Checkpoint inhibitors and autoimmune endocrinopathies

FDA

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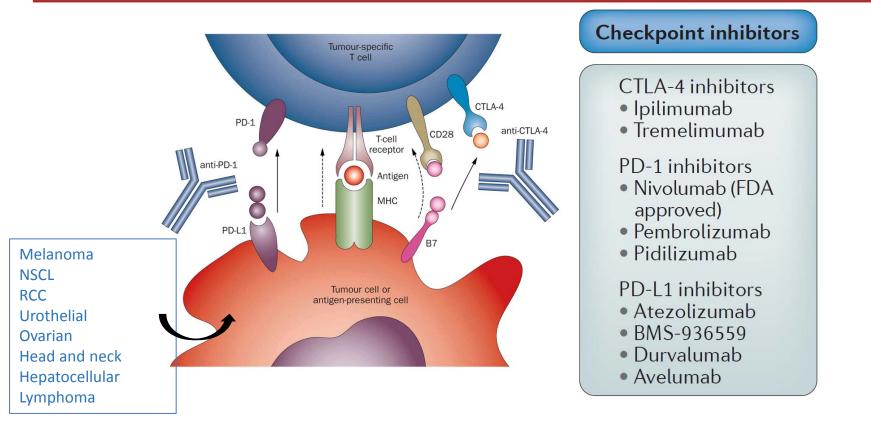
Yale University



Disclosures

- I have a patent application for a method to measure beta cell death in vivo
- I have consulted for Pfizer, BMS, Merck, Roche, Lilly, and Tiziana concerning treatment for Type 1 diabetes.
- I have no disclosures related to the material in this presentation

Immunotherapies targeting checkpoint inhibitors



This same mechanism of action would be expected to lead to immune related adverse events. Endocrine organs: pituitary, thyroid, adrenal, and β cells are prime targets for (auto)immune responses.

Cancer immunotherapy immune checkpoint blockade and associated endocrinopathies

David J. Byun^{1,2}, Jedd D. Wolchok^{1,2}, Lynne M. Rosenberg² and Monica Girotra^{1,2}

Table 1 Endocrine IRAEs in patients treated with ipilimumab									
Study	Cohort		Endocrinopathy						
	Age (range)	n	Hypophysitis	2° or other adrenal insufficiencies	2°or other hypothyroidisms	1° hypothyroidism	Thyroiditis	1° adrenal insufficiency	
Total ^{§§}		2,938	184/2,017 (9.1%)	37/608 ^Ⅲ (6.1%)	42/555 ^Ⅲ (7.6%)	23/410 (5.6%)	9/283 (3.2%)	2/256 (0.8%)	

Table 3 | Endocrine IRAEs with PD1 and PDL1 antibodies

Study C		Cohort		Endocrinopathy					
		Age (range)	n	Hypothyroidism	Hyperthyroidism	Adrenal insufficiency	Hypophysitis	Other thyroid*	T1DM
	Total#		2,702	160/2,573 (5.9%)	71/2,153 (3.3%)	2/117 (1.7%)	10/1,658 (0.6%)	3/224 (1.3%)	3/766 (0.4%)

Totals with ipilimumab: 32.4%

Totals with PD-1 and PD-L1: 13.2%

Overall rates from Barroso-Sousa et al (2017):

Hypothyroidism: 6.6% (3.8-13.2%) Hyperthyroidism: 2.9% (0.6-8.0% Hypophysitis: 0.5% (0.4-6.4%) 1° Adrenal insuff and IDD: 0.7% and 0.2%

*There have been > 15 case reports of CPI induced diabetes

Incidence of Endocrine Dysfunction Following the Use of Different Immune Checkpoint Inhibitor Regimens A Systematic Review and Meta-analysis

Romualdo Barroso-Sousa, MD, PhD; William T. Barry, PhD; Ana C. Garrido-Castro, MD; F. Stephen Hodi, MD; Le Min, MD; Ian E. Krop, MD, PhD; Sara M. Tolaney, MD, MPH (DFCI)

Hypothyroidism

	Treated	Incidence Rate	
Source	Patients, No. ^a	(95% CI)	1
PD-L1			
Fehrenbacher et al, 14 2016	142	5.6 (2.5-10.8)	HH-1
NCT01375842	558	3.8 (2.3-5.7)	H
Rosenberg et al, ¹⁵ 2016	310	0.0 (0.0-1.2)	
RE MODEL			4
PD-1			
Hamanishi et al, ¹⁶ 2015	20	40.0 (19.1-63.9)	
Muro et al, ¹⁷ 2016	39	12.8 (4.3-27.4)	⊨ ∎−−−
Robert et al, ¹⁸ 2015	555	9.4 (7.1-12.1)) i i
Larkin et al, ¹⁹ 2015	313	8.6 (5.8-12.3)	i=-1
Herbst et al, ²⁰ 2015	682	8.2 (6.3-10.5)	iei -
Weber et al, 21 2016	61	8.2 (2.7-18.1)	H=
Motzer et al. ²² 2015	406	8.1 (5.7-11.2)	in in the second
Ribas et al, ²³ 2015	357	7.3 (4.8-10.5)	in the second se
Garon et al. ²⁴ 2015	495	6.9 (4.8-9.5)	in the second se
Seiwert et al. ²⁵ 2016	60	6.7 (1.8-16.2)	
Patnaik et al, ²⁶ 2015	30	6.7 (0.8-22.1)	
Borghaei et al. ²⁷ 2015	287	6.6 (4.0-10.1)	
Motzer et al, ²⁸ 2015	167	6.0 (2.9-10.7)	
Motzer et al, 20 2015 Gettinger et al, 29 2016	52	5.8 (1.2-15.9)	
Gettinger et al. ²⁹ 2016 Weber et al. ³⁰ 2015			
	268	5.6 (3.2-9.1)	H
Robert et al, ³¹ 2015	206	4.4 (2.0-8.1)	H
Robert et al, ³² 2014	173	4.0 (1.6-8.2)	H=1
Brahmer et al, ³³ 2015	131	3.8 (1.3-8.7)	H
Nanda et al, ³⁴ 2016	32	3.1 (0.1-16.2)	
Antonia et al, ³⁵ 2016	98	3.1 (0.6-8.7)	H= H
Wolchok et al, ³⁶ 2013	33	3.0 (0.1-15.8)	H=
Rivzi et al, ³⁷ 2015	117	2.6 (0.5-7.3)	le-j
Brahmer et al, 38 2010	39	2.6 (0.1-13.5)	⊨ ∔
Topalian et al, ³⁹ 2012	296	2.4 (1.0-4.8)	H.
Nghiem et al, ⁴⁰ 2016	26	0.0 (0.0-13.2)	++++
Shimizu et al, ⁴¹ 2016	10	0.0 (0.0-30.8)	+
RE MODEL			*
CTLA-4			
Postow et al,42 2015	46	15.2 (6.3-28.9)	⊢ ∎−−1
Yamazaki et al, ⁴³ 2015	20	5.0 (0.1-24.9)	H
Larkin et al. ¹⁹ 2015	311	4.2 (2.2-7.0)	H
Robert et al. ³¹ 2015	256	2.0 (0.6-4.5)	i i
Hodi et al. ⁴⁴ 2010	131	1.5 (0.2-5.4)	H
Zimmer et al. ⁴⁵ 2015	103	1.0 (0.0-5.3)	
Zimmer et al, 46 2015	53	0.0 (0.0-6.7)	
Le et al, ⁴⁷ 2013	15	0.0 (0.0-21.8)	
Yang et al, ⁴⁸ 2007	61	0.0 (0.0-5.9)	
0'Mahony et al. ⁴⁹ 2007	11	0.0 (0.0-5.9)	1
Maki et al. ⁵⁰ 2013			
	6	0.0 (0.0-45.9)	
RE MODEL			•
Combination			
Postow et al, ⁴² 2015	94	16.0 (9.2-25.0)	⊢ •−-
Larkin et al, ¹⁹ 2015	313	15.0 (11.2-19.5)	}
Antonia et al, ³⁵ 2016	115	12.2 (6.8-19.6)	H=H
Wolchok et al, 36 2013	53	3.8 (0.5-13.0)	H=+
RE MODEL			

40	60
Incidence	%

Hyperthyroidism

	•	
	Treated	Incidence Rate
Source PD-L1	Patients, No. ^a	(95% CI)
PD-L1 NCT01375842	558	0.7 (0.2-1.8)
		· · ·
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RE MODEL		
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Zimmer et al. ⁴⁶ 2015	53	1.9 (0.0-10.1)
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Postow et al, ⁴² 2015	46	0.0 (0.0-7.7)
Zimmer et al. ⁴⁵ 2015	103	0.0 (0.0-3.5)
Yamazaki et al, ⁴³ 2015	20	0.0 (0.0-16.8)
Le et al. ⁴⁷ 2013	15	0.0 (0.0-10.8)
Le et al, 4 2013 Hodi et al, 44 2010	131	0.0 (0.0-21.8)
Yang et al. ⁴⁸ 2007	61	
		0.0 (0.0-5.9)
O'Mahony et al,49 2007	11	0.0 (0.0-28.5)
Maki et al, ⁵⁰ 2013	6	0.0 (0.0-45.9)
RE MODEL		
Combination		
Larkin et al, ¹⁹ 2015	313	9.9 (6.8-13.8)
Antonia et al, ³⁵ 2016	115	8.7 (4.2-15.4)
Postow et al, ⁴² 2015	94	4.3 (1.2-10.5)
Wolchok et al, ³⁶ 2013	53	3.8 (0.5-13.0)
RE MODEL		

0 10 20 30 40 50

Hypophysitis

Source	Treated Patients, No. ^b	Incidence Rate (95% CI)	
PD-L1	Patients, No.*	(95% CI)	
Wolchok et al. ³⁶ 2013	33	3.0 (0.1-15.8)	
Robert et al, ³² 2014	173	1.2 (0.1-4.1)	
Larkin et al, ¹⁹ 2015	313	0.6 (0.1-2.3)	# -1
Ribas et al, ²³ 2015	357	0.6 (0.1-2.0)	H
Robert et al, ¹⁸ 2015	555	0.5 (0.1-1.6)	
Robert et al, ³¹ 2015	206	0.5 (0.0-2.7)	H -1
Weber et al, ²¹ 2016	61	0.0 (0.0-5.9)	●
RE MODEL			•
CTLA-4			
Postow et al, ⁴² 2015	46	6.5 (1.4-17.9)	⊢ ∎−−−−−1
Yamazaki et al, ⁴³ 2015	20	5.0 (0.1-24.9)	
Zimmer et al, ⁴⁵ 2015	103	3.9 (1.1-9.6)	⊢ ‡∎{
Larkin et al, ¹⁹ 2015	311	3.9 (2.0-6.6)	⊢ <mark>¦</mark> ∎1
Robert et al, ³¹ 2015	256	2.3 (0.9-5.0)	H a i≓-1
Hodi et al, ⁴⁴ 2010	131	1.5 (0.2-5.4)	⊦∎∔1
Zimmer et al, ⁴⁶ 2015	53	0.0 (0.0-6.7)	↓
RE MODEL			
Combination			
Postow et al,42 2015	94	11.7 (6.0-20.0)	-
Larkin et al, ¹⁹ 2015	313	7.7 (5.0-11.2)	
Wolchok et al, ³⁶ 2013	53	3.8 (0.5-13.0)	⊢ ∎I
RE MODEL			~
			0 5 10 15 20 25
			Incidence, %

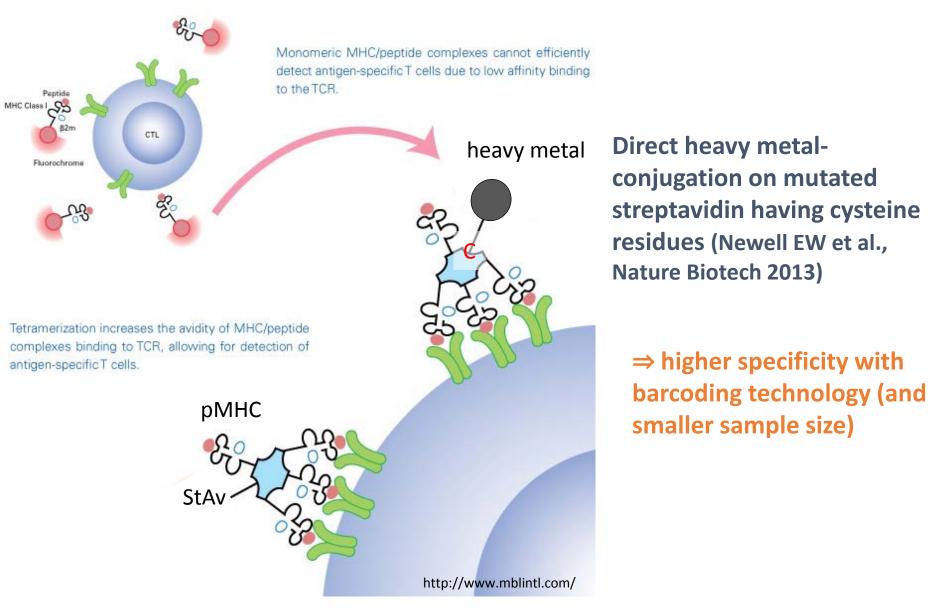
The incidence of endocrine dysfunction was higher with combo vs ipi alone. The incidence of thyroid dysfunction and hypophysitis was highest with PD-1 inhibitors and ipi respectively. Potential mechanisms of immune related adverse events

- Activation of effector T cells: Are these cells affected by checkpoint inhibitor? Are they present before treatment?
- Disturbance of normal mechanisms of tolerance? Are changes restricted to T cells?
- Tissue responses?

Features of diabetes induced with check point inhibitors

- New onset of diabetes in elderly or dramatic increase in insulin requirements in a patient with known Type 2 diabetes.
- Time to dx: mean 10 mos w/o hx of DM but 3.5 mos with a hx of DM
- 7/17 present with diabetic ketoacidosis. Avg A1c=8.09%
- BMI=28.
- Both T1D associated (HLA-DR3,4) and protective alleles identified.
- May or may not have autoantibodies
- Triggers: incr px enzymes in 6/10, imaging c/w pxitis 2/6, infection 1/17; steroids in 4/17
- 4/17 with thyroid dysfunction, 1/17 with hypophysitis
- No FH of autoimmune diabetes but frequently a family history of autoimmune diseases
- Rapidly progresses to undetectable levels of C-peptide
- It does not appear that steroids will prevent complete loss of beta cell function
- Recovery is very uncommon
- Glucose lability is consistent with absolute deficiency of insulin.

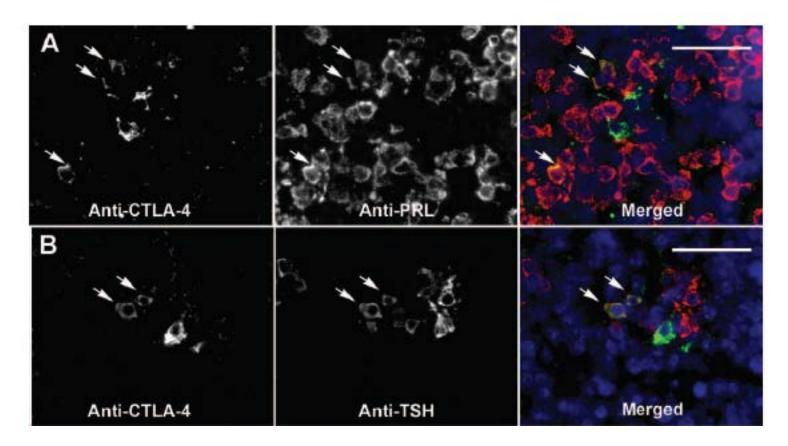
Detecting Islet Ag-Specific T Cells in CyTOF



Tissue/drug interactions?

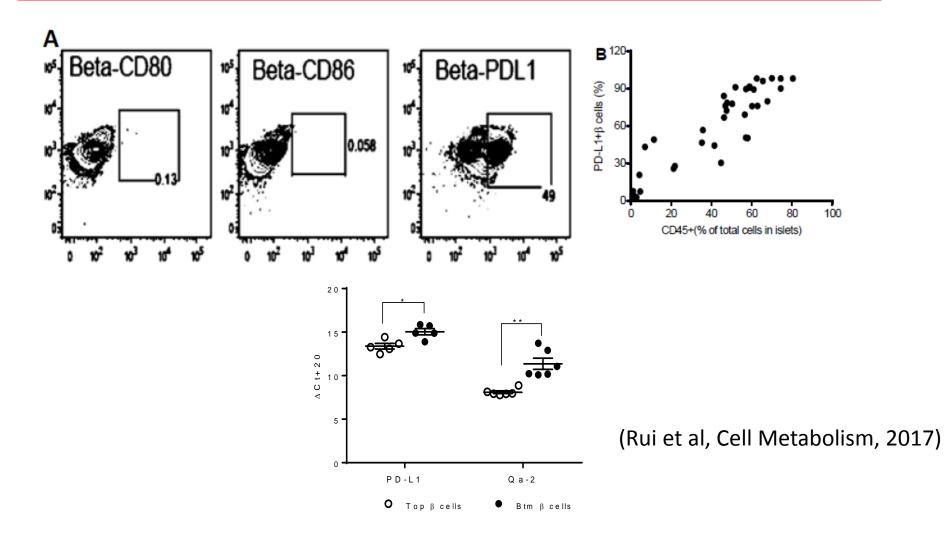
Pituitary Expression of CTLA-4 Mediates Hypophysitis Secondary to Administration of CTLA-4 Blocking Antibody

Shintaro Iwama,^{1,2} Alessandra De Remigis,¹ Margaret K. Callahan,^{3,4} Susan F. Slovin,^{3,4} Jedd D. Wolchok,^{3,4,5} Patrizio Caturegli^{1,6}*



CTLA-4 staining was found on 2±1% of PRL-secreting cells and 3±2% of the TSH-secreting cells. It was not seen on GH, ACTH, FSH, or S100+ cells.

Why is autoimmune diabetes only seen with anti-PD-1/PD-L1 antibodies while thyroiditis is seen with PD-1 and CTLA-4 checkpoint inhibitors? The new subpopulation has reduce expression of diabetes antigens and increased expression of immune inhibitory ligands



Conclusions

- Autoimmune endocrine adverse events are common after checkpoint inhibitor therapies. They can result in considerable morbidity.
- The reasons why some but not others develop these adverse events require further studies:
 - There appears to be selection of target organs based on the checkpoint inhibitor hypophysitis is more common with anti-CTLA-4 mAb, thyroid abnormalities are more common with anti-PD-1/L1 antibodies, and diabetes is exclusively with anti-PD-1/L1 antibodies.
 - Endocrine events are more common with combinations.
 - Changes in T, B cells and Tregs may be found but the relationship between these findings and risk or development of the adverse events will require further studies.
 - Tissue specific changes and associated inflammation may be important determinants of proclivity to immune attack.
- Understanding the pathogenesis of checkpoint inhibitor associated adverse events may shed light on normal immune tolerance and suggest ways to prevent autoimmunity in this setting or spontaneous disease.

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 - Mark Anderson MD PhD
 - Jeff Bluestone PhD

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