***Research Article***

***Thyroid Dysfunction After Atezolizumab and Bevacizumab is Associated with Favorable Outcomes in Hepatocellular Carcinoma***

Young Shin Songa,b\*, Hannah Yangc\*, Beodeul Kangc, Jaekyung Cheonc, Ilhwan Kimd, Hyeyeong Kime, Won Suk Leec, Yun Beom Sangc, Sanghoon Jungf, Ho Yeong Limg, Vincent E. Gaillardh, Chan Kimc, Hong Jae Chonc

aDivision of Endocrinology and Metabolism, Department of Internal Medicine, CHA Bundang Medical Center, CHA University School of Medicine, Seongnam, Korea

bDivision of Endocrinology and Metabolism, Department of Internal Medicine, Seoul Metropolitan Government Seoul National University Boramae Medical Center, Seoul National University College of Medicine, Seoul, Korea

cDivision of Medical Oncology, Department of Internal Medicine, CHA Bundang Medical Center, CHA University School of Medicine, Seongnam, Korea

dDivision of Oncology, Department of Internal Medicine, Inje University College of Medicine, Haeundae Paik Hospital, Busan, Korea

eDepartment of Internal Medicine, Ulsan University Hospital, University of Ulsan College of Medicine, Ulsan, Korea

fDepartment of Radiology, CHA Bundang Medical Center, Seongnam, Korea

gDivision of Hemato-Oncology, Department of Internal Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

hF. Hoffmann-La Roche Ltd., Basel, Switzerland

\*These authors equally contributed to this work.

Short Title: Thyroid adverse events after Ate/Bev and outcome in hepatocellular carcinoma

Corresponding authors:

Hong Jae Chon (Lead contact)

Medical Oncology, Department of Internal Medicine

CHA Bundang Medical Center, CHA University

59 Yatap-ro, Bundang-gu, Seongnam 13496 , Republic of Korea

Phone: 82-31-780-7590; Fax: 82-31-780-3929

E-mail: minidoctor@cha.ac.kr

Chan Kim

Medical Oncology, Department of Internal Medicine

CHA Bundang Medical Center, CHA University

59 Yatap-ro, Bundang-gu, Seongnam 13496 , Republic of Korea

Phone: 82-31-780-7590; Fax: 82-31-780-3929

E-mail: chan@cha.ac.kr

**Table of contents**

Supplementary Table 1. Incidence of Ate/Bev treatment-related adverse events (AEs) according to thyroid AEs

Supplementary Table 2. Hazard ratios for progression-free survival and overall survival according to immune-related adverse events

Supplementary Table 3. Baseline clinical characteristics of a validation cohort (IMbrave150)

Supplementary Figure 1. CONSORT diagram

Supplementary Figure 2. Progression-free survival and overall survival according to thyroid adverse events (AEs).

Supplementary Figure 3. Comparison of baseline cytokine levels and T cell fractions between patients with hypothyroidism and those without thyroid adverse events.

Supplementary Table 1. Incidence of Ate/Bev treatment-related adverse events (AEs) according to thyroid AEs

|  |  |  |  |
| --- | --- | --- | --- |
|  | Thyroid AE+  (n = 41) | Thyroid AE−  (n = 167) | *P* |
| Dermatological toxicity | 12 (29.3) | 25 (15.0) | **0.032** |
| Gastrointestinal toxicity | 5 (12.2) | 17 (10.2) | 0.777 |
| Hepatotoxicity | 19 (46.3) | 65 (38.9) | 0.386 |
| Pulmonary toxicity | 1 (2.4) | 2 (1.2) | 0.484 |
| Rheumatic toxicity | 2 (4.9) | 5 (3.0) | 0.626 |
| Pituitary toxicity | 2 (4.9) | 3 (1.8) | 0.256 |
| Diabetes mellitus | 1 (2.4) | 8 (4.8) | 0.507 |
| Adrenal insufficiency | 6 (14.6) | 2 (1.2) | **<0.001** |
| Fatigue | 12 (29.3) | 42 (25.1) | 0.590 |
| Hypertension | 19 (46.3) | 60 (35.9) | 0.218 |
| Proteinuria | 21 (51.2) | 76 (45.5) | 0.511 |
| Bleeding | 5 (12.2) | 16 (9.6) | 0.573 |

The incidence is presented as n (%).

Supplementary Table 2. Hazard ratios for progression-free survival and overall survival according to immune-related adverse events

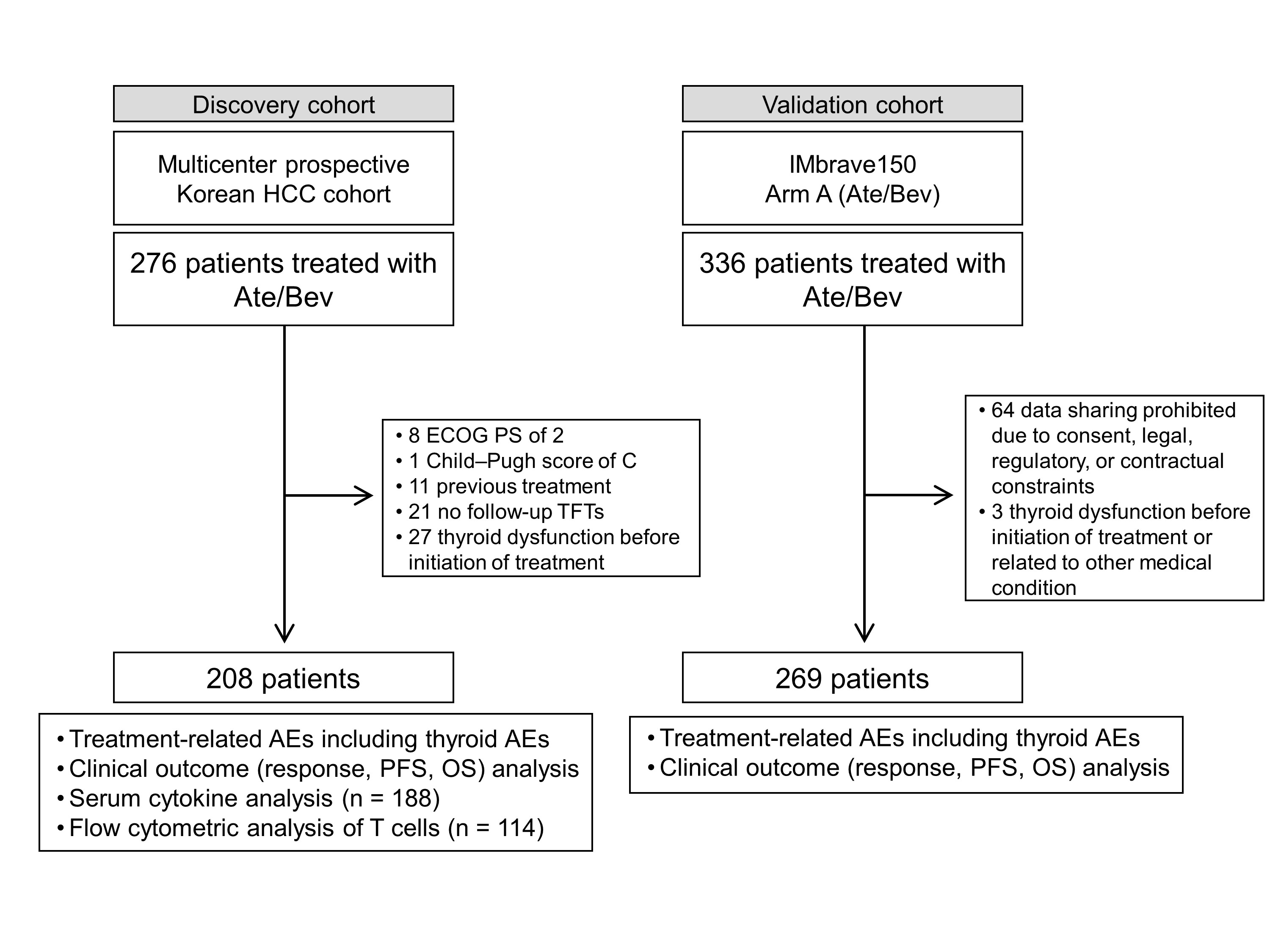
|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  |  | PFS | | OS |  |
|  | irAE, n (%) | HR | *P* | HR | *P* |
|  | (95% CI) | (95% CI) |
| Dermatological toxicity | 37 (17.8) | 0.471 | 0.005 | 0.698 | 0.231 |
|  |  | (0.275, 0.809) | (0.388, 1.257) |
| Gastrointestinal toxicity | 22 (10.6) | 0.509 | 0.052 | 0.97 | 0.931 |
|  |  | (0.258, 1.005) | (0.486, 1.933) |
| Hepatotoxicity | 84 (40.4) | 0.664 | 0.028 | 1.197 | 0.399 |
|  |  | (0.461, 0.956) | (0.788, 1.818) |
| Pulmonary toxicity | 3 (1.4) | 2.295 | 0.246 | 9.461 | < 0.001 |
|  |  | (0.564, 9.348) | (2.879, 31.097) |
| Rheumatic toxicity | 7 (3.4) | 0.495 | 0.495 | 0.227 | 0.141 |
|  |  | (0.157, 1.559) | (0.032, 1.633) |
| Pituitary toxicity | 5 (2.4) | 0.284 | 0.079 | 0.455 | 0.275 |
|  |  | (0.069, 1.158) | (0.110, 1.872) |
| Diabetes mellitus | 9 (4.3) | 0.879 | 0.759 | 0.326 | 0.118 |
|  |  | (0.387, 2.000) | (0.080, 1.328) |
| Adrenal insufficiency | 8 (3.8) | 0.429 | 0.148 | 1.101 | 0.851 |
|  |  | (0.136, 1.350) | (0.404, 3.003) |
| Thyroid AEs | 41 (19.7) | 0.279 | < 0.001 | 0.329 | 0.001 |
|  |  | (0.159, 0.489) | (0.165, 0.657) |

irAE, immune-related adverse event; PFS, progression-free survival; OS, overall survival; HR, hazard ratio; AEs, adverse events

Supplementary Table 3. Baseline clinical characteristics of a validation cohort (IMbrave150)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | All patients  (n = 269) | Thyroid AE  (n = 36) | No thyroid AE  (n = 233) | *P* |
| Age, year, median (IQR) | 66.0  (59.0–72.0) | 65.0  (61.0–65.0) | 66.0  (58.0–72.0) | 0.829 |
| Male sex, n (%) | 220 (81.8) | 32 (88.9) | 188 (80.7) | 0.235 |
| Geographic region, n (%) |  |  |  |  |
| Asia | 122 (45.4) | 13 (36.1) | 109 (46.8) | 0.340 |
| Europe | 84 (31.2) | 15 (41.7) | 69 (29.6) |  |
| North America | 56 (20.8) | 8 (22.2) | 48 (20.6) |  |
| Rest of the world | 7 (2.6) | 0 (0) | 7 (3.0) |  |
| ECOG performance status, n (%) |  |  |  | **0.017** |
| 0 | 177 (65.8) | 30 (83.3) | 147 (63.1) |  |
| 1 | 92 (34.2) | 6 (16.7) | 86 (36.9) |  |
| Child–Pugh classification, n (%) |  |  |  | N/A |
| A | 269 (100.0) | 36 (100.0) | 233 (100.0) |  |
| Barcelona clinical liver cancer stage, n (%) |  |  |  | 0.245 |
| A | 7 (2.6) | 1 (2.8) | 6 (2.6) |  |
| B | 42 (15.6) | 9 (25.0) | 33 (14.2) |  |
| C | 220 (82.8) | 26 (72.2) | 194 (83.3) |  |
| Alpha–fetoprotein ≥ 400 ng/ml, n (%) | 92 (34.2) | 9 (25.0) | 83 (35.6) | 0.211 |
| Presence of macrovascular invasion, n (%) | 105 (39.0) | 11 (30.6) | 94 (40.3) | 0.263 |
| Presence of extrahepatic spread, n (%) | 164 (61.0) | 22 (61.1) | 142 (60.9) | 0.985 |
| Etiology of HCC, n (%) |  |  |  | 0.427 |
| Hepatitis B | 106 (39.4) | 11 (30.6) | 95 (40.8) |  |
| Hepatitis C | 66 (24.5) | 8 (22.2) | 58 (24.9) |  |
| Alcohol | 34 (12.6) | 7 (19.4) | 27 (11.6) |  |
| Other or unknown | 63 (23.4) | 10 (27.8) | 53 (22.7) |  |
| Prior local therapy for HCC, n (%) | 119 (44.2) | 17 (47.2) | 102 (43.8) | 0.698 |

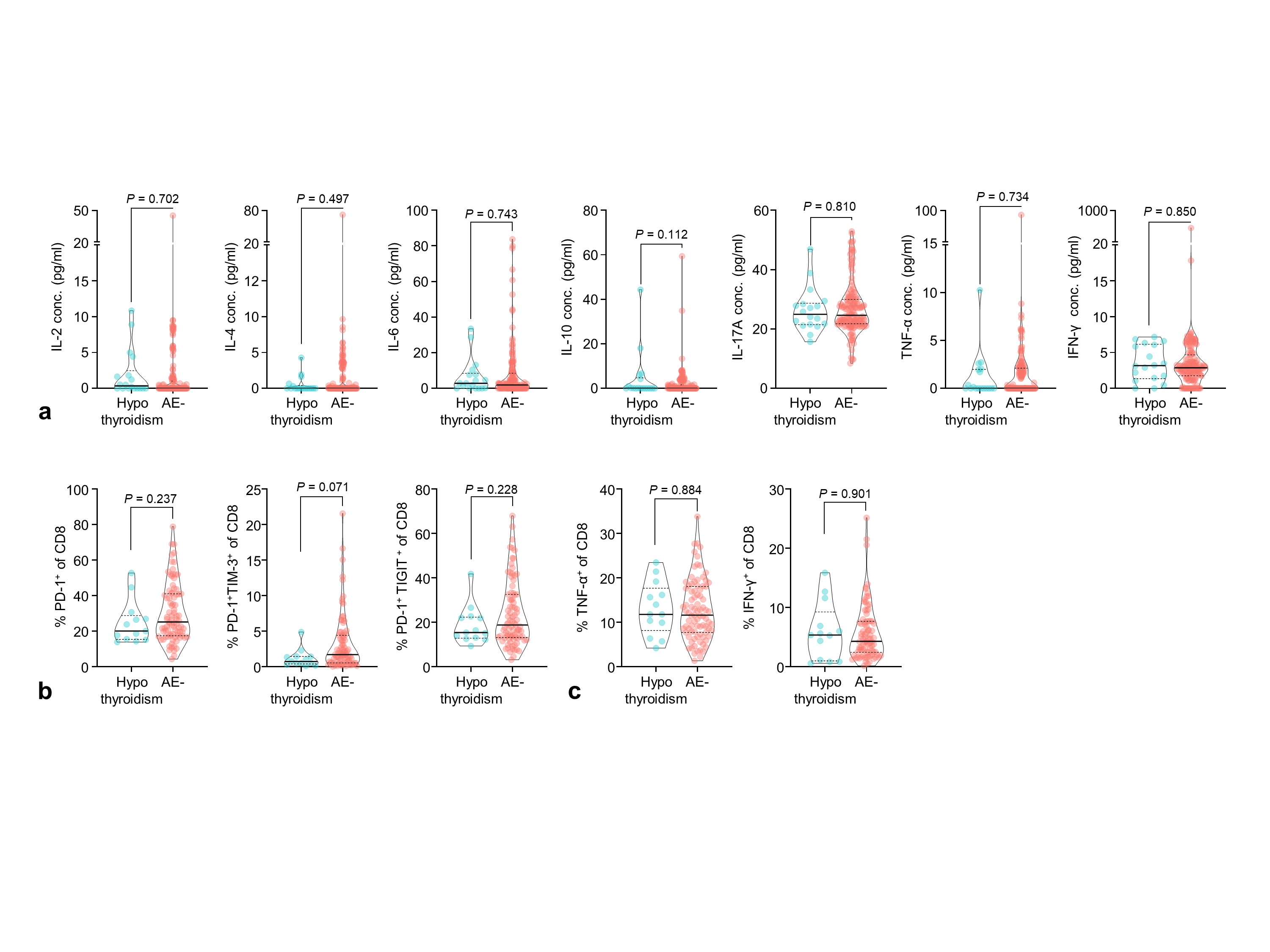
Significant *P* values in bold. AE, adverse event; IQR, interquartile range; ECOG, Eastern Cooperative Oncology Group; HCC, hepatocellular carcinoma; N/A, not applicable



Supplementary Figure 1. CONSORT diagram



Supplementary Figure 2. Progression-free survival and overall survival according to thyroid adverse events (AEs). (a and b) Time-dependent analyses using a time-dependent Cox regression model. (c and d) Patients who do not have a progressive disease response. (e and f) Patients with overt and subclinical thyroid AEs and those without thyroid AEs. (g and h) Patients with early-onset and late-onset thyroid AEs and those without thyroid AEs.



Supplementary Figure 3. Comparison of baseline cytokine levels and T cell fractions between patients with hypothyroidism and those without thyroid adverse events. Baseline cytokine levels (a and b), CD8+ cell subset fractions (c), and effector cytokines in CD8+ T-cells (d).