Cardiotoxicity associated with immune checkpoint inhibitors: A retrospective analysis of patients at an academic tertiary care center

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Research

Keywords: cardiotoxicity, immune checkpoint inhibitors, cardiomyopathy, heart failure

DOI: https://doi.org/10.21203/rs.3.rs-50662/v3

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Abstract

Background Immune checkpoint inhibitors (ICIs) are a novel class of anticancer agents that have demonstrated clinical response for both solid and hematological malignancies. ICIs are associated with development of immune-related adverse events including cardiotoxicity. We estimated the incidence of newly diagnosed cardiovascular disease ICI-related cardiotoxicity in patients treated with ICIs at a large, tertiary care center. Methods All patients with a cancer diagnosis who received any ICI treatment in the University of Florida's Integrated Data Repository from 2011-2017 were included. Cardiovascular disease was defined as a new ICD diagnosis code for cardiomyopathy, heart failure, arrhythmia, heart block, pericardial disease, or myocarditis after initiation of ICI treatment. Results Of 102,701 patients with a diagnosis of malignancy, 424 patients received at least one ICI. Sixty-two (14.6%) patients were diagnosed with at least one new cardiovascular disease after initiation of ICI therapy. Of the 374 patients receiving one ICI, 21 (5.6%) developed heart failure. Of the 49 patients who received two ICIs sequentially, three (6.1%) developed heart failure and/or cardiomyopathy. Incident cardiovascular disease was diagnosed at a median of 63 days after initial ICI exposure. One patient developed myocarditis 28 days after receiving nivolumab. Mortality in ICI treated patients with a concomitant diagnosis of incident cardiovascular disease was higher compared to those who did not (66.1% vs. 41.4%, odds ratio = 2.77, 1.55-4.95, p = 0.0006). Conclusions This study suggests a high incidence of newly diagnosed cardiovascular disease after the initiation of ICI therapy.

Background

Immune checkpoint inhibitors (ICIs) have revolutionized the management of a diverse spectrum of solid and hematological malignancies previously associated with poor prognosis. Immune checkpoint blockade removes inhibitory signals of T-cell activation enabling tumor-reactive T cells to mount an effective antitumor response by overcoming regulatory mechanisms. Currently, FDA-approved ICIs are inhibitors of either the cytotoxic T-cell lymphocyte-associated protein-4 (CTLA-4) or the programmed death receptor 1 (PD-1) or its ligand (PD-L1). Robust research efforts evaluating other checkpoint targets such as lymphocyte-activation gene-3 (LAG-3) and T-cell immunoglobulin and mucin-domain containing-3 (TIM-3) are ongoing.

ICIs have been reported to cause a range of immune-related adverse events (irAE), mostly involving the skin, endocrine system, liver, lungs, and gastrointestinal tract. These targeted therapies affect specific signaling pathways that can also induce cardiotoxicity. IrAEs occur due to inhibition of immune checkpoints that boost physiological barriers against autoimmunity, leading to local and systemic autoimmune responses. Fulminant myocarditis is currently the most recognized irAE, but complete heart block, conduction abnormalities, pericarditis, stress-induced cardiomyopathy, and left ventricular dysfunction have also been reported. Limited data are available on the incidence of cardiotoxicity after ICI initiation, and there is scarce evidence to guide prevention, surveillance, and treatment. The reported incidence of ICI-induced myocarditis ranges from 0.06% to 1.14% of patients receiving ICIs. However, absence of systematic monitoring and coding mechanisms for cardiac events in immunotherapy trials suggest that cardiac irAEs may be under-reported. Accordingly, we estimated the incidence of cardiotoxicity among patients treated with ICIs using electronic health records at a large tertiary care center.

Methods

This was an observational cohort study using data extracted from electronic health records (EHRs). Supported by the University of Florida (UF) Clinical and Translational Science Institute (CTSI), the UF Health Integrated Data Repository (IDR) is a large-scale database that collects and organizes information from across the UF-Health clinical and research enterprises, thereby including most inpatient and outpatient care services. The IDR provides access to Health Insurance Portability and Accountability Act (HIPAA) compliant and Institutional Review Board (IRB) approved limited datasets that include demographics, medications, lab results, diagnosis, and clinical encounters. For this study, the UF IDR was queried to extract information relevant to all patients receiving anticancer drugs from 2011-2017. All patients with the International Classification of Disease, ninth and tenth revisions, clinical modification (ICD-9-CM 140-239.99) and (ICD-10-CM C00-D49) codes for malignancy were included.

The current study consisted of patients who had received at least one dose for any ICI including PD-1 inhibitors (pembrolizumab, nivolumab), PD-L1 inhibitors (atezolizumab, durvalumab, avelumab), and CTLA-4 inhibitors (ipilimumab, tremelimumab). Baseline demographic information was collected at the encounter of the first ICI administration. Comorbidities such as history of hypertension, hyperlipidemia, diabetes, and ischemic heart disease were defined based on the presence of International Classification of Diseases, 9th revision, Clinical Modification (ICD-9-CM) and ICD-10-CM diagnosis codes prior to the first ICI prescription date.

Cardiotoxicity was defined by ICD-9-CM and ICD-10-CM codes for cardiomyopathy, heart failure, myocarditis, arrhythmia, pericardial disease and heart block (Supplemental Table 1). The case definition for potential ICI-induced cardiotoxicity was a new diagnosis code for any of these conditions as entered by a clinician after initiation of ICI therapy in patients with no prior history of the incident cardiac condition. The performances of these computable phenotypes were previously reported. The ranges of the estimates were 79% - 95% for sensitivity, 90% - 98.9% for specificity, 70% - 94% for positive predictive value, and of 95% - 99.4% for negative predictive value, respectively. Patients with existing diagnosis codes for cardiomyopathy, heart failure, myocarditis, arrhythmia, pericardial disease, and/or heart block before ICI initiation were considered to have pre-existing disease, thus, did not meet the case definition.
Global longitudinal strain (GLS) data were calculated from pre- and post-treatment transthoracic echocardiograms for a subset of patients who developed ICI-induced cardiotoxicity. These data were obtained using TomTec® software (Chicago, IL). Troponin, N-terminal pro-brain natriuretic peptide (NT-pro BNP), and brain natriuretic peptide (BNP) levels were included when available within the time frame of this study.

Statistical analysis: Demographic and medical history information of those with and without a diagnosis of attributable cardiotoxicity were compared using Student's unpaired t-test for continuous variables and chi-square test for categorical variables as appropriate. The percentages of patients with cardiotoxicity following exposure to each drug were estimated. Multivariable logistic regression analysis was performed to estimate the odds ratios (ORs) and 95% confidence intervals (CIs) for mortality adjusting for demographics, comorbidities, and ICIs. Covariates with univariate p-value of < 0.2 were considered in the multivariable logistic regression and variables with p < 0.05 were retained in the model. All analyses were performed in SAS v. 9.4 (Cary, NC). This study was approved by the University of Florida Institutional Review Board (IRB) (IRB# 201702876).

Results

Of 102,701 patients with a diagnosis of malignancy, 424 patients received an ICI and their pertinent demographic and clinical characteristics are summarized in Table 1. Overall, the median age was 63 years, the majority were men, Non-Hispanic whites (63.4% and 85.6%, respectively) and 7.6% were Non-Hispanic blacks. The most frequent cancer diagnoses were lung cancer (29.7%), melanoma (17.0%), and kidney cancer (12.7%) (Table 1). Almost half of the patients (49.5%) had hypertension, 30.2% had hyperlipidemia, 17.9% had diabetes, and 12.7% had ischemic heart disease before the initiation of ICI treatment as determined by ICD diagnosis codes (Table 1).

A single ICI treatment was prescribed to 374 patients. Of patients treated with PD-1 inhibitors, 217 (58%) received nivolumab and 123 (32.8%) were treated with pembrolizumab. Forty-nine patients received dual-agent therapy sequentially (39 with PD-1/PD-L1 inhibitor and CTLA-4 inhibitor combination); one patient received three different ICIs sequentially. No patients were treated with avelumab (PD-L1 inhibitor) during the study period (Table 2).

Of the 424 ICI-treated patients, sixty-two (14.6%; 95% CI, 11.3-18.0) met the definition for potential cardiotoxicity after initiation of ICI therapy. There were no statistically significant differences between those with and without a cardiotoxicity diagnosis in terms of demographics, cancer type, or comorbidities (Table 1). The most frequently diagnosed cardiac conditions were arhythmia (n = 26, 6.1%) and heart failure (n = 23, 5.4%) (Table 2). Of the 374 patients receiving only one ICI, 21 (5.6%) developed heart failure and 21 (5.6%) developed arrhythmia. Overall, in the patients treated with a single ICI, the rates of the cardiotoxicity were the highest in those treated with the CTLA-4 inhibitor ipilimumab (6/13 = 46.15%), compared to PD-L1 inhibitors (4/21 = 19.1%) and PD-1 inhibitors (44/340 = 12.94%) (p = 0.0031). Of the 39 patients receiving two ICIs sequentially (PD-1/PD-L1 inhibitor + CTLA-4 inhibitor), five patients (12.8%, 95% CI, 2.3-23.3) developed cardiomyopathy, and two patients (5.1%, 95% CI, 0.0-12.1) developed heart failure. Eight patients (1.9%) were diagnosed with pericardial disease, and seven patients (1.7%) were diagnosed with heart block (1st to 3rd degree) after PD-1 inhibitor therapy. Ten patients received PD-1/PD-L1 inhibitor therapy sequentially and one patient received three ICIs sequentially; none of these patients developed cardiotoxicity within the study period. Cardiotoxicity was diagnosed at a median time of 63 days after initial ICI exposure (interquartile range: 30-175 days) (Table 2). One patient developed myocarditis at day 28 after receiving nivolumab.

Forty-three patients including 9 (20.9%) with and 34 (79.1%) without a cardiotoxicity diagnosis had both pre-ICI treatment and post-ICI treatment transthoracic echocardiograms. There was no significant difference in mean change in ejection fraction (p=0.37) in those patients with cardiotoxicity compared to those without. Four patients also had global longitudinal (GLS) measured. Each patient demonstrated a decline in their GLS, ranging from 11% to 44% without meaningful change in ejection fraction (Supplemental Table 2).

Of the 424 ICI-treated patients, 191 (45.1%) died during the study period. The median time from ICI initiation to death was 128 days with interquartile range of 66-277 days. History of ischemic heart disease (OR: 2.11, 1.14-3.89, p = 0.017), prior use of doxorubicin (OR: 4.86, 1.31-18.11, p = 0.0184) and carboplatin use (OR: 1.86, 1.19-2.92, p = 0.0068) were also associated with higher mortality. After adjusting for the history of ischemic heart disease, and prior use of doxorubicin and carboplatin, mortality in those who developed cardiotoxicity remained higher compared to those who did not (66.1% vs. 41.4%, adjusted OR: 2.77 and 95% CI: 1.55-4.95, p = 0.0006). There was no evidence that the mortality was lower in patients treated with cardioprotective agents such as beta-blockers, angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), and statins (Table 3).

Discussion

In this study, we observed that approximately 15% of patients receiving ICI therapy developed evidence for potential cardiotoxicity. This is likely an underestimate since a standardized surveillance was not in employed at the time of or following the ICI treatment, and many cases are likely to be “subclinical” as is the case with most CVD. The most commonly observed types of cardiotoxicity were heart failure and arrhythmia. As suggested in previous reports13,14, the incidence of myocarditis was very low: only one patient (0.24%) developed myocarditis. The time to myocarditis for this patient was 28 days after initiation of nivolumab, which was consistent with the reported median time to onset of 30 days by Salem and colleagues.13 This relatively low prevalence may be related to inadequate screening, particularly since the study includes data starting from 2011,
when the autoimmune side effects of ICI s were just being recognized in a clinical setting. However, the observed incidence of other manifestations of cardiotoxicity was higher than previously suggested.\textsuperscript{13}

Estimates of the incidence of ICI-induced cardiotoxicity vary substantially across reports. This might be explained, in part, by variations in case definitions and a specific focus on certain cardiac syndromes (e.g., myocarditis). Other case series on ICI-induced cardiotoxicity suggest that cardiomyopathy, myocarditis, and conduction abnormalities are under-reported.\textsuperscript{15} The manufacturer of both ipilimumab and nivolumab reported myocarditis (0.09\%) from detailed clinical trial safety data but other cardiovascular irAEs were later described in case reports.\textsuperscript{16–19} In our study, we excluded patients with pre-existing cardiovascular disease from analysis, however this approach might have underestimated the rate of ICI-related cardiotoxicity in the real-world clinical setting as several studies have shown patients with baseline cardiovascular disease are more likely to develop cardiovascular toxicities from cancer therapies.\textsuperscript{4,20,21}

Several studies have also characterized cardiac irAEs and their incidence. Myocarditis was one of the first recognized ICI-related AEs and has been the most studied of the ICI-related cardiotoxicities.\textsuperscript{14} A multicenter registry including patients from the US, Canada, and Germany and found that the prevalence of myocarditis after ICI therapy was 1.14\% with a median time of onset of 34 days, whereas another study reported a median time of 65 days from initiation of treatment.\textsuperscript{10,22} The study of a multicenter registry by Mahmood and colleagues reported that 16 patients developed a major adverse cardiac events and 6 (38\%) occurred in patients with a normal ejection fraction.\textsuperscript{10} Pooled Food and Drug Administration (FDA) data on reported ICI-related adverse events in clinical trials suggested that the risks of cardiomyopathy, arrhythmia, myocarditis, and pericardial disease were 0.53\%, 5.56\%, 0.03\%, and 0.7\%, respectively.\textsuperscript{23} A meta-analysis of clinical trials of PD-1 inhibitors (nivolumab and pembrolizumab) and PD-L1 inhibitors (atezolizumab, avelumab and durvalumab) for treatment of non-small cell lung cancer also reported lower cardiovascular adverse event rates (1\% for cardiorespiratory arrest, 2\% for heart failure, 1\% for myocardial infarction, and 2\% for strokes).\textsuperscript{24} A case series of 30 patients with ICI-related cardiotoxicity, suggested the most frequently observed cardiotoxicities were reduced ejection fraction, arrhythmias, and pericardial disease with almost 80\% of patients having left ventricular systolic dysfunction.\textsuperscript{22}

The incidence of irAEs has been noted to be dose dependent after ipilimumab and pembrolizumab with greater toxicity at higher dose levels.\textsuperscript{7} The differences in incidence of cardiac irAEs reported may be attributable to dose of ICI and future studies should provide details on ICI dosage, number of chemotherapy cycles, and their timing. Dosing of ICIs in clinical practice follows a predominantly fixed-dosing strategy (nivolumab – 240 mg, pembrolizumab – 200 mg) and extended dosing intervals (Q4–Q6 weeks).

Previous studies have also explored early detection of chemotherapy-induced changes in cardiac function using the echocardiographic measures of ejection fraction and/or global longitudinal strain.\textsuperscript{25–28} In the subset of patients in our study who developed cardiotoxicity and had pre- and post-treatment left ventricular ejection fraction (LVEF) and GLS data available, a GLS decline was observed in the absence of a meaningful decrease in LVEF. This small dataset is congruent with the findings from Awadalla et al, who demonstrated GLS decreases were lower in patients with ICI induced myocarditis compared to control patients and was associated with the development of major adverse cardiovascular events.\textsuperscript{29}

Several studies have suggested a potential role for the early initiation of cardioprotective medications including beta blockers and angiotensin system inhibitors to prevent the development of cardiotoxicity associated with anthracyclines and trastuzumab.\textsuperscript{30–32} There is limited data regarding their benefits in the setting of ICI-induced cardiotoxicities. Interestingly, in our study we found that baseline beta-blocker use was associated with increased mortality. There is no reason to consider beta-blockers themselves problematic in patients treated with ICI, rather they likely are a marker of a sicker population with more baseline cardiovascular disease and/or risk factors.

There are several limitations to our study that should be noted. First, varying definitions of cardiotoxicity have been utilized in the literature, and currently there is no standard reference definition. Also, this is a study of retrospectively collected clinical data from ICD codes. As such we were not able to confirm these findings with direct evaluation of the electronic medical records themselves. The use of ICD code groups such as “arrhythmia” and “heart failure” represent a heterogenous collection of diseases thereby impacting the interpretation of the findings. Key biomarkers and imaging (e.g., GLS, EF) data were not measured for all patients before and after therapy. Therefore, we cannot make definitive conclusions about these findings, and we could not definitively attribute cardiac diagnosis to ICI-induced cardiotoxicity. Another limitation is that there was no compliance assessment of medication use and the dose and duration of ICI use were not easily captured. We only had one patient diagnosed with ICI-related myocarditis, so we could not evaluate the effect of corticosteroids\textsuperscript{33} or CTLA-4 agonist abatacept\textsuperscript{34} on the outcome of myocarditis patients. Finally, we cannot attribute the finding of increased mortality in patients with ICI cardiotoxicity to the cardiotoxicity as we were not able to perform competing risk analyses and there was no control group. As such, due these various limitations, the data presented should be considered hypothesis generating only and not lead to definitive conclusions.

**Conclusions**

The results of this analysis suggest that the incidence of ICI-associated cardiotoxicity may be higher than previously suggested. To better address this important knowledge gap, baseline cardiac assessment may be helpful for certain high-risk individuals (e.g., receiving combination ICI therapy,
rapid GLS decline, or a history of cardiac disease). Prospective studies are required to better characterize the incidence of specific cardiotoxicties and identify risk factors as well as long-term complications.

**List Of Abbreviations**

ICI: immune checkpoint inhibitor
CTLA-4: cytotoxic T-cell lymphocyte-associated protein-4
PD-1: the programmed death receptor 1
PD-L1: PD1 ligand
irAE: immune-related adverse events
EHR: electronic health records
UF: University of Florida
CTSI: Clinical and Translational Science Institute
IDR: Integrated Data Repository
HIPAA: Health Insurance Portability and Accountability Act
IRB: Institutional Review Board
ICD: International Classification of Disease
CM: Clinical Modification
GLS: Global longitudinal strain
NT-proBNP: N-terminal pro-brain natriuretic peptide
BNP: brain natriuretic peptide
OR: odds ratio
CI: confidence intervals
CVD: cardiovascular disease
FDA: Food and Drug Administration
LVEF: left ventricular ejection fraction
ACE: Angiotensin converting enzyme
ARB: angiotensin receptor blocker

**Declarations**

**Ethics approval and consent to participate**

This study was approved by University of Florida IRB (IRB# 201702876).

**Consent for publication**

Not applicable.

**Availability of data and materials**

The data that support the findings of this study are available from OneFlorida but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of OneFlorida with appropriate IRB approval.
Competing interests

The authors declare that they have no competing interests.

Funding

Research reported in this publication was supported by the University of Florida Clinical and Translational Science Institute, which is supported in part by the National Institute of Health National Center for Advancing Translational Sciences under award number UL1TR001427. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. The funding body has no role in the design of the study and collection, analysis, and interpretation of data and in writing of the manuscript.

Author's contributions

NW, MFG and YG wrote the manuscript. NW performed the chart review. AM performed the analysis on the echocardiography. YG performed statistical analysis. DD, TYL, GPL, KM, CJP, RMC-D and YW provided important comments to improve the manuscript. YG obtained funding for this study. All authors read and approved the final manuscript.

Acknowledgements

Not applicable.

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**Tables**

**Table 1. Demographic and clinical characteristics of patients treated with immune checkpoint inhibitors**
## Characteristics

|                        | All (n=424) | Cardiotoxicity (n=62) | No cardiotoxicity (n=362) | P      |
|------------------------|-------------|-----------------------|---------------------------|--------|
| **Age (year)**         | 62 ± 13.1   | 64.3 ± 10.2           | 62.1 ± 13.5               | 0.135  |
| **Sex**                |             |                       |                           | 0.924  |
| Women                  | 155 (36.6%) | 23 (37.1%)            | 132 (36.5%)               |        |
| Men                    | 269 (63.4%) | 39 (62.9%)            | 230 (63.5%)               |        |
| **Race/Ethnicity**     |             |                       |                           | 0.772  |
| White (non-Hispanic)   | 361 (85.6%) | 55 (88.7%)            | 306 (85.0%)               |        |
| Black (non-Hispanic)   | 32 (7.6%)   | 4 (6.5%)              | 28 (7.8%)                 |        |
| Hispanic               | 16 (3.8%)   | 1 (1.6%)              | 15 (4.2%)                 |        |
| Other                  | 13 (3.1%)   | 2 (3.2%)              | 11 (3.1%)                 |        |
| **Primary cancer diagnosis** |         |                       |                           | 0.163  |
| Lung cancer            | 126 (29.7%) | 20 (32.3%)            | 106 (29.3%)               |        |
| Melanoma               | 72 (17.0%)  | 16 (25.8%)            | 56 (15.5%)                |        |
| Kidney cancer          | 54 (12.7%)  | 7 (11.3%)             | 47 (13.0%)                |        |
| Head and neck cancer   | 45 (10.6%)  | 6 (9.7%)              | 39 (10.8%)                |        |
| Urothelial carcinoma   | 34 (8.0%)   | 6 (9.7%)              | 28 (7.7%)                 |        |
| Colorectal cancer      | 19 (4.5%)   | 4 (6.5%)              | 15 (4.1%)                 |        |
| Gastrointestinal cancers (other) |     |                       |                           |        |
| Hodgkin Lymphoma       | 7 (1.6%)    | 0                     | 7 (1.9%)                  |        |
| Other cancer           | 59 (13.9%)  | 2 (3.2%)              | 57 (15.8%)                |        |
| **Cardiovascular risk factors** |     |                       |                           |        |
| Hypertension           | 210 (49.5%) | 36 (58.1%)            | 174 (48.1%)               | 0.146  |
| Ischemic heart disease | 54 (12.7%)  | 9 (14.5%)             | 45 (12.4%)                | 0.649  |
| Hyperlipidemia         | 128 (30.2%) | 24 (38.7%)            | 104 (28.7%)               | 0.114  |
| Diabetes               | 76 (17.9%)  | 14 (22.6%)            | 62 (17.1%)                | 0.301  |
| **Other cancer medications** |     |                       |                           |        |
| Doxorubicin            | 14 (3.3%)   | 3 (4.8%)              | 11 (3.0%)                 | 0.464  |
| Carboplatin            | 114 (26.9%) | 18 (29.0%)            | 96 (26.5%)                | 0.68   |
| Paclitaxel             | 88 (20.8%)  | 15 (24.2%)            | 73 (20.2%)                | 0.47   |
| Cyclophosphamide       | 4 (0.9%)    | 1 (1.6%)              | 3 (0.8%)                  | 0.555  |

Values were reported as mean ± standard deviation for continuous variables and frequency (%) for categorical variables.

Table 2. ICI-induced cardiotoxicity
| Immune Checkpoint Inhibitor | Cardiomyopathy, n (%) | Heart failure, n (%) | Arrhythmia, n (%) | Pericardial disease, n (%) | Heart block, n (%) | Myocarditis, n (%) | Any cardiotoxicity, n (%) | Median (IQR) time to cardiotoxicity, days |
|-----------------------------|-----------------------|---------------------|------------------|--------------------------|------------------|------------------|-------------------------|---------------------------------|
| **PD-1 inhibitors**         |                       |                     |                  |                          |                  |                  |                          |                                 |
| nivolumab (n=217)           | 1 (0.46)              | 10 (4.61)           | 15 (6.91)        | 7 (3.23)                 | 6 (2.76)         | 1 (0.46)         | 33 (15.21)              | 52 (37-203)                     |
| pembrolizumab (n=123)       | 0                     | 6 (4.88)            | 3 (2.44)         | 1 (0.81)                 | 1 (0.81)         | 0                | 11 (8.94)               | 65 (30-175)                     |
| **PD-L1 inhibitors**        |                       |                     |                  |                          |                  |                  |                          |                                 |
| atezolizumab (n=17)         | 0                     | 1 (5.88)            | 2 (11.76)        | 0                        | 0                | 0                | 3 (17.65)               | 22 (2-172)                      |
| durvalumab (n=4)            | 1 (25)                | 0                   | 0                | 0                        | 0                | 0                | 1 (25.00)               | 30                              |
| **CTLA-4 inhibitor**        |                       |                     |                  |                          |                  |                  |                          |                                 |
| ipilimumab (n=13)           | 0                     | 4 (30.77)           | 1 (7.69)         | 0                        | 1 (7.69)         | 0                | 6 (46.15)               | 709 (78-1469)                   |
| **CTLA-4 + PD-1/PD-L1 inhibitor combination** | | | | | | | | |
| ipilimumab + nivolumab (n=29) | 2 (6.9)          | 1 (3.45)            | 4 (13.79)        | 0                        | 1 (3.45)         | 0                | 7 (24.14)               | 95 (11-119)                     |
| ipilimumab + pembrolizumab (n=7) | 0                  | 1 (14.29)           | 1 (14.29)        | 0                        | 0                | 0                | 1 (14.29)               | 62                              |
| tremelimumab + durvalumab (n=3) | 0                  | 0                   | 0                | 0                        | 0                | 0                | 0                        |                                 |
| **PD-1/PD-L1 dual sequential** |                       |                     |                  |                          |                  |                  |                          |                                 |
| nivolumab -> pembrolizumab (n=4) | 0              | 0                   | 0                | 0                        | 0                | 0                | 0                        |                                 |
| nivolumab -> atezolizumab (n=3) | 0              | 0                   | 0                | 0                        | 0                | 0                | 0                        |                                 |
| pembrolizumab -> atezolizumab (n=3) | 0              | 0                   | 0                | 0                        | 0                | 0                | 0                        |                                 |
| **Three drug sequential**   |                       |                     |                  |                          |                  |                  |                          |                                 |
| ipilimumab + nivolumab -> pembrolizumab (n=1) | 0              | 0                   | 0                | 0                        | 0                | 0                | 0                        |                                 |
| **Total (n=424)**           | 4 (0.94)             | 23 (5.42)           | 26 (6.13)        | 8 (1.89)                 | 9 (2.12)         | 1 (0.24)         | 62 (14.62)              | 63 (30-175)                     |

Table 3. Use of cardioprotective agents and mortality
| Drug class                   | Total (n=424) | Mortality (%) | p-value |
|-----------------------------|---------------|---------------|---------|
| Beta Blockers               |               |               |         |
| Yes (n=252)                 | 126 (50%)     | 0.013         |         |
| No (n=172)                  | 65 (37.8%)    |               |         |
| ACE Inhibitors              |               |               |         |
| Yes (n=146)                 | 69 (47.3%)    | 0.507         |         |
| No (n=278)                  | 122 (43.9%)   |               |         |
| Angiotensin Receptor Blockers|               |               |         |
| Yes (n=55)                  | 26 (47.3%)    | 0.722         |         |
| No (n=369)                  | 165 (44.7%)   |               |         |
| Statins                     |               |               |         |
| Yes (n=164)                 | 75 (45.7%)    | 0.822         |         |
| No (n=260)                  | 116 (44.6%)   |               |         |

**Supplementary Files**

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- [SupplementalTables090120.docx](#)