**Immune-related adverse events associated with immune checkpoint inhibitor: an updated comprehensive disproportionality analysis of the FDA Adverse Event Reporting System**

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**Supplementary Table 1** Summary of FDA-approved ICIs

|  |  |  |
| --- | --- | --- |
| Target | Generic name | Brand name |
| PD-1 | nivolumab | OPDIVO, MDX-1106, ONO4538, BMS-936558 |
| pembrolizumab | KEYTRUDA, MK-3475 |
| cemiplimab | LIBTAYO, SAR439684, REGN2810 |
| PD-L1 | atezolizumab | TECENTRIQ, MPDL3280A |
| durvalumab | IMFINZI, MEDI4736 |
| avelumab | BAVENCIO, MSB0010718C |
| CTLA-4 | ipilimumab  tremelimumab | YERVOY, BMS-734016, MDX-010 |

**Supplementary Table 2 Immune-related adverse events examined in ICI-associated adverse events**

|  |  |
| --- | --- |
| **Toxicity types** | **Preferred terms** |
| **Skin Toxicities** | Rash maculo-papular |
|  | Rash papular |
|  | Rash papulosquamous |
|  | Rash |
|  | Rash generalised |
|  | Rash macular |
|  | Rash maculovesicular |
|  | Pruritus |
|  | Pruritus allergic |
|  | Pruritus generalised |
|  | Rash pruritic |
|  | Lichenification |
|  | Rash morbilliform |
|  | Measles |
|  | Urticaria |
|  | Urticaria chronic |
|  | Eczema |
|  | Eczema herpeticum |
|  | Erythema |
|  | Rash erythematous |
|  | Acne |
|  | Acne pustular |
|  | Dermatitis acneiform |
|  | Papulopustular rosacea |
|  | Acne varioliformis |
|  | Psoriasis |
|  | Pustular psoriasis |
|  | Nail psoriasis |
|  | Rebound psoriasis |
|  | Vitiligo |
|  | Exfoliative rash |
|  | Dermatitis exfoliative |
|  | Dermatitis exfoliative generalised |
|  | Keratolysis exfoliativa acquired |
|  | Bullous impetigo |
|  | Dermatitis bullous |
|  | Acquired epidermolysis bullosa |
|  | Pemphigoid |
|  | Rash pustular |
|  | Itching scar |
|  | Scar pain |
|  | Stevens-Johnson syndrome |
|  | Toxic epidermal necrolysis |
|  | Acute generalised exanthematous pustulosis |
|  | Drug reaction with eosinophilia and systemic symptoms |
| **Gastrointestinal toxicities** | Acute haemorrhagic ulcerative colitis |
|  | Allergic colitis |
|  | Autoimmune colitis |
|  | Colitis |
|  | Colitis erosive |
|  | Colitis ischaemic |
|  | Colitis microscopic |
|  | Necrotising colitis |
|  | Colitis psychogenic |
|  | Enterocolitis haemorrhagic |
|  | Colitis ulcerative |
|  | Eosinophilic colitis |
|  | Pseudopolyposis |
|  | Enterocolitis |
|  | Segmental diverticular colitis |
|  | Neutropenic colitis |
|  | Acute haemorrhagic ulcerative colitis |
|  | Inflammatory bowel disease |
|  | Crohn's disease |
|  | Constipation |
|  | Abdominal distension |
|  | Abdominal pain |
|  | Abdominal pain lower |
|  | Diarrhoea |
|  | Diarrhoea haemorrhagic |
|  | Haematochezia |
|  | Intestinal angina |
|  | Abdominal distension |
|  | Gastroenteritis |
|  | Ischaemic enteritis |
|  | Enterocolitis |
|  | Allergic gastroenteritis |
|  | Enteritis |
|  | Proctitis |
|  | Duodenitis |
|  | Proctitis haemorrhagic |
|  | Duodenitis haemorrhagic |
|  | Proctitis ulcerative |
|  | Gastroenteritis radiation |
|  | Radiation proctitis |
|  | Gastrointestinal inflammation |
|  | Erosive duodenitis |
|  | Lupus enteritis |
|  | Ulcerative duodenitis |
|  | Gastric volvulus |
|  | Ileal perforation |
|  | Gastrointestinal oedema |
|  | Intestinal perforation |
|  | Intestinal angioedema |
|  | Jejunal perforation |
|  | Rectal perforation |
|  | Large intestine perforation |
|  | Duodenal perforation |
|  | Small intestinal perforation |
|  | Gastric perforation |
|  | Gastrointestinal perforation |
|  | Upper gastrointestinal perforation |
|  | Pancreatitis |
|  | Haemorrhagic necrotic pancreatitis |
|  | Pancreatitis acute |
|  | Obstructive pancreatitis |
|  | Pancreatitis chronic |
|  | Radiation pancreatitis |
|  | Pancreatitis haemorrhagic |
|  | Autoimmune pancreatitis |
|  | Pancreatitis necrotising |
|  | Oedematous pancreatitis |
|  | Ischaemic pancreatitis |
|  | Lupus pancreatitis |
|  | Amylase abnormal |
|  | Amylase increased |
|  | Lipase abnormal |
|  | Lipase increased |
| **Hepatitis** | Hepatitis |
|  | Steatohepatitis |
|  | Hepatitis mumps |
|  | Autoimmune hepatitis |
|  | Immune-mediated hepatitis |
|  | Non-alcoholic steatohepatitis |
|  | Chronic hepatitis |
|  | Hepatitis cholestatic |
|  | Steatohepatitis |
|  | Hepatitis acute |
|  | Hepatitis alcoholic |
|  | Alloimmune hepatitis |
|  | Ischaemic hepatitis |
|  | Hepatitis chronic active |
|  | Radiation hepatitis |
|  | Hepatitis chronic persistent |
|  | Lupus hepatitis |
|  | Hepatitis fulminant |
|  | Allergic hepatitis |
|  | Hepatitis toxic |
|  | Hepatotoxicity |
|  | Liver disorder |
|  | Liver injury |
|  | Drug-induced liver injury |
|  | Mixed liver injury |
|  | Hepatic failure |
|  | Acute hepatic failure |
|  | Hepatic enzyme increased |
|  | Liver function test abnormal |
|  | Liver function test increased |
|  | Transaminases abnormal |
|  | Transaminases increased |
|  | Alanine aminotransferase abnormal |
|  | Alanine aminotransferase increased |
|  | Aspartate aminotransferase abnormal |
|  | Aspartate aminotransferase increased |
|  | Blood alkaline phosphatase increased |
|  | Blood alkaline phosphatase abnormal |
|  | Bilirubin conjugated increased |
|  | Hyperbilirubinaemia |
|  | Blood bilirubin increased |
|  | Blood bilirubin unconjugated increased |
|  | Bilirubin conjugated abnormal |
|  | Blood bilirubin abnormal |
|  | Coagulopathy |
|  | Jaundice |
|  | Ocular icterus |
|  | Jaundice cholestatic |
|  | Jaundice extrahepatic obstructive |
|  | Jaundice hepatocellular |
|  | Hepatic fibrosis |
|  | Hepatic fibrosis marker increased |
|  | Hepatic cirrhosis |
|  | Hepatic encephalopathy |
|  | Minimal hepatic encephalopathy |
|  | Ascites |
| **Endocrine Toxicities** | Hypophysitis |
|  | Hypopituitarism |
|  | Blood thyroid stimulating hormone increased |
|  | Blood thyroid stimulating hormone decreased |
|  | Blood thyroid stimulating hormone abnormal |
|  | Tri-iodothyronine free decreased |
|  | Tri-iodothyronine free abnormal |
|  | Tri-iodothyronine free increased |
|  | Primary hypogonadism |
|  | Secondary hypogonadism |
|  | Diabetes insipidus |
|  | Hypothyroidism |
|  | Primary hypothyroidism |
|  | Secondary hypothyroidism |
|  | Tertiary hypothyroidism |
|  | Autoimmune hypothyroidism |
|  | Thyroid atrophy |
|  | Myxoedema |
|  | Hypothyroidic goitre |
|  | Hyperthyroidism |
|  | Thyrotoxic crisis |
|  | Thyrotoxic periodic paralysis |
|  | Toxic nodular goitre |
|  | Secondary hyperthyroidism |
|  | Toxic goitre |
|  | Primary hyperthyroidism |
|  | Thyroid dermatopathy |
|  | Hashitoxicosis |
|  | Malignant exophthalmos |
|  | Basedow's disease |
|  | Marine Lenhart syndrome |
|  | Exophthalmos |
|  | Endocrine ophthalmopathy |
|  | Atrophic thyroiditis |
|  | Thyroiditis fibrous chronic |
|  | Thyroiditis |
|  | Radiation thyroiditis |
|  | Thyroiditis acute |
|  | Hashimoto's encephalopathy |
|  | Thyroiditis chronic |
|  | Autoimmune thyroiditis |
|  | Thyroiditis subacute |
|  | Adrenal atrophy |
|  | Primary adrenal insufficiency |
|  | Addison's disease |
|  | Hypoaldosteronism |
|  | Adrenal insufficiency |
|  | Glucocorticoid deficiency |
|  | Adrenal suppression |
|  | Mineralocorticoid deficiency |
|  | Adrenocortical insufficiency acute |
|  | Adrenal androgen deficiency |
|  | Secondary adrenocortical insufficiency |
|  | Cortisol deficiency |
|  | Type 1 diabetes mellitus |
|  | Fulminant type 1 diabetes mellitus |
|  | Latent autoimmune diabetes in adults |
|  | Diabetic ketoacidosis |
|  | Euglycaemic diabetic ketoacidosis |
|  | Diabetic ketoacidotic hyperglycaemic coma |
| **Lung Toxicities** | Pneumonitis |
|  | Radiation alveolitis |
|  | Eosinophilic pneumonia |
|  | Pulmonary vasculitis |
|  | Embolic pneumonia |
|  | Eosinophilic pneumonia acute |
|  | Granulomatous pneumonitis |
|  | Alveolitis |
|  | Eosinophilic pneumonia chronic |
|  | Haemorrhagic pneumonia |
|  | Lupus pneumonitis |
|  | Immune-mediated pneumonitis |
|  | Idiopathic pneumonia syndrome |
|  | Alveolitis necrotising |
|  | Radiation pneumonitis |
|  | Pneumonia necrotising |
|  | Radiation alveolitis |
|  | Embolic pneumonia |
|  | Alveolitis |
|  | Organising pneumonia |
|  | Pulmonary interstitial emphysema syndrome |
|  | Interstitial lung disease |
|  | Acute interstitial pneumonitis |
|  | Idiopathic interstitial pneumonia |
|  | Idiopathic pulmonary fibrosis |
|  | Combined pulmonary fibrosis and emphysema |
|  | Pulmonary fibrosis |
|  | Sarcoidosis |
|  | Pulmonary sarcoidosis |
| **Musculoskeletal Toxicities** | Arthritis |
|  | Nodal osteoarthritis |
|  | Sacroiliitis |
|  | Autoimmune arthritis |
|  | Interspinous osteoarthritis |
|  | Paraneoplastic arthritis |
|  | Polyarthritis |
|  | Laryngeal rheumatoid arthritis |
|  | Rapidly progressive osteoarthritis |
|  | Antithyroid arthritis syndrome |
|  | Periarthritis calcarea |
|  | Juvenile idiopathic arthritis |
|  | Spinal osteoarthritis |
|  | Carcinomatous polyarthritis |
|  | Juvenile psoriatic arthritis |
|  | Rheumatoid arthritis |
|  | Osteoarthritis |
|  | Seronegative arthritis |
|  | Psoriatic arthropathy |
|  | SLE arthritis |
|  | Arthritis allergic |
|  | Arthritis enteropathic |
|  | Myositis |
|  | Dermatomyositis |
|  | Orbital myositis |
|  | Myositis ossificans circumscripta |
|  | Polymyositis |
|  | Myositis-like syndrome |
|  | Inclusion body myositis |
|  | Myositis ossificans |
|  | Juvenile polymyositis |
|  | Necrotising myositis |
|  | Lupus myositis |
|  | Myalgia |
|  | Malignant psoas syndrome |
|  | Eosinophilia myalgia syndrome |
|  | Tendon pain |
|  | Polymyalgia rheumatica |
|  | Musculoskeletal chest pain |
|  | Myalgia intercostal |
|  | Musculoskeletal pain |
|  | Fibromyalgia |
|  | Myofascial pain syndrome |
|  | Neuromuscular pain |
|  | Arthralgia |
|  | Joint swelling |
|  | Gouty arthritis |
| **Cardiovascular Toxicities** | Myocarditis |
|  | Autoimmune myocarditis |
|  | Lupus myocarditis |
|  | Radiation myocarditis |
|  | Hypersensitivity myocarditis |
|  | Eosinophilic myocarditis |
|  | Pericarditis |
|  | Pericarditis adhesive |
|  | Pericarditis constrictive |
|  | Pericarditis malignant |
|  | Pericarditis uraemic |
|  | Pericarditis lupus |
|  | Autoimmune pericarditis |
|  | Radiation pericarditis |
|  | Cardiac failure |
|  | Cardiac failure acute |
|  | Cardiac failure chronic |
|  | Cardiac failure congestive |
|  | Cardiac failure high output |
|  | Radiation associated cardiac failure |
|  | Chest pain |
|  | Non-cardiac chest pain |
|  | Musculoskeletal chest pain |
|  | Pleuritic pain |
|  | Epidemic pleurodynia |
|  | Dyspnoea |
|  | Heart rate abnormal |
|  | Angina unstable |
|  | Troponin increased |
|  | Vasculitis |
|  | Lupus vasculitis |
|  | Vasculitic rash |
|  | Septic vasculitis |
|  | Eosinophilic granulomatosis with polyangiitis |
|  | Rheumatoid vasculitis |
|  | Vasculitis necrotising |
|  | Radiation vasculitis |
|  | Hypersensitivity vasculitis |
|  | Cutaneous vasculitis |
|  | Anti-neutrophil cytoplasmic antibody positive vasculitis |
|  | Capillaritis |
|  | Haemorrhagic vasculitis |
|  | Diffuse vasculitis |
|  | Pseudovasculitis |
|  | Angiodermatitis |
|  | Ocular vasculitis |
|  | Nodular vasculitis |
|  | Segmented hyalinising vasculitis |
|  | Retinal vasculitis |
|  | Pulmonary vasculitis |
|  | Granulomatosis with polyangiitis |
|  | Vasculitis gastrointestinal |
|  | Renal vasculitis |
|  | Stoma site vasculitis |
|  | Urticarial vasculitis |
|  | Thromboangiitis obliterans |
|  | Vasculitic ulcer |
|  | Embolism venous |
|  | Hepatic vein embolism |
|  | Renal vein embolism |
|  | Portal vein embolism |
|  | Jugular vein embolism |
|  | Vena cava embolism |
| **Hematologic Toxicities** | Haemolytic anaemia |
|  | Autoimmune haemolytic anaemia |
|  | Cold type haemolytic anaemia |
|  | Coombs positive haemolytic anaemia |
|  | Coombs negative haemolytic anaemia |
|  | Warm type haemolytic anaemia |
|  | Haemolytic anaemia enzyme specific |
|  | Haemolytic icteroanaemia |
|  | Aplastic anaemia |
|  | Aplasia pure red cell |
|  | Hypoplastic anaemia |
|  | Autoimmune aplastic anaemia |
|  | Febrile bone marrow aplasia |
|  | Neutropenia |
|  | Febrile neutropenia |
|  | Cyclic neutropenia |
|  | Autoimmune neutropenia |
|  | Benign ethnic neutropenia |
|  | Thrombocytopenia |
|  | Platelet production decreased |
|  | Thrombocytopenic purpura |
|  | Thrombotic thrombocytopenic purpura |
|  | HELLP syndrome |
|  | Immune thrombocytopenic purpura |
|  | Acquired amegakaryocytic thrombocytopenia |
|  | Amegakaryocytic thrombocytopenia |
|  | Haemophilia |
|  | Acquired Von Willebrand's disease |
|  | Acquired haemophilia |
|  | Haemophilia A with anti factor VIII |
|  | Haemophilia A without inhibitors |
|  | Eosinophil percentage increased |
|  | Eosinophilic pleural effusion |
|  | Eosinophil count abnormal |
|  | Drug reaction with eosinophilia and systemic symptoms |
|  | Eosinophil count increased |
|  | CSF eosinophil count increased |
|  | Eosinophilia |
|  | Tropical eosinophilia |
|  | Eosinophilia myalgia syndrome |
|  | Eosinophilic fasciitis |
|  | Eosinophilic myocarditis |
|  | Eosinophilic pneumonia |
|  | Neutrophilia |
|  | Acute febrile neutrophilic dermatosis |
|  | Neutrophil count increased |
|  | Monocytosis |
|  | Mononucleosis syndrome |
|  | Haemolytic uraemic syndrome |
| **Renal Toxicities** | Nephritis |
|  | Immune-mediated nephritis |
|  | Pyelonephritis acute |
|  | Fibrillary glomerulonephritis |
|  | Glomerulonephritis membranoproliferative |
|  | Glomerulonephritis rapidly progressive |
|  | Perinephritis |
|  | Glomerulonephritis membranous |
|  | Nephritis haemorrhagic |
|  | Glomerulonephritis chronic |
|  | Glomerulonephritis |
|  | Chronic autoimmune glomerulonephritis |
|  | Autoimmune nephritis |
|  | Paraneoplastic glomerulonephritis |
|  | Pyelonephritis chronic |
|  | Glomerulonephritis minimal lesion |
|  | Nephritis allergic |
|  | Glomerulonephritis proliferative |
|  | Nephritis radiation |
|  | Nephritic syndrome |
|  | Henoch-Schonlein purpura nephritis |
|  | Tubulointerstitial nephritis |
|  | Emphysematous pyelonephritis |
|  | Pyelitis |
|  | Tubulointerstitial nephritis and uveitis syndrome |
|  | Lupus nephritis |
|  | Pyelonephritis |
|  | Glomerulonephritis acute |
|  | Mesangioproliferative glomerulonephritis |
|  | Renal vasculitis |
|  | Acute kidney injury |
|  | Postrenal failure |
|  | Hepatorenal failure |
|  | Blood creatinine increased |
|  | Blood creatinine abnormal |
|  | Blood urea nitrogen/creatinine ratio increased |
| **Nervous System Toxicities** | Autonomic neuropathy |
|  | Cardiac autonomic neuropathy |
|  | Diabetic autonomic neuropathy |
|  | Neuropathy peripheral |
|  | Thoracic outlet syndrome |
|  | Lumbosacral plexopathy |
|  | Axonal neuropathy |
|  | Neuropathic ulcer |
|  | HIV peripheral neuropathy |
|  | Lumbosacral plexus lesion |
|  | Ischaemic neuropathy |
|  | Neuritis |
|  | Peripheral sensorimotor neuropathy |
|  | Peripheral motor neuropathy |
|  | Brachial plexopathy |
|  | Peripheral sensory neuropathy |
|  | Cervical plexus lesion |
|  | Polyneuropathy |
|  | Neuronal neuropathy |
|  | Uraemic neuropathy |
|  | Notalgia paraesthetica |
|  | Encephalitis autoimmune |
|  | Subacute sclerosing panencephalitis |
|  | Encephalitis |
|  | Encephalitis brain stem |
|  | Bickerstaff's encephalitis |
|  | Panencephalitis |
|  | Lupus encephalitis |
|  | Encephalitis haemorrhagic |
|  | Encephalitis allergic |
|  | Encephalitis toxic |
|  | Acute haemorrhagic leukoencephalitis |
|  | Noninfective encephalitis |
|  | Rasmussen encephalitis |
|  | Limbic encephalitis |
|  | Myasthenic syndrome |
|  | Myasthenia gravis |
|  | Myasthenia gravis crisis |
|  | Guillain-Barre syndrome |
|  | Encephalopathy |
|  | Immune-mediated encephalopathy |
|  | Autoimmune encephalopathy |
|  | Toxic encephalopathy |
|  | Vascular encephalopathy |
|  | Encephalopathy allergic |
|  | Posterior reversible encephalopathy syndrome |
|  | Progressive multifocal leukoencephalopathy |
|  | Hashimoto's encephalopathy |
|  | Wernicke's encephalopathy |
|  | Toxic leukoencephalopathy |
|  | Rheumatic brain disease |
|  | Leukoencephalopathy |
|  | Hypertensive encephalopathy |
|  | Hepatic encephalopathy |
|  | Hyperammonaemic encephalopathy |
|  | Meningitis aseptic |
|  | Myelitis transverse |
| **Ocular Toxicities** | Uveitis |
|  | Autoimmune uveitis |
|  | Immune-mediated uveitis |
|  | Uveitic glaucoma |
|  | Keratouveitis |
|  | Immune recovery uveitis |
|  | Tubulointerstitial nephritis and uveitis syndrome |
|  | Infective uveitis |
|  | Diabetic uveitis |
|  | Swelling of eyelid |
|  | Blepharitis |
|  | Idiopathic orbital inflammation |
|  | Episcleritis |
|  | Papilloedema |
|  | Ulcerative keratitis |
|  | Choroiditis |
|  | Retinitis |
|  | Conjunctivitis |
|  | Scleritis |
|  | Blepharitis |

**Supplementary Table 3** Fourfold table of measures of disproportionality

|  |  |  |  |
| --- | --- | --- | --- |
| Drug | Adverse event of interest | All other adverse events | Total |
| Drug of interest | a | b | a＋b |
| All other drugs | c | d | c＋d |
| Total | a＋c | b＋d | N＝a＋b＋c＋d |

**Supplementary Table 4** The equations and criteria for ROR and PRR

|  |  |  |
| --- | --- | --- |
| Algorithms | Equation | Signal Criteria |
| ROR |  | a)95CI％＞1,b) N≥2 |
| PRR |  | a)N≥3, b) PRR≥2,  c) ≥4, |

Abbreviations: CI, confidence interval, N, the number of co-occurrences, PRR, proportional reporting ratio, ROR, reporting odds ratio, χ2, chi-square.

**Supplementary Table 5** the signals of ICI-associated adverse events in 11 groups.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| ICI regimens | Preferred terms | N | PRR (95%CI) | χ2 | ROR (95%CI) |
| atezolizumab | Endocrine Toxicities | 195 | 6.56 (5.72, 7.53) | 922.07 | 6.78 (5.88, 7.83) |
|  | Hematologic Toxicities | 358 | 4.03 (3.64, 4.45 | 827.78 | 4.26 (3.82, 4.74) |
|  | Hepatitis | 373 | 2.98 (2.70, 3.28) | 501.52 | 3.13 (2.82, 3.48) |
|  | Lung Toxicities | 268 | 10.15 (9.03, 11.41) | 2212.58 | 10.66 (9.52, 12.06) |
|  | Nervous System Toxicities | 190 | 3.98 (3.46, 4.58) | 427.19 | 4.10 (3.54, 4.73) |
|  | Renal Toxicities | 208 | 3.58 (3.14,4.09) | 391.08 | 3.69 (3.21, 4.24) |
| avelumab | Endocrine Toxicities | 12 | 3.50 (2.00, 6.13) | 21.53 | 3.55 (2.00, 6.29) |
|  | Hematologic Toxicities | 21 | 2.05 (1.35, 3.12) | 11.48 | 2.09 (1.35, 3.23) |
|  | Lung Toxicities | 22 | 7.21 (4.78, 10.86) | 118.23 | 7.45 (4.87, 11.41) |
|  | Nervous System Toxicities | 13 | 2.36 (1.38, 4.04) | 10.3 | 2.39 (1.38, 4.15) |
| cemiplimab | Endocrine Toxicities | 15 | 8.06 (4.92, 13.21) | 93.31 | 8.41 (5.01, 14.12) |
|  | Hematologic Toxicities | 14 | 2.52 (1.51, 4.2) | 13.04 | 2.59 (1.51, 4.42) |
|  | Hepatitis | 19 | 2.43 (1.57, 3.75) | 16.32 | 2.52 (1.58, 4.00) |
|  | Lung Toxicities | 11 | 6.64 (3.72, 11.87) | 53 | 6.84 (3.75, 12.49) |
|  | Renal Toxicities | 13 | 3.58 (2.10, 6.10) | 24.45 | 3.69 (2.12, 6.43) |
| durvalumab | Endocrine Toxicities | 103 | 8.37 (6.93, 10.10) | 670.97 | 8.74 (7.17, 10.66) |
|  | Hematologic Toxicities | 85 | 2.31 (1.87, 2.84) | 64.12 | 2.36 (1.90, 2.94) |
|  | Lung Toxicities | 588 | 54.13 (50.51, 58.00) | 30518.02 | 74.61 (67.82, 82.09) |
|  | Nervous System Toxicities | 50 | 2.53 (1.92, 3.33) | 46.61 | 2.57 (1.94, 3.40) |
| ipilimumab | Endocrine Toxicities | 788 | 14.83 (13.86, 15.86) | 10099.88 | 16.12 (14.98, 17.35) |
|  | Gastrointestinal toxicities | 2314 | 3.84 (3.71, 3.98) | 5188.46 | 4.79 (4.57, 5.03) |
|  | Hepatitis | 537 | 2.38 (2.19, 2.58) | 438.18 | 2.46 (2.26, 2.69) |
|  | Lung Toxicities | 148 | 3.10 (2.64, 3.64) | 211.16 | 3.13 (2.66, 3.69) |
|  | Nervous System Toxicities | 203 | 2.36 (2.06, 2.70) | 159.74 | 2.39 (2.08, 2.74) |
|  | Ocular Toxicities | 57 | 3.35 (2.59, 4.34) | 94 | 3.37 (2.59, 4.37) |
| nivolumab | Endocrine Toxicities | 2394 | 11.61 (11.16, 12.08) | 22507.02 | 12.35 (11.84, 12.88) |
|  | Hematologic Toxicities | 1290 | 2.03 (1.93, 2.14 | 683.21 | 2.07 (1.96, 2.19) |
|  | Hepatitis | 2433 | 2.73 (2.62, 2.83) | 2701.81 | 2.85 (2.73, 2.97) |
|  | Lung Toxicities | 1719 | 9.30 (8.87, 9.75) | 12429.93 | 9.71 (9.24, 10.20) |
|  | Nervous System Toxicities | 1063 | 3.13 (2.95, 3.32) | 1537.88 | 3.19 (3.00, 3.39) |
|  | Ocular Toxicities | 212 | 3.16 (2.76, 3.61) | 310.05 | 3.17 (2.77, 3.63) |
|  | Renal Toxicities | 1007 | 2.43 (2.29, 2.58) | 851.77 | 2.47 (2.32, 2.63) |
| pembrolizumab | Endocrine Toxicities | 1024 | 10.87 (10.24, 11.54) | 9086.25 | 11.52 (10.81, 12.28) |
|  | Hepatitis | 1037 | 2.58 (2.44, 2.74) | 1028.39 | 2.69 (2.53, 2.87) |
|  | Lung Toxicities | 1275 | 15.30 (14.51, 16.14) | 16763.1 | 16.51 (15.58, 17.49) |
|  | Nervous System Toxicities | 485 | 3.17 (2.91, 3.46) | 725.09 | 3.24 (2.96, 3.55) |
|  | Ocular Toxicities | 74 | 2.45 (1.95, 3.07) | 63.26 | 2.45 (1.95, 3.09) |
|  | Renal Toxicities | 443 | 2.38 (2.17, 2.61) | 357.52 | 2.42 (2.20, 2.66) |
| ipilimumab plus nivolumab | Endocrine Toxicities | 397 | 30.55 (27.94, 33.42) | 11347.9 | 36.92 (33.12, 41.16) |
|  | Gastrointestinal toxicities | 441 | 3.00 (2.76, 3.27) | 630.85 | 3.50 (3.15, 3.88) |
|  | Hepatitis | 261 | 4.75 (4.24, 5.32) | 790.99 | 5.24 (4.61, 5.97) |
|  | Lung Toxicities | 171 | 14.74 (12.76, 17.03) | 2196.02 | 15.88 (13.58, 18.56) |
|  | Nervous System Toxicities | 87 | 4.15 (3.38, 5.10) | 209.91 | 4.28 (3.45, 5.30) |
|  | Ocular Toxicities | 11 | 2.66 (1.47, 4.79) | 11.37 | 2.66 (1.47, 4.82) |
|  | Renal Toxicities | 70 | 2.75 (2.18, 3.46) | 78.57 | 2.80 (2.21, 3.56） |
| ipilimumab plus pembrolizumab | Endocrine Toxicities | 38 | 47.92 (36.58, 62.77) | 1755 | 66.11 (45.46, 96.16） |
|  | Gastrointestinal toxicities | 30 | 3.37 (2.45, 4.62) | 53.37 | 4.03 (2.69, 6.05) |
|  | Hepatitis | 15 | 4.49 (2.79, 7.24) | 41.74 | 4.92 (2.88, 8.42) |
|  | Lung Toxicities | 12 | 17.00 (9.90, 29.18) | 181.61 | 18.55 (10.25, 33.55) |
|  | Musculoskeletal Toxicities | 16 | 2.75 (1.73, 4.35) | 18.57 | 2.98 (1.77, 5.02) |
|  | Nervous System Toxicities | 5 | 3.93 (1.66, 9.28) | 11.01 | 4.04 (1.65, 9.87) |
|  | Renal Toxicities | 8 | 5.17 (2.64, 10.12) | 27.2 | 5.43 (2.66, 11.09) |
|  | Skin Toxicities | 22 | 2.45 (1.67, 3.59) | 20.13 | 2.72 (1.73, 4.30) |

**Supplementary Table 6 distribution of death outcomes of each ICI regimens**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| ICI regimens | Gastrointestinal toxicities | Hepatitis | Endocrine Toxicities | Lung Toxicities | Musculoskeletal Toxicities | Cardiovascular Toxicities |
| Monotherapy | 19.69% | 15.57% | 6.43% | 18.28% | 3.75% | 15.33% |
| PD-1 | 16.24% | 15.82% | 6.95% | 19.14% | 4.11% | 16.05% |
| nivolumab | 17.80% | 17.02% | 7.59% | 13.77% | 4.21% | 17.39% |
| pembrolizumab | 12.90% | 13.44% | 5.61% | 30.75% | 3.88% | 13.24% |
| cemiplimab | 16.67% | 0.00% | 5.56% | 11.11% | 5.56% | 11.11% |
| PD-L1 | 14.51% | 15.13% | 2.96% | 27.30% | 3.28% | 16.22% |
| atezolizumab | 17.16% | 17.40% | 3.19% | 17.16% | 3.43% | 18.14% |
| avelumab | 23.68% | 7.89% | 2.63% | 15.79% | 2.63% | 18.42% |
| durvalumab | 7.18% | 11.79% | 2.56% | 50.77% | 3.08% | 11.79% |
| CTLA-4 | 49.92% | 14.18% | 6.01% | 3.08% | 1.54% | 9.24% |
| ipilimumab | 49.85% | 14.20% | 6.02% | 3.09% | 1.54% | 9.26% |
| tremelimumab | 100.00% | 0.00% | 0.00% | 0.00% | 0.00% | 0.00% |
| combination therapy | 18.37% | 15.31% | 9.18% | 22.96% | 3.06% | 9.69% |
| ipilimumab plus nivolumab | 17.84% | 15.68% | 8.65% | 24.32% | 2.16% | 10.27% |
| ipilimumab plus pembrolizumab | 33.33% | 11.11% | 11.11% | 0.00% | 11.11% | 0.00% |

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| ICI regimens | Hematologic Toxicities | Renal Toxicities | Nervous System Toxicities | Ocular Toxicities | Skin Toxicities |
| Monotherapy | 5.01% | 4.64% | 5.21% | 0.28% | 5.81% |
| PD-1 | 4.94% | 4.75% | 5.32% | 0.28% | 6.40% |
| nivolumab | 5.40% | 5.00% | 5.81% | 0.31% | 5.71% |
| pembrolizumab | 3.88% | 4.08% | 4.28% | 0.20% | 7.75% |
| cemiplimab | 11.11% | 16.67% | 5.56% | 0.00% | 16.67% |
| PD-L1 | 6.86% | 5.77% | 6.24% | 0.16% | 1.56% |
| atezolizumab | 7.35% | 6.62% | 8.09% | 0.00% | 1.47% |
| avelumab | 18.42% | 5.26% | 2.63% | 2.63% | 0.00% |
| durvalumab | 3.59% | 4.10% | 3.08% | 0.00% | 2.05% |
| CTLA-4 | 3.70% | 2.77% | 3.39% | 0.46% | 5.70% |
| ipilimumab | 3.70% | 2.78% | 3.40% | 0.46% | 5.71% |
| Tremelimumab | 0.00% | 0.00% | 0.00% | 0.00% | 0.00% |
| Combination therapy | 3.57% | 3.57% | 7.14% | 0.00% | 7.14% |
| ipilimumab plus nivolumab | 3.78% | 3.78% | 6.49% | 0.00% | 7.03% |
| ipilimumab plus pembrolizumab | 0.00% | 0.00% | 22.22% | 0.00% | 11.11% |

**Supplementary Table 7 Sarcoidosis signals from ICI regimens**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **ICI regimens** | **Preferred terms** | **N** | **PRR (95%CI)** | **X2** | **ROR (95%CI)** |
| atezolizumab | Sarcoidosis | 9 | 7.37 (3.83, 14.16) | 49.36 | 7.38 (3.83, 14.20) |
| avelumab | Sarcoidosis | 4 | 28.39 (10.68, 75.43) | 105.56 | 28.57 (10.68, 76.44) |
| ipilimumab | Sarcoidosis | 22 | 7.97 (5.24, 12.12） | 133.00 | 7.98 (5.24, 12.15) |
|  | Pulmonary sarcoidosis | 4 | 6.86 (2.56, 18.33） | 19.87 | 6.86 (2.56, 18.34) |
| nivolumab | Pulmonary sarcoidosis | 8 | 4.37 (2.17, 8.78) | 20.49 | 4.37 (2.17, 8.78) |
| pembrolizumab | Sarcoidosis | 36 | 9.27 (6.67, 12.87) | 262.05 | 9.28 (6.68, 12.90) |
|  | Pulmonary sarcoidosis | 13 | 16.00 (9.24, 27.73) | 178.78 | 16.02 (9.24, 27.76) |

**Supplementary Table 8 Hypophysitis signals from ICI regimens**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **ICI regimens** | **Preferred terms** | **N** | **PRR (95%CI)** | **X2** | **ROR (95%CI)** |
| atezolizumab | Hypophysitis | 16 | 34.85 (21.29, 57.07) | 518.12 | 34.96 (21.32, 57.33) |
| durvalumab | Hypophysitis | 4 | 20.72 (7.77, 55.26) | 74.80 | 20.76 (7.77, 55.46) |
| ipilimumab | Hypophysitis | 538 | 1047.58 (929.18, 1181.08) | 272943.81 | 1098.55 (971.65, 1242.01) |
| nivolumab | Hypophysitis | 270 | 108.80 (94.76, 124.92) | 21389.68 | 109.60 (95.39, 125.94) |
| pembrolizumab | Hypophysitis | 98 | 72.24 (58.71, 88.89) | 6239.61 | 72.67 (58.99, 89.52) |