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Novel insights into cardiovascular toxicity of cancer targeted and immune therapies: Beyond ischemia with non-obstructive coronary arteries (INOCA)

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ABSTRACT

Novel immune and targeted therapies approved over the past 2 decades have resulted in dramatic improvements in cancer-specific outcomes for many cancer patients. However, many of these agents can induce cardiovascular toxicity in a subset of patients. The field of cardio-oncology was established based on observations that anti-neoplastic chemotherapies and mantle radiation can lead to premature cardiomyopathy in cancer survivors. While conventional chemotherapy, targeted therapy, and immune therapies can all result in cardiovascular adverse events, the mechanisms, timing, and incidence of these events are inherently different. Many of these effects converge upon the coronary microvasculature to involve, through endocardial endothelial cells, a more direct effect through close proximity to cardiomyocyte with cellular communication and signaling pathways. In this review, we will provide an overview of emerging paradigms in the field of Cardio-Oncology, particularly the role of the coronary microvasculature in mediating cardiovascular toxicity of important cancer targeted and immune therapies. As the number of cancer patients treated with novel immune and targeted therapies grows exponentially and subsequently the number of long-term cancer survivors dramatically increases, it is critical that cardiologists and cardiology researchers recognize the unique potential cardiovascular toxicities of these agents.

1. Introduction

With the development of intensive anti-neoplastic therapies, the prognosis of patients with cancer has substantially improved. As a result, an increasing number of cancer survivors is seen with premature cardiomyopathy despite the absence of significant cardiovascular risk factors, often decades after completion of chemotherapy and/or radiotherapy [1,2]. Cancer therapy-induced cardiovascular toxicity was almost considered to be exclusively associated with the use of anthracyclines for several decades until it became clear that other chemotherapeutic agents and radiotherapy can also have undesirable effects on the cardiovascular system, including arterial and pulmonary hypertension, supraventricular and ventricular arrhythmia, systolic and diastolic cardiac dysfunction, and coronary artery disease [2–4]. For example, among survivors of cancer, a 1.7 to 2-fold increase in cardiovascular death was reported in patients who have undergone radiotherapy [5]. Importantly, as survival time increases for patients with cancer, cardiovascular-related non-cancer mortality was shown to gradually overtake cancer-related mortality [6].

Over the past decade, there have been significant advances in understanding the biology of cancers with particular focus on the heterogeneity of their molecular drivers as well as understanding of the immune response to cancer. This has provided a new foundation towards rationally designed therapeutic regimens that target specific genes and proteins [7,8]. Cancer targeted and immune therapies have demonstrated considerable clinical efficacy and improved overall survival rates and have revolutionized the era of personalized medicine [9]. Their phenomenal success, however, has come at the cost of potential adverse events that can affect a wide variety of systems and organs, including the cardiovascular system [10] While both, conventional chemotherapy as well as novel cancer targeted and immune therapies can result in cardiovascular adverse events, the mechanisms and relative incidence of cardiovascular events are inherently different between these agents. Understanding their safety profile becomes even more complicated by the fact that the novel drugs are sometimes combined, concomitantly or sequentially, with conventional chemotherapy

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[11,12]. As a result, cardiovascular monitoring for earlier detection of subclinical myocardial dysfunction in patients on some of these novel cancer therapies has been recommended by international guidelines and position articles [10]. This further emphasizes the importance of recognizing the field of Cardio-Oncology in multidisciplinary patient care [13].

Cardiovascular toxicity can generally result from direct cardiomyocyte damage and/or ischemia [14]. While ischemia with non-obstructive coronary arteries (INOCA) has been recognized as one underlying etiology for ischemic heart disease, deeper insights into the role of the cardiac endothelium have emphasized the role of coronary microvascular dysfunction as an important underlying factor in the pathogenesis of cardiovascular toxicity [15]. The potential contributing role of cancer targeted therapy in promoting coronary microvascular dysfunction has been the subject of a variety of studies, thus providing novel and deeper insights that extended beyond INOCA [16]. In this review, we will provide an overview of emerging paradigms in the field of Cardio-Oncology, particularly the role of the coronary microvasculature in mediating cardiovascular toxicity of important cancer targeted therapies, namely ERBB-2 monoclonal antibodies and tyrosine kinase inhibitors, angiogenesis inhibitors, proteasome inhibitors, BRAF/MEK inhibitors, and immune checkpoint inhibitors (ICI) (Table 1).

2. ERBB-2 targeted therapy

2.1. ERBB-2 monoclonal antibodies

The ERBB-2 oncogene, which encodes the HER2/neu receptor tyrosine kinase, a member of the epidermal growth factor receptor (EGFR) family, is frequently overexpressed in breast cancer (20 % HER-2 positive), and was historically associated with a poor prognosis [17]. However, the introduction of HER-2 directed targeted therapies has resulted in dramatic improvements in outcomes in HER-2 + breast cancer [18]. The most commonly used targeted therapy drug in HER-2 + breast cancer is trastuzumab, a humanized monoclonal antibody that recognizes an extracellular domain of HER-2. Combination of trastuzumab with chemotherapy results in substantial improvement in progression-free survival and overall survival for both metastatic and localized HER-2 + breast cancer [19–21]. In clinically localized HER-2 + breast cancer, treatment for 12 months with trastuzumab is there standard of care; however, in the metastatic setting, patients are continued on treatment until progression which can be many years (median PFS 102 months) [22,23] Trastuzumab's efficacy, however, comes at the expense of cardiovascular toxicity with an incidence up to 28 % [20,24,25]. Cardiovascular toxicity was not limited to patients who received trastuzumab concurrent with anthracycline, which is a known cardiac toxin, but also was seen in patients who received other chemotherapeutic agents, such as paclitaxel, with 13 % of patients receiving trastuzumab and this microtubule inhibitor developing cardiac toxicity [24]. Sequential treatment of trastuzumab and chemotherapy is associated with lower risk for cardiovascular toxicity as compared to concurrent trastuzumab and chemotherapy with concurrent trastuzumab and anthracycline carrying the greatest risk among all combinations [26–28].

With at least 276,000 women worldwide newly diagnosed with HER-2 positive breast cancer each year, understanding the mechanisms of cardiovascular toxicity of trastuzumab is critical [29]. Subsequent to the early clinical trials on trastuzumab, there has been emerging evidence that HER-2 not only is an EGFR, but also serves as a co-receptor for neuregulin-1 (NRG-1)-activated ERBB-3 (HER3) or ERBB-4 (HER4) receptor tyrosine kinases [30]. NRG-1 is one of four signaling proteins in the neuregulin family that act as EGFR ligands [31]. Studies on mice where HER-2 was selectively knocked out in cardiomyocytes showed resultant cardiomyopathy and increased sensitivity to pressure overload and anthracyclines [32]. On the other hand, infusion of recombinant NRG-1 peptide fragment into four different animal models of heart

Table 1
Take-home messages on novel insights into cardiovascular toxicity for important cancer targeted therapy.

Targeted drug therapy		Postulated mechanisms
ERBB-2 Targeted Therapy	ERBB-2 Monoclonal Antibodies (e.g. Trastuzumab and Pertuzumab)	▪ Inhibition of the protective survival-promoting NRG-1 pathway ▪ Loss of HER-4/HER-4 homodimerization and HER-4/HER-2 heterodimerization ▪ NRG-1 inhibition decreases the expression of eNOS and increases iNOS, thus leading to enhanced production of ROS ▪ Cardiac endothelial cells in the myocardial capillaries and the endocardial endothelium in close proximity to cardiomyocytes ▪ Inhibition of downstream effectors that involve activation of the PI-3-K, AKT, and MAPK pathways ▪ Inhibition of autophagy, which usually protects cardiomyocytes against stress
	ERBB-2 Receptor Tyrosine Kinase Inhibitors (e.g. Lapatinib, neratinib, and tucatinib)	▪ Dual inhibition of EGFR1 and ERBB-2 ▪ Reduced downstream effectors of PI-3-K, AKT, and MAPK pathways ▪ Impaired autophagy, thus leading to accumulation of damaged mitochondria, autophagolysosomes, and free radicals and increased causing oxidative stress and cardiomyocytes toxicity ▪ Less cardiovascular toxicity rates compared to ERBB-2 monoclonal antibodies: (1) Activation of AMPK pathway, which inhibits TNF-α-induced cardiomyocyte cell death, as opposed to trastuzumab, which inhibits this pathway (2) AMPK is a major regulator of metabolic processes in the setting of stress and is critical for maintaining cardiomyocyte survival
Angiogenesis Inhibitors (e.g. Bevacizumab, sunitinib, sorafenib, and pazopanib)		▪ VEGF-signaling pathway inhibition and myocardial capillary rarefaction ▪ Induction of hypoxia and hypoxia-inducible genes in cardiomyocytes ▪ Destabilization of HIF-α in cardiomyocytes ▪ Increased incidence of hypertension: VEGF Inactivation of eNOS and production of vasoconstrictors, such as endothelin-1, and capillary rarefaction ▪ Hypertension, in turn, results in increased left ventricular afterload and peripheral vascular resistance, which can lead to pressure- and volume-mediated left ventricular remodeling
Proteasome Inhibitors (e.g. Bortezomib and Carfilzomib)		▪ eNOS uncoupling in myocardial endothelial cells ▪ Reduction in oxygen supply and increased reactive ROS ▪ Ultimate increased oxidative stress and functional and structural changes in the myocardium consistent with hypertrophic-restrictive cardiomyopathy ▪ Abnormal accumulation of ubiquitinated proteins thus forming higher order protein aggregates that are cytotoxic

(continued on next page)

Table 1 (*continued*)

Targeted drug therapy	Postulated mechanisms
	▪ These aggregates consist of soluble oligomers and aggresomes that form inclusion bodies, which, in turn, contribute to increased expression of ROS, cell injury, and caspase-mediated apoptosis ▪ Enlarged cardiomyocytes exhibiting vacuolization, mitochondrial dysfunction, and fibrosis
BRAF/MEKI Inhibitors (e.g. encorafenib/binimetinib and dabrafenib/trametinib)	▪ Inhibition of the Ras-RAF-MEK-ERK pathway is a key component in cardiomyocyte hypertrophy, cardiac remodeling, and cardiomyocyte death ▪ Cardiac hypertrophy results as a response to stressful stimuli, including mechanical overload and oxidative stress ▪ Inhibition of Ras-RAF-MEK-ERK signaling pathway by BRAF/MEK inhibitors results in loss of its cardioprotective effect ▪ Loss of ERK1/2 activation by phospholipase C, resulting in decreased eNOS and prostacyclin-mediated PKC, which usually promotes vasodilation
Immune Checkpoint Inhibitors (e.g. pembrolizumab, nivolumab, nivolumab-relatlimab, and atezolizumab)	▪ ICI-associated inflammation may influence atherosclerotic coronary plaques and promote fibrous plaque rupture, thus leading to acute myocardial infarction ▪ Significant increase in the ratio of T lymphocytes to macrophages (CD3/CD68 ratio) ▪ Interfere with immune checkpoint signaling in cardiomyocytes, thus causing breakdown of peripheral immune tolerance and lowering the threshold for T cell activation: Autoimmune myocarditis ▪ Increased cardiac-specific antimyosin autoantibodies and cardiac antigen-specific T cells ▪ Clonal expansion of T cells that target homologous antigens shared by both, the tumor and the myocardium

failure, namely rat infarct model, rat anthracycline cardiomyopathy model, rat myocarditis model, and dog rapid pacing model, resulted in improved hemodynamics and improved survival compared to angiotensin inhibitors [33]. Therefore, in vitro experiments have shown that recombinant NRG-1 demonstrates protective effect on cardiomyocytes from anthracycline-induced myofibrillar disarray [34].

NRG-1 triggers HER-4/HER-4 homodimerization and HER-4/HER-2 heterodimerization on cardiomyocytes to induce protective pathways in response to stress [35]. It also stimulates glucose uptake and protein synthesis in cardiomyocytes [36]. Preclinical data demonstrated that NRG-1 inhibition decreases the expression of endothelial nitric oxide synthase (eNOS) and increases inducible nitric oxide synthase (iNOS), thus leading to enhanced production of reactive oxygen species (ROS) [37]. As a result, NRG-1 has been shown to reduce contraction without impairing diastole by upregulating eNOS and reducing the effect of β-adrenergic stimulation [38]. In addition, NRG-1 signaling, through ERBB2-containing heterodimers, enhances cellular hypertrophy and cell survival through downstream effectors that involve activation of the phosphoinositide 3-kinase (PI-3-K), protein kinase B (also known as AKT), and mitogen-activated protein kinase (MAPK) pathways [39] (Fig. 1A). It is postulated that inhibition of these downstream pathways results in inhibition of autophagy, which is a catabolic recycling pathway triggered by intra- and extra-cellular stimuli to maintain cellular homeostasis and protect cardiomyocytes against stress. Consequently, autophagy impairment leads to massive accumulation of damaged mitochondria and free radicals, thus increased causing oxidative stress and cardiomyocytes toxicity. As such, it is hypothesized that trastuzumab can cause cardiac toxicity through inhibition of this protective survival-promoting NRG-1 pathway to which HER-2 is a coreceptor [40].

NRG-1, which acts as a paracrine factor that impacts cardiomyocytes survival, is released by cardiac endothelial cells. Preclinical data on the protective effect of NRG-1 to which HER-2 is a coreceptor suggest that the HER-2 pathway has a survival-promoting signaling pathway in the cardiac endothelial cells that can help cardiomyocytes cope with stress conditions [41]. It is important to distinguish between the role of cardiac endothelial cells in the myocardial capillaries and at the endocardium, on one hand, and that of coronary vascular endothelium in the major epicardial and smaller intramyocardial coronary arteries, on the other. The coronary vascular endothelium in the coronary conduit and resistance vessels controls the coronary artery function similar to other vascular beds in the body and contributes indirectly to the cardiac function through controlling the coronary blood supply to the myocardium. On the other hand, cardiac endothelial cells in the myocardial capillaries and the endocardial endothelium are in close proximity to cardiomyocytes, thus exerting a more direct effect through cellular communication and signaling pathways between both cell types and contributing to anti-HER-2-mediated cardiomyocyte toxicity [42].

Pertuzumab is a recombinant humanized monoclonal antibody that targets an epitope near the extracellular domain II of ERBB-2 and results in the steric inhibition of ERBB-2 dimerization [43–45]. Rates of cardiovascular toxicity in the setting of pertuzumab treatment have been reported to range between 8 and 16 % [46]. Phase II studies on patients receiving single-agent pertuzumab for HER2-negative breast cancer with prior exposure to anthracycline-containing chemotherapy showed that 10 % of patients developed a 10–15 % drop in their left ventricular ejection fraction at a median of 100 days [47]. Another study showed similar rates of cardiac dysfunction for combination therapy with pertuzumab, trastuzumab, and docetaxel, as compared to placebo, trastuzumab, and docetaxel [48]. The mechanism of pertuzumab-related cardiac toxicity is not yet fully understood. However, it is hypothesized that it also exerts this effect through inhibition of the NRG-1 pathway, similar to trastuzumab. Alteration in NRG-1 and ERBB signaling pathways due to pertuzumab and the association between circulating serum NRG-1 levels and the extent of pertuzumab-related cardiovascular toxicity are areas of active investigation [16].

Several American and European governing societies in cardiology and oncology have published guidelines on the cardiovascular monitoring for patients receiving ERBB2 monoclonal antibodies and on the management of their toxicities. These guidelines recommend a cardiological assessment before treatment initiation, including a physical examination, electrocardiogram (ECG), and cardiac imaging, preferably transthoracic echocardiography [49]. The utility of troponin levels to predict cardiac toxicity is equivocal and appears to be more helpful for patients who were exposed previously to anthracyclines [50]. Use of ERBB2 inhibitors should be avoided in patients with left ventricular ejection fraction (LVEF) that is <40 %, unless there are no effective alternative cancer therapeutic options. In patients with LVEF between 40 and 50 %, and in those exposed to prior cardiotoxic cancer treatments with a normal LVEF, ERBB2 antibodies can be used with a cardioprotective strategy using angiotensin converting enzyme inhibitors and/or beta-blockers. There are differences between the international societies' guidelines regarding subsequent cardiovascular monitoring. While most guidelines recommend cardiac imaging monitoring every 3 months during treatment, the American Society of Clinical Oncology (ASCO) leaves the choice and timing of cardiac imaging to the physician's discretion. There are also no specific recommendations regarding

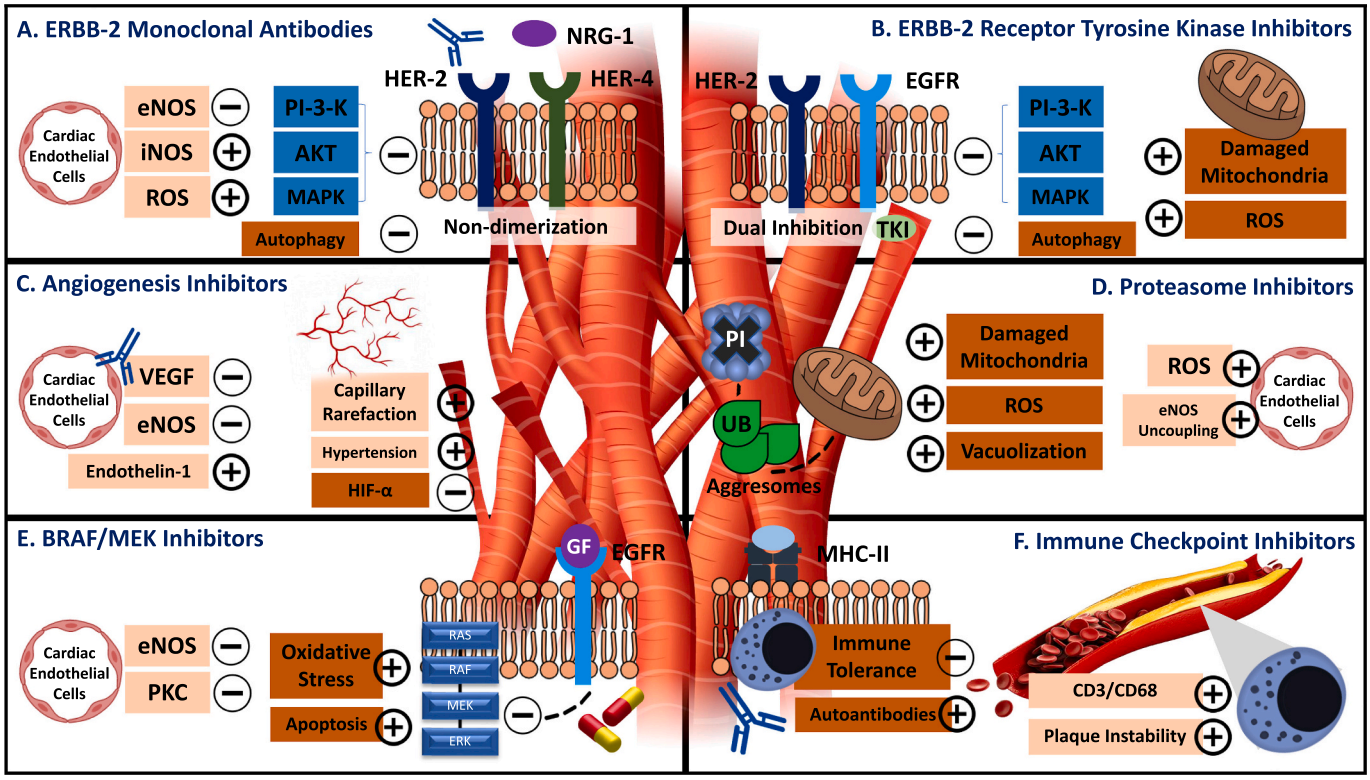

Fig. 1. Infographic summary of major pathophysiological mechanisms of cardiovascular toxicity from cancer targeted therapies.

post-treatment follow-up in cancer survivors who received ERBB2 monoclonal antibodies [49,50]. Cardiovascular toxicity from ERBB2 antibodies is considered to be reversible, and it is recommended with an absolute decrease in LVEF of ≥10 % relative to baseline, t treatment be withheld for at least 4 weeks. It can be resumed, within 4 to 8 weeks, if the LVEF returns to normal limits. If the LVEF decline persists >8 weeks or if the treatment required suspension on >3 occasions for cardiovascular toxicity, it is recommended that treatment be permanently discontinued [51,52].

2.2. *ERBB-2 receptor tyrosine kinase inhibitors*

In an attempt to prolong and maintain more potent response and overcome resistance to first-generation ERBB2 inhibitors, the second-generation ERBB-2 receptor tyrosine kinase inhibitors were developed. This generation of drugs blocks the adenosine triphosphate (ATP)-binding site and inhibits EGFR kinase activity. Indications for ERBB-2 receptor tyrosine kinase inhibitors are for treatment of metastatic HER-2 positive metastatic breast cancer, both in combination with capecitabine in patients who have been heavily pre-treated with prior lines of therapy, namely trastuzumab, taxane, and/or anthracycline, and in combination with letrozole for postmenopausal patients with hormone receptor positive and HER-2 + breast cancer [53]. Lapatinib, for example, is an oral tyrosine kinase dual inhibitor of EGFR1 and ERBB-2 that competes with ATP for binding to the ATP pocket of the kinase [54]. It is clinically efficacious in heavily pre-treated HER-2 positive breast cancer and is thought to enhance trastuzumab's effects in a synergistic fashion [19]. In fact, dual targeting of HER-2 positive tumors with lapatinib and trastuzumab can also be used as an attempt to minimize resistance to each agent when used as monotherapy [55]. Lapatinib was initially approved by the Food and Drug Administration (FDA) in 2007 for the treatment of HER-2 + metastatic breast cancer, followed by two other tyrosine kinase inhibitors, namely neratinib and tucatinib, in 2017 and 2020, respectively [56].

Although less frequent than trastuzumab, tyrosine kinase inhibitors can also be associated with cardiovascular toxicity, including decreased left ventricular ejection fraction and prolonged QTc interval requiring cardiac monitoring and dose adjustment [57,58]. Updated results of ALTERNATIVE, a phase III trial which included patients with advanced breast cancer randomized into lapatinib combined with an aromatase inhibitor with or without trastuzumab with secondary endpoints including safety, showed an incidence of 7 % of cardiac events among patients with triple therapy, compared to only 3 % among patients with trastuzumab and aromatase inhibitor without lapatinib and to 2 % among patients with receiving lapatinib and aromatase inhibitor without trastuzumab [59].

Lapatinib is considered relatively safer than trastuzumab in terms of cardiac toxicity. The proposed mechanism of this lower rate of cardiac toxicity of lapatinib is activation of the AMP-Kinase (AMPK) pathway, which inhibits TNF-α-induced cardiomyocyte cell death, as opposed to trastuzumab, which inhibits this pathway. AMPK is a major regulator of metabolic processes in the setting of stress that is critical for maintaining cardiomyocyte survival [60,61]. Furthermore, monoclonal anti-HER-2 antibodies, as opposed to tyrosine kinase inhibitors, initiate antibody-dependent cell cytotoxicity and complement-dependent cytotoxicity that could further enhance cardiomyocyte cytotoxicity [62]. Recent phase II and III clinical trials have demonstrated rates of cardiovascular toxicity with lapatinib as low as 1.5 to 2.2 %. It is important, however, to interpret these results with caution with respect to cardiac toxicity due to their limited generalizability, particularly given that enrollment is restricted to patients who do not have prior cardiovascular disease and given the variation of definitions of cardiac toxicity among clinical trials [63]. Why trastuzumab causes more cardiac toxicity than the newer HER-2 pathway inhibitors remains not fully understood, however [30,41]. Interestingly, even in published data comparing cardiovascular toxicity for lapatinib and trastuzumab, rates reported for trastuzumab have even been less than those reported from retrospective analyses from non-trial populations [64].

Preclinical studies using three-dimensional engineered myocardial tissues from neonatal rats treated with tyrosine kinase inhibitors showed

that declining contractile force was associated with impaired autophagy and increased autophagolysosomes upon ultrastructural evaluation [65]. Owing to dual inhibition of HER-1 and HER-2 by tyrosine kinase inhibitors, including lapatinib, neratinib, and tucatinib, downstream signaling of EGFR and ERBB-2 cannot be phosphorylated and thus cannot be activated. As a result, downstream targets that promote cancer growth and angiogenesis will be blocked, thus contributing to the anti-tumor effect of tyrosine kinase inhibitors [66]. In addition to their effect on tumor cells, they also result in reduced downstream effectors that involve activation of PI-3-K, AKT, and MAPK pathways in host tissue [67,68]. Inhibition of these downstream pathways results in inhibition of autophagy, thus leading to accumulation of damaged mitochondria and free radicals, thus increased causing oxidative stress and cardiomyocytes toxicity [40,65] (Fig. 1B). It has been shown that lapatinib can synergistically enhance doxorubicin toxicity in a time- and dose-dependent manner in human pluripotent stem cell-derived cardiomyocytes through iNOS signaling [69].

3. Angiogenesis inhibitors

Initially proposed by Folkman et al. >4 decades ago, inhibiting angiogenesis by targeting specific pro-angiogenic factors or their receptors has become a major target for cancer treatment [70,71]. Hypoxia-inducible factor-α (HIF-α) is a transcription factor that results in transcription of pro-tumorigenic factors, including vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF), thus mediating angiogenesis. This has been well described in clear cell renal cell carcinoma where sporadic mutations in the gene encoding for the von Hippel-Lindau (VHL) protein play a causal role in tumorigenesis. VHL protein acts as a substrate recognized by an E3 ubiquitin ligase complex that targets HIF-α to enhance its degradation. VHL mutations result in inappropriate stabilization, thus activation, of HIF-α, which leads to induction of VEGF and other HIF targets [72]. In fact, renal cell carcinoma has been the main tumor of interest for FDA approval of angiogenesis inhibitors and the only cancer in which angiogenesis are approved as single therapy [70,73].

Bevacizumab was the first FDA-approved monoclonal antibody that targets the soluble VEGF protein. Although it is given intravenously, the newer FDA-approved drugs targeting angiogenesis are given orally and target the tyrosine kinase receptors of VEGF and PDGF. These include sunitinib, sorafenib, and pazopanib. With VEGF inhibition as the common feature, these drugs are generally referred to as VEGF-signaling pathway (VSP) inhibitors. It is worth noting that tyrosine kinase inhibitors can target several tyrosine kinase receptors, and are this often referred to as “dirty” TKIs. For example, sunitinib targets all 3 VEGF receptors, namely VEGFR1, VEGFR2, and VEGFR3, in addition to PDGF receptor (PDGFR) α and β, tyrosine-protein kinase Kit, and has been approved for several types of cancers, including gastrointestinal stromal tumor, advanced renal cell carcinoma, and advanced pancreatic neuroendocrine tumors [74].

Since clinical trials on angiogenesis inhibitors have generally not included screening for heart failure or left ventricular dysfunction, the emerging awareness on cardiovascular toxicity associated with this group of drugs is largely based on retrospective analyses, which can be associated with possible misclassification bias [16]. A meta-analysis that included 5 clinical trials with 3784 breast cancer patients showed that patients who were treated with bevacizumab had a 1.6 % incidence of high-grade congestive heart failure as compared to 0.4 % among the control or placebo groups, which translated into a relative risk of 4.74 for heart failure [73]. In another meta-analysis that included 6935 patients treated with sunitinib, the incidence of all-grade and high-grade heart failure was 4.1 % and 1.5 %, respectively [75]. Moreover, the incidence of cardiovascular toxicity involving sunitinib is believed to be higher for asymptomatic cardiomyopathy according to data from individual trials which did include ejection fraction monitoring. For example, in a phase I/II trial that included 75 gastrointestinal stromal tumor patients treated with sunitinib, a 10 % decrease in left ventricular ejection fraction was reported in 28 % of patients [76].

Preclinical mouse models have shown that mice expressing a tunable transgene encoding a VEGF trap, thus mimicking the effect of bevacizumab, had decreased myocardial capillary density (a finding referred to as capillary rarefaction), induction of hypoxia and hypoxia-inducible genes in cardiomyocytes, and cardiac dysfunction. Cardiac dysfunction was reversible upon removal of the transgene [77]. Similar results were reported in mice that had genetically deleted PDGFR-β in cardiomyocytes where decreased myocardial capillary density, increased myocardial hypoxia, and enhanced heart failure after transverse aortic constriction were observed [78]. Stabilization of HIF-α in cardiomyocytes was sufficient to reverse cardiomyopathy in mice [79,80].

Myocardial capillary rarefaction, coupled with induction of hypoxia and hypoxia-inducible genes, and the resulting cardiac dysfunction demonstrated in these preclinical studies suggest that inhibition of angiogenesis by angiogenesis-inhibitors can lead to cardiomyopathy [16] (Fig. 1C). The reversibility of cardiomyopathy in these mouse models suggests that angiogenesis inhibitors-associated cardiomyopathy leads to myocardial hibernation rather than myocardial death. This is further supported by clinical data suggesting that sunitinib and sorafenib-induced cardiomyopathy may be reversible [76,81]. Uraizee et al. reported a case series of patients to highlight the reversibility of cardiomyopathy upon interruption of treatment with sunitinib or sorafenib [81]. This was later supported by ECOG 2805, a randomized, double blind phase III trial of one year of adjuvant sunitinib, sorafenib, or placebo in previously untreated patients with completely resected renal cell carcinoma at high risk for recurrence. This study showed that left ventricular dysfunction was largely reversible upon dose interruption and/or reduction of treatment [82].

In addition to their effect on myocardial capillaries, angiogenesis inhibitors can also induce hypertension in up to 25 % of patients [74,83]. There are generally two accepted mechanisms, functional and anatomic, through which VEGF signaling inhibition through angiogenesis inhibitors can contribute to hypertension: inactivation of eNOS and production of vasoconstrictors, such as endothelin-1, and capillary rarefaction, respectively [84]. Hypertension, in turn, results in increased left ventricular afterload and peripheral vascular resistance, which can lead to pressure- and volume-mediated left ventricular remodeling [85,86]. In addition to its protective cardiovascular effect by promoting left ventricular remodeling, the presence of hypertension, whether pre- or during treatment, has been shown to predict improved outcomes with VEGF-inhibitors [87]. As for VEGF inhibitor-associated proteinuria, while it does seem to be associated with hypertension, it is not clear whether hypertension causes proteinuria or vice versa or if this association lacks causality [88]. In addition, whether the development of proteinuria while on VEGF inhibitors is associated with favorable outcomes remains controversial. Karachaliou et al. reported that bevacizumab-related proteinuria was associated with a favorable outcome, while Zee et al. reported that proteinuria was associated with poor survival [89,90]. Iwasa et al. showed no correlation between VEGF inhibitor-related proteinuria and survival [91].

It is recommended that patients who are started on angiogenesis inhibitors undergo baseline assessment of their LVEF prior to initiation of therapy, followed by 1 month after treatment initiation, and at 2 to 3-month intervals during treatment. In case the LVEF decreases by 10 % from pre-treatment values to less than the institutional lower limit of normal, treatment shall be withheld. In case of symptomatic heart failure, any absolute decrease in LVEF of >20 % from baseline that is below the lower institutional limit of normal, and persistent LVEF reduction of at least 10 % from baseline that does not resolve within 4 weeks is an indication for permanently discontinuing treatment [92]. Urinary protein excretion assessment shall be tested before every administration of VEGF inhibitors. It is recommended to use serial urinalysis dipstick with a urine dipstick ≥2+ warranting further investigation with 24-hour

urine collection for protein. If the 24-hour urine protein levels are >2 g, VEGF inhibitor administration shall be withheld and then resumed when levels become <2 g. In case of nephrotic syndrome whereby the 24-hour urine protein is >3.5 g, treatment shall be discontinued. No studies have confirmed whether the use of ACE inhibitors or angiotensin II receptor blockers is warranted for VEGF inhibitor-associated proteinuria [93,94]. In case of development of grade 2 hypertension, defined as persistent (≥24 h) or symptomatic rise in the diastolic blood pressure by >20 mm Hg or in the blood pressure to over 150/100 if previously within normal limits, it is recommended to initiate anti-hypertensive medications and continue treatment as long as the blood pressure remains under 160/100. In case the blood pressure could not be controlled on one anti-hypertensive agent, this is classified as grade 3 hypertension and requires withholding VEGF inhibitor until blood pressure becomes <160/100. In case of grade 4 hypertension, defined as hypertensive crisis and/or end-organ damage, VEGF inhibitor shall be permanently discontinued [95].

4. Proteasome inhibitors

While proteasome inhibitors have led to improvement in overall survival, the post-treatment course has frequently been complicated by cardiovascular adverse events, which, in turn, contributes to treatment-associated morbidity and mortality [96]. Bortezomib received accelerated FDA approval in 2003 for patients with relapsed/refractory multiple myeloma and later emerged as the treatment of choice after failure any prior line of therapy [97,98]. Carfilzomib gained FDA approval in 2012 for patients with relapsed/refractory multiple myeloma [99]. Several studies reported an increased risk of cardiovascular adverse events with proteasome inhibitors, including hypertension, arrhythmia, heart failure, and cardiomyopathy [99,100]. In a meta-analysis that included 2594 patients, all-grade cardiovascular adverse events rate was 18.1 % [101]. In the ENDEAVOR study, for example, an increased incidence of clinically overt heart failure was detected [102]. Preclinical rat models showed that carfilzomib accumulated in the heart and resulted in strong inhibition of the cardiac proteasome [103,104]. Also, proteasome inhibition by bortezomib has been associated with enlarged cardiomyocytes exhibiting vacuolization, mitochondrial dysfunction, and fibrosis [105–107]. Being non-proliferative and having elevated proteasome activity compared to other tissues, cardiomyocytes are especially sensitive to proteasome inhibition [108]. In myeloma cells, proteasome inhibition leads to accumulation of incompatible regulatory proteins in the endoplasmic reticulum, which results in an unfolded protein response and enhanced apoptosis [109]. Similarly, proteasome inhibition in cardiomyocytes results in imbalance of proteins with abnormal accumulation of ubiquitinated proteins that associate with each other thus forming higher order protein aggregates that are cytotoxic [110]. These aggregates consist of soluble oligomers and aggresomes that form inclusion bodies, which, in turn, contribute to increased expression of reactive oxygen species, cell injury, and caspase-mediated apoptosis [111,112] (Fig. 1D). Pathological examination of human cardiomyopathies, including hypertrophic cardiomyopathy, dilated cardiomyopathy, and desmin-related cardiomyopathy, and heart failure, have also demonstrated abnormal protein aggregates [112–115]. Transcriptional activation of nuclear factor kappa B (NF-kB) in the ischemia/reperfusion model following myocardial infarction can result in pathologic remodeling. NF-kB is activated downstream of MAPK signaling pathway. While this may be cardioprotective in the short-term whereby it prevents apoptosis, prolonged NF-kB activation can be detrimental by enhancing chronic inflammation and endoplasmic reticulum stress response, thus contributing to accumulation of reactive oxygen species, promoting cardiomyocyte death and heart failure [116–118].

In addition to their effect on cardiomyocyte unfolded stress response and apoptosis, there is supporting evidence that proteasome inhibitors also alter signaling in vascular smooth muscle endothelium leading to increased vasoconstriction, vascular tone, vasospasms, and decreased response to vasodilators such as nitric oxide and acetylcholine [119–121]. The ubiquitin-proteasome system plays an important role in non-lysosomal protein quality control in order to maintain normal cellular homeostasis and adapt to physiologic changes. Its inhibition results in increased eNOS expression in endothelial cells [122]. In pig models, treatment with MLN 273, a proteasome inhibitor, results in eNOS uncoupling in myocardial endothelial cells, which leads to ultimate increased oxidative stress and functional and structural changes in the myocardium consistent with hypertrophic-restrictive cardiomyopathy [106,123]. eNOS uncoupling is a phenomenon that has been described in several cardiovascular disorders, including diabetes, hypertension, and heart failure. It describes the uncoupling of the enzyme from normal NO production due to oxidation of tetrahydrobiopterin, an essential cofactor of eNOS [124,125]. eNOS uncoupling is associated with reduction in oxygen supply and increased reactive oxygen species production [126,127]. The increased reactive oxygen species production has been hypothesized to contribute to the synergistic cardiac toxicity resulting from the concomitant use of anthracyclines and proteasome inhibitors [128]. In fact, the use of nitric oxide-releasing agents, such as nitrates or phosphodiesterase inhibitors, has been suggested for carfilzomib-induced cardiac toxicity, and that of nitroglycerine and nifedipine for reduction of vasospasms associated with endothelial dysfunction, however this was based on preclinical data, and its clinical efficacy and safety are yet to be established [129,130].

5. BRAF and MEK inhibitors

V-raf murine sarcoma viral oncogene homolog B1 (BRAF) and mitogen-activated extracellular signal-regulated kinase (MEK) inhibitors have revolutionized treatment of patients with metastatic melanoma wherein half of patients' tumors harbor a targetable BRAF mutation. The effective vertical inhibition of the Ras-RAF-MEK-ERK pathway using BRAF and MEK inhibitors has led to the FDA approval of this combination treatment for all BRAF V600E mutated solid tumors [131]. While targeting this pathway provided considerable improvement in cancer outcomes, adverse events of BRAF and MEK inhibitors can include cardiovascular toxicity [132]. For example, left ventricular systolic dysfunction in patients treated with this combination has been reported in clinical trials with a median follow-up of 9 to 16 months at an incidence up to 12 % [133,134]. Reported incidence rates may have underestimated the actual cardiovascular toxicity rate of this class of targeted therapy, particularly due to inconsistent reporting of heart failure and lack of a standardized definition of left ventricular systolic dysfunction among clinical trials across the three approved BRAF/MEK combinations. As a result, there is difficulty in comparison of results from different the different BRAF/MEK inhibitor combinations. [135,136]. Therapy with BRAF/MEK inhibitor combination was associated with a higher cardiovascular risk compared with BRAF inhibitor monotherapy, including decreased left ventricular ejection fraction, atrial fibrillation, and QTc prolongation, all of which are often reversible [133,137] It is recommended that an ECG be performed before treatment initiation and 1 month after treatment initiation or after dose modification. If QTc >500 ms, the BRAF inhibitor shall be withheld. Once QTc decreases to <500 ms, treatment can be re-initiated at a lower dose. In case QTc is both, >500 ms and >60 ms above pre-treatment value, permanent discontinuation of treatment is recommended [138]. If LVEF decreases by >10 %, it is recommended to withhold the MEK inhibitor for up to 4 weeks with rechallenge at a lower dose if the LVEF recovers. In case LVEF decreases by >20 % or if symptomatic heart failure develops, treatment with the MEK inhibitor shall be permanently discontinued [139].

Extracellular signal-regulated kinases (ERKs) 1 and 2, which are downstream effectors in the Ras-RAF-MEK-ERK pathway, play an important role in cardiac development, particularly through growth factor signaling. This pathway is a key component in cardiomyocyte

hypertrophy, cardiac remodeling, and cardiomyocyte death [140]. Cardiac hypertrophy results as a response to stressful stimuli, including mechanical overload and oxidative stress. Although this is a physiological response by the heart to enhance its contractility and cardiac output and address the increased demand, it can become pathological and lead to heart failure. Constitutive activation of Ras and BRAF in mice was associated with cardiomyocyte hypertrophy, and patients with Noonan and Leopard syndromes, which are associated with dysregulated Ras-RAF-MEK-ERK pathway, develop hypertrophic cardiomyopathy [141–143]. The MEK-ERK pathway is also needed for the protection of the myocardium after ischemic injury induced in heterozygote ERK2 gene-targeted mice by ligation of the left anterior descending artery as compared to wild-type mice [144].

Inhibition of Ras-RAF-MEK-ERK signaling pathway by BRAF/MEK inhibitors results in loss of this physiologic growth factor signaling normally present in host cells, thus resulting in loss of its cardioprotective effect of cardiac remodeling in response to stressful stimuli [140,145]. This is likely to include interleukin-10 activation of ERK1/2, which inhibits tumor necrosis factor-α-induced cardiomyocyte apoptosis [146]. In addition to its direct role in cardiomyocyte, the Ras-RAF-MEK-ERK pathway also plays a protective role in the coronary vasculature through interaction with VEGF. Phosphorylation of VEGF tyrosine kinase receptor 2 in cultured endothelial cells results in activation of phospholipase C and subsequent activation of the RAF-MEK-ERK pathway, which, in turn, enhances endothelial cell proliferation and angiogenesis via interaction with fibroblast growth factor and PDGF [147]. In addition, ERK1/2 activation by phospholipase C results in increased expression of eNOS and release of prostacyclin-mediated protein kinase C, which promotes vasodilation [148,149] (Fig. 1E).

6. Immune checkpoint inhibitors

ICI have revolutionized the treatment of a wide variety of malignancies and have gained a myriad of FDA approvals with demonstrated clinical efficacy and improved overall survival [7]. In fact, the percentage of patients eligible for treatment by ICI has increased from 1.5 % in 2011 when Ipilimumab was first approved in melanoma to 43.6 % in 2018 [150]. ICIs target the intrinsic immune inhibitory pathways, namely immune checkpoints that serve as “gate-keepers”, including cytotoxic lymphocyte-associated antigen-4 (CTLA-4), programmed cell death 1 (PD-1), its ligand (PD-L1), and lymphocyte activation gene-3 (LAG-3). Immune checkpoint inhibition essentially “takes the brakes” off of the immune system, allowing the immune system to recognize and eliminate tumors. However, activated immune cells can also attack normal host tissue, i.e. autoimmunity [151]. ICI-induced myocarditis is a rare event (1.14 %) but has a very high mortality rate of 35 to 50 % [152–156] (Fig. 1F).

There are a number of mechanisms that have been described, including T cell and B cell-mediated, with increased cardiac-specific antimyosin autoantibodies and cardiac antigen-specific T cells [157–159]. Impaired negative selection of CD4+ T cells specific for alpha myosin heavy chain has been described in the thymus of and abundance of autoreactive T cells in myocarditis of both mice and patients [159]. Immune checkpoints, such as CTLA-4 and PD-1, play an important role in promoting immune tolerance to the myocardium and prevention of autoimmune myocarditis [160]. Murine models have shown spontaneous development of myocarditis after inhibition of CTLA-4 checkpoint [161–163]. Similarly, mice deficient in CTLA-4 developed severe myocarditis and pancreatitis with multiorgan lymphocytic infiltration in another study [163]. On the other hand, Lucas et al. reported the development of lethal lymphocytic myocarditis in PD-L1-deficient mice characterized by massive CD8+ and CD4+ T cell infiltrates in the myocardium [164].

It is postulated that ICI interfere with immune checkpoint signaling in cardiomyocytes, thus causing breakdown of peripheral immune tolerance and lowering the threshold for T cell activation. In addition, ICI lead to substantial reduction of regulatory T cells, which enhances activation of cardiac-reactive T cells [156]. Another proposed mechanism of ICI-associated myocarditis is the clonal expansion of T cells that target homologous antigens shared by both, the tumor and the myocardium [165]. This was based on a report of two cases of patients with fulminant myocarditis and synchronous myositis treated with nivolumab and ipilimumab combination. Next generation sequencing of T cell receptors from myocardial T cells and tumor T cells showed that selective clonal T cell populations infiltrating the myocardium were identical to those detected in tumors and skeletal muscles [165].

ICI may also increase the risk of atherosclerosis. In a matched cohort study by Drobni et al., there was a three-fold higher risk for cardiovascular events after starting an ICI. Development of myocardial infarction in trials of pembrolizumab and atezolizumab for patients with metastatic lung cancer and urothelial cancer has also been reported [166,167]. A meta-analysis of 22 clinical trials on ICI in patients with lung cancer demonstrated an incidence of 1 % of ICI-associated myocardial infarction [168]. This association between ICI and atherosclerosis is still under current investigation. It is postulated that ICI-associated increased risk for atherosclerosis is related to chronic inflammation. The relative risk is not well-established, however, given that cancer patients often have underlying cardiovascular risk factors and, thus, comparison of rates of major adverse case events requires rigorous controls [169]. Although cardiovascular events were higher after initiation of ICI, causality has not been established, but it is rather believed that ICI might have potentially accelerated progression of pre-existing atherosclerosis. As such, optimization of cardiovascular risk factors and increased awareness of cardiovascular risk, prior to, during, and after treatment is recommended among patients on ICI [170].

In PD-1-deficient low-density lipoprotein receptor knockout mice, enhanced formation of atherosclerotic lesions was reported, thus suggesting a role of anti-PD-1 ICI in promoting the development of atherosclerosis [171]. While the exact pathophysiology of ICI-associated acute coronary syndrome is not yet fully understood, it is hypothesized that ICI-associated inflammation may influence atherosclerotic coronary plaques and promote fibrous plaque rupture, thus leading to acute myocardial infarction. This is supported by the observation that inflammatory conditions such as systemic lupus erythematosus, rheumatoid arthritis, and psoriasis have been associated with accelerated atherosclerosis and acute coronary events [172].

Patients with active cancer generally have an increased risk for development of thrombotic events [173]. Regulatory T cells have been shown to induce anti-inflammatory macrophages and inhibition of foam cell formation, thus exerting an atheroprotective effect [174]. Analysis of the composition of immune cells in coronary artery atherosclerotic plaques of ICI-treated patients revealed a significant increase in the ratio of T lymphocytes to macrophages (CD3/CD68 ratio) as compared to plaques of cancer patients who did not receive ICI treatment [175]. As such, it is postulated that ICI alter the inflammatory composition of atherosclerosis from macrophage-predominant, which is the typical composition in stable atherosclerotic plaques, to lymphocyte-predominant, which promotes plaque instability. Activation of ICI-associated inflammation triggers destabilization of pre-existing atherosclerotic plaque and plaque rupture [156]. Another possible mechanism of ICI-associated acute coronary syndrome is coronary vasospasm with several reports of transient ST segment elevation secondary to pembrolizumab used in treatment of bronchogenic adenocarcinoma. This observation, which is hypothesized to be related to systemic inflammatory response syndrome, was characterized by a normal coronary angiography, lack of cardiomarkers dynamics, and normalization of EKG changes within a few hours [176].

7. Conclusions and future directions

With the continuously evolving field of oncology, the development of cancer targeted and immune therapies has revolutionized the treatment

of a wide variety of cancers; however, these treatments also have potential toxicities, including cardiovascular toxicities. As such, it is critical to enhance our understanding of the pathophysiology and mechanisms of such toxicities The to optimize patient cancer and cardiovascular care. This includes understanding indications for cardiac monitoring, developing strategies to mitigate cardiac toxicity and developing predictive biomarkers of cardiovascular toxicity. The use of personalized approaches, i.e. patient-centered care that addresses the clinical risk scores, genomics, and biomarkers, is needed to appropriately identify high-risk patients who would benefit the most from cardiovascular protection [177]. There is a growing body of evidence that the coronary microvasculature exceeds its long-attributed role as conduit and resistance vessels to involve, through endocardial endothelial cells, a more direct effect through their close proximity to cardiomyocyte with cellular communication and signaling pathways. Clinical trials need to include more standardized definitions of left ventricular systolic dysfunction in order to better characterize the cardiovascular toxicity profiles of cancer targeted therapies and enhance their optimal utility. In addition to adequately designed clinical trials targeting the at-risk patient population, there remains an imperative need for implementing a continued multidisciplinary approach between cardiologists and oncologists.

CRediT authorship contribution statement

Firas Kreidieh: Conceptualization, Data curation. **Jennifer McQuade:** Conceptualization, Data curation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] Eve Belzile-Dugas, Mark J. Eisenberg, Radiation-induced cardiovascular disease: review of an underrecognized pathology, J. Am. Heart Assoc. 10 (18) (2021) e021686.
[2] Rui Adão, et al., Cardiotoxicity associated with cancer therapy: pathophysiology and prevention, Rev. Portuguesa Cardiol. (English Edit.) 32 (5) (2013) 395–409.
[3] J. Alexandre, J. Cautela, S. Ederhy, et al., Cardiovascular toxicity related to cancer treatment: a pragmatic approach to the American and European cardio-oncology guidelines, J. Am. Heart Assoc 9 (18) (2020) e018403.
[4] Sonia Amin Thomas, Chemotherapy agents that cause cardiotoxicity, US Pharm. 42 (9) (2017) 24–33.
[5] Maartje J. Hooning, et al., Cause-specific mortality in long-term survivors of breast cancer: a 25-year follow-up study, Int. J. Radiation Oncol. Biol. Phys. 64 (4) (2006) 1081–1091.
[6] Zhipeng Wang, et al., Higher risk of cardiovascular mortality than cancer mortality among long-term cancer survivors, Front. Cardiovasc. Med. 10 (2023) 1014400.
[7] Jun Gong, et al., Development of PD-1 and PD-L1 inhibitors as a form of cancer immunotherapy: a comprehensive review of registration trials and future considerations, J. Immunother. Cancer 6 (2018) 1–18.
[8] Khushwant S. Bhullar, et al., Kinase-targeted cancer therapies: progress, challenges and future directions, Mol. Cancer 17 (2018) 1–20.
[9] Ann Hoeben, Elbert A.J. Joosten, Marieke H.J. van den Beuken-van, Everdingen., Personalized medicine: recent progress in cancer therapy, Cancers 13 (2) (2021) 242.
[10] Gent, G. David, Rebecca. Dobson, The 2022 European Society of Cardiology Cardio-oncology guidelines in focus, European Cardiology Review 18 (2023).
[11] Alberto Zambelli, et al., Predicting and preventing cardiotoxicity in the era of breast cancer targeted therapies. Novel molecular tools for clinical issues, Breast 20 (2) (2011) 176–183.
[12] Avirup Guha, Merna Armanious, Michael G. Fradley, Update on cardio-oncology: novel cancer therapeutics and associated cardiotoxicities, Trends Cardiovasc. Med. 29 (1) (2019) 29–39 (1).
[13] Joerg Herrmann, Vascular toxic effects of cancer therapies, Nat. Rev. Cardiol. 17 (8) (2020) 503–522.
[14] Přemysl Mladěnka, et al., Comprehensive review of cardiovascular toxicity of drugs and related agents, Med. Res. Rev. 38 (4) (2018) 1332–1403 (1).
[15] R.E. Konst, et al., Ischaemia with no obstructive coronary arteries, Neth. Hear. J. 28 (2020) 66–72.
[16] Bonnie Ky, et al., Emerging paradigms in cardiomyopathies associated with cancer therapies, Circ. Res. 113 (6) (2013) 754–764.
[17] Yanjun Hou, Hiroaki Nitta, Zaibo Li, HER2 intratumoral heterogeneity in breast cancer, an evolving concept, Cancers 15 (10) (2023) 2664.
[18] Felipe da Luz, Andrés Cordero, et al., The benefits of trastuzumab in the treatment of HER2+ breast cancer as a function of exposure time, ecancermedicalscience 16 (2022).
[19] Dennis J. Slamon, et al., Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2, N. Engl. J. Med. 344 (11) (2001) 783–792.
[20] Gregory M. Cote, Douglas B. Sawyer, Bruce A. Chabner, ERBB2 inhibition and heart failure, New Engl. J. Med. 367 (22) (2012) 2150–2153.
[21] Rosie Bradley, et al., Trastuzumab for early-stage, HER2-positive breast cancer: a meta-analysis of 13 864 women in seven randomised trials, Lancet Oncol. 22 (8) (2021) 1139–1150.
[22] R. Haq, P. Gulasingam, Duration of trastuzumab in patients with HER2-positive metastatic breast cancer in prolonged remission, Curr. Oncol. 23 (2) (2016) 91–95.
[23] Izzet Dogan, et al., Termination of trastuzumab in HER2-positive metastatic breast cancer patients who received trastuzumab beyond progression, Sci. Rep. 13 (1) (2023) 8779.
[24] Dennis J. Slamon, et al., Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene, science 235 (4785) (1987) 177–182.
[25] Athanasios Koutsoukis, et al., Cardio-oncology: a focus on cardiotoxicity, Eur. Cardiol. Rev. 13 (1) (2018) 64.
[26] Helena Earl, et al., Six versus 12 months' adjuvant trastuzumab in patients with HER2-positive early breast cancer: the PERSEPHONE non-inferiority RCT, Health Technol. Assess. (Winchester, England) 24 (40) (2020) 1.
[27] Food and Drug Administration Prescribing Information on HERCEPTIN (trastuzumab), Revised 2010. http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/103792s5250lbl.pdf.
[28] Andrew Seidman, et al., Cardiac dysfunction in the trastuzumab clinical trials experience, J. Clin. Oncol. 20 (5) (2002) 1215–1221.
[29] Thirukumaran Balasubramaniam, Knowledge Ecology International, 2013.
[30] De Keulenaer, W. Gilles, Kris Doggen, Katrien Lemmens, The vulnerability of the heart as a pluricellular paracrine organ: lessons from unexpected triggers of heart failure in targeted ErbB2 anticancer therapy, Circ. Res. 106 (1) (2010) 35–46.
[31] Xihui Liu, et al., Specific regulation of NRG1 isoform expression by neuronal activity, J. Neurosci. 31 (23) (2011) 8491–8501.
[32] Steven A. Crone, et al., ErbB2 is essential in the prevention of dilated cardiomyopathy, Nat. Med. 8 (5) (2002) 459–465.
[33] Xifu Liu, et al., Neuregulin-1/erbB-activation improves cardiac function and survival in models of ischemic, dilated, and viral cardiomyopathy, J. Am. Coll. Cardiol. 48 (7) (2006) 1438–1447.
[34] Douglas B. Sawyer, et al., Modulation of anthracycline-induced myofibrillar disarray in rat ventricular myocytes by neuregulin-1β and anti-erbB2: potential mechanism for trastuzumab-induced cardiotoxicity, Circulation 105 (13) (2002) 1551–1554.
[35] Alessandra Cuomo, et al., Heart failure and cancer: mechanisms of old and new cardiotoxic drugs in cancer patients, Card. Fail. Rev. 5 (2) (2019) 112.
[36] Gregory M. Cote, et al., Neuregulin-1α and β isoform expression in cardiac microvascular endothelial cells and function in cardiac myocytes in vitro, Exp. Cell Res. 311 (1) (2005) 135–146.
[37] Francesco Timolati, et al., Neuregulin-1 beta attenuates doxorubicin-induced alterations of excitation–contraction coupling and reduces oxidative stress in adult rat cardiomyocytes, J. Mol. Cell. Cardiol. 41 (5) (2006) 845–854.
[38] Katrien Lemmens, et al., Neuregulin-1 induces a negative inotropic effect in cardiac muscle: role of nitric oxide synthase, Circulation 109 (3) (2004) 324–326.
[39] You-yang Zhao, et al., Neuregulins promote survival and growth of cardiac myocytes: persistence of ErbB2 and ErbB4 expression in neonatal and adult ventricular myocytes, J. Biol. Chem. 273 (17) (1998) 10261–10269.
[40] N. Mohan, J. Jiang, W.J. Wu, Implications of autophagy and oxidative stress in trastuzumab-mediated cardiac toxicities, Austin Pharmacol. Pharm. 2 (2017) 1.
[41] Andrew M. Bellinger, et al., Cardio-oncology: how new targeted cancer therapies and precision medicine can inform cardiovascular discovery, Circulation 132 (23) (2015) 2248–2258.
[42] Dirk L. Brutsaert, Cardiac endothelial-myocardial signaling: its role in cardiac growth, contractile performance, and rhythmicity, Physiol. Rev. 83 (1) (2003) 59–115.
[43] Toni K. Choueiri, et al., Risk of arterial thromboembolic events with sunitinib and sorafenib: a systematic review and meta-analysis of clinical trials, in: Database of Abstracts of Reviews of Effects (DARE): Quality-assessed Reviews [Internet], 2010.
[44] Carrie A. Geisberg, et al., Circulating neuregulin during the transition from stage A to stage B/C heart failure in a breast cancer cohort, J. Card. Fail. 19 (1) (2013) 10–15.
[45] Marta Capelan, et al., Pertuzumab: new hope for patients with HER2-positive breast cancer, Ann. Oncol. 24 (2) (2013) 273–282.
[46] Joseph Bubalo, HER2 Receptor Antagonist–Associated Cardiotoxicity, 2016.
[47] N.L. Sepctor, et al., Activation of AMP-activated protein kinase by human EGF receptor 2/EGF receptor tyrosine kinase inhibitor protects cardiac cells, Proc, Natl. Acad. Sci. 104 (25) (2007) 10607–10612.
[48] D. Lenihan, et al., Pooled analysis of cardiac safety in patients with cancer treated with pertuzumab, Ann. Oncol. 23 (3) (2012) 791–800.

[49] Joachim Alexandre, et al., Cardiovascular toxicity related to cancer treatment: a pragmatic approach to the American and European cardio-oncology guidelines, J. Am. Heart Assoc. 9 (18) (2020) e018403.
[50] Nazanin Fallah-Rad, et al., The utility of cardiac biomarkers, tissue velocity and strain imaging, and cardiac magnetic resonance imaging in predicting early left ventricular dysfunction in patients with human epidermal growth factor receptor II–positive breast cancer treated with adjuvant trastuzumab therapy, J. Am. Coll. Cardiol. 57 (22) (2011) 2263–2270.
[51] Richard M. Steingart, Anthony F. Yu, Chau T. Dang, Trastuzumab cures cancer and disrupts the practice of cardiology, Cardio Oncol. 1 (1) (2019) 11–13.
[52] F. Lynce, et al., Prospective evaluation of the cardiac safety of HER2-targeted therapies in patients with HER2-positive breast cancer and compromised heart function: the SAFE-HEaRt study, Breast Cancer Res. Treat. 175 (2019) 595–603.
[53] Cynthia Moreira, Virginia Kaklamani, Lapatinib and breast cancer: current indications and outlook for the future, Expert Rev. Anticancer Ther. 10 (8) (2010) 1171–1182.
[54] Adriana Albini, et al., Cardio-oncology in targeting the HER receptor family: the puzzle of different cardiotoxicities of HER2 inhibitors, Future Cardiol. 7 (5) (2011) 693–704.
[55] Carlos L. Arteaga, et al., Treatment of HER2-positive breast cancer: current status and future perspectives, Nat. Rev. Clin. Oncol. 9 (1) (2012) 16–32.
[56] Susan F. Dent, et al., Cardiovascular toxicity of novel HER2-targeted therapies in the treatment of breast cancer, Curr. Oncol. Rep. 23 (2021) 1–12.
[57] Edith A. Perez, et al., Cardiac safety of lapatinib: pooled analysis of 3689 patients enrolled in clinical trials, Mayo Clin. Proc. 83 (6) (2008). Elsevier.
[58] Mehmet A.N. Sendur, Sercan Aksoy, Kadri Altundag, Cardiotoxicity of novel HER2-targeted therapies, Curr. Med. Res. Opin. 29 (8) (2013) 1015–1024.
[59] Stephen R.D. Johnston, et al., Phase III, randomized study of dual human epidermal growth factor receptor 2 (HER2) blockade with lapatinib plus trastuzumab in combination with an aromatase inhibitor in postmenopausal women with HER2-positive, hormone receptor–positive metastatic breast cancer: ALTERNATIVE, J. Clin. Oncol. 36 (8) (2018) 741.
[60] Scott A. Shell, et al., Activation of AMPK is necessary for killing cancer cells and sparing cardiac cells, Cell Cycle 7 (12) (2008) 1769–1775.
[61] Michael Arad, Christine E. Seidman, J.G. Seidman, AMP-activated protein kinase in the heart: role during health and disease, Circ. Res. 100 (4) (2007) 474–488.
[62] Kohzoh Imai, Akinori Takaoka, Comparing antibody and small-molecule therapies for cancer, Nat. Rev. Cancer 6 (9) (2006) 714–727.
[63] Angelo Di Leo, et al., Phase III, double-blind, randomized study comparing lapatinib plus paclitaxel with placebo plus paclitaxel as first-line treatment for metastatic breast cancer, J. Clin. Oncol. 26 (34) (2008) 5544.
[64] José Baselga, et al., Lapatinib with trastuzumab for HER2-positive early breast cancer (NeoALTTO): a randomised, open-label, multicentre, phase 3 trial, The Lancet 379 (9816) (2012) 633–640.
[65] Fabian Jacob, et al., Analysis of tyrosine kinase inhibitor-mediated decline in contractile force in rat engineered heart tissue, PloS One 11 (2) (2016) e0145937.
[66] Kellie L. Jones, Aman U. Buzdar, Evolving novel anti-HER2 strategies, Lancet Oncol. 10 (12) (2009) 1179–1187.
[67] Ming Hui Chen, Risto Kerkelä, Thomas Force, Mechanisms of cardiac dysfunction associated with tyrosine kinase inhibitor cancer therapeutics, Circulation 118 (1) (2008) 84–95.
[68] Yongqiang Chen, et al., Erb-b2 receptor tyrosine kinase 2 (ERBB2) promotes ATG12-dependent autophagy contributing to treatment resistance of breast cancer cells, Cancers 13 (5) (2021) 1038.
[69] Wan-Tseng Hsu, et al., The HER2 inhibitor lapatinib potentiates doxorubicin-induced cardiotoxicity through iNOS signaling, Theranostics 8 (12) (2018) 3176.
[70] Robert S. Kerbel, Tumor angiogenesis, N. Engl. J. Med. 358 (19) (2008) 2039–2049.
[71] Judah Folkman, Tumor angiogenesis: therapeutic implications, N. Engl. J. Med. 285 (21) (1971) 1182–1186.
[72] Chuan Shen, William G. Kaelin Jr, The VHL/HIF axis in clear cell renal carcinoma, in: Seminars in Cancer Biology vol. 23, Academic Press, 2013. No. 1.
[73] Toni K. Choueiri, et al., Congestive heart failure risk in patients with breast cancer treated with bevacizumab, in: Database of Abstracts of Reviews of Effects (DARE): Quality-assessed Reviews [Internet], Centre for Reviews and Dissemination, UK, 2011.
[74] Steven M. Bair, Toni K. Choueiri, Javid Moslehi, Cardiovascular complications associated with novel angiogenesis inhibitors: emerging evidence and evolving perspectives, Trends Cardiovasc. Med. 23 (4) (2013) 104–113.
[75] Christopher J. Richards, et al., Incidence and risk of congestive heart failure in patients with renal and nonrenal cell carcinoma treated with sunitinib, in: Database of Abstracts of Reviews of Effects (DARE): Quality-assessed Reviews [Internet], Centre for Reviews and Dissemination, UK, 2011.
[76] Tammy F. Chu, et al., Cardiotoxicity associated with tyrosine kinase inhibitor sunitinib, The Lancet 370 (9604) (2007) 2011–2019.
[77] Dalit May, et al., Transgenic system for conditional induction and rescue of chronic myocardial hibernation provides insights into genomic programs of hibernation, Proc. Natl. Acad. Sci. 105 (1) (2008) 282–287.
[78] Vishnu Chintalgattu, et al., Cardiomyocyte PDGFR-β signaling is an essential component of the mouse cardiac response to load-induced stress, J. Clin. Invest. 120 (2) (2010) 472–484.
[79] Javid Moslehi, et al., Loss of hypoxia-inducible factor prolyl hydroxylase activity in cardiomyocytes phenocopies ischemic cardiomyopathy, Circulation 122 (10) (2010) 1004–1016.
[80] Raffi Bekeredjian, et al., Conditional HIF-1α expression produces a reversible cardiomyopathy, PloS One 5 (7) (2010) e11693.
[81] Imran Uraizee, Susan Cheng, Javid Moslehi, Reversible cardiomyopathy associated with sunitinib and sorafenib, New Engl. J. Med. 365 (17) (2011) 1649–1650.
[82] Naomi B. Haas, et al., Effects of adjuvant sorafenib and sunitinib on cardiac function in renal cell carcinoma patients without overt metastases: results from ASSURE, ECOG 2805, Clin. Cancer Res. 21 (18) (2015) 4048–4054.
[83] Babak Nazer, Benjamin D. Humphreys, Javid Moslehi, Effects of novel angiogenesis inhibitors for the treatment of cancer on the cardiovascular system: focus on hypertension, Circulation 124 (15) (2011) 1687–1691.
[84] Nilka de Jesus-Gonzalez, et al., Management of antiangiogenic therapy-induced hypertension, Hypertension 60 (3) (2012) 607–615.
[85] Daniel Levy, et al., The progression from hypertension to congestive heart failure, Jama 275 (20) (1996) 1557–1562.
[86] Satish Kenchaiah, Marc A. Pfeffer, Cardiac remodeling in systemic hypertension, Med. Clin. 88 (1) (2004) 115–130.
[87] Shohei Moriyama, et al., Both new-onset and pre-existing hypertension indicate favorable clinical outcomes in patients treated with anti-vascular endothelial growth factor therapy, Circ. J. (2022) CJ–22.
[88] Shirinsadat Badri, et al., Nephrotoxicity induced by vascular endothelial growth factor inhibitors, J. Nephropharmacol. 11 (1) (2021) e4.
[89] N. Karachaliou, et al., Proteinuria and favourable clinical response in a patient receiving paclitaxel+ bevacizumab for metastatic breast cancer, Ann. Oncol. 21 (8) (2010) 1729–1730.
[90] Y.K. Zee, et al., Hypertension (HTN) and proteinuria (PTN) as biomarkers of efficacy in antiangiogenic therapy for metastatic colorectal cancer (mCRC), J. Clin. Oncol. 28.15_suppl (2010) e13580.
[91] Satoru Iwasa, et al., Lack of association of proteinuria and clinical outcome in patients treated with bevacizumab for metastatic colorectal cancer, Anticancer Res 33 (1) (2013) 309–316.
[92] Nicola Maurea, et al., A recommended practical approach to the management of target therapy and angiogenesis inhibitors cardiotoxicity: an opinion paper of the working group on drug cardiotoxicity and cardioprotection, Italian Society of Cardiology, J. Cardiovasc. Med. (Hagerstown, Md.) 17 (Suppl. 1) (2016) S93.
[93] Alba A. Brandes, et al., Practical management of bevacizumab-related toxicities in glioblastoma, Oncologist 20 (2) (2015) 166–175.
[94] Terri S. Armstrong, et al., Management of treatment-associated toxicites of anti-angiogenic therapy in patients with brain tumors, Neuro-oncology 14 (10) (2012) 1203–1214.
[95] Turab Mohammed, et al., Etiology and management of hypertension in patients with cancer, Cardio-Oncology 7 (2021) 1–13.
[96] Edward T.H. Yeh, Courtney L. Bickford, Cardiovascular complications of cancer therapy: incidence, pathogenesis, diagnosis, and management, J. Am. Coll. Cardiol. 53 (24) (2009) 2231–2247.
[97] Paul G. Richardson, et al., Extended follow-up of a phase 3 trial in relapsed multiple myeloma: final time-to-event results of the APEX trial, Blood J. Am. Soc. Hematol. 110 (10) (2007) 3557–3560.
[98] San Miguel, F. Jesús, et al., Bortezomib plus melphalan and prednisone for initial treatment of multiple myeloma, New Engl. J. Med. 359 (9) (2008) 906–917.
[99] David Siegel, et al., Integrated safety profile of single-agent carfilzomib: experience from 526 patients enrolled in 4 phase II clinical studies, Haematologica 98 (11) (2013) 1753.
[100] S. Atrash, et al., Cardiac complications in relapsed and refractory multiple myeloma patients treated with carfilzomib, Blood Cancer J. 5 (1) (2015) e272.
[101] Adam J. Waxman, et al., Carfilzomib-associated cardiovascular adverse events: a systematic review and meta-analysis, JAMA Oncol. 4 (3) (2018) e174519.
[102] Meletios A. Dimopoulos, et al., Carfilzomib and dexamethasone versus bortezomib and dexamethasone for patients with relapsed or refractory multiple myeloma (ENDEAVOR): a randomised, phase 3, open-label, multicentre study, Lancet Oncol. 17 (1) (2016) 27–38.
[103] Benjamin Buck, et al., Carfilzomib-induced cardiotoxicity: an analysis of the FDA adverse event reporting system (FAERS), J. Saudi Heart Assoc. 34 (3) (2022) 134.
[104] Susan D. Demo, et al., Antitumor activity of PR-171, a novel irreversible inhibitor of the proteasome, Cancer Res. 67 (13) (2007) 6383–6391.
[105] Mingxin Tang, et al., Proteasome functional insufficiency activates the calcineurin–NFAT pathway in cardiomyocytes and promotes maladaptive remodelling of stressed mouse hearts, Cardiovasc. Res. 88 (3) (2010) 424–433.
[106] Joerg Herrmann, et al., Primary proteasome inhibition results in cardiac dysfunction, Eur. J. Heart Fail. 15 (6) (2013) 614–623.
[107] Dominika Nowis, et al., Cardiotoxicity of the anticancer therapeutic agent bortezomib, Am. J. Pathol. 176 (6) (2010) 2658–2668.
[108] M.B. Patel, M. Majetschak, Distribution and interrelationship of ubiquitin proteasome pathway component activities and ubiquitin pools in various porcine tissues, Physiol. Res. 56 (3) (2007) 341–350.
[109] Esther A. Obeng, et al., Proteasome inhibitors induce a terminal unfolded protein response in multiple myeloma cells, Blood 107 (12) (2006) 4907–4916.
[110] Monte S. Willis, Cam Patterson, Proteotoxicity and cardiac dysfunction—Alzheimer's disease of the heart? New Engl. J. Med. 368 (5) (2013) 455–464.
[111] Brian B. Hasinoff, Daywin Patel, Wu. Xing, Molecular mechanisms of the cardiotoxicity of the proteasomal-targeted drugs bortezomib and carfilzomib, Cardiovasc. Toxicol. 17 (2017) 237–250.
[112] Paul Tannous, et al., Intracellular protein aggregation is a proximal trigger of cardiomyocyte autophagy, Circulation 117 (24) (2008) 3070–3078.
[113] Atsushi Sanbe, et al., Desmin-related cardiomyopathy in transgenic mice: a cardiac amyloidosis, Proc. Natl. Acad. Sci. 101 (27) (2004) 10132–10136.

[114] Jaime M. Predmore, et al., Ubiquitin proteasome dysfunction in human hypertrophic and dilated cardiomyopathies, Circulation 121 (8) (2010) 997–1004.
[115] Yaron D. Barac, et al., The ubiquitin-proteasome system: a potential therapeutic target for heart failure, J. Heart Lung Transplant. 36 (7) (2017) 708–714.
[116] Joseph W. Gordon, James A. Shaw, Lorrie A. Kirshenbaum, Multiple facets of NF-κB in the heart: to be or not to NF-κB, Circ. Res. 108 (9) (2011) 1122–1132.
[117] Nikolaos G. Frangogiannis, C. Wayne Smith, Mark L. Entman, The inflammatory response in myocardial infarction, Cardiovasc. Res. 53 (1) (2002) 31–47.
[118] Richard C.X. Li, et al., PKCε modulates NF-κB and AP-1 via mitogen-activated protein kinases in adult rabbit cardiomyocytes, Am. J. Physiol.-Heart Circ. Physiol. 279 (4) (2000) H1679–H1689.
[119] Carol Chen-Scarabelli, et al., Spasmogenic effects of the proteasome inhibitor carfilzomib on coronary resistance, vascular tone and reactivity, EBioMedicine 21 (2017) 206–212.
[120] Robert F. Furchgott, John V. Zawadzki, The obligatory role of endothelial cells in the relaxation of arterial smooth muscle by acetylcholine, nature 288 (5789) (1980) 373–376.
[121] Richard M.J. Palmer, A.G. Ferrige, Salvador Moncada, Nitric oxide release accounts for the biological activity of endothelium-derived relaxing factor, Nature 327 (6122) (1987) 524–526.
[122] Karl Stangl, Verena Stangl, The ubiquitin-proteasome pathway and endothelial (dys) function, Cardiovasc. Res. 85 (2) (2010) 281–290.
[123] Joerg Herrmann, et al., Chronic proteasome inhibition contributes to coronary atherosclerosis, Circ. Res. 101 (9) (2007) 865–874.
[124] Sheldon Milstien, Zvonimir Katusic, Oxidation of tetrahydrobiopterin by peroxynitrite: implications for vascular endothelial function, Biochem. Biophys. Res. Commun. 263 (3) (1999) 681–684.
[125] Nermin Kuzkaya, et al., Interactions of peroxynitrite, tetrahydrobiopterin, ascorbic acid, and thiols: implications for uncoupling endothelial nitric-oxide synthase, J. Biol. Chem. 278 (25) (2003) 22546–22554.
[126] Ulf Landmesser, et al., Oxidation of tetrahydrobiopterin leads to uncoupling of endothelial cell nitric oxide synthase in hypertension, J. Clin. Invest. 111 (8) (2003) 1201–1209.
[127] Francesco Cosentino, Thomas F. Lüscher, Tetrahydrobiopterin and endothelial nitric oxide synthase activity, Cardiovasc. Res. 43 (2) (1999) 274–278.
[128] Eva-Margarete Spur, et al., Inhibition of chymotryptic-like standard proteasome activity exacerbates doxorubicin-induced cytotoxicity in primary cardiomyocytes, Toxicology 353 (2016) 34–47.
[129] Perry Wu, et al., Proteasome inhibitor-related cardiotoxicity: mechanisms, diagnosis, and management, Curr. Oncol. Rep. 22 (2020) 1–14 (1).
[130] Tiziano M. Scarabelli, et al., Cardiovascular effects of carfilzomib, a new proteasome inhibitor, on coronary resistencies, vascular tone and vascular reactivity, J. Am. Coll. Cardiol. 65 (10S) (2015) A2143.
[131] Alexander M. Menzies, Georgina V. Long, Dabrafenib and trametinib, alone and in combination for BRAF-mutant metastatic melanoma, Clin. Cancer Res. 20 (8) (2014) 2035–2043 (1).
[132] Claire Glen, et al., Mechanistic and clinical overview cardiovascular toxicity of BRAF and MEK inhibitors: JACC: CardioOncology state-of-the-art review, Cardio Oncol. 4 (1) (2022) 1–18.
[133] Raluca I. Mincu, et al., Cardiovascular adverse events associated with BRAF and MEK inhibitors: a systematic review and meta-analysis, JAMA Netw. Open 2 (8) (2019) e198890.
[134] Sarah J. Welsh, Pippa G. Corrie, Management of BRAF and MEK inhibitor toxicities in patients with metastatic melanoma, Ther. Adv. Med. Oncol. 7 (2) (2015) 122–136.
[135] Janice M. Bonsu, et al., Reporting of cardiovascular events in clinical trials supporting FDA approval of contemporary cancer therapies, J. Am. Coll. Cardiol. 75 (6) (2020) 620–628 (1).
[136] National Cancer Institute (US), Cancer Therapy Evaluation Program. Common Terminology Criteria for Adverse Events:(CTCAE). Cancer Therapy Evaluation Program, 2003, p. 1.
[137] Dimitri Arangalage, et al., Pathophysiology, diagnosis and management of cardiac toxicity induced by immune checkpoint inhibitors and BRAF and MEK inhibitors, Cancer Treat. Rev. 100 (2021) 102282.
[138] Elisabeth Livingstone, et al., BRAF, MEK and KIT inhibitors for melanoma: adverse events and their management, Chin. Clin. Oncol. 3 (2014) 3.
[139] Mary Banks, et al., Cardiovascular effects of the MEK inhibitor, trametinib: a case report, literature review, and consideration of mechanism, Cardiovasc. Toxicol. 17 (2017) 487–493 (1).
[140] Beth A. Rose, Thomas Force, Yibin Wang, Mitogen-activated protein kinase signaling in the heart: angels versus demons in a heart-breaking tale, Physiol. Rev. 90 (4) (2010) 1507–1546.
[141] Yoko Aoki, et al., The RAS/MAPK syndromes: novel roles of the RAS pathway in human genetic disorders, Hum. Mutat. 29 (8) (2008) 992–1006.
[142] John J. Hunter, et al., Ventricular expression of a MLC-2v-ras fusion gene induces cardiac hypertrophy and selective diastolic dysfunction in transgenic mice (*), J. Biol. Chem. 270 (39) (1995) 23173–23178.
[143] Ian S. Harris, et al., Raf-1 kinase is required for cardiac hypertrophy and cardiomyocyte survival in response to pressure overload, Circulation 110 (6) (2004) 718–723.
[144] Daniel J. Lips, et al., MEK1-ERK2 signaling pathway protects myocardium from ischemic injury in vivo, Circulation 109 (16) (2004) 1938–1941.
[145] Yanlin Song, et al., Targeting RAS–RAF–MEK–ERK signaling pathway in human cancer: current status in clinical trials, Genes Dis. 10 (1) (2023) 76–88.
[146] Sanjiv Dhingra, et al., IL-10 attenuates TNF-α-induced NFκB pathway activation and cardiomyocyte apoptosis, Cardiovasc. Res. 82 (1) (2009) 59–66.
[147] Tomoko Takahashi, Hikaru Ueno, Masabumi Shibuya, VEGF activates protein kinase C-dependent, but Ras-independent Raf-MEK-MAP kinase pathway for DNA synthesis in primary endothelial cells, Oncogene 18 (13) (1999) 2221–2230.
[148] Anne Bouloumié, Valérie B. Schini-Kerth, Rudi Busse, Vascular endothelial growth factor up-regulates nitric oxide synthase expression in endothelial cells, Cardiovasc. Res. 41 (3) (1999) 773–780.
[149] Ian Zachary, Signaling mechanisms mediating vascular protective actions of vascular endothelial growth factor, Am. J. Phys. Cell Phys. 280 (6) (2001) C1375–C1386.
[150] Alyson Haslam, Vinay Prasad, Estimation of the percentage of US patients with cancer who are eligible for and respond to checkpoint inhibitor immunotherapy drugs, JAMA Netw. Open 2 (5) (2019) e192535.
[151] Gilda Varricchi, et al., Immune checkpoint inhibitors and cardiac toxicity: an emerging issue, Curr. Med. Chem. 25 (11) (2018) 1327–1339.
[152] Daniel Y. Wang, et al., Fatal toxic effects associated with immune checkpoint inhibitors: a systematic review and meta-analysis, JAMA Oncol. 4 (12) (2018) 1721–1728.
[153] Hassan Mir, et al., Cardiac complications associated with checkpoint inhibition: a systematic review of the literature in an important emerging area, Can. J. Cardiol. 34 (8) (2018) 1059–1068.
[154] Daniel Y. Wang, et al., Cardiovascular toxicities associated with cancer immunotherapies, Curr. Cardiol. Rep. 19 (2017) 1–11.
[155] Syed S. Mahmood, et al., Myocarditis in patients treated with immune checkpoint inhibitors, J. Am. Coll. Cardiol. 71 (16) (2018) 1755–1764.
[156] Arjun Khunger, et al., New insights into mechanisms of immune checkpoint inhibitor-induced cardiovascular toxicity, Curr. Oncol. Rep. 22 (2020) 1–11.
[157] Caforio Al, Identification of alpha-and beta-cardiac myosin heavy chain isoforms as major autoantigens in dilated cardiomyopathy, Circulation 85 (1992) 1734–1742.
[158] Bernward Lauer, et al., Antimyosin autoantibodies are associated with deterioration of systolic and diastolic left ventricular function in patients with chronic myocarditis, J. Am. Coll. Cardiol. 35 (1) (2000) 11–18.
[159] HuiJuan Lv, et al., Impaired thymic tolerance to α-myosin directs autoimmunity to the heart in mice and humans, J. Clin. Invest. 121 (4) (2011) 1561–1573.
[160] Daniel L. Mueller, Mechanisms maintaining peripheral tolerance, Nat. Immunol. 11 (1) (2010) 21–27.
[161] Paul Waterhouse, et al., Lymphoproliferative disorders with early lethality in mice deficient in Ctla-4, Science 270 (5238) (1995) 985–988.
[162] Haiyan Ying, et al., Cutting edge: CTLA-4–B7 interaction suppresses Th17 cell differentiation, J. Immunol. 185 (3) (2010) 1375–1378.
[163] Elizabeth A. Tivol, et al., Loss of CTLA-4 leads to massive lymphoproliferation and fatal multiorgan tissue destruction, revealing a critical negative regulatory role of CTLA-4, Immunity 3 (5) (1995) 541–547.
[164] Julie A. Lucas, et al., Programmed death ligand 1 regulates a critical checkpoint for autoimmune myocarditis and pneumonitis in MRL mice, J. Immunol. 181 (4) (2008) 2513–2521.
[165] Douglas B. Johnson, et al., Fulminant myocarditis with combination immune checkpoint blockade, New Engl. J. Med. 375 (18) (2016) 1749–1755.
[166] Arjun V. Balar, et al., Atezolizumab as first-line treatment in cisplatin-ineligible patients with locally advanced and metastatic urothelial carcinoma: a single-arm, multicentre, phase 2 trial, The Lancet 389 (10064) (2017) 67–76.
[167] Roy S. Herbst, et al., Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial, Lancet 387 (10027) (2016) 1540–1550.
[168] Yang-Bo Hu, et al., Evaluation of rare but severe immune related adverse effects in PD-1 and PD-L1 inhibitors in non-small cell lung cancer: a meta-analysis, Transl. Lung Cancer Res. 6 (Suppl. 1) (2017) S8.
[169] Peter Libby, Paul M. Ridker, Göran K. Hansson, Progress and challenges in translating the biology of atherosclerosis, Nature 473 (7347) (2011) 317–325.
[170] Zsofia D. Drobni, et al., Association between immune checkpoint inhibitors with cardiovascular events and atherosclerotic plaque, Circulation 142 (24) (2020) 2299–2311.
[171] De-xiu Bu, et al., Impairment of the programmed cell death-1 pathway increases atherosclerotic lesion development and inflammation, Arterioscler. Thromb. Vasc. Biol. 31 (5) (2011) 1100–1107.
[172] C.E.N.G.İ.Z. Korkmaz, D.U. Cansu, T. Kaşifoğlu, Myocardial infarction in young patients (≤ 35 years of age) with systemic lupus erythematosus: a case report and clinical analysis of the literature, Lupus 16 (4) (2007) 289–297.
[173] Babak B. Navi, et al., Risk of arterial thromboembolism in patients with cancer, J. Am. Coll. Cardiol. 70 (8) (2017) 926–938.
[174] Jing Lin, et al., The role of CD4+ CD25+ regulatory T cells in macrophage-derived foam-cell formation, J. Lipid Res. 51 (5) (2010) 1208–1217.
[175] Justine L. Newman, James R. Stone, Immune checkpoint inhibition alters the inflammatory cell composition of human coronary artery atherosclerosis, Cardiovasc. Pathol. 43 (2019) 107148.
[176] Radomir Nykl, et al., 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.-Atherosclerotic Dis. 2 (1) (2017) 100–102.
[177] Marie-A Chaix, et al., Machine learning identifies clinical and genetic factors associated with anthracycline cardiotoxicity in pediatric cancer survivors, Cardio Oncol. 2 (5) (2020) 690–706.