Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

Incidence of endocrine dysfunction following the use of different immune checkpoint inhibitor regimens: a systematic review and meta-analysis

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eTable 1. Incidence of endocrine dysfunctions in all studies included in the meta-analysis

Study[(reference)]	ICI regimen	Tumor type	No of patients treated	Hypothyroidism (all grades)	G3/4	Hyperthyroidism (all grades)	G3/4	Hypophysisitis (all grades)	G3/4	Adrenal Insufficiency (all grades)	G3/4	Insulin deficient diabetes (all grades)	G3/4
Anti-PD-L1													
Fehrenbacher et al. 2016[1]	Atezo	NSCLC	142	8	1	1	0	0	0	0	0	0	0
NCT01375842	Atezo	Solid tumors	558	21	0	4	0	1	1	4	2	0	0
Rosenberg et al. 2016[2]	Atezo	Urothelial carcinoma	310	0	0	0	0	0	0	0	0	0	0
Anti-PD-1													
Hamanishi et al. 2015[3]	Nivo	Ovarian	20	8	0	NA	NA	NA	NA	NA	NA	NA	NA
Muro et al. 2016[4]	Pembro	Gastric	39	5	1	3	0	0	0	0	0	0	0
Robert et al. 2015[5]	Pembro	Melanoma	555	52	1	27	0	3	2	0	0	2	0
Larkin et al. 2015[6]	Nivo	Melanoma	313	27	0	13	0	2	1	NA	NA	NA	NA
Herbst et al. 2015[7]	Pembro	NSCLC	682	56	0	32	1	2	2	5	1	3	2
Weber et al. 2016[8]	Nivo	Melanoma	61	5	0	3	0	0	0	4	2	0	0
Motzer et al.	Nivo	RCC	406	33	2	10	0	2	1	8	3	6	3

Study	Drug	Cancer											
Ribas et al. 2015[10]	Pembro	Melanoma	357	26	0	9	0	2	1	0	0	0	0
Garon et al. 2015[11]	Pembro	NSCLC	495	34	NA	9	NA	NA	NA	NA	NA	NA	NA
Seiwert et al. 2016[12]	Pembro	Head and Neck	60	4	0	1	0	0	0	2	0	0	0
Patnaik et al. 2015[13]	Pembro	Solid tumors	30	2	0	0	0	0	0	0	0	0	0
Borghaei et al. 2015[14]	Nivo	NSCLC	287	19	0	4	0	0	0	0	0	0	0
Motzer et al. 2015[15]	Nivo	RCC	167	10	1	0	0	0	0	0	0	0	0
Gettinger et al. 2016[16]	Nivo	NSCLC	52	3	0	1	0	0	0	1	0	0	0
Weber et al. 2015[17]	Nivo	Melanoma	268	15	0	5	0	NA	NA	NA	NA	NA	NA
Robert et al. 2015[18]	Nivo	Melanoma	206	9	0	7	1	1	1	0	0	1	0
Robert et al. 2014[19]	Pembro	Melanoma	173	7	0	3	0	2	1	1	1	0	0
Brahmer et al. 2015[20]	Nivo	NSCLC	131	5	0	0	0	0	0	0	0	0	0
Nanda et al. 2016[21]	Pembro	Breast	32	1	0	0	0	0	0	0	0	0	0
Antonia et al. 2016[22]	Nivo	SCLC	98	3	0	2	0	0	0	0	0	0	0
Rivzi et al. 2015[23]	Nivo	NSCLC	117	3	0	0	0	0	0	1	1	0	0
Brahmer et al.	Nivo	Solid tumors	39	1	0	0	0	0	0	0	0	0	0

Study	Drug	Tumor type	N										
2010[24]													
Topalian et al. 2012[25]	Nivo	Advanced solid tumors	296	7	1	3	1	NA	NA	0	0	0	0
Nghiem et al. 2016[26]	Pembro	Merkel carcinoma	26	0	0	0	0	0	0	0	0	0	0
Shimizu et al. 2016[27]	Pembro	Solid tumors	10	0	0	0	0	0	0	0	0	0	0
Wolchok et al. 2013[28]	Nivo	Melanoma	33	1	0	0	0	1	1	1	1	0	0
Anti-CTLA-4													
Postow et al. 2015[29]	Ipi	Melanoma	46	7	0	0	0	3	2	2	1	0	0
Yamazaki et al. 2015[30]	Ipi	Melanoma	20	1	0	0	0	1	0	0	0	1	1
Larkin et al. 2015[6]	Ipi	Melanoma	311	13	0	3	0	12	6	NA	NA	NA	NA
Robert et al. 2015[5]	Ipi	Melanoma	256	5	0	6	1	6	4	0	0	0	0
Hodi et al. 2010[31]	Ipi	Melanoma	131	2	0	0	0	2	2	2	0	0	0
Zimmer et al. 2015[32]	Ipi	Melanoma	103	1	0	0	0	4	1	0	0	0	0
Zimmer et al. 2015[33]	Ipi	Melanoma	53	0	0	1	0	0	0	0	0	0	0
Le et al. 2013[34]	Ipi	Pancreas	15	0	0	0	0	2	0	0	0	0	0
Yang et al. 2007[35]	Ipi	RCC	61	0	0	0	0	2	NA	1	NA	0	0
O´Mahony et al. 2007[36]	Ipi	Solid tumors	11	0	0	0	0	0	0	0	0	0	0

Maki et al. 2013[37]	Ipi	Synovial Sarcoma	6	0	0	0	0	0	0	0	0	0	0
Combination*													
Wolchok et al. 2013[28]	Concurrent	Melanoma	53	2	0	2	NA	2	1	2	0	0	0
Postow et al. 2015[29]	Concurrent	Melanoma	94	15	0	4	0	11	2	6	1	0	0
Larkin et al. 2015[6]	Concurrent	Melanoma	313	47	1	31	3	24	5	NA	NA	NA	NA
Antonia et al. 2016[22]	Concurrent	SCLC	115	14	1	10	0	0	0	3	1	0	0
TOTAL			7689	502	9	194	7	92	36	52	17	13	6

Abbreviations: Atezo, Atezolizumab; CTLA-4, Cytotoxic T-Lymphocyte Associated Protein 4; ICI, immune checkpoint inhibitor; IPi, Ipilimumab; NA, not available; NSCLC, non–small cell lung cancer; PD-1, programmed cell death 1; PD-L1, programmed cell death ligand 1; Nivo, Nivolumab; Pembro, Pembrolizumab; RCC, renal cell carcinoma; SCLC, small cell lung cancer. *Combination = nivolumab plus ipilimumab.

eTable 2. Meta-regression model results for all grade hypothyroidism and hyperthyrodism

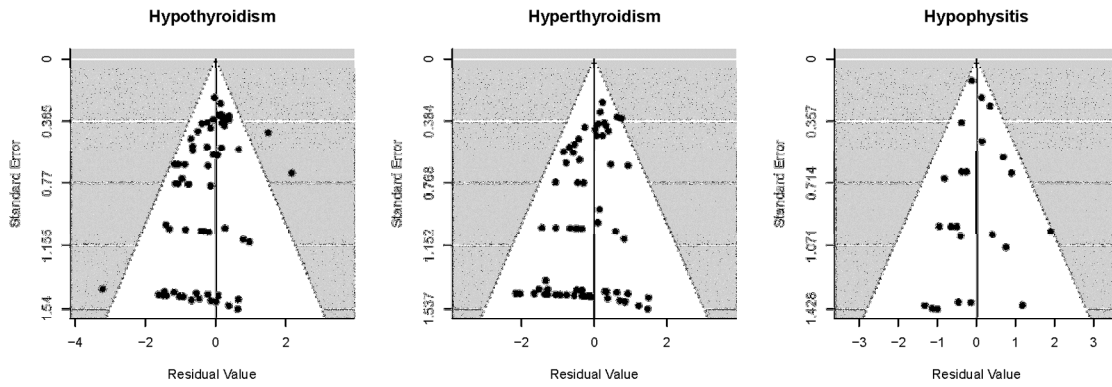| All grade hypothyroidism			
Variable	Predicted Incidence, % (95% PI)	Odds ratio (95% CI)	*P* Value
ICI regimens			
CTLA-4	3.8 (1.9 - 7.8)	Reference	
PD-1	7.0 (3.9 - 12.3)	1.89 (1.17 - 3.05)	0.0089
PD-L1	3.9 (1.7 - 8.4)	1.01 (0.49 - 2.07)	0.9861
Combination*	13.2 (6.9 - 23.8)	3.81 (2.10 - 6.91)	<.0001
All grade hyperthyroidism			
Variable	Predicted Incidence, % (95% PI)	Odds ratio (95% CI)	*P* Value
ICI regimens			
CTLA-4	1.7 (0.8 - 3.8)	Reference	
PD-1	3.2 (1.7 - 5.7)	1.89 (1.02 - 3.52)	0.0438
PD-L1	0.6 (0.2 - 1.8)	0.35 (0.12 - 1.07)	0.0653
Combination*	8.0 (4.1 - 15.3)	5.07 (2.45 - 10.52)	<.0001
PD-1 agent			
Nivolumab	2.5 (1.3 - 4.6)	Reference	
Pembrolizumab	3.8 (2.1 - 6.9)	1.56 (1.01 - 2.39)	0.0428

Abbreviations: CI, Confidence interval; CTLA-4, Cytotoxic T-Lymphocyte Associated Protein-4; PD-1, programmed cell death-1; PD-L1, programmed cell death ligand-1; PI, Prediction interval; *Combination = nivolumab plus ipilimumab.

eTable 3. Meta-regression model results for any grade hypophisitis in patients with melanoma
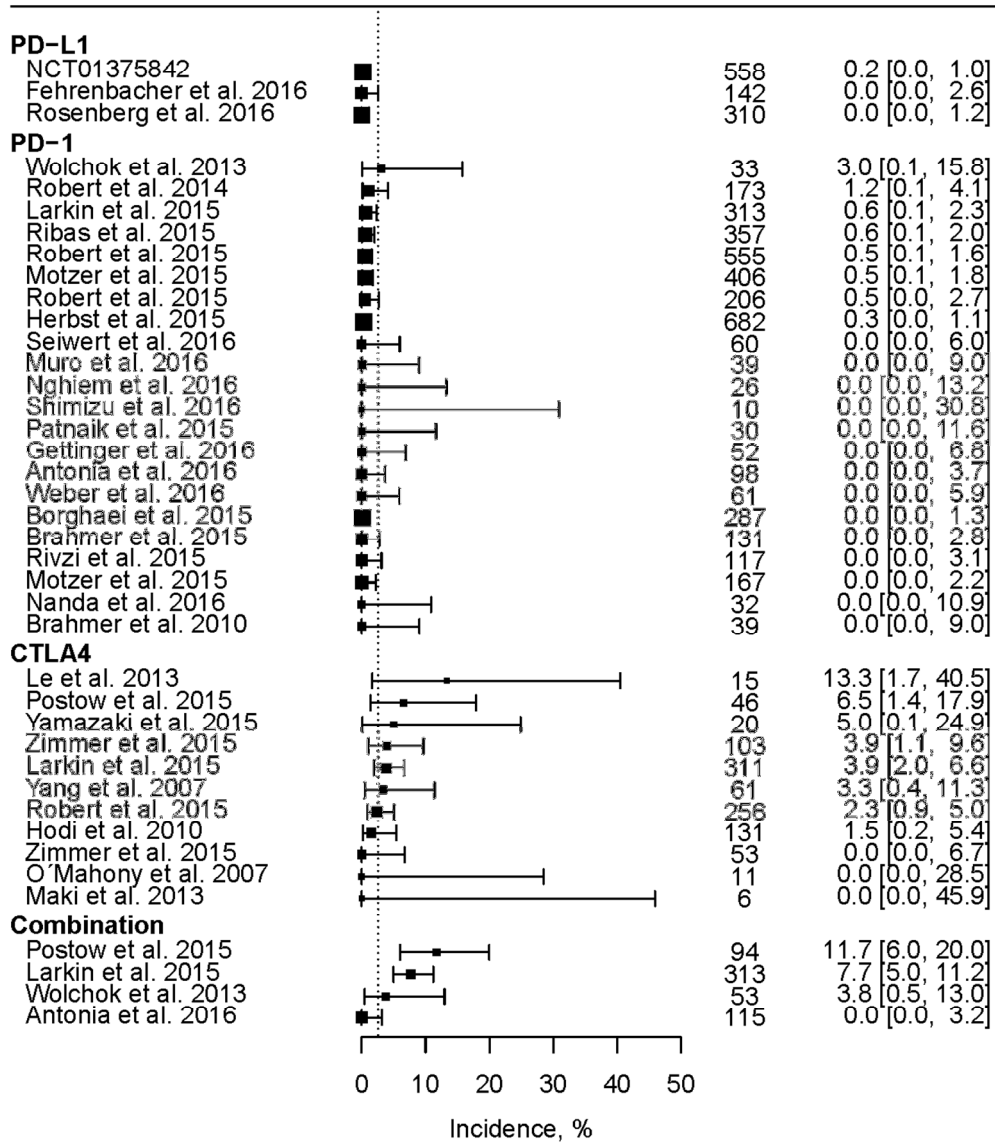
Class	Predicted Incidence, % (95% PI)	Odds ratio (95% CI)	*P* Value
ICI regimens			
CTLA-4	3.8 (2.7 - 5.2)	Reference	
PD-1	1.1 (0.8 - 1.6)	0.29 (0.18 - 0.49)	<.0001
Combination	8.0 (5.9 - 10.8)	2.24 (1.39 - 3.60)	0.0009

Abbreviations: CTLA-4, Cytotoxic T-Lymphocyte Associated Protein 4; PD-1, programmed cell death 1; PD-L1, programmed cell death ligand 1; *Combination = nivolumab plus ipilimumab.

eFigure 1. Funnel Plots for ICI Studies included in the meta-analysis for all grades hypothyroidism, hyperthyroidism and hypophysitis

eFigure 2. Forest plots of the incidence of all grade hypophysitis during treatment with different ICI regimens

PD-L1		
NCT01375842	558	0.2 [0.0, 1.0]
Fehrenbacher et al. 2016	142	0.0 [0.0, 2.6]
Rosenberg et al. 2016	310	0.0 [0.0, 1.2]
PD-1		
Wolchok et al. 2013	33	3.0 [0.1, 15.8]
Robert et al. 2014	173	1.2 [0.1, 4.1]
Larkin et al. 2015	313	0.6 [0.1, 2.3]
Ribas et al. 2015	357	0.6 [0.1, 2.0]
Robert et al. 2015	555	0.5 [0.1, 1.6]
Motzer et al. 2015	406	0.5 [0.1, 1.8]
Robert et al. 2015	206	0.5 [0.0, 2.7]
Herbst et al. 2015	682	0.3 [0.0, 1.1]
Seiwert et al. 2016	60	0.0 [0.0, 6.0]
Muro et al. 2016	39	0.0 [0.0, 9.0]
Nghiem et al. 2016	26	0.0 [0.0, 13.2]
Shimizu et al. 2016	10	0.0 [0.0, 30.8]
Patnaik et al. 2015	30	0.0 [0.0, 11.6]
Gettinger et al. 2016	52	0.0 [0.0, 6.8]
Antonia et al. 2016	98	0.0 [0.0, 3.7]
Weber et al. 2016	61	0.0 [0.0, 5.9]
Borghaei et al. 2015	287	0.0 [0.0, 1.3]
Brahmer et al. 2015	131	0.0 [0.0, 2.8]
Rivzi et al. 2015	117	0.0 [0.0, 3.1]
Motzer et al. 2015	167	0.0 [0.0, 2.2]
Nanda et al. 2016	32	0.0 [0.0, 10.9]
Brahmer et al. 2010	39	0.0 [0.0, 9.0]
CTLA4		
Le et al. 2013	15	13.3 [1.7, 40.5]
Postow et al. 2015	46	6.5 [1.4, 17.9]
Yamazaki et al. 2015	20	5.0 [0.1, 24.9]
Zimmer et al. 2015	103	3.9 [1.1, 9.6]
Larkin et al. 2015	311	3.9 [2.0, 6.6]
Yang et al. 2007	61	3.3 [0.4, 11.3]
Robert et al. 2015	256	2.3 [0.9, 5.0]
Hodi et al. 2010	131	1.5 [0.2, 5.4]
Zimmer et al. 2015	53	0.0 [0.0, 6.7]
O´Mahony et al. 2007	11	0.0 [0.0, 28.5]
Maki et al. 2013	6	0.0 [0.0, 45.9]
Combination		
Postow et al. 2015	94	11.7 [6.0, 20.0]
Larkin et al. 2015	313	7.7 [5.0, 11.2]
Wolchok et al. 2013	53	3.8 [0.5, 13.0]
Antonia et al. 2016	115	0.0 [0.0, 3.2]

Incidence, %

Abbreviations: CTLA4, Cytotoxic T-Lymphocyte Associated Protein-4; PD-1, programmed cell death-1; PD-L1, programmed cell death ligand-1; Combination = nivolumab plus ipilimumab.
Study-level data are displayed as box-and-whiskers using binomial exact 95% confidence intervals.

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