

## Supplemental Materials for

### A case of nivolumab-induced acute-onset type 1 diabetes mellitus in melanoma

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### Listing of Supplemental Material(s):

Supplemental Appendix 1: Supplemental Table 1

Supplemental Table 1: Review of previously reported cases of immuno-checkpoint inhibitor-induced type 1 diabetes mellitus

**Supplemental Table 1. Review of previously reported cases of immuno-checkpoint inhibitor-induced type 1 diabetes mellitus**

Author, year	Age /Sex	Primary Diagnosis	immuno-CPI drugs	Duration of immuno-CPIs treatment	Islet auto-antibodies	HLA typing	Style of diabetes	GCT
Present case	68/F	Melanoma	NIV	60 weeks	None	DRB1*09:01	DKA+	+
Hughes J., 2015 <sup>1</sup>	55/F	Melanoma	NIV+IPI	5 months	None	A2.1+, DR4	DKA+	+
	83/F	NSCLC	NIV	<1 month	GAD+	A2.1+, DR4	DKA+	-
	63/M	RCC	NIV	4 months	GAD+/ICA+ /IAA+	A2.1+, DR4	DKA-	-
58/M	SCLC	NIV	1 week	GAD+	A2.1+	DKA+	-	
	64/F	Melanoma	PEM	< 1 month	None	DR4+	DKA+	-
Martin-Liberal J., 2015 <sup>2</sup>	54/F	Melanoma	PEM	9 weeks	GAD+/IAA+ /ICA-	DRB1*4, DQB1*0302 (HLA A2 DR4 DQ8)	DKA+	-
Mellati M., 2015 <sup>3</sup>	70/M	NSCLC	PDL1 antibody	15 weeks	GAD-/IA2- /IAA-/ZnT8-	N/A	DKA+	-
	66 /F	Head & neck carcinoma	PD-1 antibody	7 weeks	GAD+/IA2- /IAA-/ZnT8-	DR3-DQ2, DR4-DQ8	DKA+	-
Aleksova J., 2016 <sup>4</sup>	60 /M	Melanoma	(IPI)→ PEM	5 weeks	GAD-/IA2-	N/A	DKA+	+
Hansen E., 2016 <sup>5</sup>	58 /M	Melanoma	PEM	12 months	GAD+/ICA-	N/A	N/A	-
Araújo M., 2017 <sup>6</sup>	73/F	NSCLC	NIV	25 days	GAD+/ICA-	DRB*03:01-DQA1*05:01- DQB1*02:01/DRB1*04:01- DQA1*03:01DQB1*03:02; A*02:01, *24:06; B*40:01,	DKA+/Flu	-

Hoffman L., 2016 <sup>7</sup>	70 /F	Melanoma	NIV	6 weeks	GAD-/IA2-	N/A	N/A	-
	78 /F	Melanoma	(IPI→) NIV	3 weeks	GAD+	N/A	DKA+	-
	40/M	Melanoma	NIV	6 weeks	N/A	N/A	N/A	-
	58 /F	Melanoma	(IPI→) PEM	3 weeks	GAD+/IA2±	N/A	N/A	-
Miyoshi Y., 2016 <sup>8</sup>	66 /F	Melanoma	NIV	17 weeks	GAD-/IA2- /ZnT8-	DRB1*11:01, 13:02;01; DQB1*03:01:01, 06:04:01	DKA+/Flu	-
	55 /F	Melanoma	NIV	12 months	GAD-/IA2- /IAA-ZnT8-	DRB1*04:05, DQB1*04:01	DKA+/Flu	-
Chae YK., 2017 <sup>10</sup>	76/M	NSCLC	PEM	6 weeks	GAD+/IA2+ /ICA-	N/A	DKA-	+
Changizzadeh PN., 2017 <sup>11</sup>	42/M	Melanoma	NIV+IPI	9 weeks	GAD-/ZnT8- /IA2-	N/A	DKA+	+
Gauci ML., 2017 <sup>12</sup>	73/M	Melanoma	NIV	6 weeks	GAD+/ZnT8+ /IA2+/IAA+	N/A	DKA+	-
Godwin JL., 2017 <sup>13</sup>	34/F	NSCLC	NIV	2 weeks	GAD+/IA2+/ZnT8+ nT8+	A30:01, 30:02; D09:CTZ,09:CTZ	DKA+	-
Hickmott L., 2017 <sup>14</sup>	57/M	Urothelial carcinoma	ATE	15 weeks	GAD-/ICA-	DRB1*11, DRB1*04; DRB3*02, DRB4*01; DQB1*03, DQB1*03	DKA+	-
Ishikawa K., 2017 <sup>15</sup>	54/F	Melanoma	NIV	2 months	GAD-/IA2-	B*15:01, *40:06; DRB1*04:05, *04:06; DQB1*03:02, 04:01	DKA-/Flu	-

Lowe JR., 2018 <sup>16</sup>	68/M	Melanoma	NIV+IPI	4 months	GAD-	N/A	DKA+	+
Matsumura K., 2018 <sup>17</sup>	67/M	NSCLC	NIV	30 days	GAD-/IA2-	A*24:02, DRB1*09:01; DRB1*15:02	DKA-/Flu	+
Kapke J., 2017 <sup>18</sup>	83/M	Head & neck carcinoma	NIV	3 months	GAD+	DRB1*08, DRB1*11, DQB1*03, DQB1*04	DKA+	-
	63/F	Urothelial carcinoma	ATE	6 weeks	GAD+	DRB1*03, DRB1*04, DQB1*02, DQB1*03	DKA+	-
	62/F	NSCLC	NIV	10 weeks	GAD-	DRB*09:01- DQB1*03:03	DKA-	-
Kumagai R., 2017 <sup>19</sup>	73/M	NSCLC	NIV	25 weeks	GAD-/IA2- /IAA-/ZnT8-	DRB1*09:01- DQB1*03:03; DRB1+01:01- DQB1*05:01	DKA-	-
Li L., 2017 <sup>20</sup>	63/M	NSCLC	NIV	27 days	GAD+	N/A	DKA+	-
Marchand L., 2017 <sup>21</sup>	55/M	Pleomorphic carcinoma	NIV	9 courses	GAD-/ICA- /IA2-/ZnT8-	N/A	DKA+/Flu	N/A
Munakata W., 2017 <sup>22</sup>	72/M	HL	NIV	10 weeks	GAD-/ZnT8-	B*4002	DKA-	-
Smith-Cohn MA., 2017 <sup>23</sup>	67/F	Cholangio carcinoma	PEM	3 months	GAD+/ICA- /IA2-/ZnT8-	N/A	DKA+	+
Teramoto Y., 2017 <sup>24</sup>	63/F	Melanoma	NIV	30 weeks	GAD-/IA2- /IAA-	N/A	DKA+/Flu	-
Usui Y., 2017 <sup>25</sup>	31/M	NSCLC	NIV	13 days	GAD+	DR1*04:05- DQB1*04:01	DKA+/Flu	-

To date, there have been 35 reports of immuno-CPI-induced T1DM in literature.

†, Glucocorticoid was administered in all 7 patients who developed immune-CPIs-induced T1DM. T1DM could not be reversed in any of the patients.

immuno-CPIs, immuno-checkpoint inhibitors; T1DM, type 1 diabetes mellitus; NIV, nivolumab; IPI, ipilimumab; PEM, pembrolizumab; PDL1 antibody, programmed cell death-1 ligand; ATE, atezolizumab; DKA, diabetic ketoacidosis; GC; glucocorticoid; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer; RCC, renal cell carcinoma; HL, Hodgkin's lymphoma; NIV, nivolumab; IPI, ipilimumab; PEM; pembrolizumab, ATE, atezolizumab; N/A, not applicable; GAD, glutamic acid decarboxylase; IA2, insulinoma-associated antigen-2; IAA, insulin autoantibody; ZnT8, zinc transporter 8; ICA, islet cell antibody; N/A, not applicable.

## REFERENCES

1. Hughes J, Vudattu N, Sznol M, et al. Precipitation of autoimmune diabetes with anti-PD-1 immunotherapy. *Diabetes Care* 2015;38:e55–7.
2. Martin-Liberal J, Furness AJ, Joshi K, Peggs KS, Quezada SA, Larkin J. Anti-programmed cell death-1 therapy and insulin-dependent diabetes: a case report. *Cancer Immunol Immunother* 2015;64:765–7.
3. Mellati M, Eaton KD, Brooks-Worrell BM, et al. Anti-PD-1 and Anti-PDL-1 Monoclonal Antibodies Causing Type 1 Diabetes. *Diabetes Care* 2015;38:e137–8.
4. Aleksova J, Lau PK, Soldatos G, McArthur G. Glucocorticoids did not reverse type 1 diabetes mellitus secondary to pembrolizumab in a patient with metastatic melanoma. *BMJ Case Rep* 2016;pii: bcr2016217454
5. Hansen E, Sahasrabudhe D, Sievert L. A case report of insulin-dependent diabetes as immune-related toxicity of pembrolizumab: presentation, management and outcome. *Cancer Immunol Immunother* 2016;65:765–7.
6. Araújo M, Ligeiro D, Costa L, et al. A case of fulminant Type 1 diabetes following anti-PD1 immunotherapy in a genetically susceptible patient. *Immunotherapy* 2017;9:531–5.
7. Hofmann L, Forschner A, Loquai C, et al. Cutaneous, gastrointestinal, hepatic, endocrine, and renal side-effects of anti-PD-1 therapy. *Eur J Cancer* 2016;60:190–209.
8. Miyoshi Y, Ogawa O, Oyama Y. Nivolumab, an Anti-Programmed Cell Death-1 Antibody, Induces Fulminant Type 1 Diabetes. *Tohoku J Exp Med* 2016;239:155–8.
9. Okamoto M, Okamoto M, Gotoh K, et al. Fulminant type 1 diabetes mellitus with anti-programmed cell death-1 therapy. *J Diabetes Investig* 2016;7:915–8.
10. Chae YK, Chiec L, Mohindra N, Gentzler R, Patel J, Giles F. A case of pembrolizumab-induced type-1 diabetes mellitus and discussion of immune checkpoint inhibitor-induced type 1 diabetes. *Cancer Immunol Immunother* 2017;66:25–32.
11. Changizzadeh PN, Mukkamalla SKR, Armenio VA. Combined checkpoint inhibitor therapy causing diabetic ketoacidosis in metastatic melanoma. *J Immunother Cancer* 2017;5:97.
12. Gauci ML, Laly P, Vidal-Trecan T, et al. Autoimmune diabetes induced by PD-1 inhibitor-retrospective analysis and pathogenesis: a case report and literature review. *Cancer Immunol Immunother* 2017;66:1399–410.
13. Godwin JL, Jaggi S, Sirisena I, et al. Nivolumab-induced autoimmune diabetes mellitus presenting as diabetic ketoacidosis in a patient with metastatic lung cancer. *J Immunother Cancer* 2017;5:40.
14. Hickmott L, De La Peña H, Turner H, et al. Anti-PD-L1 Atezolizumab-Induced Autoimmune Diabetes: a Case Report and Review of the Literature. *Target Oncol* 2017;12:235–41.
15. Ishikawa K, Shono-Saito T, Yamate T, et al. A case of fulminant type 1 diabetes mellitus, with a precipitous decrease in pancreatic volume, induced by nivolumab for malignant melanoma: analysis of HLA and CTLA-4 polymorphisms. *Eur J Dermatol* 2017;27:184–5.
16. Lowe JR, Perry DJ, Salama AK, Mathews CE, Moss LG, Hanks BA. Genetic risk analysis of a patient with fulminant autoimmune type 1 diabetes mellitus secondary to combination ipilimumab and nivolumab immunotherapy. *J Immunother Cancer* 2016;4:89.
17. Matsumura K, Nagasawa K, Oshima Y, et al. Aggravation of diabetes, and incompletely deficient insulin secretion in a case with type 1 diabetes-resistant human leukocyte antigen DRB1\*15:02 treated with nivolumab. *J Diabetes Investig* 2017. doi: 10.1111/jdi.12679. [Epub ahead of print]
18. Kapke J, Shaheen Z, Kilari D, Knudson P, Wong S. Immune Checkpoint Inhibitor-Associated Type 1 Diabetes Mellitus: Case Series, Review of the Literature, and Optimal Management. *Case Rep Oncol* 2017;10:897–909.
19. Kumagai R, Muramatsu A, Nakajima R, et al. Acute-onset type 1 diabetes mellitus caused by nivolumab in a patient with advanced pulmonary adenocarcinoma. *J Diabetes Investig* 2017;8:798–9.

20. Li L, Masood A, Bari S, Yavuz S, Grosbach AB. Autoimmune Diabetes and Thyroiditis Complicating Treatment with Nivolumab. *Case Rep Oncol* 2017;10:230–4.
21. Marchand L, Paulus V, Fabien N, et al. Nivolumab-Induced Acute Diabetes Mellitus and Hypophysitis in a Patient with Advanced Pulmonary Pleomorphic Carcinoma with a Prolonged Tumor Response. *J Thorac Oncol* 2017;12:e182–4.
22. Munakata W, Ohashi K, Yamauchi N, Tobinai K. Fulminant type I diabetes mellitus associated with nivolumab in a patient with relapsed classical Hodgkin lymphoma. *Int J Hematol* 2017;105:383–6.
23. Smith-Cohn MA, Gill D, Voorhies BN, Agarwal N, Garrido-Laguna I. Case report: pembrolizumab-induced Type 1 diabetes in a patient with metastatic cholangiocarcinoma. *Immunotherapy* 2017;9:797–804.
24. Teramoto Y, Nakamura Y, Asami Y, et al. Case of type 1 diabetes associated with less-dose nivolumab therapy in a melanoma patient. *J Dermatol* 2017;44:605–6.
25. Usui Y, Udagawa H, Matsumoto S, et al. Association of Serum Anti-GAD Antibody and HLA Haplotypes with Type 1 Diabetes Mellitus Triggered by Nivolumab in Patients with Non-Small Cell Lung Cancer. *J Thorac Oncol* 2017;12:e41–3.