Thyroid Immune-Related Adverse Events in Cancer Patients Treated with Anti-PD1/Anti-CTLA4 Immune-Checkpoint Inhibitor Combination

Lui DTW[1], Lee CH[1], Tang V[1], Fong CHY[1], Lee ACH[1], Chiu JWY[1], Leung RCY[1], Kwok GGW[1], Li BCW[1], Cheung TT[2], Woo YC[1], Lam KSL[1], Yau T[1]

[1]Department of Medicine, [2]Department of Surgery; Queen Mary Hospital, The University of Hong Kong

Background and Aims

- **Combination anti-PD1/anti-CTLA4 immune checkpoint inhibitors** (ICIs) can further **improve** the **overall survival** (OS) of **cancer patients**, at the expense of **more immune-related adverse events** (irAEs), **including thyroid** irAEs
- A number of cancer types, including hepatocellular carcinoma (HCC), have gained recent FDA approval for combination ICIs
- **Most published data** in the literature about the **prognostic significance of thyroid irAEs** reported **only among single ICIs** (anti-PD1, anti-PDL1) mainly in **non-small cell lung cancer**
- We carried out a **territory-wide study** of patients with advanced cancer treated with combination anti-PD1/anti-CTLA4, to
  1. describe the clinical course and sequelae of thyroid irAEs following combination ICIs,
  2. identify the potential predictors of thyroid irAEs, and
  3. evaluate the association between thyroid irAEs and OS

Methods

- All patients who received ≥1 cycle(s) of combination anti-PD1/anti-CTLA4 between 1 January 2015 and 31 December 2019 were identified from the territory-wide electronic health record of the Hong Kong Hospital Authority
- Demographics, treatment course, FDG-PET scans and baseline thyroid function tests (TFTs) were retrieved
- TFTs monitored every three weeks
- Exclusion criteria
  - History of thyroid disorder or thyroid cancer
  - History of ICI-related endocrinopathies
  - On concurrent tyrosine kinase inhibitors (TKIs)
  - Absent / abnormal baseline TFTs
  - Duration of follow-up <30 days
- Thyroid irAE: ≥2 abnormal TFTs after initiation of combination anti-PD1/anti-CTLA4 without other causes; initial presentation classified into:
  - Hypothyroidism (overt if TSH >4.8 mIU/L and fT4 <12 pmol/L; subclinical if TSH >4.8 mIU/L and fT4 12–23 pmol/L) and
  - Thyrotoxicosis (overt if TSH <0.35 mIU/L and fT4 >23 pmol/L; subclinical if TSH <0.35 mIU/L and fT4 12–23 pmol/L)
- Events were censored on 30 June 2020

Results

- **103 patients** were included
  - Median **age**: **59 years** (IQR 51–65); **71.8% male**
  - **50.5% had HCC**, a prevalent cancer type among Asians
  - **24.3%** had **prior TKI** exposure (majority: sorafenib)
  - **44.7%** had **prior anti-PD1** exposure
- Median **follow-up**: **6.8 months** (IQR 3.0–16.0)
- **17 patients (16.5%)** had **thyroid irAEs occurring at** a median of **12.9 weeks** (IQR 6.2–39.8)
- 71 patients (68.9%) died during follow-up

1. Clinical course and sequelae of thyroid irAEs

- 6 patients (**35.3%**) **initially** presented with **thyrotoxicosis** (overt thyrotoxicosis, n=4; subclinical thyrotoxicosis, n=2)
- 11 patients (**64.7%**) **initially** presented with **hypothyroidism** (overt hypothyroidism, n=2; subclinical hypothyroidism, n=9)
- **Time of onset appeared** to be **earlier** in those initially presented with **thyrotoxicosis** than hypothyroidism, although not reaching statistically significance (median 10.4 weeks [IQR: 4.0-31.7] vs 17.4 weeks [IQR: 7.7-93.9], p=0.462)
- **Diffuse thyroid uptake on FDG-PET** preceded or coincided with abnormal TFT in 3 patients (**50%**) of the **thyrotoxic group**
- Patients who **initially presented with thyrotoxicosis evolved** along a **typical trajectory of thyroiditis** over 3-9 weeks into hypothyroid state
- 10 (**58.8%**) of the 17 patients **who developed thyroid irAEs** required **continuous thyroxine replacement**
- Systemic steroid was not required in all cases

2. Clinical predictors of thyroid irAEs

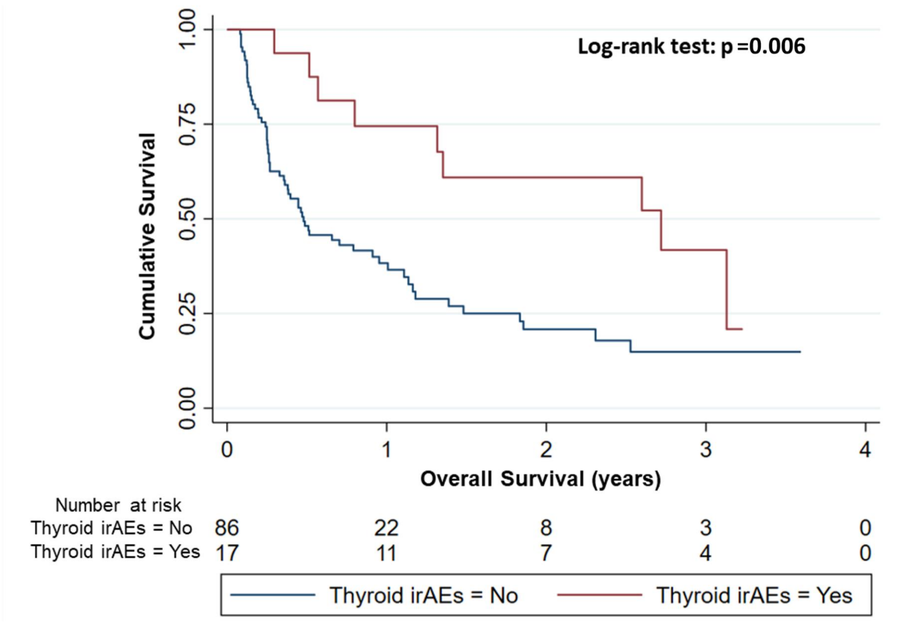
	Thyroid irAE (+)	Thyroid irAE (-)	p-value
Number	17 (16.5%)	86 (83.5%)	—
Age, years	55.0 (46.0–63.5)	59.0 (51.0–68.0)	0.188
Female	4 (23.5%)	25 (29.1%)	0.773
HCC	7 (41.2%)	45 (52.3%)	0.401
History of prior systemic therapy			
Treatment-naïve	3 (17.6%)	28 (32.6%)	0.221
Prior chemotherapy	10 (58.8%)	36 (41.9%)	0.199
Prior anti-PD1	**12 (70.6%)**	**34 (39.5%)**	**0.019**
Prior TKI	5 (29.4%)	20 (23.3%)	0.552
Anti-PD1 in the combo			0.899
Nivolumab	7 (41.2%)	34 (39.5%)	
Pembrolizumab	10 (58.8%)	52 (60.5%)	
Diffuse thyroid uptake on FDG-PET	0/15 (0%)	1/67 (1.5%)	0.999
Baseline TSH, mIU/L	1.50 (1.10–2.90)	1.55 (1.18–2.43)	0.742
Baseline free T4, pmol/L	16.0 (15.0–18.0)	16.0 (15.0–19.0)	0.886

▲**Table 1. Characteristics of patients with and without thyroid irAEs**

- Logistic regression analysis showed that **prior anti-PD1 therapy** was associated with **more than 3-fold risk of thyroid irAEs** (**odds ratio 3.67**, 95% CI 1.19–11.4, **p=0.024**)

3. Factors associated with OS

- Patients who **developed thyroid irAEs** had **median OS** of **17.9 months** (IQR: 7.8–35.0), **longer** than those who **did not develop thyroid irAEs** (**median OS 5.7 months**, IQR: 2.6–12.3; **p<0.001**)



▲ **Figure 1. Kaplan-Meier curve for patients who developed thyroid irAEs compared with those who did not**

- Among various baseline clinical characteristics, only the occurrence of thyroid irAEs was associated with a significant protective effect in terms of OS (crude hazard ratio 0.38, 95% CI 0.19–0.78, p=0.008)
- In **multivariable Cox regression model** which included prior anti-PD1 exposure, prior TKI exposure and occurrence of thyroid irAEs, **occurrence of thyroid irAEs predicted better OS** (**adjusted hazard ratio 0.36**, 95% CI 0.18–0.75, **p=0.006**) **independent of prior anti-PD1** (p=0.386) **and TKI exposure** (p=0.155)

Conclusion

- **Thyroid irAEs are common in advanced cancer patients treated with combination anti-PD1/anti-CTLA4 in routine clinical practice**
- **Prior anti-PD1 exposure increases the risk of thyroid irAEs**
- **Occurrence of thyroid irAEs may be associated with better OS**
- **Regular TFT monitoring is advised for timely treatment of thyroid irAEs to avoid morbidities due to untreated thyroid disorders**