Supplemental Material Comment to the Editor (Separate before submission)

Supplemental figures and tables are necessary in order to provide readers with further data into the exact schedule and exposure of immunotherapies administered, and presentation of diabetes mellitus cases that may be difficult to appropriately illustrate within the character and figure limitations of the main manuscript. The addition of these tables and figures may assist clinicians in diagnosing and treating suspected new cases of immunotherapy-induced diabetes mellitus in their own practices, and provide them with a precedence in best-practice patterns for novel adverse events.

Online-Only Supplemental Material (Separate before submission)

Table S1—Supplemental—Demographics and baseline clinical characteristics

Characteristic	**n=18**
Median age at DM diagnosis, years (range)	63.5 (27-78)
Gender, n (%)	
Female	8 (44)
Male	10 (56)
Median BMI, kg/m^2 (range)	27 (18-34)
History of HTN, n (%)	5 (28)
Primary tumor histology, n (%)	
Melanoma	5 (28)
Ovarian serous carcinoma	2 (11)
Renal cell carcinoma, clear cell	2 (11)
Urothelial carcinoma	2 (11)
Breast lobular carcinoma	1 (6)
Colon adenocarcinoma	1 (6)
Endometrial adenocarcinoma	1 (6)
Esophageal adenocarcinoma	1 (6)
Follicular lymphoma	1 (6)
Lung adenocarcinoma	1 (6)
Ovarian rhabdomyosarcoma and endometrial adenocarcinoma	1 (6)
Clinical stage at cancer diagnosis, n (%)	
I	3 (17)
II	1 (6)
III	4 (22)
IV	8 (44)
Unknown	2 (11)
Treatments received for primary cancer prior to initiation of immunotherapy, n (%)	
Yes	17 (94)
Concurrent	1 (6)
Surgery	16 (89)
Chemotherapy	12 (67)
Radiation therapy	8 (44)
Clinical stage at initiation of immunotherapy, n (%)	
III	1 (6)
IV	16 (89)
Unknown	1 (6)
History of DM prior to immunotherapy initiation, n (%)	
No	12 (67)
Prediabetes	5 (28)
T2D, diet-controlled	1 (6)
Family history of diabetes, n (%)	
T1D	1 (6)
T2D	7 (39)
None	10 (56)

DM, diabetes mellitus; BMI, body mass index; HTN, hypertension; T1D, type 1 diabetes; T2D, type 2 diabetes.

Table S2—Supplemental—Immune checkpoint inhibitor exposure (n=18)

Combination Therapy	No. of Patients (%)
Any combination therapy	9 (50)
CTLA-4 + PD-1	6 (33)
Ipilimumab + nivolumab	6/6 (100)
CTLA-4 + PD-L1	2 (11)
Durvalumab + tremelimumab	2/2 (100)
CTLA-4 + PD-1 + PD-L1	1 (6)
Ipilimumab + nivolumab + pembrolizumab	1/1 (100)
Monotherapy	
Any monotherapy	9 (50)
PD-1	6 (33)
Nivolumab	5/6 (83)
Pembrolizumab	1/6 (17)
PD-L1	3 (17)
Atezolizumab	1/3 (33)
Durvalumab	2/3 (67)
PD-1/PD-L1 Agent	
Any PD-1 or PD-L1 exposure	18 (100)
PD-1	12 (67)
Nivolumab	11/12 (92)
Pembrolizumab	1/12 (8)
PD-1 + PD-L1	1 (6)
Pembrolizumab, nivolumab	1/1 (100)
PD-L1	5 (28)
Atezolizumab	1/5 (20)
Durvalumab	4/5 (80)

CTLA-4, cytotoxic T-lymphocyte-associated antigen 4; PD-1, programmed cell death protein 1; PD-L1, programmed cell death protein ligand 1.

Table S3—Supplemental—Results pertaining to insulin-dependent diabetes mellitus presentation

	Time from first dose PD-1 to IDDM dx (mo.)	DKA*	Initial glucose* (mmol/L)	Random glucose prior to IDDM dx (mmol/L) median of 16 days before ICI-DM (range, 11-51)	Random C-peptide*† (nmol/L)	Lowest random C-peptide† on f/u (nmol/L)	Elev amylase* (y/n)	Elev lipase* (y/n)	HbA1C* (%)	HbA1C* (mmol/mol)	GAD Ab+ (y/n)	Insulin TDD 3-6 mo. after IDDM dx (U/kg)	Response to ICI therapy
Median (range)	3.65 (0.56-12.23)		27.92 (18.59-46.9)	6.35 (4.38-14.49)	0.07 (<0.01-0.55)	<0.01 (<0.01-0.2)			7.25 (5.8-9.5)	56 (40-80)		0.49 (0.2-1.03)	
Patient													
1	3.4	+	43.57	8.16	0.07	0.02	NR	NR	NR	NR	y	0.20	SD
2	3.7	-	28.31	4.55	<0.07	<0.07	y	y	6.9	52	NR	NR	POD
3	9.3	-	25.64	5	0.26	<0.01	n	n	7.0	53	n	0.40	CR
4	3.0	+	NR	NR	<0.01	<0.01	NR	NR	NR	NR	NR	0.39	POD
5	12.2	+	46.9	6.94	0.03	<0.01	NR	NR	8.4	68	n	0.59	CR
6	3.3	-	18.76	13.82	0.17	<0.01	n	n	9.0	75	y	0.34	CR
7	0.6	-	23.09	6.11	NR	NR	NR	NR	6.3	45	y	NR	SD
8	12.4	+	21.53	14.49	0.04	0.04	y	y	8.8	73	NR	0.28	POD
9	5.6	-	18.59	NR	0.18	<0.03	NR	NR	6.4	46	n	0.48	POD
10	4.2	+	31.19	6.49	0.14	<0.01	n	n	8.3	67	n	0.68	POD
11	2.3	-	27.92	9.77	<0.01	<0.01	NR	NR	NR	NR	NR	0.89	POD
12	10.6	+	44.9	5.88	0.05	<0.01	n	y	6.9	52	NR	0.62	PR
13	6.0	+	21.7	7.38	0.2	0.2	n	y	7.5	58	n	NR	POD
14	0.8	-	19.98	5.72	<0.01	<0.01	NR	NR	NR	NR	NR	0.49	POD
15	1.4	-	20.7	6.22	0.55	0.02	n	n	7	53	y	NR	POD
16	3.7	+	46.34	4.38	0.11	0.11	y	n	9.4	79	n	0.73	POD
17	0.8	+	32.69	5.44	<0.07	<0.07	n	n	5.8	40	y	NR	NR
18	9.9	-	30.36	11.88	0.29	0.04	NR	NR	9.5	80	n	1.03	CR

PD-1, programmed cell death protein 1; IDDM dx, insulin-dependent diabetes mellitus diagnosis; mo, months; DKA, diabetic ketoacidosis; f/u, follow-up; Elev, elevated; y, yes; n, no; GAD, glutamic acid decarboxylase; Ab+, antibody-positive; TDD, total daily dose; ICI, immune checkpoint inhibitor; +, positive; -, negative; NR, not reported; SD, stable disease; POD, progression of disease; CR, complete response; PR, partial response. *At IDDM presentation. †Random C-peptide reference range=0.23-0.81 nmol/L.

Table S4—Supplemental—HLA Class I data

Patient	HLA Class I Germline Alleles
1	A2601, A2601, B3801, B3801, C1203, C1203
2	-
3	A2902, A3101, B3501, B4403, C0401, C1601
4	-
5	-
6	-
7	A0301, A6802, B0702, B5301, C0401, C0702
8	A0101, A2402, B0801, B5601, C0102, C0701
9	-
10	A2902, A2601, B4403, B4402, C1601, C0501
11	A0301, A0201, B3501, B5801, C1203, C0701
12	A0201, A6901, B4901, B3501, C1502, C0401
13	A0301, A3002, B5701, B1801, C0501, C0602
14	A1101, A2402, B4901, B5201, C1202, C0701
15	-
16	A6601, A2601, B3801, B3801, C1203, C1203
17	-
18	A0101, A0201, B4402, B4402, C0501, C0501

HLA, human leukocyte antigen; T1D, type 1 diabetes.

Table S5—Supplemental—Pancreatic atrophy. Volumetric pancreatic parenchymal estimates were quantified in all 18 patients by a single board-certified radiologist. “Baseline” and “last follow-up” pancreatic volumes were derived from 3-dimensional imaging available approximately 4-24 months before and 4-24 months following ICI-DM diagnosis, respectively. Volume changes around ICI-DM diagnosis, referred to as “pre-DM” and “post-DM” pancreatic volumes, were assessed by available scans 3 months pre- and post-IDDM, respectively.

Time of Pancreas Volume Measurement	**Median (Range), cm^3**	**Wilcoxon Rank Sum Test p Value**	**Median Percent Change (Range)**
Baseline	76.6 (42.3, 159.3)	Reference	Reference
Pre-DM	75.1 (37.9, 147.2)	0.007	5.6% (-11.1%, 39.2%)
Post-DM	63.7 (34.9, 150.7)	< .001	-16.1% (-59.1%, 1.0%)
Last follow-up	53.9 (26.9, 109.36)	< .001	-30.8% (-70.9%, 0.0%)

IDDM, insulin-dependent diabetes mellitus

Table S6—Supplemental—Immune checkpoint inhibitor dosing

Patient	PD-1 or PD-L1 exposure	PD-1 dose per cycle		PD-1 cumulative dose prior to IDDM dx	PD-1 cycles prior to IDDM dx	CTLA-4 exposure	CTLA-4 dose per cycle		CTLA-4 cumulative dose prior to IDDM dx	CTLA-4 cycles prior to IDDM dx
		(mg)	(mg/kg)*	(mg)			(mg)	(mg/kg)	(mg)	
1	pembrolizumab	200	3.6	1000	5	-	-	-	-	-
2	nivolumab + pembrolizumab	N: 72 P: 130	N:1 P:2	N: 72 P: 130	N: 1 P: 1	ipilimumab	215	3	215	1
3	nivolumab	230	3	1410	9	ipilimumab	225	3	900	4
4	nivolumab	NR	NR	NR	NR	ipilimumab	NR	NR	NR	NR
5	nivolumab	310	3	6720	23	ipilimumab	330	3	330	1
6	nivolumab	240	3	1680	7	-	-	-	-	-
7	nivolumab	90	1	175	2	ipilimumab	270	3	530	2
8	nivolumab	240	3	4467	19	-	-	-	-	-
9	nivolumab	NR	NR	NR	NR	-	-	-	-	-
10	nivolumab	240	3	720	3	-	-	-	-	-
11	nivolumab	330	3	1650	5	-	-	-	-	-
12	nivolumab	229	3	4731	21	ipilimumab	68	1	280	4
13	nivolumab	211	3	2321	11	ipilimumab	70	1	140	2
14	durvalumab	NR	-	NR	NR	-	-	-	-	-
15	durvalumab	750	-	2250	3	-	-	-	-	-
16	durvalumab	1500	-	3000	2	tremelimumab	75	-	150	2
17	durvalumab	1500	-	1500	1	tremelimumab	75	-	75	1
18	atezolizumab	1200	-	16800	14	-	-	-	-	-

PD-1, programmed cell death protein 1; PD-L1, programmed cell death protein ligand 1; IDDM dx, insulin-dependent diabetes mellitus diagnosis; CTLA-4, cytotoxic T-lymphocyte-associated antigen 4; N, nivolumab; P, pembrolizumab; NR, not reported. *Doses are reported in mg/kg only if weight-based dosing is applicable for the specific agent.

Table S7—Supplemental—Steroid exposure

Patient	Steroids prior to IDDM dx	Time from last steroid dose to IDDM dx (days)
1	dexamethasone	133
8	prednisone	71
10*	prednisone	7
11	dexamethasone	97
13	prednisone	87
14	dexamethasone	201
17	dexamethasone	84
18*	prednisone	0

IDDM dx, insulin-dependent diabetes mellitus diagnosis.

***2 patients who received steroids within 7 prior to ICI-DM diagnosis had follow-up C-peptide levels that remained low when off steroids and continued to require exogenous insulin.**

Table S8—Supplemental—GAD-positive versus GAD-negative

	All (n=18) GAD status known (n=12) + GAD status unknown (n=6)	GAD+ (n=5)	GAD- (n=7)
Median time to IDDM onset, months (range)	3.6 (0.6-12.2)	1.4 (0.6-3.4)	6.0 (3.7-12.2)
Number of cycles of a PD-1/PD-L1 agent pre-IDDM dx, median (range)	5 (1-23)	3 (1-7)	10 (2-23)
Patient response to immunotherapy, n (%)[§]			
Complete response	4 (22%)	1 (20%)	3 (43%)
Partial response	1 (6%)	0 (0%)	0 (0%)
Stable disease	2 (11%)	2 (40%)	0 (0%)
Progression of disease	10 (56%)	1 (20%)	4 (57%)
Method of DM diagnosis, n (%)[§]			
DKA	9 (50%)	2 (40%)	4 (57%)
Random blood glucose	9 (50%)	3 (60%)	3 (43%)
Initial DM median glucose, mmol/L (range)	27.92 (18.59-46.9)	23.09 (18.76-43.57)	30.36 (21.7-46.9)
Most recent median random glucose prior to IDDM dx, mmol/L (range)	6.35 (4.38-14.49)	6.22 (5.44-13.82)	6.72 (4.38-11.88)
Random C-peptide closest to diagnosis, nmol/L (range)	0.07 (<0.01-0.55)	0.12 (<0.07-0.55)	0.18 (0.03-0.29)
Lowest random C-peptide, nmol/L (range)	<0.01 (<0.01-0.2)	0.01 (<0.01-0.02)	<0.01 (<0.01-20.19)
HbA1C at diagnosis, % (range)	7.25 (5.8-9.5)	6.7 (6.3-9.0)	8.3 (6.4-9.5)
HbA1C at diagnosis, mmol/mol (range)	56 (40-80)	50 (45-75)	67 (46-80)
Amylase close to diagnosis, n (%)[§]			
Elevated	3 (17%)	0 (0%)	1 (14%)
Normal	7 (39%)	3 (60%)	3 (43%)
Unknown	8 (44%)	2 (40%)	3 (43%)
Lipase close to diagnosis, n (%)[§]			
Elevated	4 (22%)	0 (0%)	1 (14%)
Normal	6 (33%)	3 (60%)	3 (43%)
Unknown	8 (44%)	2 (40%)	3 (43%)

GAD, glutamic acid decarboxylase; GAD+, GAD-positive; GAD-, GAD-negative; T1D, type 1 diabetes; IDDM dx, insulin-dependent diabetes mellitus diagnosis; DM, diabetes mellitus; DKA, diabetic ketoacidosis. [§]Percentages are all based on the n value in that specific column.

Table S9—Supplemental—Single class versus combination immune checkpoint inhibitor therapy

	All (n=18)	Single Class (n=9)	Combination with CTLA-4 (n=9)
Median time to IDDM onset*, months (range)	3.6 (0.6-12.2)	3.4 (0.75-12.2)	3.7 (0.6-12.0)
Median OS since immunotherapy	NR	NR	NR
Total # of cycles - median (range)	5 (1-23)	5 (3-19)	5.5 (1-23)
Patient response to immunotherapy, n (%)†			
Complete response	4 (22%)	2 (22%)	2 (22%)
Partial response	1 (6%)	0 (0%)	1 (11%)
Stable disease	2 (11%)	1 (11%)	1 (11%)
Progression of disease	10 (56%)	6 (67%)	4 (44%)
Other adverse events, n (%)†			
Other endocrine‡	4 (22%)	2 (22%)	2 (22%)
Gastrointestinal	4 (22%)	1 (11%)	3 (33%)
Liver	6 (33%)	2 (22%)	4 (44%)
Dermatologic	8 (44%)	2 (22%)	6 (67%)
Other§	3 (17%)	1 (11%)	2 (22%)

CTLA-4, cytotoxic T-lymphocyte-associated antigen 4; IDDM, insulin-dependent diabetes mellitus; T1D, type 1 diabetes; OS, overall survival; NR, not reported; PD-1, programmed cell death protein 1. *"Median time to T1D onset" is time from first dose of anti-PD–1/anti-PD-L1 therapy to DM onset in months**.** †Percentages for the patient response to immunotherapy and toxicities are all based on the n in that specific column. ‡"Other endocrine adverse events" include one or more of the following: primary hypothyroidism, hypophysitis. §"Other" includes one or more of the following: myalgia, joint pain, pneumonitis, anemia.

Table S10—Supplemental—Immune checkpoint inhibitor toxicities: PD-1 versus PD-L1

	All (n=17)*	PD-1 (n=12)	PD-L1 (n=5)
Median time to IDDM onset†, months (range)	3.7 (0.6-12.2)	4.8 (0.6-12.2)	2.5 (0.75-9.7)
Median OS since immunotherapy	NR	NR	NR
Total # of cycles, median (range)	6 (1-23)	8 (2-23)	2.5 (1-14)
Patient response to immunotherapy, n (%)‡			
Complete response	4 (24%)	3 (25%)	1 (20%)
Partial response	1 (6%)	1 (8%)	0 (0%)
Stable disease	2 (12%)	2 (17%)	0 (0%)
Progression of disease	9 (59%)	6 (50%)	3 (60%)
Other adverse events, n (%)‡			
Other endocrine§	4 (24%)	3 (25%)	1 (20%)
Gastrointestinal	3 (17%)	3 (25%)	0 (0%)
Liver	6 (35%)	5 (42%)	1 (20%)
Dermatologic	7 (41%)	6 (50%)	1 (20%)
Other‖	2 (12%)	1 (8%)	1 (20%)

IDDM, insulin-dependent diabetes mellitus; PD-1, programmed cell death protein 1; PD-L1, programmed cell death protein ligand 1, T1D, type 1 diabetes; OS, overall survival; NR, not reported. *For the table above, one patient was classified as PD-1 + PD-L1. This patient was not included in the table.†"Median time to T1D onset" is time from first dose of anti-PD–1/anti-PD-L1 therapy to T1D onset in months. ‡Percentages for the patient response to immunotherapy and adverse events are all based on the n in that specific column. §"Other endocrine adverse events" include one or more of the following: primary hypothyroidism, hypophysitis. ‖"Other" includes one or more of the following: myalgia, joint pain, pneumonitis, anemia.

Figure S1—Supplemental—Random C-peptide trend. Patients who had 2 or more random C-peptide levels measured are included on this graph. Patients with random C-peptide levels measured only at the time of initial disease onset were excluded.

IDDM, insulin-dependent diabetes mellitus.

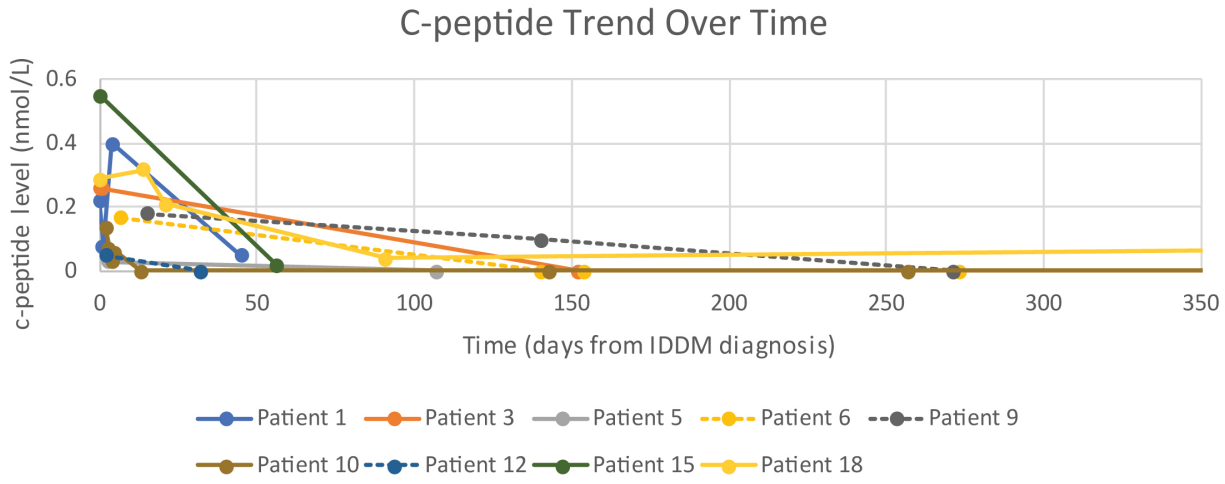

Figure S2—Supplemental—HbA1C trend. Patients who had 2 or more measured HbA1C levels are included on this graph.

IDDM, insulin-dependent diabetes mellitus.

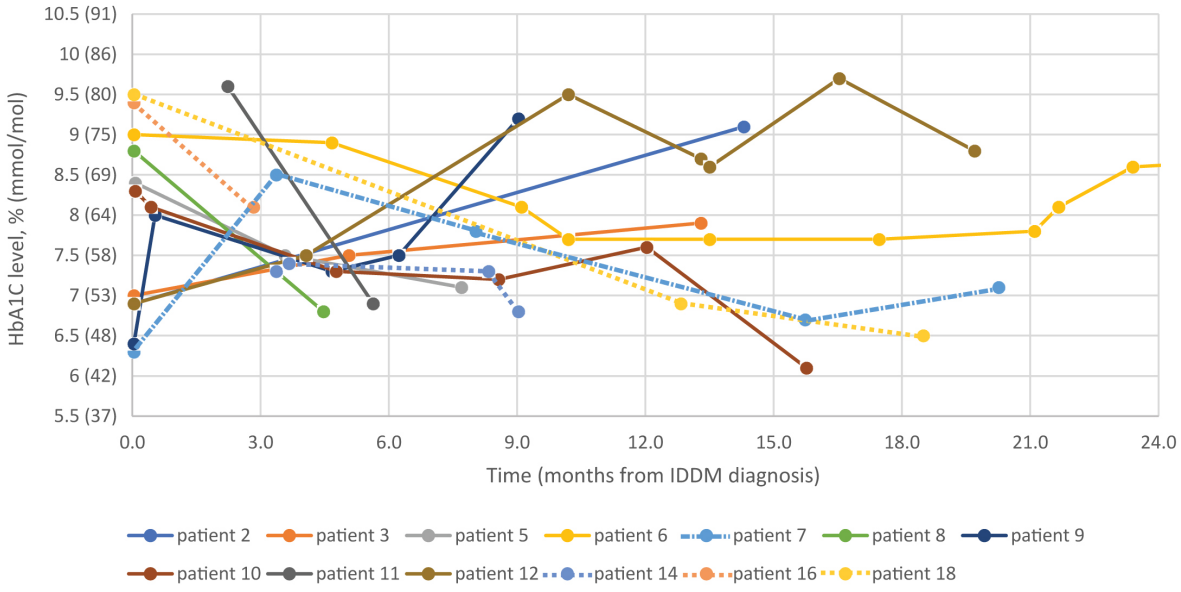

Figure S3—Supplemental—Toxicity box plot demonstrating the time course of various toxicities after treatment with ICI. Toxicity onset after ICI therapy (either anti-PD-1 or anti-PD-L1 alone, or in combination with anti-CTLA-4 therapy). Dermatologic AEs tend to occur early on in treatment; ICI-DM onset was variable after ICI treatment. Four patients (22%) experienced other endocrine AEs attributed to immunotherapy, including secondary adrenal insufficiency from hypophysitis (n=1) and primary hypothyroidism (n=3). Other ICI-related AEs included gastrointestinal tract toxicity (n=4; 22%), hepatotoxicity (n=6; 33%), and dermatologic toxicity (n=8; 44%). Other AEs included anemia, myalgia, fatigue, joint pain, and pneumonitis.

ICI, immune checkpoint inhibitor; AE, adverse event; PD-1, programmed cell death protein 1; PD-L1, programmed cell death protein ligand 1; CTLA-4, cytotoxic T-lymphocyte–associated antigen 4; ICI-DM, ICI-associated insulin-dependent diabetes mellitus; Derm, dermatologic; IDDM, insulin-dependent diabetes mellitus; Endo, endocrine; GI, gastrointestinal