41P: Cardiotoxicity of Immune Checkpoint Inhibitors: a Systematic Review and Meta-Analysis of Randomized Clinical Trials

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Background

- **Immune checkpoint inhibitors (ICI)** represent a class of drugs that has dramatically **improved the outcomes of several cancers**, including melanoma, non-small cell lung cancer (NSCLC), renal cancer and hematological malignancies (1)
- The toxicity of ICI is different to other cancer treatments: due to their mechanism of action, treatment related adverse events (AEs) are **mostly immune-related AEs** which can **affect any organ**, including the **cardiovascular system** (2,3)
- The WHO database shows that the **mortality associated with ICI-related myocarditis** ranges from **36% to 67%** (4)
- Although there is increasing awareness of **cardiotoxicity induced by ICI**, its incidence in the most recent data has **not been systematically analyzed**

Methods & Objectives

- This systematic review and meta-analysis was conducted according to PRISMA guidelines and was registered in the PROSPERO database (ID: CRD42020183524)
- The **primary objective** was to assess whether ICI, either alone or in combination with other non-ICI treatment, are associated with a higher risk of cardiac AEs compared to other cancer treatments.
- The **secondary objective** was to compare the risk of cardiotoxicity associated with dual-agent ICI (immunotherapy combinations) with the risk of cardiotoxicity associated with single-agent ICI.
- Systematic search of PubMed, MEDLINE, Embase databases, and conference proceedings up to June 30, 2020.
- Inclusion of all randomized clinical trials comparing ICI with other treatments (primary objective) or dual-agent ICI vs single-agent ICI (secondary objective) in any solid tumor
- Pooled risk ratios (RR) with 95% confidence intervals (95%CI) for cardiotoxicity events were calculated using random effect models.
- **Subgroup analyses** were performed to evaluate the impact of tumor type, setting of disease, line of treatment, major class of ICI, type of ICI combination, presence of treatment associated with ICI (yes or no), type of treatment associated with ICI (where applicable), and type of treatment in the control arm.

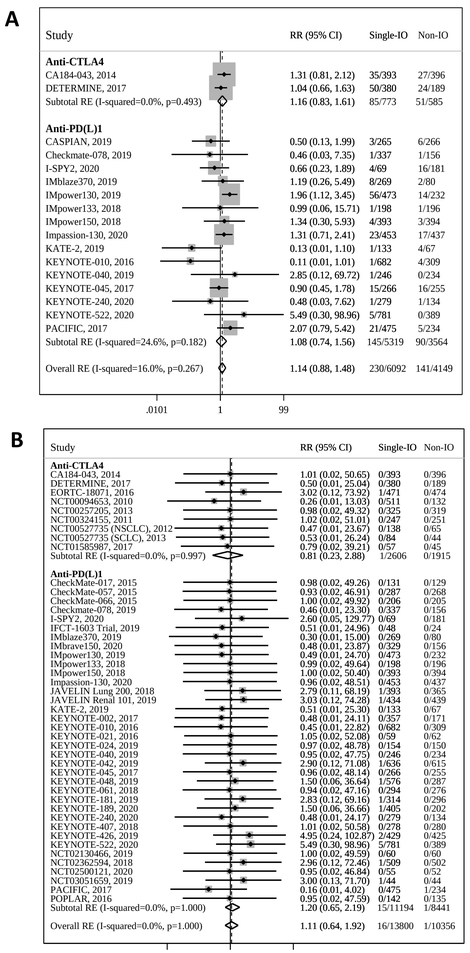
Results

- **Eighty studies** including **35,337 patients** were included in the analysis (66 studies with 34,664 patients for the primary endpoint and 14 studies with 673 patients for the secondary endpoint)
- Overall, any cardiac AEs occurred in ≤4% of patients and myocarditis in ≤0.2% of patients (Table 1).
- **No significant differences in terms of cardiac AEs** were observed between ICI and non-ICI groups (RR 1.14, 95%CI 0.88-1.48, p=0.326) (Fig. A) nor between dual-ICI and single-ICI groups (RR 1.91, 95%CI 0.52-7.01, p=0.329) (Fig. C)
- **Myocarditis** incidence **did not significantly differ** between ICI and non-ICI groups (RR 1.11, 95%CI 0.64-1.92, p=0.701) (Fig. B) nor between dual-ICI and single-ICI groups (RR 1.10, 95%CI 0.31-3.87, p=0.881) (Fig D).
- No differences were observed in subgroup analyses according to tumor type, setting of disease, treatment line, and type of treatment.
- Funnel plots of reported cardiac endpoints are shown in figures A1-D1.

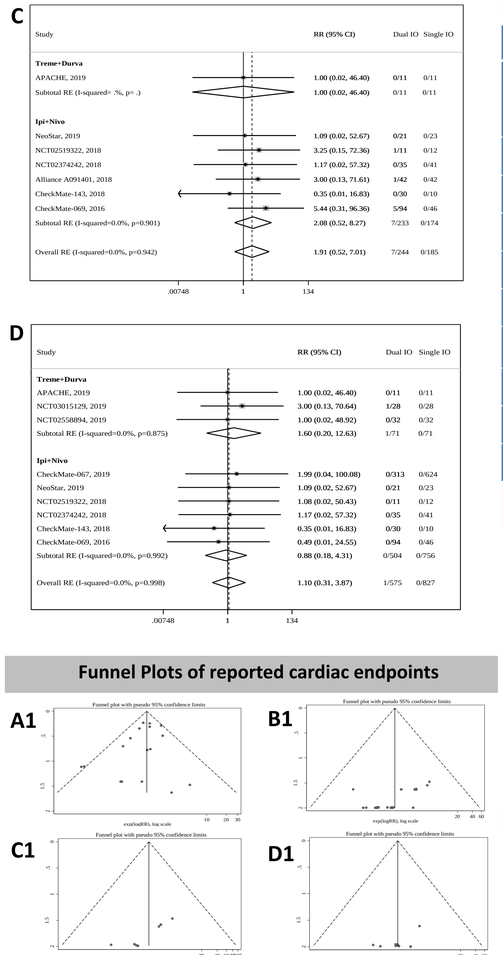
References

1. *Ramos-Casals M et al., Nat Rev Dis Primers 2020*
2. *Haanen JBAG et al., Ann Oncol 2017*
3. *Brahmer JR et al., J Clin Oncol 2018*
4. *Brumbaugh AD et al., Cardiol Rev 2019*

Forest Plots for "all cardiac events (any)" (A) and "myocarditis events" (B) in Single ICI vs non-ICI group



Forest Plots for "all cardiac events (any)" (C) and "myocarditis events" (D) in Dual ICI vs Single-ICI group



Funnel Plots of reported cardiac endpoints

Table 1 – Number of cardiac adverse events per number of patients, pooled incidence, and relative risk-ratios with 95% confidence intervals in the immune-checkpoint inhibitors (ICI) group vs non-ICI group and in the dual-ICI group vs single-ICI group.

	ICI vs non-ICI groups			Dual ICI vs Single ICI groups		
	ICI-group events/N (%)	Non-ICI group events/N (%)	RR (95% CI)	Dual ICI events/N (%)	Single ICI events/N (%)	RR (95% CI)
Any cardiac AEs	230/6092 (3.78)	141/4149 (3.40)	1.14 (0.88-1.48), p=0.326	7/244 (2.87)	1/248 (0.40)	1.91 (0.52-7.01), p=0.329
Myocarditis	16/13800 (0.12)	1/10356 (0.01)	1.11 (0.64-1.92), p=0.701	2/1151 (0.17)	0	1.10 (0.31-3.87), p=0.881
Myocardial infarction	27/6607 (0.41)	12/4477 (0.27)	1.19 (0.63-2.23), p=0.596	1/202 (0.50)	0	0.98 (0.21-4.47), p=0.978
Pericarditis	31/6113 (0.51)	9/4162 (0.22)	1.14 (0.62-2.10), p=0.668	0	1/206 (0.49)	0.67 (0.16-2.76), p=0.580
Arrhytmias	104/5826 (1.79)	58/3894 (1.49)	1.32 (0.94-1.84), p=0.108	5/202 (2.48)	0	1.65 (0.40-6.89), p=0.491
Heart failure	28/6548 (0.43)	28/4415 (0.63)	0.61 (0.35-1.07), p=0.087	1/263 (0.38)	0	1.04 (0.25-4.26), p=0.962
Valvular disease	0	1/3894 (0.03)	0.63 (0.24-1.64), p=0.340	0	0	0.79 (0.16-3.83), p=0.770
Cardiac arrest	19/7854 (0.24)	5/5399 (0.09)	1.23 (0.61-2.47), p=0.558	0	0	0.79 (0.16-3.83), p=0.770
Cardiac death	55/16620 (0.33)	27/12987 (0.21)	1.07 (0.72-1.59), p=0.751	4/1458 (0.27)	0	1.28 (0.48-3.42), p=0.623

Conclusions

- In our meta-analysis of RCT, **use of ICI** was **not associated** with a higher **risk of cardiotoxicity** compared to non-ICI treatments. Moreover, **ICI combinations** were **not associated** with a higher **risk of cardiotoxicity** compared to ICI in monotherapy, which is **reassuring for patients.**
- Our study is the **largest meta-analysis** to date of cardiotoxicity induced by ICI, and we investigated not only myocarditis events, which are known to have a potential immune-related aetiology, but also a **broader range of cardiac AEs** including myocardial infarction, pericarditis, heart failure, arrhythmias, valvular disease, cardiac arrest and cardiac death.
- Nonetheless, **not all studies** included in the meta-analyses provided **complete data about cardiac AEs** among participants. Several studies presented only AEs occurring above a specified incidence, which might have ranged from 1% to 20%. This could favour **underreporting of rare AEs**, like cardiac events, and could mask the real incidence of this toxicity
- Despite the apparent cardiac safety of ICI, investigators of clinical trials should be strongly encouraged to **report cardiac AEs** systematically and **as completely as possible**

Disclosures

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