

Myocarditis: An Immune-Related Adverse Event of Checkpoint Inhibitors

December 15, 2017 Workshop

Pfizer Peapack Campus, Peapack, NJ

Hosted by **Project Data Sphere, LLC**, an independent, non-profit initiative
of the **CEO Roundtable on Cancer Life Sciences Consortium**

Workshop objectives

- Bring together key stakeholders from academia, industry, and regulatory agencies to assess current state of knowledge, identify knowledge gaps, and establish priorities for improved prevention, recognition/early detection, and treatment of immune checkpoint inhibitor (ICI)–associated myocarditis.
- Identify optimal ways to collect, share, and make available for analysis data on ICI-associated myocarditis.
- Establish cross-functional teams, including representatives from industry, academia, and regulatory bodies, to develop a case definition, a diagnostic work-up, and treatment algorithms for ICI-associated myocarditis.

Current knowledge on immune checkpoint inhibitor–associated myocarditis

- ICI-associated myocarditis is a rare but potentially fatal AE that was first reported in 2015; due to its subtle manifestations and unpredictable clinical course as well as the rapidly growing use of ICIs in academic and community hospital settings, there is an urgent need to coordinate efforts to establish a case definition, algorithm for diagnostic work-up, and approach to treatment.
 - In addition, since patients with ICI-associated myocarditis may first seek care from healthcare workers unfamiliar with this syndrome (eg, family physicians, internists, ER physicians, hospitalists, or even cardiologists), a priority is to further efforts to heighten awareness of this syndrome to these groups.
- Patients with myocarditis may present with chest pain, dyspnea, and/or arrhythmia, but may also be asymptomatic; sudden cardiac death due to myocarditis in asymptomatic patients is a potential concern.
- Diagnosis of ICI-associated myocarditis may be complex and challenging:
 - Troponin elevation is common but is not a specific marker for myocarditis diagnosis.
 - ECGs may be entirely normal or show subtle, non-specific changes, such as dysrhythmias.
 - Cardiac MRIs with contrast are more sensitive but are expensive and not widely available.
 - Endomyocardial biopsy is considered the gold standard for myocarditis diagnosis; however, endocardial involvement may not be uniform, and therefore myocarditis is not always evident at the biopsy site.
- The incidence of myocarditis in patients with cancer treated with ICIs is likely underestimated due to:
 - Symptoms that are subclinical, atypical, or attributed to underlying disease/comorbidities.
 - A lack of awareness and common definition of ICI-associated myocarditis.
- Because most ICIs were approved for various tumor indications based on single-arm trials in small populations of patients, and via an expedited approval process by the US FDA, some safety information, including reporting of rare AEs (such as myocarditis), which would be acquired through a standard clinical development process involving larger numbers of patients, may only now become evident as clinical experience has grown.
- Observations from cardio-oncologists and cardiologists (T Neilan, Massachusetts General Hospital; R Steingart, Memorial Sloan Kettering Cancer Center; and J Moslehi, Vanderbilt University) indicate myocarditis generally occurs early during the course of treatment (typically within 3 months) and is frequently diagnosed based on an abnormal ECG and elevated troponin.
 - Unpublished findings from a multicenter registry (presented by T Neilan) showed elevated serum troponin was common in those patients that subsequently had a major adverse cardiac event during ICI treatment, and a higher initial steroid dose for treatment of myocarditis was associated with a lower major adverse cardiac event rate.
 - Based on these findings, the group recommended ECG and troponin testing at baseline and during early cycles of ICIs and myocarditis be initially treated with high-dose steroids (eg, 1000 mg SoluMedrol for 3–5 days); lower-dose steroids may be less successful in preventing deaths due to myocarditis.
- Some patients with ICI-associated myocarditis may also have ICI-associated AEs (myositis, in particular) in

other organs.

- The risk of myocarditis increases when ICIs are administered in combination regimens; it is important to be aware of the risk of immune-related AEs, eg, myocarditis, as these combination regimens become more widely used and as ICIs are increasingly tested in combination with drugs that have different mechanisms of action.

Key data gaps and priorities for future efforts

- There is currently no case definition for ICI-associated myocarditis to enable uniform assessment by different clinicians in different settings.
 - A standardized definition is needed to capture these events in a harmonized manner so data may be pooled for subsequent analyses; this should be built into clinical trial protocols and data collection forms.
 - Development of the case definition will be an iterative process (using broader designations for the initial retrospective analysis) to balance sensitivity and specificity.
 - It is also recognized that certain diagnostic tests may not be available in all clinical settings to which such patients may present; therefore, one suggestion was that there be one set of criteria established with adequate sensitivity for identifying potential cases of ICI-associated myocarditis and a more extensive set of criteria, with improved specificity, for confirming the diagnosis.
- The benefit:risk ratio of increased monitoring for myocarditis in clinical trials of ICIs, especially as part of combination regimens, must be evaluated.
 - We need a consensus guideline for myocarditis monitoring to present to sponsors according to the trial phase and setting.
 - More aggressive monitoring may be appropriate for phase 1/2 studies, in particular, those using dose escalation strategies or testing in the adjuvant setting.
 - It may be sufficient to screen and monitor a subset of patients in large phase 3 trials.
- Risk factors for ICI-associated myocarditis are unknown.
 - It may be possible to analyze existing biospecimens from clinical trials using large-scale proteomics.
 - Recommendations for specific biospecimens to collect in future clinical trials are needed.

Immediate next steps

- Establish three working groups to:
 1. Develop a case definition for ICI-associated myocarditis (led by B Gregory).
 - a. Consider whether one set of criteria should be established for all situations, or whether one set could be established for screening (ie, high sensitivity) and another set for more definitive diagnosis (ie, high specificity).
 - b. High cost and limited availability of some diagnostic tests and/or expertise may make one set of criteria appropriate for use in community hospital settings, whereas another may be appropriate for use in tertiary care medical centers.
 - c. This two-tier approach may also be used prospectively in clinical trials.
 2. Establish a single, integrated database of de-identified, patient-level data within Project Data Sphere and gain agreement from industry sponsors, NCTN organizations, and high-volume cancer centers to contribute to this; identify and prioritize research questions to guide queries and analyses from the Project Data Sphere database.
 3. Develop guidelines for clinical trial investigators and treating physicians on how to identify patients who may be at increased risk, facilitate early diagnosis, and institute early and appropriate treatment for ICI-associated myocarditis.

ACTION ITEM: Individuals interested in participating in working groups should inform Eliza Silvester (ESilvester@SatoriConsulting.com).

- Industry participants are to submit relevant data sets to Project Data Sphere.
- Develop a publication from the December 15, 2017 workshop describing what is currently known and unknown about ICI-associated myocarditis, with a call to action to address this unmet need.
 - Planned submission of a Sounding Board article to *New Engl J Med* by January 31, 2018.