

Supplementary Online Content

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

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eMethods

Data source

The study is based on adverse drug reactions reported in VigiBase, the WHO global Individual Safety Case Reports (ISCRs) database, originating from >130 countries. VigiBase is managed by the Uppsala Monitoring Center (UMC) and contains >16,000,000 ISCRs submitted by national pharmacovigilance centers since 1968. These reports originate from different sources such as healthcare professionals, patients, and pharmaceutical companies and are generally notified post-marketing.

Search

Vigilyze was accessed and queried on January 30, 2018. Drug terms searched were “ipilimumab,” and “tremelimumab” (anti-CTLA-4); “nivolumab,” and “pembrolizumab” (anti-PD-1); and “atezolizumab,” “avelumab,” and “durvalumab” (anti-PD-L1), yielding 31,059 unique reports. Combination therapy was defined as anti-PD-1 or anti-PD-L1 given concurrently with anti-CTLA-4. Each report contains general administrative information (country of origin, date of reporting, reporter qualification), patient characteristics (sex, age), drugs (indication for the drug, start and end dates, dosage regimen, route of administration), reactions/events (reported terms, MedDRA classification terms, onset date, end date, seriousness, final outcome). Date of treatment initiation, date of symptom onset and death, patient demographics, and cancer type were collected when reported.

eTable 1: List of irAEs included

Toxicity
Endocrine
Addison's disease
Adrenal insufficiency
Adrenocortical insufficiency acute
Adrenocorticotrophic hormone deficiency
Autoimmune thyroiditis
Diabetic ketoacidosis
Fulminant type 1 diabetes mellitus
Hyperthyroidism
Hypophysitis
Hypopituitarism
Hypothalamo-pituitary disorder
Hypothyroidism
Lymphocytic hypophysitis
Pituitary enlargement
Secondary adrenocortical insufficiency
Thyroiditis
Type 1 diabetes mellitus
Gastrointestinal
Acute hepatic failure
Autoimmune colitis
Autoimmune hepatitis
Autoimmune pancreatitis
Colitis
Colitis microscopic
Diarrhoea
Diarrhoea haemorrhagic
Drug-induced liver injury
Duodenitis
Enteritis
Enterocolitis
Enterocolitis haemorrhagic
Eosinophilic oesophagitis
Hepatic failure
Hepatitis
Hepatitis acute
Hepatotoxicity
Pancreatitis
Ulcerative gastritis
Pulmonary

Pneumonitis
Organising pneumonia
Cardiac
Myocarditis
Autoimmune myocarditis
Neurologic
Autoimmune neuropathy
Demyelinating polyneuropathy
Encephalitis
Encephalitis autoimmune
Encephalopathy
Guillain-Barre syndrome
Limbic encephalitis
Meningitis
Meningitis aseptic
Myasthenia gravis
Myasthenia gravis crisis
Myasthenic syndrome
Myositis
Necrotising myositis
Neuropathy peripheral
Ocular myasthenia
Peripheral motor neuropathy
Peripheral sensorimotor neuropathy
Peripheral sensory neuropathy
Polymyositis
Rhabdomyolysis
Hematologic
Autoimmune haemolytic anaemia
Haemolytic anaemia
Histiocytosis haematophagic
Immune thrombocytopenic purpura
Renal
Nephritis
Skin
Pemphigoid
Skin toxicity
Dermatitis
Dermatitis psoriasiform
Drug eruption

Toxic skin eruption
Acute febrile neutrophilic dermatosis
Other
Granulomatosis with polyangiitis
Infusion related reaction

eTable 2: Additional demographic of fatal immune related adverse events in Vigilyze

	Ipilimumab (n = 193)	Anti-PD- 1/PD-L1	Combination (n = 87)	P value

		(n = 333)		
Type of fatal irAE (n, %)				
Neurologic	11 (6)	50 (15)	7 (8)	0.003
Myasthenia Gravis	1	22	2	
Guillan Barre Syndrome	3	4	0	
Encephalitis/Meningitis	2	20	4	
Other*	5	4	1	
Hematologic	3 (2)	14 (4)	2 (2)	0.22
ITP	1	3	0	
Pancytopenia	2	1	1	
Agranulocytosis	0	1	0	
Hemolysis/Hemolytic anemia	0	3	0	
HLH	0	2	0	
TTP	0	1	1	
Reporting Region				
Americas	105 (54)	157 (47)	74 (85)	<0.001
Europe	69 (36)	128 (38)	12 (14)	
Asia	2 (1)	37 (11)	1 (1)	
Oceania	17 (9)	11 (3)	0 (0)	

*Includes chronic idiopathic demyelinating polyneuropathy, posterior reversible encephalopathy syndrome, amyotrophy, neuritis, unspecified neuropathy, unspecified neurotoxicity. ITP: idiopathic thrombocytopenic purpura; HLH: hemophagocytic lymphohistiocytosis; TTP: thrombotic thrombocytopenic purpura.

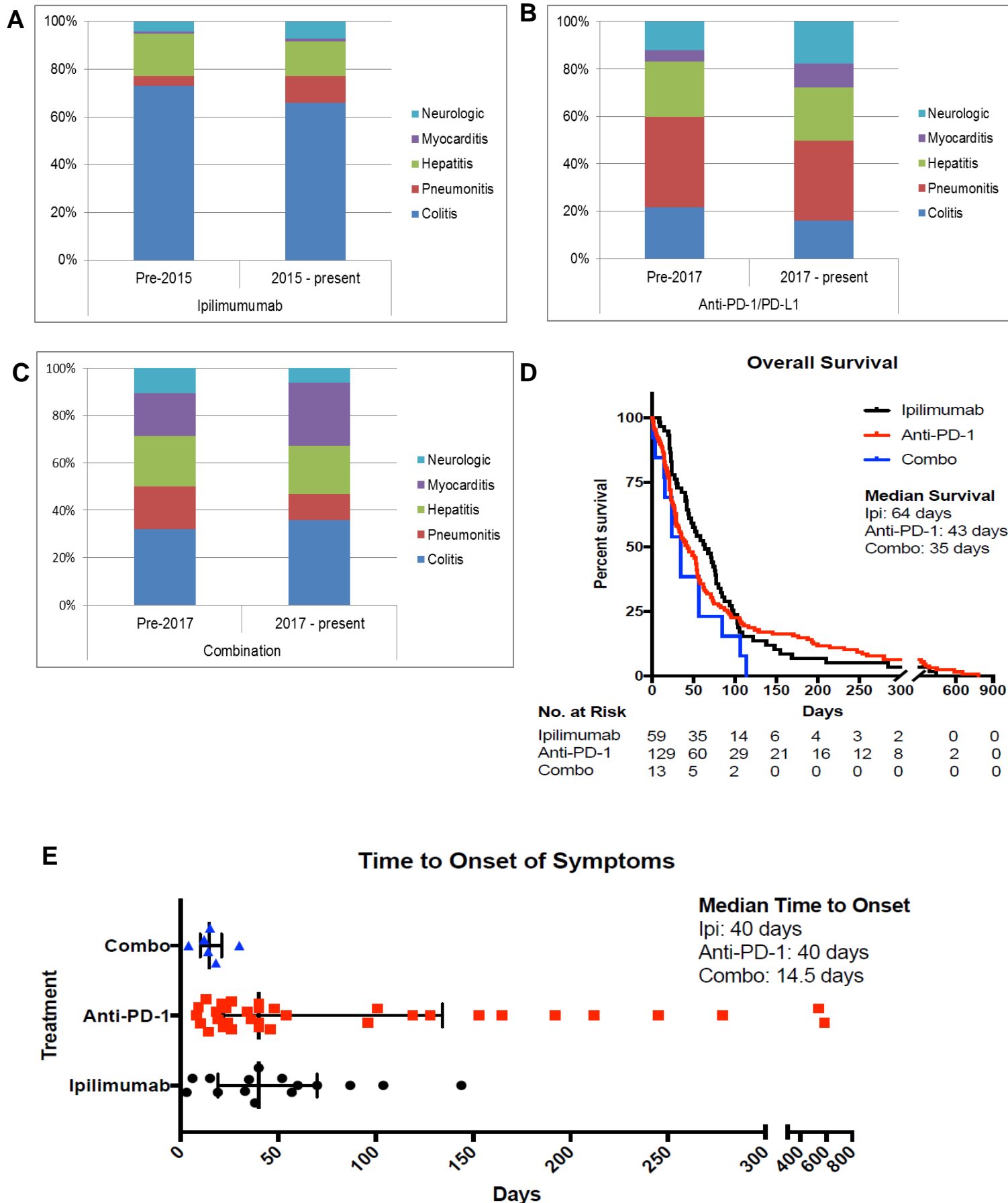
eTable 3: Clinical features of 21 ICI-related fatalities from six large academic centers

Characteristic (n=21)	Number (%)
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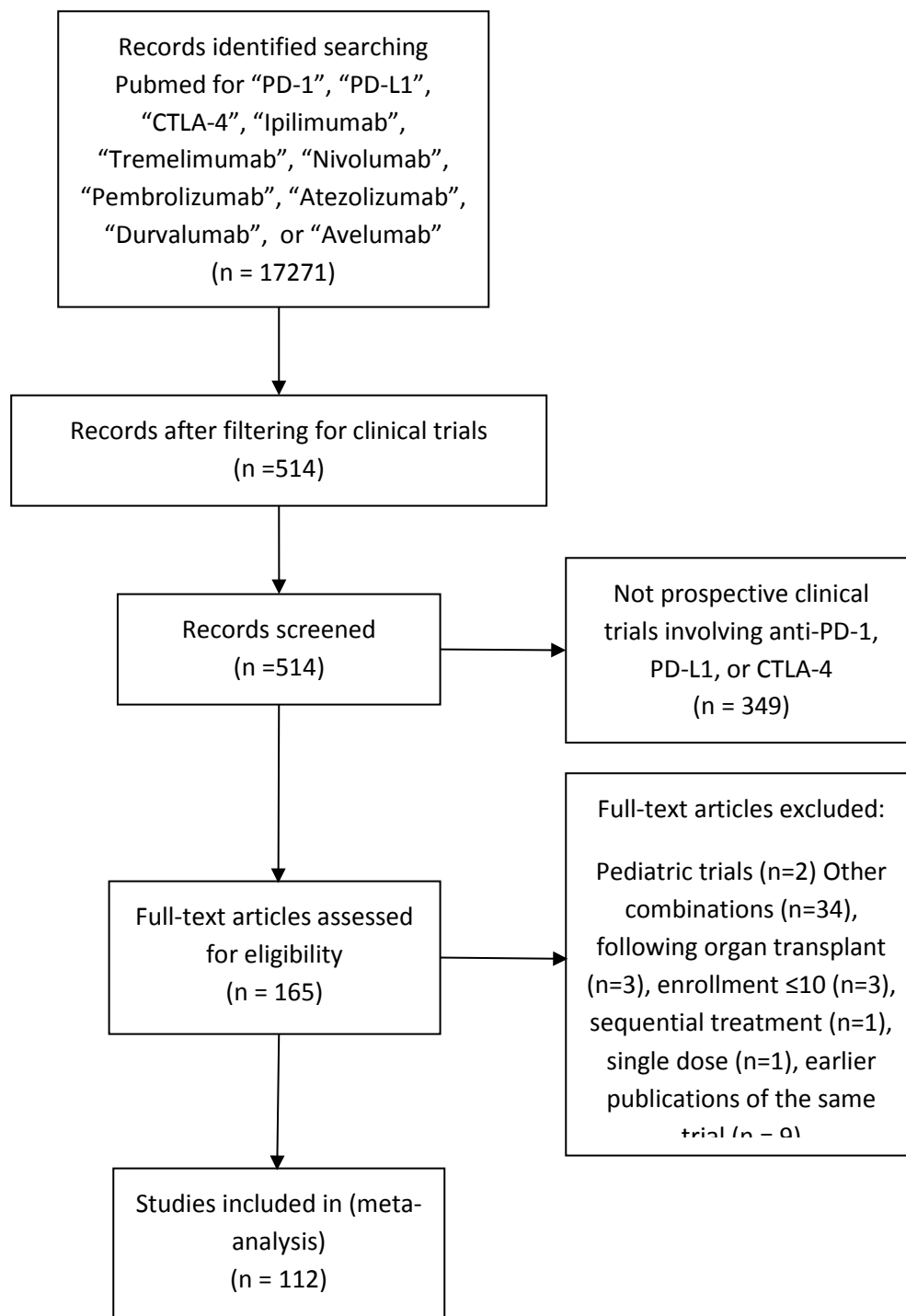
Female gender	8 (38)
Age (years; median, range)	72 (37 – 84)
Melanoma	19 (90)
Merkel or squamous cell carcinoma	2 (10)
Prior therapies	
Other immune therapy	4 (19)
BRAF and/or MEK inhibitors	4 (19)
Chemotherapy	3 (14)
Co-morbidities	
Hypertension	12 (57)
Cardiac*	6 (29)
Prior organ transplant	2 (10)
Autoimmune disease [†]	2 (10)
Diabetes	1 (5)
Regimen	
Pembrolizumab	7 (33)
Nivolumab	2 (10)
Ipilimumab	7 (33)
Ipilimumab + nivolumab	5 (24)
Type of fatal irAE	
Myocarditis	6 (29)
Neurologic [#]	5 (24)
Colitis/enteritis	6 (29)
Hepatic failure	5 (24)
Myositis	3 (14)
Inflammatory syndrome and hypophysitis	2 (10)
Stevens Johnson Syndrome	1 (5)
Time to symptom onset (days; median, range)	15 (3 – 543)
Time to steroids (days; median, range)	5 (0 – 112)
Time to death (days; median, range)	85 (10 – 585)
Symptom onset to death (days; median, range)	32 (3 – 355)
Chronicity	
Single hospitalization	13 (62)
Multiple hospitalizations	8 (38)
Treatment	
High dose steroids	21 (100)
Infliximab	4 (19)
Intravenous immunoglobulin	5 (24)
Rituximab	1 (5)

*Atrial arrhythmias (n=5), coronary artery disease (n=1), #Encephalitis (n=2), Guillain-Barré Syndrome/acute inflammatory demyelinating polyneuropathy (n=1), undefined progressive weakness (n=2). †Graves disease in both cases.

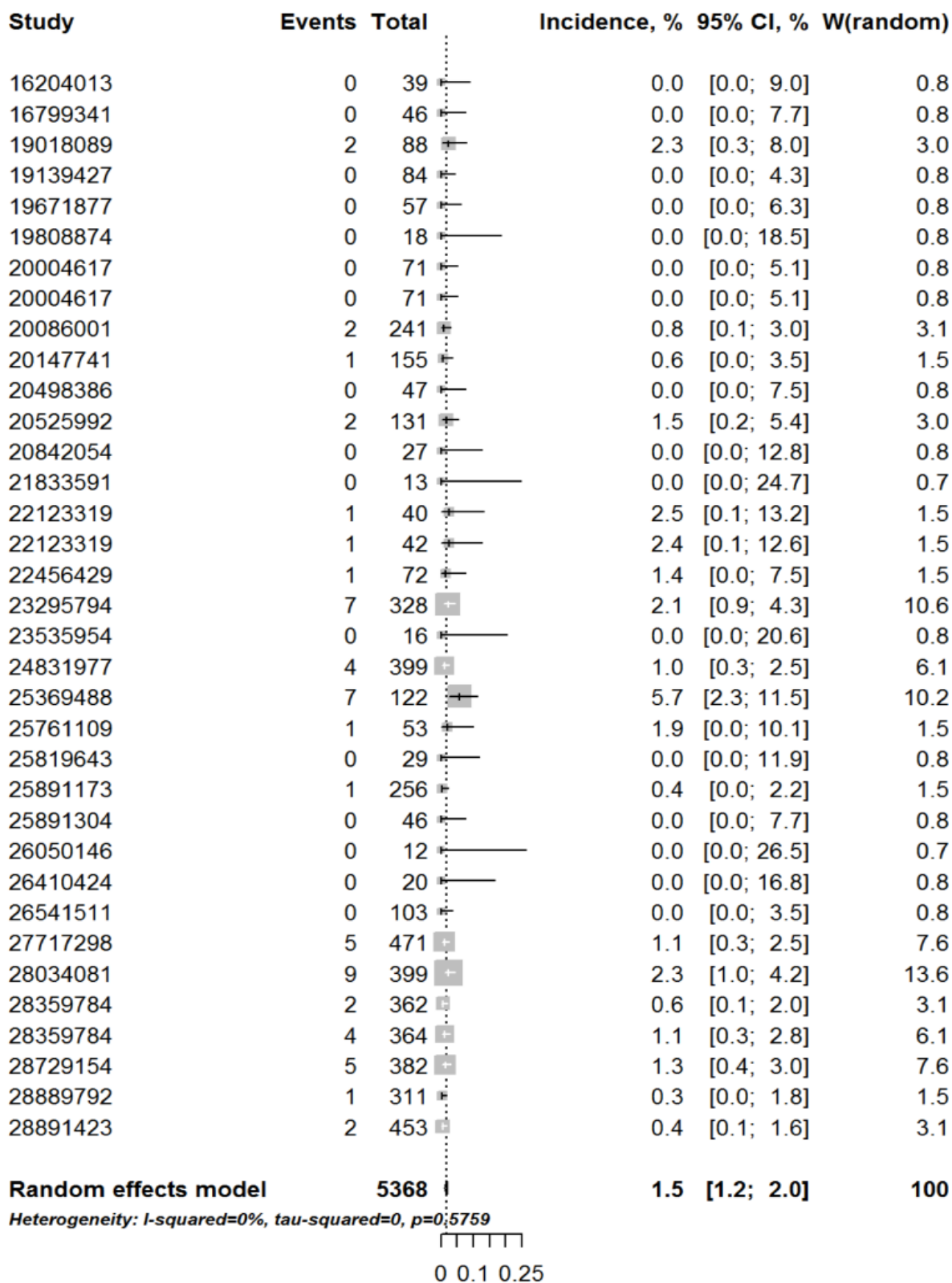
eFigure 1



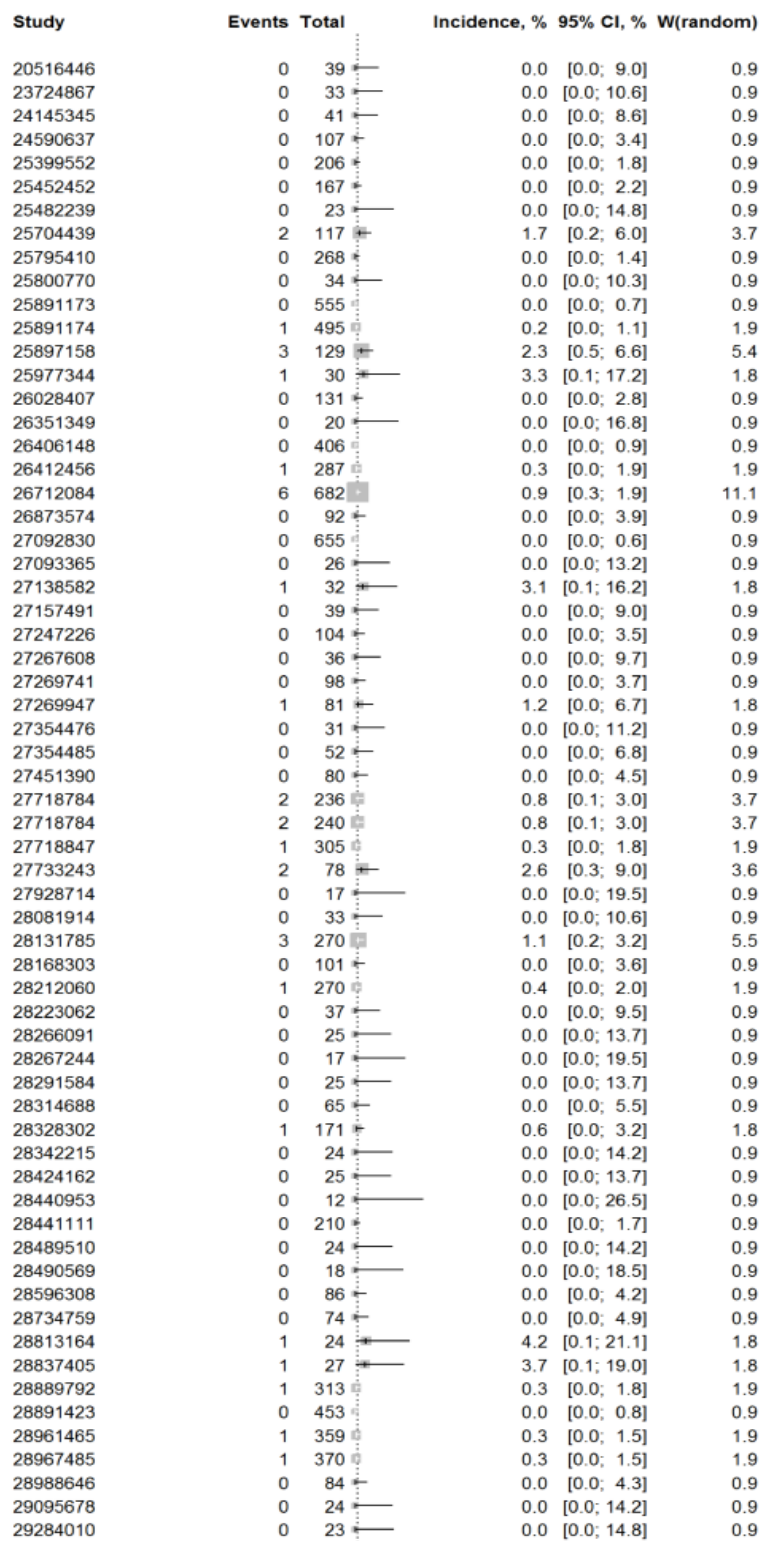
eFigure 2



eFigure 3: Forest plot of incidence of death due to immune related adverse events with anti-CTLA-4 therapy



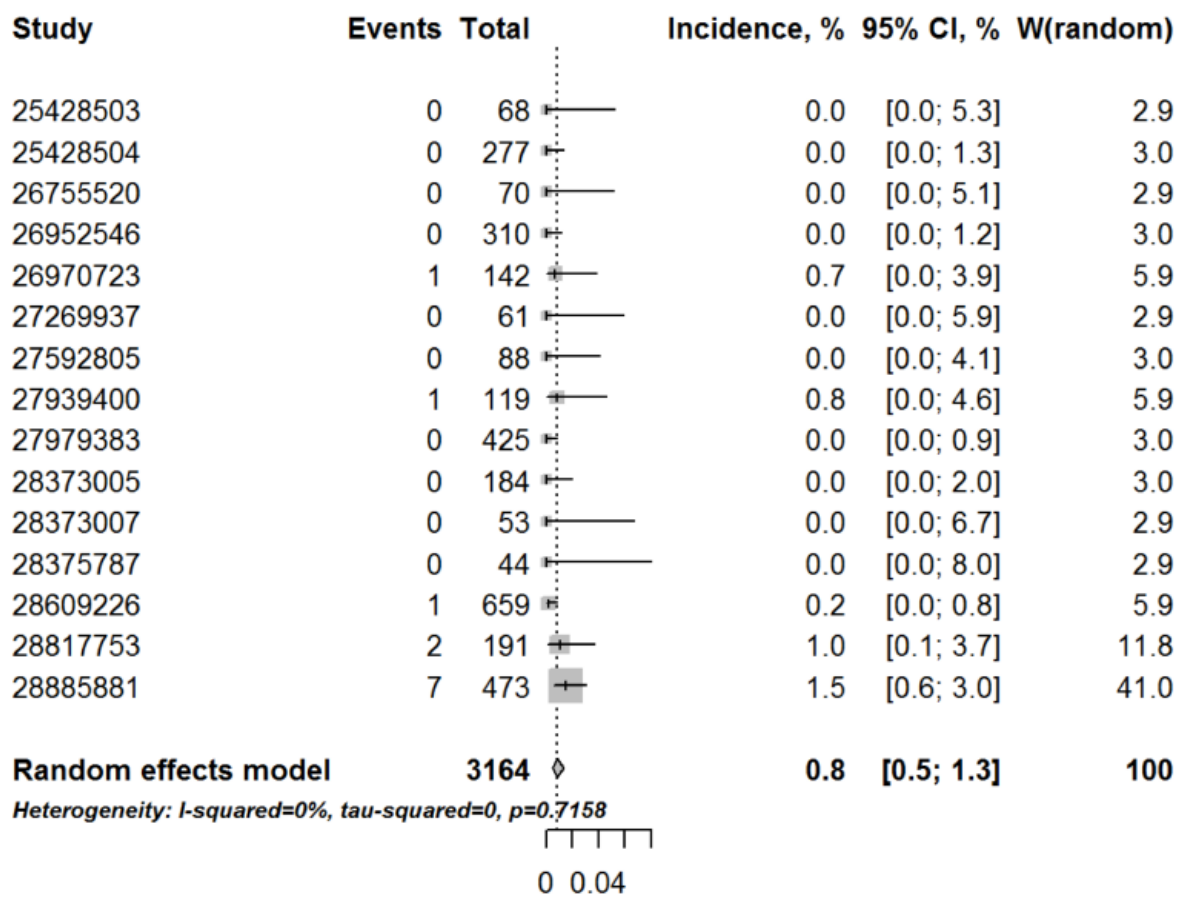
eFigure 4: Forest plot of incidence of death due to immune related adverse events with anti-PD-1 therapy



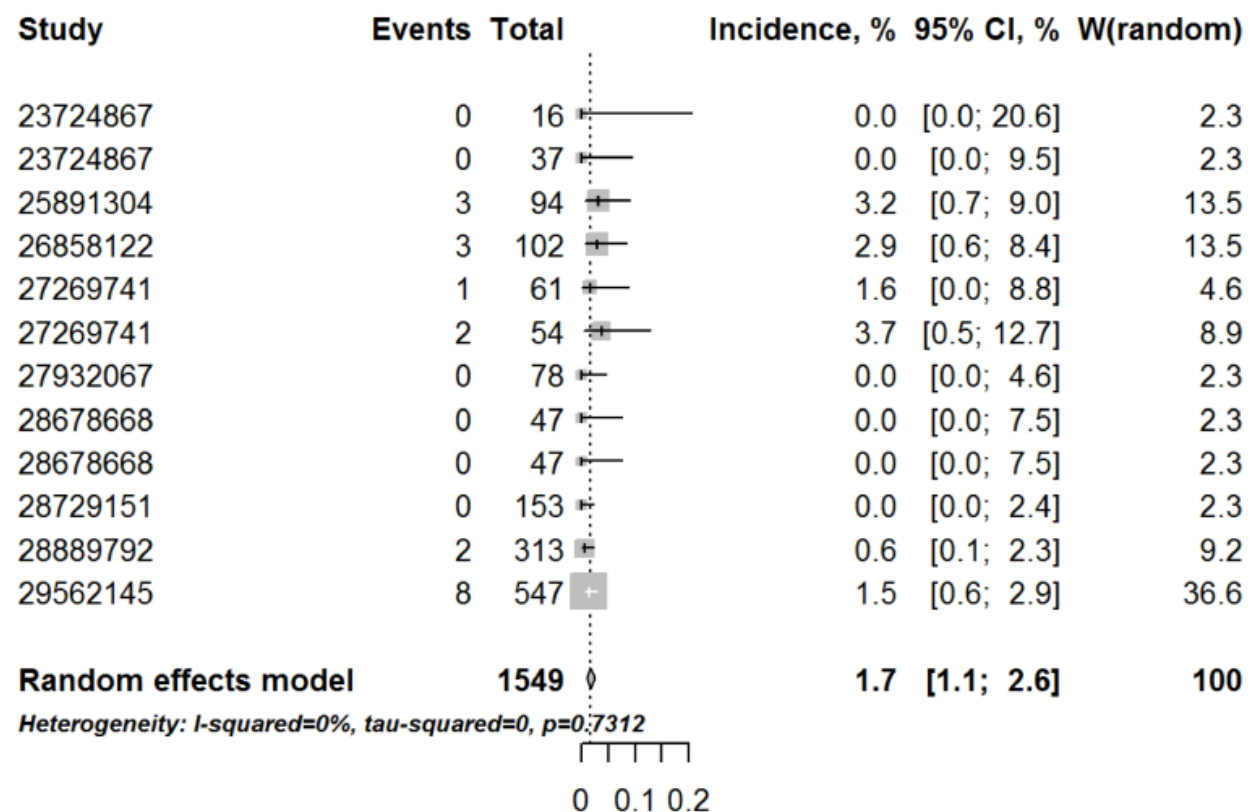
Random effects model 9136 0.9 [0.7; 1.2] 100

Heterogeneity: I-squared=0%, tau-squared=0, p=0.9503

eFigure 5: Forest plot of incidence of death due to immune related adverse events with anti-PD-L1 therapy



eFigure 6: Forest plot of incidence of death due to immune related adverse events with combination anti-CTLA-4 and anti-PD-1 therapy



eTable 4.

Tumor Type	Treatment	Class of Drug	Dose, if Ipi (mg/kg)	Phase	# of total patients	# deaths	Death types	Pubmed ID
Solid cancers	Tremelimumab	Anti-CTLA 4	-	1	39	0		16204013
Solid cancers	Ipilimumab	Anti-CTLA 4	-	1	46	0		16799341
Melano ma	Ipilimumab	Anti-CTLA 4	up to 20	1	88	2	cardiac arrest, ischemia/edema	19018089
Melano	Tremelimu	Anti-	-	1	84	0		19139427

ma	mab	CTLA 4						
Melano ma	Ipilimumab	Anti- CTLA 4	10	2	57	0		19671877
Hodgki n	Ipilimumab	Anti- CTLA 4	3	1	18	0		19808874
Melano ma	Ipilimumab	Anti- CTLA 4	3	2	71	0		20004617
Melano ma	Ipilimumab	Anti- CTLA 4	10	2	71	0		20004617
Melano ma	Tremelimu mab	Anti- CTLA 4	-	2	241	2	Perforatio n, sudden death	20086001
Melano ma	Ipilimumab	Anti- CTLA 4	10	2	155	1	hepatitis	20147741
Colon	Tremelimu mab	Anti- CTLA 4	-	2	47	0		20498386
Melano ma	Ipilimumab	Anti- CTLA 4	3	3	131	2	colitis, liver failure	20525992
Pancre as	Ipilimumab	Anti- CTLA 4	3	1	27	0		20842054
Melano ma	Ipilimumab	Anti- CTLA 4	10	2	13	0		21833591
Melano ma	Ipilimumab	Anti- CTLA 4	3	2	40	1	Perforatio n	22123319
Melano ma	Ipilimumab	Anti- CTLA 4	10	2	42	1	Perforatio n	22123319
Melano ma	Ipilimumab	Anti- CTLA 4	10	2	72	1	colitis	22456429
Melano ma	Tremelimu mab	Anti- CTLA 4	-	3	328	7	cardiac arrest, pneumon ia, sepsis, electrolyt e imbalanc	23295794

							e, pulmonar y embolism , hemorrhage, colitis	
Prostate	Ipilimumab	Anti-CTLA4	10	2	16	0		23535954
Prostate	Ipilimumab	Anti-CTLA4	10	3	399	4	pneumonia x3, general deterioration	24831977
Melanoma	Ipilimumab	Anti-CTLA4	10	2	122	7	colitis x2, multiorgan failure x2, cardiac arrest, pneumonitis x2, hepatic failure	25369488
Melanoma (uveal)	Ipilimumab	Anti-CTLA4	3	2	53	1	pancytopenia	25761109
Mesothelioma	Tremelimumab	Anti-CTLA4	-	2	29	0		25819643
Melanoma	Ipilimumab	Anti-CTLA4	3	3	256	1	diarrhea	25891173
Melanoma	Ipilimumab	Anti-CTLA4	3	2	46	0		25891304
Uveal melanoma	Tremelimumab	Anti-CTLA4	-	2	12	0		26050146
Melanoma	Ipilimumab	Anti-CTLA4	3	2	20	0		26410424
Melanoma	Ipilimumab	Anti-CTLA4	3	2	103	0		26541511
Melanoma	Ipilimumab	Anti-CTLA4	10	3	471	5	colitis x3, myocarditis, GBS	27717298
Prostate	Ipilimumab	Anti-	10	3	399	9	colitis,	28034081

e		CTLA 4					hepatotoxicity x2, cardiac arrest x3, renal failure, pneumonia, pneumonitis	
Melanoma	Ipilimumab	Anti-CTLA 4	3	3	362	2	colitis x2	28359784
Melanoma	Ipilimumab	Anti-CTLA 4	10	3	364	4	colitis x2, multiorgan failure, diarrhea	28359784
Mesothelioma	Tremelimumab	Anti-CTLA 4	10	2	382	5	colitis x2, perforation, lung infection, skin ulcer	28729154
Melanoma	Ipilimumab	Anti-CTLA 4	3	3	311	1	colitis	28889792
Melanoma	Ipilimumab	Anti-CTLA 4	10	3	453	2	colitis, marrow aplasia	28891423
					5368	58	0.01080	
Solid cancers	Nivolumab	Anti-PD1	-	1	39	0		20516446
Melanoma	Nivolumab	Anti-PD1	-	1	33	0		23724867
Melanoma	Nivolumab	Anti-PD1	-	1	41	0		24145345
Melanoma	Nivolumab	Anti-PD1	-	1	107	0		24590637
Melanoma	Nivolumab	Anti-PD1	-	3	206	0		25399552
RCC	Nivolumab	Anti-PD1	-	2	167	0		25452452
Hodgkin	Nivolumab	Anti-PD1	-	2	23	0		25482239
NSCLC	Nivolumab	Anti-PD1	-	2	117	2	hypoxic pneumonia, ischemic stroke	25704439

Melano ma	Nivolumab	Anti- PD1	-	3	268	0		25795410
RCC	Nivolumab	Anti- PD1	-	1	34	0		25800770
Melano ma	Pembrolizu mab	Anti- PD1	-	3	555	0		25891173
NSCLC	Pembrolizu mab	Anti- PD1	-	1	495	1	pneumon itis	25891174
NSCLC	Nivolumab	Anti- PD1	-	1	129	3	pneumon itis x 3	25897158
Solid cancers	Pembrolizu mab	Anti- PD1	-	1	30	1	cryptococ cus after gastritis	25977344
NSCLC (squamo us)	Nivolumab	Anti- PD1	-	3	131	0		26028407
Ovarian	Nivolumab	Anti- PD1	-	2	20	0		26351349
RCC	Nivolumab	Anti- PD1	-	3	406	0		26406148
NSCLC (non- squamo us)	Nivolumab	Anti- PD1	-	3	287	1	encephali tis	26412456
NSCLC	Pembrolizu mab	Anti- PD1	-	3	682	6	[pneumo nia, pneumon itis x 2] @ 2 mg/kg, [myocardi al infarction, pneumon ia, pneumon itis] @ 10 mg/kg	26712084
Melano ma	Nivolumab	Anti- PD1	-	2	92	0		26873574
Melano ma	Pembrolizu mab	Anti- PD1	-	1	655	0		27092830
Merkel cell carcino ma	Pembrolizu mab	Anti- PD1	-	2	26	0		27093365
Breast	Pembrolizu mab	Anti- PD1	-	1	32	1	DIC?	27138582
Gastric	Pembrolizu mab	Anti- PD1	-	1	39	0		27157491

SCCHN	Pembrolizumab	Anti-PD1	-	1	104	0		27247226
Brain mets	Pembrolizumab	Anti-PD1	-	2	36	0		27267608
SCLC	Nivolumab	Anti-PD1	-	1	98	0		27269741
Heme	Nivolumab	Anti-PD1	-	2	81	1	ARDS	27269947
Hodgkin	Pembrolizumab	Anti-PD1	-	2	31	0		27354476
NSCLC	Nivolumab	Anti-PD1	-	2	52	0		27354485
Hodgkin	Nivolumab	Anti-PD1	-	2	80	0		27451390
SCCHN	Nivolumab	Anti-PD1	-	3	236	2	pneumonitis, hypercalcemia	27718784
HNSCC	Nivolumab	Anti-PD1	-	3	240	2	pneumonitis, hypercalcemia	27718784
NSCLC	Pembrolizumab	Anti-PD1	-	3	305	1	sudden death of unknown cause	27718847
Bladder	Nivolumab	Anti-PD1	-	2	78	2	pneumonitis, ITP	27733243
Solid cancers	Nivolumab	Anti-PD1	-	1	17	0		27928714
Bladder	Pembrolizumab	Anti-PD1	-	1	33	0		28081914
Bladder	Nivolumab	Anti-PD1	-	2	270	3	pneumonitis, cardiac failure, respiratory failure	28131785
NSCLC	Pembrolizumab	Anti-PD1	-	1	101	0		28168303
Bladder	Pembrolizumab	Anti-PD1	-	3	270	1	pneumonitis	28212060
Anal	Nivolumab	Anti-PD1	-	2	37	0		28223062
NSCLC	Nivolumab	Anti-PD1	-	2	25	0		28266091
Hodgkin	Nivolumab	Anti-PD1	-	2	17	0		28267244
Mesothelioma	Pembrolizumab	Anti-PD1	-	2	25	0		28291584

Esophageal	Nivolumab	Anti-PD1	-	2	65	0		28314688
HNSCC	Pembrolizumab	Anti-PD1	-	2	171	1	pneumonitis	28328302
Melanoma	Nivolumab	Anti-PD1	-	2	24	0		28342215
CLL	Pembrolizumab	Anti-PD1	-	2	25	0		28424162
Uterine leiomyosarcoma	Nivolumab	Anti-PD1	-	2	12	0		28440953
Hodgkin	Pembrolizumab	Anti-PD1	-	2	210	0		28441111
Endometrial	Pembrolizumab	Anti-PD1	-	2	24	0		28489510
PMBCL	Pembrolizumab	Anti-PD1	-	2	18	0		28490569
MMR cancers	Pembrolizumab	Anti-PD1	-	2	86	0		28596308
MSI colon	Nivolumab	Anti-PD1	-	2	74	0		28734759
SCLC	Pembrolizumab	Anti-PD1	-	2	24	1	Colitis	28813164
Nasopharyngeal	Pembrolizumab	Anti-PD1	-	2	27	1	Sepsis	28837405
Melanoma	Nivolumab	Anti-PD1	-	3	313	1	neutropenia	28889792
Melanoma	Nivolumab	Anti-PD1	-	3	453	0		28891423
Melanoma	Pembrolizumab	Anti-PD1	-	2	359	1	diarrhea and pneumonia	28961465
Bladder	Pembrolizumab	Anti-PD1	-	2	370	1	Myocarditis/myositis	28967485
Sarcoma	Pembrolizumab	Anti-PD1	-	2	84	0		28988646
Cervical	Pembrolizumab	Anti-PD1	-	2	24	0		29095678
Colon	Pembrolizumab	Anti-PD1	-	2	23	0		29284010
					9136	33	0.00361	
Melanoma	Nivolumab +	Anti-PD1	1	1	16	0		23724867

	Ipilimumab	+ Anti- CTLA 4						
Melano ma	Nivolumab + Ipilimumab	Anti- PD1 + Anti- CTLA 4	3	1	37	0		23724867
Melano ma	Nivolumab + Ipilimumab	Anti- PD1 + Anti- CTLA 4	3	2	94	3	arrhythmi a, pneumon itis/pneu mothorax , pneumon ia	25891304
NSCLC	Durvaluma b + tremelimu mab	Anti- PD1 + Anti- CTLA 4	-	1	102	3	myasthen ia, pericardi al effusion, neuromu scular disorder	26858122
SCLC	Nivolumab + Ipilimumab	Anti- PD1 + Anti- CTLA 4	1	1	61	1	pneumon itis	27269741
SCLC	Nivolumab + Ipilimumab	Anti- PD1 + Anti- CTLA 4	3	1	54	2	myasthen ia, renal failure	27269741
NSCLC	Nivolumab + Ipilimumab	Anti- PD1 + Anti- CTLA 4	1	1	78	0		27932067
RCC	Nivolumab + Ipilimumab	Anti- PD1 + Anti- CTLA 4	1	2	47	0		28678668

RCC	Nivolumab + Ipilimumab	Anti-PD1 + Anti-CTLA 4	3	2	47	0		28678668
Melano ma	Pembrolizumab + ipilimumab	Anti-PD1 + Anti-CTLA 4	1	2	153	0		28729151
Melano ma	Nivolumab + Ipilimumab	Anti-PD1 + Anti-CTLA 4	3	3	313	2	myocarditis, liver failure	28889792
RCC	Nivolumab + Ipilimumab	Anti-PD1 + Anti-CTLA 4	1	3	547	8	pneumonitis, pneumonia, aplastic anemia, bronchitis, GI hemorrhage, sudden death, HLH, hepatitis, lung infection	29562145
					1549	19	0.01227	
Bladder	Atezolizumab	Anti-PDL1	-	1	68	0		25428503
Solid cancers	Atezolizumab	Anti-PDL1	-	1	277	0		25428504
RCC	Atezolizumab	Anti-PDL1	-	2	70	0		26755520
Bladder cancer	Atezolizumab	Anti-PDL1	-	2	310	0		26952546
NSCLC	Atezolizumab	Anti-PDL1	-	2	142	1	cardiac failure	26970723
Bladder	Durvalumab	Anti-PDL1	-	2	61	0		27269937

Merckel	Avelumab	Anti-PDL1	-	2	88	0		27592805
Bladder	Atezolizumab	Anti-PDL1	-	2	119	1	Sepsis	27939400
NSCLC	Atezolizumab	Anti-PDL1	-	3	425	0		27979383
NSCLC	Avelumab	Anti-PDL1	-	1	184	0		28373005
Solid tumors	Avelumab	Anti-PDL1	-	1	53	0		28373007
Bladder	Avelumab	Anti-PDL1	-	1	44	0		28375787
NSCLC	Atezolizumab	Anti-PDL1	-	2	659	1	pneumonia	28609226
Bladder	Durvalumab	Anti-PDL1	-	2	191	2	hepatitis, pneumonia	28817753
NSCLC	Durvalumab	Anti-PDL1	-	3	473	7	pneumonia x4, cardiomyopathy, RV failure, respiratory failure	28885881
					3164	12	0.00379	
				Total	19217	122	0.00630	
	Extracted	3/24/2018						