FIGURE 3

Management of Immune-Related Hypothyroidism[4,6,10,14,21]

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. Hypothyroidism was reported in approximately 2% of patients treated with ipilimumab, and 8.3% of patients treated with PD-1 inhibitors. Time of onset for hypothyroidism ranged from 0.7 weeks to 19 months. Hypothyroidism is diagnosed if TSH level is increased with a low free T4 level. When thyroid replacement is given, dose adjustments should occur no sooner than 4-6 weeks. An endocrinologist should be consulted with the exception of grade 1 or uncomplicated grade 2 hypothyroidism.

HYPO-THYROIDISM	Description	Referral	MANAGEMENT: Corticosteroids	MANAGEMENT: Supportive Therapy	MANAGEMENT: Immune Therapy
GRADE 1	Asymptomatic FT4 normal TSH >10mUI/L.	Monitor TSH before each cycle.	Not recommended.	Intervention not indicated.	Monitor closely and continue immune therapy.
GRADE 2	Moderate symptoms[§] Low FT4 and/or TSH >10mUI/L.	Monitor TSH and FT4 before each cycle. Consider consultation with endocrinologist.	Not recommended.	Initiate levothyroxine therapy at 0.5-1.5 mcg/kg if no heart disease or severe co-morbidities; otherwise, start at 12 to 25mcg daily and increase dose slowly (no sooner than every 4-6 weeks)[¥].	Consider holding therapy until symptoms are controlled, the patient is stable on hormone therapy, and is receiving <7.5 mg of prednisone or equivalent daily.
GRADE 3	Severe symptoms[‡] Very low FT4 and TSH very high.	Monitor TSH and FT4. Hospitalization indicated.	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. Commence IV hydration if indicated.	Above plus supportive therapy for severe cardio-respiratory symptoms.	
GRADE 4	Life-threatening Very low FT4 and TSH very high.				Discontinue therapy.

§ fatigue, constipation, weight gain, loss of appetite, dry skin, eyelid edema, puffy face, hair loss

‡bradycardia, hypotension, pericardial effusion, depression, hypoventilation, stupor, lethargy to myxedema coma

¥ if patient has both adrenal insufficiency and hypothyroidism, start corticosteroid for 2-3 days before levothyroxine