**Table S1** Reporting frequencies of ICIs-associated (total and common) endocrine events in male compared with female\*

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | **a** | **b** | **c** | **d** | **ROR** | **ROR025** | **ROR975** |
| **Total**  **(N=29294335)** | 3428 | 69180 | 2095 | 41550 | 0.98 | 0.93 | 1.04 |
| Hypothyroidism | 425 | 72183 | 374 | 43271 | 0.68 | 0.59 | 0.78 |
| Adrenal insufficiency | 447 | 72161 | 203 | 43442 | 1.33 | 1.12 | 1.56 |
| Hypophysitis | 336 | 72272 | 176 | 43469 | 1.15 | 0.96 | 1.38 |
| Hyperthyroidism | 241 | 72367 | 189 | 43456 | 0.77 | 0.63 | 0.93 |
| **Melanoma**  **(N=136963)** | 1235 | 15238 | 950 | 10694 | 0.91 | 0.84 | 1.00 |
| Hypothyroidism | 124 | 16349 | 169 | 11475 | 0.52 | 0.41 | 0.65 |
| Adrenal Insufficiency | 138 | 16335 | 79 | 11565 | 1.24 | 0.94 | 1.63 |
| Hypophysitis | 210 | 16263 | 101 | 11543 | 1.47 | 1.16 | 1.87 |
| Hyperthyroidism | 79 | 16394 | 81 | 11563 | 0.69 | 0.51 | 0.94 |
| **Non-small cell lung cancer (N=190307)** | 706 | 14710 | 296 | 7129 | 1.16 | 1.01 | 1.33 |
| Hypothyroidism | 108 | 15308 | 52 | 7373 | 1.00 | 0.72 | 1.39 |
| Adrenal Insufficiency | 102 | 15314 | 32 | 7393 | 1.53 | 1.03 | 2.29 |
| Hypophysitis | 33 | 15383 | 13 | 7412 | 1.22 | 0.64 | 2.32 |
| Hyperthyroidism | 63 | 15353 | 33 | 7392 | 0.92 | 0.60 | 1.40 |
| **Other indications**  **(N=28967065)** | 1487 | 39232 | 849 | 23727 | 1.06 | 0.97 | 1.15 |
| Hypothyroidism | 193 | 40526 | 153 | 24423 | 0.76 | 0.61 | 0.94 |
| Adrenal Insufficiency | 207 | 40512 | 92 | 24484 | 1.36 | 1.06 | 1.74 |
| Hypophysitis | 93 | 40626 | 62 | 24514 | 0.91 | 0.66 | 1.25 |
| Hyperthyroidism | 99 | 40620 | 75 | 24501 | 0.80 | 0.59 | 1.08 |

\* In **Table S1**, N: number of total records; a: the number of records with endocrine AEs reported for ICIs; b: the number of records with any other AEs reported for ICIs; c: the number of records with any endocrine AEs for other drugs; d: the number of records reported other AEs for other drugs. ROR025: the lower end of the 95% confidence interval of ROR. ROR975: the upper end of the 95% confidence interval of ROR. ROR025 exceeds 1 was deemed significant difference.

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**Figure S1** Comparisons of ICIs-related endocrine events (total and common) between male and female.

**Table S2** Disproportionality analysis results for ICI monotherapy strategies and endocrine complications\*

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Drug** | **PT** | **a** | **b** | **c** | **d** | **IC** | **IC025** | **IC975** | **ROR** | **ROR025** | **ROR975** |
| Nivolumab | Hypothyroidism | 466 | 56997 | 11260 | 29225613 | 4.311 | **4.158** | 4.464 | 20.771 | **18.926** | 22.795 |
|  | Adrenal insufficiency | 222 | 57241 | 3965 | 29232908 | 4.674 | **4.452** | 4.897 | 26.924 | **23.514** | 30.829 |
|  | Hyperthyroidism | 167 | 57296 | 6434 | 29230439 | 3.639 | **3.382** | 3.895 | 12.775 | **10.953** | 14.900 |
|  | Fulminant type 1 diabetes mellitus | 130 | 57333 | 425 | 29236448 | 6.360 | **6.069** | 6.651 | 97.868 | **80.399** | 119.132 |
|  | Diabetic ketoacidosis | 111 | 57352 | 17452 | 29219421 | 1.674 | **1.359** | 1.989 | 3.208 | **2.662** | 3.867 |
|  | Diabetes mellitus | 110 | 57353 | 28504 | 29208369 | 0.964 | **0.648** | 1.281 | 1.957 | **1.622** | 2.360 |
|  | Type 1 diabetes mellitus | 103 | 57360 | 2988 | 29233885 | 3.979 | **3.652** | 4.306 | 16.266 | **13.363** | 19.800 |
|  | Hypercalcaemia | 89 | 57374 | 6037 | 29230836 | 2.838 | **2.486** | 3.190 | 7.247 | **5.878** | 8.936 |
|  | Thyroiditis | 85 | 57378 | 1528 | 29235345 | 4.544 | **4.184** | 4.905 | 24.436 | **19.639** | 30.406 |
|  | Hyperglycaemia | 83 | 57380 | 16287 | 29220586 | 1.356 | **0.992** | 1.721 | 2.571 | **2.072** | 3.190 |
|  | Hypophysitis | 81 | 57382 | 1602 | 29235271 | 4.422 | **4.053** | 4.792 | 22.363 | **17.887** | 27.960 |
|  | Thyroid disorder | 73 | 57390 | 7826 | 29229047 | 2.200 | **1.811** | 2.590 | 4.633 | **3.678** | 5.834 |
|  | Adrenal disorder | 52 | 57411 | 637 | 29236236 | 4.826 | **4.363** | 5.288 | 29.985 | **22.599** | 39.785 |
|  | Adrenocorticotropic hormone deficiency | 52 | 57411 | 188 | 29236685 | 5.757 | **5.294** | 6.220 | 60.403 | **44.426** | 82.125 |
|  | Hypopituitarism | 50 | 57413 | 967 | 29235906 | 4.339 | **3.867** | 4.812 | 21.051 | **15.840** | 27.975 |
|  | Hypoglycaemia | 43 | 57420 | 25532 | 29211341 | -0.220 | -0.730 | 0.290 | 0.858 | 0.636 | 1.158 |
|  | Autoimmune thyroiditis | 34 | 57429 | 1358 | 29235515 | 3.417 | **2.841** | 3.993 | 10.892 | **7.749** | 15.308 |
|  | Secondary adrenocortical insufficiency | 33 | 57430 | 866 | 29236007 | 3.888 | **3.303** | 4.473 | 15.219 | **10.749** | 21.548 |
|  | Type 2 diabetes mellitus | 29 | 57434 | 20594 | 29216279 | -0.473 | -1.099 | 0.152 | 0.720 | 0.500 | 1.036 |
|  | Inappropriate antidiuretic hormone secretion | 20 | 57443 | 7702 | 29229171 | 0.390 | -0.371 | 1.150 | 1.311 | 0.845 | 2.033 |
|  | Adrenocortical insufficiency acute | 15 | 57448 | 731 | 29236142 | 2.981 | **2.094** | 3.867 | 8.005 | **4.800** | 13.347 |
|  | Hypothalamo-pituitary disorder | 15 | 57448 | 686 | 29236187 | 3.047 | **2.161** | 3.934 | 8.388 | **5.028** | 13.991 |
|  | Endocrine disorder | 13 | 57450 | 625 | 29236248 | 2.946 | **1.988** | 3.904 | 7.812 | **4.510** | 13.530 |
|  | Gynaecomastia | 13 | 57450 | 34690 | 29202183 | -2.345 | -3.303 | -1.387 | 0.196 | 0.114 | 0.338 |
|  | Diabetes mellitus inadequate control | 11 | 57452 | 7417 | 29229456 | -0.390 | -1.440 | 0.660 | 0.763 | 0.422 | 1.378 |
|  | Goitre | 9 | 57454 | 1708 | 29235165 | 1.296 | **0.122** | 2.470 | 2.463 | **1.279** | 4.743 |
|  | Silent thyroiditis | 8 | 57455 | 52 | 29236821 | 3.782 | **2.527** | 5.038 | 14.115 | **6.705** | 29.715 |
|  | Diabetes insipidus | 7 | 57456 | 928 | 29235945 | 1.684 | **0.329** | 3.039 | 3.228 | **1.534** | 6.789 |
|  | Lymphocytic hypophysitis | 7 | 57456 | 231 | 29236642 | 2.956 | **1.600** | 4.311 | 7.862 | **3.706** | 16.677 |
|  | Metastases to adrenals | 7 | 57456 | 262 | 29236611 | 2.868 | **1.512** | 4.223 | 7.390 | **3.488** | 15.655 |
|  | Hypoparathyroidism | 6 | 57457 | 263 | 29236610 | 2.661 | **1.178** | 4.144 | 6.392 | **2.846** | 14.359 |
|  | Primary hypothyroidism | 6 | 57457 | 96 | 29236777 | 3.215 | **1.732** | 4.698 | 9.439 | **4.137** | 21.534 |
|  | Autoimmune hypothyroidism | 5 | 57458 | 85 | 29236788 | 3.023 | **1.368** | 4.678 | 8.245 | **3.346** | 20.320 |
|  | Hypercalcaemia of malignancy | 5 | 57458 | 98 | 29236775 | 2.970 | **1.315** | 4.624 | 7.941 | **3.233** | 19.506 |
|  | Adrenalitis | 4 | 57459 | 33 | 29236840 | 2.974 | **1.074** | 4.874 | 7.967 | **2.822** | 22.488 |
|  | Tetany | 4 | 57459 | 949 | 29235924 | 0.925 | -0.975 | 2.825 | 1.903 | 0.713 | 5.080 |
|  | Adrenal gland cancer | 3 | 57460 | 90 | 29236783 | 2.359 | **0.068** | 4.649 | 5.171 | **1.637** | 16.336 |
|  | Diabetic hyperglycaemic coma | 3 | 57460 | 167 | 29236706 | 2.070 | -0.220 | 4.360 | 4.226 | **1.349** | 13.237 |
|  | Diabetic nephropathy | 3 | 57460 | 754 | 29236119 | 0.818 | -1.472 | 3.108 | 1.766 | 0.568 | 5.488 |
|  | Exophthalmos | 3 | 57460 | 607 | 29236266 | 1.045 | -1.245 | 3.335 | 2.067 | 0.665 | 6.428 |
|  | Hyperprolactinaemia | 3 | 57460 | 6667 | 29230206 | -1.956 | -4.247 | 0.334 | 0.257 | 0.083 | 0.798 |
|  | Neuroendocrine carcinoma of the bladder | 3 | 57460 | 676 | 29236197 | 0.934 | -1.356 | 3.224 | 1.914 | 0.616 | 5.950 |
|  | Thyroid cancer | 3 | 57460 | 3423 | 29233450 | -1.045 | -3.335 | 1.245 | 0.484 | 0.156 | 1.502 |
| Pembrolizumab | Hypothyroidism | 172 | 29158 | 11554 | 29253452 | 3.817 | **3.564** | 4.069 | 14.356 | **12.344** | 16.695 |
|  | Adrenal insufficiency | 144 | 29186 | 4043 | 29260963 | 4.945 | **4.669** | 5.221 | 31.880 | **26.987** | 37.660 |
|  | Hyperthyroidism | 99 | 29231 | 6502 | 29258504 | 3.807 | **3.473** | 4.141 | 14.223 | **11.658** | 17.351 |
|  | Diabetes mellitus | 81 | 29249 | 28533 | 29236473 | 1.483 | **1.114** | 1.853 | 2.806 | **2.255** | 3.491 |
|  | Hyperglycaemia | 69 | 29261 | 16301 | 29248705 | 2.041 | **1.640** | 2.442 | 4.135 | **3.263** | 5.239 |
|  | Type 1 diabetes mellitus | 56 | 29274 | 3035 | 29261971 | 3.974 | **3.529** | 4.420 | 15.977 | **12.263** | 20.816 |
|  | Hypophysitis | 53 | 29277 | 1630 | 29263376 | 4.614 | **4.155** | 5.072 | 25.108 | **19.094** | 33.017 |
|  | Diabetic ketoacidosis | 47 | 29283 | 17516 | 29247490 | 1.393 | **0.906** | 1.881 | 2.633 | **1.977** | 3.507 |
|  | Adrenocorticotropic hormone deficiency | 37 | 29293 | 203 | 29264803 | 5.663 | **5.111** | 6.214 | 53.328 | **37.559** | 75.717 |
|  | Thyroiditis | 35 | 29295 | 1578 | 29263428 | 4.069 | **3.502** | 4.637 | 17.070 | **12.209** | 23.866 |
|  | Hypopituitarism | 33 | 29297 | 984 | 29264022 | 4.464 | **3.879** | 5.049 | 22.557 | **15.943** | 31.916 |
|  | Thyroid disorder | 30 | 29300 | 7869 | 29257137 | 1.859 | **1.244** | 2.474 | 3.639 | **2.542** | 5.210 |
|  | Hypothalamo-pituitary disorder | 29 | 29301 | 672 | 29264334 | 4.617 | **3.992** | 5.243 | 25.153 | **17.341** | 36.484 |
|  | Adrenal disorder | 28 | 29302 | 661 | 29264345 | 4.582 | **3.945** | 5.219 | 24.530 | **16.803** | 35.810 |
|  | Autoimmune hypothyroidism | 25 | 29305 | 65 | 29264941 | 5.433 | **4.757** | 6.109 | 45.126 | **28.447** | 71.583 |
|  | Autoimmune thyroiditis | 25 | 29305 | 1367 | 29263639 | 3.751 | **3.075** | 4.427 | 13.644 | **9.185** | 20.268 |
|  | Fulminant type 1 diabetes mellitus | 25 | 29305 | 530 | 29264476 | 4.594 | **3.918** | 5.270 | 24.740 | **16.562** | 36.955 |
|  | Hypercalcaemia | 24 | 29306 | 6102 | 29258904 | 1.885 | **1.194** | 2.576 | 3.705 | **2.481** | 5.534 |
|  | Hypoglycaemia | 20 | 29310 | 25555 | 29239451 | -0.349 | -1.109 | 0.411 | 0.785 | 0.506 | 1.217 |
|  | Inappropriate antidiuretic hormone secretion | 11 | 29319 | 7711 | 29257295 | 0.482 | -0.567 | 1.532 | 1.398 | 0.774 | 2.525 |
|  | Secondary adrenocortical insufficiency | 11 | 29319 | 888 | 29264118 | 3.038 | **1.988** | 4.088 | 8.275 | **4.566** | 14.999 |
|  | Autoimmune endocrine disorder | 10 | 29320 | 3 | 29265003 | 4.355 | **3.248** | 5.462 | 20.875 | **5.745** | 75.854 |
|  | Type 2 diabetes mellitus | 9 | 29321 | 20614 | 29244392 | -1.155 | -2.329 | 0.020 | 0.449 | 0.233 | 0.863 |
|  | Hypoglycaemic coma | 7 | 29323 | 2112 | 29262894 | 1.516 | **0.161** | 2.872 | 2.867 | **1.365** | 6.021 |
|  | Adrenocortical insufficienc | 6 | 29324 | 740 | 29264266 | 2.382 | **0.899** | 3.865 | 5.236 | **2.344** | 11.693 |
|  | Gynaecomastia | 6 | 29324 | 34697 | 29230309 | -2.439 | -3.922 | -0.956 | 0.184 | 0.083 | 0.410 |
|  | Adrenalitis | 5 | 29325 | 32 | 29264974 | 3.356 | **1.702** | 5.011 | 10.337 | **4.027** | 26.532 |
|  | Diabetes insipidus | 5 | 29325 | 930 | 29264076 | 1.937 | **0.283** | 3.592 | 3.841 | **1.595** | 9.251 |
|  | Endocrine disorder | 5 | 29325 | 633 | 29264373 | 2.272 | **0.617** | 3.927 | 4.849 | **2.011** | 11.691 |
|  | Secondary hypothyroidism | 5 | 29325 | 217 | 29264789 | 2.929 | **1.274** | 4.584 | 7.666 | **3.159** | 18.606 |
|  | Autoimmune thyroid disorder | 4 | 29326 | 25 | 29264981 | 3.088 | **1.188** | 4.988 | 8.571 | **2.983** | 24.628 |
|  | Endocrine ophthalmopathy | 4 | 29326 | 198 | 29264808 | 2.680 | **0.780** | 4.580 | 6.443 | **2.394** | 17.339 |
|  | Glucocorticoid deficiency | 4 | 29326 | 104 | 29264902 | 2.887 | **0.987** | 4.787 | 7.448 | **2.743** | 20.219 |
|  | Neuroendocrine carcinoma of the bladder | 4 | 29326 | 675 | 29264331 | 1.931 | **0.031** | 3.831 | 3.825 | **1.431** | 10.222 |
|  | Primary adrenal Primary adrenal insufficiency | 4 | 29326 | 105 | 29264901 | 2.885 | **0.985** | 4.785 | 7.435 | **2.739** | 20.182 |
|  | Silent thyroiditis | 4 | 29326 | 56 | 29264950 | 3.006 | **1.106** | 4.906 | 8.092 | **2.934** | 22.316 |
|  | Adrenal neoplasm | 3 | 29327 | 217 | 29264789 | 2.281 | -0.009 | 4.571 | 4.878 | **1.561** | 15.245 |
|  | Adrenomegaly | 3 | 29327 | 77 | 29264929 | 2.593 | **0.303** | 4.883 | 6.064 | **1.913** | 19.219 |
|  | Diabetic nephropathy | 3 | 29327 | 754 | 29264252 | 1.476 | -0.814 | 3.766 | 2.787 | 0.897 | 8.663 |
|  | Hypoparathyroidism | 3 | 29327 | 266 | 29264740 | 2.186 | -0.104 | 4.476 | 4.566 | **1.463** | 14.248 |
| Atezolizumab | Hypothyroidism | 29 | 7294 | 11697 | 29275316 | 3.104 | **2.478** | 3.730 | 8.640 | **5.997** | 12.448 |
|  | Adrenal insufficiency | 23 | 7300 | 4164 | 29282849 | 3.925 | **3.219** | 4.632 | 15.279 | **10.135** | 23.033 |
|  | Hyperthyroidism | 21 | 7302 | 6580 | 29280433 | 3.322 | **2.581** | 4.063 | 10.042 | **6.539** | 15.422 |
|  | Hyperglycaemia | 18 | 7305 | 16352 | 29270661 | 2.010 | **1.206** | 2.814 | 4.038 | **2.542** | 6.415 |
|  | Hypercalcaemia | 14 | 7309 | 6112 | 29280901 | 2.836 | **1.915** | 3.756 | 7.158 | **4.235** | 12.100 |
|  | Diabetic ketoacidosis | 10 | 7313 | 17553 | 29269460 | 1.102 | -0.004 | 2.209 | 2.149 | **1.156** | 3.997 |
|  | Hypophysitis | 10 | 7313 | 1673 | 29285340 | 3.511 | **2.405** | 4.618 | 11.441 | **6.142** | 21.312 |
|  | Diabetes mellitus | 7 | 7316 | 28607 | 29258406 | -0.029 | -1.384 | 1.326 | 0.980 | 0.467 | 2.057 |
|  | Type 1 diabetes mellitus | 6 | 7317 | 3085 | 29283928 | 2.353 | **0.869** | 3.836 | 5.115 | **2.295** | 11.398 |
|  | Type 2 diabetes mellitus | 6 | 7317 | 20617 | 29266396 | 0.201 | -1.282 | 1.684 | 1.150 | 0.516 | 2.560 |
|  | Inappropriate antidiuretic hormone secretion | 4 | 7319 | 7718 | 29279295 | 0.889 | -1.011 | 2.789 | 1.852 | 0.695 | 4.938 |
|  | Autoimmune thyroiditis | 3 | 7320 | 1389 | 29285624 | 2.045 | -0.245 | 4.335 | 4.131 | **1.330** | 12.828 |
|  | Hypopituitarism | 3 | 7320 | 1014 | 29285999 | 2.214 | -0.076 | 4.504 | 4.645 | **1.495** | 14.431 |
|  | Thyroiditis | 3 | 7320 | 1610 | 29285403 | 1.954 | -0.336 | 4.244 | 3.878 | **1.249** | 12.041 |
| Avelumab | Diabetes mellitus | 6 | 995 | 28608 | 29264727 | 2.137 | **0.654** | 3.620 | 4.414 | **1.978** | 9.849 |
|  | Hyperglycaemia | 3 | 998 | 16367 | 29276968 | 1.724 | -0.566 | 4.014 | 3.308 | **1.065** | 10.277 |
|  | Hyperthyroidism | 3 | 998 | 6598 | 29286737 | 2.270 | -0.020 | 4.560 | 4.829 | **1.554** | 15.001 |
|  | Neuroendocrine carcinoma of the bladder | 3 | 998 | 676 | 29292659 | 2.742 | **0.452** | 5.032 | 6.692 | **2.149** | 20.836 |
|  | Secondary adrenocortical insufficiency | 3 | 998 | 896 | 29292439 | 2.721 | **0.431** | 5.011 | 6.597 | **2.120** | 20.529 |
| Durvalumab | Hyperthyroidism | 16 | 1892 | 6585 | 29285843 | 4.149 | **3.293** | 5.005 | 17.830 | **10.894** | 29.181 |
|  | Diabetes mellitus | 14 | 1894 | 28600 | 29263828 | 2.617 | **1.697** | 3.537 | 6.167 | **3.645** | 10.435 |
|  | Hypothyroidism | 11 | 1897 | 11715 | 29280713 | 3.186 | **2.136** | 4.236 | 9.134 | **5.049** | 16.527 |
|  | Adrenal insufficiency | 6 | 1902 | 4181 | 29288247 | 3.072 | **1.589** | 4.556 | 8.425 | **3.778** | 18.788 |
|  | Hyperglycaemia | 3 | 1905 | 16367 | 29276061 | 1.160 | -1.130 | 3.450 | 2.236 | 0.721 | 6.941 |
|  | Hypophysitis | 3 | 1905 | 1680 | 29290748 | 2.521 | **0.231** | 4.812 | 5.745 | **1.849** | 17.846 |
| Ipilimumab | Hypophysitis | 267 | 10725 | 1416 | 29281928 | 7.885 | **7.683** | 8.088 | 262.607 | **230.102** | 299.703 |
|  | Adrenal insufficiency | 102 | 10890 | 4085 | 29279259 | 5.629 | **5.300** | 5.958 | 50.759 | **41.667** | 61.834 |
|  | Hypothyroidism | 49 | 10943 | 11677 | 29271667 | 3.337 | **2.859** | 3.814 | 10.174 | **7.680** | 13.478 |
|  | Hypopituitarism | 33 | 10959 | 984 | 29282360 | 5.248 | **4.663** | 5.833 | 38.583 | **27.260** | 54.608 |
|  | Lymphocytic hypophysitis | 32 | 10960 | 206 | 29283138 | 5.785 | **5.191** | 6.380 | 56.316 | **38.787** | 81.767 |
|  | Hypothalamo-pituitary disorder | 24 | 10968 | 677 | 29282667 | 5.005 | **4.314** | 5.696 | 32.512 | **21.629** | 48.869 |
|  | Hyperthyroidism | 19 | 10973 | 6582 | 29276762 | 2.712 | **1.930** | 3.493 | 6.572 | **4.188** | 10.315 |
|  | Thyroiditis | 18 | 10974 | 1595 | 29281749 | 4.065 | **3.261** | 4.869 | 16.852 | **10.586** | 26.828 |
|  | Diabetes mellitus | 14 | 10978 | 28600 | 29254744 | 0.368 | -0.552 | 1.288 | 1.291 | 0.764 | 2.181 |
|  | Pituitary enlargement | 14 | 10978 | 93 | 29283251 | 4.747 | **3.826** | 5.667 | 27.110 | **15.451** | 47.564 |
|  | Endocrine disorder | 13 | 10979 | 625 | 29282719 | 4.190 | **3.233** | 5.148 | 18.384 | **10.611** | 31.850 |
|  | Adrenocortical insufficiency acute | 12 | 10980 | 734 | 29282610 | 4.002 | **3.002** | 5.003 | 16.124 | **9.112** | 28.533 |
|  | Thyroid disorder | 12 | 10980 | 7887 | 29275457 | 1.851 | **0.851** | 2.852 | 3.615 | **2.051** | 6.370 |
|  | Adrenal disorder | 10 | 10982 | 679 | 29282665 | 3.791 | **2.684** | 4.898 | 13.914 | **7.450** | 25.985 |
|  | Hyperglycaemia | 10 | 10982 | 16360 | 29266984 | 0.661 | -0.446 | 1.767 | 1.582 | 0.851 | 2.941 |
|  | Type 1 diabetes mellitus | 10 | 10982 | 3081 | 29280263 | 2.661 | **1.554** | 3.768 | 6.342 | **3.408** | 11.803 |
|  | Diabetic ketoacidosis | 8 | 10984 | 17555 | 29265789 | 0.262 | -0.993 | 1.517 | 1.199 | 0.599 | 2.399 |
|  | Adrenocorticotropic hormone | 5 | 10987 | 235 | 29283109 | 3.221 | **1.566** | 4.875 | 9.351 | **3.855** | 22.680 |
|  | Hypercalcaemia | 5 | 10987 | 6121 | 29277223 | 0.975 | -0.680 | 2.629 | 1.966 | 0.818 | 4.727 |
|  | Hypogonadism | 5 | 10987 | 659 | 29282685 | 2.876 | **1.221** | 4.531 | 7.360 | **3.053** | 17.746 |
|  | Autoimmune thyroiditis | 4 | 10988 | 1388 | 29281956 | 2.138 | **0.238** | 4.038 | 4.408 | **1.652** | 11.764 |
|  | Diabetes insipidus | 4 | 10988 | 931 | 29282413 | 2.403 | **0.503** | 4.303 | 5.298 | **1.984** | 14.149 |
|  | Secondary adrenocortical insufficiency | 4 | 10988 | 895 | 29282449 | 2.426 | **0.526** | 4.326 | 5.384 | **2.016** | 14.379 |
|  | Goitre | 3 | 10989 | 1714 | 29281630 | 1.613 | -0.677 | 3.903 | 3.061 | 0.986 | 9.503 |
|  | Hypoglycaemia | 3 | 10989 | 25572 | 29257772 | -1.528 | -3.819 | 0.762 | 0.346 | 0.112 | 1.074 |
|  | Inappropriate antidiuretic hormone secretion | 3 | 10989 | 7719 | 29275625 | 0.043 | -2.247 | 2.333 | 1.030 | 0.332 | 3.195 |

\*In **Table S2**, PT: preferred term; a: the number of records with endocrine AEs reported for ICIs; b: the number of records with any other AEs reported for ICIs; c: the number of records with any endocrine AEs for other drugs; d: the number of records reported other AEs for other drugs. IC025: the lower end of the 95% confidence interval of IC. IC975: the upper end of the 95% confidence interval of IC. IC025 greater than 0 was deemed a signal. ROR025: the lower end of the 95% confidence interval of ROR. ROR975: the upper end of the 95% confidence interval of ROR.ROR025 exceeds 1 was deemed a signal. Bold text denotes a significant signal. Only PTs with at least 3 records were listed.

**Table S3** Disproportionality analysis results for ICI combination therapy strategies and endocrine complications\*

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Drug** | **PT** | **a** | **b** | **c** | **d** | **IC** | **IC025** | **IC975** | **ROR** | **ROR025** | **ROR975** |
| Nivolumab+ pembrolizumab+ ipilimumab | Hypothalamo-pituitary disorder | 9 | 300 | 692 | 29293335 | 4.227 | **3.053** | 5.401 | 18.734 | **9.613** | 36.510 |
|  | Lymphocytic hypophysitis | 9 | 300 | 229 | 29293798 | 4.241 | **3.067** | 5.415 | 18.911 | **9.623** | 37.164 |
|  | Type 1 diabetes mellitus | 9 | 300 | 3082 | 29290945 | 4.157 | **2.983** | 5.331 | 17.872 | **9.200** | 34.717 |
|  | Primary hypothyroidism | 8 | 301 | 94 | 29293933 | 4.084 | **2.829** | 5.339 | 16.967 | **8.171** | 35.231 |
|  | Hypophysitis | 5 | 304 | 1678 | 29292349 | 3.409 | **1.754** | 5.064 | 10.630 | **4.387** | 25.756 |
|  | Hypothyroidism | 4 | 305 | 11722 | 29282305 | 2.851 | **0.951** | 4.751 | 7.234 | **2.697** | 19.401 |
|  | Adrenal insufficiency | 3 | 306 | 4184 | 29289843 | 2.685 | **0.395** | 4.975 | 6.437 | **2.064** | 20.078 |
|  | Fulminant type 1 diabetes mellitus | 3 | 306 | 552 | 29293475 | 2.791 | **0.500** | 5.081 | 6.920 | **2.213** | 21.642 |
|  | Hyperthyroidism | 3 | 306 | 6598 | 29287429 | 2.619 | **0.329** | 4.909 | 6.152 | **1.973** | 19.185 |
| Nivolumab+ ipilimumab | Hypophysitis | 258 | 22543 | 1425 | 29270110 | 7.158 | **6.952** | 7.364 | 161.816 | **141.628** | 184.881 |
|  | Adrenal insufficiency | 199 | 22602 | 3988 | 29267547 | 5.730 | **5.495** | 5.965 | 55.730 | **48.306** | 64.295 |
|  | Hypothyroidism | 140 | 22661 | 11586 | 29259949 | 3.867 | **3.587** | 4.147 | 14.832 | **12.549** | 17.530 |
|  | Hyperthyroidism | 135 | 22666 | 6466 | 29265069 | 4.587 | **4.302** | 4.872 | 24.601 | **20.735** | 29.187 |
|  | Diabetic ketoacidosis | 128 | 22673 | 17435 | 29254100 | 3.181 | **2.888** | 3.474 | 9.170 | **7.703** | 10.917 |
|  | Hyperglycaemia | 127 | 22674 | 16243 | 29255292 | 3.267 | **2.973** | 3.562 | 9.741 | **8.176** | 11.605 |
|  | Diabetes mellitus | 99 | 22702 | 28515 | 29243020 | 2.127 | **1.794** | 2.461 | 4.395 | **3.607** | 5.357 |
|  | Type 1 diabetes mellitus | 81 | 22720 | 3010 | 29268525 | 4.810 | **4.440** | 5.179 | 28.732 | **23.033** | 35.841 |
|  | Thyroiditis | 64 | 22737 | 1549 | 29269986 | 5.199 | **4.783** | 5.616 | 37.868 | **29.482** | 48.641 |
|  | Hypopituitarism | 49 | 22752 | 968 | 29270567 | 5.260 | **4.783** | 5.737 | 39.523 | **29.654** | 52.677 |
|  | Fulminant type 1 diabetes mellitus | 46 | 22755 | 509 | 29271026 | 5.641 | **5.148** | 6.134 | 51.915 | **38.381** | 70.221 |
|  | Hypercalcaemia | 36 | 22765 | 6090 | 29265445 | 2.793 | **2.233** | 3.352 | 6.969 | **5.021** | 9.674 |
|  | Thyroid disorder | 29 | 22772 | 7870 | 29263665 | 2.150 | **1.524** | 2.775 | 4.453 | **3.092** | 6.414 |
|  | Hypothalamo-pituitary disorder | 27 | 22774 | 674 | 29270861 | 4.717 | **4.068** | 5.366 | 26.845 | **18.268** | 39.448 |
|  | Lymphocytic hypophysitis | 23 | 22778 | 215 | 29271320 | 5.100 | **4.394** | 5.806 | 35.216 | **22.904** | 54.147 |
|  | Autoimmune thyroiditis | 22 | 22779 | 1370 | 29270165 | 3.829 | **3.106** | 4.552 | 14.366 | **9.426** | 21.896 |
|  | Adrenocorticotropic hormone deficiency | 20 | 22781 | 220 | 29271315 | 4.900 | **4.139** | 5.660 | 30.541 | **19.320** | 48.280 |
|  | Endocrine disorder | 17 | 22784 | 621 | 29270914 | 4.134 | **3.305** | 4.963 | 17.796 | **10.990** | 28.817 |
|  | Secondary adrenocortical insufficiency | 17 | 22784 | 882 | 29270653 | 3.867 | **3.038** | 4.695 | 14.749 | **9.125** | 23.838 |
|  | Adrenocortical insufficiency acute | 15 | 22786 | 731 | 29270804 | 3.842 | **2.956** | 4.729 | 14.499 | **8.694** | 24.179 |
|  | Hypoglycaemia | 14 | 22787 | 25561 | 29245974 | -0.493 | -1.413 | 0.427 | 0.710 | 0.421 | 1.200 |
|  | Inappropriate antidiuretic | 10 | 22791 | 7712 | 29263823 | 0.690 | -0.417 | 1.796 | 1.614 | 0.868 | 3.001 |
|  | Thyrotoxic crisis | 10 | 22791 | 586 | 29270949 | 3.445 | **2.339** | 4.552 | 10.980 | **5.876** | 20.518 |
|  | Adrenal disorder | 9 | 22792 | 680 | 29270855 | 3.197 | **2.022** | 4.371 | 9.228 | **4.780** | 17.814 |
|  | Hypoparathyroidism | 9 | 22792 | 260 | 29271275 | 3.743 | **2.569** | 4.917 | 13.524 | **6.957** | 26.289 |
|  | Type 2 diabetes mellitus | 9 | 22792 | 20614 | 29250921 | -0.801 | -1.975 | 0.373 | 0.574 | 0.298 | 1.103 |
|  | Diabetes insipidus | 8 | 22793 | 927 | 29270608 | 2.791 | **1.536** | 4.047 | 6.957 | **3.468** | 13.954 |
|  | Pituitary enlargement | 8 | 22793 | 99 | 29271436 | 3.865 | **2.610** | 5.120 | 14.729 | **7.166** | 30.276 |
|  | Diabetes mellitus inadequate control | 6 | 22795 | 7422 | 29264113 | 0.049 | -1.434 | 1.533 | 1.035 | 0.465 | 2.304 |
|  | Diabetic metabolic decompen | 5 | 22796 | 1372 | 29270163 | 1.807 | **0.152** | 3.462 | 3.506 | **1.457** | 8.439 |
|  | Adrenalitis | 4 | 22797 | 33 | 29271502 | 3.089 | **1.189** | 4.989 | 8.560 | **3.032** | 24.164 |
|  | Hypogonadism | 4 | 22797 | 660 | 29270875 | 2.146 | **0.246** | 4.046 | 4.438 | **1.660** | 11.860 |
|  | Thyroiditis acute | 4 | 22797 | 237 | 29271298 | 2.710 | **0.810** | 4.610 | 6.573 | **2.447** | 17.661 |
|  | Diabetic coma | 3 | 22798 | 686 | 29270849 | 1.756 | -0.534 | 4.046 | 3.384 | **1.089** | 10.519 |
|  | Glucocorticoid deficiency | 3 | 22798 | 105 | 29271430 | 2.583 | **0.293** | 4.873 | 6.016 | **1.909** | 18.957 |
|  | Pituitary infarction | 3 | 22798 | 23 | 29271512 | 2.750 | **0.460** | 5.040 | 6.758 | **2.029** | 22.509 |
|  | Secondary hypogonadism | 3 | 22798 | 268 | 29271267 | 2.300 | **0.009** | 4.590 | 4.938 | **1.583** | 15.410 |
| Pembrolizumab+ ipilimumab | Fulminant type 1 diabetes mellitus | 17 | 733 | 538 | 29293048 | 5.089 | **4.260** | 5.918 | 34.082 | **20.917** | 55.534 |
|  | Type 1 diabetes mellitus | 14 | 736 | 3077 | 29290509 | 4.646 | **3.726** | 5.566 | 25.116 | **14.784** | 42.669 |
|  | Adrenal insufficiency | 9 | 741 | 4178 | 29289408 | 3.968 | **2.794** | 5.142 | 15.684 | **8.123** | 30.285 |
|  | Diabetic ketoacidosis | 9 | 741 | 17554 | 29276032 | 3.322 | **2.148** | 4.497 | 10.060 | **5.213** | 19.415 |
|  | Thyroiditis | 9 | 741 | 1604 | 29291982 | 4.133 | **2.959** | 5.308 | 17.574 | **9.091** | 33.971 |
|  | Hyperthyroidism | 8 | 742 | 6593 | 29286993 | 3.667 | **2.412** | 4.922 | 12.743 | **6.346** | 25.587 |
|  | Hypophysitis | 8 | 742 | 1675 | 29291911 | 3.968 | **2.713** | 5.223 | 15.670 | **7.795** | 31.503 |
|  | Hypothyroidism | 7 | 743 | 11719 | 29281867 | 3.228 | **1.873** | 4.584 | 9.406 | **4.468** | 19.804 |
|  | Diabetes mellitus | 4 | 746 | 28610 | 29264976 | 1.868 | -0.032 | 3.768 | 3.661 | **1.370** | 9.780 |
|  | Autoimmune hypothyroidism | 3 | 747 | 87 | 29293499 | 2.801 | **0.511** | 5.091 | 6.969 | **2.200** | 22.080 |
| Durvalumab+ tremelimumab | Adrenal insufficiency | 17 | 138 | 4170 | 29290011 | 5.067 | **4.238** | 5.896 | 33.677 | **20.330** | 55.786 |
|  | Hypopituitarism | 8 | 147 | 1009 | 29293172 | 4.072 | **2.817** | 5.327 | 16.830 | **8.239** | 34.377 |

\* In **Table S3**, PT: preferred term; a: the number of records with endocrine AEs reported for ICIs; b: the number of records with any other AEs reported for ICIs; c: the number of records with any endocrine AEs for other drugs; d: the number of records reported other AEs for other drugs. IC025: the lower end of the 95% confidence interval of IC. IC975: the upper end of the 95% confidence interval of IC. IC025 greater than 0 was deemed a signal. ROR025: the lower end of the 95% confidence interval of ROR. ROR975: the upper end of the 95% confidence interval of IC. ROR025 exceeds 1 was deemed a signal. Bold text denotes a significant signal. Bold text denotes a significant signal. Only PTs with at least 3 records were listed.

**Table S4** PTs related to endocrine AEs after receiving ICIs in FAERS 2014 Q1-2019Q1, by descending frequency\*

|  |  |
| --- | --- |
| PT | Frequency |
| Hypothyroidism | 885 |
| Adrenal Insufficiency | 730 |
| Hypophysitis | 688 |
| Hyperthyroidism | 472 |
| Diabetes Mellitus | 335 |
| Hyperglycaemia | 317 |
| Diabetic Ketoacidosis | 316 |
| Type 1 Diabetes Mellitus | 283 |
| Fulminant Type 1 Diabetes Mellitus | 224 |
| Thyroiditis | 218 |
| Hypopituitarism | 182 |
| Hypercalcaemia | 173 |
| Thyroid Disorder | 149 |
| Adrenocorticotropic Hormone Deficiency | 115 |
| Hypothalamo-Pituitary Disorder | 106 |
| Adrenal Disorder | 101 |
| Autoimmune Thyroiditis | 91 |
| Hypoglycaemia | 84 |
| Lymphocytic Hypophysitis | 76 |
| Secondary Adrenocortical Insufficiency | 72 |
| Type 2 Diabetes Mellitus | 53 |
| Endocrine Disorder | 52 |
| Adrenocortical Insufficiency Acute | 51 |
| Inappropriate Antidiuretic Hormone Secretion | 50 |
| Autoimmune Hypothyroidism | 40 |
| Diabetes Insipidus | 24 |
| Pituitary Enlargement | 23 |
| Diabetes Mellitus Inadequat | 21 |
| Gynaecomastia | 20 |
| Hypoparathyroidism | 18 |
| Goitre | 17 |
| Primary Hypothyroidism | 16 |
| Adrenalitis | 14 |
| Metastases to Adrenals | 13 |
| Thyrotoxic Crisis | 13 |
| Secondary Hypothyroidism | 12 |
| Silent Thyroiditis | 12 |
| Autoimmune Endocrine Disorder | 11 |
| Neuroendocrine Carcinoma of the Bladder | 11 |
| Diabetic Metabolic Decompensation | 10 |
| Glucocorticoid Deficiency | 9 |
| Hypogonadism | 9 |
| Endocrine Ophthalmopathy | 8 |
| Primary Adrenal Insufficiency | 8 |
| Hypoglycaemic Coma | 7 |
| Autoimmune Thyroid Disorder | 6 |
| Diabetic Nephropathy | 6 |
| Secondary Hypogonadism | 6 |
| Thyroid Cancer | 6 |
| Thyroiditis Acute | 6 |
| Adrenal Gland Cancer | 5 |
| Adrenal Neoplasm | 5 |
| Adrenomegaly | 5 |
| Exophthalmos | 5 |
| Hypercalcaemia Of Malignancy | 5 |
| Pituitary Haemorrhage | 5 |
| Thyroid Mass | 5 |
| Adrenal Mass | 4 |
| Diabetic Coma | 4 |
| Diabetic Hyperosmolar Coma | 4 |
| Infectious Thyroiditis | 4 |
| Polydipsia | 4 |
| Tetany | 4 |
| Androgen Deficiency | 3 |
| Diabetic Hyperglycaemic Coma | 3 |
| Diabetic Ketoacidotic Hyperglycaemic Coma | 3 |
| Hyperglycaemic Hyperosmolar Nonketotic Syndrome | 3 |
| Hyperparathyroidism | 3 |
| Hyperprolactinaemia | 3 |
| Latent Autoimmune Diabetes | 3 |
| Pituitary Infarction | 3 |
| Pituitary-dependent Cushing's syndrome | 3 |
| Hashitoxicosis | 2 |
| Thyroiditis Chronic | 2 |
| Polyglandular Disorder | 1 |

\*In **Table S4**, PTs: preferred terms (PTs); FAERS: FDA Adverse Event Reporting System; Q1: first quarter.