A MULTICENTER RETROSPECTIVE COHORT STUDY INVESTIGATING IMMUNE-RELATED THYROID TOXICITY IN ADJUVANT MELANOMA PATIENTS TREATED WITH A PD-1 INHIBITOR

OUH Odense University Hospital SDU

E-poster #925 – MASCC/ISOO Annual Meeting 2023

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Introduction

- Immune checkpoint inhibitor (ICI) related thyroiditis (irTAE) is a common adverse reaction
- IrTAEs are observed more frequently after PD-1 inhibitors compared to CTLA-4 inhibitors
- PD-1 inhibitors are used in the adjuvant setting after resection of melanoma
- IrTAE is frequently resulting in lifelong hormone replacement therapy
- The real-world incidence, clinical timeline characteristics, and associated factors in the adjuvant setting are unexplored

Objectives

- In a national cohort of adjuvant melanoma patients treated with a PD-1 inhibitor, to
  - describe the incidence of irTAEs
  - describe the clinical timeline characteristics of the transient and persistent irTAEs
  - test if age and sex were associated with the risk of developing irTAE
  - investigate associations between irTAE with recurrence-free survival (RFS) and overall survival (OS)

Methods

- Melanoma patients receiving first cycle of adjuvant PD-1 inhibitor between Nov 2018 and Dec 2020
- Demographics, treatment characteristics, laboratory findings and FDG-PET/CT scan results were extracted from the Danish Metastatic Melanoma Database
- Data cut off March 2022
- Key exclusion criteria: known thyroid illness, ir-hypophysitis, fewer than two reported TSH values, no baseline TSH value

Results

- Of 554 adjuvant melanoma patients 454 passed the exclusion criteria
- 56.6% were men and 43.4% were women
- Patients with irTAE had a median age of 59.9 years (17.6-86.1) and without irTAE 62.2 years (21.1-86.3)
- 99 developed irTAEs (21.8%), of these were 46.5% transient and 53.5% persistent
- Age per 10 years increase was significantly associated with a lower risk of developing irTAEs (HR 0.86; 95% CI 0.75 - 0.98; p = 0.024)

- The table compares clinical timeline characteristics between transient and persistent irTAE

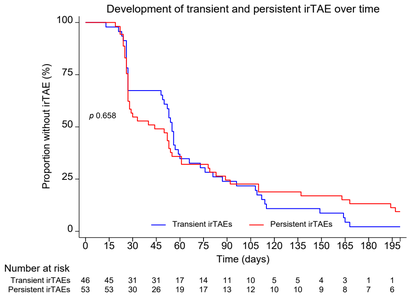
All irTAE

	Transient irTAE N=46	Persistent irTAE N=53	p-value
Time to irTAE (days), median (range)	55 (13-280)	44 (19-427)	0.57
Levothyroxine treatment, n (%)	0 (0%)	53 (100%)	
Time to start levothyroxine after first abnormal TSH value (days), median (IQR)		57 (29-63)	
Duration of irTAE* (days), median (IQR)	84 (57-140)		
Time to hyperthyroid (days), median (range)	53 (13-280)	28 (19-349)	0.16
Time to hypothyroid (days), median (range)	109 (26-336)	84 (36-447)	0.48
The phases of the irTAE n (%)			
Hyperthyroid + hypothyroid	6 (13)	39 (73.6)	**<0.001**
Hypothyroid + hyperthyroid	0 (0)	1 (1.9)	
Isolated hyperthyroid	29 (63)	2 (3.8)	**<0.001**
Isolated hypothyroid	11 (24)	11 (20.7)	0.81

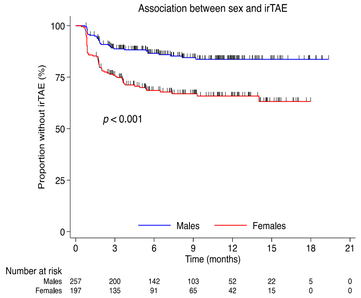
Definitions of irTAE

- Transient: ≥ two consecutive abnormal TSH values *not requiring* hormone replacement
- Persistent: ≥ two consecutive abnormal TSH values *requiring* hormone replacement

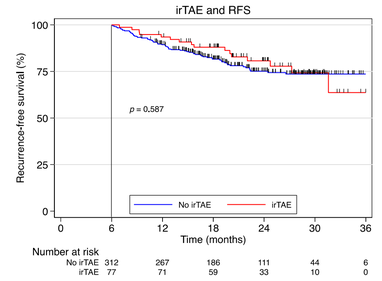
- IR 0-3 months:2.7/1,000 pers-day
- IR 3-6 months: 0.5/1,000 pers-day

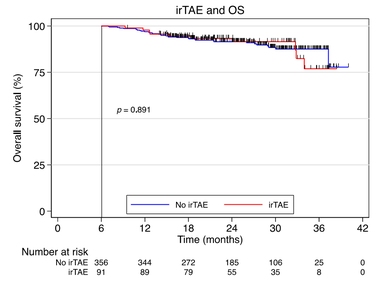


- Female sex associated with a greater risk of developing irTAEs (HR 2.52; 95% CI 1.67 - 3.80; p < 0.001



- No significant association between irTAE and RFS (HR 0.86; 95% CI 0.50 - 1.48; p = 0.587), or OS (HR 1.05; 95% CI 0.52 - 2.12, p = 0.589)





Conclusion

- IrTAE is a common side-effect to adjuvant PD-1 inhibitors primarily occurring within the first three months, with different degrees of severity
- Female sex and younger age are predictors for developing irTAEs
- IrTAE was not associated with better clinical outcome measurements
- Future prospective studies are needed to understand additional predictors and competing risk factors in the adjuvant setting of melanoma patients

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