

## Supplementary Online Content

Wang Y, Zhou S, Yang F, et al. Treatment-related adverse events of PD-1 and PD-L1 inhibitors in clinical trials: a systematic review and meta-analysis. *JAMA Oncol*. Published online April 25, 2019. doi:10.1001/jamaoncol.2019.0393

**eTable 1.** List of the Studies Included in This Meta-Analysis

**eTable 2.** Relative Ratios of Grade 3 or Higher Adverse Event Incidences to Respective All-grade Adverse Event Incidences

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**eFigure 1.** Incidences of All Adverse Events, (A) Incidences of All-grade Adverse Events and (B) Incidences of Grade 3 or Higher Adverse Events

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**eFigure 3.** Heterogeneity of Adverse Event Incidence in This Meta-Analysis

**eFigure 4.** Mean Incidences of All-grade Adverse Events by Study if Ignoring Missing Data

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

**eTable 1. List of the Studies Included in This Meta-Analysis**

Study	Ref	Phase	NCT number	Trial name or ID	Cancer type	cancer type category	Total Patient number	Dosing schedule	Patient number	Patients with any grade AEs	Patients with grade 3 or higher AEs	Note on AE report criteria
<b>Nivolumab</b>												
2010-Brahmer-J Clin Oncol	6	1	00441337	CA209-001	Advanced solid tumors	Mixed cancer types	33	1 mg/kg Q4W	6			Treatment-related/ Drug-related; Grade ≥ 2
								3 mg/kg Q4W	6			Treatment-related/ Drug-related; Grade ≥ 2
								10 mg/kg Q4W	21			Treatment-related/ Drug-related; Grade ≥ 2
2012-Topalian-N Engl J Med	7	1	00730639	CA209-003	Advanced tumors	Mixed cancer types	259	1 mg/kg Q2W	79	39	5	Treatment-related; ≥ 1% All patients
								3 mg/kg Q2W	50	19	2	Treatment-related; ≥ 1% All patients
								10 mg/kg Q2W	130	50	11	Treatment-related; ≥ 1% All patients
2014-Topalian-J Clin Oncol	8	1	00730639	CA209-003	Melanoma	Melanoma	72	1 mg/kg Q2W	35	34	5	Treatment-related; ≥ 3%

												All patients
								3 mg/kg Q2W	17	15	6	Treatment-related; ≥ 3% All patients
								10 mg/kg Q2W	20	14	5	Treatment-related; ≥ 3% All patients
2015-Ansell-N Engl J Med	9	1	0159 2370	CA209-039	Hodgkin lymphoma	Hematologic malignancy	23	3 mg/kg Q2W	23	18	5	Drug-related in ≥ 5% All patients ; Drug-related serious adverse events
2015-Borghaei-N Engl J Med	10	3	0167 3867	CheckMate 057	Nonsquamous NSCLC	Lung cancer	287	3 mg/kg Q2W	287	199	30	Treatment-related; ≥ 10% Patients treated with Nivolumab or Docetaxel
2015-Brahmer-N Engl J Med	11	3	0164 2004	CheckMate 017	Squamous NSCLC	Lung cancer	131	3 mg/kg Q2W	131	76	9	Treatment-related; ≥ 5% Patients treated with Nivolumab or Docetaxel
2015-Gettinger-J Clin Oncol	12	1	0073 0639	CA209-003	NSCLC	Lung cancer	129	1, 3, 10 mg/kg Q2W	129	53	6	Treatment-related select (with potential

												immunologic etiologies that require more frequent monitoring or intervention)
								1 mg/kg Q2W	33	21	5	Treatment-related; ≥ 3% All patients
								3 mg/kg Q2W	37	25	5	Treatment-related; ≥ 3% All patients
								10 mg/kg Q2W	59	45	8	Treatment-related; ≥ 3% All patients
2015-Hamanishi-J Clin Oncol	13	2		UMIN00005714	Ovarian	Other cancer	20	1 mg/kg Q2W	10	9	4	Treatment-related of special interest ; ≥ 20% All patients
								3 mg/kg Q2W	10	10	4	Treatment-related of special interest ; ≥ 20% All patients
2015-McDermott-J Clin Oncol	14	1	00730639	CA209-003	RCC	GU cancer	34	1 mg/kg Q2W	18	15	2	Treatment-related; ≥ 3% All patients
								10 mg/kg Q2W	16	14	4	Treatment-

													related; ≥ 3% All patients
2015-Motzer-N Engl J Med	1 5	3	0166 8784	CheckMate 025	RCC	GU cancer	40 6	3 mg/kg Q2W	40 6	319	76	Treatm ent- related; ≥ 10% Patient s treated with Nivolu mab or Everoli mus	
2015-Motzer-J Clin Oncol	1 6	2	0135 4431	CA209-010	RCC	GU cancer	54	10 mg/kg Q3W	54	42	7	Treatm ent- related in ≥ 10% Patient s in any group; Potenti al immun e- mediat ed	
2015-Rizvi-Lancet Oncol	1 7	2	0172 1759	CheckMate 063	NSCLC	Lung cancer	11 7	3 mg/kg Q2W	11 7	87	20	Treatm ent- related, ≥ 5% All patients	
2015-Robert-N Engl J Med	1 8	3	0172 1772	CheckMate 066	Melanoma	Melanom a	20 6	3 mg/kg Q2W	20 6	153	24	Treatm ent- related; ≥ 2% Patient s in either group	
2016-Antonia- Lancet Oncol	1 9	1/ 2	0192 8394	CheckMate 032	SCLC	Lung cancer	98	3 mg/kg Q2W	98	52	13	Treatm ent- related; ≥ 10% Patient s in any cohort (Grade 1-2) and all events	

												(Grade 3-4)
2016-Choueiri-Clin Cancer Res	20	3	01358721		RCC	GU cancer	69	2 mg/kg Q3W, Previously Treated	22	22	8	Treatment-related; ≥ 15% Patients in all treatment groups (any grade) and ≥ 2 patients in any treatment group (select AEs with potential immunologic causes)
								10 mg/kg Q3W, Previously Treated	23	23	13	Treatment-related; ≥ 15% Patients in all treatment groups (any grade) and ≥ 2 patients in any treatment group (select AEs with potential immunologic causes)
								10 mg/kg Q3W, Treatment-naïve	24	24	12	Treatment-related; ≥ 15%

																					Patient s in all treatme nt groups (any grade) and ≥ 2 patients in any treatme nt group (select AEs with potenti al immun ologic causes)
2016-Ferris-N Engl J Med	2 1	3	0210 5636	CheckMate 141	Head and neck carcinoma	Other cancer	23 6	3 mg/kg Q2W	23 6	139	31										Treatm ent- related; ≥ 5% Patient s in either group
2016-Gettinger-J Clin Oncol	2 2	1	0145 4102		NSCLC	Lung cancer	52	3 mg/kg Q2W	52	37	10										Treatm ent- related; ≥ 5% All Patient s; Combin ed with treatme nt- related irAEs
2016-Lesokhin-J Clin Oncol	2 3	1b	0159 2370		Hematologic malignancy	Hematolo gic malignanc y	81	1 or 3 mg/kg Q2W	81	53	17										Drug- related; ≥ 5% Patient s (any grade) and all events (grade ≥ 3); Combin ed with drug-

												related irAEs
2016-Sharma-Lancet Oncol	2/4	1/2	01928394	CheckMate 032	Urothelial carcinoma	GU cancer	78	3 mg/kg Q2W	78	63	17	Treatment-related; ≥ 10% Patients (any grade) and all events (grade 3-4)
2016-Weber-Cancer Immu Res	2/5	1/2	01176461	CA209-006/007	Melanoma	Melanoma	61	3 mg/kg Q2W	61			Drug-related; Any irAEs or > 5% of total patients
2017-Ben-Ami-Cancer	2/6	2	02428192	NCI-2014-02403	Uterus leiomyosarcoma	Other cancer	12	3 mg/kg Q2W	12		9	All grade ≥ 3 AEs including unrelated, possible, probable, definite related to drug
2017-Carbone-N Engl J Med	2/7	3	02041533	CheckMate 026	NSCLC	Lung cancer	267	3 mg/kg Q2W	267	190	47	Treatment-related; ≥ 10% Patients in either group
2017-El-Khoueiry-Lancet	2/8	1/2	01658878	CheckMate 040	Hepatocellular carcinoma	GI cancer	33	1 mg/kg Q2W	10	8	5	Treatment-related; ≥ 5% of all patients, any grade
								3 mg/kg Q2W	10	9	2	Treatment-related; ≥ 5% of all patients





												All patients
2017-Maruyama-Cancer Sci	3 2	2		JapicCTI-142755	Hodgkin lymphoma	Hematologic malignancy	17	3 mg/kg Q2W	17	17	4	Drug-related; ≥ 10% All patients or immunerelated
2017-Morris-Lancet Oncol	3 3	2	0231 4169		Anal cancer	GI cancer	37	3 mg/kg Q2W	37			Treatment-related/ Drug-related; All AEs
2017-Overman-Lancet Oncol	3 4	2	0206 0188	CheckMate 142	Colorectal cancer	GI cancer	74	3 mg/kg Q2W	74	51	15	Treatment-related; ≥ 10% Patients (grade 1-2) and all events (grade 3-4)
2017-Sharma-Lancet Oncol	3 5	2	0238 7996		Urothelial carcinoma	GU cancer	27 0	3 mg/kg Q2W	27 0	170	47	Treatment-related; ≥ 5% All patients and select (immunomediated)
2017-Weber-N Engl J Med	3 6	3	0238 8906	CheckMate 238	Melanoma	Melanoma	45 2	3 mg/kg Q2W	45 2	385	65	Treatment-related; ≥ 10% Patients in either group
2017-Yamamoto-Invest New Drugs	3 7	1	0044 1337		Solid tumors	Mixed cancer types	14	1 mg/kg Q2W	3	3	0	Drug-related; ≥ 2 Patients
								3 mg/kg Q2W	5	5	1	Drug-related; ≥ 2

													Patient s
							10 mg/kg Q2W	6	6	0			Drug- related; ≥ 2 Patient s
2017-Yamazaki- Cancer Sci	3 8	2		JapicCTI- 142533	Melanoma	Melanom a	23	3 mg/kg Q2W	23	20	3		Treatm ent- related AEs in ≥10% Patient s; Treatm ent- related serious AEs; Treatm ent- related select AEs
2018-Armand-J Clin Oncol	3 9	2	0218 1738	CheckMate 205	Hodgkin lymphoma	Hematolo gic malignanc y	80	3 mg/kg Q2W	80				Drug- related; ≥ 10% Patient s (grade 1-2) and all events (grade 3-4)
2018-D'Angelo- Lancet Oncol	4 0	2	0250 0797	Alliance A091401	Sarcoma	Mixed cancer types	42	3 mg/kg Q2W	42		3		≥ 10% Patient s (grade 1-2) or ≥ 1 Patient (grade 3-5)
2018-Forde-N Engl J Med	4 1	2	0225 9621		NSCLC	Lung cancer	22	3 mg/kg Q2W	22	5	1		Treatm ent- related
2018-Gettinger-J Clin Oncol	4 2	1	0073 0639	CA209-003	NSLCL	Lung cancer	12 9	1 (n=33), 3 (n=37) or 10 (n=59) mg/kg Q2W	12 9	91	22		Treatm ent- related (with potenti al immun ologic cause)

2018-Hellmann-N Engl J Med	4 3	3	0247 7826	CheckMate 227	NSCLC	Lung cancer	39 1	240 mg Q2W	39 1	251	74	Treatm ent- related; ≥ 10% Patient s (any grade) in any group
2018-Hodi-Lancet Oncol	4 4	3	0184 4505	CheckMate 067	Melanoma	Melanoma	31 3	3 mg/kg Q2W	31 3	270	71	Treatm ent- related; ≥ 10% Patient s (any grade) or ≥ 2% Patient s (grade 3-4) in any group
2018-Janjigian-J Clin Oncol	4 5	1/ 2	0192 8394	CheckMate -032	Esophagogastric cancer	GI cancer	59	3 mg/kg Q2W	59	41	10	Treatm ent- related; ≥ 15% Patient s (any grade) in any group
2018-Lee-Lung Cancer	4 6	2	0217 5017		NSCLC	Lung cancer	10 0	3 mg/kg Q2W	10 0			Treatm ent- related; ≥ 1 Patient (any grade and grade ≥ 3)
					NSCLC (Squamous)			3 mg/kg Q2W	44			Treatm ent- related; ≥ 1 Patient (any grade and grade ≥ 3)
					NSCLC (Non-squamous)			3 mg/kg Q2W	56			Treatm ent- related; ≥ 1

												Patient (any grade and grade ≥ 3)
2018-Long-Lancet Oncol	47	2	02374242		Melanoma (brain metastases; No previous local brain therapy)	Melanoma	41	3 mg/kg Q2W	25	20	4	Treatment-related; ≥ 10% Patients (any grade) or ≥ 1 Patient (grade 3-4) in any group
					Melanoma (brain metastases; Failed local therapy, or who had neurological symptoms, or leptomeningeal disease)	Melanoma	41	3 mg/kg Q2W	16	9	0	Treatment-related; ≥ 10% Patients (any grade) or ≥ 1 Patient (grade 3-4) in any group
2018-Ma-J Clin Oncol	48	2	02339558	NCI-9742	Nasopharyngeal carcinoma	Other cancer	45	3 mg/kg Q2W	45		10	All treatment-related
2018-Omuro-Neuro Oncol	49	1	02017717	CheckMate 143	Glioblastoma	Other cancer	10	3 mg/kg Q2W	10	9	0	Treatment-related; ≥ 2 Patients in any arm or treatment-related serious AEs
2018-Quispel-Janssen-J Thorac Oncol	50	2	02497508		Pleural mesothelioma	Other cancer	34	3 mg/kg Q2W	34	26	9	All treatment-related
2018-Ready-J Thorac Oncol	51	1/2	01928394	CheckMate 32	SCLC	Lung cancer	109	3 mg/kg Q2W	109	60	13	Treatment-related; ≥ 5%

													Patient s (any grade)
<b>Pembrolizumab</b>													
2015-Garon-N Engl J Med	5 2	1	0129 5827	KEYNOTE- 001	NSCLC	Lung cancer	49 5	2 mg/kg Q3W	6				Treatm ent- related; ≥ 2% Patient s in any group
								10 mg/kg Q3W	28 7				Treatm ent- related; ≥ 2% Patient s in any group
								10 mg/kg Q2W	20 2				Treatm ent- related; ≥ 2% Patient s in any group
2015-Le-N Engl J Med	5 3	2	0187 6511	MK-3475- 016	Advanced solid tumors	Mixed cancer types	41	10 mg/kg Q2W	41	40	17		> 5% Patient s
2015-Patnaik-Clin Cancer Res	5 4	1	0129 5827	KEYNOTE- 001	Advanced solid tumors	Mixed cancer types	23	10 mg/kg Q2W	10	4	0		Treatm ent- related; ≥ 1 Patient
								2 mg/kg Q3W	7	7	0		Treatm ent- related; ≥ 1 Patient
								10 mg/kg Q3W	6	4	0		Treatm ent- related; ≥ 1 Patient
2015-Ribas-Lancet Oncol	5 5	2	0170 4287	KEYNOTE- 002	Melanoma	Melanom a	35 7	2 mg/kg Q3W	17 8	120	19		Treatm ent- related; ≥ 5% Patient s in any group
								10 mg/kg Q3W	17 9	132	25		Treatm ent- related; ≥ 5% Patient

													s in any group
2015-Robert-N Engl J Med	56	3	01866319	KEYNOTE-006	Melanoma	Melanoma	555	10 mg/kg Q2W	278	221	37		Treatment-related; ≥ 1% Patients in any group and AEs of special interest (autoimmune or immune-related)
								10 mg/kg Q3W	277	202	28		Treatment-related; ≥ 1% Patients in any group and AEs of special interest (autoimmune or immune-related)
2016-Armand-J Clin Oncol	57	1b	01953692	KEYNOTE-013	Classical Hodgkin Lymphoma	Hematologic malignancy	31	10 mg/kg Q2W	31	21	5		Treatment-related; ≥ 2 Patients of any grade
2016-Chow-J Clin Oncol	58	1b	01848834	KEYNOTE-012	Head and neck carcinoma	Other cancer	132	200 mg Q3W	132	82	12		Treatment-related; ≥ 10% Patients (grade 1-2) and any event (grade 3-4)

2016-Herbst-Lancet	59	2/3	01905657	KEYNOTE-010	NSCLC	Lung cancer	682	2 mg/kg Q3W	339	215	43	Treatm ent-related ≥ 1% of patients in any group; Special interest ≥ 2 patients in the pembrolizumab groups
								10 mg/kg Q3W	343	226	55	Treatm ent-related ≥ 1% of patients in any group; Special interest ≥ 2 patients in the pembrolizumab groups
2016-Goldberg-Lancet Oncol	60	2	02085070		Melanoma	Melanoma	36	10 mg/kg Q2W	18			Neurological; Treatm ent-related non-neurological
					NSCLC	Lung cancer		10 mg/kg Q2W	18			Neurological; Treatm ent-related non-neurological
2016-Muro-Lancet Oncol	61	1b	01848834	KEYNOTE-012	Gastric cancer	GI cancer	39	10 mg/kg Q2W	39	26	5	Treatm ent-related; ≥ 10% Patients (grade 1-2) and all events



												(grade 3-5)
2016-Nanda-J Clin Oncol	6 2	1b	0244 7003	KEYNOTE- 012	TNBC	Other cancer	32	10 mg/kg Q2W	32	18	5	Treatm ent-related; ≥ 2 Patient s (any grade) and ≥ 1 Patient s (grade 3-5)
2016-Nghiem-N Engl J Med	6 3	2	0226 7603	MK-3475	Merkel cell Carcinoma	Other cancer	26	2 mg/kg Q3W	26	20	4	Drug-related
2016-Reck-N Engl J Med	6 4	3	0214 2738	KEYNOTE- 024	NSCLC	Lung cancer	15 4	200 mg Q3W	15 4	113	41	Treatm ent-related; ≥10% Patient s in either group
2016-Ribas-JAMA	6 5	1b	0129 5827	KEYNOTE- 001	Melanoma	Melanom a	65 5	10 mg/kg Q2W, 2,10 mg/kg Q3W	65 5	544	92	Treatm ent-related/ Drug-related; ≥ 5% Patient s
2016-Seiwert-Lancet Oncol	6 6	1b	0184 8834	KEYNOTE- 012	Head and neck carcinoma	Other cancer	60	10 mg/kg Q2W	60	38	10	Treatm ent-related
2016-Shimizu-Invest New Drugs	6 7	1	0184 0579	MK-3475	Advanced solid tumors	Mixed cancer types	7	10 mg/kg Q2W	7			Treatm ent-related/ Drug-related
2017-Alley-Lancet Oncol	6 8	1b	0205 4806	KEYNOTE- 028	Pleural mesothelioma	Other cancer	25	10 mg/kg Q2W	25	16	5	Treatm ent-related
2017-Balar-Lancet Oncol	6 9	2	0233 5424	KEYNOTE- 052	Urothelial carcinoma	GU cancer	37 0	200 mg Q3W	37 0	229	57	Treatm ent-related; ≥ 10% Patient s (grade 1-2) and all events (grade 3-5)

2017-Bellmunt-N Engl J Med	70	3	02256436	KEYNOTE-045	Advanced urothelial carcinoma	GU cancer	266	200 mg Q3W	266	162	40	Treatment-related in ≥ 10% Patients in either group; Event of interest (immune-related cause)
2017-Bauml-J Clin Oncol	71	2	02255097	KEYNOTE-055	Head and neck cancer	Other cancer	171	200 mg Q3W	171	109	26	Treatment-related; ≥ 2% Patients
2017-Chen-J Clin Oncol	72	2	02453594	KEYNOTE-087	Hodgkin lymphoma	Hematologic malignancy	210	200 mg Q3W	210			Treatment-related; ≥ 5% All patients
2017-Ding-Blood	73	2	02332980	NCI-2014-02561	CLL	Hematologic malignancy	25	200 mg Q3W	25	25	15	Drug-related; ≥ 5% Patients
2017-Doi-J Clin Oncol	74	1b	02054806	KEYNOTE-028	Esophageal carcinoma	GI cancer	23	10 mg/kg Q2W	23	9	4	Treatment-related; ≥ 1 Patient
2017-Frenel-J Clin Oncol	75	1b	02054806	KEYNOTE-028	Cervical cancer	Other cancer	24	10 mg/kg Q2W	24	18	5	Treatment-related; ≥ 2 Patients of any grade
2017-Gangadhar-J Immunother	76		02083484	KEYNOTE-030	Melanoma	Melanoma	947	2 mg/kg Q3W	947	181	29	Treatment-related of interest based on possible immun

													e etiology
2017-Hsu-J Clin Oncol	7 7	1b	0205 4806	KEYNOTE- 028	Nasopharyngeal carcinoma	Other cancer	27	10 mg/kg Q2W	27	20	8	Treatm ent- related/ Drug- related; ≥ 5% Patient s (any grade) and any event (grade 3-5)	
2017-Ott-J Clin Oncol	7 8	1b	0205 4806	KEYNOTE- 028	Endometrial cancer	Other cancer	24	10 mg/kg Q2W	24	13	4	Treatm ent- related; ≥ 1 Patient	
2017-Ott-Ann Oncol	7 9	1b	0205 4806	KEYNOTE- 028	Anal canal carcinoma	GI cancer	25	10 mg/kg Q2W	25	16	3	Treatm ent- related; ≥ 2 Patient s (any grade) and ≥ 1 Patient (grade 3-4)	
2017-Ott-J Clin Oncol	8 0	1b	0205 4806	KEYNOTE- 028	SCLC	Lung cancer	24	10 mg/kg Q2W	24	16	1	Treatm ent- related; ≥ 5% Patient s	
2017-O'Neil-PLoS One	8 1	1b	0205 4806	KEYNOTE- 028	Colorectal carcinoma	GI	23	10 mg/kg Q2W	23	8	1	Treatm ent- related	
2017-Plimack-Lancet Oncol	8 2	1b	0184 8834	KEYNOTE- 012	Urothelial cancer	GU cancer	33	10 mg/kg Q2W	33	20	5	Treatm ent- related; ≥ 10% Patient s (grade 1-2) and all events (grade 3-4)	
2017-Schachter-Lancet	8 3	3	0186 6319	KEYNOTE- 006	Melanoma	Melanoma	55 5	10 mg/kg Q2W	27 8	229	47	Treatm ent- related;	

													≥ 10% Patients in any group
							10 mg/kg Q3W	277	213	46			Treatment-related; ≥ 10% Patients in any group
2017-Tawbi-Lancet Oncol	84	2	02301039	SARC028	Bone sarcoma	Other cancer	84	200 mg Q3W	42	40	21		Events with maximum grade 2 occurring in <10% of patients overall have been suppressed
					Soft-tissue sarcoma	Other cancer		200 mg Q3W	42	38	21		Events with maximum grade 2 occurring in <10% of patients overall have been suppressed
2017-Yamazaki-Cancer Chemother Pharmacol	85	1b	02180061	KEYNOTE-041	Melanoma	Melanoma	42	2 mg/kg Q3W	42	34	8		Treatment-related; ≥ 2 Patients
2017-Zinzani-Blood	86	1b	01953692	KEYNOTE-013	PMBCL	Hematologic malignancy	18	10 mg/kg Q2W, 200mg/kg Q3W	18	11	2		Drug-related adverse events
2018-Adams-Ann Oncol	87	2	02447003	KEYNOTE-086	TNBC	Other cancer	107	200 mg Q3W	107	103	22		Treatment-related ≥ 5%

																						Patient s or immun e- mediat ed ≥ 1 Patient
2018-Adra-Ann Oncol	8 8	2	0249 9952	GU14-206	Germ cell tumors	GU cancer	12	200 mg Q3W	12													All commo n and ≥ grade 3 AEs observ ed
2018-Cho-J Clin Oncol	8 9	2	0260 7631		Thymic epithelial tumor	Other cancer	33	200 mg Q3W	33													Treatm ent- related; > 5% Patient s (any grade) in any histolog ic group or ≥ 1 Patient (irAE)
2018-Cohen-Am J Clin Oncol	9 0	1b	0205 4806	KEYNOTE- 028	Salivary gland carcinoma	Other cancer	26	10 mg/kg Q2W	26	22												Treatm ent- related; ≥ 2 Patient s (any grade) or ≥ 1 Patient (grade 3-5)
2018-Cohen- Lancet	9 1	3	0225 2042	KEYNOTE- 040	Head and neck carcinoma	Other cancer	24 6	200 mg Q3W	24 6	155												Treatm ent- related ≥ 10% Patient s or immun e- related (regard less of attributi on to treatme nt) ≥ 1% Patient

													s in either group
2018-Eggermont-N Engl J Med	9 2	3	0236 2594	EORTC 1325	Melanoma	Melanoma	50 9	200 mg Q3W	50 9	396	75	Treatment-related or irAE; ≥ 10% Patients	
2018-Fuchs-JAMA Oncol	9 3	2	0233 5411	KEYNOTE-059	Gastric or gastro-oesophageal junction cancer	GI cancer	25 9	200 mg Q3W	25 9	156	46	Treatment-related; ≥ 5% Patients (any grade)	
2018-Gadgeel-J Thorac Oncol	9 4	2			SCLC	Lung cancer	45	200 mg Q3W	45			Treatment-related; ≥ 10% Patients (any grade)	
2018-Giaccone-Lancet Oncol	9 5	2	0236 4076		Thymic carcinoma	Other cancer	40	200 mg Q3W	40			All treatment-related	
2018-Hansen-Ann Oncol	9 6	1b	0205 4806	KEYNOTE-028	Prostate adenocarcinoma	GU cancer	23	10 mg/kg Q2W	23	14	3	Treatment-related; ≥ 2 Patients (any grade) or ≥ 1 Patient (grade 3-4)	
2018-Necchi-J Clin Oncol	9 7	2	0273 6266	PURE-01	Urothelial bladder carcinoma	GU cancer	50	200 mg Q3W	50			All treatment-related	
2018-Rugo-Clin Cancer Res	9 8	1b	0205 4806	KEYNOTE-028	Breast cancer	Other cancer	25	10 mg/kg Q2W	25	16	4	Treatment-related; ≥ 2 Patients (any grade) or ≥ 1 Patient (grade 3-4)	
2018-Shitara-Lancet	9 9	3	0237 0498	KEYNOTE-061	Gastric or gastro-oesophageal junction cancer	GI cancer	29 4	200 mg Q3W	29 4	155	42	Treatment-	

												related ≥ 10% Patient s (any grade) in either group or AEs of special interest (based on their likely immun e aetiolog y, irrespe ctive of attributi on to study treatme nt)
2018-Zhu-Lancet Oncol	1 0 0	2	0270 2414	KEYNOTE- 224	Hepatocellular carcinoma	GI cancer	10 4	200 mg Q3W	10 4	76	27	Treatm ent- related; ≥ 10% Patient s (grade 1-2) or ≥ 1 Patient (grade 3-5)
<b>Atezolizumab</b>												
2014-Herbst- Nature	1 0 1	1a	0137 5842	2011- 001422-23	Advanced incurable cancers	Mixed cancer types	27 7	0.01, 0.03, 0.1, 0.3, 1, 3, 10, 20 mg/kg Q3W	27 7	194	35	Treatm ent- related; ≥ 4% Patient s (any grade) and ≥ 2 Patient s (grade 3-4)
2016- Fehrenbacher- Lancet	1 0 2	2	0190 3993	POPLAR	NSCLC	Lung cancer	14 2	1200 mg Q3W	14 2	95	16	Treatm ent- related; ≥ 10%

													Patient s in either group (any grade)
2016-McDermott-J Clin Oncol	1 0 3	1a	0137 5842	2011- 001422-23	RCC	GU cancer	70	3, 10, 15, 20, 1200 mg/kg Q3W	70	59	12	Treatm ent- related; ≥ 2 Patient s (all grades) and ≥ 1 Patient (grade 3-4)	
2016-Rosenberg- Lancet	1 0 4	2	0210 8652	IMvigor 210	Urothelial carcinoma	GU cancer	31 0	1200 mg Q3W	31 0	215	50	Treatm ent- related	
2017-Balar-Lancet	1 0 5	2	0210 8652	IMvigor 210	Urothelial carcinoma	GU cancer	11 9	1200 mg Q3W	11 9	79	19	Treatm ent- related; ≥ 3 Patient s (any grade) and ≥ 1 Patient (grade 3-4)	
2016-Mizugaki- Invest New Drugs	1 0 6	1			Advanced solid tumors	Mixed cancer types	6	10, 20 mg/kg Q3W	6	6	0	≥ 2 Patient s	
								10 mg/kg Q3W	3		0	≥ 2 Patient s	
								20 mg/kg Q3W	3		0	≥ 2 Patient s	
2017-Peters-J Clin Oncol	1 0 7	2	0203 1458	BIRCH	NSCLC	Lung cancer	65 9	1200 mg Q3W	65 9	429	81	Treatm ent- related ≥ 5% Patient s; Combin ed with special interest AEs > 1% Patient s	



2017-Rittmeyer-Lancet	1 0 8	3	0200 8227		NSCLC	Lung cancer	60 9	1200 mg Q3W	60 9	390	90	Treatm ent- related; ≥ 10% Patient s in any group (any grade)
2018-Colevas-Ann Oncol	1 0 9	1	0137 5842		Head and neck carcinoma	Other cancer	32	15 or 20 mg/kg or 2000 mg Q3W	32	21	4	Treatm ent- related; ≥ 5% Patient s (any grade) or ≥ 1 Patient (grade 3-4)
2018-Emens-JAMA Oncol	1 1 0	1	0137 5842		Breast cancer	Other cancer	11 6	15 or 20 mg/kg or 2000 mg Q3W	11 6	73	13	Treatm ent- related; ≥ 3% Patient s (any grade)
2018-Horn-Eur J Cancer	1 1 1	1	0137 5842	PCD4989g	NSLCL	Lung cancer	89	10, 15 or 20 mg/kg or 2000 mg Q3W	89	68	10	Treatm ent- related; > 5% Patient s (any grade)
2018-Lukas-J Neurooncol	1 1 2	1a	0137 5842	PCD4989g	Glioblastoma	Other cancer	16	2000 mg Q3W	16	10	3	Treatm ent- related
2018-McDermott- Nat Med	1 1 3	2	0198 4242	IMmotion1 50	RCC	GU cancer	10 3	1200 mg Q3W	10 3	86	17	All- cause AEs ≥ 20% Patient s (any grade) in any group or AEs of special interest (based on their likely immune

												aetiolog y.
2018-Petrylak- JAMA Oncol	1 1 4	1	0137 5842	2011- 001422-23	Urothelial carcinoma	GU cancer	95	15 mg/kg Q3W	95	64	9	Treatm ent- related; ≥ 1 Patient s
2018-Powles- Lancet	1 1 5	3	0230 2807	IMvigor211	Urothelial carcinoma	GU cancer	45 9	1200 mg Q3W	45 9	319	91	Treatm ent- related; ≥ 5% Patient s (any grade) or ≥ 2% Patient s (grade 3-4) in either group
<b>Avelumab</b>												
2016-Kaufman- Lancet Oncol	1 1 6	2	0215 5647		Merkel cell carcinoma	Other cancer	88	10 mg/kg Q2W	88	62	5	Treatm ent- related; ≥ 5% Patient s (any grade) and ≥ 1 Patient (grade 3-5)
2017-Apolo-J Clin Oncol	1 1 7	1b	0177 2004		Urothelial carcinoma	GU cancer	44	10 mg/kg Q2W	44	29	3	Treatm ent- related; > 5% Patient s (any grade) and ≥ 1 Patient (grade ≥ 3)
2017-Gulley-Lancet Oncol	1 1 8	1b	0177 2004		NSCLC	Lung cancer	18 4	10 mg/kg Q2W	18 4	142	22	Treatm ent- related; ≥ 5% Patient s (any grade) and ≥ 1 Patient

												(grade ≥ 3)
2017-Heery-Lancet Oncol	1 1 9	1a	0177 2004		Advanced solid tumors	Mixed cancer types	15	10 mg/kg Q2W	15	14	5	Treatm ent-related; ≥ 10% Patient s (any grade) and ≥ 1 Patient (grade ≥ 3)
2018-Bang-Ann Oncol	1 2 0	3	0262 5623	JAVELIN Gastric 300	Gastric or gastro-oesophageal junction cancer	GI cancer	18 4	10 mg/kg Q2W	18 4	90	17	Treatm ent-related; > 10% Patient s (any grade) or > 1% Patient s (grade 3)
2018-Barlesi-Lancet Oncol	1 2 1	3	0239 5172	JAVELIN Lung 200	NSLCL	Lung cancer	39 3	10 mg/kg Q2W	39 3	251	39	Treatm ent-related; ≥ 10% Patient s (grade 1-2) and ≥ 1% Patient (grade 3-5)
2018-DAngelo-JAMA Oncol	1 2 2	2	0215 5647	JAVELIN Merkel 200 part B	Merkel cell carcinoma	Other cancer	39	10 mg/kg Q2W	39	28	8	Treatm ent-related; ≥ 5% Patient s (any grade) or ≥ 1 Patient (grade 3-4)
2018-Dirix-Breast Cancer Res Treat	1 2 3	1b	0177 2004	JAVELIN	Breast cancer	Other cancer	16 8	10 mg/kg Q2W	16 8	115	21	Treatm ent-related; ≥ 5% Patient s (any grade)

												or ≥ 1 Patient (grade ≥ 3)
2018-Le Tourneau-J Immunother Cancer	1 2 4	1b	0177 2004	JAVELIN Solid Tumor	Adrenocortical carcinoma	GU cancer	25	10 mg/kg Q2W	25	20	2	Treatm ent- related; ≥ 10% Patient s (any grade) or ≥ 1 Patient (grade 3) in either group
<b>Durvalumab</b>												
2016-Massard-J Clin Oncol	1 2 5	1/ 2	0169 3562		Urothelial Bladder Cancer	GU cancer	61	10 mg/kg Q2W	61	39	3	Treatm ent- related; ≥ 5% patients or ≥ 1 Patient (grade ≥ 3) or ≥ 2 Patient s (AESIs)
2017-Antonia-N Engl J Med	1 2 6	3	0212 5461	PACIFIC	NSCLC	Lung cancer	47 5	10 mg/kg Q2W	47 5	322	56	Treatm ent- related; ≥ 5% Patient s in either group
2017-Powles-JAMA Oncol	1 2 7	1/ 2	0169 3562	CD-ON- MEDI4736- 1108	Solid cancer	Mixed cancer types	97 0	10 mg/kg Q2W	97 0	565	92	Treatm ent- related; ≥ 5% Patient s in either group (all grades) and ≥ 1 Patient in UC cohort (grade ≥ 3)

2018-Garassino-Lancet Oncol	1 2 8	2	0208 7423	ATLANTIC	NSLCL (EGFR+/ALK+)	Lung cancer	44 4	10 mg/kg Q2W	11 1	53	6	Treatm ent-related; ≥ 10% Patient s (grade 1-2) or ≥ 1 Patient (grade 3-4) in any corhot
					NSLCL (EGFR-/ALK-)	Lung cancer		10 mg/kg Q2W	26 5	157	22	Treatm ent-related; ≥ 10% Patient s (grade 1-2) or ≥ 1 Patient (grade 3-4) in any corhot
					NSLCL (EGFR-/ALK- with ≥ 90% tumour cells expressing PD-L1)	Lung cancer		10 mg/kg Q2W	68	46	12	Treatm ent-related; ≥ 10% Patient s (grade 1-2) or ≥ 1 Patient (grade 3-4) in any corhot
2018-Necchi-Eurology	1 2 9	2	0308 1923	APACHE	Germ cell tumors	GU cancer	22	1500 mg Q4W	22			
2018-Siu-JAMA Oncol	1 3 0	2	0231 9044	CONDOR	Head and neck carcinoma	Other cancer	65	10 mg/kg Q2W	65	41	8	Treatm ent-related; > 5% Patient s (any grade) or > 2% Patient s (grade



**eTable 2. Relative Ratios of Grade 3 or Higher Adverse Event Incidences to Respective All-grade Adverse Event Incidences**

AE type	Incidence of all-grade AE (95% CI)	Incidence of grade 3 or higher AE (95% CI)	Risk ratio (95% CI)
Hepatitis	0.85 (0.64-1.10)	0.43 (0.30-0.62)	50.59 (32.01-80.31)
Lipase increased	1.69 (1.35-2.08)	0.71 (0.51-0.98)	42.01 (28.37-61.82)
GGT increased	1.12 (0.85-1.46)	0.47 (0.30-0.69)	41.96 (25.27-66.53)
Type 1 diabetes	0.43 (0.27-0.65)	0.18 (0.10-0.30)	41.86 (20.20-84.44)
Colitis	1.24 (0.99-1.54)	0.47 (0.34-0.65)	37.90 (25.49-56.49)
Increased transaminases	0.38 (0.22-0.62)	0.13 (0.05-0.27)	34.21 (12.46-84.56)
Neutropenia	0.89 (0.69-1.12)	0.28 (0.19-0.41)	31.46 (19.58-49.31)
Hypertension	0.81 (0.56-1.13)	0.23 (0.12-0.40)	28.40 (13.69-55.70)
Hypophosphatemia	0.89 (0.62-1.23)	0.25 (0.14-0.41)	28.09 (14.27-51.00)
Pneumonia	0.66 (0.43-0.98)	0.18 (0.09-0.32)	27.27 (12.56-55.87)
Hypoxia	0.55 (0.30-0.89)	0.15 (0.06-0.30)	27.27 (9.50-66.34)
Hypopituitarism	0.26 (0.12-0.50)	0.07 (0.02-0.16)	26.92 (6.72-85.86)
Hypophysitis	0.60 (0.42-0.82)	0.16 (0.09-0.27)	26.67 (13.66-50.00)
Lymphopenia	1.52 (1.18-1.92)	0.40 (0.26-0.60)	26.32 (16.18-42.17)
Adrenal insufficiency	0.69 (0.50-0.93)	0.18 (0.10-0.30)	26.09 (13.75-47.87)
Dehydration	0.61 (0.40-0.90)	0.15 (0.07-0.27)	24.59 (11.11-51.22)
Pneumonitis	2.79 (2.39-3.23)	0.67 (0.50-0.89)	24.01 (17.41-33.22)
Hyponatremia	1.73 (1.37-2.16)	0.39 (0.25-0.59)	22.54 (13.91-36.02)
ALT increased	3.14 (2.71-3.62)	0.70 (0.52-0.93)	22.29 (15.94-30.57)
AST increased	3.39 (2.94-3.89)	0.75 (0.56-0.99)	22.12 (15.95-30.25)
Amylase increased	1.39 (1.06-1.78)	0.30 (0.17-0.47)	21.58 (11.83-36.73)
Anemia	3.84 (3.35-4.38)	0.78 (0.59-1.02)	20.31 (14.88-27.25)
Hyperglycemia	1.20 (0.91-1.55)	0.24 (0.13-0.38)	20.00 (10.58-34.26)
Platelet count decreased	1.16 (0.85-1.52)	0.20 (0.11-0.35)	17.24 (8.78-32.99)
Pancreatitis	0.42 (0.25-0.67)	0.07 (0.02-0.15)	16.67 (5.1-41.87)
ALP increased	1.86 (1.50-2.28)	0.27 (0.16-0.43)	14.52 (8.47-24.06)
Bilirubin increase	1.05 (0.75-1.41)	0.15 (0.07-0.28)	14.29 (6.16-28.88)
Hypotension	0.79 (0.53-1.11)	0.11 (0.05-0.23)	13.92 (5.42-32.04)
Dyspnea	3.88 (3.38-4.45)	0.42 (0.30-0.59)	10.82 (7.61-15.5)
Blood creatinine increased	1.70 (1.35-2.12)	0.18 (0.09-0.30)	10.59 (5.37-18.56)
Autoimmune thyroiditis	0.20 (0.07-0.45)	0.02 (0.00-0.09)	10.00 (1.36-63.79)
Rash maculo-papular	2.78 (2.38-3.23)	0.25 (0.16-0.37)	8.99 (5.48-13.71)
White blood cell decreased	0.83 (0.59-1.14)	0.07 (0.03-0.15)	8.43 (3.19-19.78)
Back pain	2.12 (1.76-2.54)	0.16 (0.09-0.27)	7.55 (3.97-12.99)
Pain in extremity	1.21 (0.87-1.62)	0.09 (0.04-0.20)	7.44 (2.90-17.82)
Infusion-related reaction	3.63 (3.15-4.17)	0.26 (0.16-0.40)	7.16 (4.33-11.34)
Stomatitis	1.27 (1.02-1.58)	0.09 (0.04-0.17)	7.09 (3.13-13.72)
Uveitis	0.29 (0.15-0.51)	0.02 (0.00-0.07)	6.90 (0.90-29.38)
Abdominal pain	2.19 (1.82-2.62)	0.15 (0.08-0.26)	6.85 (3.47-12.18)
Diarrhea	9.47 (8.43-10.58)	0.59 (0.45-0.77)	6.23 (4.62-8.29)
Asthenia	5.58 (4.92-6.31)	0.34 (0.25-0.48)	6.09 (4.30-8.73)

TSH increased	1.01 (0.72-1.37)	0.06 (0.02-0.14)	5.94 (1.66-14.40)
TSH decreased	0.37 (0.18-0.64)	0.02 (0.00-0.08)	5.41 (0.76-25.40)
Vomiting	3.53 (3.06-4.05)	0.19 (0.12-0.29)	5.38 (3.35-8.46)
Thyroiditis	0.75 (0.52-1.04)	0.04 (0.01-0.10)	5.33 (1.32-14.61)
Fatigue	18.26 (16.49-20.11)	0.89 (0.69-1.14)	4.87 (3.70-6.34)
Mucosal inflammation	1.10 (0.83-1.44)	0.05 (0.02-0.12)	4.55 (1.36-11.12)
Pain	2.03 (1.63-2.48)	0.09 (0.03-0.19)	4.43 (1.57-9.43)
Myalgia	2.95 (2.53-3.44)	0.12 (0.06-0.20)	4.07 (2.15-6.90)
Hypersensitivity	0.81 (0.55-1.15)	0.03 (0.01-0.10)	3.70 (0.77-12.58)
Peripheral neuropathy	0.94 (0.73-1.20)	0.03 (0.01-0.08)	3.19 (1.14-9.03)
Rash	9.31 (8.29-10.41)	0.27 (0.19-0.38)	2.90 (2.02-4.14)
Headache	3.37 (2.90-3.90)	0.09 (0.04-0.17)	2.67 (1.17-5.02)
Influenza-like illness	1.89 (1.49-2.35)	0.05 (0.01-0.12)	2.65 (0.62-6.67)
Decreased appetite	7.18 (6.36-8.06)	0.19 (0.13-0.27)	2.65 (1.72-3.85)
Arthralgia	5.83 (5.15-6.59)	0.15 (0.10-0.23)	2.57 (1.64-4.02)
Malaise	1.42 (1.06-1.84)	0.03 (0.01-0.10)	2.11 (0.49-7.67)
Nausea	8.39 (7.46-9.39)	0.17 (0.12-0.24)	2.03 (1.35-2.96)
Insomnia	1.02 (0.71-1.41)	0.02 (0.00-0.07)	1.96 (0.27-7.20)
Dizziness	1.58 (1.22-2.00)	0.03 (0.01-0.08)	1.9 (0.37-5.46)
Alopecia	0.53 (0.38-0.73)	0.01 (0.00-0.05)	1.89 (0.38-9.03)
Pyrexia	4.77 (4.18-5.42)	0.08 (0.04-0.14)	1.68 (0.93-3.01)
Constipation	3.60 (3.12-4.13)	0.06 (0.03-0.12)	1.67 (0.74-3.31)
Erythema	1.30 (0.96-1.71)	0.02 (0.00-0.08)	1.54 (0.23-6.08)
Hyperthyroidism	2.82 (2.40-3.29)	0.04 (0.02-0.10)	1.42 (0.57-3.64)
Weight decreased	2.14 (1.74-2.60)	0.03 (0.01-0.09)	1.40 (0.29-4.25)
Dry mouth	2.16 (1.74-2.63)	0.03 (0.01-0.09)	1.39 (0.28-4.22)
Hypothyroidism	6.07 (5.35-6.85)	0.08 (0.04-0.13)	1.32 (0.71-2.22)
Cough	4.17 (3.64-4.77)	0.05 (0.02-0.10)	1.20 (0.42-2.34)
Edema peripheral	1.72 (1.40-2.11)	0.02 (0.01-0.07)	1.16 (0.29-4.13)
Chills	2.36 (1.96-2.83)	0.02 (0.01-0.07)	0.85 (0.23-3.20)
Dysgeusia	1.28 (1.01-1.59)	0.01 (0.00-0.05)	0.78 (0.17-3.90)
Dry skin	2.59 (2.17-3.08)	0.02 (0.00-0.06)	0.77 (0.10-2.25)
Vitiligo	3.26 (2.80-3.79)	0.02 (0.00-0.06)	0.61 (0.15-1.99)
Pruritus	10.61 (9.46-11.83)	0.06 (0.03-0.11)	0.57 (0.33-1.04)

AE: adverse event; CI: confidence interval; ALT: alanine transaminase; AST: aspartate aminotransferase; ALP: alkaline phosphatase; GGT: Gamma-glutamyltransferase; TSH: Thyroid-stimulating hormone.



**eTable 3. List of Studies That Reported At Least One Treatment-related Death**

Study	Ref	Total Patient number	Cancer type	Cancer type category	Patient number	Dosing schedule	Number of treatment-related death	Causes of death
<b>Nivolumab</b>								
2015-Gettinger-J Clin Oncol	12	129	NSCLC	Lung cancer	33	1 mg/kg Q2W	2	Pneumonitis
					37	3 mg/kg Q2W	1	Pneumonitis
					59	10 mg/kg Q2W	0	
2015-Rizvi-Lancet Oncol	17	117	NSCLC	Lung cancer	117	3 mg/kg Q2W	2	Hypoxic pneumonia (n=1), ischemic stroke (n=1)
2016-Ferris-N Engl J Med	21	236	Head and neck carcinoma	Other cancer	236	3 mg/kg Q2W	2	Pneumonitis(n=1), hypercalcemia/pulmonary embolism (n=1)
2016-Lesokhin-J Clin Oncol	23	81	Hematologic malignancy	Hematologic malignancy	81	1, 3 mg/kg Q2W	1	Pneumonitis/ARDS
2016-Sharma-Lancet Oncol	24	78	Urothelial carcinoma	GU cancer	78	3 mg/kg Q2W	2	Pneumonitis (n=1), thrombocytopenia (n=1)
2017-Carbone-N Engl J Med	27	267	NSCLC	Lung cancer	267	3 mg/kg Q2W	2	Multiorgan failure (n=1), pneumonitis (n=1)
2017-Kang-Lancet	29	330	Gastric or gastro-oesophageal junction cancer	GI cancer	330	3 mg/kg Q2W	5	Hepatitis (n=1), cardiac arrest (n=1), death (unknown cause; n=1), exertional dyspnea (n=1), and pneumonia (n=1)
2017-Sharma-Lancet Oncol	35	270	Urothelial carcinoma	GU cancer	270	3 mg/kg Q2W	3	Pneumonitis (n=1), acute respiratory failure (n=1), cardiovascular failure (n=1)
2018-Gettinger-J Clin Oncol	42	129	NSLCL	Lung cancer	129	1 (n=33), 3 (n=37) or 10 (n=59) mg/kg Q2W	1	Sepsis
2018-Hellmann-N Engl J Med	43	391	NSCLC	Lung cancer	391	240 mg Q2W	2	Pneumonitis with sepsis (n=1), neutropenia with sepsis (n=1)
2018-Hodi-Lancet Oncol	44	313	Melanoma	Melanoma	313	3 mg/kg Q2W	1	Neutropenia
2018-Lee-Lung Cancer	46	100	NSCLC	Lung cancer	100	3 mg/kg Q2W	1	Pneumonitis
2018-Ma-J Clin Oncol	48	45	Nasopharyngeal carcinoma	Other cancer	45	3 mg/kg Q2W	1	Sepsis
2018-Quispel-Janssen-J Thorac Oncol	50	34	Pleural mesothelioma	Other cancer	34	3 mg/kg Q2W	1	Pneumonitis
2018-Ready-J Thorac Oncol	51	109	SCLC	Lung cancer	109	3 mg/kg Q2W	1	Pneumonitis
<b>Pembrolizumab</b>								

2015-Garon-N Engl J Med	5 2	4 9 5	NSCLC	Lung cancer	6	2 mg/kg Q3W	0	
					287	10 mg/kg Q3W	1	Pneumonitis/Interstitial lung disease
					202	10 mg/kg Q2W	0	
2016-Herbst-Lancet	5 9	6 8 2	NSCLC	Lung cancer	339	2 mg/kg Q3W	3	Pneumonitis (n=2), pneumonia (n=1)
					343	10 mg/kg Q3W	3	Pneumonitis (n=1), pneumonia (n=1), myocardial infarction (n=1)
2016-Nanda-J Clin Oncol	6 2	3 2	TNBC	Other cancer	32	10 mg/kg Q2W	1	DIC accompanied by grade 4 decreased blood fibrinogen
2016-Reck-N Engl J Med	6 4	1 5 4	NSCLC	Lung cancer	154	200 mg Q3W	1	Sudden death of unknown cause
2017-Balar-Lancet Oncol	6 9	3 7 0	Urothelial carcinoma	GU cancer	370	200 mg Q3W	1	Myositis
2017-Bellmunt-N Engl J Med	7 0	2 6 6	Advanced urothelial carcinoma	GU cancer	266	200 mg Q3W	4	Pneumonitis (n=1), urinary tract obstruction (n=1), malignant neoplasm progression (n=1), unspecified cause (n=1)
2017-Bauml-J Clin Oncol	7 1	1 7 1	Head and neck cancer	Other cancer	171	200 mg Q3W	1	Pneumonitis
2017-Hsu-J Clin Oncol	7 7	2 7	Nasopharyngeal carcinoma	Other cancer	27	10 mg/kg Q2W	1	Sepsis
2017-Schachter-Lancet	8 3	5 5 5	Melanoma	Melanoma	278	10 mg/kg Q2W	1	Sepsis
					277	10 mg/kg Q3W	0	
2017-Tawbi-Lancet Oncol	8 4	8 4	Bone sarcoma	Other cancer	42	200 mg Q3W	2	Neoplasms (n=1), respiratory, thoracic and mediastinal disorders (n=1)
			Soft-tissue sarcoma	Other cancer	42	200 mg Q3W	4	Sepsis (n=1), neoplasms (n=1), respiratory failure (n=1), cause not specified (n=1)
2017-Yamazaki-Cancer Chemother Pharmacol	8 5	4 2	Melanoma	Melanoma	42	2 mg/kg Q3W	2	Unknown cause (n=1), cerebral hemorrhage (n=1)
2018-Cohen-Am J Clin Oncol	9 0	2 6	Salivary gland carcinoma	Other cancer	26	10 mg/kg Q2W	1	Interstitial lung disease
2018-Cohen-Lancet	9 1	2 4 6	Head and neck carcinoma	Other cancer	246	200 mg Q3W	1	Severe skin reaction
2018-Eggermont-N Engl J Med	9 2	5 0 9	Melanoma	Melanoma	509	200 mg Q3W	1	Myositis
2018-Gadgeel-J Thorac Oncol	9 4	4 5	SCLC	Lung cancer	45	200 mg Q3W	1	Acute coronary syndrome
2018-Shitara-Lancet	9 9	2 9 4	Gastric or gastro-oesophageal junction cancer	GI cancer	294	200 mg Q3W	2	Colitis (n=1), interstitial lung disease (n=1)
2018-Zhu-Lancet Oncol	1 0 0	1 0 4	Hepatocellular carcinoma	GI cancer	104	200 mg Q3W	1	Ulcerative oesophagitis
<b>Atezolizumab</b>								
2016-Fehrenbacher-Lancet	1 0 2	1 4 2	NSCLC	Lung cancer	142	1200 mg Q3W	1	Cardiac failure

2017-Balar-Lancet	1 0 5	1 1 9	Urothelial carcinoma	GU cancer	119	1200 mg Q3W	1	Sepsis
2018-Emens-JAMA Oncol	1 1 0	1 1 6	Breast cancer	Other cancer	116	15 or 20 mg/kg or 2000 mg Q3W	2	Pulmonary hypertension (n=1), cause not specified (n=1)
2018-Powles-Lancet	1 1 5	4 5 9	Urothelial carcinoma	GU cancer	459	1200 mg Q3W	4	General physical health deterioration (n=1), respiratory failure (n=1), intestinal perforation (n=1), toxic epidermal necrolysis (n=1)
<b>Avelumab</b>								
2017-Gulley-Lancet Oncol	1 1 8	1 8 4	NSCLC	Lung cancer	184	10 mg/kg Q2W	1	Radiation pneumonitis
2018-Dirix-Breast Cancer Res Treat	1 2 3	1 6 8	Breast cancer	Other cancer	168	10 mg/kg Q2W	2	Acute hepatic failure (n=1), respiratory distress (n=1)
<b>Durvalumab</b>								
2017-Antonia-N Engl J Med	1 2 6	4 7 5	NSCLC	Lung cancer	475	10 mg/kg Q2W	7	Pneumonitis (n=4), cardiomyopathy (n=1), right ventricular failure (n=1), respiratory distress (n=1), respiratory failure (n=1), brain natriuretic peptide increased (n=1), radiation pneumonitis (n=1)
2017-Powles-JAMA Oncol	1 2 7	9 7 0	Solid cancer	Mixed cancer types	970	10 mg/kg Q2W	4	Pneumonia in the setting of pneumonitis (n=1), autoimmune hepatitis and pneumonitis (n=1), and immune thrombocytopenic purpura (n=1)

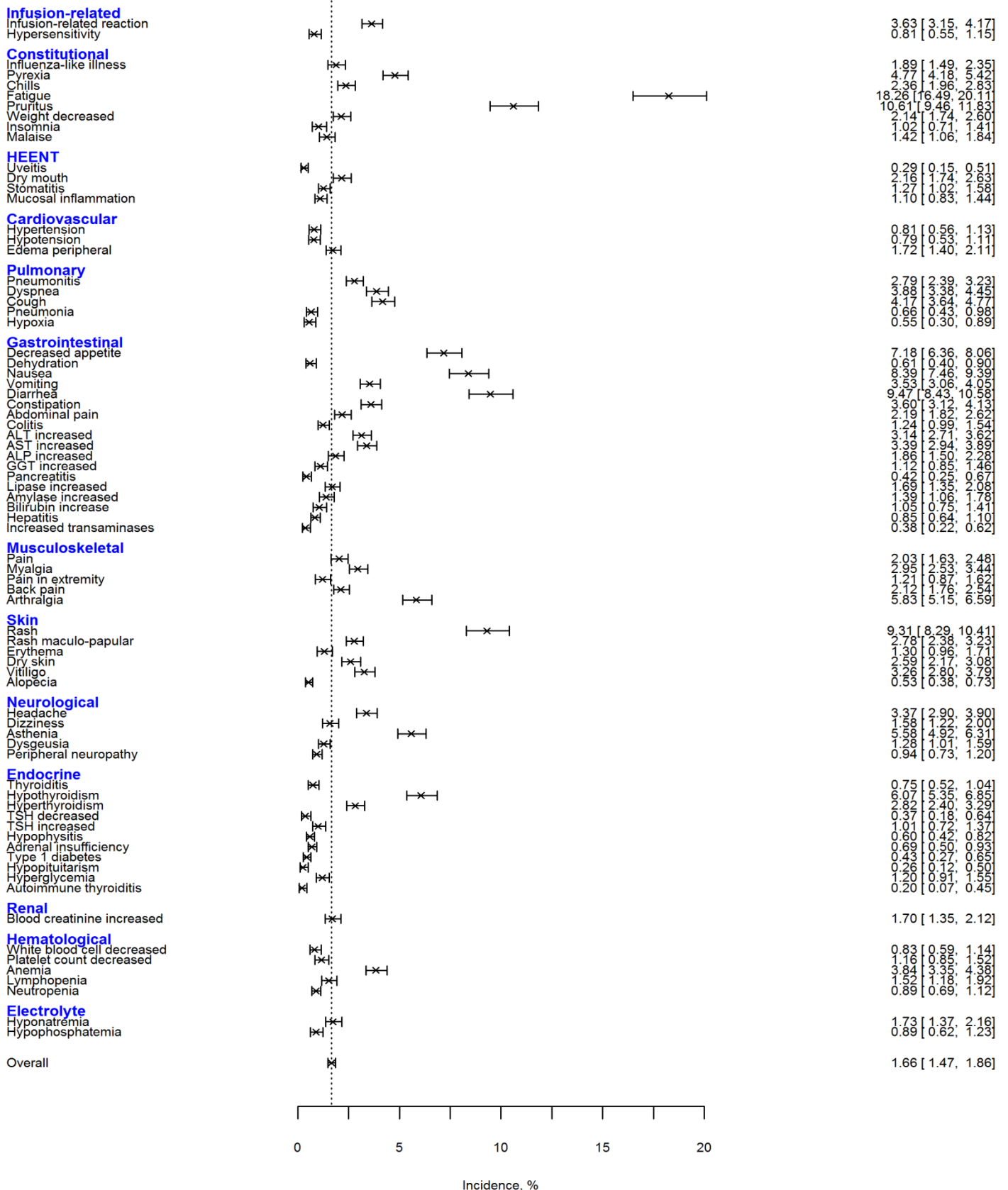
AE: adverse event; NSCLC: non-small cell lung cancer; SCLC: small cell lung cancer; RCC: renal cell carcinoma; TNBC: triple-negative breast cancer; GI: gastrointestinal; GU: genitourinary; Q2W: every 2 weeks; Q3W: every 3 weeks; ARDS: acute respiratory distress syndrome.

# eFigure 1. Incidences of All Adverse Events

## A. Incidences of All-grade Adverse Events

All-grade AEs

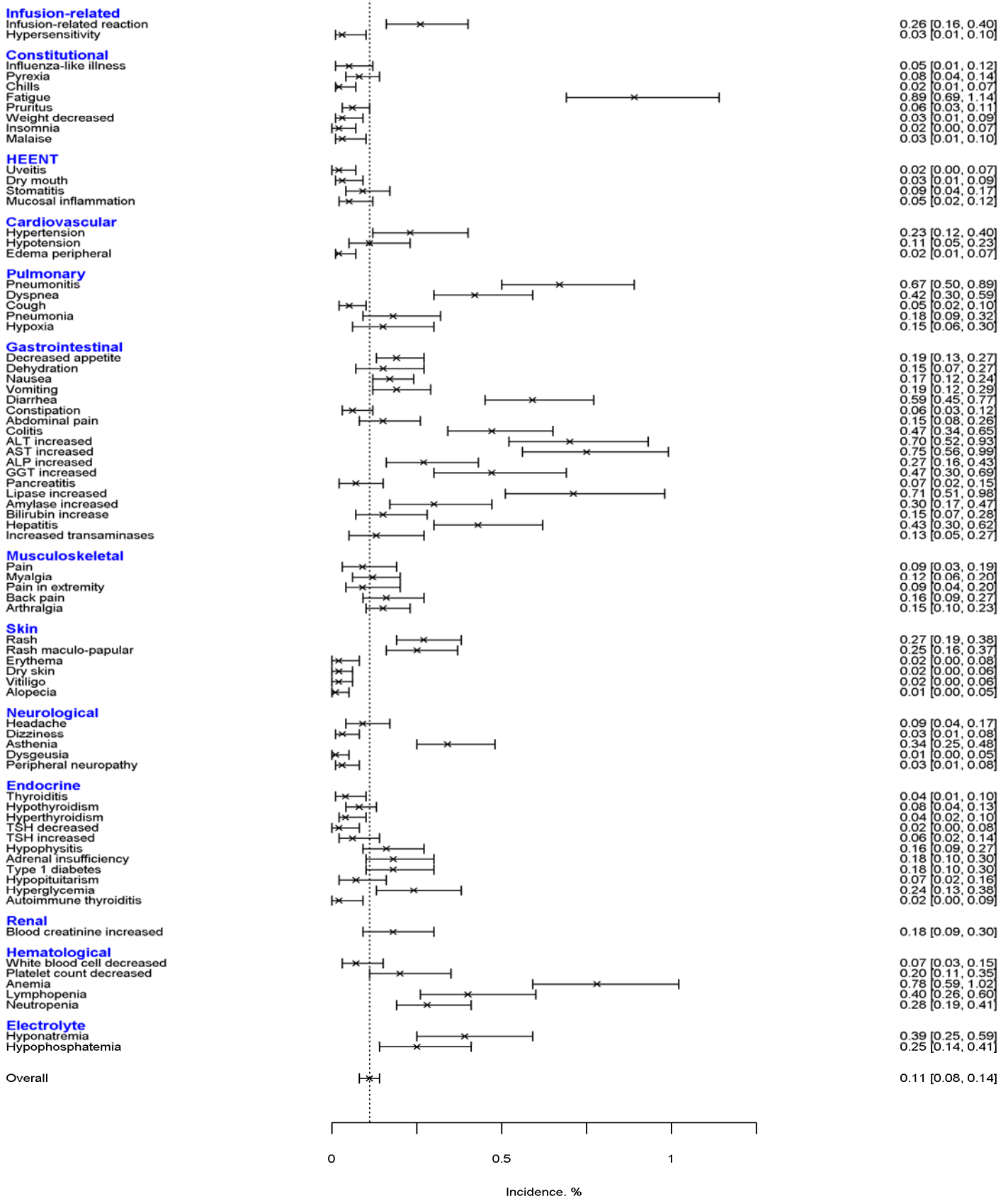
Incidence [95% CI]



## B. Incidences of Grade 3 or Higher Adverse Events

Grade 3 and above AEs

Incidence [95% CI]

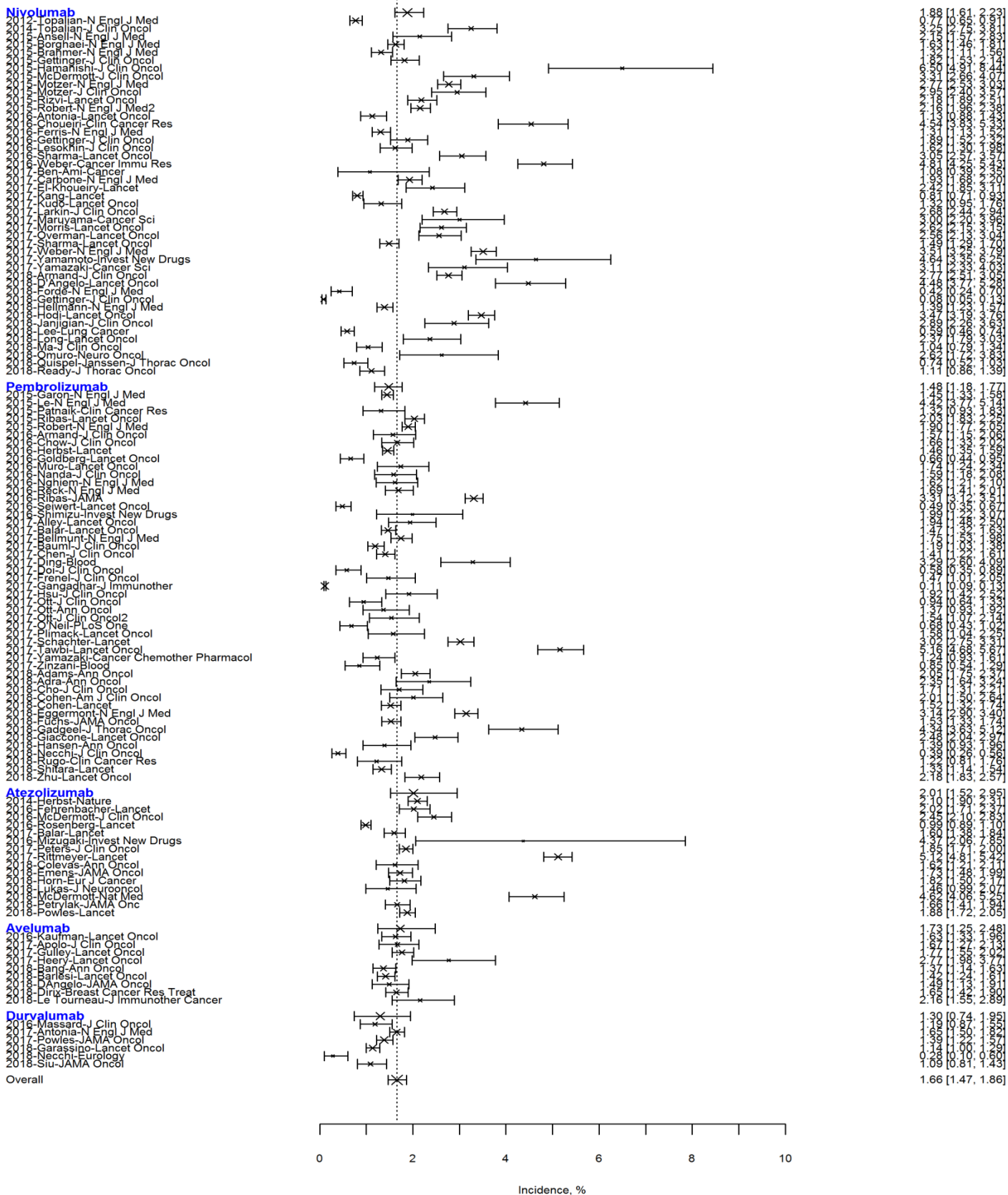


# eFigure 2. Mean Incidences of Adverse Events by Study

## A. Mean Incidences of All-grade Adverse Events by Study

All-grade AEs

Incidence [95% CI]



## B. Mean Incidences of Grade 3 or Higher Adverse Events by Study

Grade 3 and above AEs

Incidence [95% CI]

### Nivolumab

Brannmer-J Clin Oncol  
 Lobianco-J Clin Oncol  
 Soballe-J Clin Oncol  
 Yamazaki-Lancet Oncol  
 Brannmer-N Engl J Med  
 Gettinger-J Clin Oncol  
 Vaidyanathan-J Clin Oncol  
 McDermott-J Clin Oncol  
 Wolzner-J Clin Oncol  
 Rizvi-Lancet Oncol  
 Robert-N Engl J Med  
 Antonia-Lancet Oncol  
 Khoury Clin Cancer Res  
 Ferris-N Engl J Med  
 Lesokhin-J Clin Oncol  
 Sharma-Lancet Oncol  
 Ribera-Lancet Oncol  
 Re-Amer Cancer Res  
 Carbone-N Engl J Med  
 Khoury-Lancet  
 Kudo-Lancet Oncol  
 Varkin-J Clin Oncol  
 Waruya-Lancet Oncol  
 Morris-Lancet Oncol  
 Overman-Lancet Oncol  
 Sharma-Lancet Oncol  
 Weber-N Engl J Med  
 Yamamoto-Invest New Drugs  
 Armand-J Clin Oncol  
 D'Angelo-Lancet Oncol  
 Lowery-Lancet Oncol  
 Leung-Engl J Med  
 Hellmann-N Engl J Med  
 Rodriguez-Lancet Oncol  
 Langhahn-J Clin Oncol  
 Lee-Lung Cancer  
 Long-Lancet Oncol  
 Vignani-Lancet Oncol  
 Omuro-Neuro Oncol  
 Quispel-Janssen-J Thorac Oncol  
 Ready-J Thorac Oncol

### Pembrolizumab

Le-N Engl J Med  
 Patnaik-J Clin Cancer Res  
 Robert-N Engl J Med  
 Armand-J Clin Oncol  
 Lowery-Lancet Oncol  
 Goldberg-Lancet Oncol  
 Wuro-Lancet Oncol  
 Nghiem-N Engl J Med  
 Seck-N Engl J Med  
 Siewert-Lancet Oncol  
 Shimizu-Invest New Drugs  
 Alley-Lancet Oncol  
 Hellmunt-N Engl J Med  
 Nishimura-J Clin Oncol  
 Ding-Blood  
 Loriot-Lancet Oncol  
 Shenel-J Clin Oncol  
 Gangadhar-J Immunother  
 Chau-J Clin Oncol  
 Ott-Ann Oncol  
 Ott-Neu Oncol  
 Jimack-Lancet Oncol  
 Schachter-Lancet  
 Lawler-Lancet Oncol  
 Yamazaki-Cancer Chemother Pharmacol  
 Kinzani-Blood  
 Adra-Ann Oncol  
 Cho-J Clin Oncol  
 Cohen-Amer Cancer Res  
 Gggermont-N Engl J Med  
 Gadgeel-J Thorac Oncol  
 Giaccone-Lancet Oncol  
 Jansen-Ann Oncol  
 Lecchi-J Clin Oncol  
 Lugo-Clin Cancer Res  
 Jhara-Lancet  
 Zhu-Lancet Oncol

### Atezolizumab

Berbst-Nature  
 Schrenbacher-Lancet  
 McDermott-J Clin Oncol  
 Rosenber-Lancet  
 Salar-Lancet  
 Wuzgaki-Invest New Drugs  
 Peters-J Clin Oncol  
 Rittmeyer-Lancet  
 Colevas-Ann Oncol  
 Timens-JAMA Oncol  
 Horn-Lung Cancer  
 Lukas-J Neurooncol  
 McDermott-Nat Med  
 Petrylak-JAMA Oncol  
 Powles-Lancet

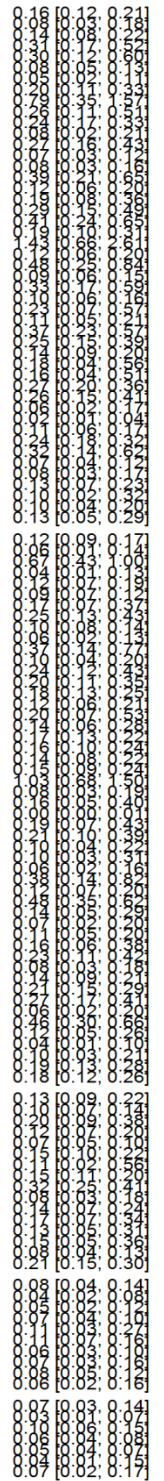
### Avelumab

B-Kaufman-Lancet Oncol  
 Apolo-J Clin Oncol  
 Gulley-Lancet Oncol  
 Leery-Lancet Oncol  
 Wang-Ann Oncol  
 D'Angelo-JAMA Oncol  
 Dirix-Breast Cancer Res Treat  
 Le Tourneau-J Immunother Cancer

### Durvalumab

Massard-J Clin Oncol  
 Antonia-N Engl J Med  
 Powles-JAMA Oncol  
 Garassino-Lancet Oncol  
 Necchi-Lancet Oncol  
 Liu-JAMA Oncol

Overall

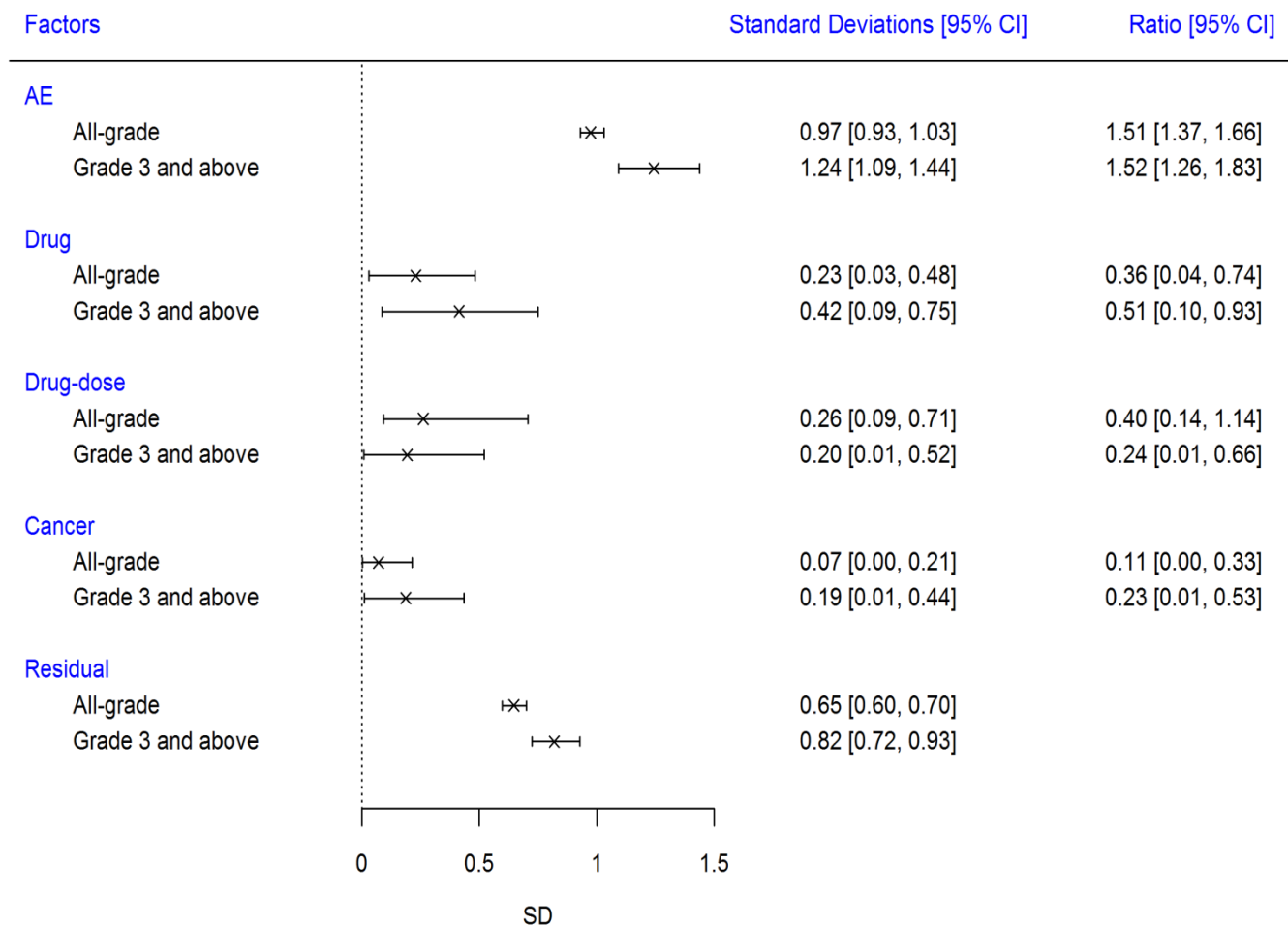


0.11 [0.08, 0.14]

0 1 2 3

Incidence, %

**eFigure 3. Heterogeneity of Adverse Event Incidence in This Meta-Analysis**





eFigure 4. Mean Incidences of All-grade Adverse Events by Study if Ignoring Missing Data

All-grade AEs

Incidence [95% CI]

