**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.