, acquired haemophilia, thrombocytopenia

Cytokine Release Syndrome (CRS) – rarely seen with checkpoint inhbitors

- Mainly seen in CAR-T cell therapy and therapeutic monoclonal antibodies in haem malignancies against T-cells
- On-target effect → binding of bispecific antibody or CAR T cell receptor to antigen and activation of bystander cells.
- Bystander immune/ non-immune cell activation → massive cytokine release
- "First dose" effect

Treatment
- ICU/ supportive care
- IL6 and IL6R monoclonol antibodies e.g. Siltuximab and Tocilizumab
- Steroids
- TNF alpha antagonist



Shimabukuro-Vornhagen et al. Journal for Immuno Therapy of Cancer **(2018) 6:56**

The case of Mdm F….

- 83y; Recurrent transitional cell carcinoma renal pelvis (L renal mass and lung mets)
- Increasing size of lung mets on repeat CT
- ECOG 1
- Commenced on treatment with PD-1 inhibitor

End of Cycle 1 PD-1 inhibitor review:

- **G1 fatigue, G1 diarrhoea and….**

Thyroid Screen				
Thyroxine, Free	43.8 ^	H	pmol/L	8.0 - 20.0
TSH	0.04 v	L	mIU/L	0.45 - 4.50
T3, Free	6.0 ^	N	pmol/L	3.5 - 6.0
Anti-TPO Ab	224	H	IU/mL	<50
Anti-Thyroglobulin	859	H	IU/mL	<40
TSH Receptor Ab	1.3		IU/L	

No thyroid signs/ symptoms:
→ G1 hyperthyroidism (Asymptomatic; clinical or diagnostic observations only; intervention not indicated)

Referred to Endocrinology – no Rx required

Cycle 2, D12

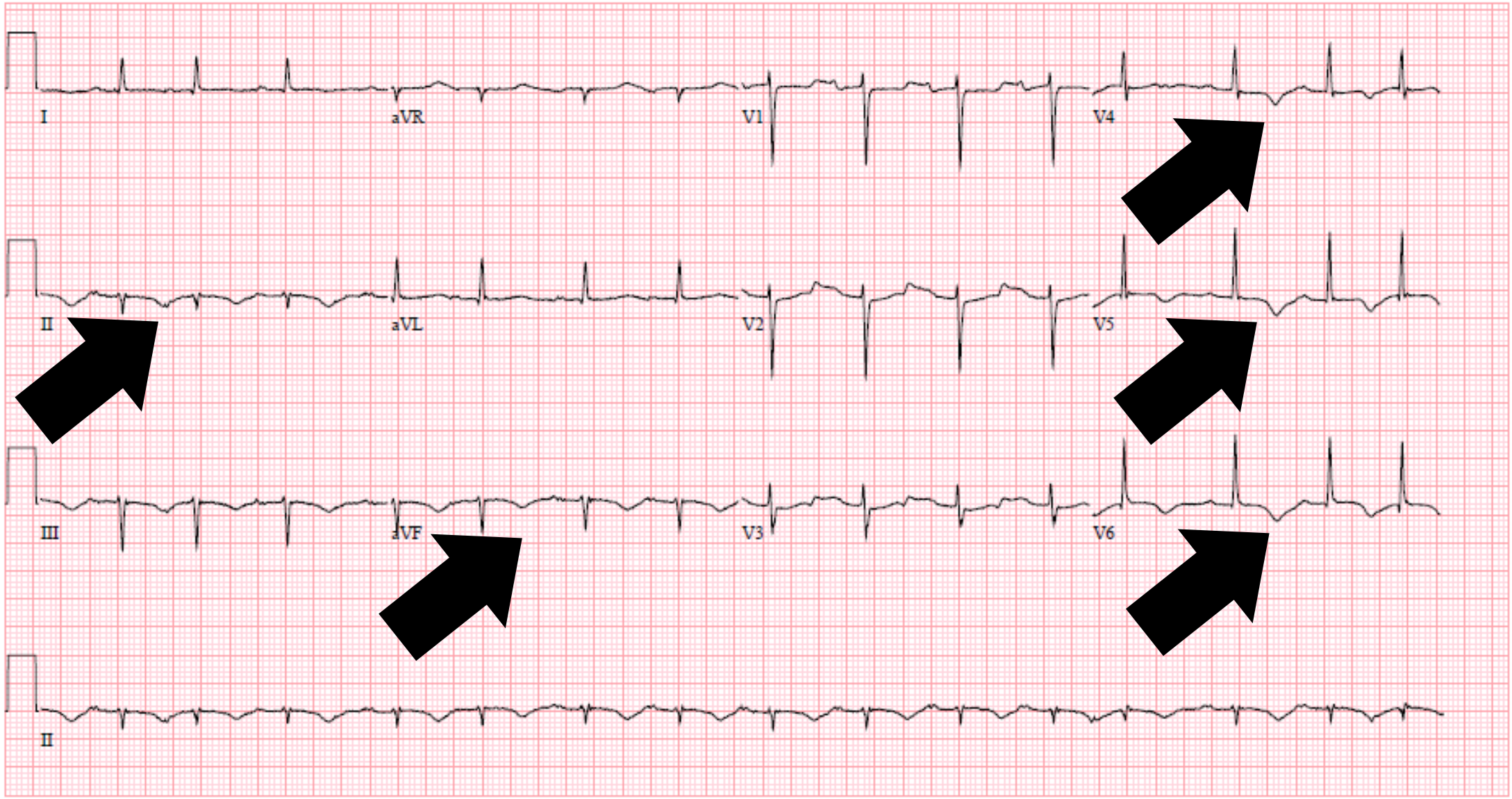
- **Left Buttock pain**
- **G2 fatigue**
- **G2 musculoskeletal pain**
- **Alert, oriented**
- **No dyspnoea/ chest pain**

Cycle 2, D16

- **Ptosis**
- **Worsening myalgia**
- **G3 fatigue**

Cycle 2, D16 blood results

	Level	Normal range
Creatinine Kinase	9902	20-300 U/L
Creatinine Kinase MB	145	5-25 U/L
Troponin I	1.59	0-0.039 ug/L
Albumin	32	38-48 umol/L
Bilirubin	6	5-30 5-30 umol/L
AST	700	10-50 U/L
ALT	456	10-70 U/L
ALP	90	40-130 U/L
LDH	3457	250-580 U/L



ECG: prolonged QTc of 650, and new T inversions

Diagnosis: Immune toxicity to PD-1 inhibitor

- Polymyositis → raised CK, ALT, AST
- Carditis → ECG changes, raised CK-MB and Trop I
- Thyroiditis → Raised T4, Anti TPO, Anti thyroglobulin
- ?Autoimmune hepatitis (raised ALT/ AST)
- ?Myasthenia gravis (Ptosis/ fatigue)

?Myasthenia Gravis ?Autoimmune hepatitis

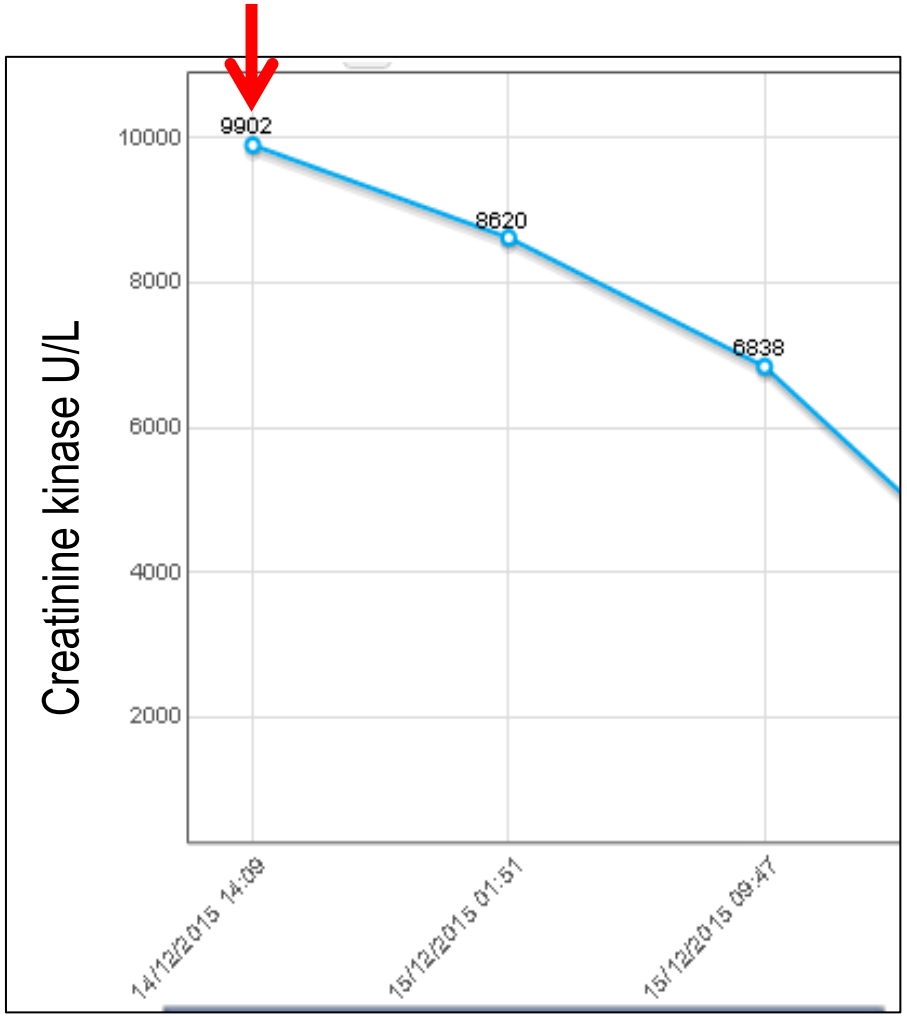
- EMG → myopathic process
- Nerve Conduction Study → normal
- Repetitive Nerve Stimulation test → no neuromuscular defect
- Ocular ice pack test → negative

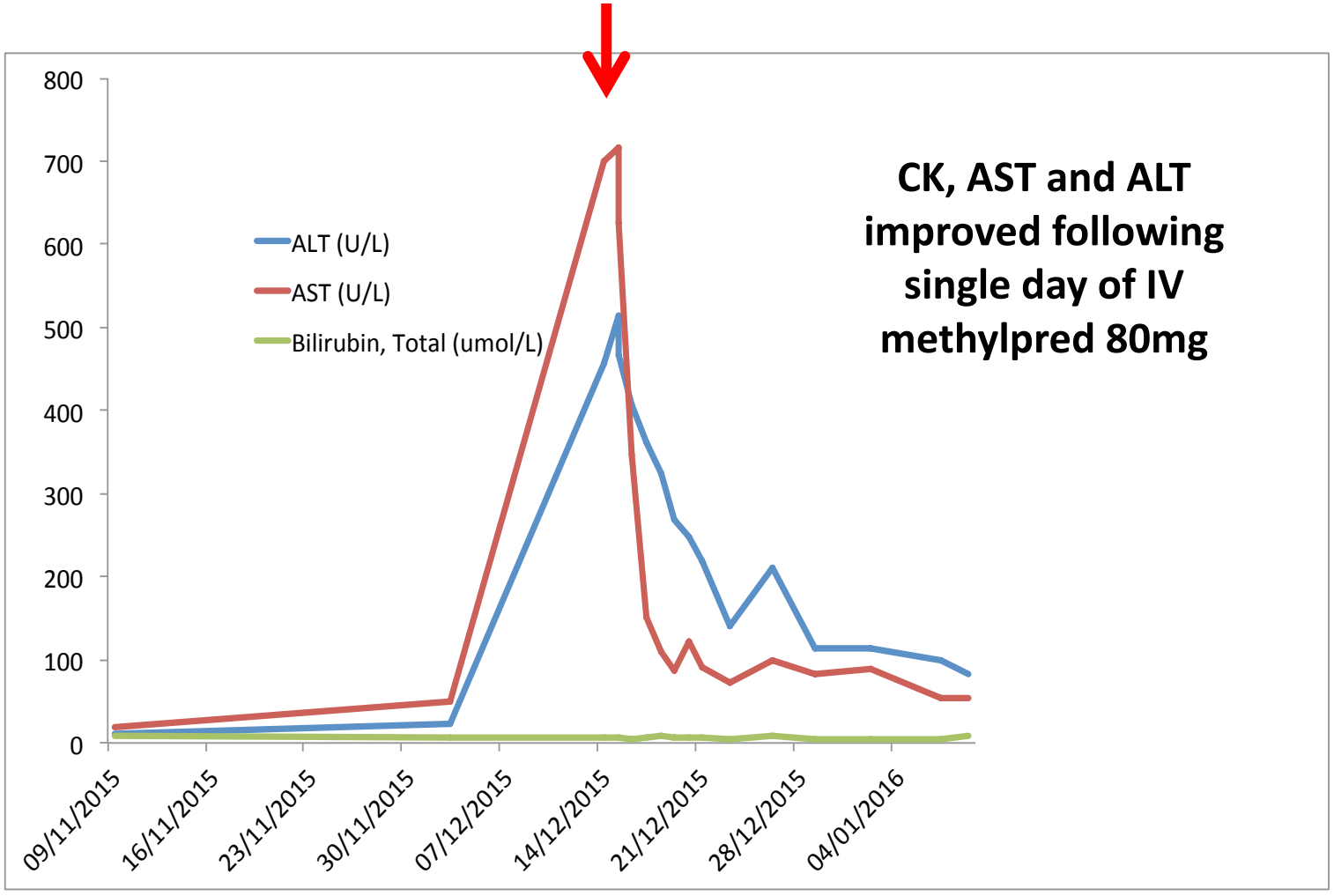
Acetycholine Rcpt Ab	< 0.07
Anti-LKM	Negative
Anti-Nuclear Ab	1:320 Titre
ANA Pattern	Homogeneous
Anti-Smooth Muscle	4

ANA was noted to be strongly positive at 1:320

- **But other markers of autoimmune hepatitis were negative.**
- **elevated AST/ALT in presence of normal bilirubin thought likely to be due to polymyositis**

Following C2 D16 single dose of methylprednisolone 80mg:



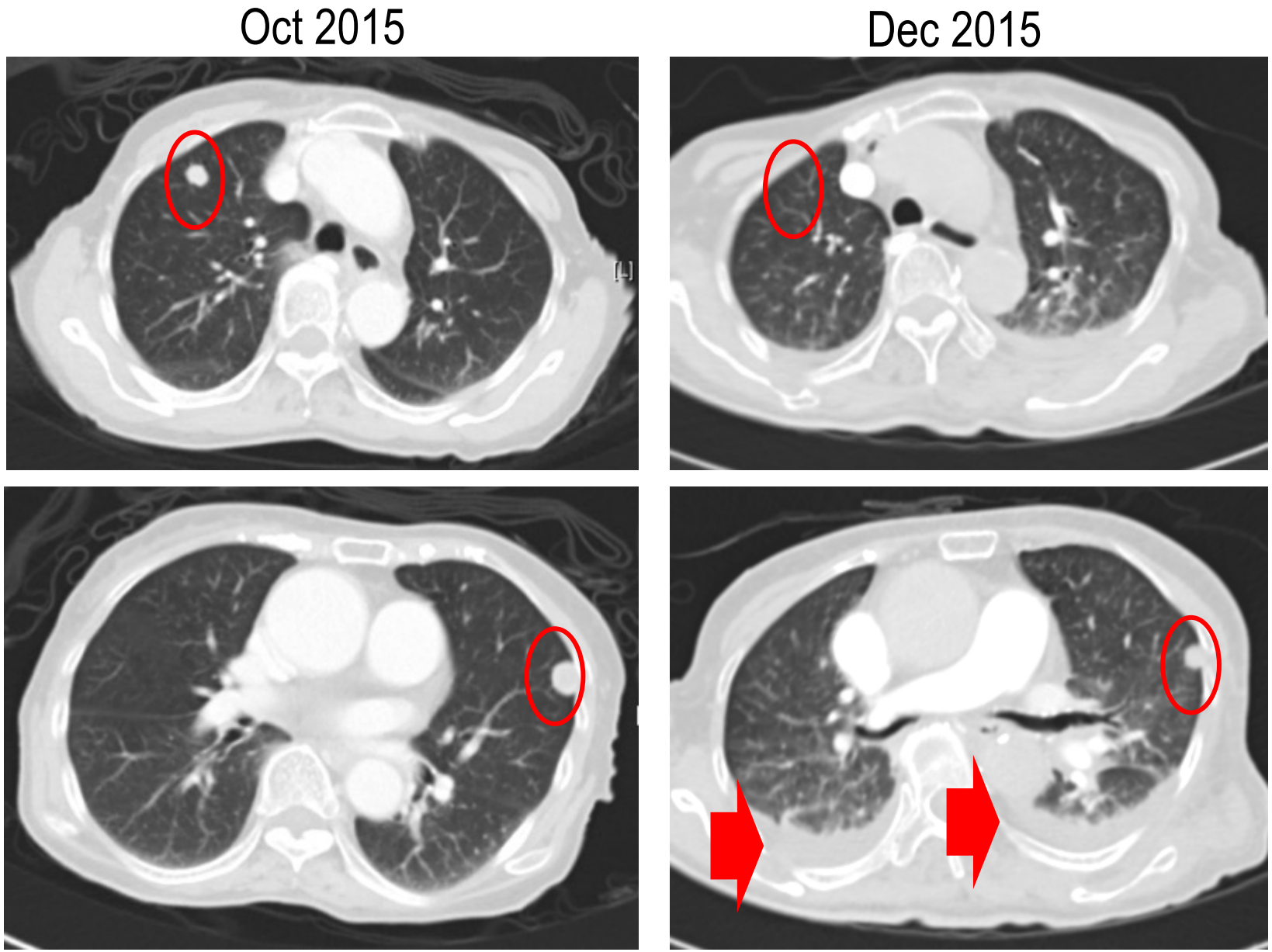


C2 D19: Cardiac arrhythmias and desaturation

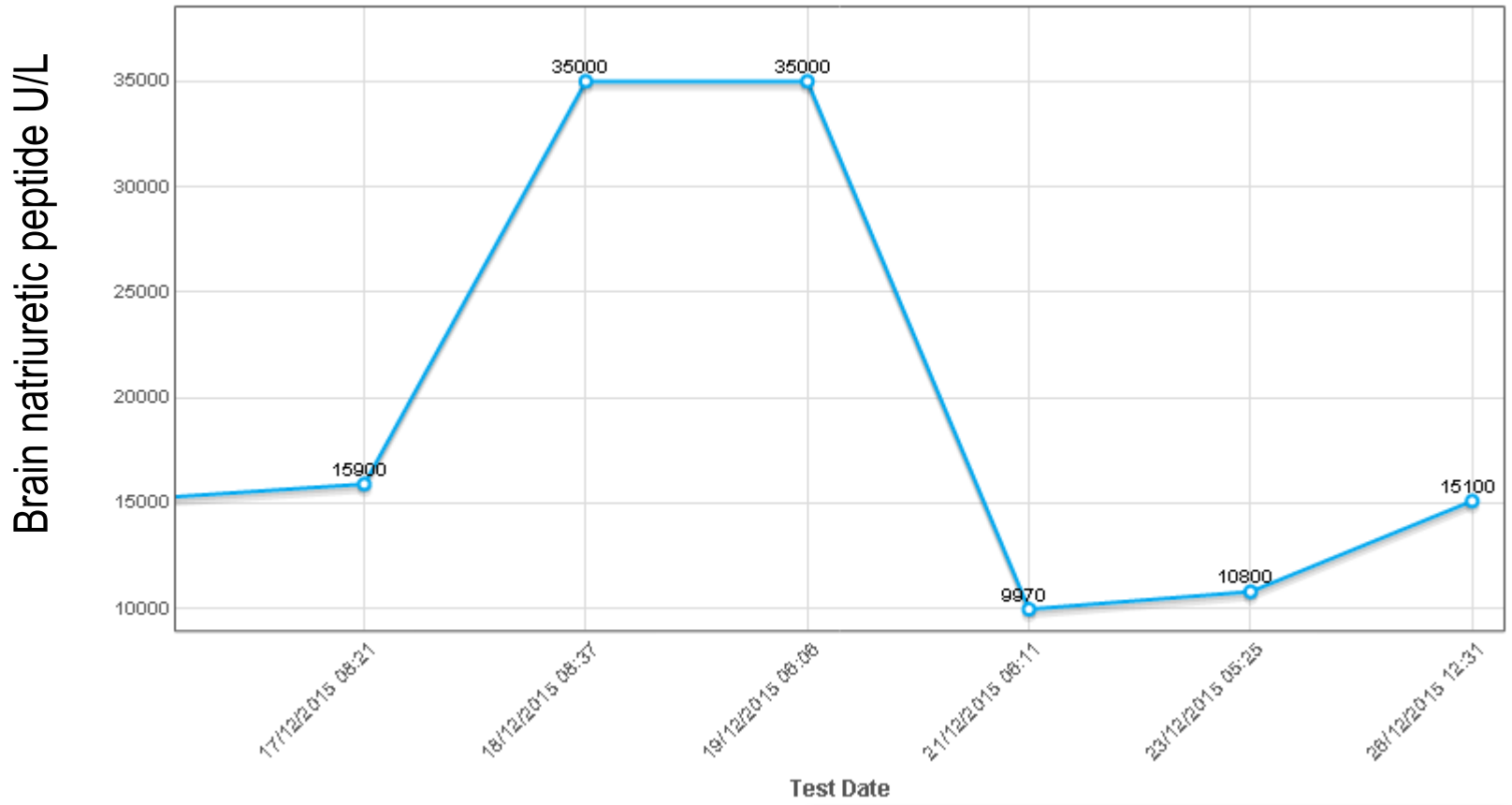
- **Weakness and ptosis persisted → patient desaturated**
- **Supraventricular tachycardia max rate 160 bpm - refractory to adenosine.**
- **2D-ECHO - LVEF preserved at 60%**
- **Assessed by cardiology → arrhythmia related to autoimmune myocarditis**
- **In view of desaturation → started on 500mg IV methylprednisone for 3 days**

CTPA performed on C2 D19 (tachycardia/ desaturation)

- No PE
- Bilateral pleural effusions
- Evidence of partial response to treatment

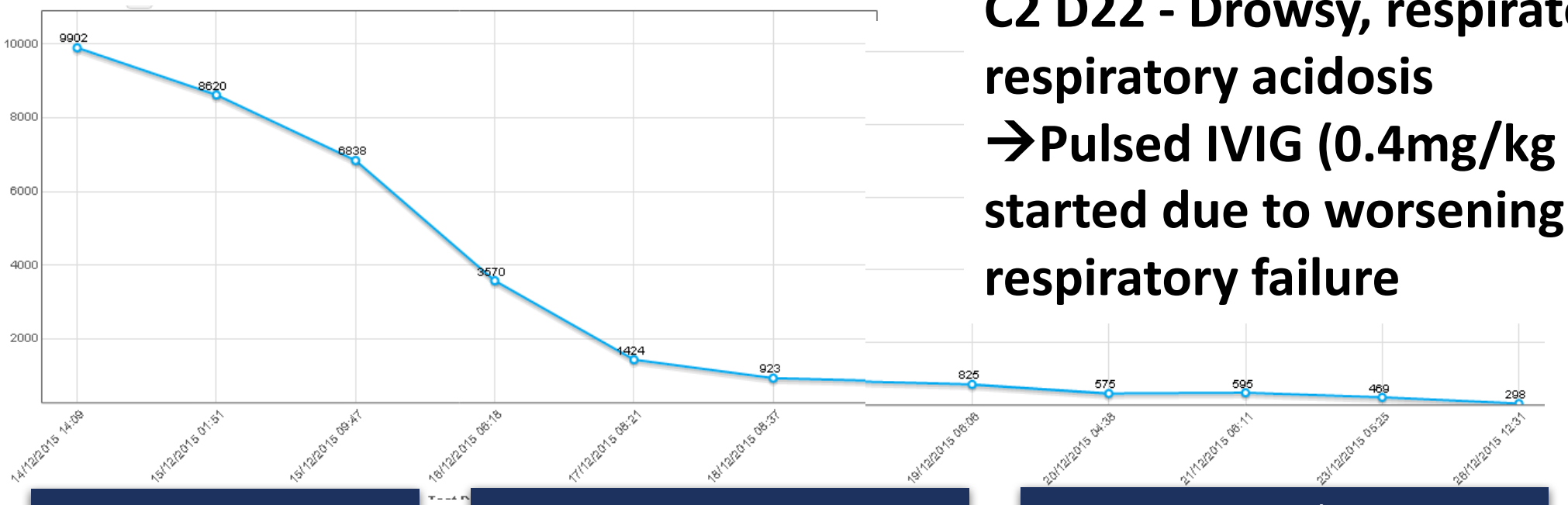


Cardiac Decompensation C2 D19 – raised BNP



Metoprolol 12.5 to 50mg tds

CK trend with time



C2 D22 - Drowsy, respiratory distress, respiratory acidosis
→Pulsed IVIG (0.4mg/kg daily) started due to worsening type 2 respiratory failure

IV methylpred 80mg

IV methylpred 500mg x 3 days

IV IVIG 0.4mg/kg x 5days

C2 D16

C2 D19

C2 D22

But..

Test Name	UoM	15-Dec-2015 11:11	17-Dec-2015 18:27	18-Dec-2015 11:02	18-Dec-2015 17:50	19-Dec-2015 01:20	19-Dec-2015 12:14	19-Dec-2015 17:57	20-Dec-2015 06:14	26-Dec-2015 12:31	26-Dec-2015 16:09
Bicarbonate (HCO3)	mmol/L	22.7	28.2	31.3	35.3	35.2	36.5			41.0	
Bicarbonate, POCT (HCO3P)	mmol/L							33.6	32.3		34.0
O2 Saturation(calc) (SAT)	%	96.9	96.3	95.7	96.3	94.8	95.6	97.0	97.8	83.1	95.3
pCO2 (PCO2)	mmHg	37.4	50.5	53.6	62.1	61.8	75.6			93.7	
pCO2, POCT (PCO2P)	mmHg							55.3	43.0		52.1
pH, Arterial (PH)		7.40	7.37	7.38	7.37	7.37	7.30			7.26	
pH, POCT (PHP)								7.40	7.49		7.43

IV methylpred 500mg x 3 days

IV IVIG 0.4mg/kg x 5days

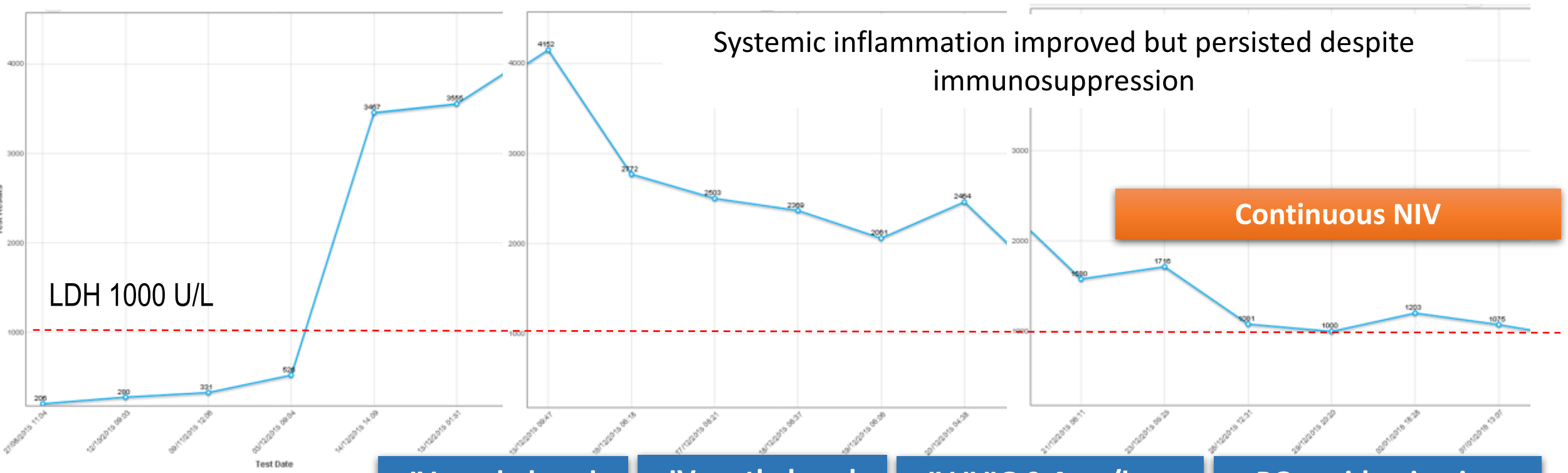
Nocturnal BiPAP

Continuous NIV

C2 D28

- **Increasing lethargy → Thyroid function rechecked**
- **FT4 <3.2, TSH 20.57 → hypothyroid phase of pembrolizumab-induced thyroiditis.**
- **Thyroxine replacement 25mcg daily → Increased to 50mcg daily 4 days later**

Lactate dehydrogenase (LDH) level over course of immunotoxicity



IV methylpred 80mg

IV methylpred 500mg x 3 days

IV IVIG 0.4mg/kg x 5days

PO pyridostigmine 30mg om/ bd

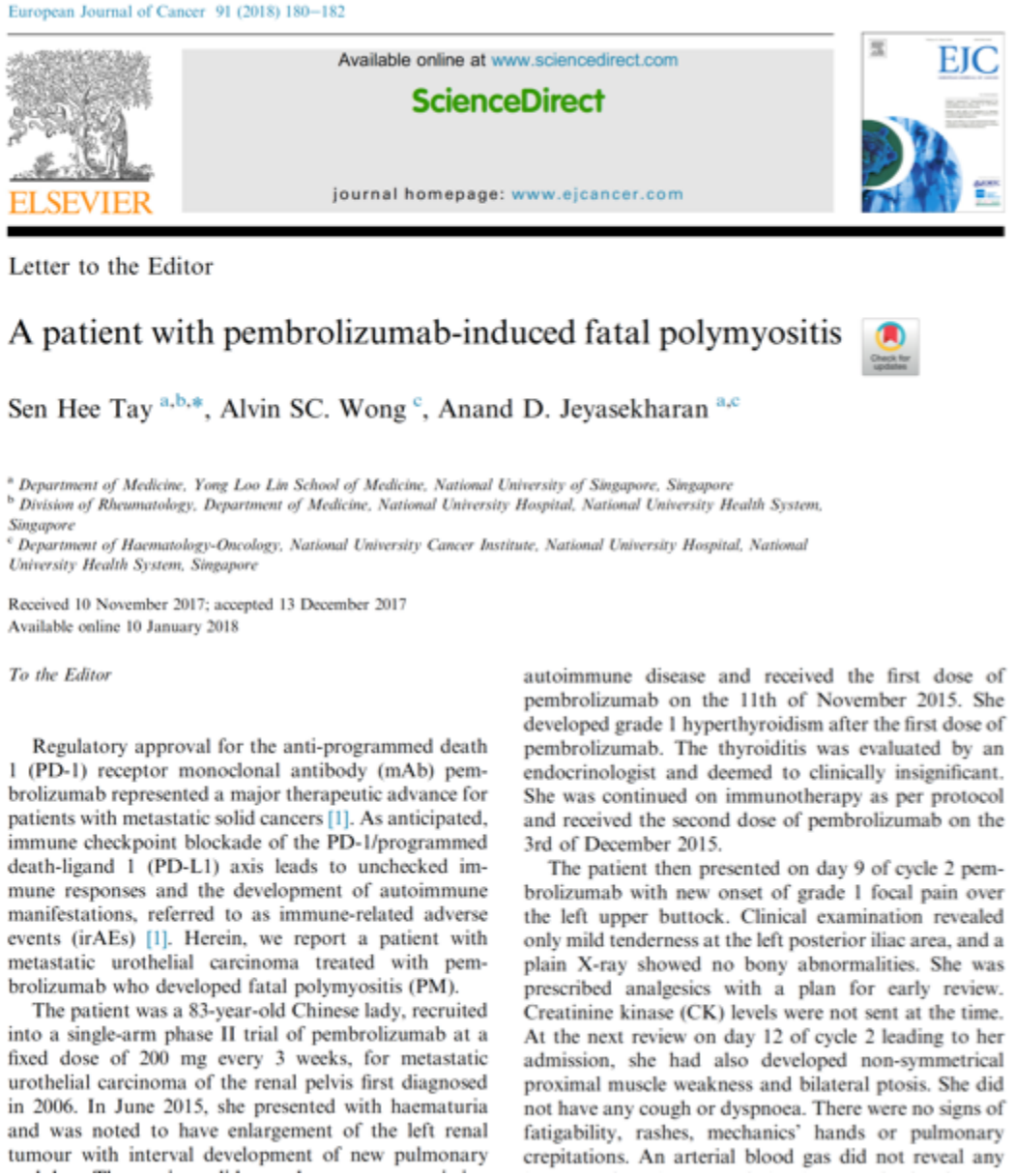
Metoprolol 12.5 to 50mg tds

Outcome: Patient demise 2 weeks later after developing further episode of pneumonia

Thyroxine 25mcg->50

Lessons from Mdm F:

- Multiorgan failure from immunotoxicity – endocrinopathy, polymyositis, autoimmune myocarditis, respiratory failure
- Multidisciplinary input crucial
- Earlier/ combined use of alternative immunosuppressive agents in patients with G3/4 irAEs? → e.g. IVIG/ Infliximab?
- Removal of drug from the system
  → ?plasmapheresis
- Predictive markers for immune toxicities?



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Letter to the Editor

A patient with pembrolizumab-induced fatal polymyositis

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To the Editor

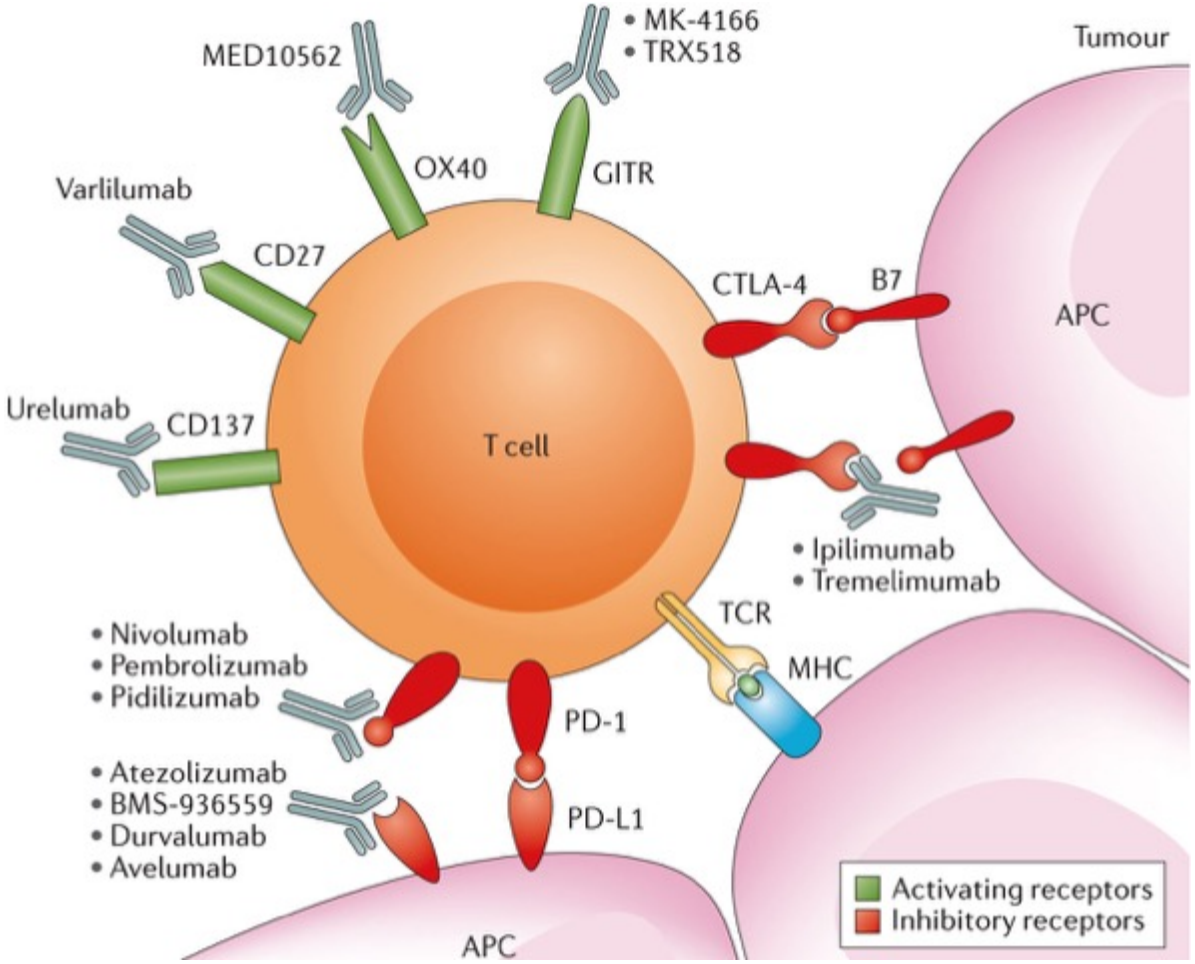
Regulatory approval for the anti-programmed death 1 (PD-1) receptor monoclonal antibody (mAb) pembrolizumab represented a major therapeutic advance for patients with metastatic solid cancers [1]. As anticipated, immune checkpoint blockade of the PD-1/programmed death-ligand 1 (PD-L1) axis leads to unchecked immune responses and the development of autoimmune manifestations, referred to as immune-related adverse events (irAEs) [1]. Herein, we report a patient with metastatic urothelial carcinoma treated with pembrolizumab who developed fatal polymyositis (PM).

The patient was a 83-year-old Chinese lady, recruited into a single-arm phase II trial of pembrolizumab at a fixed dose of 200 mg every 3 weeks, for metastatic urothelial carcinoma of the renal pelvis first diagnosed in 2006. In June 2015, she presented with haematuria and was noted to have enlargement of the left renal tumour with interval development of new pulmonary

autoimmune disease and received the first dose of pembrolizumab on the 11th of November 2015. She developed grade 1 hyperthyroidism after the first dose of pembrolizumab. The thyroiditis was evaluated by an endocrinologist and deemed to clinically insignificant. She was continued on immunotherapy as per protocol and received the second dose of pembrolizumab on the 3rd of December 2015.

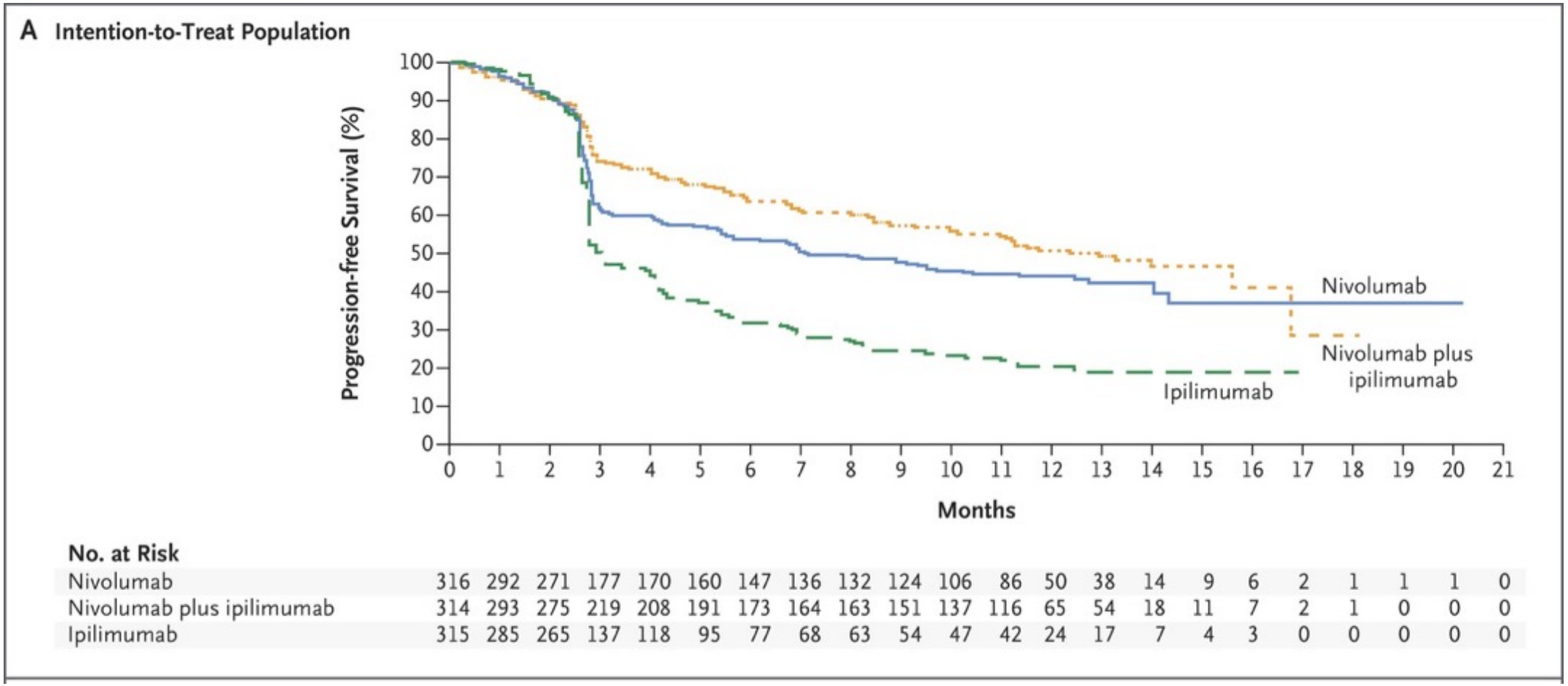
The patient then presented on day 9 of cycle 2 pembrolizumab with new onset of grade 1 focal pain over the left upper buttock. Clinical examination revealed only mild tenderness at the left posterior iliac area, and a plain X-ray showed no bony abnormalities. She was prescribed analgesics with a plan for early review. Creatinine kinase (CK) levels were not sent at the time. At the next review on day 12 of cycle 2 leading to her admission, she had also developed non-symmetrical proximal muscle weakness and bilateral ptosis. She did not have any cough or dyspnoea. There were no signs of fatigability, rashes, mechanics' hands or pulmonary crepitations. An arterial blood gas did not reveal any

Combined immune checkpoint therapy?



Carlo, M. I. *et. al. Nat. Rev. Urol.* 2016

Combined immunotherapy: Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma



No. at Risk																						
Nivolumab	316	292	271	177	170	160	147	136	132	124	106	86	50	38	14	9	6	2	1	1	1	0
Nivolumab plus ipilimumab	314	293	275	219	208	191	173	164	163	151	137	116	65	54	18	11	7	2	1	0	0	0
Ipilimumab	315	285	265	137	118	95	77	68	63	54	47	42	24	17	7	4	3	0	0	0	0	0

Larkin et al. N Engl J Med 2015; 373: 23–34.

AEs in combined PD-1/ CTLA 4 blockade

Adverse events, %	NIVO + IPI (n = 313)		NIVO (n = 313)		IPI (n = 311)	
	All grades	CTCAE grade 3–4	All grades	CTCAE grade 3–4	All grades	CTCAE grade 3–4
Treatment-related	95.5	55.0	82.1	16.3	86.2	27.3
Treatment-related, prompting treatment discontinuation	36.4	29.4	7.7	5.1	14.8	13.2
Treatment-related deaths	0					arrest)

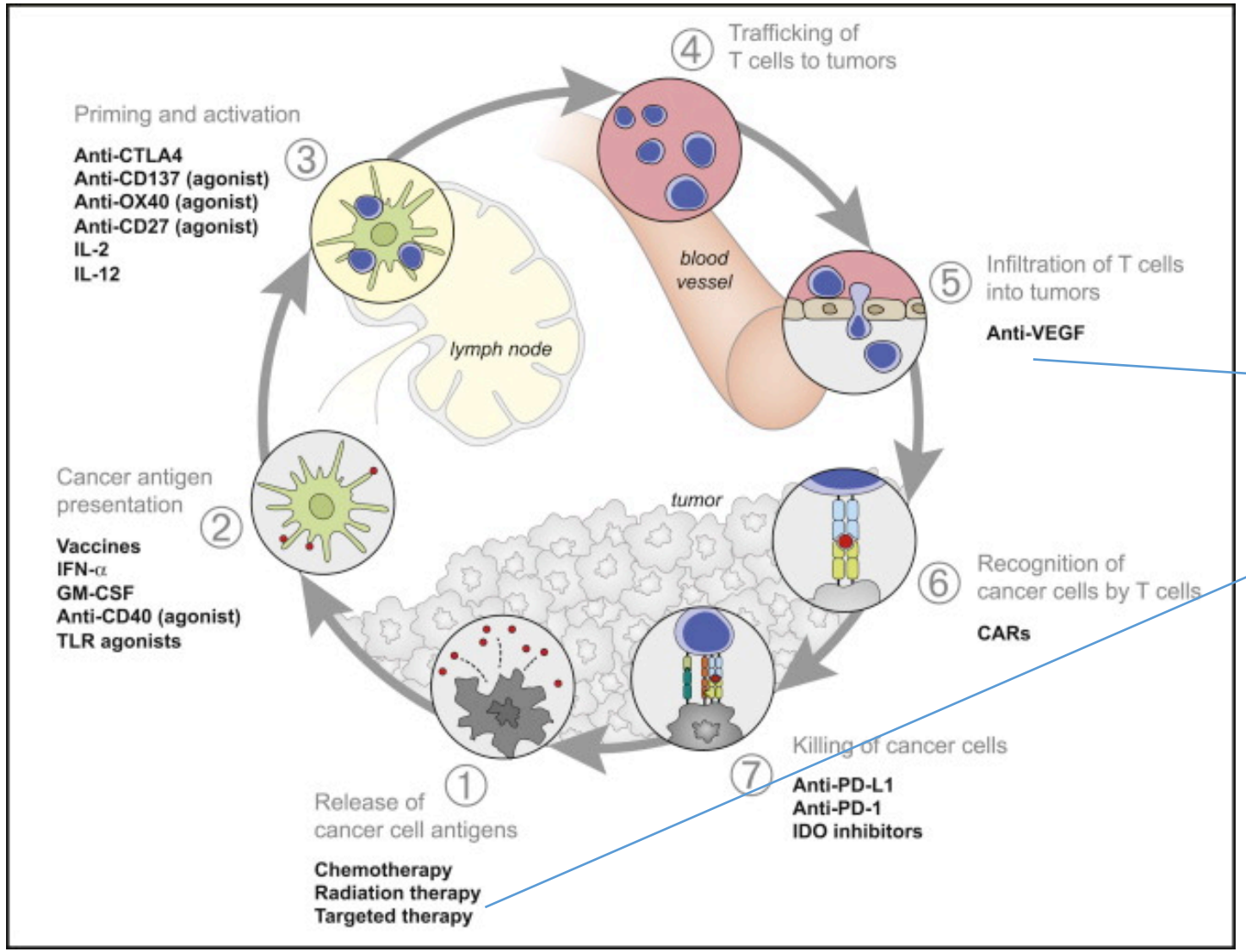
In 120 patients who discontinued combination therapy because of toxic effects, the response rate was 67.5%

Larkin et al. N Engl J Med 2015; 373: 23–34.

Treatment selected irAEs in >10% patients from Checkmate 067: Ipi+Nivo vs Nivolumab vs Ipilimumab groups

Patients Reporting Event, %	NIVO + IPI (N=313)		NIVO (N=313)		IPI (N=311)	
	Any Grade	Grade 3–4	Any Grade	Grade 3–4	Any Grade	Grade 3–4
Skin	59.1	5.8	41.9	1.6	54.0	2.9
Pruritus	33.2	1.9	18.8	0	35.4	0.3
Rash	28.4	2.9	21.7	0.3	20.9	1.6
Rash maculo-papular	11.8	1.9	4.2	0.3	11.9	0.3
Gastrointestinal	46.3	14.7	19.5	2.2	36.7	11.6
Diarrhea	44.1	9.3	19.2	2.2	33.1	6.1
Colitis	11.8	7.7	1.3	0.6	11.6	8.7
Hepatic	30.0	18.8	6.4	2.6	7.1	1.6
Increase in alanine aminotransferase	17.6	8.3	3.8	1.3	3.9	1.6
Increase in aspartate aminotransferase	15.3	6.1	3.8	1.0	3.5	0.6
Endocrine	30.0	4.8	14.4	0.6	10.9	2.3
Hypothyroidism	15.0	0.3	8.6	0	4.2	0

Cancer-immunity cycle and therapeutic options



Targeted therapy:

BRAF/MEK inhibitors

PIK3CA/AKT inhibitors

PARP inhibitors

Antiangiogenic agents

Chen DS, Mellman I. Immunity. 2013;39:1-8

Combination Immune Checkpoint Studies in Ovarian Cancer

Combination	Treatment setting	Line of therapy	Phase	Trial identifier
aCTLA-4 + PARPi	Tremelimumab + olaparib	2L+	I/II	NCT02571725
aCTLA-4 + PARPi	Tremelimumab tremelimumab + olaparib	2L	I/II	NCT02485990
aCTLA-4 + aPD-1	Nivolumab versus nivolumab + ipilimumab	2–4L	II[a]	NCT02498600
aPD-1 + TC	Pembrolizumab + paclitaxel + carboplatin	1L	II	NCT02520154
aPD-1 + ddT	Pembrolizumab + dose-dense paclitaxel	2L+	II	NCT02440425
aPD-1 + TKI	ACP-196 (TKI) versus pembrolizumab + ACP-196	2–4L	II[a]	NCT02537444
aPD-L1 + PARPi	Durvalumab + olaparib vs durvalumab + cediranib	Any	I/II[a]	NCT02484404
aPD-L1 + aCTLA-4	Durvalumab + tremelimumab	Any	I	NCT02261220
aPD-L1 + Bev	Atezolizumab + bevacizumab	2L-	II[a]	NCT02659384
aPD-L1 + TLRa + PLD	Durvalumab + motolimod + PLD	2–3L	I/II	NCT02431559
aPD-L1 + PLD	Avelumab versus avelumab + PLD versus PLD	2–4L	III[a]	NCT02580058

Hamanishi et al 2016

Combination of BRAF inhibitor and Immune checkpoint blocking therapy – Vemurafenib and Ipilimumab

Ribas et al NEJM 2014

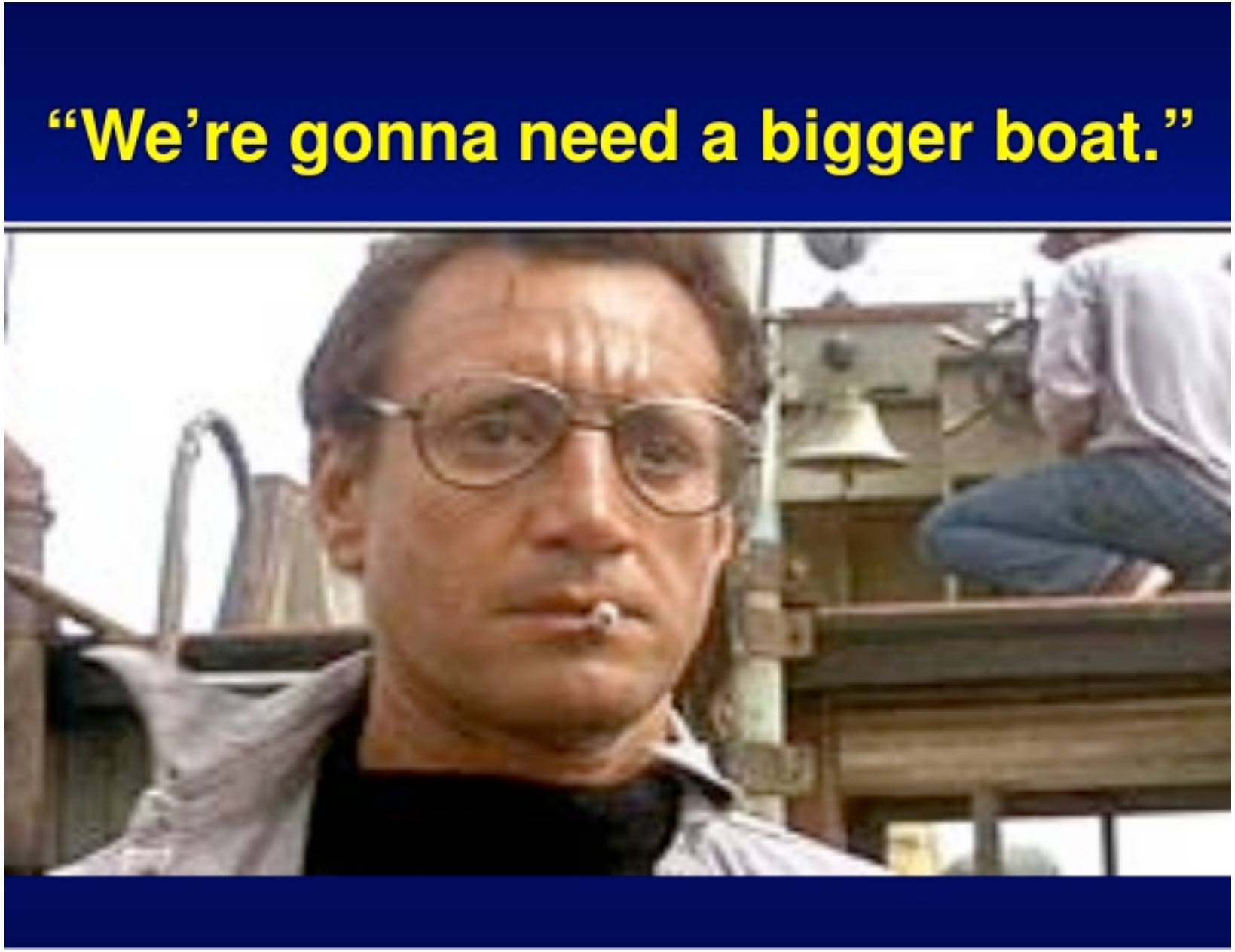
Inhibition of the MAPK pathway with MEK or $BRAF^{V600E}$ inhibitors in melanoma cell lines results in increased levels of melanocyte differentiation antigens

→ associated with improved recognition by antigen-specific T lymphocytes.

Table 1. Data for Patients with Grade 3 Elevations in Alanine Aminotransferase (ALT) and Aspartate Aminotransferase (AST) Levels While Receiving Combination Therapy with Vemurafenib and Ipilimumab.*

Study Cohort and Patient No.	No. of Doses of Ipilimumab before ALT–AST Elevation	Time to Onset of ALT–AST Elevation after First Dose of Ipilimumab	Treatment	Time to Resolution of ALT–AST Elevation	Toxicity Relapse with Repeated Ipilimumab
First cohort					
4	1	21	rticoids; vemurafenib discontinu… then restarted with…	…ys	NA
5	2	36 days	…4 da… …uc-	6 days	No
6†	1	21 d…	…then restarted with… …ipilimumab continued (1 dose)	…ys	No
8	1	19 da…	Glucocorticoids; vemurafenib discontinued for 4 days and then restarted with dose reduction; ipilimumab continued (1 dose)	…ays	Yes
Second cohort					
10	1	15 days	Glucocorticoids; vemurafenib discontinued for 7 days and then restarted with dose reduction; ipilimumab permanently discontinued	10 days	NA
16‡	1	13 days	Vemurafenib and ipilimumab permanently discontinued	20 days	NA

Stopped due to liver toxicity



Chief Brody, *Jaws* 1975

NUH Immune-related Toxicity (irTox) Team

- NUH irTox team
  - Designated organ specialists
  - Modelled after Hopkins irTox team
  - Inception in Mar 2018
    - First to be established in the region
  - Cardiology, dermatology, endocrinology, gastroenterology, hematology, hepatology, nephrology, neurology, ophthalmology, pulmonology and rheumatology disciplines

- Rapid direct referrals for collaborative management and research

- Local irAE screening checklist developed


Document

NUH Immune-related Toxicity (irTox) Team

Discipline	1st Line Consultants
Gastroenterology	Juanda Leo
Hepatology	Mark Muthiah
Pulmonology	Felicia Teo
Rheumatology	Frank Tay
Dermatology	Nisha Suyien Chandran/Chris Tan
Endocrine	Samantha Yang
Neurology	Kay Ng
Cardiology	Tan Li Ling
Nephrology	Martin Lee
Hematology	Yap Eng Soo
Ophthalmology	Dawn Lim

Spectrum of irAE Referrals

Table 1. irAEs by Grade						
irAEs	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Pericarditis			1			1
Dermatitis	4	1		1		6
Hypophysitis		4				5
Diabetes				1		1
Thyroid gland disorders	6					6
Hepatitis		2	3			5
Aseptic meningitis			1			1
Peripheral neuropathy	1					1
Uveitis	1					1
Pneumonitis		1		1		2
Inflammatory arthritis		2				2
Myositis	1	1		1	1	4
Cytokine release syndrome	1	2			2	4
Total	14	13	5	4	3	39

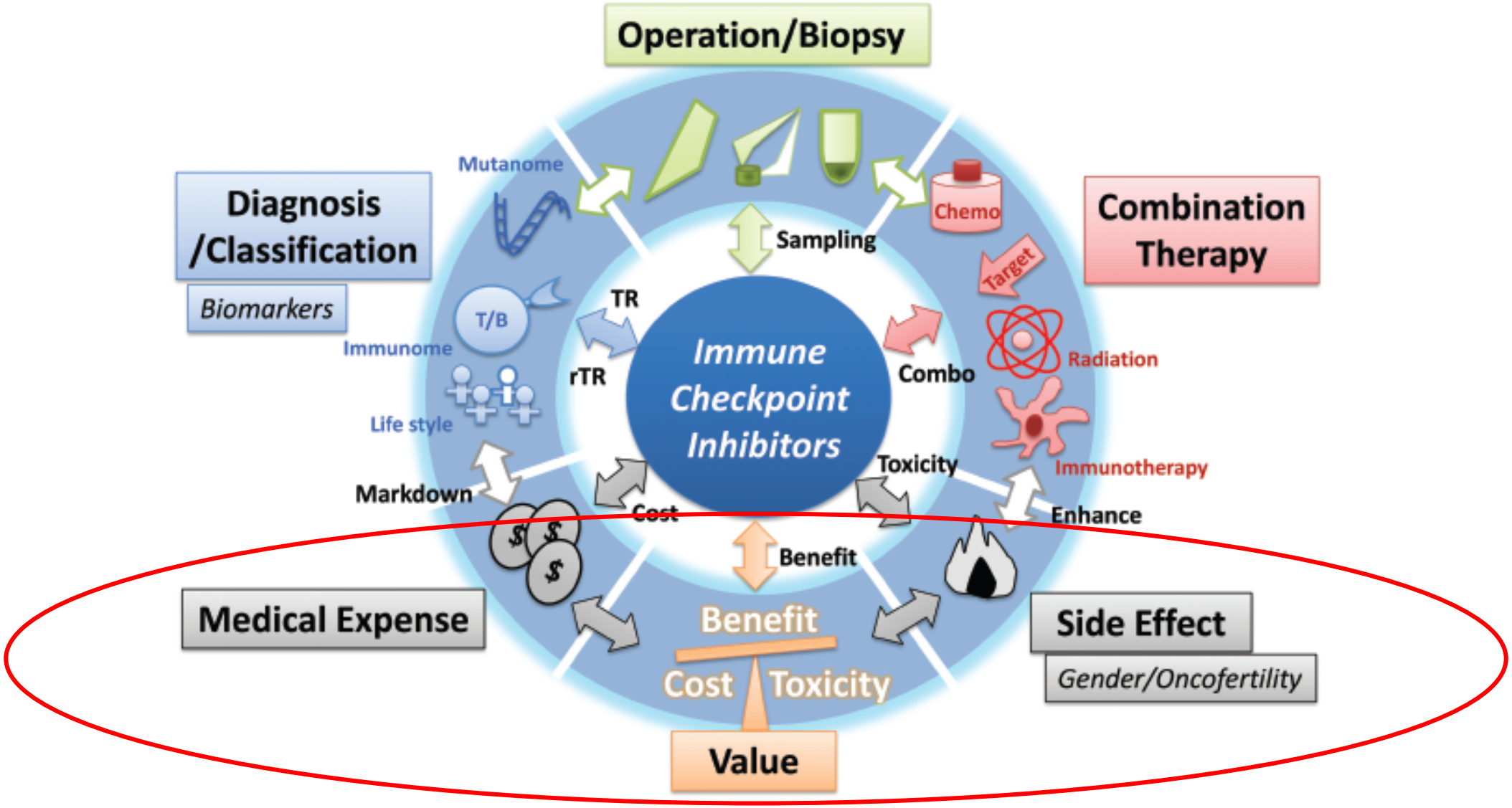
30.8% of irAE referrals to the NUH irTox Team were ≥ Grade 3

?Predicting irAEs

- Baseline sarcopenia and low muscle attenuation (Daly et al, 2017)
- Family history of autoimmune diseases,
- Tumour infiltration and location,
- Previous viral infections - HIV or hepatitis
- Concomitant use of medicines with known autoimmune toxicities such as antiarrhythmics, antibiotics, anticonvulsants or antipsychotics

  (Champiat et al, 2016; Manson et al, 2016).
- Diversification of the T-cell repertoire (Fong et al, 2016; Oh et al,2017)
- Increased eosinophils (Schindler et al, 2014)
- Increased circulating IL-17 levels → gastrointestinal toxicity (Tarhini et al, 2015)

More research needed for predictors of IO toxicity
Larger numbers required → national IO tox database



Hamanishi et al 2016

Summary and future considerations:

- **Unique spectrum of side effects for checkpoint inhibitors → mostly manageable but expert input should be available**
- **Most patients completely recover with immunosuppression**
- **Immunosuppression does not appear to affect therapeutic efficacy**

  → ?Patients with autoimmune conditions
- **Combinations – toxicity evaluation and management will be key to feasibility**
- **Is fixed dose appropriate for all patients? → modified dosing based on tumour characteristics?**
- **Collaborative databases to identify predictive biomarkers for efficacy and toxicity → risk/cost-benefit**

Annals of Oncology 28 (Supplement 4): iv119–iv142, 2017
doi:10.1093/annonc/mdx225

CLINICAL PRACTICE GUIDELINES

Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

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†Approved by the ESMO Guidelines Committee: May 2017.

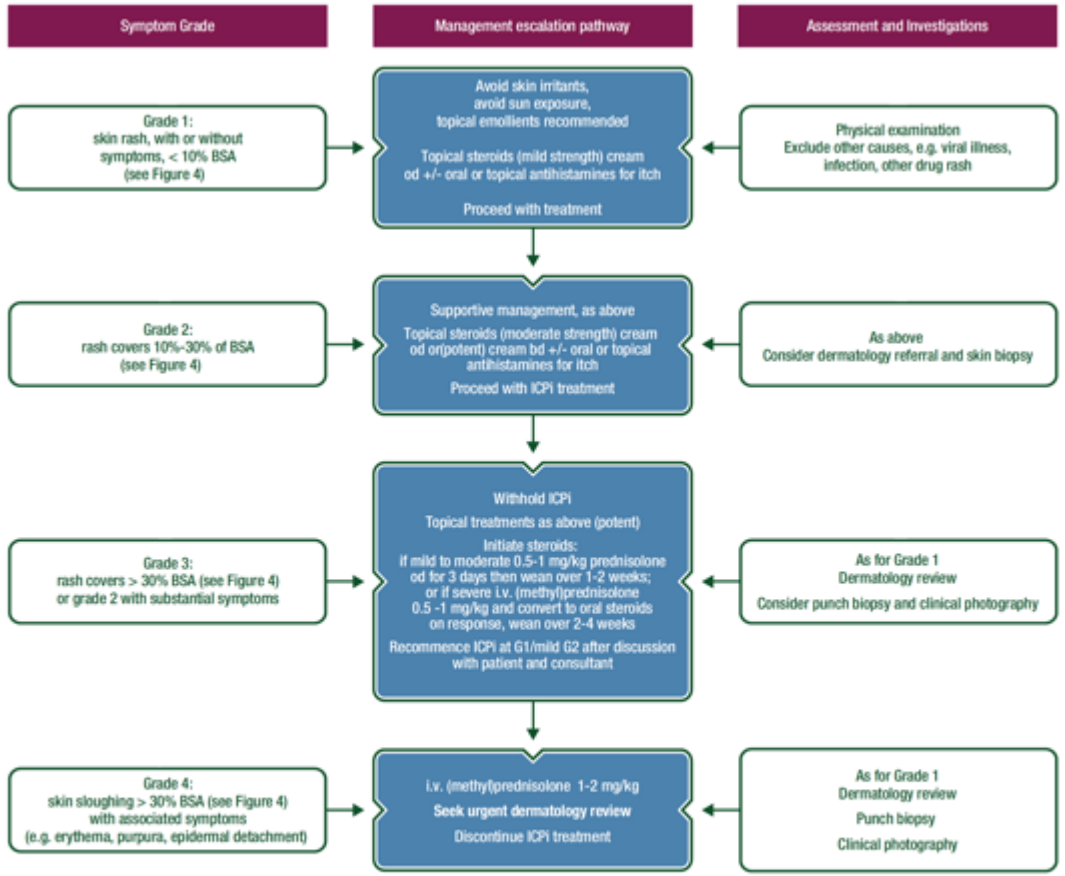

Figure 3. ICPi-related toxicity: management of skin rash/toxicity.
Recognised skin AEs include: (i) most common: erythema, maculopapular and pustulopapular rash; (ii) rare: toxic epidermal necrolysis, Steven-Johnson syndrome and DRESS; (iii) vasculitis may also be present with purpuric rash.
AE, adverse event; bd, twice daily; BSA, body surface area; DRESS, drug rash with eosinophilia and systemic symptoms; ICPi, immune checkpoint inhibitor; i.v., intravenous; od, once daily.

National University Cancer Institute, Singapore

Thank You

Committed To The Research of Cancers in Asia

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NUH National University Hospital

NUS National University of Singapore

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Faculty of Dentistry
Saw Swee Hock School of Public Health