Royal Brisbane and Women's Hospital

2023

6th Annual

CANCER PRECEPTORSHIP

FOR GENERAL PRACTITIONERS

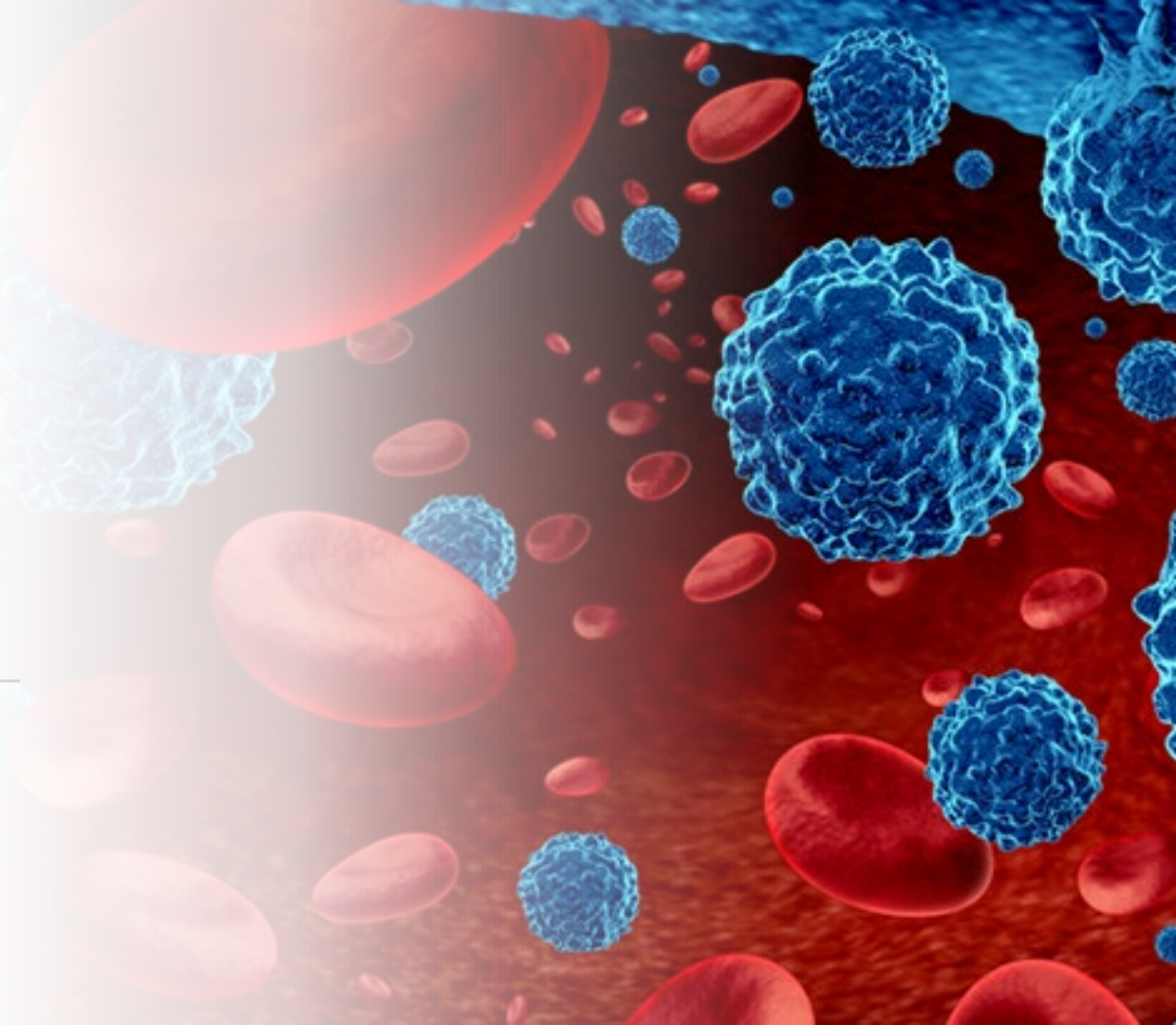
Metro North Health

Queensland Government

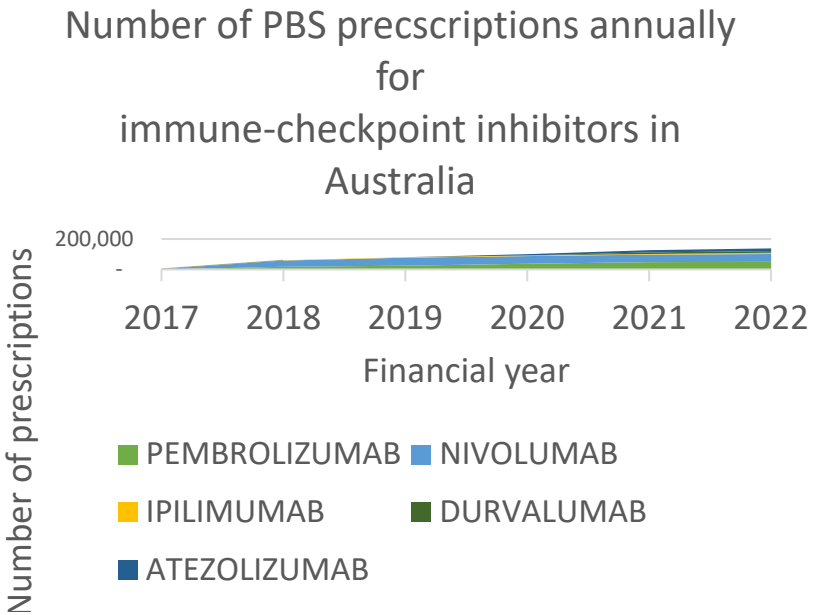
Immunotherapy – what should a GP be looking for?

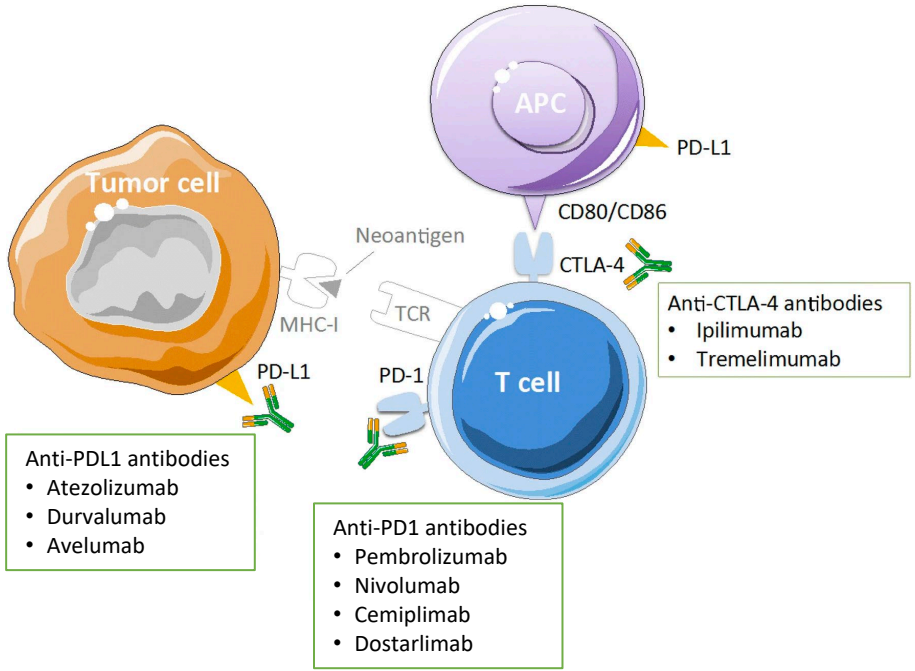
A/Prof Melissa Eastgate

A/Executive Director, MNHHS Cancer Care Stream

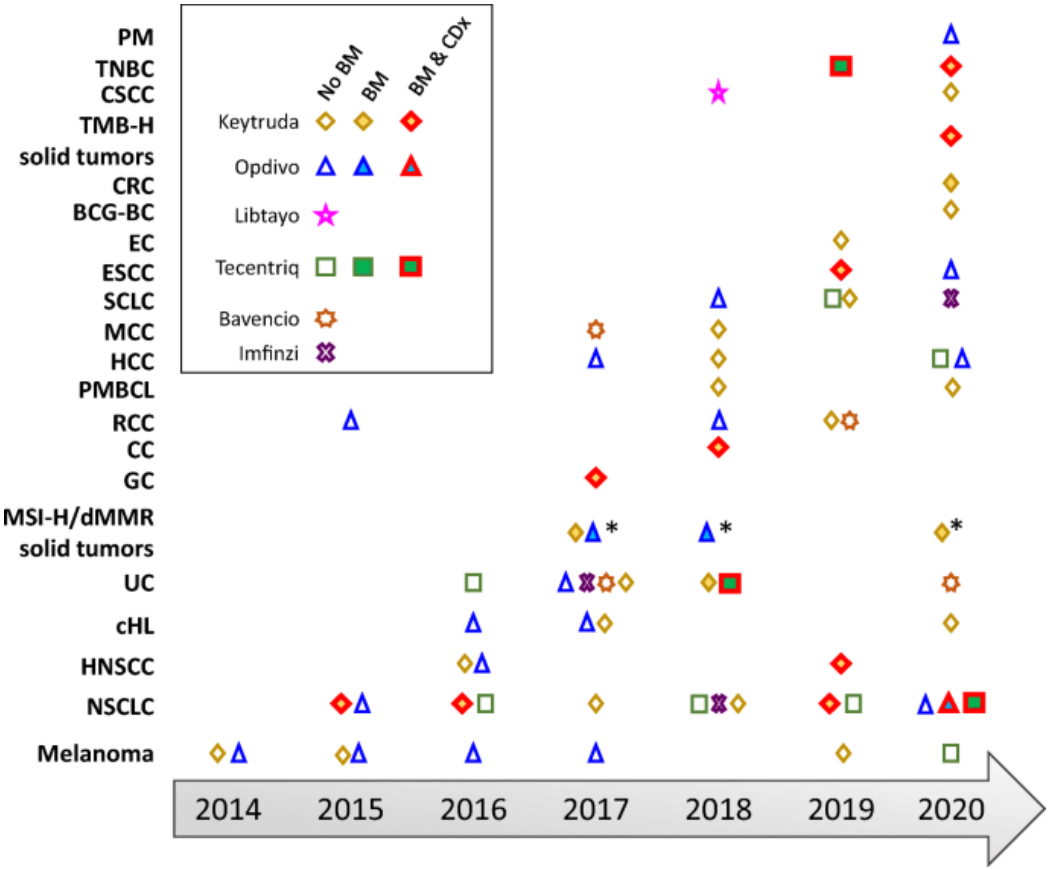


Immune checkpoint inhibitors

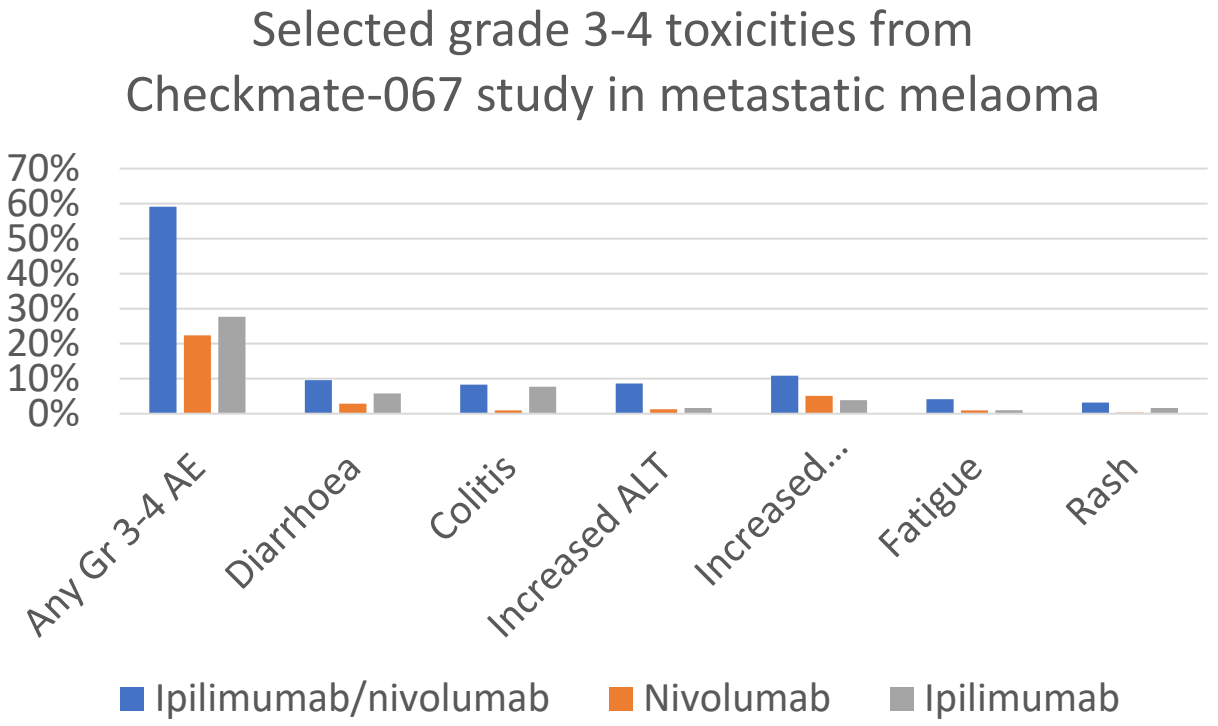




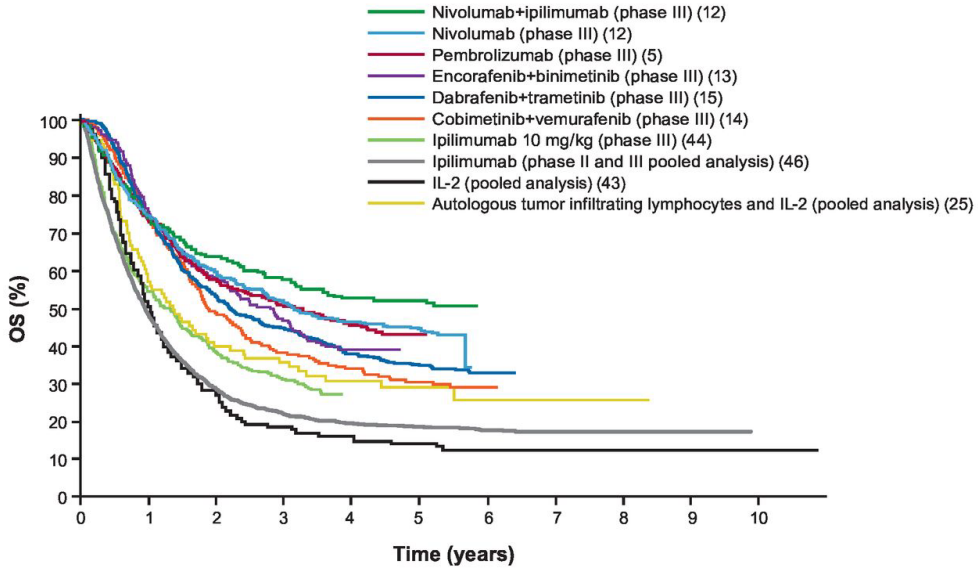
Rouanne et al, *World J Urology*, 2018


No BM
BM
BM & CDx
Keytruda
Opdivo
Libtayo
Tecentriq
Bavencio
Imfinzi
PM
TNBC
CSCC
TMB-H
solid tumors
CRC
BCG-BC
EC
ESCC
SCLC
MCC
HCC
PMBCL
RCC
CC
GC
MSI-H/dMMR
solid tumors
UC
cHL
HNSCC
NSCLC
Melanoma
2014
2015
2016
2017
2018
2019
2020

Immune checkpoint inhibitors



Immune checkpoint inhibitors – melanoma survival

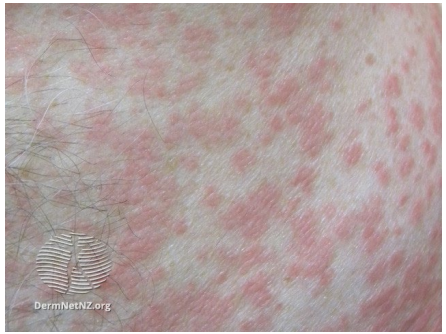


Case 1

72F

Metastatic clear cell renal cell carcinoma

- Ipilimumab/nivolumab x4 from June 2021
- Complicated by gr 2 hepatitis post C4
  - Responded to prednisone
- Maintenance nivolumab from Oct 21
  - Responded to further low dose prednisone
- Treatment continued with stable disease radiologically
- Distal pancreatectomy Nov 2022 for presumed pNET
  - Histology, met RCC
  - Loose BM post – on Creon



Case 1

- Presented to ED 4.1.23 with:
  - Abdominal and ‘burning’ chest pain worsening over weeks
  - Nausea and vomiting
  - 3 loose bowel motions / day stable over months
- CT: multiple new enlarged abdominal lymph nodes and mesenteric stranding. Suggestive of nodal metastases from RCC. Enteritis with reactive lymphadenopathy is thought less likely. Fluid in pancreatic bed
- Admitted 48 hours, analgesia and antiemetics for symptomatic management

Sample Appearance	Clear		
Sodium	137	mmol/L	(135 - 145)
Potassium	3.7	mmol/L	(3.5 - 5.2)
Chloride	103	mmol/L	(95 - 110)
Bicarbonate	28	mmol/L	(22 - 32)
Anion Gap	6	mmol/L	(4 - 13)
Glucose	8.1	mmol/L	(3.0 - 7.8)
		(Fasting	3.0 - 6.0)
Urea	5.2	mmol/L	(2.9 - 8.2)
Creatinine	76	umol/L	(36 - 73)
Urea/Creat	68		(40 - 100)
GFR (estimated)	68	mL/min/1.73m^2	(> 90)
Urate	0.31	mmol/L	(0.15 - 0.45)
Protein (Total)	56	g/L	(60 - 80)
Albumin	30	g/L	(35 - 50)
Globulin	26	g/L	(25 - 45)
Bilirubin (Total)	7	umol/L	(< 20)
Bilirubin (Conj.)	< 4	umol/L	(< 4)
Alkaline Phosphatase	114	U/L	(30 - 110)
Gamma-GT	82	U/L	(< 38)
Alanine Transaminase	37	U/L	(< 34)
Aspartate Transaminase	30	U/L	(< 31)
Lipase (Serum)	103	U/L	(< 60)

Faeces Microbiology

SPECIMEN : Faeces

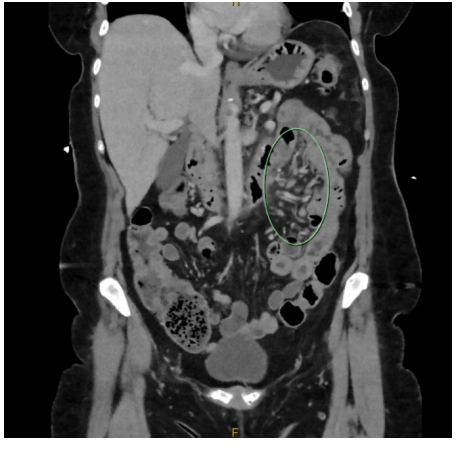
Viral PCR:

Adenovirus 40/41 PCR	Not Detected
Norovirus PCR	Not Detected
Rotavirus PCR	Not Detected

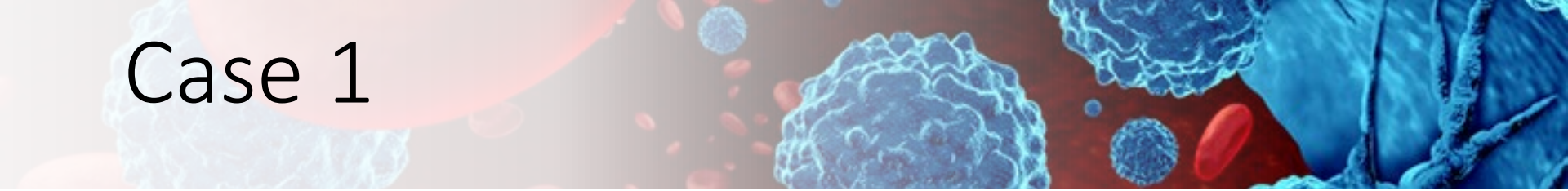
Bacterial PCR:

Salmonella species PCR	Not Detected
Shigella species PCR	Not Detected
Campylobacter species PCR	Not Detected
Yersinia enterocolitica PCR	Not Detected
Vibrio cholerae PCR	Not Detected
Vibrio parahaemolyticus PCR	Not Detected

C.difficile Screen: Negative



Case 1



- Re-presented 48 hours after discharge; family frustrated
- Ongoing nausea, vomiting and abdominal pain

Immunotherapy Question 1

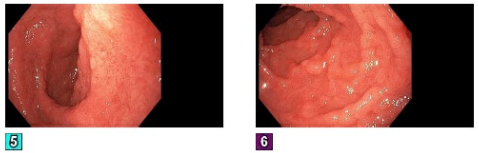
What next?

- CT Brain with contrast
- Endoscopy
- Palliative care consult to manage refractory nausea
- Psychology input

Case 1

- Symptoms escalated during hospital stay with worsening vomiting and minimal oral intake. Now 20 bowel motions/24 hours

Sample Appearance	Clear	Clear		
Sodium	135	137	mmol/L	(135 - 145)
Potassium	3.1	2.8	mmol/L	(3.5 - 5.2)
Chloride	96	100	mmol/L	(95 - 110)
Bicarbonate	26	23	mmol/L	(22 - 32)
Anion Gap	13	14	mmol/L	(4 - 13)
Glucose	7.1	6.1	mmol/L	(3.0 - 7.8)
			(Fasting	3.0 - 6.0)
Urea	7.4	6.3	mmol/L	(2.9 - 8.2)
Creatinine	74	73	umol/L	(36 - 73)
Urea/Creat	100	87		(40 - 100)
GFR (estimated)	70	71	mL/min/1.73m^2	(> 90)
Urate	0.32	0.31	mmol/L	(0.15 - 0.45)
Protein (Total)	60	51	g/L	(60 - 80)
Albumin	28	23	g/L	(35 - 50)
Globulin	32	27	g/L	(25 - 45)
Bilirubin (Total)	9	8	umol/L	(< 20)
Bilirubin (Conj.)	< 4	< 4	umol/L	(< 4)
Alkaline Phosphatase	133	100	U/L	(30 - 110)
Gamma-GT	79	61	U/L	(< 38)
Alanine Transaminase	31	23	U/L	(< 34)
Aspartate Transaminase	18	13	U/L	(< 31)
Lactate Dehydrogenase	214	187	U/L	(120 - 250)
Calcium	2.23	2.01	mmol/L	(2.10 - 2.60)
Calcium (Alb. Corr.)	2.47	2.34	mmol/L	(2.10 - 2.60)
Phosphate	1.28	1.25	mmol/L	(0.75 - 1.50)
Lipase (Serum)	26		U/L	(< 60)
Magnesium	0.68	0.91	mmol/L	(0.70 - 1.10)
Osmolality (Calculated)	290	293	mmol/L	(275 - 295)



Reduced folds in duodenum, flattening
Colon macroscopically normal appearance

1. Duodenum 1: This specimen shows mild villous blunting. There is diffuse hypercellularity of the lamina propria with increased plasma cells and neutrophils. There is also surface epithelial injury with increased intraepithelial neutrophils and lymphocytes. Viral cytopathic changes and parasites have not been identified.

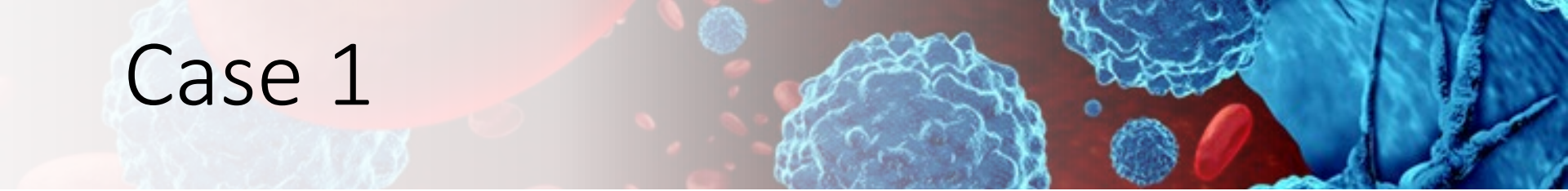
SUMMARY

1. Duodenum 1: Moderate active duodenitis.
2. Duodenum 2: Moderate active duodenitis.
3. Colon random colon: Mild active inflammation with epithelial lymphocytosis and increased apoptosis.

COMMENT

Given the clinical history, the inflammatory changes in the duodenum and random colonic biopsies are highly suspicious for immune checkpoint inhibitor enterocolitis. Severe coeliac disease could conceivably cause the duodenal changes, but the histological features are atypical for that diagnosis.

Case 1

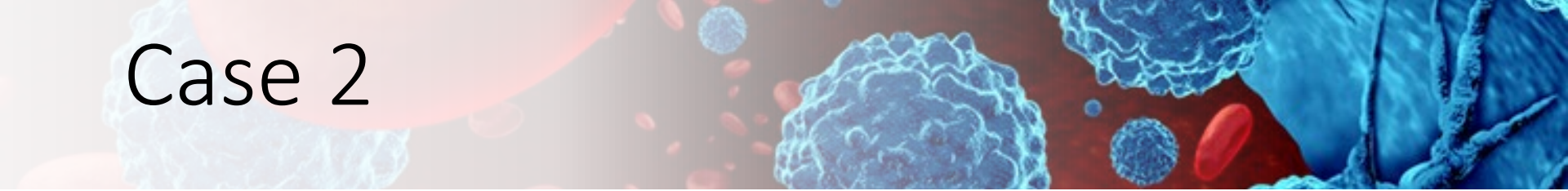


- IV methylprednisolone 2mg/kg commenced
- Improvement but not resolution of symptoms
- Infliximab 5mg/kg on D5 of methylpred with ongoing resolution of symptoms

Gastritis/duodenitis

- Much less common than lower GI toxicity; can occur together
- Incidence unclear, case reports/series; estimated <1%
- Symptoms include:
  - Nausea/vomiting (50-100%)
  - Abdominal pain (30-75%)
  - Dyspepsia (38%)
  - Bleeding (18% in one case series)
  - Concomitant lower GI symptoms eg. diarrhoea up to 50%
- Management guided by case series - as for lower GI toxicity with steroids and anti-TNF-α agents in refractory cases

Case 2



69M

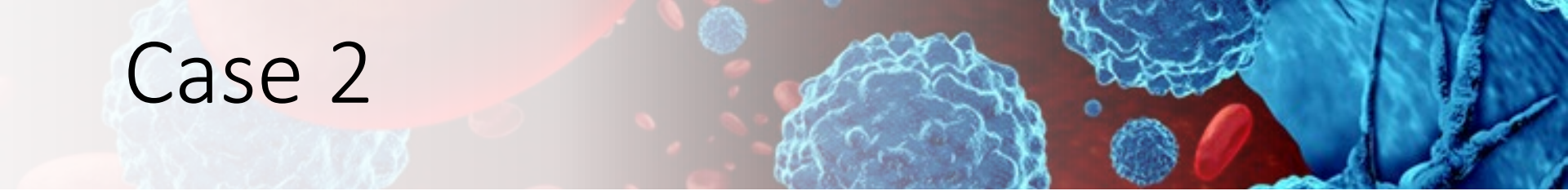
- Resected stage IIIC (pT3bN2bM0) melanoma
- BG: AF with prior tachycardia induced CMP, asthma
- Treated with adjuvant nivolumab from June 2022
- Presented for cycle 9 treatment, reporting:
  - Fatigue/lethargy
  - Postural dizziness
  - Anorexia, abdominal pain, nausea/vomiting
  - No diarrhoea

Immunotherapy – Question 2

What do you think this is likely to be?

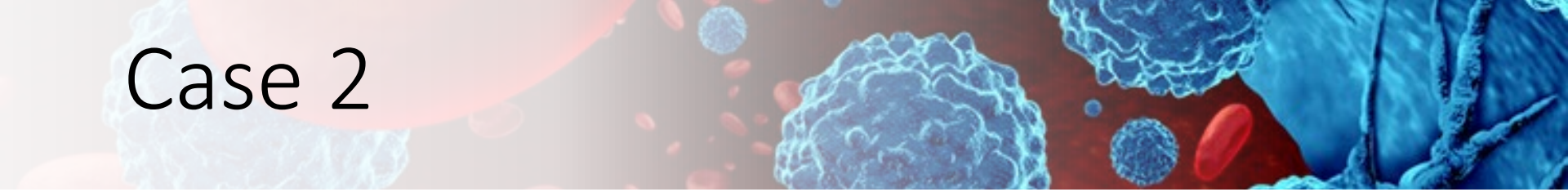
- Non specific immunotherapy toxicity
- Gastritis/duodenitis
- Brain metastasis
- New onset diabetes
- Pituitary dysfunction

Case 2



Sample Appearance	Clear		
Sample Integrity			
Status	Fasting		
Sodium	130	mmol/L	(135 - 145)
Potassium	5.5	mmol/L	(3.5 - 5.2)
Chloride	99	mmol/L	(95 - 110)
Bicarbonate	15	mmol/L	(22 - 32)
Anion Gap	16	mmol/L	(4 - 13)
Glucose	19.1	mmol/L	(3.0 - 7.8)
		(Fasting	3.0 - 6.0)
Urea	4.7	mmol/L	(2.9 - 8.2)
Creatinine	98	umol/L	(64 - 108)
Urea/Creat	48		(40 - 100)
GFR (estimated)	68	mL/min/1.73m^2	(> 90)
Urate	0.44	mmol/L	(0.15 - 0.50)
Protein (Total)	77	g/L	(60 - 80)
Albumin	39	g/L	(35 - 50)
Globulin	38	g/L	(25 - 45)
Bilirubin (Total)	6	umol/L	(< 20)
Bilirubin (Conj.)	< 4	umol/L	(< 4)
Alkaline Phosphatase	72	U/L	(30 - 110)
Gamma-GT	90	U/L	(< 55)
Alanine Transaminase	22	U/L	(< 45)
Aspartate Transaminase	16	U/L	(< 35)
Lactate Dehydrogenase	179	U/L	(120 - 250)
Calcium	2.30	mmol/L	(2.10 - 2.60)
Calcium (Alb. Corr.)	2.32	mmol/L	(2.10 - 2.60)
Phosphate	0.85	mmol/L	(0.75 - 1.50)
Lipase (Serum)		U/L	(< 60)
Magnesium	0.82	mmol/L	(0.70 - 1.10)
Osmolality (Calculated)	290	mmol/L	(275 - 295)

Case 2



Arterial Gas Parameters

pH	7.03		(7.35 - 7.45)
pCO2	26	mmHg	(32 - 48)
pO2	27	mmHg	(83 - 108)
Oxygen Saturation	45	%	(94 - 98)
Bicarbonate	6	mmol/L	(22 - 33)
p50	28.9	mmHg	(25.0 - 29.0)
Base Excess	-24.9	mmol/L	(-2.0 - 3.0)

Corrected Values

Corrected pH	7.03	
Corrected pCO2	26	mmHg
Corrected pO2	27	mmHg

Electrolytes

Sodium	138	mmol/L	(135 - 145)
Potassium	4.8	mmol/L	(3.5 - 5.2)
Chloride	113	mmol/L	(95 - 110)
Anion Gap	19	mmol/L	(4 - 13)
Creatinine Blood Gas	85	umol/L	(64 - 108)
Calcium (Ionised) (Bld Gas)	1.37	mmol/L	(1.15 - 1.32)

Metabolites

Glucose	21.5	mmol/L	(3.9 - 5.5)
Lactate	1.3	mmol/L	(0.5 - 2.2)

Sample Appearance	Clear	Clear		
Sample Integrity				
Status	Fasting			
Sodium	130	137	mmol/L	(135 - 145)
Potassium	5.5	5.0	mmol/L	(3.5 - 5.2)
Chloride	99	106	mmol/L	(95 - 110)
Bicarbonate	15	7	mmol/L	(22 - 32)
Anion Gap	16	24	mmol/L	(4 - 13)
Glucose	19.1	20.2	mmol/L	(3.0 - 7.8)
			(Fasting	3.0 - 6.0)
Urea	4.7	4.0	mmol/L	(2.9 - 8.2)
Creatinine	98	114	umol/L	(64 - 108)
Urea/Creat	48	35		(40 - 100)
GFR (estimated)	68	56	mL/min/1.73m^2	(> 90)
Urate	0.44	0.47	mmol/L	(0.15 - 0.50)
Protein (Total)	77	84	g/L	(60 - 80)
Albumin	39	44	g/L	(35 - 50)
Globulin	38	40	g/L	(25 - 45)
Bilirubin (Total)	6	< 4	umol/L	(< 20)
Bilirubin (Conj.)	< 4	< 4	umol/L	(< 4)
Alkaline Phosphatase	72	92	U/L	(30 - 110)
Gamma-GT	90	99	U/L	(< 55)
Alanine Transaminase	22	27	U/L	(< 45)
Aspartate Transaminase	16	13	U/L	(< 35)
Lactate Dehydrogenase	179	269	U/L	(120 - 250)
Calcium	2.30	2.37	mmol/L	(2.10 - 2.60)
Calcium (Alb. Corr.)	2.32	2.29	mmol/L	(2.10 - 2.60)
Phosphate	0.85	1.00	mmol/L	(0.75 - 1.50)
Lipase (Serum)		41	U/L	(< 60)
Magnesium	0.82	0.92	mmol/L	(0.70 - 1.10)
Osmolality (Calculated)	290	305	mmol/L	(275 - 295)

Case 2

- Diagnosed with immunotherapy related diabetes mellitus
- IV rehydration, IV insulin and IV dextrose
- Vomiting and abdominal pain resolved with correction of ketoacidosis

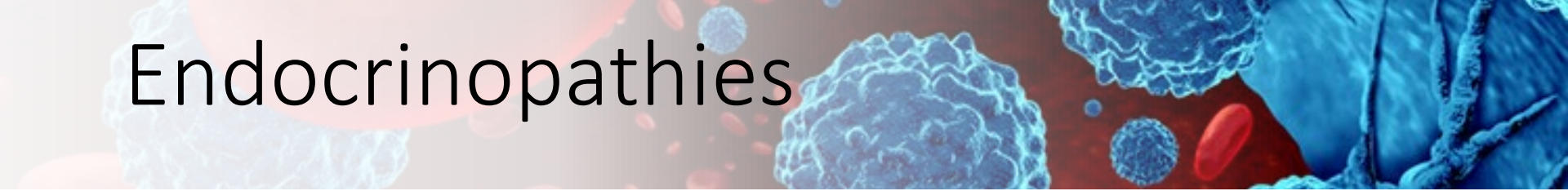
Year 2023 / ALERTS												
Date	10/02	10/02	10/02	10/02	10/02	10/02	10/02	10/02	10/02	10/02	10/02	10/02
Time BGL	0030	0130	0230	0330	0430	0500	0530	0630	0725	0835	0930	1030
Greater than 20 Notify Dr immediately	21.6	21.7	20.4									
15.1–20 Notify Dr immediately				16.4	15.9	—						
10.1–15 Notify Dr if 3 consecutive BGLs greater than 10							13.2	11.9	10.8	10.2	10.2	10.3
Write BGL (mmol/L) in corresponding range box 5.1–10												
Less than 5 Notify Dr immediately Treat hypoglycaemia if less than 4												
Insulin infusion rate (units/hr)	4	4	7	10	10	13	13	13	13	13	13	13
Meal / Snack bolus (units given)												
Nurse(s) initials	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]		[illegible]	[illegible]	[illegible]	[illegible]
Ketones / Hypo intervention	5.8	5.8	5.5	5.4	5.6	—	5.8	5.3	5.1	4.0	2.9	2.4
Dr notified	✓	✓	✓	✓	✓	✓	✓		✓			✓

Year 2023 / ALERTS												
Date	10/02	10/02	10/02	10/02	10/02	10/02	10/02	10/2	10/2	10/2	10/2	10/2
Time BGL	1130	1230	1325	1430	1530	1630	1730	1830	1955	2050	2150	2250
Greater than 20 Notify Dr immediately												
15.1–20 Notify Dr immediately												
10.1–15 Notify Dr if 3 consecutive BGLs greater than 10	11.3	11.5	11.1						10.1	11.2		
Write BGL (mmol/L) in corresponding range box 5.1–10				9.0	8.6	7.8	6.4	8.1			8.6	6.5
Less than 5 Notify Dr immediately Treat hypoglycaemia if less than 4												
Insulin infusion rate (units/hr)	15	15	6	4	4	4	4/2	4	6	6	4	2
Meal / Snack bolus (units given)												
Nurse(s) initials	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Ketones / Hypo intervention	1.8	0.9	0.8	0.5	0.9	0.9	0.7	0.6	1.6	1.1	0.6	0.5
Dr notified												

OTHER TISSUE AUTOANTIBODIES

anti-Pancreatic Islet Cell	Negative
GAD Ab	< 5.0
IA2 Ab	<15.0
C-Peptide	<0.1

Endocrinopathies



- Clinically significant endocrinopathies in up to 10% patients
  - Most commonly hypothyroidism
  - Can include: hypoadrenalism, hypopituitarism / hypophysitis, diabetes
  - Incidence of ICI-associated diabetes <1%
- Irreversible
- Steroids rarely indicated
- Do not preclude further immunotherapy

Case 3

43M

- Unresectable stage III melanoma with multifocal chest wall recurrence after several prior resections
- No medical history, runs earth moving business
- Commenced on ipilimumab/nivolumab Jan 2023
- Presented post C2 with fevers, chills and rigors
  - No localising symptoms

Haemoglobin	144	g/L	(135 - 180)
White Cell Count	7.2	x 10^9/L	(4.0 - 11.0)
Platelets	398	x 10^9/L	(140 - 400)
Haematocrit	0.43		(0.39 - 0.52)
MCH	30.8	pg	(27.0 - 33.0)
Red Cell Count	4.67	x 10^{12}/L	(4.50 - 6.00)
MCV	92	fL	(80 - 100)
Neutrophils	4.24	x 10^9/L	(2.00 - 8.00)
Lymphocytes	2.12	x 10^9/L	(1.00 - 4.00)
Monocytes	0.68	x 10^9/L	(0.10 - 1.00)
Eosinophils	0.01	x 10^9/L	(< 0.60)
Basophils	0.13	x 10^9/L	(< 0.20)

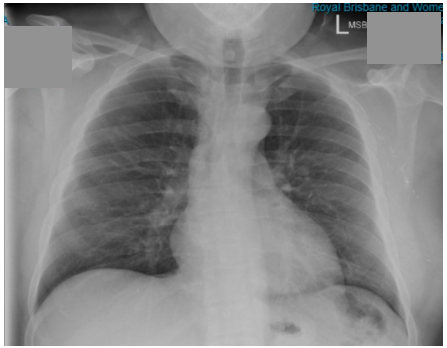
CRP	124

Urine Microbiology

SPECIMEN : Urine ? Collection

MICROSCOPY

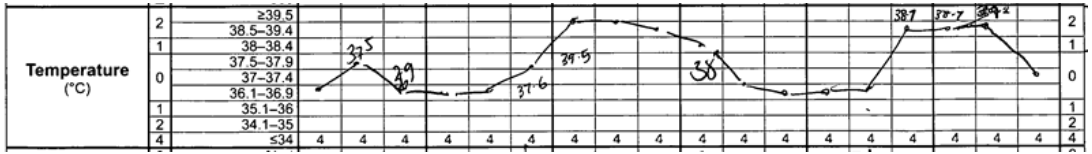
Leucocytes	< 10	x10^6/L	RR (< 10)
Erythrocytes	< 10	x10^6/L	RR (< 10)
Epithelials	< 10	x10^6/L	



Case 3

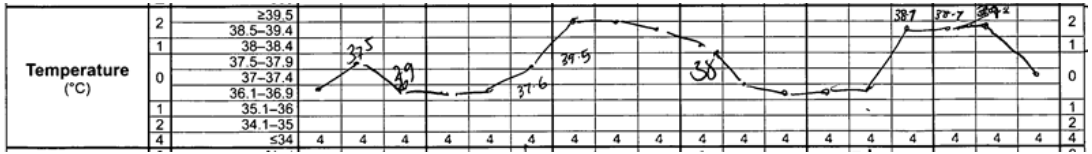
- Continued episodes fever, rigors, tachypnoea on D4 IV piptaz
- Mild transaminitis
- Remained culture negative

Sample Appearance	Clear	Clear	Clear	Clear	Clear		
Sodium	141	142	141	139	141	mmol/L	(135 - 145)
Potassium	4.1	4.3	4.0	3.9	4.0	mmol/L	(3.5 - 5.2)
Chloride	105	106	106	103	106	mmol/L	(95 - 110)
Bicarbonate	26	24	22	23	23	mmol/L	(22 - 32)
Anion Gap	10	13	12	13	12	mmol/L	(4 - 13)
Glucose	5.1	4.0	5.3	7.0	4.9	mmol/L	(3.0 - 7.8)
						(Fasting	3.0 - 6.0)
Urea	3.1	3.2	3.3	3.5	3.9	mmol/L	(2.1 - 7.1)
Creatinine	70	66	66	64	64	umol/L	(60 - 110)
Urea/Creat	44	49	50	55	61		(40 - 100)
GFR (estimated)	>90	>90	>90	>90	>90	mL/min/1.73m^2	(> 90)
Urate	0.25	0.30	0.21	0.24	0.22	mmol/L	(0.15 - 0.50)
Protein (Total)	66	69	62	63	66	g/L	(60 - 80)
Albumin	34	35	31	30	31	g/L	(35 - 50)
Globulin	32	34	31	33	35	g/L	(25 - 45)
Bilirubin (Total)	12	9	12	14	14	umol/L	(< 20)
Bilirubin (Conj.)	6	< 4	5	6	6	umol/L	(< 4)
Alkaline Phosphatase	64	67	72	77	91	U/L	(30 - 110)
Gamma-GT	51	50	75	84	97	U/L	(< 55)
Alanine Transaminase	52	73	84	103	118	U/L	(< 45)
Aspartate Transaminase	50	74	93	106	104	U/L	(< 35)
Lactate Dehydrogenase	353	496	616	701	668	U/L	(120 - 250)



Case 3

Sample Appearance	Clear	Clear	Clear	Clear	Clear		
Sodium	141	142	141	139	141	mmol/L	(135 - 145)
Potassium	4.1	4.3	4.0	3.9	4.0	mmol/L	(3.5 - 5.2)
Chloride	105	106	106	103	106	mmol/L	(95 - 110)
Bicarbonate	26	24	22	23	23	mmol/L	(22 - 32)
Anion Gap	10	13	12	13	12	mmol/L	(4 - 13)
Glucose	5.1	4.0	5.3	7.0	4.9	mmol/L (Fasting	(3.0 - 7.8) 3.0 - 6.0)
Urea	3.1	3.2	3.3	3.5	3.9	mmol/L	(2.1 - 7.1)
Creatinine	70	66	66	64	64	umol/L	(60 - 110)
Urea/Creat	44	49	50	55	61		(40 - 100)
GFR (estimated)	>90	>90	>90	>90	>90	mL/min/1.73m^2	(> 90)
Urate	0.25	0.30	0.21	0.24	0.22	mmol/L	(0.15 - 0.50)
Protein (Total)	66	69	62	63	66	g/L	(60 - 80)
Albumin	34	35	31	30	31	g/L	(35 - 50)
Globulin	32	34	31	33	35	g/L	(25 - 45)
Bilirubin (Total)	12	9	12	14	14	umol/L	(< 20)
Bilirubin (Conj.)	6	< 4	5	6	6	umol/L	(< 4)
Alkaline Phosphatase	64	67	72	77	91	U/L	(30 - 110)
Gamma-GT	51	50	75	84	97	U/L	(< 55)
Alanine Transaminase	52	73	84	103	118	U/L	(< 45)
Aspartate Transaminase	50	74	93	106	104	U/L	(< 35)
Lactate Dehydrogenase	353	496	616	701	668	U/L	(120 - 250)



Immunotherapy Question 3

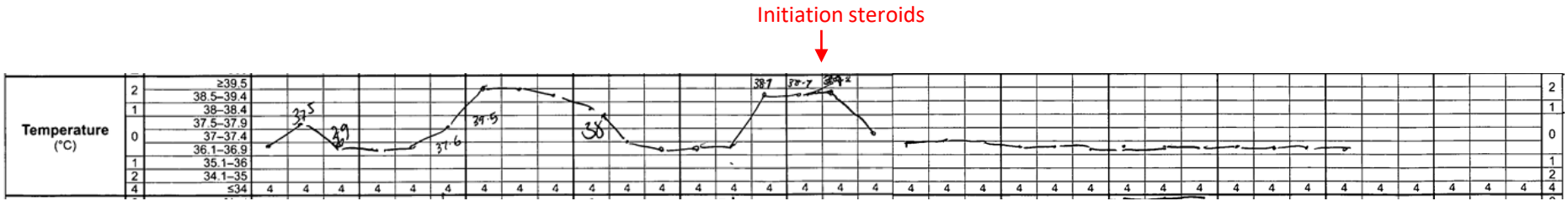
What next?

- ID consult
- Escalate antibiotics
- Stop antibiotics and reculture
- Start steroids
- CT head/CAP

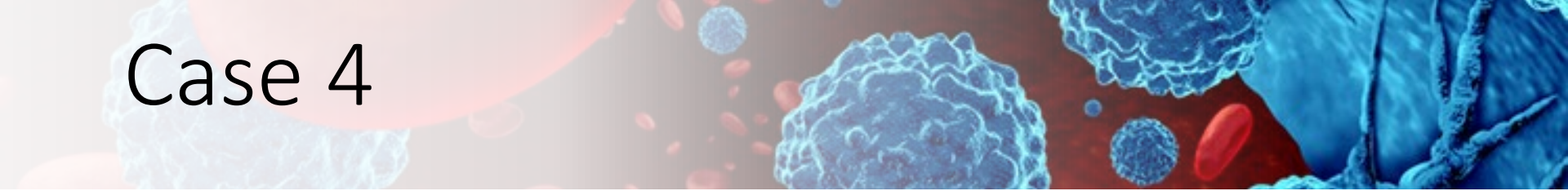
Case 3

- Antibiotics were stopped
- Prednisone initiated 1mg/kg with rapid resolution of symptoms

- Presented to outpatient follow-up with fever and rigors having forgotten prednisone that morning
- Mycophenolate added to facilitate steroid wean



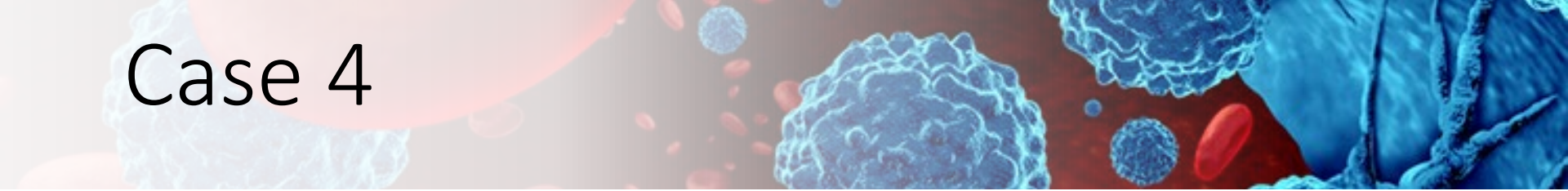
Case 4



43M

- Metastatic melanoma – brain, lymph node and lung metastases, BRAF V600E mutation
- Resection of left occipital brain metastasis with post-op SBRT
- Unable to tolerate first line treatment with BRAF/MEK inhibitor
- Treated with ipilimumab/nivolumab from April 2020 → maintenance nivolumab from August 2020

Case 4



- Treatment complicated by:
  - Arthralgias and rash - responded to low dose steroid
  - Hypophysitis
- A number of brain metastases treated with gamma-knife radiotherapy over course of 2020-2021

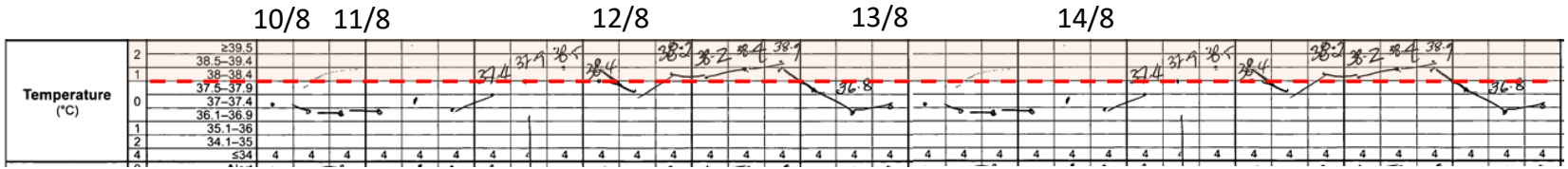
- Re-induction with ipilimumab/nivolumab May 2022 due to progression with subcut lesions and further brain metastases
  (*remains on prednisone 10mg)*

Case 4

- Presented post C4 with fevers, myalgias/arthralgias, slight exacerbation of chronic cough
- Commenced on broad spectrum antibiotics
- Multiple BC negative, urine clear, CXR normal, respiratory viral panel negative
- Remained febrile after 5 days IVABs *(incl piptaz, azithromycin, vancomycin)*

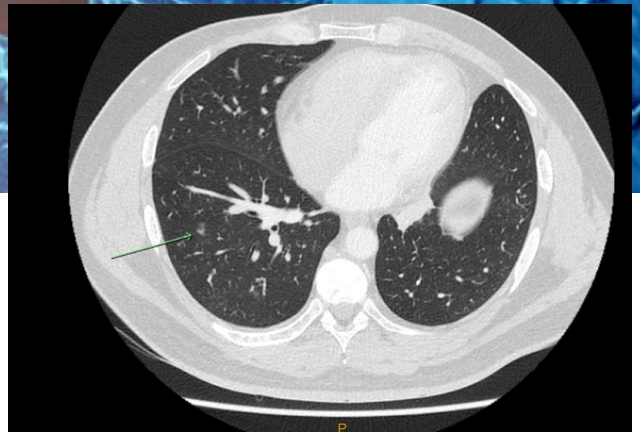
Time Collected	13:45	06:50
Date Collected	10-Aug-22	11-Aug-22
Time Registered	14:05	07:18
Date Registered	10-Aug-22	11-Aug-22
Year Collected	2022	2022
Req. Officer	ROTS~RBWH	PATU1~RBWH
Consultant	ROTS~RBWH	THAD1_2~RBWH
Lab No	2220956879	2222327190
Specimen Type	Blood	Blood

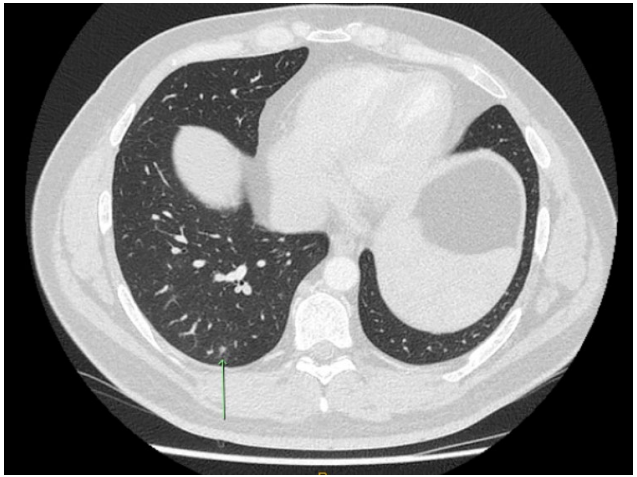
Haemoglobin	146	125
White Cell Count	8.1	6.3
Platelets	146	129
Haematocrit	0.44	0.38
MCH	29.1	28.9
Red Cell Count	5.02	4.33
MCV	88	89
Neutrophils	6.28	4.59
Lymphocytes	0.84	0.91
Monocytes	0.74	0.63
Eosinophils	0.16	0.18
Basophils	0.03	0.02
ESR		20
CRP		132



Case 4

- CT BCAP: multiple small opacities RUL, nil other new findings
- 1/3 urine MCS cultured *S. aureus*
- Treated with total 2/52 IVABs
- Admission complicated by COVID infection (5/7 Paxlovid); *C difficile* diarrhoea (PO vancomycin)
- Discharged home after 2/52



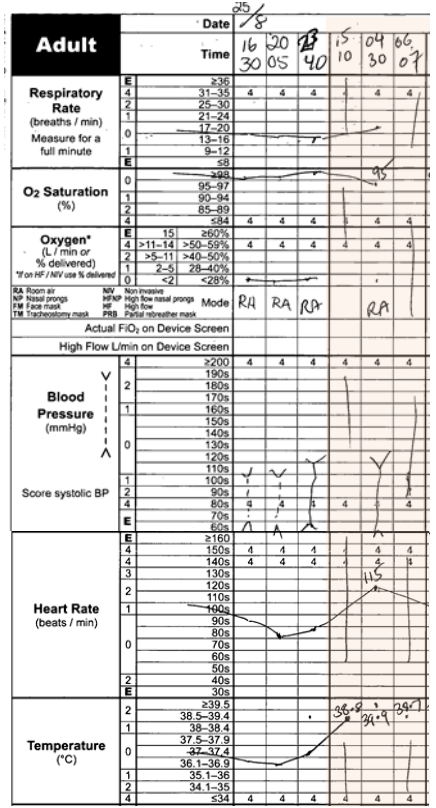


Case 4

- Readmitted 24 hours later with further fevers and SIRS response

Time Collected	18:11	07:55	17:12	07:15	07:57	**10:15**		
Date Collected	27-Aug-22	28-Aug-22	28-Aug-22	29-Aug-22	30-Aug-22	**31-Aug-22**		
Time Registered	18:59	09:26	18:11	08:29	09:12	**11:26**		
Date Registered	27-Aug-22	28-Aug-22	28-Aug-22	29-Aug-22	30-Aug-22	**31-Aug-22**		
Year Collected	2022	2022	2022	2022	2022	**2022**		
Req. Officer	EASM_2~RBWH	EASM_2~RBWH	POSJ1~RBWH	HARH11~RBWH	EASM_2~RBWH	**EASM_2~RBWH**		
Consultant	EASM_2~RBWH	EASM_2~RBWH	EASM_2~RBWH	EASM_2~RBWH	EASM_2~RBWH	**EASM_2~RBWH**		
Lab No	2225266755	2225284266	2225285126	2170948026	2222325439	**2225288826**		
Specimen Type	Blood	Blood	Blood	Blood	Blood	**Blood**	**Units**	**Ref Range**
Haemoglobin	100	101	95	100	89	88	g/L	(135 - 180)
White Cell Count	3.2	2.6	2.5	2.6	4.6	7.0	x 10^9/L	(4.0 - 11.0)
Platelets	58	30	21	9	37	85	x 10^9/L	(140 - 400)
Haematocrit	0.31	0.32	0.30	0.31	0.28	0.28		(0.39 - 0.52)
MCH	27.9	27.5	27.8	28.2	27.5	27.5	pg	(27.0 - 33.0)
Red Cell Count	3.59	3.67	3.42	3.55	3.24	3.20	x 10^{12}/L	(4.50 - 6.00)
MCV	87	87	88	89	87	87	fL	(80 - 100)
Neutrophils	2.78	2.07	2.17	2.10	3.79	5.74	x 10^9/L	(2.00 - 8.00)
Lymphocytes	0.24	0.23	0.15	0.27	0.66	0.88	x 10^9/L	(1.00 - 4.00)
Monocytes	0.10	0.10	0.10	0.17	0.17	0.35	x 10^9/L	(0.10 - 1.00)
Eosinophils	0.10	0.15	0.05	0.07	0.01	0.00	x 10^9/L	(< 0.60)
Basophils	0.01	0.01	0.00	0.00	0.00	0.01	x 10^9/L	(< 0.20)
ESR				40			mm/Hr	(< 10)

- Normal renal function, no neurological symptoms, no GI symptoms, rash or bruising



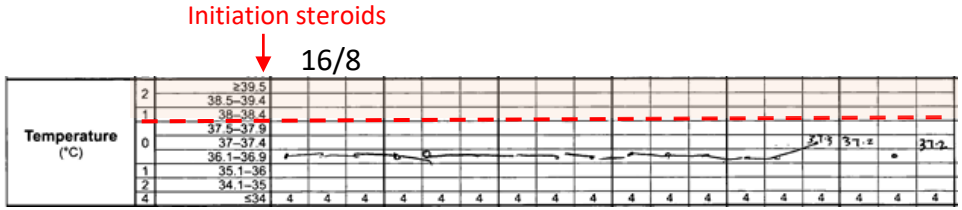
Case 4

Platelet Autoantibodies

SPECIMEN : Blood

Platelet Autoantibodies: (PIFT Method) POSITIVE

- Haematology input – consistent with ITP
  - Started on 1mg/kg prednisone
  - IVIg x 2 doses
  - Platelets normalised
- Discharged after 2/52 on oral prednisone 75mg



Case 4

- Represented within 24 hours with further fevers, hypotension requiring inotrope support
- Again reinitiated broad spectrum Abs (piptaz, azithromycin, vancomycin)
- Cultures all negative
- Arthralgias but no other symptoms
- CT CAP no cause
- Ongoing fevers despite antibiotics

Anti Nuclear Antibodies

Antinuclear Antibody	POS	titre	
Speckled	40	titre	(< 40)

Anti dsDNA

dsDNA (RIA)	5	IU/mL	(< 7)

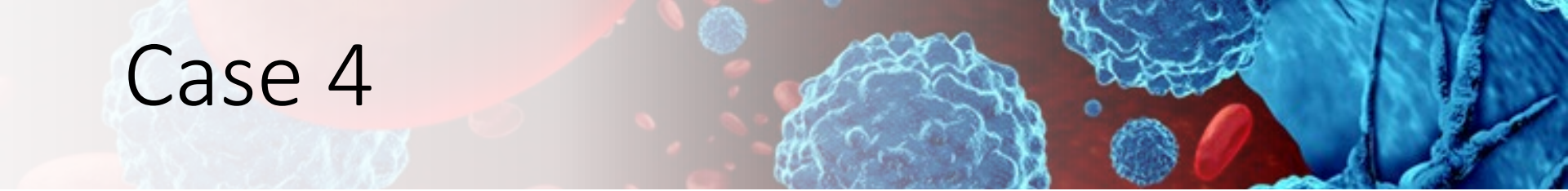
Rheum. Factor (Neph)	<20	IU/mL	(< 20)
Anti-Cardiolipin (IgG) Abs (aCL-IgG)	9	CU	(< 20)

Anti-Neutrophil Cytoplasmic Antibodies (ANCA)

C-ANCA	Negative
P-ANCA	Negative
Anti-GBM (Quant)	4

Sample Appearance	Clear		
Sample Integrity			
Iron	< 2	umol/L	(12 - 31)
Transferrin	1.3	g/L	(2.0 - 3.6)
Transferrin Saturation	< 6	%	(15 - 45)
Ferritin	3790	ug/L	(45 - 715)

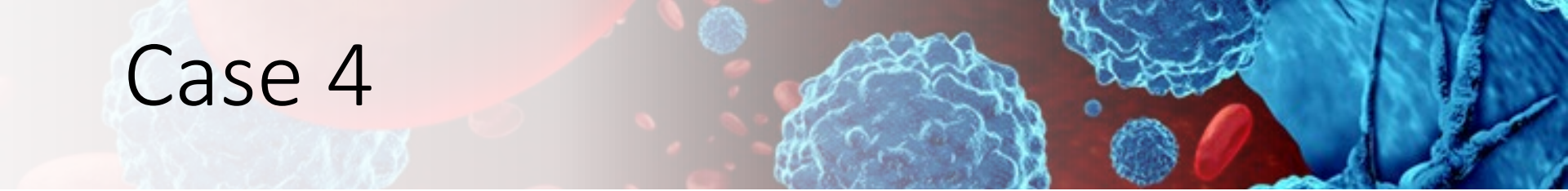
Case 4



- Antibiotics ceased
- Immunology consult
- Mycophenolate 500mg bd added with plan to uptitrate and wean steroids
- Successfully discharged home

- 3 months later imaging showed progression with new cervical lymph node disease
- Rechallenged with dabrafenib + trametinib with reduced dose
  Remains on prednisone 17.5mg and weaning + MMF 1g bd

Case 4



- Presented 1mo after reinitiating treatment with:
  - Fever 39.1°C
  - Nausea
  - Haemodynamically stable
  - Prednisone dose now down to 8mg; remains on MMF 1g bd

Immunotherapy – Question 4

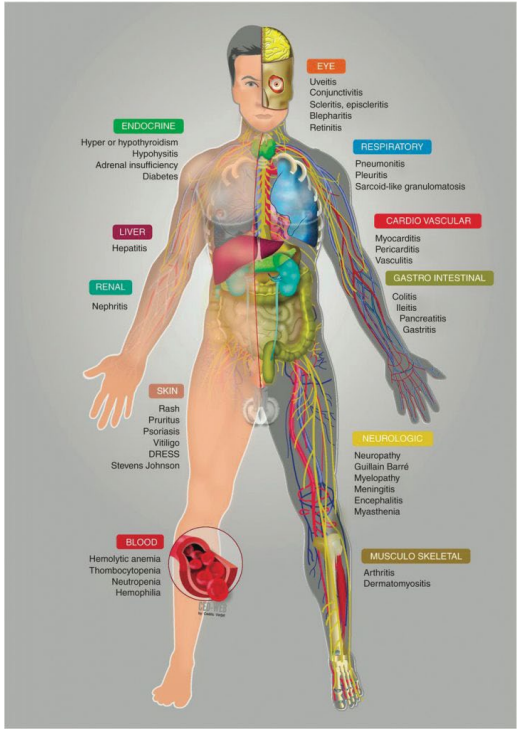
What next?

- Septic screen
- Start antibiotics
- Stop dabrafenib + trametinib
- Double prednisone dose to 15mg
- Reinitiate prednisone 1mg/kg
- Fungal cultures + induced sputum for PJP

Fever and systemic inflammatory syndromes

- Fever and systemic inflammatory complications of immunotherapy can occur including cytokine release syndrome (CRS) and haemophagocytic lymphohistiocytosis (HLH)
- Requires usual workup to exclude infectious causes
- Limited data to guide management but can be steroid responsive

Summary



Champiat et al, Ann Oncol, 2016