

Supplementary-Table-2. Diagnostic work-up for suspected ICI-myocarditis and evaluation of severity criteria (adapted from(1))

Work-up and evaluation		
Investigation	Diagnosis	Prognosis (severity criteria)
ECG, Holter ECG, telemetry - ECG are particularly useful when compared to pre-ICI baseline ECG(2,3)	- Tachycardia - QRS duration lengthening and voltage decrease - QTc lengthening - Appearance of conductive disorders (sinus dysfunction, bundle branch & atrio-ventricular blocks), ventricular arrhythmias, premature ventricular contractions and pathological Q-waves	- Decreased QRS voltage (Sokoloff-Lyon index) / Micro-voltage - Appearance of pathological Q-waves - Appearance of high degree atrio-ventricular blocks (up to 25%) - Appearance of ventricular arrhythmias (up to 25%)
Cardio-muscular circulating biomarkers (troponins, creatine kinase)(1,4) - Biomarkers are particularly useful when compared to pre-ICI baseline values as they may be already abnormal in a subset of patients(5)	- Troponins increased in almost all patients (high sensitivity; >90%) - Creatine kinase increased in over three-quarter of patients - Caution in interpretation when concurrent cardiotoxic drug is used in combination with ICI (anti-angiogenics, anthracyclines, ...)(5)	- Resistance to immunosuppressant treatment is likely evaluable by troponin-T kinetics evolution(1,4)
Echocardiography(1,3,6)	- Often (>50%) normal - Possible appearance of decreased LVEF or decreased LV longitudinal strain or LV motion abnormality (non-Takotsubo pattern)	- Conflicting data on LV longitudinal strain - Systolic dysfunction leading to acute symptomatic heart failure
Cardiac and/or muscular pathology(1,7,8)	- Definite diagnosis established when identification of T-cells and macrophages infiltrating muscles with associated myocytes death	- Unclear
Cardiac MRI(6,9-11) - Caution concerning a high proportion of pre-existing abnormality before ICI start and expected T1/T2 mapping alteration on ICI in non-myocarditis ICI treated cancer patients(9)	- Variable sensitivity (25-75%); poorer when realized soon upon first suspicion - Multi-parametric criteria for cardiac tissue assessment (seeking for fibrosis, edema) required using quantitative T1/T2 mapping and late gadolinium enhancement with variable levels of certainty for diagnosis - Possible appearance of decreased LVEF or decreased LV longitudinal strain or LV motion abnormality (non-Takotsubo pattern)	- Conflicting data on LV late gadolinium enhancement - Unclear for quantitative analysis relying on T1/T2 mapping - Systolic dysfunction leading to acute heart failure
Search for concomitant and severity of myositis frequently associated with myocarditis(12-15) - Clinical assessment - Pulmonary functional respiratory tests - Electromyogram - Muscle MRI - Blood capnia - Diaphragm imaging (echography, MRI)#	- Clinical signs of concurrent myositis (myalgia, muscles weaknesses), eventually presenting as myasthenia-gravis syndrome (ptosis, diplopia, dysphagia, dysphonia, dyspnea, abdominal paradoxical breathing) - Pulmonary functional respiratory test identifying respiratory muscles dysfunction identified by presence of restrictive ventilatory defect, and/or vital capacity drop >15% in the supine position - Electromyogram with a myopathic pattern and normal repetitive nerve stimulation test (no neuromuscular junction function disorder) - Muscle MRI identifying hypersignals (muscle edema on T2-sequences) - Blood capnia to evaluate hypercapnia	- Overt respiratory muscle failure leading to hypercapnia(3,14) - Dysphagia requiring (par)enteral nutrition - Myositis symptoms impairing significantly quality of life - Role of diaphragm imaging and phrenic nerve electromyogram evaluation to be further assessed
Search for concomitant hepatitis(13)	- hepatic biomarkers often abnormally increased	- Unclear
<i>Require further assessment:</i> Brain Natriuretic Peptide (BNP), or NT-proBNP(1)	- Might be increased - Association with heart failure to be confirmed in this setting	- Unclear
<i>Exams guided by physician judgment:</i> Chest X-ray, stress test, thoracic & cardiac/coronary scanner, coronary angiogram, PET scanner, c-reactive protein, creatinine, cell blood count with differential, D-dimers	- Rule-out an alternative diagnosis (cardiac thrombus, metastasis, pulmonary embolism, systemic infection, cardiac ischemia, acute coronary syndrome, pneumothorax, kidney failure, Tako-tsubo, ...) - Cardiac 18FDG PET-scanner is poorly sensitive for ICI-myocarditis(16)	- Concurrent association between ICI-myocarditis and acute coronary syndrome requiring urgent revascularization occurring in up to 10% of cases is a predictor of poor outcomes.(17) Caution is required to not delay an eventual diagnosis of ICI-myocarditis.

Abbreviations: FDG: Fluoro-desoxy-glucose ; ICI: immune checkpoint inhibitors ; LV(EF): left ventricular ejection fraction ; MRI: magnetic resonance imaging

Deserve further evaluation to establish norms and standards in control cancer population on ICI with no myotoxicities

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