

Appendix

Supplementary Table 1. Cardiovascular adverse events grouping as a function of Medical Dictionary for Regulatory Activities (MedDRA) Classification Version 20.1.

Groups	MedDRA Terms used
Hypertension and related end-organ damages	Hypertension (SMQ narrow 20.1)
Arterial systemic ischemia	Embolic and thrombotic events, arterial (SMQ narrow 20.1)
Myocardial infarction	Myocardial infarction (SMQ narrow 20.1)
Cerebral arterial ischemia	Ischaemic central nervous system vascular conditions (SMQ narrow 20.1)
Cardiac valve disorders	Cardiac valve disorders (HLGT narrow 20.1)
Endocardial disorders	Endocardial disorders (HLGT 20.1)
Cardiac supra-ventricular arrhythmias	Supraventricular tachyarrhythmias (SMQ narrow 20.1)
Cardiac ventricular arrhythmias	Ventricular tachyarrhythmias (SMQ narrow 20.1)
Torsade de pointes / QT prolongation	Torsade de pointes/ QT prolongation (SMQ narrow 20.1)
Cardiac conductive disorders	Cardiac conduction disorders (HLT 20.1)
Heart Failure	Cardiac Failure (SMQ narrow 20.1)
Cardiac death or shock	Shock-associated circulatory or cardiac conditions (excl torsade de pointes) (SMQ narrow 20.1)
Myocarditis	Non-infectious myocarditis (HLT 20.1)
Pericardial diseases	Non-infectious pericarditis (HLT 20.1) and Pericardial disorders NEC (HLT 20.1)
Vascular neoplasm	Vascular neoplasm (HLT 20.1)
Hemorrhage (clinical events)	Haemorrhage terms (excl laboratory terms) (SMQ narrow 20.1)
Biological hemostatic disorders favoring hemorrhage	Haemorrhage laboratory terms (SMQ narrow 20.1)
Cerebral hemorrhage	Haemorrhagic central nervous system vascular conditions (SMQ narrow 20.1)
Pulmonary hypertension and related cardiac involvement	Pulmonary hypertension (SMQ narrow 20.1)
Vasculitis	Vasculitis (SMQ narrow 20.1)
Temporal arteritis / Polymyalgia rheumatica	Polymyalgia rheumatica (PT 20.1) and Temporal arteritis (PT 20.1)
Dyslipidemia	Dyslipidaemia (SMQ 20.1 narrow)

Abbreviations: HL(G)T: High Level (Group) Term; NEC: Not elsewhere classified; PT: Preferred Term; SMQ: Standardized MedDRA Query.

Supplementary Table 2. Example of calculation of the reporting Odds-Ratios (ROR) from VigiBase.

	Reports with the suspected AE:	Reports without the suspected AE
Reports with suspected group of drugs (example: mono-immunotherapy)	A	B
Reports with comparator group of drugs (example: combination immunotherapy)	C	D

A: Number of reports of drug-induced AE of interest (e.g; myocarditis) associated with the given group of drug (mono-immunotherapy).

B: Number of reports of other AE (e.g; all AE excluding myocarditis) associated with the given group of drug (mono-immunotherapy).

C: Number of reports of AE of interest (e.g; myocarditis) associated with a comparator group of drugs (combination immunotherapy).

D: Number of reports of other AE (e.g; all AE excluding myocarditis) associated with a comparator group of drugs (combination immunotherapy).

$$\text{ROR} = (A/C)/(B/D) = AD/BC. \quad (1)$$

Abbreviations: AE, adverse event; CV-irAE: immune related cardiovascular adverse events; ROR: Reporting Odds-Ratio

Supplementary Table 3. Details concerning patients with immune checkpoint inhibitors (ICI) associated cardiac supra-ventricular arrhythmias collected from VigiBase (last accessed: 01/2018)

Characteristics	N (%)	Data availability, n (%)
Region reporting, n (%) Americas: Europe Australia Asia Africa	156 (70.3) 59 (26.6) 5 (2.3) 1 (0.4) 1 (0.4)	222(100.0)
Reporting Year 2018 (<i>thru January 2018</i>) 2017 2016 2015 2014 2013 2012 2009-2011	11 (5.0) 85 (38.3) 45 (20.3) 43 (19.4) 19 (8.5) 6 (2.7) 8 (3.6) 5 (2.2)	222 (100.0)
Gender Male Female	157 (72.0) 61 (28.0)	218 (98.2)
Age at onset, mean ± SD (years) [min-max]	68.1 ± 10.3 [23-90]	199 (89.6)
Suspected Drugs * Only ICI ICI + 1 other drug ICI + ≥2 other drugs	168 (75.7) 38 (17.1) 16 (7.2)	222(100.0)
Drugs <u>Monotherapy with Anti PD-1/PD-L1</u> - Nivolumab - Pembrolizumab - Atezolizumab - Avelumab - Durvalumab <u>Monotherapy with Anti CTLA-4</u> - Ipilimumab <u>Combination therapy</u> - Nivolumab + Ipilimumab - Pembrolizumab + Ipilimumab	122 (55.0) 72 (32.4) 37 (16.7) 4 (1.8) 6 (2.7) 3 (1.4) 65 (29.3) 35 (15.7) 34 (15.3) 1 (0.4)	222(100.0)
Number of ICI administration before onset, median [IQR] [min-max]	2 [1-4.3] [1-69]	82 (37.0)
Time to irAE onset, days: Median delay between treatment and irAE, median [IQR] [min-max]	14 [1-52] [1- 925]	102 (46.0)
Severe AE	189 (87.5)	216 (97.3)
Death	53 (23.9)	222 (100.0)
Malignant neoplasm progression	22 (9.9)	222 (100.0)
Indications Malignant melanoma Lung cancer Renal carcinoma Prostate cancer	101 (50.5) 55 (27.5) 9 (4.5) 5 (2.5)	200 (90.0)

Urothelial carcinoma	4 (2.0)	
Lymphoma (all variants)	4 (2.0)	
Neoplasm malignant (tissue not specified)	3 (1.5)	
Squamous cell carcinoma of head and neck	3 (1.5)	
Head and neck carcinoma	3 (1.5)	
Plasma cell myeloma	2 (1.0)	
Merkel cell carcinoma	2 (1.0)	
Chronic lymphocytic leukemia	2 (1.0)	
Breast cancer	2 (1.0)	
Colon cancer	1 (0.5)	
Salivary gland cancer	1 (0.5)	
Ovarian epithelial cancer	1 (0.5)	
Glioblastoma	1 (0.5)	
Esophageal carcinoma	1 (0.5)	
Reported cardiac supra-ventricular arrhythmias		222 (100.0)
Atrial fibrillation	172 (77.5)	
Supraventricular tachycardia and extra-systoles	23 (10.4)	
Atrial flutter	16 (7.2)	
Sinus Tachycardia	11 (4.9)	
Concurrent irAE favoring cardiac supra-ventricular arrhythmias		222 (100.0)
<u>None (lone)</u>	38 (17.1)	
<u>Gastro-intestinal disorders (any)</u>	93 (41.9)	
Diarrhea / Colitis / Gastroenteritis/ Enteritis/ Dehydration	58 (26.1)	
Hepatitis / Hepatic failure / Gallbladder disorders	19 (8.6)	
Gastrointestinal bleeding	14 (6.3)	
Nausea / Vomiting	13 (5.9)	
Abdominal pain	10 (4.5)	
Gastrointestinal obstruction	7 (3.2)	
Pancreatitis	2 (0.9)	
Other gastrointestinal conditions / unspecified gastrointestinal disorders	22 (9.9)	
<u>Endocrino-metabolic disorders</u>	66 (29.7)	
Thyroid disorders	29 (13.1)	
Fever	18 (8.1)	
Potassium imbalance	8 (3.6)	
Adrenal insufficiency	7 (3.2)	
Diabetes/ blood glucose increased / hyperglycemia / Diabetic Ketoacidosis	4 (1.8)	
Hypophysitis	2 (0.9)	
Other endocrine-metabolic conditions / unspecified endocrine-metabolic disorders	12 (5.4)	
<u>Pulmonary condition</u>	47 (21.2)	
Pneumonia/ Pneumonitis	29 (13.1)	
Pleural effusion	9 (4.1)	
Respiratory failure	8 (3.6)	
Bronchitis	1 (0.4)	
Interstitial lung disease	1 (0.4)	
Other pulmonary conditions / unspecified pulmonary disorders	9 (4.1)	
<u>Cardiac condition</u>	69 (31.1)	
Cardiac failure/ decreased EF/ Pulmonary edema/ Pulmonary Hypertension	27 (12.2)	
Pulmonary thromboembolism	11 (5.0)	
Myocardial infarction/ Coronary artery disease/Cardiac ischemia	8 (3.6)	
Cardiac arrhythmias (Long QT, ventricular arrhythmias, Torsade de pointes, syncope)	7 (3.2)	
Pericardial effusion/ Tamponade/ Pericarditis	6 (2.7)	
Cardiomyopathy	5 (2.3)	
Cardiogenic shock/ Cardiac arrest	5 (2.3)	
Myocarditis	4 (1.8)	
Other cardiovascular conditions / unspecified cardiovascular disorders	14 (6.3)	
<u>Renal condition</u>	23 (10.4)	
Renal failure /Acute kidney injury	19 (8.6)	

Nephrotic syndrome	1 (0.4)	
Other renal conditions / unspecified renal conditions	3 (1.4)	
<u>Neurologic condition</u>	28 (12.6)	
Decreased level of consciousness	11 (5.0)	
Stoke (ischemic or hemorrhagic)	4 (1.8)	
Encephalitis /meningitis	3 (1.4)	
Ophthalmological abnormality (vision)	1 (0.5)	
Peripheral neuropathy (Guillain-Barre)	2 (0.9)	
Other neurologic conditions / unspecified neurologic conditions	11 (5.0)	
<u>Dermatologic and Rheumatologic condition</u>	37 (16.7)	
myositis / myasthenia gravis / muscular involvement	15 (6.8)	
Rash / Alopecia	9 (4.1)	
Erysipelas/ fasciitis /Dermatitis bullous	3 (1.4)	
Pruritis	1 (0.4)	
Other dermatologic and rheumatologic conditions / unspecified dermatologic and rheumatologic conditions	11 (5.0)	
<u>Hematologic condition</u>	27 (12.2)	
Anemia	18 (8.1)	
Cytopenia (pancytopenia, leukocytopenia, thrombocytopenia)	9 (4.1)	
Other hematologic conditions/ Unspecified hematologic conditions	4 (1.8)	

* Other concomitant reported suspected medications were alkylating agents and antimetabolites (n: 28), tyrosine kinase inhibitors (n: 24), other immunotherapies e.g. interleukin-2 (n: 22), and anticoagulants (n: 6).

Abbreviations: CTLA-4, cytotoxic T-lymphocyte-associated protein 4; ICI, immune checkpoint inhibitor; IQR, interquartile range; irAE, immune related adverse event; [min-max], minimum-maximum; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1; SD, standard deviation