Cardiotoxicity with immune system targeting drugs: a meta-analysis of anti-PD/PD-L1 immunotherapy randomized clinical trials

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Background: With antiprogrammed death receptor-1 (anti-PD-L1) therapy, a recent meta-analysis reported higher incidence of cutaneous, endocrine and gastrointestinal complications especially with dual anti-PD-L1 immunotherapy (IMM). **Methods:** Our primary outcome was assessment of all cardiotoxicity grades in IMM compared with different treatments, thus a systemic review and a meta-analysis on randomized clinical trials (RCTs) were done. **Results:** We included 11 RCTs with 6574 patients (3234 patients in IMM arm vs 3340 patients in the other arm). Three non-small-cell lung cancer RCTs, seven melanoma RCTs and only one prostatic cancer RCT met the inclusion criteria. There were five RCTs that compared monoimmunotherapy to chemotherapy "(n = 2631 patients)". No difference exists in all cardiotoxicity grades or high-grade cardiotoxicity (p > 0.05). Lung cancer exhibited a higher response rate and lower mortality in IMM. **Conclusion:** There was no reported statistically significant cardiotoxicity associated with anti-PD/PD-L1 use. Lung cancer subgroups showed better response and survival rates.

In the era of immunotherapy, specifically, immune-checkpoint blocking antibodies as antiprogrammed death receptor-1 (anti-PD/PD-L1) and anticytotoxic T lymphocyte-associated antigen 4 (anti-CTLA-4) used in various malignancies, mainly melanoma, non-small-cell lung cancer (NSCLC) and renal cell carcinoma, a plethora of immune-mediated adverse events have been frequently encountered. In previous case series and meta-analyses, a higher incidence of cutaneous, gastrointestinal and endocrine complications was reported with anti-PD-L1 therapy and some even reported cadiotoxicity. Consequently, a higher incidence with dual anti-PD-L1 therapy was reported [1–4]. In this study, our aim was to determine if anti-PD/PD-L1 had higher incidence of cardiotoxicity compared with other treatment protocols.

Methods

Search strategy and study selection of this systematic review were conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [5]. In February 2017, the PubMed,

MEDLINE and EMBASE databases were searched for publications containing anti-PD/PD-L1 immunotherapy (IMM) by the words 'Atezolizumab' OR 'Avelumab' OR 'BMS936559' OR 'Durvalumab' OR 'Ipilimumab' OR 'Nivolumab' OR 'Pembrolizumab' OR 'Pidilizumab' OR 'Tremelimumab' that were obtained from a previously published review [6]. All studies comparing mono-immunotherapy versus other single/multiple treatments and reporting any cardiac complications were identified. Cardiac complications included arrhythmias as ventricular tachycardia and atrial fibrillation, pericardial effusion, pericarditis, myocardial infarction, cardiac myositis, cardiomyopathy, death from cardiac arrest or acute heart failure [4].

The bibliography of all studies and any related meta-analyses were searched to identify further articles that potentially could be recruited, in other words, backward snowballing.

Inclusion criteria for the present analysis were: cancer-related, Phase (II/III), randomized clinical trials (RCTs) on humans published in English language with availability of full article that reports any previously mentioned cardiotoxicity.

In case of absence of monoimmunotherapy in one treatment arm, the study was excluded. In case of multiple publications from the same center or overlapping between studies, only the publication with the largest sample size was considered. Non-English studies, studies on animals, case reports, review articles, editorials and expert opinions were also excluded.

Two authors (M Baudo and M Rahouma) independently inspected the electronic reports identified by the searches. In case of discrepancies, they were resolved by the third author (M Gaudino) opinion and consensus meeting.

The quality of included studies was assessed using The Cochrane Collaboration's tool for assessing risk of bias in RCTs [7] (Supplementary figure 1).

Study outcomes

Cardiotoxicity grades in IMM in comparison to other treatments were our primary end point. The secondary end points were: comparing cardiotoxicity grades in IMM to others in lung cancer and subgroups; the cardiotoxicity grade difference in between IMM and other studies having lung cancer and other cancer subgroups and in IMM compared with chemotherapy (CTH)-only studies; outcome of IMM compared with others (in all studies and in lung cancer/other cancers subgroups) as well as in IMMs compared with CTH only studies; and difference in mortality in the same groups. High-grade adverse events were defined as grade 3 or higher identified by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAEv.4) [8] that means Severe, Life-threatening and Death for grade 3, 4 and 5, respectively.

Data extraction & statistical analysis

Microsoft Office Excel 2010 (Microsoft, Redmond, Washington) was the used program for data extraction. Continuous variables are expressed as median (25th, 75th percentile) or as mean $\pm$ standard deviation. Categorical variables are reported as (%).

Study design, study period, country, study center, trial Phase (II/III), cancer type, comparison arms, doses of drug administered, inclusion/exclusion criteria, treatments arms and sample size were documented. The following patient characteristics were registered: age, sex, smoking, Eastern Cooperative Oncology Group performance status (ECOG-PS), stage, cardiotoxicity complications (see earlier; all grade/high grade), response (complete and partial responders were considered as responders) and all-cause mortality.

All-cause mortality was derived from Kaplan–Meier overall survival curves at the end of follow-up using a previously described method [9–11] with aid of GetData Graph Digitizer software 2.26 (http://getdata-graph-digitizer.com/). Relative ratios (RR) with 95% confidence intervals (95% CI) for cardiotoxicity events were calculated by means of the DerSimonian-Laird (inverse variance [IV]) method [12]. Exploiting the assumption that HRs are asymptotically similar to relative risks, we calculated relative risks according to the formula described by Grant *et al.* [13]. Random-effect model was used for statistical outcome pooling, computing risk estimates with CI and in case of heterogeneity (I^2) >25, otherwise, fixed model was used.

Funnel plots were used for assessment of publication bias by graphical inspection. We have set the hypothesis testing for equivalence using the two-tailed 0.05 level. The hypothesis testing for statistical homogeneity was setting the two-tailed 0.10 level. Cochran Q-test was used as a base with I^2 values of 25, 50 and 75%. (each of those value show mild, moderate and severe homogeneity)
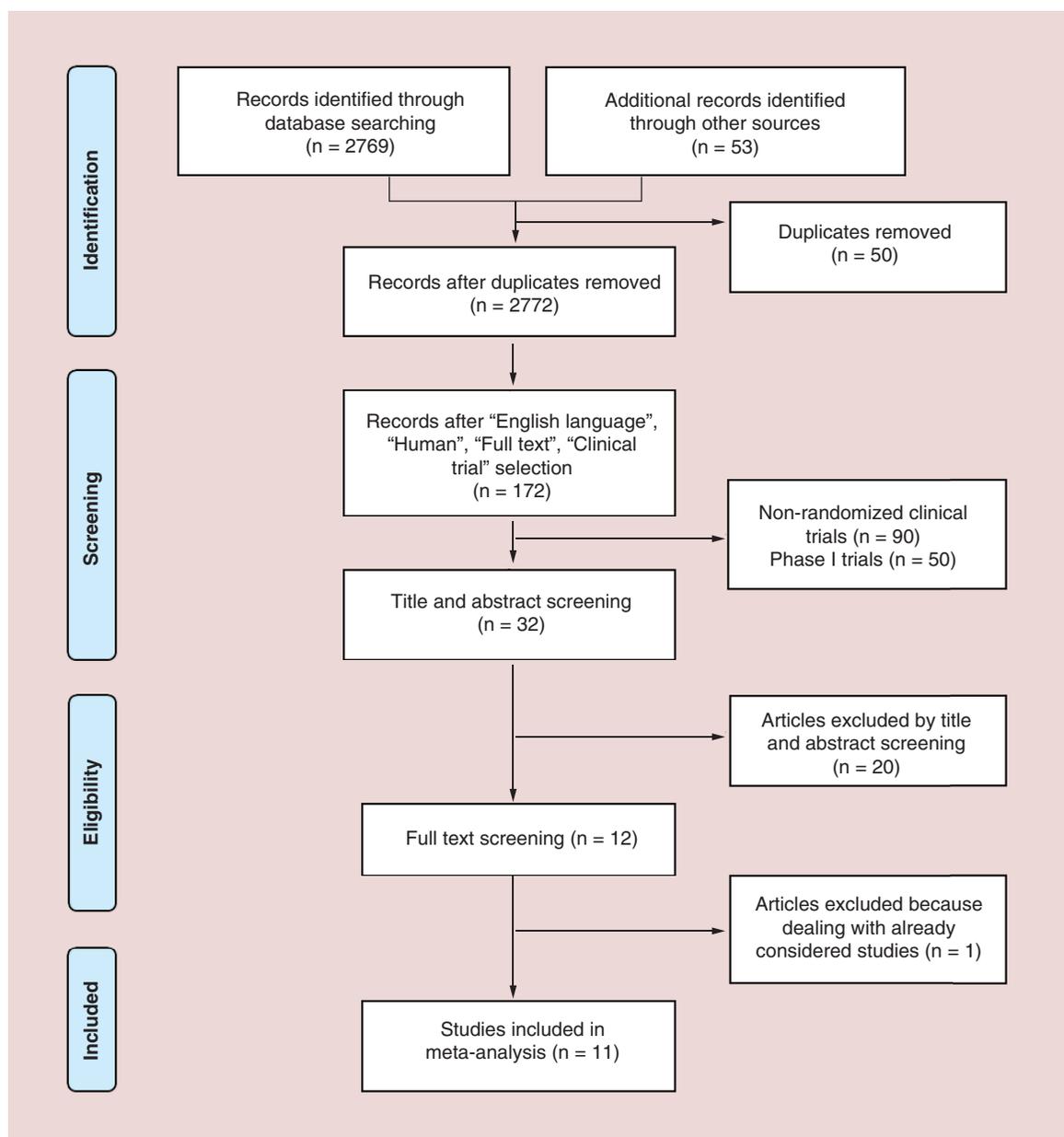
Figure 1.   PRISMA flowchart of our recruited articles. Among 2769 searched articles from database searching and 53 additional articles, 11 articles met our inclusion criteria.

We used Review Manager version 5.3 to do this meta-analysis and comprehensive meta-analysis version 2 for sensitivity analysis using 'one study removed analysis'.

Results

Eligible studies & characteristics of studies

Figure 1 shows an outline of the systematic review process. We identified 2822 studies for clinical outcomes, which ended at 2772 studies after removal of duplicates. We also assessed 32 full text articles for eligibility. Eleven RCTs met our inclusion criteria, we included 6574 patients. We found 3234 (49.19%) patients in IMM arm and in the other arm we had 3340 (50.88%) patients. We analyzed three NSCLC RCTs that included 1588 patients, subclassification of those showed 782 in IMM arm and 776 in other arm. Moreover, seven RCTs were included for melanoma patients (n = 4190), and only one RCT for prostate cancer that had been included according our inclusion
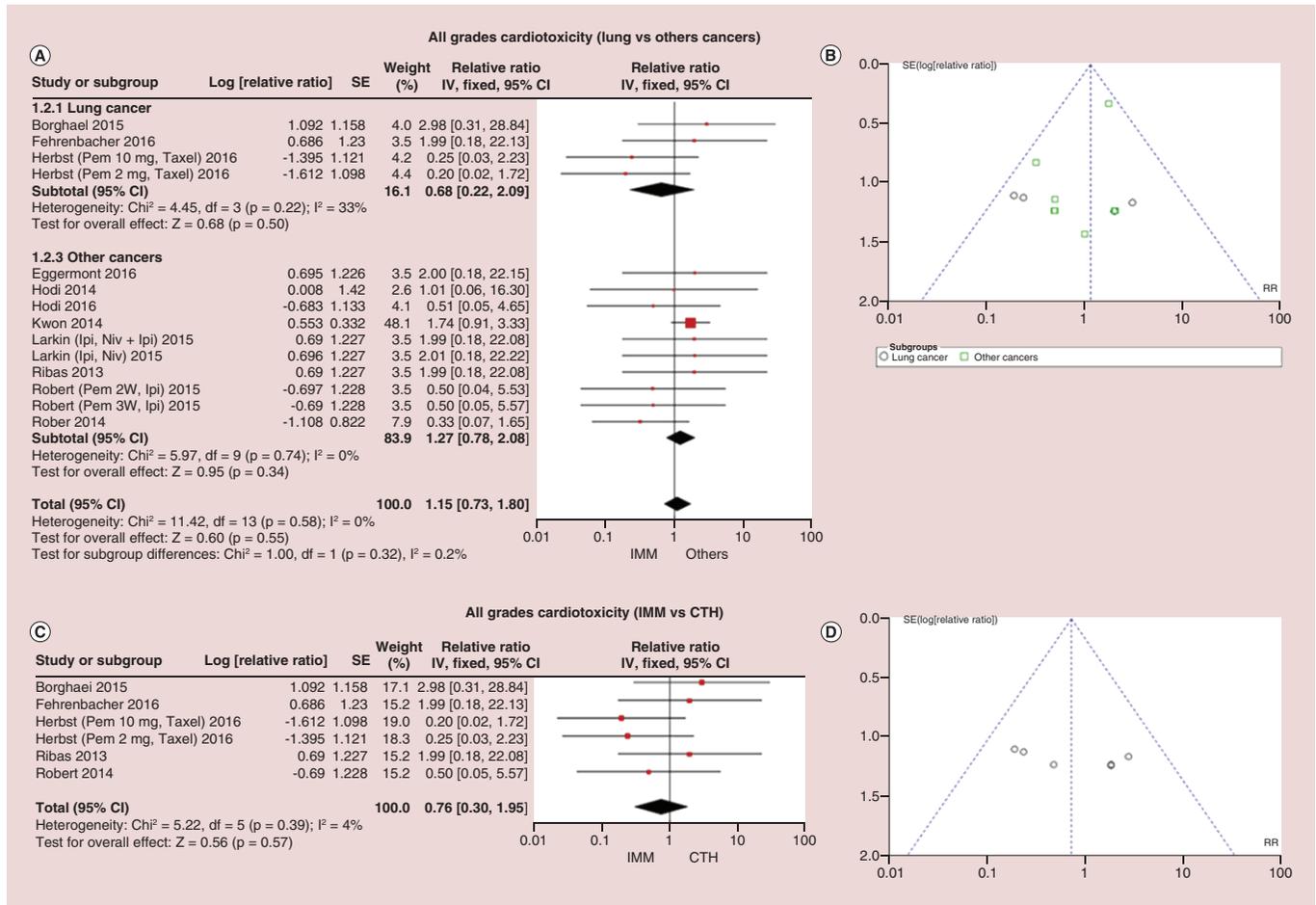
Figure 2.   Forest & Funnel plots of all-grade cardiotoxicity in different subgroups. (A & B) Forest & Funnel plots of lung versus other cancers studies. **(C & D)** Forest & Funnel plots of immunotherapy versus chemotherapy-only studies.

criteria. In addition to the above-mentioned studies, we included five RCTs that compared monoimmunotherapy to CTH (four studies used docetaxel, one study used temozolomide or dacarbazine), those studies had 2631 patients, subclassification showed 1320 in IMM arm and 1311 patients in CTH arm. The pooled mean follow-up was 18.69 and 18.52 months in IMM and other arm, respectively. Criteria of the included studies are shown in Table 1 and Supplementary Table 1.

Meta-analysis of the outcomes
Cardiotoxicity in immunotherapy

There was no difference in all grades cardiotoxicity among all recruited studies (RR: 1.15; 95% CI: 0.73–1.80; p = 0.55) or in subgroups of lung cancer (RR: 0.68; 95% CI: 0.22–2.09; p = 0.50) or other cancers (RR = 1.27; 95% CI: 0.78–2.08; p = 0.34) (Figure 2). One study removed analysis for all grades cardiotoxicity was shown in Supplementary Figure 1. Similarly, no difference in high grades cardiotoxicity among all recruited studies (RR: 1.47; 95% CI: 0.87–2.46; p = 0.15) or in subgroups of lung cancer (RR: 0.80; 95% CI: 0.25–2.50; p = 0.70) or other cancers (RR: 1.71, 95% CI: 0.96–3.06; p = 0.07) (Supplementary Figure 3; Table 2).

Response in immunotherapy

No difference in response between comparative arms (IMM vs others) could be identified (RR: 1.41; 95% CI: 0.91–2.17; p = 0.12). While lung cancer showed a higher response rate (RR: 1.65; 95% CI: 1.27–2.15; p = 0.0002), no statistically significant difference in response regarding other types of cancers could be identified but heterogeneity exists (I2 = 93; p < 0.0001). On restricting studies to those comparing response in IMM versus CTH only,

Table 1. Criteria of the included studies.

Study [ref.]	Year	Study period	Country	Center	Study type	Trial phase	Cancer type	Comparison arms (immunotherapy vs CTH)	Doses of drug administration
Borghaei et al. [14]	2015	2012–2013	International	Multicenter	RCT	Phase III	NSCLC	Nivolumab vs docetaxel	Nivolumab 3 mg/kg vs docetaxel 75 mg/m²
Eggermont et al. [15]	2016	2008–2011	International	Multicenter	RCT	Phase III	Melanoma	Ipilimumab vs placebo	Ipilimumab 10 mg/kg vs placebo
Fehrenbacher et al. [16]	2016	2013–2014	International	Multicenter	RCT	Phase II	NSCLC	Atezolizumab vs docetaxel	Atezolizumab 1200 mg vs docetaxel 75 mg/m²
Herbst et al. [17] (Pem 2 mg vs Taxol)	2016	2013–2015	International	Multicenter	RCT	Phase II/III	NSCLC	Pembrolizumab vs docetaxel	Pembrolizumab 2 mg/kg vs docetaxel 75 mg/m²
Herbst et al. [17] (Pem 10 mg vs Taxol)	2016	2013–2015	International	Multicenter	RCT	Phase II/III	NSCLC	Pembrolizumab vs docetaxel	Pembrolizumab 10 mg/kg vs docetaxel 75 mg/m²
Hodi et al. [18]	2014	2010–2011	US-based	Multicenter	RCT	Phase II	Melanoma	Ipilimumab vs Ipilimumab + sargramostim	Ipilimumab 10 mg/kg iv. plus sargramostim 250 µg
Hodi et al. [19]	2016	2013–2014	USA + France	Multicenter	RCT	Phase II	Melanoma	Ipilimumab + placebo vs nivolumab + ipilimumab	Nivolumab 1 mg/kg plus ipilimumab 3 mg/kg or ipilimumab 3 mg/kg plus placebo
Kwon et al. [13]	2014	2009–2012	International	Multicenter	RCT	Phase III	Prostate cancer	Ipilimumab vs placebo	Ipilimumab 10 mg/kg or placebo
Larkin et al. [20] (Ipi vs Niv)	2015	2013–2014	International	Multicenter	RCT	Phase III	Melanoma	Nivolumab alone, nivolumab plus ipilimumab, or ipilimumab alone	3 mg/kg of Nivolumab (plus ipilimumab-matched placebo); or 3 mg /kg of ipilimumab (plus Nivolumab-matched placebo)
Larkin [20] (Ipi vs Niv + Ipi)	2015	2013–2014	International	Multicenter	RCT	Phase III	Melanoma	Nivolumab alone, nivolumab plus ipilimumab, or ipilimumab alone	1 mg/kg of nivolumab plus 3 mg/kg of ipilimumab, followed by 3 mg/kg of nivolumab for cycle 3 and beyond; or 3 mg/kg of Ipilimumab (plus nivolumab-matched placebo)
Ribas et al. [21]	2013	2006–2007	International	Multicenter	RCT	Phase III	Melanoma	Tremelimumab vs standard of care CTH (temozolomide or dacarbazine)	Tremelimumab 15 mg/kg vs (dacarbazine 1000 mg/m² or temozolomide 200 mg/m²)
Robert et al. [22]	2014	2013–2014	International	Multicenter	RCT	Phase III	Melanoma	Nivolumab vs dacarbzine	Nivolumab 3 mg/kg vs dacarbazine 1000 mg/m²
Robert et al. [23] (Pem 2W vs Ipi)	2015	2013–2014	International	Multicenter	RCT	Phase III	Melanoma	Pembrolizumab every 2 weeks vs ipilimumab	Pembrolizumab 10 mg/kg or ipilimumab 3 mg/kg
Robert et al. [23] (Pem 3W vs Ipi)	2015	2013–2014	International	Multicenter	RCT	Phase III	Melanoma	Pembrolizumab every 2 weeks vs pembrolizumab every 3 weeks vs ipilimumab	Pembrolizumab 10 mg/kg or ipilimumab 3 mg/kg

NSCLC: Non-small-cell lung cancer; RCT: Randomized clinical trial.

Table 2. Summary of outcomes among anti PD-L1 immunotherapy recruited studies.					
Outcome or subgroup	Studies	Effect estimate (RR; 95% CI)	Heterogeneity (I^2), p-value	Overall effect	Favors
I. Cardiotoxicity in immunotherapy					
All grades cardiotoxicity (All studies)	11	1.15 (0.73, 1.80)	$I^2 = 0$; p = 0.58	Z = 0.60; p = 0.55	None
All grades cardiotoxicity in immunotherapy (lung vs others subgroups)					
● Lung cancer	3	0.68 (0.22, 2.09)	$I^2 = 33$; p = 0.22	Z = 0.68; p = 0.50	None
● Other cancers	8	1.27 (0.78, 2.08)	$I^2 = 0$; p = 0.74	Z = 0.95; p = 0.34	None
All grades cardiotoxicity in immunotherapy (IMM vs CTH only)	5	0.76 (0.30, 1.95)	$I^2 = 4$; p = 0.39	Z = 0.56; p = 0.57	None
High-grade cardiotoxicity (all studies)	11	1.47 (0.87, 2.46)	$I^2 = 0$; p = 0.72	Z = 0.45; p = 0.15	None
High-grade cardiotoxicity in immunotherapy (lung vs others subgroups)					
● Lung cancer	3	0.80 (0.25, 2.50)	$I^2 = 14$; p = 0.32	Z = 0.39; p = 0.70	None
● Other cancers	8	1.71 (0.96, 3.06)	$I^2 = 0$; p = 0.85	Z = 1.82; p = 0.07	None
High-grade cardiotoxicity in immunotherapy (IMM vs CTH only)	5	0.95 (0.36, 2.50)	$I^2 = 0$; p = 0.56	Z = 0.10; p = 0.92	None
II. Response in IMM					
Response in IMM vs others	10	1.41 (0.91, 2.17)	$I^2 = 90$; p < 0.0001	Z = 1.55; p = 0.12	None
Response in lung vs other cancers	10	1.41 (0.91, 2.17)			
● Lung cancer	3	1.65 (1.27, 2.15)	$I^2 = 13$; p = 0.33	Z = 3.74; p = 0.0002	IMM
● Other cancers	7	1.32 (0.71, 2.45)	$I^2 = 93$; p < 0.0001	Z = 0.87; p = 0.38	None
Response in IMM vs CTH	5	1.68 (1.25, 2.26)	$I^2 = 53$; p = 0.06	Z = 3.46; p < 0.001	IMM
III. OS at end of follow-up					
OS at end of follow-up (all studies)	10	0.84 (0.69, 1.02)	$I^2 = 59$; p = 0.005	Z = 1.77; p = 0.08	None
OS at end of follow-up (lung vs other cancers)	10	0.84 (0.69, 1.02)			
● Lung cancer	3	0.80 (0.65, 0.97)	$I^2 = 0$; p = 0.83	Z = 2.24; p = 0.03	IMM
● Other cancers	7	0.86 (0.63, 1.16)	$I^2 = 72$; p < 0.001	Z = 1.00; p = 0.32	None
OS at end of follow-up (IMM vs CTH)	5	0.73 (0.56, 0.95)	$I^2 = 58$; p = 0.04	Z = 2.35; p = 0.02	IMM

CTH: Chemotherapy; IMM: Immunotherapy; OS: Overall survival; RR: Relative ratio.

immunotherapy arm showed a higher response rate (RR: 1.68; 95% CI: 1.25–2.26; p < 0.001) (Figure 3 & Table 2).

End of follow-up overall mortality

There was no statistically significant difference in the end of follow-up overall mortality in immunotherapy versus others in all recruited studies (RR: 0.84; 95% CI: 0.69–1.02; p = 0.08), but heterogeneity exists ($I^2 = 59$; p = 0.005). On subgroups analysis, patients received immunotherapy showed lower mortality versus the other arm in lung cancer (RR: 0.80; 95% CI: 0.65–0.97; p = 0.03), but this was not statistically evident in the other included types of cancer (RR: 0.86; 95% CI: 0.63–1.16; p = 0.32) but heterogeneity exists ($I^2 = 72\%$; p = 0.0007). After including IMM versus CTH studies only, lower mortality was evident in IMM arm (RR: 0.73; 95% CI: 0.56–0.95; p = 0.02) (Figure 4).

Outcomes summary is shown in Table 2.

Discussion

Up-to-date and up-to-our knowledge, this is the first meta-analysis reporting cardiotoxicity outcomes in immunotherapy.

With the current era of immunotherapy in cancer treatment, we aimed to assess the cardiotoxicity associated with anti-PD/PD-L1 use that included arrhythmias, pericardial effusion or inflamation, myocardial infarction, cardiac myositis, cardiomyopathy, death from cardiac arrest or acute heart failure. Four Prior RCT reported two cases of cardiac arrest and two cases of cardio-respiratory arrest in Ipilimumab 10 mg/kg arm when compared with placebo-related death [16] and another one reported acute cardiac failure-related mortality in Atezolizumab 1200 mg when compared with Docetaxel 75 mg/m² [17]. Myocardial infarction death was reported in Herbst *et al.* three arm trial when they compared Pembrolizumab 10 mg versus docetaxel arms but not in Pembrolizumab
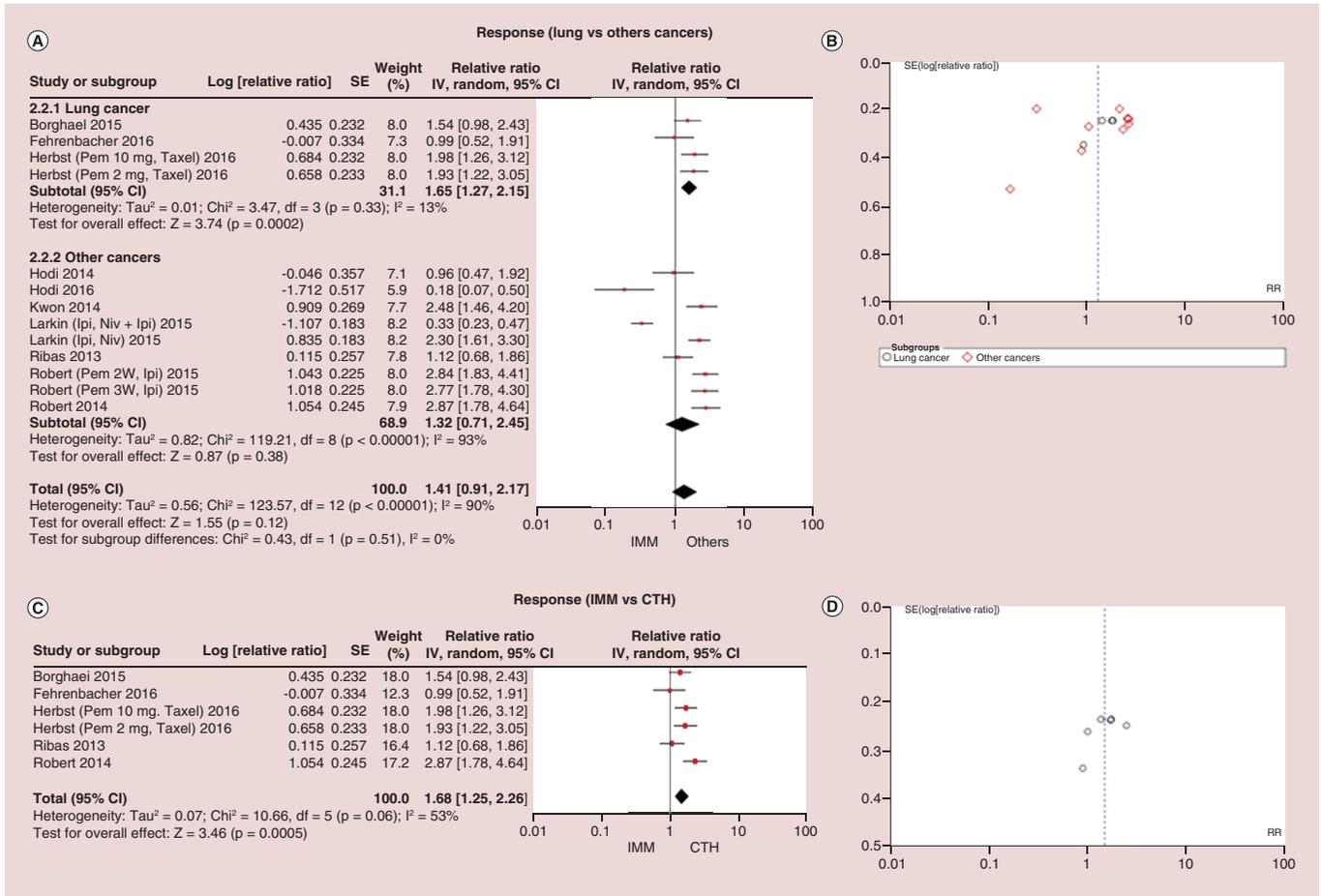
Figure 3.   Forest & Funnel plots of response in different subgroups. (A & B) Forest & Funnel plots of lung versus other cancers studies. **(C & D)** Forest & Funnel plots of immunotherapy versus chemotherapy-only studies.

2 mg versus docetaxel arms [14,15]. So, we aimed to pool many studies to identify the actual incidence and properly estimate the risk of those apparently rare events with such effective treatments. No difference in all/high grades cardiotoxicity was evident in our meta-analysis.

No difference in response except after comparing IMM versus CTH only and in RCTs on lung cancer patients. Although individual studies showed better response to IMM but pooling of several studies with heterogeneous pathology omit this response difference; however, this statistical difference re-appears after isolation of NSCLC as a separate subgroup analysis as outcomes drawn from lung cancer reported RCTs were generally homogenous (the highest I2 in all reported outcomes was 33%) and elaborate the previously confirmed results of several recruited [14,17,24] or unrecruited RCTs [15] in this meta-analysis that IMM was associated with higher response and survival.

This meta-analysis met its end point of providing an evidence for absence of significantly higher horrific cardiotoxicity mentioned by some of the published RCTs as mentioned earlier.

Being the first meta-analysis reporting cardiotoxicity outcomes in immunotherapy represents an inherited strength in our study; however, among the limitation of our meta-analysis is that it included heterogeneous types of cancers (three NSCLC RCTs, seven melanoma RCTs, one prostate cancer RCT) and heterogeneous second treatment arm (CTH, dual IMM, Sargramostim and placebo); however, in order to make it more homogenous, we did several subgroup analyses.

Conclusion

Despite the fact that anti-PD/PD-L1 previously showed greater incidence of complications including gastrointestinal, cardiotoxicity was statistically insignificant regardless the treatment regimen either chemotherapy or dual
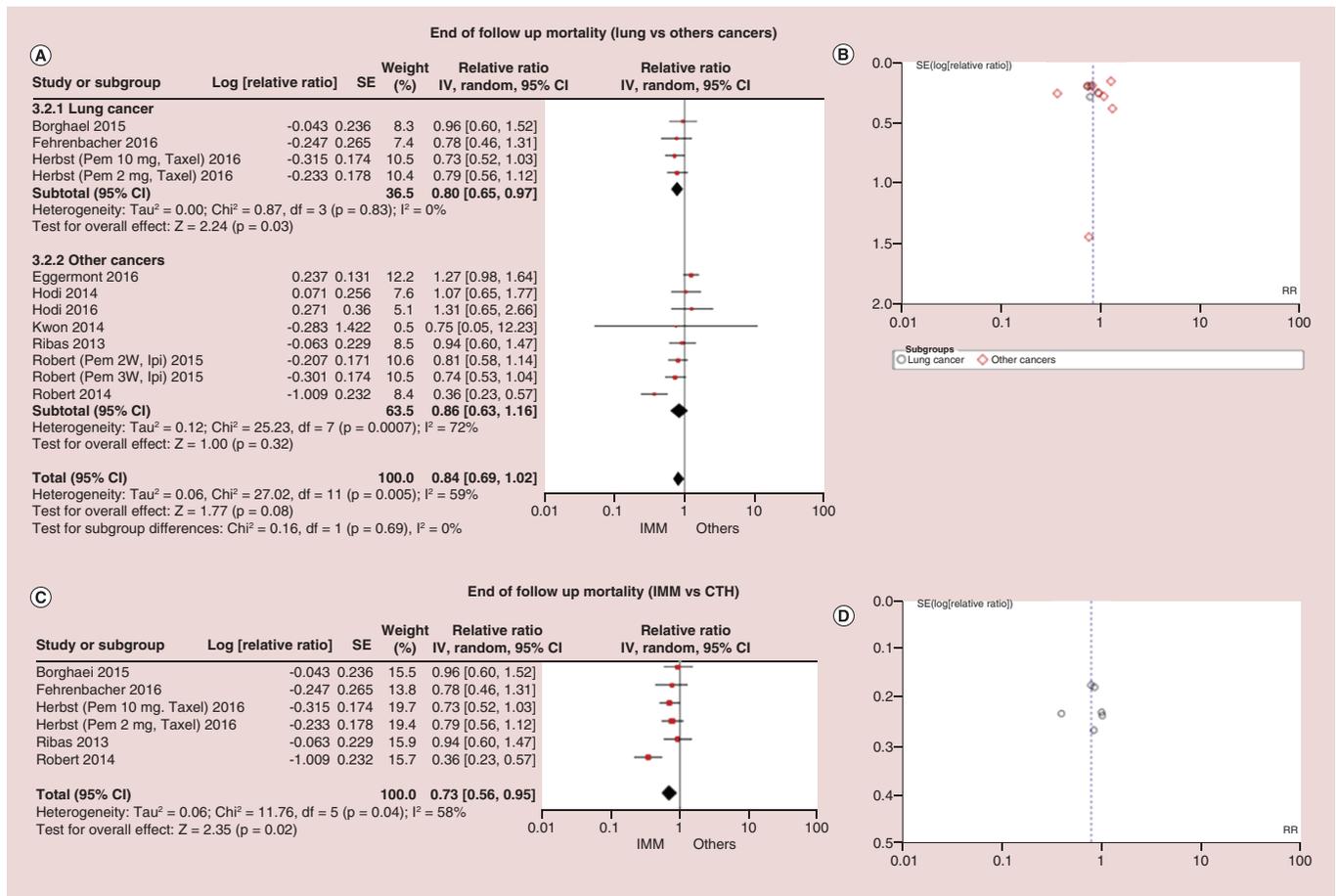
Figure 4.   Forest & Funnel plots of overall mortality at end of follow-up in different subgroups. (A & B) Forest & Funnel plots of lung versus other cancers studies. **(C & D)** Forest & Funnel plots of immunotherapy versus chemotherapy-only studies.

immunotherapy. The use of anti-PD/PD-L1 provided better response and survival rates when used in lung cancer subgroup.

Future perspective

Due to the efficacy of anti-PD/PD-L1 and anti-CTLA-4 in treatment of various malignancies, growing number of patients are assigned to this line of treatment. Devastating as it may seem, cardiotoxicity due to these drugs has to be detected and managed as early as possible. The involvement of cardiologists in the initial planning for treatment or in the early cardiac dysfunction assessment is not a standard of care yet [25], that is why a multidisciplinary approach is recommended, including oncologist and an expert cardiologist for early identification and management of cardiotoxicities. Despite being a specific and sensitive marker of cardiotoxicity, troponin-I is not routinely monitored in most immunotherapy trials [26,27]. We recommend inclusion of thorough cardiac monitoring in the treatment plan, including assessment of troponin level, routine electrocardiograms, as well as echocardiographs to enhance our knowledge of the real incidence of early and late cardiotoxicities associated with immune checkpoint inhibitors. Nevertheless, clear validated guidelines for management of checkpoint inhibitors-associated myocarditis are urgently needed through prospective studies.

While various grades of cardiotoxic events were described with the use of immune checkpoint inhibitors including myocarditis, heart failure, heart block, myocardial fibrosis and cardiomyopathy, the exact mechanism of such complications is not fully understood. Johnson *et al.* [28] described two cases of fulminant myocarditis and myositis associated with combination of ipilimumab plus nivolumab where histological analysis showed that the myocardium, the cardiac sinus and the atrioventricular nodes were infiltrated by lymphocytes, and macrophages. Also, high expression of PD-L1 was demonstrated on affected cardiomyocytes and on infiltrating CD8$^+$ T cells.

Thus, we may conclude that cardiac toxicities that arise with the use of immune checkpoint inhibitors are mostly immune mediated. In previous reports, these toxicities were successfully managed using systemic high dose steroids [29,30]. Based on this, we recommend exploring the role of low dose steroids in decreasing immune checkpoint inhibitors cardiotoxicities in future prospective studies.

Executive summary

Background
- Immune-mediated adverse events have been frequently encountered with the use of antiprogrammed death receptor-1 (anti-PD/PD-L1) and anticytotoxic T lymphocyte-associated antigen 4 in treatment of various malignancies.
- These adverse effects include cutaneous, gastrointestinal, endocrine complications as well as various degrees of cardiotoxicities.
- We aimed to determine if there was a higher incidence of cardiotoxicity with the use of anti-PD/PD-L1 compared with other treatment protocols.

Methods
- We searched the PubMed, MEDLINE and EMBASE databases for publications containing anti-PD/PD-L1 immuotherapy (IMM) by the words 'Atezolizumab' OR 'Avelumab' OR 'BMS936559' OR 'Durvalumab' OR 'Ipilimumab' OR 'Nivolumab' OR 'Pembrolizumab' OR 'Pidilizumab' OR 'Tremelimumab' that were obtained from a previously published review [6].

Study outcome
- The primary end point was all grade difference in cardiotoxicity in IMM versus other treatments.
- The secondary end points were:
  - The difference of all cardiotoxicity grades in IMM in comparison to others in lung cancer, in addition comparing IMM to CTH.
  - Comparing cardiotoxicity higher grades in between IMM (within different cancer subgroups) and IMM to CTH.
  - Outcome of IMM compared with others (in all studies and in lung cancer/other cancers subgroups) as well as in IMMs compared with CTH only studies.
  - Difference in mortality in the same groups.

Results

Meta-analysis of the outcomes

Cardiotoxicity in immunotherapy
- Regarding all grades cardiotoxicity, no difference was found in all recruited studies (p = 0.55) or subgroups of lung cancer (p = 0.50) or other cancers p = 0.34).
- There was no difference in high grades cardiotoxicity among all recruited studies (p = 0.15) or in subgroups of lung cancer; (p = 0.70) or other cancers (p = 0.07).

Response in immunotherapy
- There was no difference in response between comparative arms (IMM vs others) (p = 0.12).
- Lung cancer showed a higher response rate (p = 0.0002).
- There was no statistically significant difference in response regarding other types of cancers, but heterogeneity exists (p < 0.0001).
- Immunotherapy arm showed a higher response rate on restricting studies to those comparing response in IMM versus CTH only (p < 0.001).

Discussion
- This is the first meta-analysis reporting cardiotoxicity outcomes in immunotherapy, up-to-date and up-to-our knowledge.
- Our aim was to assess the cardiotoxicity associated with anti-PD/PD-L1 use.
- There was no evident difference in all/high grades cardiotoxicity in our meta-analysis.
- No difference in response could be identified except after comparing IMM versus CTH only and in RCTs on lung cancer patients.
- This statistical difference reappears after isolation of non-small-cell lung cancer as a separate subgroup analysis.
- We met our end point in this meta-analysis by proving the absence of IMM associated higher cardiotoxicity rates mentioned by some of the published RCTs.

Conclusion
- Anti-PD/PD-L1 previously showed higher incidence of cutaneous, gastrointestinal, endocrine complications.
- There was no statistically significant cardiotoxicity was associated with anti-PD/PD-L1 in contrast to other treatment regimens.

Since human and murine hearts express PD-L1 [31,32] and the fact that many experiments suggested that PD-1/PD-L1 and CTLA-4 play important roles in limiting T cell-mediated autoimmune myocarditis [33–39], we suggest further research to find a cardioprotective drug against the decrease in cardiac PD-1/PD-L1 and CTLA-4 levels.

Financial & competing interests disclosure

Open access

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.future-science.com/doi/suppl/10.2217/imt-2018-0118

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