Supplementary-Table-5. Proposed management algorithm for ICI-myotoxicities as a function of severity criteria grading (adapted from (1))

Grading and treatment		
Grade	**Definition**	**Management**
Grade 1 (mild)	Asymptomatic with abnormal cardiac biomarker testing (troponin) potentially associated with mild ECG or LVEF abnormalities (no severity criteria)#	- Hold ICI and monitor troponin 6 hours later and then daily for ≥3 days to evaluate if steep increase - Urgent cardiology consultation and decision to hospitalize upon this first assessment - No systematic immunossupressant start(2) - Evaluate an alternative diagnosis(3) - Search for cardiac and peripheral muscles diagnostic and severity criteria - Resume ICI if cardiac event believed not to be related to ICI - The appropriateness of re-challenging confirmed ICI-myocarditis upon resolution of abnormalities is unknown.
Grade 2 (moderate)	Mild symptoms with abnormal cardiac biomarker testing (troponin) with moderate LVEF or ECG abnormalities	- Hold ICI and monitor troponin 6 hours later and then daily for ≥3 days to evaluate if steep increase or unfavorable trend in biomarker evolution upon immunosuppressive treatment start - Admit for cardiology consultation and inpatient surveillance for few days - Search for cardiac and peripheral muscles diagnostic and severity criteria - Discuss start of corticosteroids (≥1mg/kg/day of prednisone, oral or IV depending on symptoms) as it may be beneficial for prevention of evolution of cardiac symptoms(4) but long-term effects on tumor are unknown* - The appropriateness of re-challenging confirmed ICI-myocarditis upon resolution of abnormalities is unknown.
Grade 3 (Severe)	Abnormal cardiac biomarker testing (troponin) with appearance of severe cardiac pro-arrhythmias, or acute heart failure (but not cardiogenic shock) or concurrent respiratory muscle failure leading to hypoventilation (but no urgent need for mechanical ventilation) or cortico-resistance**	- Hold ICI and monitor troponin 6 hours later and then daily for ≥3 days seeking for unfavorable evolution trend upon treatment start. Subsequent troponin and symptoms monitoring to guide treatment. - Immediate transfer to an acute coronary/arrhythmia care unit should be considered for patients - Search for cardiac and peripheral muscles diagnostic and severity criteria - Monitor for appearance of ventricular pro-arrythmia and high-degree conduction disorders. Use with caution anti-arrhythmic drugs which might precipitate high-degree conduction disorders. Permanent (eventually leadless) vs. temporary implantation of pacemakers must be evaluated thoroughly, given the risk for infections, and vascular complications of patients with implantable chambers. These rhythmic events are often reversible upon effective immunossupressant start. - Discuss start of a combination of corticosteroids (≥0.5mg/kg/day of prednisone, oral or IV depending on symptoms), with a CTLA4 agonist and/or a JAK inhibitor.*(5-8) - The appropriateness of re-challenging confirmed ICI-myocarditis upon resolution of abnormalities is unknown.
Grade 4 (life-threatening)	Abnormal cardiac biomarker testing (troponin) with sustained/symptomatic cardiac arrythmias or cardiogenic shock; or concurrent overt respiratory muscle failure requiring urgent mechanical ventilation.	- Hold ICI and monitor troponin 6 hours later and then daily for ≥3 days seeking for unfavorable evolution trend upon treatment start. Subsequent troponin and symptoms monitoring to guide treatment. - Immediate transfer to intensive care unit should be considered for patients - Search for cardiac and peripheral muscles diagnostic and severity criteria - Monitor for appearance of ventricular pro-arrythmia and high-degree conduction disorders. Use with caution anti-arrhythmic drugs which might precipitate high-degree conduction disorders. Permanent (eventually leadless) vs. temporary implantation of pacemakers must be evaluated thoroughly, given the risk for infections, and vascular complications of patients with implantable chambers. These rhythmic events might be reversible upon effective immunossupressant start. - Discuss start of a combination of corticosteroids (≥0.5 mg/kg/day of prednisone, oral or IV depending on symptoms), with a CTLA4 agonist and a JAK inhibitor.*(5-8) - Consider anti-thymoglobulin or alemtuzumab (CD52 blockade) if the previous line of treatment is not effective.(1) - The appropriateness of re-challenging confirmed ICI-myocarditis upon resolution of abnormalities is unknown.
Grade 5 (fatal)	Fatal	

Abbreviations: CD: cluster of differentiation; CTLA4: cytotoxic T-lymphocyte antigen 4; ICI: immune checkpoint inhibitors ; JAK: Janus-kinase; LV(EF) : left ventricular ejection fraction ; URL: upper reference limit

* A major challenge to consider while treating patient with immune related toxicity is how to mitigate the potential adverse events and lethality associated with this side effect while preserving anti-tumor beneficial effects. Most immunossupressant have been flagged with a potential risk for pro-tumorigenicity particularly when used chronically, including corticosteroids, abatacept and JAK inhibitors.(5,9) Further research is indeed required to assess the question of the optimal drug mix, dosage and duration to be used to preserve ICI therapeutic effect while treating a pauci-symptomatic vs. a severe ICI-related adverse event. Start of corticosteroids might justify starting associated measures including prevention of gastric ulcer (proton pomp inhibitor), iono-glycemic monitoring and anti-infective prophylaxis.

** Cortico-resistance is defined by deteriorating symptoms; or decrease in Troponin levels <20% of peak level (within 72h of admission) despite at least 72 hours of ≥0.5mg/kg/day of equivalent oral prednisone

severity criteria on ECG include appearance of pathological Q-waves, micro-voltage, QRS≥150msec or delta≥30msec vs. baseline pre-ICI, ventricular tachycardia, high-degree atrioventricular block or sinus dysfunction[10]

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