

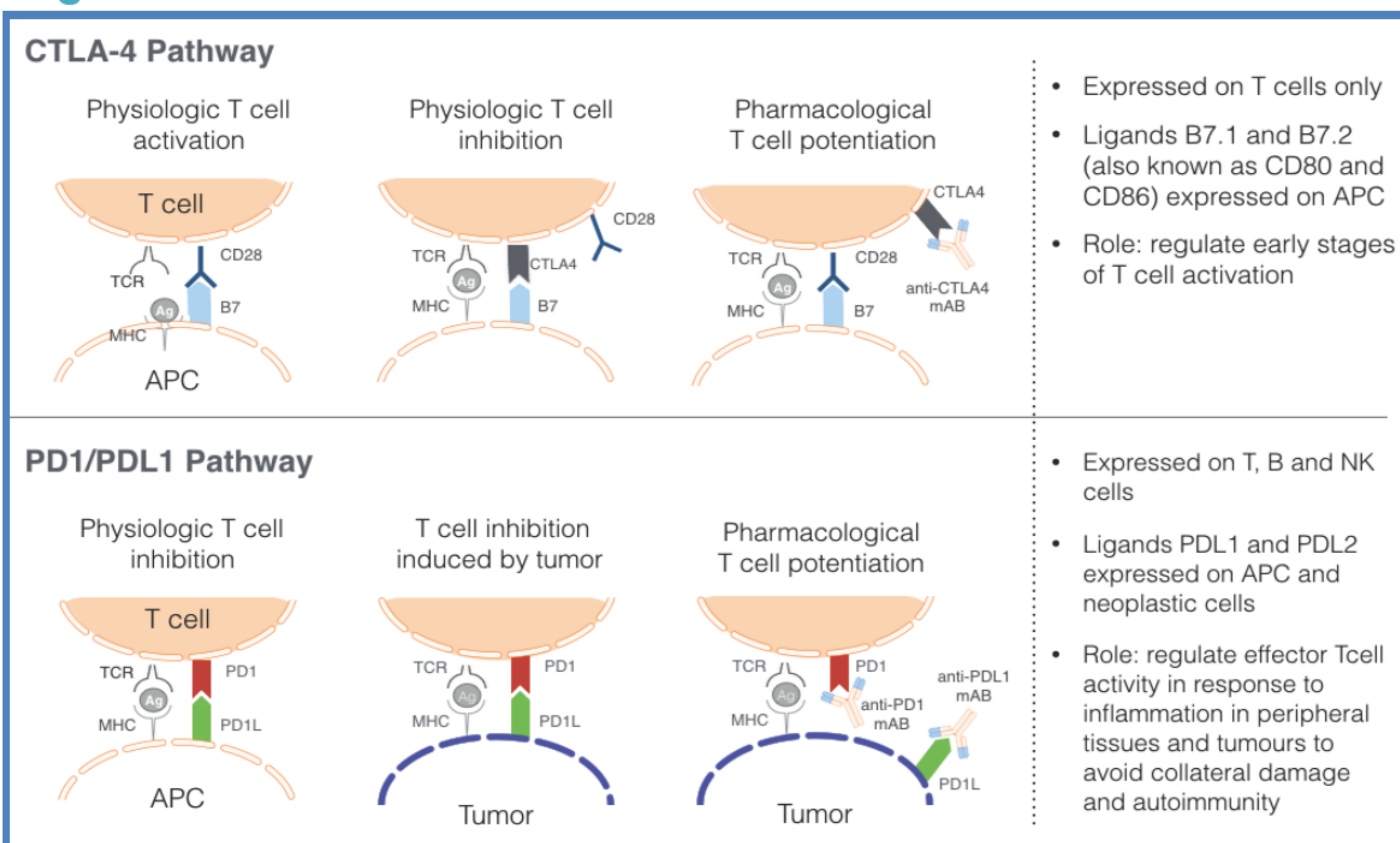
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## Introduction

Immune checkpoint inhibitors (ICIs) are a new drug generation used for advanced neoplasias. They are monoclonal antibodies (mAbs) which enhance the immune system to combat cancer cells (Figure 1). As a result, immunologic tolerance can be altered and autoimmunity triggered. Toxicities associated to ICIs have been named immune-related adverse events (irAEs). "Time to resolution" of endocrine irAEs have not been well described as this term has not been defined in clinical trials. The aim of this study was to describe the frequency and characteristics of endocrine irAEs in the patients treated with ICIs at our centre.

### Figure 1: Mechanism of action of the most common ICIs



## Methods

Between 2010 and 2015, 91 patients have been treated with anti CTLA-4 (Ipilimumab), PD1 and PD-L1mAbs for advanced neoplasias (melanoma, lung cancer and Hodgkin's Lymphoma). This report is based on the retrospective review of the records of 81 patients considered suitable for inclusion, as they had been screened regularly for endocrinopathies throughout their treatment. For thyroidopathies, we defined "time to resolution" as the time it took to normalize TSH levels.

**Table 1: Characteristics of patients presenting endocrine toxicities**

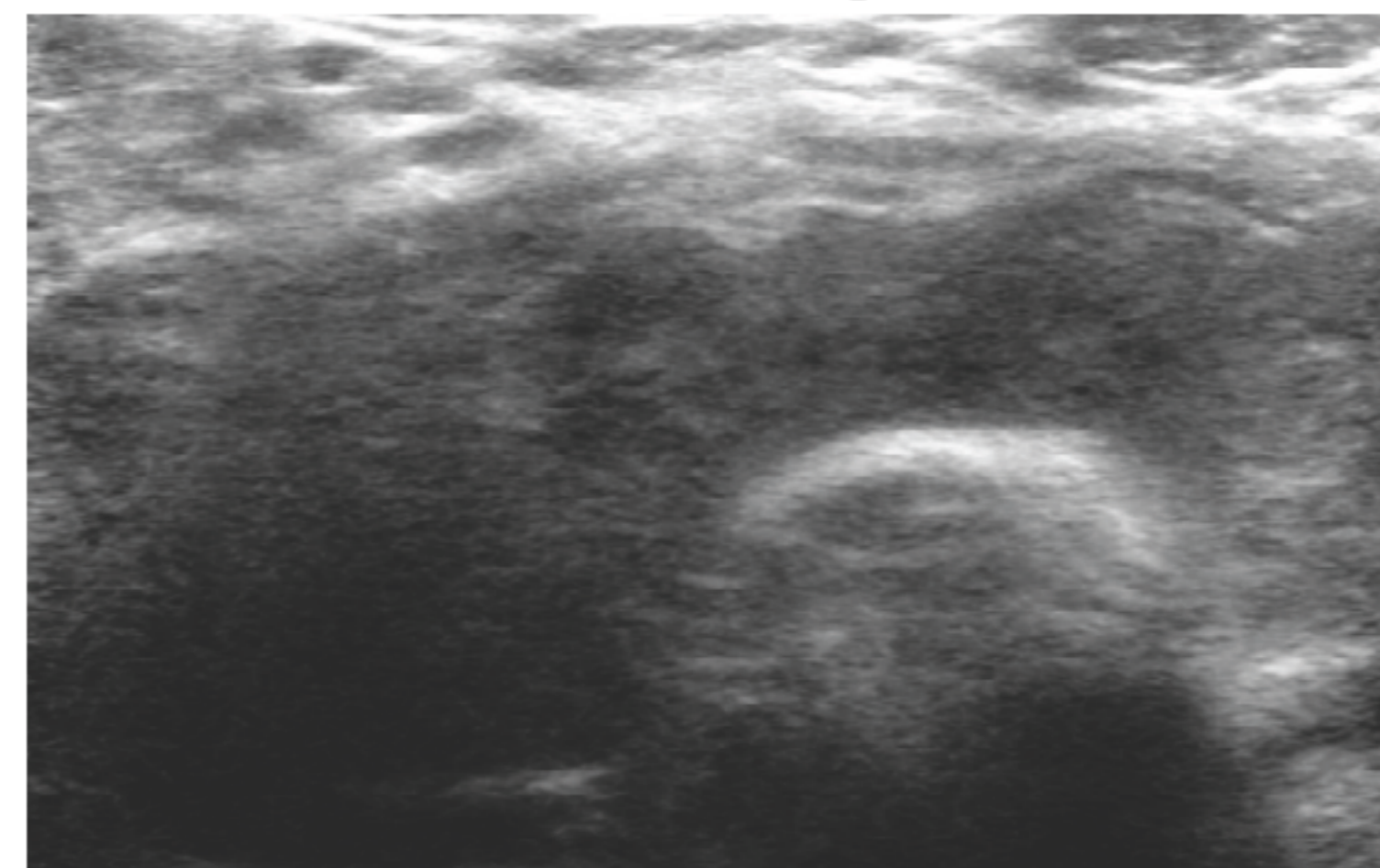
Age	Gender	Diagnosis	Treatment	Toxicity	Thyroid autoAb (TPO/TSI)	Nº Doses to toxicity	Nº weeks to toxicity	Nº weeks hyperfx	Time to resolution (weeks)	Evolution	Duration treatment (weeks)	Response	Response duration (doses)
61	M	Melanoma	Anti PD1	Thyroiditis	+/+	2	6	6	16	Permanent hypothyroidism	18	PD	-
70	M	Lung	Anti PD1	Thyroiditis	+/-	1	2	8	27	Permanent hypothyroidism	52	SD	52
72	M	Lung	Anti PD1	Thyroiditis	-/Grey zone	6	10	6	Not reached	Permanent hypothyroidism	Ongoing	SD	Ongoing (21)
60	M	Lung	Anti PD1	Thyroiditis	-/-	5	8	10	18	Euthyroidism	Ongoing	SD	Ongoing (29)
74	M	Lung	Anti PD1	Thyroiditis	-/-	3	7	4	6	Permanent hypothyroidism	Ongoing	SD	Ongoing
77	M	Lung	Anti PD1	Hypothyroidism	NR	6	12	-	15	Permanent hypothyroidism	Ongoing	PR	Ongoing
52	W	Melanoma	Ipilimumab	Hypophysitis		4	11	-	-	Permanent ACTH and TSH deficiency	No	PD	-

(NR: not recorded; SD: stable disease; PR: partial response; PD: progressive disease)

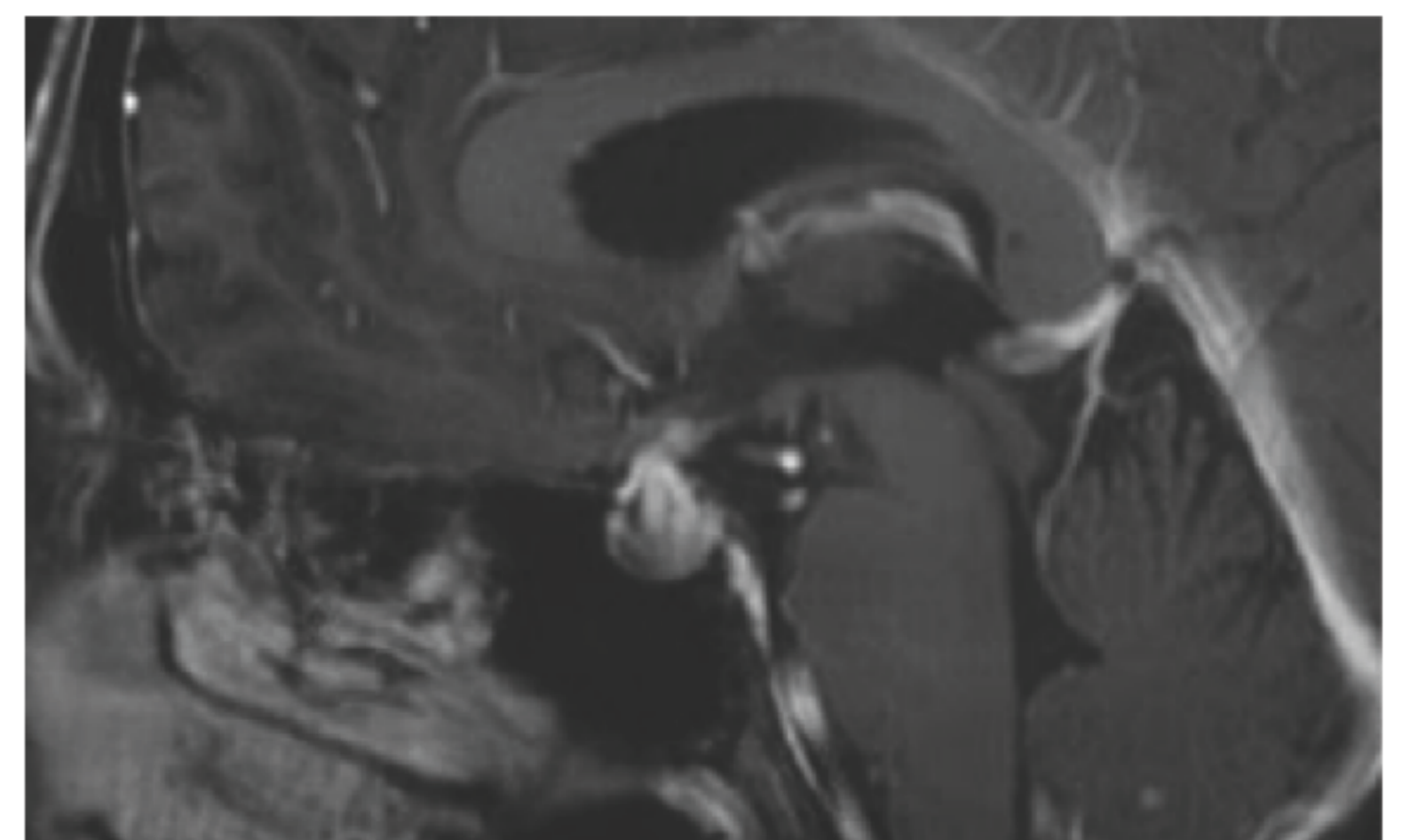
## Results

7 patients (8.6%) presented endocrine irAEs. 5 patients (6.2%) developed painless thyroiditis, 1 (1.2%) Hashimoto's thyroiditis and 1 (1.2%) hypophysitis. Endocrinopathies presented after a median of 8 weeks (2-12) once treatment started, and the patients had received a median number of doses of 4. Thyroiditis where all secondary to antiPD1mAbs (Figure 2). All patients presented with the classic triphasic presentation with a median of 6 weeks of hyperfunction and a mean time to resolution of 17 weeks. 4 of 5 patients developed permanent hypothyroidism. The patient with hypophysitis presented with asthenia, intense headache and blurred vision 11 weeks after starting Ipilimumab. An MRI revealed enlargement and enhancement of the pituitary gland and stalk (Figure 3). Corticotroph and thyrotroph axes were affected and have not recovered 9 months after the event. On addition, 5 more patients (6.2%) showed a transitory decrease in TSH with normal T4 and T3 levels which could correspond to Sick Euthyroid Syndromes or short, subclinical thyroiditis.

**Figure 2: Thyroid US of an anti-PD1 mAb induced thyroiditis**



**Figure 3: MRI of a hypophysitis induced by Ipilimumab**



## Conclusions

Endocrinopathies due to the use of ICIs are common and generally mild. In our series, thyroiditis was the most frequent irAE, especially associated to antiPD1mAbs. Clinical presentation and duration of ICIs-induced thyroiditis is similar to sporadic cases, although there could possibly be a higher tendency to develop permanent hypothyroidism. Hypophysitis is an unfrequent but serious irAE. Endocrinologists must be aware of this emerging cause of autoimmune endocrinopathies as the use of ICIs is expected to increase exponentially in the near future.

## References

- Pardoll DM. *Nat Rev Cancer*. 2012;12(4):252-264.
- Postow MA. *ASCO Educ B*. 2015.
- Corsello SM, Barnabei A, Marchetti P et al. *J Clin Endocrinol Metab*. 2013;98(4):1361-1375.
- González-Rodríguez E, Rodríguez-Abreu D. *The Oncologist*, 2016; (In press).