# Checkpoint inhibitor monotherapy is associated with less cardiac toxicity than combination therapy


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## INTRODUCTION

- Immune checkpoint inhibitors (ICI) demonstrate impressive clinical benefit across a variety of cancers
- Guidelines now support both ICI monotherapy and ICI combination therapy as options at the same clinical stage for several cancers
- Cardiac toxicity is a rare but catastrophic ICI-related adverse drug reaction (ADR)
- ***We retrospectively analyzed the cardiac events reported for immune checkpoint inhibitor monotherapy versus combination therapy with ipilimumab/nivolumab***

## METHODS

1. Retrospective analysis using **VigiBase**
   - Spontaneous drug safety reports from > 130 countries
   - Administered by the World Health Organization
2. Studied cardiovascular reactions relating to monotherapy (**pembrolizumab, nivolumab, ipilimumab, atezolizumab, durvalumab**) or combination with **ipilimumab/nivolumab**
   - Subcategorized as **myocardial infarction** (MI), **heart failure** (HF), **carditis** (cardiomyopathies, pericarditis, and myocarditis), **new valvular dysfunction, new arrythmias**, and **other**
3. Analyzed using pharmacovigilance method – **Disproportionality Analysis**
   - No comparison group, so use all individuals in the database taking other drugs as comparator
   - If the proportion reporting an event while taking a drug is higher than the proportion taking other drugs with same event = signal of disproportionality
4. Reported both **empirical Bayes estimator** (EBE) and **reporting odds ratio** (ROR)
   - **ROR** = frequentist, similar to relative risk
     - Large variability with small counts
   - **EBE** = Bayesian, less susceptible to low counts
     - Calculates pre and post odds assuming Poisson distribution
5. Per prior work, EBE used for signal, with ROR and 95% CIs calculated for significant signals

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## RESULTS

**Table 2.** Number of reports, expected number, empirical Bayes estimator (EBE), and reporting odds ratio for cardiac events in patients receiving either monotherapy or combination therapy with immune checkpoint inhibitors. EBE reports the lower (5th percentile) bounds of the posterior distribution of odds.

| | Count | Expected Count | Empirical Bayes Estimator | Reporting Odds Ratio (95% CI) |
|---|---|---|---|---|
| **Any cardiac event** | | | | |
| Monotherapy | 2278 | 3350 | 0.7 | NA |
| Combination Therapy | 353 | 410 | 0.8 | NA |
| **Heart Failure** | | | | |
| Monotherapy | 313 | 333.2 | 0.9 | NA |
| Combination Therapy | 25 | 40.8 | 0.4 | NA |
| **Myocardial Infarction** | | | | |
| Monotherapy | 415 | 753.6 | 0.5 | NA |
| Combination Therapy | 48 | 92.3 | 0.4 | NA |
| **Carditis** | | | | |
| Monotherapy | 630 | 128.6 | **4.6** | **5.0 (4.6-5.4)** |
| Combination Therapy | 107 | 15.8 | **5.7** | **6.9 (5.7-8.3)** |
| **Arrythmia** | | | | |
| Monotherapy | 701 | 1105.0 | 0.6 | NA |
| Combination Therapy | 150 | 135.4 | 1.0 | NA |
| **Valvular Dysfunction** | | | | |
| Monotherapy | 9 | 109.9 | 0.05 | NA |
| Combination Therapy | 2 | 13.5 | 0.05 | NA |
| **Other** | | | | |
| Monotherapy | 210 | 912 | 0.20 | NA |
| Combination Therapy | 21 | 111.7 | 0.13 | NA |

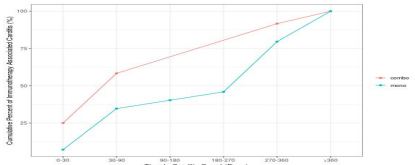


**Figure 1.** Cumulative incidence of time to carditis onset from initiation of atezolizumab (red) durvalumab (yellow) ipilumumab (green) nivolumab (blue) pembrolizumab (pink) or combination ipilimumab/nivolumab (teal).

| Drug Indication | Cardiac events n (%) |
|---|---|
| Bladder and Upper Tracts | 86 (3.3) |
| Brain | 7 (0.2) |
| Breast | 25 (0.9) |
| Colon | 21 (0.8) |
| Gynecologic | 37 (1.4) |
| Head and Neck | 59 (2.2) |
| Hematologic | 78 (3.0) |
| Kidney | 209 (7.9) |
| Lung | 1005 (38.1) |
| Melanoma | 514 (19.5) |
| Non-colon GI | 46 (1.7) |
| Non-melanoma skin | 13 (0.5) |
| Other | 282 (10.7) |
| Prostate | 18 (0.7) |

**Table 3.** Number of cardiac events by indication

**Table 1**. Characteristics of cardiac ADRs associated with ICI monotherapy vs combination therapy in VigiBase (last accessed 11/23/2019).[+,*]

| Adverse Drug Reaction | Monotherapy (n=2278) | Combination Therapy (n=353) | Total (n=2631) |
|---|---|---|---|
| **Region Reporting** | | | |
| Americas | 1,012 (44.4) | 259 (73.4) | 1,271 (48.3) |
| Europe | 877 (38.5) | 83 (23.5) | 960 (36.5) |
| Australia | 368 (16.2) | 11 (3.1) | 379 (14.4) |
| Asia | 12 (0.5) | 0 (0.0) | 12 (0.5) |
| Africa | 3 (0.1) | 0 (0.0) | 3 (0.1) |
| Eastern Mediterranean | 6 (0.3) | 0 (0.0) | 6 (0.2) |
| **Reported Outside Clinical Trial** | 1420 (62.3) | 134 (38.0) | 1,554 (59.1) |
| **Reported by non-healthcare worker** | 283 (12.5) | 65 (18.5) | 348 (13.3) |
| **Age at onset (years)** | | | |
| 75 or older | 420 (18.4) | 50 (14.2) | 470 (17.9) |
| 65-74 | 623 (27.3) | 105 (29.7) | 728 (27.7) |
| 45-64 | 526 (23.1) | 86 (24.4) | 612 (23.3) |
| < 45 | 84 (3.7) | 20 (5.6) | 104 (4.0) |
| unknown | 625 (27.4) | 92 (26.1) | 717 (27.3) |
| **Male Sex** | 1431 (66.6) | 194 (61.4) | 1625 (65.9) |
| **Suspected drugs** | | | |
| Only drug of interest | 1786 (78.4) | 288 (81.6) | 2074 (78.8) |
| 1 other drug | 282 (12.4) | 37 (10.5) | 319 (12.1) |
| 2+ other drugs | 210 (9.2) | 28 (7.9) | 238 (9.0) |
| **Time to ADR (days): mean (SD)** | 83.4 (133.2) | 100.1 (167) | 84.4 (135.3) |
| **Severe ADR*** | 1841 (84.1) | 308 (88.3) | 2149 (84.7) |
| **Death as outcome** | 430 (18.9) | 58 (16.4) | 488 (18.5) |

* Values are reported as n (%) or n/N (%) unless otherwise indicated
+ Percentage ratios may vary by category owing to missing data (i.e., 1 event may account for a different column percent in Region Reporting vs Time to ADR)
* Defined in VigiBase as life-threatening, leading to persistent or significant disability, birth defect, congenital anomaly, or to any other medically important condition, requiring hospitalization of causing death

## CONCLUSIONS

- ***We found increased risks for myocarditis and pericarditis for all immune checkpoint inhibitor therapy, with higher risks for combination therapy compared to monotherapy***
- These events were frequently fatal
- The next step is to identify patients at high risk of cardiac complications

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