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| Table S1. Neuro-psychiatric adverse events grouping as a function of Medical Dictionary for Regulatory Activities (MedDRA) Classification Version 21.0. |
| Groups | **MedDRA Terms used** |
| Noninfectious meningitis  | Meningitis (PT) and/or Meningitis aseptic (PT)  |
| Noninfectious encephalitis and/or myelitis | Encephalitis NEC (HLT) and/or Myelitis transverse (PT) and/or Myelitis (PT) |
| Noninfectious encephalopathy/delirium  | Noninfectious encephalopathy/delirium (SMQ narrow) |
| Epilepsy/Seizures | Seizures (incl subtypes) (HLGT) |
| Dementia | Dementia (SMQ narrow) |
| Headaches and migraines  | Headaches (HLGT) |
| Sleep disturbances | Sleep disturbances (incl subtypes) (HLGT) |
| Coma | Coma states (HLT)  |
| Demyelination (excluding Guillain-Barre syndrome) | Demyelinating disorders (HLGT) |
| Spinal cord and nerve root disorders | Cervical spinal cord and nerve root disorders (HLT) and/or lumbar spinal cord and nerve root disorders (HLT) and/or spinal cord and nerve root disorders traumatic (HLT) |
| Increased intracranial pressure and hydrocephalus | Increased intracranial pressure and hydrocephalus (HLGT)  |
| Benign nervous system neoplasms  | Nervous system neoplasms benign (HLGT) |
| Central nervous system vascular ischemia | Ischaemic central nervous system vascular conditions (SMQ narrow) |
| Central nervous system vascular hemorrhage | Haemorrhagic central nervous system vascular conditions (SMQ narrow) |
| Cerebral artery vasculitis | Vasculitis cerebral (PT) and/or Temporal arteritis (PT) |
| Movement disorders (including parkinsonism and dyskinesia) | Movement disorders (incl parkinsonism) (HLGT) |
| Extrapyramidal syndrome | Extrapyramidal syndrome (SMQ broad) |
| Sensory abnormalities | Paraesthesias and dysaesthesias (HLT) and/or Sensory abnormalities NEC (HLT) |
| Speech and language abnormalities | Speech and language abnormalities (HLT) |
| Vertigos | Vertigos NEC (HLT) |
| Cranial Nerve Disorders | Cranial nerve disorders (excl neoplasms, HLGT) |
| Peripheral neuropathy | Peripheral neuropathy (SMQ narrow) |
| Acute polyneuropathies | Acute polyneuropathies (HLT) |
| Chronic polyneuropathies | Chronic polyneuropathies (HLT) |
| Mononeuropathies | Mononeuropathies (HLT) |
| Guillain-Barre syndrome | Guillain-Barre syndrome (SMQ narrow) |
| Neuromuscular junction dysfunction | Neuromuscular junction dysfunction (HLT) |
| Anticholinergic syndrome  | Anticholinergic syndrome (SMQ broad) |
| Psychosis and psychotic disorders  | Psychosis and psychotic disorders (SMQ broad) |

*Abbreviations*:HL(G)T: High Level (Group) Term; incl: including; NEC: Not elsewhere classified; PT: Preferred Term;SOC: System Organ Class;SMQ: Standardized MedDRA Query.

***Table S2***: Example of calculating reporting odds ratio (ROR) in Vigibase

|  |  |  |
| --- | --- | --- |
|  | Reports with the AE | Reports without the AE |
| Reports with suspected class of drugs (e.g. anti-PD-1/PD-L1) | A | B |
| Reports with comparator class of drugs (e.g. anti-CTLA-4) | C | D |

A: Number of reports of drug-induced AE of interest (e.g; myasthenia gravis) associated with the given group of drug (anti-PD-1/PD-L1).

B: Number of reports of all other AE (e.g; all AE excluding myasthenia gravis) associated with the given group of drug (anti-PD-1/PD-L1).

C: Number of reports of AE of interest (e.g; myasthenia gravis) associated with a comparator group of drugs (anti-CTLA-4).

D: Number of reports of other AE (e.g; all AE excluding myasthenia gravis) associated with a comparator group of drugs (anti-CTLA-4).

ROR = (A/C)/(B/D) = AD/BC.

***Table S3****:* Clinical characteristics of patients with ICI-associated **cerebral vasculitis** collected from VigiBase

|  |  |  |
| --- | --- | --- |
| **Characteristics** | ***N* (%)** | **Data available,** ***N* (%)** |
| **Reporting region**AmericasEuropeAsiaOceana | 17 (50.00)16 (47.06)1 (2.94)0 (0.00) | 34 (100.00) |
| **Reporting year**2018 (through November)20172016201520142012-2013 | 15 (44.12)7 (20.59)5 (14.71)3 (8.82)0 (0.00)4 (11.76) | 34 (100.00) |
| **Reporters** Healthcare professionalNon-healthcare professional | 31 (91.18)3 (8.82) | 34 (100.00) |
| **Gender**MaleFemale | 15 (46.88)17 (53.13) | 32 (94.12) |
| **Age at onset,** mean ± SD, years[min-max] | 68.48±12.50[36-88] | 25 (73.53) |
| **Drugs***Monotherapy with Anti PD-1/PD-L1** *Nivolumab*
* *Pembrolizumab*
* *Atezolizumab*
* *Durvalumab*
* *Avelumab*

*Monotherapy with Anti CTLA-4** *Ipilimumab*

*Combination therapy** *Nivolumab + Ipilimumab*
* *Pembrolizumab + Ipilimumab*
* *Tremelimumab + Durvalumab*
 | 20 (58.82)9 (45.00)9 (45.00)1 (5.00)0 (0)1 (5.00)10 (29.41)10 (100)4 (11.76)3 (75.00)1 (25.00)0 (0) | 34 (100.00) |
| **Suspected Drugs\***Only ICIICI + 1 other drugICI + ≥2 other drugs | 30 (88.24)3 (8.82)1 (2.94) | 34 (100.00) |
| **Number of ICI administration before onset***,*median [IQR], [min-max] | 4, [2.5-6][1-21] | 15 (44.12) |
| **Severe AE** | 31 (100.0)  | 31 (91.18) |
| **Indications**Malignant melanomaLung cancer Non-small cell lung cancer Small cell lung cancer Not specifiedColorectal cancerMerkel cell carcinomaRenal cell carcinomaSkin cancer- Unspecified  | 11 (44.00)9 (36.00)7 (28.00)0 (0.00)2 (8.00)2 (8.00)1 (4.00)1 (4.00)1 (4.00) | 25 (73.53) |
| **Main CNS Toxicity:** Temporal arteritisVasculitis cerebralRetinal vasculitis | 23 (67.65)8 (23.53)3 (8.82) | 34 (100.0) |
| **Time to irAE onset,** days**:** Median, [IQR][min-max]*Data available* | 80 [47-113] [14-300] | 15 (44.12) |
| **Death** | 1 (2.94) | 34 (100.0) |
| **Concurrent neurologic symptoms/syndromes**Myasthenia gravisEncephalitis/myelitisCerebral vasculitisGuillain Barre syndromePeripheral NeuropathyMeningitisDemyelinationSeizureStrokeBlindness (unilateral or bilateral)Coma/loss of consciousness | 0 (0)1 (2.94)N/A0 (0)0 (0)0 (0)0 (0)0 (0)1 (2.94)3 (8.82)2 (5.88) | 34 (100.0) |
| **Other irAEs**Colitis/diarrheaPneumonitisMyocarditisMyositisDermatitisThyroiditis/hypothyroidismHypophysitis/hypopituitarismHepatitisNephritisOther**None** | 3 (8.82)1 (2.94)0 (0)0 (0)0 (0)1 (2.94)0 (0)0 (0)0 (0)2 (5.88)28 (82.35) | 34 (100.0) |

\* Other concomitant reported suspected medications were Bevacizumab (n:3), Brentuximab vedotin (n:2), Carboplatin (n:2), Cobimetinib (n:2), Aldesleukin (n:1), Azithromycin (n:1), Cabozantinib (n:1), Crizotinib (n:1), Entinostat (n:1), Etanercept (n:1), Ethanol (n:1), Etoposide (n:1), Golimumab (n:1), Influenza vaccine (n:1), Interferon alfa-2b (n:1), Metronidazole(n:1), Oxycodone (n:1), Pemetrexed, (n:1), Radium (n:1), Simvastatin (n:1), Tizanidine (n:1), and Drug names under assessment (n:4).

***Table S4****:* Clinical characteristics of patients with ICI-associated **myasthenia gravis** collected from VigiBase

|  |  |  |
| --- | --- | --- |
| **Characteristics** | ***N* (%)** | **Data Available** ***N* (%)** |
| **Reporting Region**North AmericaEuropeAustraliaAsiaAfrica | 103 (45.18)64 (28.07)12 (5.26)48 (21.05)1 (0.44) | 228 (100.00) |
| **Reporters**Healthcare ProfessionalNon-Healthcare Professional | 188 (87.44)27 (12.56) | 215 (94.30) |
| **Suspected Drugs**1Only ICIICI + 1 other drugICI + 2+ drugs | 216 (94.74)10 (4.39)2 (0.88) | 228 (100.00) |
| **Number of ICI doses before onset**, median [IQR][min – max] | 2 [2 – 3][1 – 21] | 19 (8.33) |
| **Severe AE** | 215 (100.00) | 215 (94.30) |
| **Indication for ICI**MelanomaLung Non-small cell lung cancer Small cell lung cancer Not specifiedRenalBladderGastricHead and neck squamous cellThymicAdenocarcinoma, unknown primaryHematologic cancersColorectalMerkelLiverBoneThyroid**Prostate****Uterine** | 47 (25.54)73 (39.67)48 (26.09)6 (3.26)19 (10.33)25 (13.59)9 (4.89)6 (3.26)6 (3.26)4 (2.17)3 (1.63)2 (1.09)2 (1.09)2 (1.09)1 (0.54)1 (0.54)1 (0.54)1 (0.54)1 (0.54) | 184 (80.70) |
| **Main CNS Toxicity**Myasthenia GravisOcular MyastheniaMyasthenia Gravis CrisisMyasthenic SyndromeMyasthenia Gravis + Myasthenic SyndromeMyasthenia Gravis + Myasthenia Gravis Crisis | 164 (71.93)45 (19.74)11 (4.82)5 (2.19)2 (0.88)1 (0.44) | 228 (100.00) |

1 Other concomitant reported suspected medications were Ambenonium, Axitinib, Azathioprine, Bevacizumab, Carboplatin, Cefoperazone;Sulbactam, Entinostat, Gemcitabine, Immunoglobulin human normal, Leuprorelin, Paracetamol, Peginterferon alfa-2a, Prednisolone, Pyridostigmine, Thiamazole, and Thrombomodulin alfa (n = 1 for all).

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

***Table S5****:* Clinical characteristics of patients with ICI-associated **encephalitis/myelitis** collected from VigiBase

|  |  |  |
| --- | --- | --- |
| **Characteristics** | ***N* (%)** | **Data available,** ***N* (%)** |
| **Reporting region**AmericasEuropeAsiaOceana | 129 (51.60)92 (36.80)20 (8.00)9 (3.60) | 250 (100.00) |
| **Reporters** Healthcare professionalNon-healthcare professional | 209 (87.08)31 (12.92) | 240 (96.00) |
| **Suspected Drugs\***Only ICIICI + 1 other drugICI + ≥2 other drugs | 230 (92.00)16 (6.40)4 (1.60) | 250 (100.00) |
| **Number of ICI administration before onset***,*median [IQR], [min-max] | 3, [1-8.5][1-34] | 51 (20.40) |
| **Severe AE** | 240 (100.0)  | 240 (96.00) |
| **Death** | 33 (13.2) | 250 (100.00) |
| **Indications**Lung cancer Non-small cell lung cancer Small cell lung cancer Not specifiedMalignant melanomaHematologic cancer and lymphomaRenal cell carcinoma Malignant neoplasm non-specifiedUrothelial cancer Gastrointestinal cancer Breast cancer Bile duct cancers and Cholangiocarcinoma Hepatocellular carcinoma Cervix carcinoma Mesothelioma Squamous cell carcinoma of head and neck  | 91 (39.39)53 (22.94)5 (2.16)33 (14.29)54 (23.38)19 (8.23)14 (6.06)12 (5.19)7 (3.03)4 (1.73)2 (0.87)2 (0.87)2 (0.87)1 (0.43)1 (0.43)1 (0.43) | 231 (85.20) |
| **Main CNS Toxicity:** EncephalitisMyelitisParaneoplastic EncephalomyelitisCNS Inflammation | 225 (90.00)20 (8.00)4 (1.60)1 (0.40) | 250 (100.0) |

\* Other concomitant reported suspected medications were Bevacizumab (n:3), Brentuximab vedotin (n:2), Carboplatin (n:2), Cobimetinib (n:2), Aldesleukin (n:1), Azithromycin (n:1), Cabozantinib (n:1), Crizotinib (n:1), Entinostat (n:1), Etanercept (n:1), Ethanol (n:1), Etoposide (n:1), Golimumab (n:1), Influenza vaccine (n:1), Interferon alfa-2b (n:1), Metronidazole(n:1), Oxycodone (n:1), Pemetrexed, (n:1), Radium (n:1), Simvastatin (n:1), Tizanidine (n:1), and Drug names under assessment for who-dd (n:4).

***Table S6****:* Clinical characteristics of patients with ICI-associated **Guillain-Barre Syndrome** collected from VigiBase

|  |  |  |
| --- | --- | --- |
| **Characteristics** | ***N* (%)** | **Data Available, *N* (%)** |
| **Reporting Region**North AmericaEuropeOceanaAsia | 65 (53.3)42 (34.4)10 (8.2) 5 (4.1) | 122 (100) |
| **Reporters**Healthcare personnelNon-healthcare personnel | 92 (80)23 (20) | 115 (94) |
| **Suspected Drugs\***Only ICIICI + 1 other drugICI + >2 other drugs | 114 (93.4)5 (4.1)3 (2.5) | 122 (100) |
| **Number ICI admin before onset**Median[min – max] | 3[1-31] | 21 (17.2) |
| **Indications**Malignant MelanomaLung Cancer Non-small cell lung cancer Small cell lung cancer Not specifiedRenal Cell CarcinomaUrothelial CancerHematologic cancer and lymphomaUterine cancerHead/neck cancerMesotheliomaSimultaneous Lung (unspecified) and Melanoma | 65 (67.7)18 (18.75) 12 (12.5) 0 6 (6.25)5 (5.2)3 (3.1)1 (1.0)1 (1.0)1 (1.0)1 (1.0)1 (1.0) | 96 (78.7) |
| **Main CNS Toxicity:**Guillain-Barre SyndromeDemyelinating Polyneuropathy Chronic Inflammatory Demyelinating PolyneuropathyAcute Axonal NeuropathyMiller Fisher Syndrome | 97 (79.51)15 (12.30)6 (4.92)3 (2.46)1 (0.82) | 122 (100.00) |

\*Other concomitant reported suspected medications were: dabrafenib(4), trametinib(3), vemurafenib(2), influenza vaccine(1), interleukins(1), cyclophosphamide(1), fludarabine(1), and brentuximab(1).

***Table S7****:* Clinical characteristics of patients with ICI-associated **non-infectious meningitis** collected from VigiBase

|  |  |  |
| --- | --- | --- |
| **Characteristics** | ***N* (%)** | **Data Available** |
| **Reporting Region**North AmericaEuropeOceanaAsia | 36 (50.00)29 (40.28)1 (1.39)6 (8.33) | 72 (100) |
| **Reporters**Healthcare PersonnelNon-healthcare Personnel | 63 (90.00)7 (10.00) | 70 (97.2) |
| **Suspected Drugs**Only ICIICI + 1 other drug | 65 (90.27)7 (9.72) | 72 (100) |
| **Number of ICI admin before onset****Median [IQR]** **[min-max]** | 1 [1 -4.5][1-20] |  17 (23.61) |
| **Time to onset, weeks**Median[min, max] | 10[0 - 49] |  23 (31.94) |
| **Indication**Malignant MelanomaLung Cancer Non-small cell lung cancer Small cell lung cancer Not specifiedRenal Cell CancerHodgkin's DiseaseBladder CarcinomaBile Duct CancerSCC of head/neckGlioblastomaB-cell lymphomaAdenocarcinoma (unspecified)Breast CancerConcurrent Lung (unspecified) and Bladder Cancer | 38 (60.12)7 (11.11) 5 (7.94)0 (0.00)2 (3.17)5 (7.94)3 (4.76)3 (4.76)1 (1.59)1 (1.59)1 (1.59)1 (1.59)1 (1.59)1 (1.59)1 (1.59) | 63 (87.5) |
| **Main CNS Toxicity:**Aseptic Meningitis Meningitis | 40 (55.56)32 (44.44) | 72 (100.00) |

\*Other concomitant reported suspected medications were cabozantinib(n:1), cobimetinib(n:1), dacarbazine(n:1), dendritic cells/cytokine induced killer cells(n:1), rituximab (n:1) and an unspecified investigational drug (n:2).