ICIs-Related Cardiotoxicity in Different Types of Cancer

Mei Dong 1,†, Ting Yu 2,†, Zhenzhen Zhang 1, Jing Zhang 1, Rujian Wang 3, Gary Tse 4,5, Tong Liu 4,6,* and Lin Zhong 1,6,*

1 Department of Cardiology, The Affiliated Yantai Yuhuangding Hospital of Qingdao University, Yantai 264000, China;dongmei0212@126.com (M.D.); m18663817808@163.com (Z.Z.); zhangjingfriend@126.com (J.Z.)
2 Medical College, Qingdao University, Qingdao 266003, China; 13061487578@163.com
3 Department of Oncology, The Affiliated Yantai Yuhuangding Hospital of Qingdao University, Yantai 264000, China; w15066122363@126.com
4 Tianjin Key Laboratory of Ionic-Molecular Function of Cardiovascular Disease, Department of Cardiology, Tianjin Institute of Cardiology, Second Hospital of Tianjin Medical University, Tianjin 300070, China; gary.tse@doctors.org.uk
5 Kent and Medway Medical School, Canterbury CT2 7FS, UK
6 Correspondence: liutong@tmu.edu.cn (T.L.); linzhongyhd1971@sina.com (L.Z.); Tel.: +86-139-0218-3163 (T.L.); +86-159-5355-0726 (L.Z.)
† These authors contributed equally to this work.

Abstract: Immune checkpoint inhibitors (ICIs) are rapidly developing immunotherapy cancer drugs that have prolonged patient survival. However, ICIs-related cardiotoxicity has been recognized as a rare, but fatal, consequence. Although there has been extensive research based on different types of ICIs, these studies have not indicated whether cardiotoxicity is specific to a type of cancer. Therefore, we conducted a systematic review to analyze a variety of ICIs-related cardiotoxicity, focusing on different types of cancer. We found that the incidence of ICIs-related cardiac adverse events (CAEs) and common cardiotoxic manifestations vary with cancer type. This inspired us to explore the underlying mechanisms to formulate targeted clinical strategies for maintaining the cardiovascular health of cancer patients.

Keywords: immune checkpoint inhibitors; cardiotoxicity; cardio-oncology; cancer-type-specific

1. Introduction

Cardiovascular disease (CVD) and cancer are global health issues with high morbidity and mortality [1], and numerous published studies suggest that there is an overlap in epidemiology, risk factors, and pathophysiologic processes (Figure 1) [1–5].

With the widespread application of anticancer drugs, the survival of patients has significantly improved, but the related cardiotoxicity affects long-term therapeutic outcomes, and this has attracted considerable attention. Immune checkpoint inhibitors (ICIs), antibodies that target the checkpoints in immune cells, work to activate inhibited T-cells and other cells of the innate and adaptive arms, resulting in the robust activation of the immune system and productive antitumor immune responses. This new type of immunotherapy drug has significantly improved the survival of cancer patients [6–8]. ICIs have been widely used in the treatment of melanomas, non-small cell lung cancer (NSCLC), advanced renal cell carcinomas (RCCs), urothelial carcinomas, hepatocellular carcinomas (HCCs), and hematological malignancies [7,9–12]. However, their use is associated with adverse side effects involving different organs [13,14]. ICIs-related cardiotoxicity, which may develop even without a history of significant cardiac risk factors, includes myocarditis, pericarditis, heart failure, arrhythmias, and vasculitis [15]. In reported cases of adverse ICIs-related events, 6.2% were cardiac adverse events (CAEs), which can be the main determinants of quality of life and increased mortality [3,16,17]. Recent cohort data from a large healthcare network
suggested that the most common CAEs were arrhythmia (9.3%) and myocarditis (2.1%) [18]. Cardiotoxicity associated with ICIs is known for its vast array of clinical presentations, which makes it unfavorable for an early diagnosis [19,20]. To date, there has been little agreement on the incidence or specific mechanisms of ICIs-related cardiotoxicity in different types of cancer. We hypothesize that ICIs may exhibit cancer-type-specific cardiotoxicity.

Figure 1. (a) Risk factors for CVD and cancer; (b) Common pathophysiologic processes of CVD and cancer.

2. Methods

We systematically reviewed articles published up to 28 February 2022 in PubMed, Web of Science, and Google Scholar databases without any language restrictions. The keywords included “PD-1”, “PD-L1”, “CTLA-4”, “LAG-3”, “nivolumab (anti-PD-1 antibody)”, “pembrolizumab (anti-PD-1 antibody)”, “atezolizumab (anti-PD-L1 antibody)”, “durvalumab (anti-PD-L1 antibody)”, “ipilimumab (anti-CTLA-4 antibody)” (with their chemical names and brand names), “cancer”, “tumor”, “carcinoma”, “neoplasm”, “malignancy”, “adverse events”, “complications”, and “cardiotoxicity”. The inclusion criteria of papers were (1) retrospective and prospective studies, case reports, meta-analysis, reviews involving PD-1, PD-L1, CTLA-4 and LAG-3 inhibitors for all cancers; (2) data on the rates of any ICIs-related adverse events associated with cardiac disorders. The exclusion criteria were as follows: (1) patients treated with anthracyclines (such as doxorubicin, daunorubicin, or idarubicin); (2) patients treated with tyrosine inhibitor kinase drugs, T-cell activated cells, activated dendritic cells, stem cell transplantation, or other antibodies; and (3) patients treated with ICIs with concomitant vaccines. A total of 549 papers were found of which 102 were kept for this review. Eventually, more than 40 clinical trials and case reports of 14 different cancers were collected.
3. Cardiotoxicity in Different Types of Cancer

3.1. Melanoma

In 16 studies, 24 of 6710 patients on ICIs [21–36] developed CAEs. This corresponded with an incidence of 0.20–4.93% in which grade 3–5 CAEs accounted for 41.7%. Commonly encountered cardiotoxicities included hypertension (50%), hypotension (16.7%), and myocarditis (8.3%). Treatment-related hypertension was linked to the application of lambrolizumab (58.3%) (PD-1). Nivolumab may have had a correlation with ICIs-related hypotension. Patients treated with a higher dose of ipilimumab, particularly 10 mg/kg × 4 doses/3 weeks, were more prone to fatal adverse events such as cardiac arrest (Table 1).

3.2. Lung Cancer

A total of 11 studies [37–47] included 5404 patients on ICIs, and 101 developed CAEs for an incidence of 0.15–37.78% in which grade 3–5 CAEs accounted for 55.4%. Commonly encountered cardiotoxicities included arrhythmia (32.7%), cardiac-related chest pain (24.8%), elevated cTnI or myocarditis (23.8%), cardiomyopathy (20.8%), pericardial disease (11.9%), and acute coronary syndrome (10.9%). One study indicated that major adverse cardiovascular events (MACEs) were dose-independent of nivolumab and pembrolizumab in lung cancer patients [37]. Those treated with a higher dose of durvalumab, particularly 10 mg/kg × 4 doses/2 weeks, were more prone to fatal adverse events such as a cardiac arrest and cardiogenic shock [41]. One patient treated with pembrolizumab at 10 mg/kg for 3 weeks underwent a myocardial infarction, which led to death (Table 2) [43].

3.3. Renal Cell Carcinoma

In seven studies [48–54] comprising 1971 patients with renal cell carcinomas on ICIs, 14 developed CAEs with an incidence of 0.20–2.19% in which grade 3–5 CAEs accounted for 35.7%. Commonly encountered cardiotoxicities included hypertension (85.7%) and myocarditis (7.1%). Treatment-related hypertension was linked to a nivolumab plus ipilimumab therapy (100%). Compared with melanomas and lung cancer, the ICI therapy caused mild cardiotoxicity in renal cell carcinomas. Fatal CAEs were not found (Table 3).

3.4. Urothelial Carcinoma

In Seven studies [55–61] 111 of 2550 patients with urothelial carcinomas on ICIs developed CAEs with an incidence of 0.22–10.60% in which grade 3–5 CAEs accounted for 52.3%. Commonly encountered cardiotoxicities included hypertension (28.8%), arrhythmia (14.4%) and hypotension (6.3%). The fluctuation of blood pressure was linked to treatment with atezolizumab. Hypertension was observed in 21 patients and hypotension was observed in 7 after application of atezolizumab. Patients treated with 200 mg pembrolizumab for 3 weeks (maximum 35 cycles) or at 1200 mg every three weeks were more prone to fatal adverse events such as a cardiac arrest (Table 4).
## Table 1. Cardiotoxicity in melanoma.

| Author, Year                  | Study Type | Phase | Sample Size | Drug | Dose and Frequency | Non-CAE | CAE | Manifestation                  | 3–5 Grade CAE |
|-------------------------------|------------|-------|-------------|------|--------------------|---------|-----|--------------------------------|----------------|
| Omid Hamid et al., 2017 [21]  | Prospective study II | 528 (178 vs. 179 vs. 171) | Pembrolizumab vs. Pembrolizumab vs. chemotherapy | 2 mg/kg/3 weeks vs. 10 mg/kg/3 weeks vs. standard dose | 528 | 0 | 0                            | 0              |
| Caroline Robert et al., 2014 [22] | Prospective study III | 418 (210 vs. 208) | Nivolumab vs. Dacarbazine | 3 mg/kg/2 weeks vs. standard dose | 308 (153 vs. 155) | 5 | Hypotension 1 vs. 4           | 0              |
| Jeffrey S Weber et al., 2015 [23] | Prospective study III | 370 (268 vs. 102) | Nivolumab vs. ICC (Dacarbazine al) | 3 mg/kg/2 weeks vs. standard dose | 362 (181 vs. 81) | 0 | 0                            | 0              |
| Paolo A Ascierto et al., 2017 [24] | Prospective study III | 726 (364 vs. 362) | Ipilimumab | 10 mg/kg/4 doses/3 weeks vs. 3 mg/kg/4 doses/3 weeks | 514 (286 vs. 228) | 3 | Hypertension 1 vs. 0; Heart arrest 1 vs. 0; Pericarditis 1 vs. 0 | 3              |
| F Stephen Hodi et al., 2016 [25] | Prospective study II | 142 (95 vs. 47) | Nivolumab + Ipilimumab vs. Ipilimumab + placebo | 1 mg/kg + 3 mg/kg/4 doses/3 weeks vs. 3 mg/kg + placebo/4 doses/3 weeks | 140 (94 vs. 46) | 7 | Hypotension 3 vs. 0; Ventricular arrhythmia 1 vs. 0; Ventricular tachycardia 1 vs. 0; Atrial fibrillation 1 vs. 0; Myocardial infarction 1 vs. 0 | 5              |
| Caroline Robert et al., 2015 [26] | Prospective study III | 834 (278 vs. 277 vs. 256) | Pembrolizumab vs. Pembrolizumab vs. Ipilimumab | 10 mg/kg/2 weeks/doses vs. 10 mg/kg/3 weeks/doses vs. 3 mg/kg/3 weeks/4 doses | 610 (221 vs. 202 vs. 187) | 4 | Hypertension 3 vs. 1 vs. 0 | 2              |
| J. Weber, M. et al., 2017 [27] | Prospective study III | 906 (453 vs. 453) | Nivolumab vs. Ipilimumab | 3 mg/kg/4 doses/2 weeks vs. 10 mg/kg/4 doses/3 weeks | 884 (438 vs. 446) | 0 | 0                            | 0              |
| J.D. Wolchok et al., 2017 [28] | Prospective study III | 937 (313 vs. 313 vs. 311) | Nivolumab + Ipilimumab vs. Nivolumab + p vs. Ipilimumab + p (placebo) | 1 mg/kg/3 mg/kg/3 weeks/4 doses vs. 3 mg/kg/2 weeks + placebo vs. 3 mg/kg/3 weeks/4 doses + placebo | 847 (300 vs. 279 vs. 268) | 0 | 0                            | 0              |
| Jedd D Wolchok et al., 2010 [29] | Prospective study II | 217 (73 vs. 72 vs. 72) | Ipilimumab | 10 mg/kg vs. 3 mg/kg vs. 0.3 mg/kg/3 weeks/4 doses | 115 (50 vs. 46 vs. 19) | 0 | 0                            | 0              |
| Ines Pires da Silva et al., 2021 [30] | Retrospective study NR (Not Reported) | 355 (193 vs. 162) | Ipilimumab + Nivolumab/ Pembrolizumab/ Atezolizumab vs. Ipilimumab | 3 mg/kg/3 weeks vs. 4 doses + standard dose vs. 3 mg/kg/3 weeks/4 doses | 287 (163 vs. 124) | 1 | Myocarditis 0 vs. 1            | 1              |
### Table 1. Cont.

| Author, Year | Study Type     | Phase | Sample Size | Drug                                                                 | Dose and Frequency                                                                 | Non-CAE | CAE    | Manifestation          | 3–5 Grade CAE |
|--------------|----------------|-------|-------------|----------------------------------------------------------------------|----------------------------------------------------------------------------------|---------|--------|------------------------|----------------|
| Patrick Schöffski et al., 2022 [31] | Retrospective study | I/II  | 255 (134 vs. 121) | LAG-3 inhibitor leramilimab vs. leramilimab + Spartalizumab         | leramilimab (escalating 1–15 mg/kg)/ 2 weeks or once/ 4 weeks vs. leramilimab + Spartalizumab q2w or q3w or q4w or leramilimab q2w + Spartalizumab q4w | 159 (75 vs. 84) | 0      | 0                       | 0              |
| Alexander M.M. et al., 2020 [32] | Prospective study | III   | 1011 (509 vs. 502) | Pembrolizumab vs. placebo                                      | 200 mg/3 weeks for 18 doses                                                                 | 235 (190 vs. 45) | 1 (1 vs. 0) | Myocarditis 1 vs. 0   | NR             |
| Omid Hamid et al., 2013 [33] | Prospective study | I     | 135 (57 vs. 56 vs. 22) | Lambrolizumab                                               | 10 mg/kg/2 weeks vs. 10 mg/kg/3 weeks vs. 2 mg/kg/3 weeks                          | 132 (55 vs. 55 vs. 22) | 7 (2 vs. 4 vs. 1) | Hypertension 2 vs. 4 vs. 1 | NR             |
| Margaret K. et al., 2018 [34] | Retrospective study | I     | 94 (53 vs. 41) | Ipilimumab + Nivolumab (Niv) Ipilimumab (Ipi) | Niv+Ipi(escalating doses)/3 weeks for four doses, followed by Niv 3 weeks for four doses, then Niv + Ipi/12 weeks for eight doses vs. Niv 1 mg/kg + Ipi 3 mg/kg/3 weeks for 4 doses, followed by Niv 3 mg/kg/2 weeks | 87      | 0      | 0                       | 0              |
| Ulrich Keilholz et al., 2019 [35] | Prospective study | I     | 51           | Avelumab                                                 | 10 mg/kg for one-hour intravenous infusion/2 weeks                              | 39      | 0      | 0                       | 0              |
| Hussein A et al., 2022 [36] | Retrospective study | II-III | 714 (355 vs. 359) | Relatlimab + Nivolumab vs. Nivolumab | Relatlimab 160 mg + Nivolumab 480 mg vs. Nivolumab 480 mg | 504 (288 vs. 216) | 0      | 0                       | 0              |

The severity of adverse events was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. Grade 3: severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living. Grade 4: life-threatening consequences; urgent intervention indicated. Grade 5: Death related to adverse events.
Table 2. Cardiotoxicity in lung cancer.

| Author, Year | Study Type | Phase | Sample Size | Drug | Dose and Frequency | Non-CAE | CAE | Manifestation | 3–5 Grade CAE |
|--------------|------------|-------|-------------|------|-------------------|---------|-----|---------------|---------------|
| Kalyan R et al., 2019 [37] | Retrospective study | NR | 252 (117 vs. 135) | Non-ICI vs. ICI (Nivolumab/ Pembrolizumab) Nivolumab (Niv) Pembrolizumab (Pem) | Standard dose vs. increasing dose (Niv < 540 mg; 540–1440 mg; > 1440 mg Pem < 600 mg; 600–1707 mg; >1707 mg) | NR | 93 (42 vs. 51) | Arhythmia 31 vs. 25; Cardiac-related chest pain 12 vs. 25; Valvular heart disease 4 vs. 2; Cardiomyopathy 13 vs. 20; Myopericardial disease 11; Pericardial disease 8; Myocarditis 1; Valvular disease 2; Venous arterial thromboembolic events 8 | 40 (major CAE) |
| Scott N et al., 2015 [38] | Prospective study (NSCLC) | I | 129 (33 vs. 37 vs. 59) | Nivolumab | 1 mg/kg vs. 3 mg/kg vs. 10 mg/kg intravenously/2 weeks in 8-week cycles for up to 96 weeks. | 91 (21 vs. 25 vs. 45) | 0 | 0 | 0 |
| Tony S K Mok et al., 2019 [39] | Prospective study (NSCLC) | III | 1251 (636 vs. 615) | Pembrolizumab vs. platinum-based chemotherapy | 200 mg/3 weeks for up to 35 cycles vs. platinum-based chemotherapy for four to six cycles. | 1112 (515 vs. 597) | 1 (1 vs. 0) | Myocarditis 1 vs. 0 | 1 |
| Achim Rittmeyer et al., 2017 [40] | Prospective study (NSCLC) | III | 1187 (609 vs. 578) | Atezolizumab vs. Docetaxel | 1200 mg/3 weeks vs. 75 mg/m²/3 weeks | 886 (390 vs. 496) | 0 | 0 | 0 |
| S.J. Antonia et al., 2017 [41] | Prospective study (NSCLC) | III | 718 (475 vs. 234) | Durvalumab vs. Placebo | 10 mg/kg/2 weeks for up to 12 months vs. placebo | 421 (301 vs. 120) | 26 (21 vs. 5) | ACS 9 vs. 2; Arhythmia 7 vs. 1; Heart failure 7 vs. 0; Cardiac arrest 2 vs. 1; Cardiogenic shock 1 vs. 0; Cardiomyopathy 1 vs. 0; Myocarditis 0 vs. 1; Pericardial effusion 2 vs. 0 | NR |
| Yuequan Shi et al., 2021 [42] | Observational study (NSCLC/SCLC) | NR | 1905 (1162 vs. 743) (598 vs. 455 vs. 273 vs. 176 vs. 125 vs. 81 vs. 62 vs. 34 vs. 23) | ICI (Pembrolizumab/Nivolumab/ Camrelizumab/ Trepotizumab/ Tesilizumab/ Atezolizumab/ Durvalumab/Iplimumab) only vs. combination therapy | at least one dose | 647 | 22 (22 vs. 0) | Elevated cTnI or myocarditis 22 | 9 |
| Roy S Herbst et al., 2016 [43] | Prospective study (NSCLC) | II/III | 991 (339 vs. 343 vs. 309) | Pembrolizumab vs. Docetaxel | Pemb 2 mg/kg; Pemb 10 mg/kg vs. Docetaxel 75 mg/m²/3 weeks | 690 (215 vs. 225 vs. 250) | 1 (0 vs. 1 vs. 1) | Myocardial infarction 0 vs. 1 vs. 0; Acute cardiac failure 0 vs. 0 vs. 1 | 1 |
| Martin Reck et al., 2016 [44] | Prospective study (NSCLC) | III | 304 (154 vs. 150) | Pembrolizumab vs. platinum-based chemotherapy | 200 mg/3 weeks vs. standard dose | 52 (45 vs. 7) | 0 | 0 | 0 |
Table 2. Cont.

| Author, Year          | Study Type          | Phase | Sample Size | Drug                        | Dose and Frequency                          | Non-CAE | CAE                     | Manifestation                                      | 3–5 Grade CAE |
|-----------------------|---------------------|-------|-------------|-----------------------------|---------------------------------------------|---------|-------------------------|----------------------------------------------------|---------------|
| H. Borghaei et al., 2015 [45] | Prospective study (NSCLC) | III   | 555 (278 vs. 268) | Nivolumab vs. Docetaxel     | 3 mg/kg/2 weeks vs. 75 mg/m²/3 weeks         | 432 (196 vs. 236) | 3 (3 vs. 0) | Cardiac tamponade 1 vs. 0; Pericardial effusion 1 vs. 0; Tachycardia 1 vs. 0 | 3             |
| Julie Brahmer et al., 2015 [46] | Prospective study (NSCLC) | III   | 272 (135:137) | Nivolumab vs. Docetaxel     | 3 mg/kg/2 weeks vs. 75 mg/m²/3 weeks         | 187 (76 vs. 111) | 0 | 0 | 0 | 0 |
| D.P. Carbone et al., 2017 [47] | Prospective study (NSCLC) | III   | 530 (267 vs. 263) | Nivolumab vs. Chemotherapy(platinum-based) | 3 mg/kg/2 weeks vs. standard dose for six cycles. | 431 (188 vs. 243) | 2 (2 vs. 0) | Myocardial infarction 1 vs. 0; Pericardial effusion malignant 1 vs. 0 | 2             |

Table 3. Cardiotoxicity in renal cell carcinoma.

| Author, Year          | Study Type          | Phase | Sample Size | Drug                        | Dose and Frequency                          | Non-CAE | CAE                     | Manifestation                                      | 3–5 Grade CAE |
|-----------------------|---------------------|-------|-------------|-----------------------------|---------------------------------------------|---------|-------------------------|----------------------------------------------------|---------------|
| Sarah Abou Alaiwi et al., 2019 [48] | Retrospective study | III   | 499         | Anti-PD-1/PD-L1 (Nivolumab/ Pembrolizumab/Atezolizumab/Avelumab/Durvalumab) | NR                                      | 79 | 1 | Myocarditis 1 | 1 |
| Emre Yekedüz et al., 2021 [49] | Retrospective study | II/III | 173         | Nivolumab               | Nivolumab 240 mg/2wks                       | 11 (treatment discontinuation) | 0 | 0 | 0 | 0 |
| Robert J Motzer et al., 2018 [50] | Retrospective study | III   | 1082 (547 vs. 535) | Nivolumab + Ipilimumab vs. sunitinib | 3 mg/kg + 1 mg/kg/3 weeks for four doses, followed by Niv 3 mg/kg/2 weeks; or SUN 50 mg orally once daily for 4 weeks (6-week cycle). | 273 vs. 305 | 12 (12 vs. 0) | Hypertension 12 vs. 0 | 4 |
| Robert J. Motzer et al., 2015 [51] | Prospective study   | II    | 167 (59 vs. 54 vs. 54) | Nivolumab               | 0.3, 2 or 10 mg/kg intravenously once/3 weeks | 47 vs. 45 vs. 49 | 1 (1 vs. 0 vs. 0) | Cardiac disorder 1 vs. 0 vs. 0 | 0 |
| Joshua J et al., 2020 [52] | Prospective study   | IIIb/IV | 97          | Nivolumab               | 240 mg/2 weeks for ≤24 months               | 68 | 0 | 0 | 0 |
| Robert J. Motzer et al., 2015 [53] | Prospective study   | III   | 406 vs. 397 | Nivolumab vs. Everolimus | 3 mg/kg intravenously ≥60 min/2 weeks vs. 10 mg orally once daily. | 319 vs. 349 | 0 | 0 | 0 | 0 |
| Ulka Vaishampayan et al., 2019 [54] | Prospective study   | I     | 82 (62 vs. 20) (1Line vs. 2 Line) | Avelumab | 10 mg/kg by intravenous Infusion/2 weeks | 51 vs. 14 | 0 | 0 | 0 | 0 |
Table 4. Cardiotoxicity in urothelial carcinoma.

| Author, Year          | Study Type            | Phase | Sample Size | Drug | Dose and Frequency | Non-CAE | CAE | Manifestation                                                                 | 3–5 Grade CAE |
|-----------------------|-----------------------|-------|-------------|------|--------------------|---------|-----|--------------------------------------------------------------------------------|----------------|
| Joaquim Bellmunt et al., 2021 [55] | Prospective study     | III   | 406 vs. 403 | Atezolizumab vs. observation group | 1200 mg intravenously vs. observation | 378 vs. 389 | 51 (27 vs. 24) | Hypertension 15 vs. 0; Arrhythmia 10 vs. 0; Myocardial infarction 1 vs. 0; Cardiac discomfort 2 vs. 0 | 9              |
| Dingwei Ye et al., 2021 [56]     | Retrospective study   | II    | 113         | Tislelizumab | 200 mg intravenously /3weeks | 106 (31 immune-related AEs) | 0 | 0 |                                                                              | 0              |
| Thomas Powles et al., 2020 [57]  | Prospective study     | III   | 345 vs. 340 vs. 313 | Durvalumab vs. Durvalumab + Tremelimumab vs. Chemotherapy | 1500 mg intravenously / 4 weeks vs. Dur + Tre 75 mg intravenously / 4 weeks for 4 doses vs. standard dose | 193 vs. 254 vs. 282 | 0 | 0 |                                                                              | 0              |
| Padmanee Sharma et al., 2017 [58] | Prospective study     | II    | 270         | Nivolumab | 3 mg/kg/2weeks | 173 | 1 | Cardiovascular failure 1 | 1                                |
| Michiel S. van der Heijden et al., 2021 [59] | Prospective study     | III   | 443 vs. 459 | Chemotherapy vs. Atezolizumab | standard dose vs. 1200 mg/3weeks | 435 vs. 436 | 2 (1 vs. 1) | Cardiac arrest 0 vs. 1 | 1                                |
| Jonathan E Rosenberg et al., 2016 [60] | Prospective study     | II    | 315         | Atezolizumab | Intravenously given/3weeks | 202 | 13 | Hypotension 7; Hypertension 6 | 5                                |
| Thomas Powles et al., 2021 [61]  | Prospective study     | III   | 349 vs. 302 vs. 342 | Pembrolizumab (Pem)+ chemotherapy vs. Pembrolizumab vs. Chemotherapy | Pemb 200 mg/3 weeks for a max of 35 cycles + standard dose vs. Pem only vs. chemo only | NR | 98 (40 vs. 29 vs. 29) | Hypertension 8 vs. 3 vs. 2; Atrial fibrillation 4 vs. 2 vs. 2; ACS 4 vs. 2 vs. 3; Cardiac arrest 3 vs. 2 vs. 1 (specific number NR) | 42 (18 vs. 14 vs. 10) |
3.5. Other Types of Cancer

The most commonly encountered ICIs-related type of cardiotoxicity in hematological malignancies was hypertension [62–65]. In other cancers, such as hepatocellular carcinomas and malignant pleural mesotheliomas, the relevant research did not present many cases [66–71]; these were almost all case reports of myocarditis [72–74].

4. Discussion

A total of 23,090 subjects from more than 40 studies were analyzed and the major findings were (1) ICIs-related CAEs commonly occur in melanomas, lung cancer, urothelial and renal cell carcinomas, and hematological malignancies. The incidence of ICIs-related CAEs ranged from 0.15 to 10%. The most commonly encountered type of cardiotoxicity in melanomas, renal cell carcinomas, and urothelial carcinomas was hypertension, whereas in lung cancer it was arrhythmia. ICIs-related cardiotoxicities for other cancer types appeared mostly in case reports and presented with myocarditis. (2) Among the abovementioned five cancers, the incidence of grade 3–5 ICIs-related CAEs ranged from 35.7 to 55.4%. Compared with RCCs, the other four types had a higher incidence of CAEs, including sudden cardiac arrest. (3) In different types of cancer, different ICIs had manifested different cardiotoxicities. In melanomas, PD-1/PD-L1 inhibitor use was closely related to a fluctuation in blood pressure. Treatment-related hypertension was linked to lambrolizumab. Nivolumab appeared to have a correlation with ICIs-related hypotension. Abnormal blood pressures might also be caused by the toxic effect of ICIs on other organs (e.g., vasculature). In addition, fatal myocarditis was reported after a single treatment with the combination of nivolumab and ipilimumab [75]. Recent evidence suggests that abatacept, a CTLA-4 agonist, may be used as additional immunosuppression for severe ICI–related myocarditis [76]. In lung cancer, the common cardiotoxic manifestations of durvalumab were acute coronary syndrome, arrhythmia, and heart failure. The common cardiotoxic manifestations of nivolumab and pembrolizumab were arrhythmia, cardiac-related chest pain, cardiomyopathy, myopericardial disease, and pericardial disease. In renal cell carcinomas, nivolumab combined with ipilimumab appeared to cause hypertension. In urothelial carcinoma, atezolizumab was related to hypertension and arrhythmia. (4) In melanomas, we observed that the growing incidence of CAEs correlated with increased dosage [24] and frequency [26] of an ICI application. Regarding the cardiotoxicity of an ICI monotherapy compared with a combination therapy, two studies had inconsistent conclusions [25,30]. In lung cancer, two studies showed contradictory conclusions on the relationship between the ICI dose and ICIs-related cardiotoxicity [37,43]. As different drugs are used for different cancer types, the dosage and therapeutic regimens can also influence toxicity. Therefore, our conclusions require further evidence to be confirmed.

The pathogenic mechanism underlying ICIs-related cardiotoxicity has not been comprehensively studied [77]. Tumor cells escaping immune surveillance by promoting checkpoint activation have been recognized as a major mechanism (Figure 2). Direct T cell-mediated cytotoxicity leads to the inflammation of the His-Purkinje system. Furthermore, macrophage infiltration, inflammation, fibrosis of myocardium hyperactivation [78–80], infiltration of cytotoxic T cells into myocardial tissue, inhibition of cardioprotective PD-1 and PD-L1 pathways in cardiomyocytes, and clonal expansion of T cells against homologous tumors and myocardium antigens have been observed (Figure 2) [75,81]. Other hypotheses that have attracted attention are ICIs-associated inflammation-triggering destabilization [82–84], cytotoxic T cell activation leading to the pseudo-progression of pericardial micro-metastases [85–88], and direct action on the coronary vascular bed [89–91].

Tumor-intrinsic factors (such as a tumor-associated stroma) [92], patient-intrinsic factors, and environmental factors may be implicated in different cardiotoxicities of ICIs of different cancer types [93]. Tumor-intrinsic factors relating to the genetic, transcriptional, or functional profile of the tumor cells themselves [92,94] appear to be the decisive factors for ICIs-related cardiotoxicity. Patients with tumors having parallel histological and genetic features had a similar incidence of ICIs-related CAEs [92,95]. Tumor-intrinsic factors
According to ASCO guidelines, permanent discontinuation of ICIs is recommended for grade 4 toxicities, except for endocrinopathies that have been controlled by hormone replacement [99–101]. The interval of time required for cardiotoxicity to occur has not yet been precisely indicated [97,98], so further work is required to elucidate this. There are still many unanswered questions about the effect of patient-intrinsic factors on ICIs-related cardiotoxicity because the mechanisms differ, even in patients treated with the same agent.

With a wide range of ICI applications in anticancer therapy, there is growing recognition of a broad spectrum of ICIs-related CAEs. More attention must be paid to cancer-type-specific ICIs-related cardiotoxicity to target high-risk patients so that effective prevention and treatment measures can be applied. For patients treated with ICIs, clinical management—including the observation of clinical symptoms, the detection of cardiac biomarkers, and the performance of electrocardiograms and echocardiograms—are strongly suggested. More importantly, cancer-type-specific clinical management is urgently required. In patients with NSCLC, we suggest that the dynamic monitoring of electrocardiograms be performed after ICI application to evaluate the occurrence of arrhythmias such as atrial fibrillation, conduction blocks, and even malignant arrhythmias. Regarding patients with cancers such as melanomas, renal cell carcinomas, and uroepithelial carcinomas, we suggest that blood pressure be monitored dynamically during ICI therapy.

For ICIs-related cardiac complications, a high dose of steroids a common treatment; however, there are some circumstances in which aggressive therapy may be ineffective [99–101]. According to ASCO guidelines, permanent discontinuation of ICIs is recommended for grade 4 toxicities, except for endocrinopathies that have been controlled by hormone replacement [102]. It is prudent for cardiologists and oncologists to spread awareness about the manifestations of ICIs-related cardiotoxicity for each cancer type and cooperate closely for its successful diagnosis and management. Rigorous follow-ups of patients receiving ICI therapy with cardiac biomarkers, EKGs, and echocardiograms are recommended. It should be borne in mind that different drugs are used for different cancer types, and if a drug causes a different toxicity in a particular cancer type, the composition of each drug should be compared. The dosage and therapeutic regimen should also be compared because they influence toxicity. Further studies focusing on exploring cancer-type-specific ICIs-related car-

Figure 2. Tumor cells facilitate checkpoint activation to evade immune surveillance.
diotoxic manifestations and potential mechanisms are required and helpful for maintaining the cardiac health of cancer patients treated by chemotherapy.

**Author Contributions:** Conceptualization, M.D.; formal analysis, M.D. and J.Z.; investigation, Z.Z.; data curation, R.W.; writing—original draft preparation, T.Y.; writing—review and editing, G.T. and T.L.; supervision, T.L. and L.Z.; project administration, L.Z. All authors have read and agreed to the published version of the manuscript.

**Funding:** This research received no external funding.

**Informed Consent Statement:** Not applicable.

**Data Availability Statement:** All data can be found in the references.

**Conflicts of Interest:** The authors declare no conflict of interest.

**References**

1. Narayan, V.; Thompson, E.W.; Demissei, B.; Ho, J.E.; Januzzi, J.L., Jr.; Ky, B. Mechanistic Biomarkers Informative of Both Cancer and Cardiovascular Disease: JACC State-of-the-Art Review. *J. Am. Coll. Cardiol.* 2020, 75, 2726–2737. [CrossRef] [PubMed]

2. Vincent, L.; Leedy, D.; Masri, S.C.; Cheng, R.K. Cardiovascular Disease and Cancer: Is There Increasing Overlap? *Curr. Oncol. Rep.* 2019, 21, 47. [CrossRef] [PubMed]

3. Giza, D.E.; Iliescu, G.; Hassan, S.; Marmagkiolis, K.; Iliescu, C. Cancer as a Risk Factor for Cardiovascular Disease. *Curr. Oncol. Rep.* 2017, 19, 39. [CrossRef]

4. Blaes, A.; Prizment, A.; Koene, R.J.; Konety, S. Cardio-oncology Related to Heart Failure: Common Risk Factors Between Cancer and Cardiovascular Disease. *Heart Fail. Clin.* 2017, 13, 367–380. [CrossRef]

5. Navi, B.B.; Reiner, A.S.; Kamel, H.; Iadecola, C.; Okin, P.M.; Elkind, M.S.; Panageas, K.S.; DeAngelis, L.M. Risk of arterial thromboembolism in patients with cancer. *J. Am. Coll. Cardiol.* 2017, 70, 926–938. [CrossRef]

6. Kaushik, I.; Ramachandran, S.; Zabel, C.; Gaikwad, S.; Srivastava, S.K. The evolutionary legacy of immune checkpoint inhibitors. *In Seminars in Cancer Biology;* Academic Press: Cambridge, MA, USA, 2022. [CrossRef]

7. Lee, J.B.; Kim, H.R.; Ha, S.J. Immune Checkpoint Inhibitors in 10 Years: Contribution of Basic Research and Clinical Application in Cancer Immunotherapy. *Immunet.* 2022, 22, e2. [CrossRef]

8. Park, J.; Kwon, M.; Shin, E.C. Immune checkpoint inhibitors for cancer treatment. *Arch. Pharmacal Res.* 2016, 39, 1577–1587. [CrossRef]

9. Zaha, V.G.; Meijers, W.C.; Moslehi, J. Cardio-Immuo-Oncology. *Circulation* 2020, 141, 87–89. [CrossRef]

10. Wang, F.; Qin, S. Progress in Diagnosis and Treatment of Immune Checkpoint Inhibitor-Associated Cardiotoxicity. *J. Cancer Immunol.* 2020, 2, 96–102.

11. Ronen, D.; Boul, A.; Lotem, M.; Abedat, S.; Yarkoni, M.; Amir, O.; Asleh, R. Exploring the Mechanisms Underlying the Cardiotoxic Effects of Immune Checkpoint Inhibitor Therapies. *Vaccines* 2022, 10, 540. [CrossRef]

12. Chen, C.H.; Yu, H.S.; Yu, S. Cutaneous Adverse Events Associated with Immune Checkpoint Inhibitors: A Review Article. *Curr. Oncol.* 2022, 29, 2871–2886. [CrossRef] [PubMed]

13. Zhou, J.; Chau, Y.A.; Yoo, J.W.; Lee, S.; Ng, K.; Dee, E.C.; Liu, T.; Wai, A.K.C.; Zhang, Q.; Tse, G. Liver Immune-related Adverse Effects of Programmed Cell Death 1 (PD-1) and Programmed Cell Death Ligand 1 (PD-L1) Inhibitors: A Propensity Score Matched Study with Competing Risk Analyses. *Clin. Oncol. (R Coll. Radiol.)* 2022, 34, e316–e317. [CrossRef] [PubMed]

14. Zhou, J.; Lee, S.; Lakhani, I.; Yang, L.; Liu, T.; Zhang, Y.; Xia, Y.; Wong, W.T.; Bao, K.K.H.; Wong, I.C.K.; et al. Adverse Cardiovascular Complications following prescription of programmed cell death 1 (PD-1) and programmed cell death ligand 1 (PD-L1) inhibitors: A propensity-score matched Cohort Study with competing risk analysis. *Cardiooncology* 2022, 8, 5. [CrossRef] [PubMed]

15. Dolladille, C.; Akroun, J.; Morice, P.M.; Dompmartin, A.; Eznine, E.; Sassier, M.; Da-Silva, A.; Plane, A.F.; Legallois, D.; L'Orphelin, J.M.; et al. Cardiovascular immunotoxicities associated with immune checkpoint inhibitors: A safety meta-analysis. *Eur. J. Heart J.* 2021, 42, 4964–4977. [CrossRef]

16. Gumusay, O.; Callan, J.; Rugo, H.S. Immunotherapy toxicity: Identification and management. *Breast Cancer Res. Treat.* 2022, 192, 1–17. [CrossRef]

17. Master, S.R.; Robinson, A.; Mills, G.M.; Mansour, R.P. Cardiovascular complications of immune checkpoint inhibitor therapy. *J. Clin. Oncol.* 2019, 37, 2568. [CrossRef]

18. Li, C.; Bhatti, S.A.; Ying, J. Immune Checkpoint Inhibitors—Associated Cardiotoxicity. *Cancers* 2022, 14, 1145. [CrossRef]

19. Salem, J.-E.; Manouchehri, A.; Moey, M.; Lebrun-Vignes, B.; Bastarache, L.; Pariente, A.; Gobert, A.; Spano, J.-P.; Balko, J.M.; Bonaca, M.P. Cardiovascular toxicities associated with immune checkpoint inhibitors: An observational, retrospective, pharmacovigilance study. *Lancet Oncol.* 2018, 19, 1579–1589. [CrossRef]

20. Upadhrasta, S.; Elias, H.; Patel, K.; Zheng, L. Managing cardiotoxicity associated with immune checkpoint inhibitors. *Chronic Dis. Transl. Med.* 2019, 5, 6–14. [CrossRef]
21. Hamid, O.; Puzanov, I.; Dummer, R.; Schachter, J.; Daud, A.; Schadendorf, D.; Blank, C.; Cranmer, L.D.; Robert, C.; Pavlick, A.C.; et al. Final analysis of a randomised trial comparing pembrolizumab versus investigator-choice chemotherapy for ipilimumab-refractory advanced melanoma. *Eur. J. Cancer* 2017, 86, 37–45. [CrossRef]

22. Robert, C.; Long, G.V.; Brady, B.; Dutriaux, C.; Maio, M.; Mortier, L.; Hassel, J.C.; Rutkowski, P.; McNeil, C.; Calinka-Warzocha, E.; et al. Nivolumab in previously untreated melanoma without BRAF mutation. *N. Engl. J. Med.* 2015, 372, 320–330. [CrossRef] [PubMed]

23. Weber, J.S.; D’Angelo, S.P.; Minor, D.; Hodi, F.S.; Gutzmer, R.; Neyns, B.; Khushalani, N.I.; Miller, W.H.; Jr.; Lao, C.D.; et al. Nivolumab versus chemotherapy in patients with advanced melanoma who progressed after anti-CTLA-4 treatment (CheckMate 037): A randomised, controlled, open-label, phase 3 trial. *Lancet Oncol.* 2015, 16, 375–384. [CrossRef]

24. Ascierto, P.A.; Del Vecchio, M.; Robert, C.; Mackiewicz, A.; Chiarion-Sileni, V.; Arance, A.; Lebbé, C.; Bastholt, L.; Hamid, O.; Rutkowski, P.; et al. Ipilimumab 10 mg/kg versus ipilimumab 3 mg/kg in patients with unresectable or metastatic melanoma: A randomised, double-blind, multicentre, phase 3 trial. *Lancet Oncol.* 2017, 18, 611–622. [CrossRef]

25. Hodi, F.S.; Chesney, J.; Pavlick, A.C.; Robert, C.; Grossmann, K.F.; McDermott, D.F.; Linette, G.P.; Meyer, N.; Giguere, J.K.; et al. Combined nivolumab and ipilimumab alone in patients with advanced melanoma: 2-year overall survival outcomes in a multicentre, randomised, controlled, phase 2 trial. *Lancet Oncol.* 2016, 17, 1558–1568. [CrossRef]

26. Robert, C.; Schachter, J.; Long, G.V.; Arance, A.; Grob, J.J.; Mortier, L.; Daud, A.; Carlino, M.S.; McNeil, C.; Lotem, M.; et al. Pembrolizumab versus Ipilimumab in Advanced Melanoma. *N. Engl. J. Med.* 2015, 372, 2521–2532. [CrossRef] [PubMed]

27. Weber, J.; Mandala, M.; Del Vecchio, M.; Gogas, H.J.; Arance, A.; Rutkowski, P.; Grob, J.J.; Courey, C.L.; Dalle, S.; Schenker, M.; Chiarion-Sileni, V.; Marquez-Rodas, I.; et al. Adjuvant Nivolumab versus Ipilimumab in Resected Stage III or IV Melanoma. *N. Engl. J. Med.* 2017, 377, 1824–1835. [CrossRef]

28. Wolchok, J.D.; Chiarion-Sileni, V.; Gonzalez, R.; Rutkowski, P.; Grob, J.J.; Cowey, C.L.; Lao, C.D.; Wagstaff, J.; Schadendorf, D.; Ferrucci, P.E.; et al. Overall Survival with Combined Nivolumab and Ipilimumab in Advanced Melanoma. *N. Engl. J. Med.* 2017, 377, 1345–1356. [CrossRef]

29. Wolchok, J.D.; Neyns, B.; Linette, G.; Negrier, S.; Lutzky, J.; Thomas, L.; Waterfield, W.; Schadendorf, D.; Smylie, M.; Guthrie, T.; Jr.; et al. Ipilimumab monotherapy in patients with pretreated advanced melanoma: A randomised, double-blind, multicentre, phase 2, dose-ranging study. *Lancet Oncol.* 2010, 11, 155–164. [CrossRef]

30. Pires da Silva, I.; Ahmed, T.; Reijers, I.L.M.; Weppier, A.M.; Betof Warner, A.; Patrinely, J.R.; Serra-Bellver, P.; Allayouz, C.; Mangana, J.; Nguyen, K.; et al. Ipilimumab alone or ipilimumab plus anti-PD-1 therapy in patients with metastatic melanoma resistant to anti-PD-(L)1 monotherapy: A multicentre, retrospective, cohort study. *Lancet Oncol.* 2021, 22, 836–847. [CrossRef]

31. Schöffski, P.; Tan, D.S.W.; Martin, M.; Ochoa-de-Olza, M.; Sarantopoulos, J.; Carvajal, R.D.; Kyi, C.; Esaki, T.; Frawria, A.; Akerley, W.; et al. Phase I/II study of the LAG-3 inhibitor ieramilimab (LAG525) ± anti-PD-1 spartalizumab (PDR001) in patients with advanced malignancies. *J. Immunother. Cancer* 2022, 10, e003776. [CrossRef]

32. Eggermont, A.M.M.; Kicinski, M.; Blank, C.U.; Mandala, M.; Long, G.V.; Atkins, V.; Dalle, S.; Haydon, A.; Khattak, A.; Carlino, M.S.; et al. Association Between Immune-Related Adverse Events and Recurrence-Free Survival Among Patients With Stage III Melanoma Randomized to Receive Pembrolizumab or Placebo: A Secondary Analysis of a Randomized Clinical Trial. *JAMA Oncol.* 2020, 6, 519–527. [CrossRef] [PubMed]

33. Hamid, O.; Robert, C.; Daud, A.; Hodi, F.S.; Hwu, W.J.; Kefferd, R.; Wolchok, J.D.; Hersey, P.; Joseph, R.W.; Weber, J.S.; et al. Safety and tumor response with pembrolizumab in melanoma. *N. Engl. J. Med.* 2013, 369, 134–144. [CrossRef] [PubMed]

34. Callahan, M.K.; Kluger, H.; Postow, M.A.; Segal, N.H.; Lesokhin, A.; Atkins, M.B.; Kirkwood, J.M.; Krishnan, S.; Bho, R.; Horak, C.; et al. Nivolumab Plus Ipilimumab in Patients With Advanced Melanoma: Updated Survival, Response, and Safety Data in a Phase I Dose-Escalation Study. *J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol.* 2018, 36, 391–398. [CrossRef] [PubMed]

35. Keilholz, U.; Mehnhert, J.M.; Bauer, S.; Bourgeois, H.; Patel, M.R.; Gravenor, D.; Nemunaitis, J.J.; Taylor, M.H.; Wyrwicz, L.; Lee, K.W.; et al. Avelumab in patients with previously treated metastatic melanoma: Phase Ib results from the JAVELIN Solid Tumor trial. *J. Immunother. Cancer* 2019, 7, 12. [CrossRef] [PubMed]

36. Tabbi, H.A.; Schadendorf, D.; Lipson, E.J.; Ascierto, P.A.; Matamala, L.; Castillo Gutiérrez, E.; Rutkowski, P.; Gogas, H.J.; Lao, C.D.; De Menezes, J.J.; et al. Relatlimab and Nivolumab versus Nivolumab in Untreated Advanced Melanoma. *N. Engl. J. Med.* 2022, 386, 24–34. [CrossRef]

37. Chitturi, K.R.; Xu, J.; Araujo-Gutierrez, R.; Bhimaraj, A.; Guha, A.; Hussain, I.; Kassi, M.; Bernicker, E.H.; Trachtenberg, B.H. Immune Checkpoint Inhibitor-Related Adverse Cardiovascular Events in Patients With Lung Cancer. *JACC CardioOncol.* 2019, 1, 182–192. [CrossRef]

38. Gettinger, S.N.; Horn, L.; Gandhi, L.; Spigel, D.R.; Antonia, S.J.; Rizvi, N.A.; Powderly, J.D.; Heist, R.S.; Carvajal, R.D.; Jackman, D.M.; et al. Overall Survival and Long-Term Safety of Nivolumab (Anti-Programmed Death 1 Antibody, BMS-936558, ONO-4538) in Patients With Previously Treated Advanced Non-Small-Cell Lung Cancer. *J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol.* 2015, 33, 2004–2012. [CrossRef]

39. Mok, T.S.K.; Wu, Y.L.; Kudaba, I.; Kowalski, D.M.; Cho, B.C.; Turna, H.Z.; Castro, G., Jr.; Srimuninnimit, V.; Laktionov, K.K.; Bondarenko, I.; et al. Pembrolizumab versus chemotherapy for previously untreated, PD-L1-expressing, locally advanced or metastatic non-small-cell lung cancer (KEYNOTE-042): A randomised, open-label, controlled, phase 3 trial. *Lancet* 2019, 393, 1819–1830. [CrossRef]

*J. Cardiovasc. Dev. Dis.* 2022, 9, 203
56. Ye, D.; Liu, J.; Zhou, A.; Zou, Q.; Li, H.; Fu, C.; Hu, H.; Huang, J.; Zhu, S.; Jin, J.; et al. Tislelizumab in Asian patients with non-small-cell lung cancer: Results from a phase 3, open-label, multicentre randomised controlled trial. *Lancet* 2017, 389, 255–265. [CrossRef]

57. Antonia, S.J.; Villegas, A.; Daniel, D.; Vicente, D.; Murakami, S.; Hui, R.; Yokoi, T.; Chiapporri, A.; Lee, K.H.; de Wit, M.; et al. Durvalumab after chemoradiotherapy in Stage III Non-Small-Cell Lung Cancer. *N. Engl. J. Med.* 2017, 377, 1919–1929. [CrossRef]

58. Shi, Y.; Fang, J.; Zhou, C.; Liu, A.; Wang, Y.; Meng, Q.; Ding, C.; Ai, B.; Gu, Y.; Yao, Y.; et al. Immune checkpoint inhibitor-related adverse events in lung cancer: Real-world incidence and management practices of 1905 patients in China. *Thorac. Cancer* 2022, 13, 412–422. [CrossRef] [PubMed]

59. Herbst, R.S.; Baas, P.; Kim, D.W.; Felip, E.; Pérez-Gracia, J.L.; Han, J.Y.; Molina, J.; Kim, J.H.; Arvis, C.D.; Ahn, M.J.; et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): A randomised controlled trial. *Lancet* 2016, 387, 1540–1550. [CrossRef]

60. Reck, M.; Rodriguez-Aruebá, D.; Robinson, A.G.; Hui, R.; Csöszi, T.; Fülöp, A.; Gottfried, M.; Peled, N.; Tafreshi, A.; Cuffe, S.; et al. Pembrolizumab versus Chemotherapy for Non-Small-Cell Lung Cancer. *N. Engl. J. Med.* 2016, 375, 1823–1833. [CrossRef] [PubMed]

61. Borchgrevink, C.; Paz-Ares, L.; Horn, L.; Spigel, D.R.; Steins, M.; Ready, N.E.; Chow, L.Q.; Vokes, E.E.; Felip, E.; Golgardo, E.; et al. Nivolumab versus Docetaxel in Advanced Nonsmall-Non-Small-Cell Lung Cancer. *N. Engl. J. Med.* 2015, 373, 1627–1639. [CrossRef]

62. Brahmer, J.; Reckamp, K.L.; Baas, P.; Crinò, L.; Eberhardt, W.E.; Poddubskaya, E.; Antonia, S.; Pluzanski, A.; Vokes, E.E.; Golgardo, E.; et al. Nivolumab versus Docetaxel in Advanced Squamous-Cell Non-Small-Cell Lung Cancer. *N. Engl. J. Med.* 2015, 373, 123–135. [CrossRef]

63. Carbone, D.P.; Reck, M.; Paz-Ares, L.; Cereelan, B.; Horn, L.; Steins, M.; Felip, E.; van den Heuvel, M.M.; Ciuleanu, T.E.; Badin, F.; et al. First-Line Nivolumab in Stage IV or Recurrent Non-Small-Cell Lung Cancer. *N. Engl. J. Med.* 2017, 376, 2415–2426. [CrossRef]

64. Abou Alaïwi, S.; Xie, W.; Nassar, A.H.; Dudani, S.; Martini, D.; Bakoueny, Z.; Steinhalter, J.A.; Nuzzo, P.V.; Flippot, R.; Martinez-Chanza, N.; et al. Safety and efficacy of restarting immune checkpoint inhibitors after clinically significant immune-related adverse events in metastatic renal cell carcinoma. *J. Immunother. Cancer* 2020, 8, e00144. [CrossRef]

65. Yekedüz, E.; Ertürk, İ.; Tural, D.; Karadurmuş, N.; Karakaya, S.; Hızal, M.; Arıkan, R.; Arslan, Ç.; Taban, H.; Küçükarda, A.; et al. Nivolumab in metastatic renal cell carcinoma: Results from the Turkish Oncology Group Kidney Cancer Consortium database. *Future Oncol.* 2021, 17, 4861–4869. [CrossRef]

66. Motzer, R.J.; Tannir, N.M.; McDermott, D.F.; Aréñ Frontera, O.; Melichar, B.; Choueiri, T.K.; Plimack, E.R.; Barthélémy, P.; Porta, C.; George, S.; et al. Nivolumab plus Ipilimumab versus Sunitinib in Advanced Renal-Cell Carcinoma. *N. Engl. J. Med.* 2018, 378, 1277–1290. [CrossRef]

67. Motzer, R.J.; Rini, B.I.; McDermott, D.F.; Redman, B.G.; Kuzel, T.M.; Harrison, M.R.; Vaishampayan, U.N.; Drabkin, H.A.; George, S.; Logan, T.F.; et al. Nivolumab for Metastatic Renal Cell Carcinoma: Results of a Randomized Phase II Trial. *J. Clin. Oncol.* 2015, 33, 1430–1437. [CrossRef]

68. McFarlane, J.J.; Kochenderfer, M.D.; Olsen, M.R.; Bauer, T.M.; Molina, A.; Hauke, R.J.; Reeves, J.A.; Babu, S.; Van Veldenhuizen, P.; Somer, B.; et al. Safety and Efficacy of Nivolumab in Patients With Advanced Clear Renal Cell Carcinoma: Results From the Phase IIIb/IV CheckMate 374 Study. *Clin. Genitourin. Cancer* 2020, 18, 469–476.e464. [CrossRef]

69. Motzer, R.J.; Escudier, B.; McDermott, D.F.; George, S.; Hammers, H.J.; Srinivas, S.; Tykodi, S.S.; Sosman, J.A.; Procopio, G.; Plimack, E.R.; et al. Nivolumab versus Everolimus in Advanced Renal-Cell Carcinoma. *N. Engl. J. Med.* 2015, 373, 1803–1813. [CrossRef] [PubMed]

70. Vaishampayan, U.; Schöffski, P.; Ravaud, A.; Borel, C.; Pegoerro, J.; Chaves, J.; Morris, J.C.; Kotecki, N.; Smakal, M.; Zhou, D.; et al. Avelumab monotherapy as first-line or second-line treatment in patients with metastatic renal cell carcinoma: Phase Ib results from the JAVELIN Solid Tumor trial. *J. Immunother. Cancer* 2019, 7, 279. [CrossRef] [PubMed]

71. Bellmunt, J.; Hussain, M.; Gschwend, J.E.; Albers, P.; Oudard, S.; Castellano, D.; Daneshmand, S.; Nishiyama, H.; Majchrowicz, M.; Degaonkar, V.; et al. Adjuvant atezolizumab versus observation in muscle-invasive urothelial carcinoma (IMvigor010): A multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol.* 2021, 22, 525–537. [CrossRef]

72. Ye, D.; Liu, J.; Zhou, A.; Zou, Q.; Li, H.; Fu, C.; Hu, H.; Huang, J.; Zhu, S.; Jin, J.; et al. Tislelizumab in Asian patients with previously treated locally advanced or metastatic urothelial carcinoma. *Cancer Sci.* 2021, 112, 305–313. [CrossRef] [PubMed]

73. Powles, T.; van der Heijden, M.S.; Castellano, D.; Galsky, M.D.; Loriot, Y.; Petrylak, D.P.; Ogawa, O.; Park, S.H.; Lee, J.L.; De Giorgi, U.; et al. Durvalumab alone and durvalumab plus tremelimumab versus chemotherapy in previously untreated patients with unresectable, locally advanced or metastatic urothelial carcinoma (DANUBE): A randomised, open-label, multicentre, phase 3 trial. *Lancet Oncol.* 2020, 21, 1574–1588. [CrossRef]

74. Sharma, P.; Retz, M.; Sieffker-Radtke, A.; Baron, A.; Necchi, A.; Bedke, J.; Plimack, E.R.; Vaena, D.; Grimm, M.O.; Bracarda, S.; et al. Nivolumab in urothelial urothelial carcinoma after platinum therapy (CheckMate 275): A multicentre, single-arm, phase 2 trial. *Lancet Oncol.* 2017, 18, 312–322. [CrossRef]

75. Van der Heijden, M.S.; Loriot, Y.; Durán, I.; Ravaud, A.; Retz, M.; Vogelzang, N.J.; Nelson, B.; Wang, J.; Shen, X.; Powles, T. Atezolizumab Versus Chemotherapy in Patients with Platinum-treated Locally Advanced or Metastatic Urothelial Carcinoma: A Long-term Overall Survival and Safety Update from the Phase 3 IMvigor211 Clinical Trial. *Eur. Urol.* 2021, 80, 7–11. [CrossRef]
60. Rosenberg, J.E.; Hoffman-Censits, J.; Powles, T.; van der Heijden, M.S.; Balar, A.V.; Necchi, A.; Dawson, N.; O’Donnell, P.H.; Balmanoukian, A.; Lorigi, Y.; et al. Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: A single-arm, multicentre, phase 2 trial. *Lancet* **2016**, *387*, 1909–1920. [CrossRef]

61. Powles, T.; Cézeti, T.; Ozguroglu, M.; Matsubara, N.; Géczi, L.; Cheng, S.Y.; Fradet, Y.; Oudard, S.; Vulsteke, C.; Morales Barrera, R.; et al. Pembrolizumab alone or combined with chemotherapy versus chemotherapy as first-line therapy for advanced urothelial carcinoma (KEYNOTE-361): A randomised, open-label, phase 3 trial. *Lancet Oncol.* **2021**, *22*, 931–945. [CrossRef]

62. André, T.; Shiu, K.K.; Kim, T.W.; Jensen, B.V.; Jensen, L.H.; Punt, C.; Smith, D.; García-Carbonero, R.; Benavides, M.; Gibbs, P.; et al. Pembrolizumab in Microsatellite-Instability-High Advanced Colorectal Cancer. *N. Engl. J. Med.* **2020**, *383*, 2207–2218. [CrossRef] [PubMed]

63. Shi, Y.; Su, H.; Song, Y.; Jiang, W.; Sun, X.; Qian, W.; Zhang, W.; Gao, Y.; Jin, Z.; Zhou, J.; et al. Safety and activity of sintilimab in patients with relapsed or refractory classical Hodgkin lymphoma (ORIENT-1): A multicentre, single-arm, phase 2 trial. *Lancet Haematol.* **2019**, *6*, e12–e19. [CrossRef]

64. Shi, Y.; Wu, J.; Wang, Z.; Zhang, L.; Wang, Z.; Zhang, M.; Cen, H.; Peng, Z.; Li, Y.; Fan, L.; et al. Efficacy and safety of geptanolimab (GB226) for relapsed or refractory peripheral T cell lymphoma: An open-label phase 2 study (Explore-002). *J. Hematol. Oncol.* **2021**, *14*, 12. [CrossRef]

65. Heinzerling, L.; Ott, P.A.; Hodi, F.S.; Husain, A.N.; Tajmir-Riahi, A.; Tawbi, H.; Pauschinger, M.; Gajewski, T.F.; Lipson, E.J.; Luke, J.J. Cardiotoxicity associated with CTLA4 and PD1 blocking immunotherapy. *J. Immunother. Cancer* **2016**, *4*, 50. [CrossRef]

66. Kang, Y.K.; Boku, N.; Satoh, T.; Ryu, M.H.; Chao, Y.; Kato, K.; Chung, H.C.; Chen, J.S.; Muro, K.; Kang, W.K.; et al. Nivolumab in patients with advanced gastric or gastro-oesophageal junction cancer refractory to, or intolerant of, at least two previous chemotherapy regimens (ONO-4538-12, ATTRACTION-2): A randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet* **2017**, *380*, 2461–2471. [CrossRef]

67. Wadhwa, D.; Fallah-Rad, N.; Grenier, D.; Krahn, M.; Fang, T.; Ahmadie, R.; Walker, J.R.; Lister, D.; Arora, R.C.; Barac, I.; et al. Trastuzumab mediated cardiotoxicity in the setting of adjuvant chemotherapy for breast cancer: A retrospective study. *Breast Cancer Res. Treat* **2009**, *117*, 357–364. [CrossRef] [PubMed]

68. Zhu, A.X.; Finn, R.S.; Edeline, J.; Cattan, S.; Ogasawara, S.; Palmer, D.; Verslype, C.; Zagonel, V.; Fartoux, L.; Vogel, A.; et al. Pembrolizumab in patients with advanced hepatocellular carcinoma previously treated with sorafenib (KEYNOTE-224): A non-randomised, open-label phase 2 trial. *Lancet Oncol.* **2018**, *19*, 940–952. [CrossRef]

69. Quispel-Janssen, J.; van der Noort, V.; de Vries, J.F.; Zimmerman, M.; Lalezari, F.; Thunnissen, E.; Monkhorst, K.; Schouten, R.; Schunselfaar, L.; Disselhorst, M.; et al. Programmed Death 1 Blockade With Nivolumab in Patients With Recurrent Malignant Pleural Mesothelioma. *J. Thorac. Oncol. Off. Publ. Int. Assoc. Study Lung Cancer* **2018**, *13*, 1569–1576. [CrossRef]

70. Vos, J.L.; Elbers, J.B.W.; Krijgsman, O.; Traets, J.J.H.; Qiao, X.; van der Leun, A.M.; Lubeck, Y.; Seignette, I.M.; Smit, L.A.; Willems, S.M.; et al. Neoadjuvant immunotherapy with nivolumab and ipilimumab induces major pathological responses in patients with head and neck squamous cell carcinoma. *Nat. Commun.* **2021**, *12*, 7348. [CrossRef]

71. Nghiem, P.T.; Bhatia, S.; Lipson, E.J.; Kuchchadkar, R.R.; Miller, N.J.; Annamalai, L.; Berry, S.; Chartash, E.K.; Daud, A.; Fling, S.P.; et al. PD-1 Blockade with Pembrolizumab in Advanced Merkel-Cell Carcinoma. *N. Engl. J. Med.* **2016**, *374*, 2524–2532. [CrossRef] [PubMed]

72. Johnson, D.B.; Balko, J.M.; Compton, M.L.; Matsubara, N.; Géczi, L.; Cheng, S.Y.; Fradet, Y.; Oudard, S.; Vulsteke, C.; Morales Barrera, R.; et al. Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: A single-arm, multicentre, phase 2 trial. *Lancet* **2016**, *387*, 1909–1920. [CrossRef]

73. Heinzerling, L.; Ott, P.A.; Hodi, F.S.; Husain, A.N.; Tajmir-Riahi, A.; Tawbi, H.; Pauschinger, M.; Gajewski, T.F.; Lipson, E.J.; Luke, J.J. Cardiotoxicity associated with CTLA4 and PD1 blocking immunotherapy. *J. Immunother. Cancer* **2016**, *4*, 50. [CrossRef]

74. Kang, Y.K.; Boku, N.; Satoh, T.; Ryu, M.H.; Chao, Y.; Kato, K.; Chung, H.C.; Chen, J.S.; Muro, K.; Kang, W.K.; et al. Nivolumab in patients with advanced gastric or gastro-oesophageal junction cancer refractory to, or intolerant of, at least two previous chemotherapy regimens (ONO-4538-12, ATTRACTION-2): A randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet* **2017**, *380*, 2461–2471. [CrossRef]

75. Wadhwa, D.; Fallah-Rad, N.; Grenier, D.; Krahn, M.; Fang, T.; Ahmadie, R.; Walker, J.R.; Lister, D.; Arora, R.C.; Barac, I.; et al. Trastuzumab mediated cardiotoxicity in the setting of adjuvant chemotherapy for breast cancer: A retrospective study. *Breast Cancer Res. Treat* **2009**, *117*, 357–364. [CrossRef] [PubMed]

76. Zhu, A.X.; Finn, R.S.; Edeline, J.; Cattan, S.; Ogasawara, S.; Palmer, D.; Verslype, C.; Zagonel, V.; Fartoux, L.; Vogel, A.; et al. Pembrolizumab in patients with advanced hepatocellular carcinoma previously treated with sorafenib (KEYNOTE-224): A non-randomised, open-label phase 2 trial. *Lancet Oncol.* **2018**, *19*, 940–952. [CrossRef]

77. Khunger, A.; Battel, L.; Wadhawan, A.; More, A.; Kapoor, A.; Agrawal, N. New Insights into Mechanisms of Immune Checkpoint Inhibitor-Associated Myocarditis. *Curr. Oncol. Rep.* **2017**, *19*, 1749–1755. [CrossRef] [PubMed]

78. Li, Y.; Wang, Z.; Zhang, L.; Zhang, M.; Cen, H.; Peng, Z.; Li, Y.; Fan, L.; et al. Efficacy and safety of geptanolimab (GB226) for relapsed or refractory peripheral T cell lymphoma: An open-label phase 2 study (Explore-002). *J. Hematol. Oncol.* **2021**, *14*, 12. [CrossRef]

79. Ganatra, S.; Neilan, T.G. Immune checkpoint inhibitor-associated myocarditis. *Oncologist* **2018**, *23*, 879–886. [CrossRef]

80. Lyon, A.R.; Yousaf, N.; Battisti, N.M.L.; Moslehi, J.; Larkin, J. Immune checkpoint inhibitors and cardiovascular toxicity. *Lancet Oncol.* **2018**, *19*, e447–e458. [CrossRef]
83. Newman, J.L.; Stone, J.R. Immune checkpoint inhibition alters the inflammatory cell composition of human coronary artery atherosclerosis. *Cardiovasc. Pathol. Off. J. Soc. Cardiovasc. Pathol.* 2019, 43, 107148. [CrossRef] [PubMed]

84. Nykl, R.; Fischer, O.; Vykoupek, K.; Taborsky, M. A unique reason for coronary spasm causing temporary ST elevation myocardial infarction (inferior STEMI)—systemic inflammatory response syndrome after use of pembrolizumab. *Arch. Med. Sci. Atheroscler. Dis.* 2017, 2, e100–e102. [CrossRef] [PubMed]

85. Love, V.A.; Grabie, N.; Duramad, P.; Stavarakis, G.; Sharpe, A.; Lichtman, A. CTLA-4 ablation and interleukin-12–driven differentiation synergistically alters cardiac pathogenicity of cytotoxic T lymphocytes. *Circ. Res.* 2007, 101, 248–257. [CrossRef]

86. Di Giacomo, A.M.; Danielli, R.; Guidoboni, M.; Calabrò, L.; Carlucci, D.; Miracco, C.; Volterrani, L.; Mazzei, M.A.; Biagioli, M.; Altomonte, M.; et al. Therapeutic efficacy of ipilimumab, an anti-CTLA-4 monoclonal antibody, in patients with metastatic melanoma unresponsive to prior systemic treatments: Clinical and immunological evidence from three patient cases. *Cancer Immunol. Immunother.* 2009, 58, 1297–1306. [CrossRef]

87. Chen, D.Y.; Huang, W.K.; Chien-Chia Wu, V.; Chang, W.C.; Chen, J.S.; Chuang, C.K.; Chu, P.H. Cardiovascular toxicity of immune checkpoint inhibitors in cancer patients: A review when cardiology meets immuno-oncology. *J. Formos. Med. Assoc. Taiwan Yi Zhi* 2020, 119, 1461–1475. [CrossRef]

88. Altan, M.; Toki, M.I.; Gettinger, S.N.; Carvajal-Hausdorf, D.E.; Zugazagoitia, J.; Sinard, J.H.; Herbst, R.S.; Rimm, D.L. Immune Checkpoint Inhibitor-Associated Pericarditis. *J. Thorac. Oncol.* 2019, 14, 1102–1108. [CrossRef]

89. Chen, D.S.; Mellman, I. Oncology meets immunology: The cancer-immunity cycle. *Immunity* 2013, 39, 1–10. [CrossRef]

90. Varrieci, G.; Galdiero, M.R.; Tocchetti, C.G. Cardiac toxicity of immune checkpoint inhibitors: Cardio-oncology meets immunology. *Circulation* 2017, 136, 1989–1992. [CrossRef]

91. Coen, V.; Grabie, N.; Duramad, P.; Stavarakis, G.; Sharpe, A.; Lichtman, A. CTLA-4 ablation and interleukin-12–driven differentiation synergistically alters cardiac pathogenicity of cytotoxic T lymphocytes. *Circ. Res.* 2007, 101, 248–257. [CrossRef]

92. Giatromanolaki, A.; Koukourakis, M.I.; Koutsopoulos, A.; Mendrinos, S.; Sivridis, E. The metabolic interactions between tumor cells and tumor-associated stroma (TAS) in prostatic cancer. *Cancer Biol.* 2012, 13, 1284–1289. [CrossRef] [PubMed]

93. Kalbasi, A.; Ribas, A. Tumour-intrinsic resistance to immune checkpoint blockade. *Nat. Rev. Immunol.* 2020, 20, 25–39. [CrossRef] [PubMed]

94. Van Rooij, N.; van Buuren, M.M.; Philips, D.; Velds, A.; Toebes, M.; Rimm, D.L. Immune Checkpoint Inhibitor-Associated Pericarditis. *J. Thorac. Oncol.* 2019, 14, 1102–1108. [CrossRef]

95. Liu, Z.; Ahn, M.; Kurokawa, T.; Ly, A.; Zhang, G.; Wang, F.; Yamada, T.; Sadagopan, A.; Cheng, J.; Ferrone, C.; et al. A fast, simple, and cost-effective method of expanding patient-derived xenograft mouse models of pancreatic ductal adenocarcinoma. *J. Transl. Med.* 2020, 18, 255. [CrossRef] [PubMed]

96. Oudin, M.J.; Barbier, L.; Kosciuk, T.; Kreidl, E.; Gertler, F. Abstract 4031: Novel tumor intrinsic vs. extrinsic mechanisms of resistance to chemotherapy in metastatic disease. *Cancer Res.* 2018, 78, 4031. [CrossRef]

97. Llovet, J.M.; Castet, F.; Heikenwalder, M.; Maini, M.K.; Mazzaferro, V.; Pinato, D.J.; Pikarsky, E.; Zhu, A.X.; Finn, R.S. Immunotherapies for hepatocellular carcinoma. *Nat. Rev. Clin. Oncol.* 2022, 19, 151–172. [CrossRef]

98. Mocan-Hognogi, D.L.; Trancali, S.; Farcaș, A.D.; Mocan-Hognogi, R.F.; Pârvu, A.V.; Bojan, A.S. Immune Checkpoint Inhibitors and the Heart. *Front. Cardiovasc. Med.* 2021, 8, 726426. [CrossRef]

99. Tajiri, K.; Ieda, M. Cardiac complications in immune checkpoint inhibition therapy. *Front. Cardiovasc. Med.* 2019, 6, 3. [CrossRef]

100. Johnson, D.B.; Sullivan, R.J.; Menzies, A.M. Immune checkpoint inhibitors in challenging populations. *Cancer* 2017, 123, 1904–1911. [CrossRef]

101. Schneider, B.J.; Naidoo, J.; Santomasso, B.D.; Lacchetti, C.; Adkins, S.; Anadkat, M.; Atkins, M.B.; Brassil, K.J.; Caterino, J.M.; Chau, I.; et al. Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: ASCO Guideline Update. *J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol.* 2021, 39, 4073–4126. [CrossRef] [PubMed]