

**FIGURE 4**  
**Management of Immune-Related Hyperthyroidism**<sup>6,10,14,21</sup>

**Background:** Around 5-10% of patients receiving CLTA-4 and anti-PD-1/PD-L1 antibodies are likely to develop an endocrine adverse event of any grade. Patients with thyroid disorders may be asymptomatic. Detection of hyperthyroidism is through laboratory testing of TSH and T4 levels. The incidence of hyperthyroidism has been lower than hypothyroidism with a time of onset ranging from 24 days to 12 months. Hyperthyroidism is characterized by high or normal levels of free T4 in the body and presents with low TSH. Most patients later become hypothyroid due to autoimmune thyroiditis and require thyroid hormone replacement. An endocrinologist should be involved and consulted as soon as hyperthyroidism is suspected.

	Description	Referral	MANAGEMENT		
			Corticosteroids	Supportive Therapy	Immune Therapy
<b>HYPER-THYROIDISM</b>	<b>GRADE 1</b> Asymptomatic FT4 normal; TSH suppressed (<0.3mUI/L).	Monitor TSH and FT4 before each cycle.	Not recommended.	Intervention not indicated.	Monitor closely and continue immune therapy.
	<b>GRADE 2</b> Moderate symptoms <sup>§</sup> Suppressed TSH (<0.1mUI/L); high FT4.	Monitor TSH and FT4 before each cycle. Consult with endocrinologist.	Consider a short period of 1 mg/kg/day PO prednisone or equivalent for acute thyroiditis presenting as hyperthyroidism.	Typically patients are asymptomatic, if symptomatic initiate an oral beta-blocker (e.g. propranolol 10-40 mg QID or atenolol 25-50 mg daily). Refer to endocrinologist for consultation.	Withhold therapy until symptoms are controlled, the patient is stable on hormone therapy, and is receiving <7.5 mg of prednisone or equivalent daily.
	<b>GRADE 3</b> Severe symptoms <sup>‡</sup> Suppressed TSH (<0.1mUI/L); FT4 high.	Hospitalization indicated. Monitor TSH and FT4. Rule out sepsis.	Initiate corticosteroids at a dose of 1-2 mg/kg/day methylprednisolone IV and continue until improvement to mild severity, resolve or return to baseline. Taper over at least 1 month.	If urgent, consider initiating therapy with methimazole (e.g. 20-30 mg/day, reduced after 4-6 weeks to maintenance doses 5-15 mg/day) or propylthiouracil (e.g. 200-300 mg/day, then reduced to maintenance of 50-150 mg/day) in cases of Grave's disease.	
	<b>GRADE 4</b> Life-threatening Suppressed TSH (<0.1mUI/L); FT4 high.			Initiate thyroid replacement if hypothyroid after several weeks (see management of hypothyroidism algorithm).	Discontinue therapy.

<sup>§</sup> weight loss, increased appetite, anxiety and irritability, muscle weakness, menstrual irregularities, fatigue, tachycardia  
<sup>‡</sup> arrhythmia, atrial fibrillation, tremor, sweating, insomnia, diarrhea