**Table 1. Study laboratory parameters**

|  |  |  |  |
| --- | --- | --- | --- |
| **Parameter** | **Type of sample** | **Method** | **Reference range** |
| ACTH | Plasma | Electrochemiluminescence immunoassay; Cobas 6000 Module e601 (Roche, Switzerland) | 7.2–63.3 pg/mL |
| Cortisol | Serum | Electrochemiluminescence immunoassay; Cobas 6000 Module e601 (Roche, Switzerland) | 171–536 nmol/L |
| TSH | Serum | Chemiluminescence immunoassay; ARCHITECT i2000 (Abbott, USA) | 0.25–3.5 mIU/L |
| fТ4 | Serum | Chemiluminescence immunoassay; ARCHITECT i2000 (Abbott, USA) | 9–19 pmol/L |
| fТ3 | Serum | Chemiluminescence immunoassay; ARCHITECT i2000 (Abbott, USA) | 2.6–5.7 pmol/L |
| TPOAb | Serum | Chemiluminescence immunoassay; ARCHITECT i2000 (Abbott, USA) | 0–5.6 IU/mL |
| TgAb | Serum | Electrochemiluminescence immunoassay; Cobas 6000 Module e601 (Roche, Switzerland) | 0–115 IU/mL |
| rTSHAb | Serum | Chemiluminescence immunoassay; ARCHITECT i2000 (Abbott, USA) | 0–1.75 IU/mL |
| Glucose | Serum | Chemiluminescence immunoassay; ARCHITECT c8000 (Abbott, USA) | 3.1–6.1 mmol/L |
| Total calcium | Serum | Chemiluminescence immunoassay; ARCHITECT c8000 (Abbott, USA) | 2.15–2.55 mmol/L |
| Na | Serum | Chemiluminescence immunoassay; ARCHITECT c8000 (Abbott, USA) | 136–145 mmol/L |
| K | Serum | Chemiluminescence immunoassay; ARCHITECT c8000 (Abbott, USA) | 3.5–5.1 mmol/L |
| Cl | Serum | Chemiluminescence immunoassay; ARCHITECT c8000 (Abbott, USA) | 98–107 mmol/L |

ACTH, adrenocorticotropic hormone; Cl, chlorine; fТ3, free triiodthyronine; fТ4, free thyroxin; K, potassium; Na, sodium; rTSHAb, antibodies to thyroid stimulating hormone receptors; TgAb, anti-thyroglobulin antibodies; TPOAb, anti-thyroperoxidase antibodies; TSH, thyroid stimulating hormone

**Table 2. Types and frequencies of immune-related adverse events under treatment with immune checkpoints inhibitors**

|  |  |  |
| --- | --- | --- |
| **Syndrome, disorder** | **irAEs numbers, n** | **Proportion of patients with irAEs in the cohort (n = 102), %** |
| Endocrine irAEs: |  |  |
| Thyroid disorders | 13 | 12.7 |
| Hypophysitis | 2 | 1.9 |
| Diabetes mellitus | 1 | 0.9 |
| Non-endocrine irAEs: |  |  |
| Skin disorders | 13 | 12.7 |
| Gastrointestinal toxicity | 7 | 6.9 |
| Liver toxicity | 4 | 3.9 |
| Nephritis | 2 | 1.9 |
| Hematological toxicity | 1 | 0.9 |
| Pneumonitis | 1 | 0.9 |
| Guillain-Barre syndrome | 1 | 0.9 |

irAEs, immune-related adverse events

**Table 3. Laboratory parameters and the development of any immune-related adverse events in the study sample (n = 102)**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Parameter** | **Any irAE: yes** |  | **Any irAE: no** | | **р** |
| **N** | **n (%) / Me [Q1; Q3]** | **N** | **n (%) / Me [Q1; Q3]** |
| Demographic characteristics | | | | | |
| Gender, male /female | 38 | 16 / 22 (42 / 58) | 64 | 34 / 30 (53 / 47) | 0.331\* |
| Age, years | 38 | 61 [52; 67] | 64 | 59 [51; 68] | 0.613\*\* |
| Laboratory parameters | | | | | |
| TSH, мIU/L | 38 | 1.022 [0.707; 1.624] | 64 | 1.078 [0.747; 1.555] | 0.920\*\* |
| fТ4, pmol/L | 38 | 12.45 [11.70; 13.39] | 64 | 12.55 [11.80; 13.51] | 0.677\*\* |
| fТ3, pmol/L | 38 | 4.28 [3.99; 4.57] | 64 | 4.39 [3.64; 4.72] | 0.861\*\* |
| rTSHAb, IU/mL | 10 | 0.8 [0.8; 0.971] | 4 | 0.8 [0.8; 0.8] | 0.304\*\* |
| TPOAb, IU/mL | 29 | 2.4 [0.6; 53.6] | 32 | 0.85 [0.49; 2.19] | 0.021\*\* |
| TgAb, IU/mL | 29 | 14.42 [10.22; 41.13] | 32 | 11.36 [10.00; 15.10] | 0.024\*\* |
| ACTH, pg/mL | 37 | 18.81 [11.85; 29.68] | 64 | 18.90 [13.88; 29.49] | 0.766\*\* |
| Cortisol, nmol/L | 38 | 288.05 [214.4; 406.5] | 64 | 370.2 [251.2; 485.8] | 0.126\*\* |
| Glucose, mmol/L | 38 | 5.49 [5.09; 6.70] | 62 | 5.1 [4.8; 5.7] | 0.012\*\* |
| Total calcium, mmol/L | 37 | 2.3 [2.27; 2.37] | 62 | 2.31 [2.25; 2.42] | 0.798\*\* |
| Na, mmol/L | 27 | 139 [137; 142] | 46 | 139.9 [137.0; 141.0] | 0.825\*\* |
| K, mmol/L | 27 | 4.1 [3.9; 4.5] | 45 | 4.2 [4.1; 4.5] | 0.233\*\* |
| Cl, mmol/L | 27 | 104.0 [101.0; 106.0] | 46 | 104.9 [102.0; 106.0] | 0.637\*\* |
| Past history of endocrine disorders before the initiation of immunotherapy with ICIs | | | | | |
| History of any endocrine disorder | 38 | 14 (37) | 64 | 34 (53) | 0.151\* |
| History of treatment for an endocrine disorder | 36 | 5 (14) | 64 | 10 (16) | 1.000\* |

ACTH, adrenocorticotropic hormone; Cl, chlorine; fТ3, free triiodthyronine; fТ4, free thyroxin; ICIs, immune checkpoint inhibitors; irAEs, immune-related adverse events; K, potassium; Me [Q1; Q3], median and quartiles; N, number of patients in the group; n (٪), absolute numbers and their proportion from total patient numbers in the group; Na, sodium; rTSHAb, antibodies to thyroid stimulating hormone receptors; TgAb, anti-thyroglobulin antibodies; TPOAb, anti-thyroperoxidase antibodies; TSH, thyroid stimulating hormone

\* Fischer’s exact test

\*\* U test

Bonferroni adjustment Р0 = 0.05 / 17 = 0.003

**Table 4. Laboratory parameters and the development of thyroid immune-related adverse events in the study sample (n = 102)**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Parameter** | **Thyroid irAE: yes** |  | **Thyroid irAE: no** | | **р** |
| **N** | **n (%) / Me [Q1; Q3]** | **N** | **n (%) / Me [Q1; Q3]** |
| Demographic characteristics | | | | | |
| Gender, male /female | 13 | 7 / 6 (54 / 46) | 89 | 43 / 46 (48 / 52) | 0.773\* |
| Age, years | 13 | 58 [48; 65] | 89 | 59 [52; 68] | 0.684\*\* |
| Laboratory parameters | | | | | |
| TSH, мIU/L | 13 | 1.022 [0.861; 1.606] | 89 | 1.053 [0.745; 1.606] | 0.992\*\* |
| fТ4, pmol/L | 13 | 12.73 [12.27; 13.03] | 89 | 12.46 [11.76; 13.41] | 0.781\*\* |
| fТ3, pmol/L | 13 | 4.13 [3.96; 4.54] | 89 | 4.37 [3.90; 4.62] | 0.551\*\* |
| rTSHAb, IU/mL | 7 | 0.8 [0.8; 0.971] | 7 | 0.8 [0.8; 0.8] | 0.456\*\* |
| TPOAb, IU/mL | 12 | 63.45 [4.56; 192.72] | 49 | 0.85 [0.49; 2.76] | < 0.001\*\* |
| TgAb, IU/mL | 12 | 40.55 [22.69; 197.65] | 49 | 11.54 [10.00; 14.48] | < 0.001\*\* |
| ACTH, pg/mL | 13 | 18.81 [10.15; 24.35] | 88 | 18.89 [13.62; 29.89] | 0.564\*\* |
| Cortisol, nmol/L | 13 | 309.4 [129; 406.5] | 89 | 352.9 [261.2; 481.7] | 0.278\*\* |
| Glucose, mmol/L | 13 | 5.84 [5.12; 6.64] | 87 | 5.15 [4.85; 6.25] | 0.076\*\* |
| Total calcium, mmol/L | 13 | 2.29 [2.27; 2.39] | 86 | 2.31 [2.25; 2.40] | 0.641\*\* |
| Na, mmol/L | 10 | 139.0 [137.0; 142.0] | 63 | 139.8 [137.0; 141.0] | 0.831\*\* |
| K, mmol/L | 10 | 4.1 [3.9; 4.4] | 62 | 4.2 [4.0; 4.5] | 0.298\*\* |
| Cl, mmol/L | 10 | 104.5 [102.0; 106.0] | 63 | 104.7 [101.0; 106.0] | 0.868\*\* |
| Past history of endocrine disorders before the initiation of immunotherapy with ICIs | | | | | |
| History of any endocrine disorder | 13 | 5 (38) | 89 | 43 (48) | 0.564\* |
| History of treatment for an endocrine disorder | 13 | 0 (0) | 87 | 15 (17) | 0.207\* |

ACTH, adrenocorticotropic hormone; Cl, chlorine; fТ3, free triiodthyronine; fТ4, free thyroxin; ICIs, immune checkpoint inhibitors; irAEs, immune-related adverse events; K, potassium; Me [Q1; Q3], median and quartiles; N, number of patients in the group; n (٪), absolute numbers and their proportion from total patient numbers in the group; Na, sodium; rTSHAb, antibodies to thyroid stimulating hormone receptors; TgAb, anti-thyroglobulin antibodies; TPOAb, anti-thyroperoxidase antibodies; TSH, thyroid stimulating hormone

\* Fischer’s exact test

\*\* U test

Bonferroni adjustment Р0 = 0.05 / 17 = 0.003

**Table 5. ROC characteristics and cut-off levels of anti-thyroperoxidase and anti-thyroglobulin antibodies for prediction of thyroid immune-related adverse events in the study patient sample (n = 102)**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Variable** | **AUC, 95% CI** | **Cut-off value** | **DSn 95% CI** | **DSp 95% CI** | **PVPR, 5% CI** | **PVNR, 95% CI** |
| TPOAb | 0.828 [0.678–0.979] | ≥ 7.54 МЕ/мл | 75% [48–92] | 92% [85–96] | 69% [44–85] | 94% [87–98] |
| TgAb | 0.875 [0.742–1.000] | ≥ 16.45 МЕ/мл | 92% [64–100] | 84% [77–86] | 58% [40–63] | 98% [90–100] |

AUC, area under the ROC curve; CI, confidence interval; DSn, diagnostic sensitivity; DSp, diagnostic specificity; PVNR, prognostic value of negative result; PVRP, prognostic value of positive result; TgAb, anti-thyroglobulin antibodies; TPOAb, anti-thyroperoxidase antibodies

**Table 6. Confusion matrix: yes / no for combination of factors: anti-thyroperoxidase antibodies ≥ 7.54 IU/mL and anti-thyroglobulin antibodies ≥ 16.45 IU/mL in the groups depending on the development of thyroid immune-related adverse events**

| **TPOAb ≥ 7.54 IU/mL**  **TgAb ≥ 16.45 IU/mL** | **Any irAE: yes** | **Any irAE: no** |
| --- | --- | --- |
| Combination of the factors: yes | 9 | 2 |
| Combination of the factors: no | 3 | 47 |

irAE, immune-related adverse event; TgAb, anti-thyroglobulin antibodies; TPOAb, anti-thyroperoxidase antibodies

**Table 7. Laboratory parameters of the patients depending on the development of skin immune-related adverse events in the study sample (n = 102)**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Parameter** | **Skin irAE: yes** |  | **Skin irAE: no** | | **р** |
| **N** | **n (%) / Me [Q1; Q3]** | **N** | **n (%) / Me [Q1; Q3]** |
| Demographic characteristics | | | | | |
| Gender, male /female | 13 | 2 / 11 (15 / 85) | 89 | 48/41 (54 / 46) | 0.015\* |
| Age, years | 13 | 61 [59; 67] | 89 | 59 [51; 68] | 0.335\*\* |
| Laboratory parameters | | | | | |
| TSH, мIU/L | 13 | 1.026 [0.574; 1.976] | 89 | 1.053 [0.749; 1.503] | 0.786\*\* |
| fТ4, pmol/L | 13 | 12.20 [11.96; 12.80] | 89 | 12.58 [11.76; 13.41] | 0.699\*\* |
| fТ3, pmol/L | 13 | 4.25 [4.04; 4.44] | 89 | 4.39 [3.84; 4.60] | 0.880\*\* |
| rTSHAb, IU/mL | 2 | 0.923; 1.06 | 12 | 0.8 [0.8; 0.8] | 0.121\*\* |
| TPOAb, IU/mL | 12 | 1.29 [0.56; 4.58] | 49 | 1.21 [0.50; 4.13] | 0.935\*\* |
| TgAb, IU/mL | 12 | 11.60 [10.00; 18.29] | 49 | 12.70 [10.00; 18.74] | 0.670\*\* |
| ACTH, pg/mL | 13 | 13.81 [11.50; 27.46] | 88 | 19.23 [13.88; 29.89] | 0.280\*\* |
| Cortisol, nmol/L | 13 | 283.2 [272.7; 439.4] | 89 | 361.7 [218.9; 481.7] | 0.710\*\* |
| Glucose, mmol/L | 13 | 5.49 [5.11; 6.36] | 87 | 5.15 [4.90; 6.37] | 0.282\*\* |
| Total calcium, mmol/L | 12 | 2.29 [2.25; 2.39] | 87 | 2.31 [2.25; 2.39] | 0.719\*\* |
| Na, mmol/L | 8 | 139.5 [137.0; 141.0] | 65 | 139.0 [137.0; 141.0] | 1.000\*\* |
| K, mmol/L | 8 | 4.5 [3.6; 4.6] | 64 | 4.2 [4.0; 4.5] | 0.513\*\* |
| Cl, mmol/L | 8 | 104.5 [101.0; 106.2] | 65 | 104.7 [102.0; 106.0] | 0.986\*\* |
| Past history of endocrine disorders before the initiation of immunotherapy with ICIs | | | | | |
| History of any endocrine disorder | 13 | 5 (38) | 89 | 43 (48) | 0.564\* |
| History of treatment for an endocrine disorder | 12 | 2 (17) | 88 | 13 (15) | 1.000\* |

ACTH, adrenocorticotropic hormone; Cl, chlorine; fТ3, free triiodthyronine; fТ4, free thyroxin; ICIs, immune checkpoint inhibitors; irAEs, immune-related adverse events; K, potassium; Me [Q1; Q3], median and quartiles; N, number of patients in the group; n (٪), absolute numbers and their proportion from total patient numbers in the group; Na, sodium; rTSHAb, antibodies to thyroid stimulating hormone receptors; TgAb, anti-thyroglobulin antibodies; TPOAb, anti-thyroperoxidase antibodies; TSH, thyroid stimulating hormone

\* Fischer’s exact test

\*\* U test

Bonferroni adjustment Р0 = 0.05 / 17 = 0.003