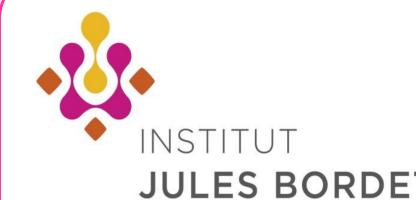
41P: Cardiotoxicity of Immune Checkpoint Inhibitors: a Systematic Review and Meta-Analysis of Randomized Clinical Trials



Agostinetto E^{1,2}, Eiger D¹, Lambertini M^{3,4}, Ceppi M⁵, Bruzzone M⁵, Pondé N⁶, Plummer C⁷, Awada AH⁸, Piccart-Gebhart M⁸, de Azambuja E¹

L. Academic Trials Promoting Team, Institut Jules Bordet and l'Université Libre de Bruxelles (U.L.B), Brussels, Belgium, 2. Medical Oncology and Hematology Unit, Humanitas Cancer Center, Humanitas Clinical and Research Center – IRCCS, Rozzano (Milan), Italy, 3. Department of Internal Medicine and Medical Specialties (DiMI), School of Medicine, University of Genova, Italy, 4. Department of Medical Oncology, U.O. Clinical Epidemiology, IRCCS Ospedale Policlinico San Martino, Genova, Italy, 6. Clinical Oncology Department, AC Camargo Cancer Center, São Paulo, Brazil, 7. Translational and Clinical Research Institute, Newcastle University, Newcastle upon Tyne, UK, 8. Oncology Department, Institut Jules Bordet, Brussels, Belgium

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

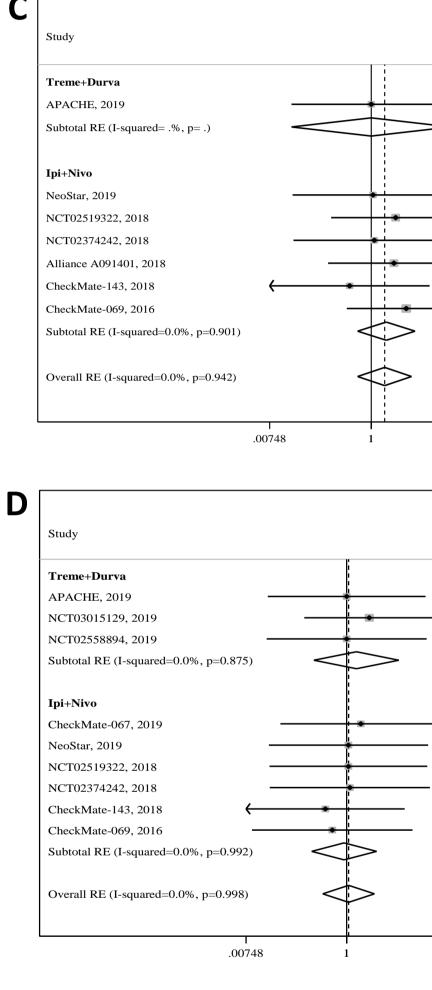
- Eighty studies including 35,337 patients were included in the analysis (66 studies with 34,664 patients for the primary endpoint and 14 studies with 673 patients for the secondary endpoint)
- Overall, any cardiac AEs occurred in $\leq 4\%$ of patients and myocarditis in $\leq 0.2\%$ of patients (Table 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
- 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

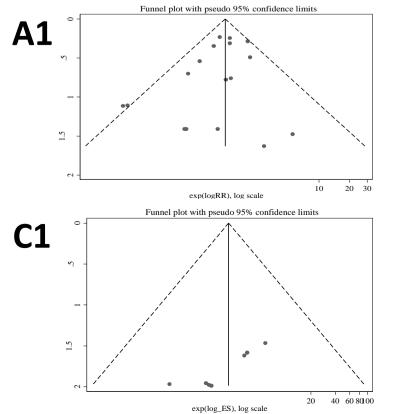
- Ramos-Casals M et al., Nat Rev Dis Primers 2020
- Haanen JBAG et al., Ann Oncol 2017
- Brahmer JR et al., J Clin Oncol 2018
- Brumbaugh AD et al., Cardiol Rev 2019

Forest Plots for "all cardiac events (any)" (A) and "myocarditis events" (B) in Single ICI vs non-ICI group RR (95% CI) Single-IO Non-IO Study Anti-CTLA4 CA184-043, 2014 1.31 (0.81, 2.12) 35/393 27/396 DETERMINE, 2017 1.04 (0.66, 1.63) 50/380 24/189 Subtotal RE (I-squared=0.0%, p=0.493) 1.16 (0.83, 1.61) 85/773 51/585 Anti-PD(L)1 CASPIAN, 2019 0.50 (0.13, 1.99) 3/265 6/266 Checkmate-078, 201 1/337 1/156 0.46 (0.03, 7.35) I-SPY2, 2020 0.66 (0.23, 1.89) 16/181 4/69 IMblaze370, 2019 2/801.19 (0.26, 5.49) 8/269 IMpower130, 2019 14/232 1.96 (1.12, 3.45) 56/473 IMpower133, 2018 0.99 (0.06, 15.71) 1/198 1/196 IMpower150, 2018 1.34 (0.30, 5.93) 4/393 3/394 Impassion-130, 2020 1.31 (0.71, 2.41) 23/453 17/437 KATE-2, 2019 1/133 4/67 0.13 (0.01, 1 KEYNOTE-010, 2016 4/309 0.11 (0.01, 1/682 KEYNOTE-040, 2019 0/234 1/246 KEYNOTE-045, 2017 16/255 0.90 (0.45, 1.78) 15/266 KEYNOTE-240, 2020 1/134 1/279 KEYNOTE-522, 2020 5.49 (0.30, 98.96) 5/781 0/389 PACIFIC, 2017 5/234 2.07 (0.79, 5.42) 21/475 Subtotal RE (I-squared=24.6%, p=0.182) 1.08 (0.74, 1.56) 145/5319 90/3564 Overall RE (I-squared=16.0%, p=0.267) 1.14 (0.88, 1.48) 230/6092 141/4149 .0101 RR (95% CI) Single-IO Non-IO Anti-CTLA4 0/396 1.01 (0.02, 50.65) A184-043. 201 DETERMINE, 2017 0.50 (0.01, 25.04) 0/380 0/189 EORTC-18071, 2016 3.02 (0.12, 73.92) 1/471 0/474 -----0.26 (0.01, 13.03) 0/511 NCT00094653, 2010 0/132 NCT00257205, 2013 0.98 (0.02, 49.32) 0/325 0/319 NCT00324155, 201 1.02 (0.02, 51.01) 0/247 0/251 NCT00527735 (NSCLC), 2012 0.47 (0.01, 23.67) 0/138 0/65NCT00527735 (SCLC), 2013 0/44 _____• ' 0.53 (0.01, 26.24) 0/84 0.79 (0.02, 39.21) 0/57 0/45 NCT01585987, 2017 Subtotal RE (I-squared=0.0%, p=0.997) 0/1915 0.81 (0.23, 2.88) 1/2606 Anti-PD(L)1 CheckMate-017, 2015 0.98 (0.02, 49, 26) 0/131 0/129 CheckMate-057, 2015 0/268 0.93 (0.02, 46.91) 0/287 0/205 0/156 CheckMate-066, 2015 1.00 (0.02, 49.92) 0/206 0.46 (0.01, 23.30) 0/337 Checkmate-078, 2019 I-SPY2, 2020 -----2.60 (0.05, 129.77) 0/69 0/181IFCT-1603 Trial, 2019 0.51 (0.01, 24.96) 0/48 0/24 IMblaze370, 2019 0/80 0.30 (0.01, 15.00) 0/269 IMbrave150, 2020 0.48 (0.01, 23.87) 0/329 0/156 IMpower130, 2019 IMpower133, 2018 0/232 0.49 (0.01, 24.70) 0/473 0.99 (0.02, 49.64) 0/198 0/196 0/394 IMpower150, 2018 1.00 (0.02, 50.40) 0/393 Impassion-130, 2020 JAVELIN Lung 200, 2018 0.96 (0.02, 48.51) 0/453 0/437.79 (0.11, 68.19) 1/393 0/365 _____ JAVELIN Renal 101, 2019 -----.03 (0.12, 74.28) 1/434 0/439 KATE-2, 2019 0.51 (0.01, 25.30) 0/133 0/67 • KEYNOTE-002, 2017 0.48 (0.01, 24.11) 0/357 0/171KEYNOTE-010, 2016 0/309 0.45 (0.01, 22.82) 0/682 KEYNOTE-021, 2016 1.05 (0.02, 52.08) 0/59 0/62 KEYNOTE-024, 2019 0.97 (0.02, 48.78) 0/154 0/150 KEYNOTE-040, 2019 0.95 (0.02, 47.75) 0/246 0/234 0/615**KEYNOTE-042**, 2019 2.90 (0.12, 71.08) 1/636 **KEYNOTE-045**, 2017 0.96(0.02, 48.14) 0/2660/255 **KEYNOTE-048**, 2019 1.50 (0.06, 36.64) 1/576 0/287**KEYNOTE-061**, 2018 0/276 0.94 (0.02, 47.16) 0/294 **KEYNOTE-181, 2019** 2.83 (0.12, 69.16) 1/314 0/296 0/202 0/134 KEYNOTE-189, 2020 1.50 (0.06, 36.66) 1/405 **KEYNOTE-240, 2020** 0.48 (0.01, 24.17) 0/279 **KEYNOTE-407**, 2018 1.01 (0.02, 50.58) 0/278 0/280 0/425 KEYNOTE-426, 2019 4.95 (0.24, 102.87) 2/429 KEYNOTE-522, 2020 0/389 5.49 (0.30, 98.96) 5/781 NCT02130466, 2019 0/60 1.00 (0.02, 49.59) 0/60 0/502 0/52 NCT02362594, 2018 2.96 (0.12, 72.46) 1/509 NCT02500121, 2020 0.95 (0.02, 46.84) 0/55 -----0/44 NCT03051659, 2019 3.00 (0.13, 71.70) 1/44 1/234 **PACIFIC. 2017** 0.16 (0.01, 4.02) 0/475 0/135 **POPLAR**, 2016 0.95 (0.02, 47.59) 0/142 Subtotal RE (I-squared=0.0%, p=1.000) 1.20 (0.65, 2.19) 15/11194 1/8441 Overall RE (I-squared=0.0%, p=1.000) 1.11 (0.64, 1.92) 16/13800 1/10356

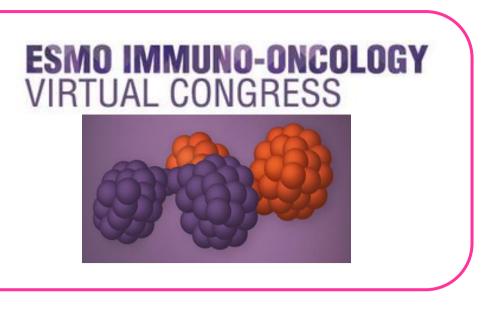
Forest Plots for "all cardiac events (any)" (C) and "myocarditis events" (D) in Dual ICI vs Single-ICI group



Funnel Plots of reported cardiac endpoints



.00518



	RR (95% CI)	Dual IO	Single IO
>	1.00 (0.02, 46.40) 1.00 (0.02, 46.40)	0/11 0/11	0/11 0/11
	1.09 (0.02, 52.67)	0/21	0/23
	 3.25 (0.15, 72.36) 1.17 (0.02, 57.32) 3.00 (0.13, 71.61) 	1/11 0/35 1/42	0/12 0/41 0/42
-	0.35 (0.01, 16.83) 5.44 (0.31, 96.36) 2.08 (0.52, 8.27)	0/30 5/94 7/233	0/10 0/46 0/174
	1.91 (0.52, 7.01)	7/244	0/185
13	34		

	RR (95% CI)	Dual IO	Single IO
	1.00 (0.02, 46.40)	0/11	0/11
_	3.00 (0.13, 70.64)	1/28	0/28
	1.00 (0.02, 48.92)	0/32	0/32
	1.60 (0.20, 12.63)	1/71	0/71
	1.99 (0.04, 100.08)	0/313	0/624
•	1.09 (0.02, 52.67)	0/21	0/23
	1.08 (0.02, 50.43)	0/11	0/12
-	1.17 (0.02, 57.32)	0/35	0/41
	0.35 (0.01, 16.83)	0/30	0/10
	0.49 (0.01, 24.55)	0/94	0/46
	0.88 (0.18, 4.31)	0/504	0/756
	1.10 (0.31, 3.87)	1/575	0/827

134

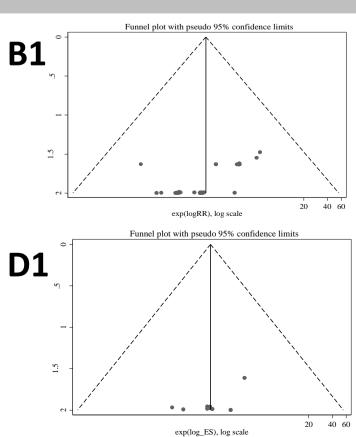


Table 1 – Number of cardiac adverse events per number of patients, pooled incidence, and relative risk-ratios with 95% confidence intervals in the immune-checkpoint inhibitors (ICI) group vs non-ICI group and in the dual-ICI group vs single-ICI group.

	ICI vs non-ICI groups			Dual ICI vs Single ICI groups		
	ICI-group	Non-ICI group	RR (95% CI)	Dual ICI	Single ICI	RR (95% CI)
	events/N (%)	events/N (%)		events/N (%)	events/N (%)	
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

The authors have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this poster. Elisa Agostinetto has no conflict of interests to declare. Daniel Eiger: Funding for his ESMO fellowship (2018-2019): Novartis. Speaker honoraria: Janssen (outside the submitted work). Matteo Lambertini acted as a consultant for Roche and Novartis, and received honoraria from Theramex, Takeda, Roche, Lilly, Pfizer and Novartis (outside the submitted work). Marcello Ceppi has no conflicts of interest to declare. Marco Bruzzone has no conflicts of interest to declare. Noam Ponde acted as a consultant for Lilly, and has received honoraria from Roche, Lilly, Novartis and AstraZeneca (outside the submitted work). Chris Plummer has received honoraria for speaking at educational meetings from Amgen, Ferring, Incyte, Ipsen, Novartis, Pfizer and Roche (outside the submitted work). Ahmad Hussein Awada: Advisory role, speaker fees and research funding for his institute from: Roche, Lilly, Amgen, EISAI, BMS, Pfizer, Novartis, MSD, Genomic Health, Ipsen, AstraZeneca, Bayer, Leo Pharma (outside the submitted work). Armando Santoro: Advisory board: BMS, Servier, Gilead, Pfizer, Eisai, Bayer, MSD. Partecipation in Conferences: Takeda, Roche, Abb-vie- Amgen, Celgene, Astrazeneca, Lilly, Sandoz, Novartis, BMS, Servier, Gilead, Pfizer, Argule, Eisai Consultant: Argule (outside the submitted work). Martine Piccart: Board Member (Scientific Board): Oncolytics, Radius; Consultant (honoraria): AstraZeneca, Camel-IDS, Crescendo Biologics, Debiopharm, G1 Therapeutics, Genentech, Huya, Immunomedics, Lilly, Menarini, MSD, Novartis, Odonate, Oncolytics, Periphagen, Pfizer, Roche, Seattle Genetics; Research grants to her Institute : AstraZeneca, Lilly, MSD, Novartis, Pfizer, Radius, Roche-Genentech, Servier, Synthon (outside the submitted work). Evandro de Azambuja: honoraria and advisory board: Roche/GNE, Novartis, Seattle Genetics, Zodiacs and Libbs; travel grants: Roche/GNE, GSK/Novartis. Research grant for his institute: Roche/GNE, Astra-Zeneca, Novartis, and Servier (outside the submitted work).