Government of Western Australia
Department of Health

FIONA STANLEY hospital

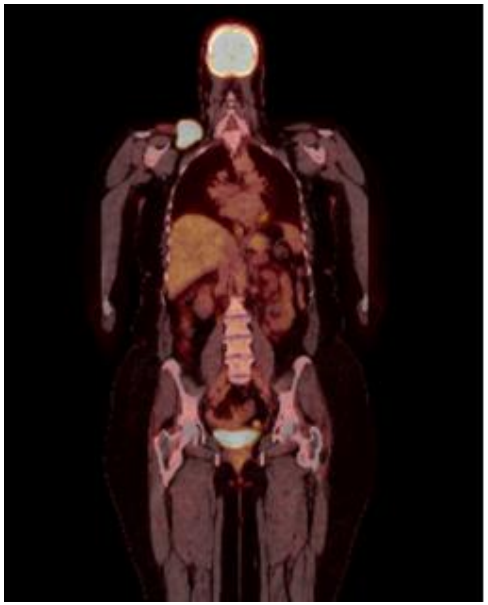
An unusual presentation of diabetes

Lydia Lamb

Endocrinology Registrar

History

- 54yo female from Port Hedland
- Metastatic melanoma diagnosed Dec 2016
  - Right supraclavicular mass 5cm, left 8th rib bony metastasis, pulmonary nodules
- PMHx
  - Gastro-oesophageal reflux disease
  - Multinodular goitre
- FHx
  - Nil significant



History

- Enrolled in clinical trial Jan 2017
  - Treatment with ipilimumab and nivolumab Jan-March 2017, three cycles
- Transient thyroid dysfunction

	22/9/16	27/1/17	20/2/17	21/4/17	19/6/17
TSH	0.44	**0.18**	**<0.01**	**0.08**	1.70
T4	14	14		14	12
T3	4.7	4.4		4.2	4.1

- Complicated by Grade 3 colitis requiring treatment with IV methylprednisolone followed by high dose prednisolone tapered and ceased June 2017
- Complete response to therapy

History

- Initial review via telehealth August 2017
- Symptoms of polyuria, polydipsia, lethargy, oral thrush and unintentional weight loss 96kg → 75.5kg
- Treatment with metformin and lantus commenced by G.P.
- Blood glucose levels
  - Fasting 10-12mmol/L
  - Post prandial 20mmol/L

Investigations

	13/3/17	21/4/17	19/6/17	27/7/17	15/9/2017
HbA1c				**10.5%**	**11.0%**
Fasting glucose	4.3mmol/L			**14.9mmol/L**	
Fasting c-peptide				0.29 (0.20-0.90nmol/L)	
Insulin				3 (<12mU/L)	
GAD antibodies					<10 (<10U/mL)
IA2 antibodies					<10 (<10U/mL)
ZNT8 antibodies					<15 (<15U/mL)
Lipase		**95 (<60 U/L)**	**932 (<60 U/L)**		
Amylase			**127 (<100 U/L)**		

Immunotherapy Jan - March

Treatment with glucocorticoids for colitis ceased June

Symptoms of hyperglycaemia

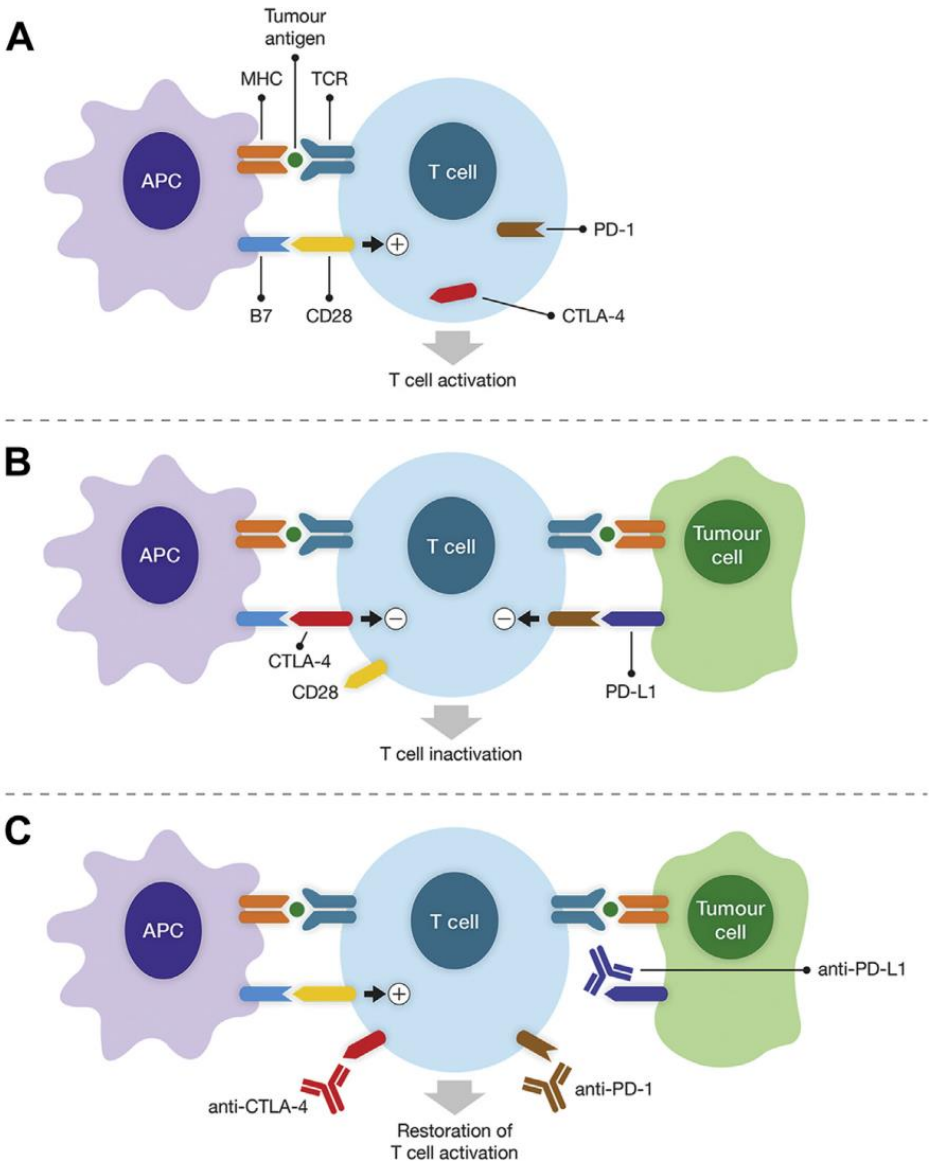
Aetiology of diabetes?

- ? Type 1 Diabetes
  - Low normal c-peptide
  - Negative antibodies
- ? Type 2 Diabetes
- ? Steroid induced diabetes

- ? Due to immunotherapy

Immune checkpoint inhibitors

T cell activation requires co-stimulation via B7 binding CD28



CTLA 4 and PD1 are **inhibitory receptors** on the T cell to regulate immune response

CTLA4 binds to B7 with higher affinity than CD 28

PD1 binds PD-L1 expressed by tumour cells

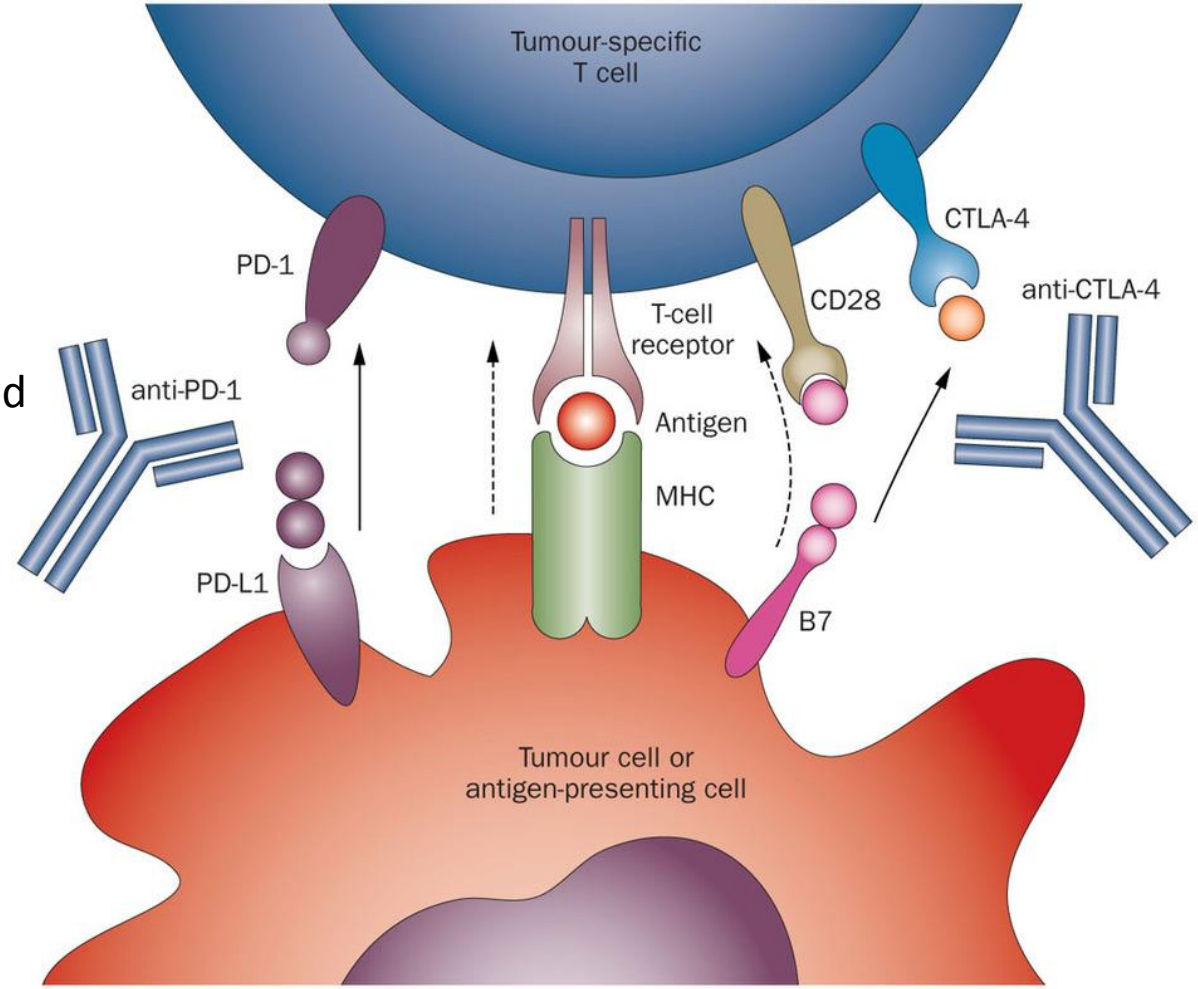
→ **T cell inactivation**

ICIs block inhibitory signals

→ Restoration of T cell activation

Immune checkpoint inhibitors

Co-inhibitory pathway 2:
Antibodies directed against <u>PD-1</u>
Nivolumab
Pembrolizumab



Co-inhibitory pathway 1:
Antibodies directed against <u>CTLA-4</u>
Ipilimumab
Tremilimumab

Adverse effects of check point inhibitors

2 Incidence of immune-related adverse events associated with immune checkpoint inhibitors[7-14]

Immune-related adverse event	Ipilimumab[7-9]		Ipilimumab–nivolumab[8,9]		Nivolumab[9-12]		Pembrolizumab[7,13,14]	
	All grades	Grade 3 or 4	All grades	Grade 3 or 4	All grades	Grade 3 or 4	All grades	Grade 3 or 4
Dermatological								
Rash	15–33%	0–2%	28–41%	3–5%	4–26%	0–1%	10–15%	< 1%
Pruritus	25–35%	0–2%	33–35%	1–2%	6–19%	0–1%	11–14%	0
Vitiligo	2–9%	0	7–11%	0	7–11%	0	9–11%	0
Gastrointestinal								
Diarrhoea	23–37%	3–11%	44–45%	9–11%	8–19%	0–3%	8–17%	1–3%
Colitis	8–13%	7–9%	12–23%	7–8%	1%	< 1%	1–4%	1–3%
Hepatitis	1–4%	0–2%	22–30%	11–19%	1–6%	0–3%	1–3%	0–2%
Endocrine								
Hypothyroidism	2–15%	0	15–16%	< 1%	4–9%	0	8–10%	< 1%
Hyperthyroidism	1–2%	< 1%	10%	1%	2–4%	< 1%	2–4%	0
Hypophysitis	2–7%	2–4%	8–12%	2%	< 1%	< 1%	< 1%	< 1%
Pneumonitis	0–4%	0–2%	6–11%	1–2%	1–5%	0–3%	0–5%	0–2%
Rheumatological								
Myalgia	2–13%	< 1%	10%	0	2–6%	0–1%	2–7%	< 1%
Arthralgia	5–9%	< 1%	11%	< 1%	5–8%	0	9–12%	< 1%
Arthritis	0	0	nr	nr	nr	nr	0–2%	0
Neurological								
Headache	2–8%	< 1%	3–10%	0–1%	4–7%	0	2–3%	0
Paraesthesia	1%	< 1%	nr	nr	2%	0	< 1%	0
Renal	0–3%	< 1%	3–6%	1–2%	1–2%	< 1%	< 1%	0
Haematological								
Anaemia	< 1%	< 1%	nr	nr	2–4%	1%	1–3%	0–1%

nr = not recorded. ◆

Bourke et al. MJA 2016

Endocrinopathies

- Occur in up to 15% of patients with CTLA4 inhibition
- Occur in up to 10% of patients with anti-PD1 therapy
- Thyroid dysfunction and hypophysitis most common
- Rare cases of adrenal insufficiency and T1DM
- May be irreversible and require long term hormone replacement (unlike other immune related adverse events)

Bourke et al. 2016. MJA
Spain et al. 2016. Cancer Treatment Reviews
Friedman et al. 2016. JAMA Oncology
Heinzerling et al. 2017. Co Oncology

Diabetes and immune checkpoint inhibitors

- Autoimmune diabetes is an emerging complication of immune checkpoint inhibitors
- Previously unrecognised in clinical trials
- Variable time to onset of symptoms from 1 week up to 12 months following therapy
- Varying severity of clinical presentation
  - Cases of severe DKA reported
- Antibodies may be positive or negative

ICI	Disease	Other treatment	Time to onset	HbA1c	DKA	C-peptide	Antibodies	High risk HLA genotype	Reference
Nivolumab	Melanoma	Ipilimumab	5 months	6.9%	+	<0.1	None	A02:01, DRB1*04	Hughes
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Nivolumab	Hodgkins lymphoma	Chemo	10 weeks	7.3%	-	Low	None	B*4002	Munakata
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Pembrolizumab	Melanoma	None	<1 month	7.4%	-	0.5	None	DR4	Hughes
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Nivolumab	Melanoma	Ipilimumab	6 weeks	NR	NR	NR	NR	NR	Hoffman
Nivolumab	Melanoma	ipilimumab	3 weeks	NR	+	Low	Anti GAD	NR	Hoffman
Nivolumab	Melanoma	Chemo	7 months	8.9%	+	0.08	None	NR	Teramoto
Nivolumab	Melanoma	None	4 months	7.3%	+	UD	None	DRB1 11:01 13:02:01, DQB1 03:01:01 06:04:01	Miyoshi
Nivolumab	Melanoma	Chemo	12 months	7.0%	-	1.00	None	DRB1*04:05, DQB1*04:01	Okamoto
Nivolumab	Hodgkins lymphoma	Chemo	10 weeks	7.3%	-	Low	None	B*4002	Munakata
Nivolumab	SCC	None	12 weeks	7.4%	+	0.32	Anti GAD	DRB1*08:11, DQB1*03:04, DQA1*04,05	Kapke
Pembrolizumab	Melanoma	None	<1 month	7.4%	-	0.5	None	DR4	Hughes
Pembrolizumab	Melanoma	Ipilimumab	3 cycles	NR	+	NR	Anti GAD	DRB1*04, DQB1*03:02	Martin-Liberal
Pembrolizumab	Melanoma	Ipilimumab	After 2nd injection	6.85%	+	UD	None	None	Gaudy
Pembrolizumab	Melanoma	Ipilimumab	3 weeks	NR	-	Low	Anti GAD, Anti IA2	NR	Hoffman
Pembrolizumab	Melanoma	Ipilimumab	51 weeks	9.7%	-	2.4	Anti GAD	NR	Hansen
Pembrolizumab	NSCLC	Chemo	After 2nd injection	5.8%	-	<0.1	Anti GAD, Anti IA2	NR	Chae
PD-1	Lung	NR	7 weeks	9.4%	+	<0.1	None	DR3-DQ2, DR4-DQ8	Mellati
PD-L1 AB	SCC	NR	15 weeks	9.8%	+	0.3	None	NR	Mellati
Atezolizumab	Urothelial Ca	Chemo	24 weeks	7.8%	-	0.02	Anti GAD	DRB1*03, DRB1*04, DQB1*02, DQB1*03, DQA1*03, DAQ1*05	Kapke

ICI	Disease	Other treatment	Time to onset	HbA1c	DKA	C-peptide	Antibodies	High risk HLA genotype	Reference
Nivolumab	Melanoma	Ipilimumab	5 months	6.9%	+	<0.1	None	A02:01, DRB1*04	Hughes
Nivolumab	NSCLC	None	<1 month	7.7%	+	<0.1	Anti GAD	A02:01, DRB1*04	Hughes
Nivolumab	RCC	Chemo	4 months	8.2%	-	1.3	Anti GAD, Anti-ICA512, Anti IA2	A02:01, DRB1*04	Hughes
Nivolumab	SLC	Chemo	1 week	9.7%	+	<0.1	Anti GAD	A02:01	Hughes
Nivolumab	Melanoma	None	6 weeks	NR	-	<0.1	None	NR	Hoffman
Nivolumab	Melanoma	Ipilimumab	6 weeks	NR	NR	NR	NR	NR	Hoffman
Nivolumab	Melanoma	ipilimumab	3 weeks	NR	+	Low	Anti GAD	NR	Hoffman
Nivolumab	Melanoma	Chemo	7 months	8.9%	+	0.08	None	NR	Teramoto
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Pembrolizumab	Melanoma	None	<1 month	7.4%	-	0.5	None	DR4	Hughes
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Pembrolizumab	Melanoma	Ipilimumab	After 2nd injection	6.85%	+	UD	None	None	Gaudy
Pembrolizumab	Melanoma	Ipilimumab	3 weeks	NR	-	Low	Anti GAD, Anti IA2	NR	Hoffman
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Atezolizumab	Urothelial Ca	Chemo	24 weeks	7.8%	-	0.02	Anti GAD	DRB1*03, DRB1*04, DQB1*02, DQB1*03, DQA1*03, DAQ1*05	Kapke

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Nivolumab	Melanoma	Ipilimumab	6 weeks	NR	NR	NR	NR	NR	Hoffman
Nivolumab	Melanoma	ipilimumab	3 weeks	NR	+	Low	Anti GAD	NR	Hoffman
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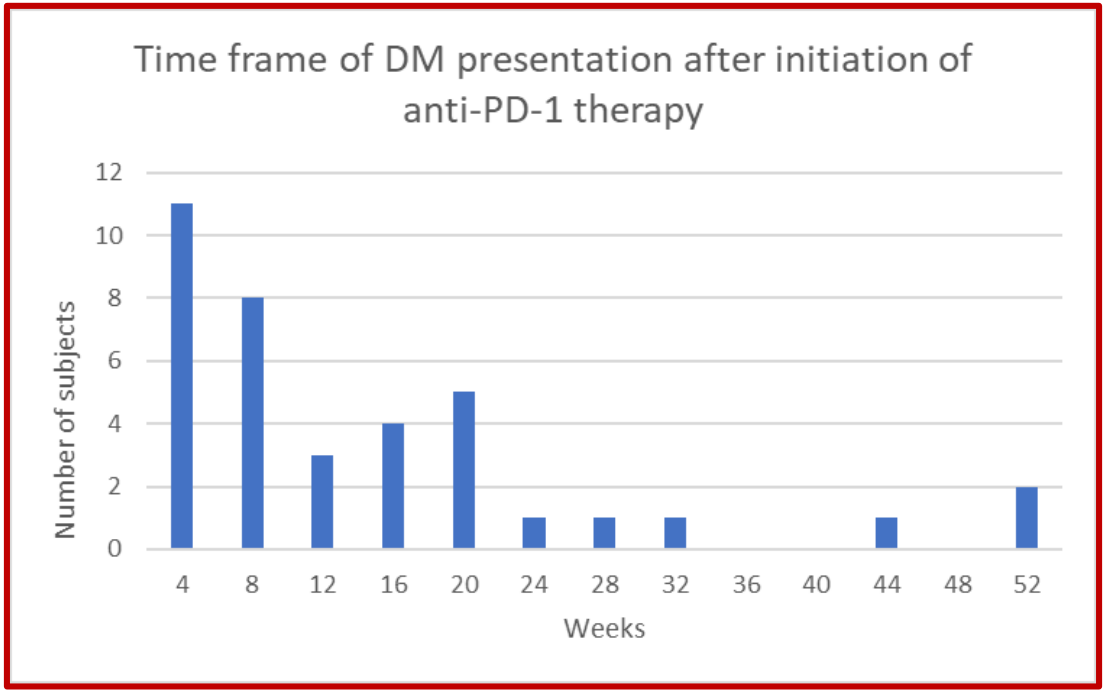
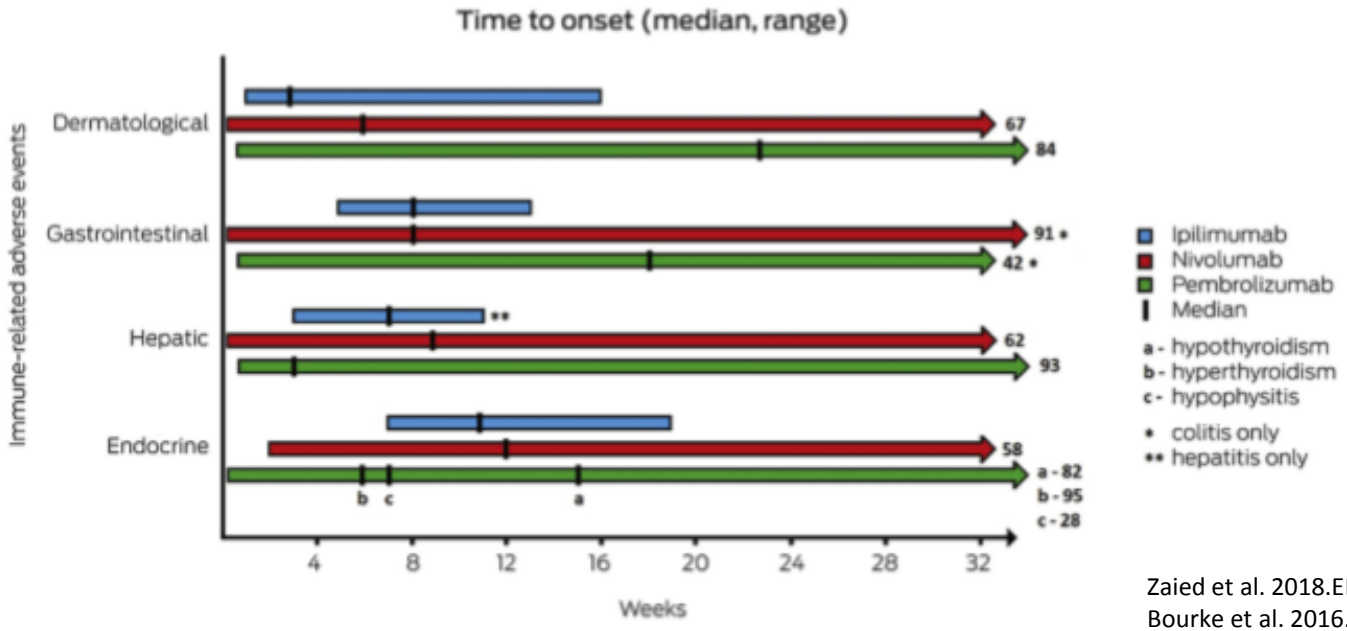
Time to onset of adverse events



3 Time to onset of immune-related adverse events with different immune checkpoint inhibitors



Zaied et al. 2018.EDM Case reports.
Bourke et al. 2016. MJA

Pathogenesis of autoimmune diabetes secondary to ICIs: PD-1 pathway

- PD-1 pathway is an inhibitory pathway in the development of T1DM

- Studies in mice
  - PD1 blockade can promote T1DM
  - No correlation between autoantibody levels and development of diabetes
- Reduced activity of PD1 is common to conventional autoimmune T1DM and anti-PD1 therapy related diabetes
  - Reduction in PD1 expression on T cells has been demonstrated in T1DM compared with other types of DM
  - Lower expression of PD-1 on T cells causes inappropriate activation of these cells in T1DM
- Anti-PD1 therapy may cause inappropriate activation of autoreactive T cells resulting in autoimmune responses against pancreatic β cells
  - Unclear whether activation of autoreactive T cells is due to decreased Treg activity or direct activation through removal of inhibitory PD1 pathway.

Ansari et al. 2003. J Exp Med
Kochupurakkal et al. 2014. PLoS One
Fujisawa et al. 2015. Clin Exp Immunol
Okamoto et al. 2016. J Diabetes Investig
Kanke et al. 2017. Case reports in oncology

Pathogenesis of autoimmune diabetes secondary to ICIs

- Unclear role of CTLA-4 inhibition in the development of diabetes
  - CTLA-4 inhibitors well described in association with various immune-related effects but there are only two reports of T1DM with CTLA-4 inhibition alone
  - CTLA-4 blockade in mice induces T1DM in neonates but not adult mice
  - Low CTLA-4 levels have been demonstrated in patients with fulminant T1DM
  - Reduction of CTLA-4 in CD4+ T helper cells may promote an immune reaction causing accelerated beta cell destruction

- Reported cases have shown high risk HLA genotypes
  - HLA could be involved with autoimmune diabetes developing in at risk patients who are given anti-PD1 drugs

Chae et al. 2017. Cancer Immunol Immunother
Ikegami et al. 2016. Diabetol Int
Zaied et al. 2018. EDM Case Reports
Haseda et al. 2011 Immunology Letters

Predicting autoimmune diabetes in patients on ICIs

- Review of clinical trial data and case reports
  - No risk factors identified
- HLA haplotypes could be a biomarker predictive of PD1 therapy related diabetes
- Elevated pancreatic enzymes may precede the onset of diabetes in patients treated with ICIs

Chan et al. 2017. Journal of pharmacy practice and research
Munakata et al. 2016. Int J Haematol

Patient summary

- 54yo female treated with ipilimumab and nivolumab
- Subsequent symptomatic hyperglycaemia significant unintentional weight loss
- Low c-peptide, negative antibodies
- Ongoing insulin requirement
- Diagnosis: Anti PD-1 therapy related diabetes mellitus

Patient summary

Immune-related adverse events

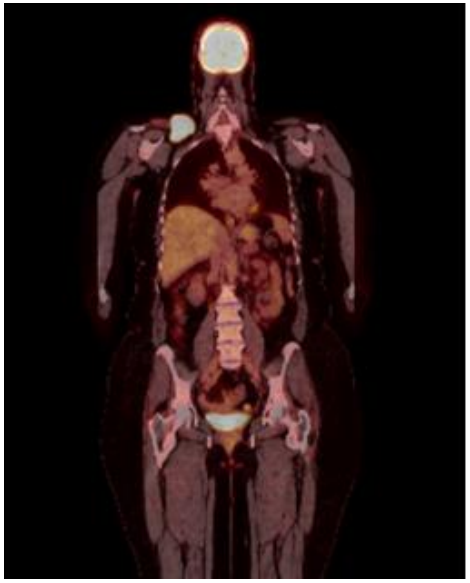
?Thyroiditis **Colitis** **Diabetes Mellitus** **Vitiligo**

1 2 3 4 5 6 7 8 9 10 11 12

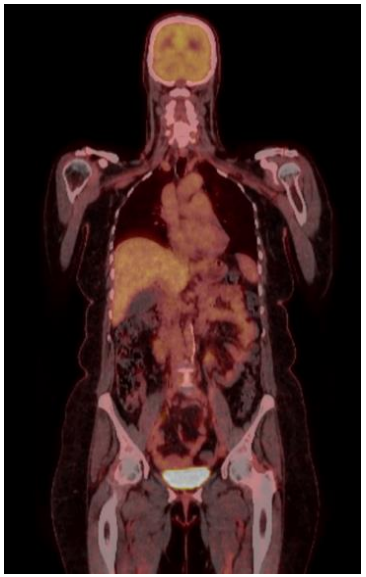
Time to onset (months)

Complete response to therapy

Jan 2017



Jan 2018



Conclusions

- Multiple endocrinopathies are known to occur as a result of immune checkpoint inhibitor therapy
- Autoimmune diabetes caused by ICIs is an emerging complication and not well described
- Patients should be screened for diabetes if treated with ICIs and diabetes should be considered in unwell patients on this treatment.
- Further research needed to identify potential risk factors/biomarkers for autoimmune diabetes as a result of immunotherapy

Acknowledgements

- Department of Endocrinology and Department of Oncology, Fiona Stanley Hospital
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  - Ashley Makepeace
  - Adnan Khattak