Universal Definition of Cardiovascular Toxicities of Cancer Therapies -

An International Cardio-Oncology Society (IC-OS) Consensus Statement

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Abstract

The discipline of Cardio-Oncology (CO) has seen tremendous growth over the past decade. It is devoted to the cardiovascular care of the cancer patient, especially to the mitigation and management of cardiovascular complications or toxicities of cancer therapies, which can have profound implications on prognosis. To that effect, many studies have assessed cardiovascular toxicities in patients undergoing various types of cancer therapies; however, direct comparisons has proven difficult due to lack of uniformity in cardiovascular toxicity endpoints. Similarly, in clinical practice there can be substantial differences in the understanding of what constitutes cardiovascular toxicity, which can lead to significant variation in patient management and outcomes. This document addresses these issues and provides consensus definitions for the most commonly reported cardiovascular toxicities including: cardiomyopathy/heart failure and myocarditis, vascular toxicity and hypertension, as well as arrhythmias and QTc prolongation.

Introduction

As advancements in cancer therapy have led to improvement in survival, there has been increasing recognition of the short and late-term complications of cancer therapies that affect morbidity and mortality, including cardiovascular (CV) toxicities.[1, 2] The discipline of Cardio-Oncology (CO) has emerged, in particular, to prevent, mitigate and manage CV diseases and complications in cancer patients. [3, 4] A critical element of such efforts, important for both clinical practice and research endeavors, is a uniform understanding and agreement regarding what constitutes a CV toxicity.

CV toxicities of cancer therapies encompass a broad spectrum of entities; however, this document will focus on the categories most commonly reported in the literature and illustrated in **Figure 1**.[3] Furthermore, it is outside the scope of this document to provide specific management recommendations for CV toxicities. The intent of this document was to provide clinically meaningful definitions of commonly encountered CV adverse events during contemporary cancer therapy. It is to facilitate cross-disciplinary communication to allow effective clinical description of CV events and enhance the clinical research that is ongoing in CO (thereby universal). By incorporation of these standards into routine clinical practice and research, direct comparisons of clinically relevant events in various subpopulations of patients will be strengthened to allow advances in evidence-based CO practice.

Methodology

The consensus definitions of CV toxicities encountered during cancer therapy were developed by a writing group consisting of multidisciplinary experts in the fields of cardiology, hematology, and oncology convened by the Scientific Council of the International Cardio-Oncology Society

(IC-OS). Bimonthly webinars/teleconferences were held from July 2020 until January 2021, during which subgroups discussed individual topics with an accompanying extensive literature review, and consensus discussions were developed applicable to clinical practice as well as clinical trials following accepted guidelines.[5] The definitions described in this document represent unanimous agreement among the writing group. The most common adverse CV events during contemporary cancer therapy can be categorized into 5 main categories: 1) Cardiac Dysfunction: Cardiomyopathy/Heart Failure, 2) Myocarditis, 3) Vascular Toxicity, 4) Hypertension, 5) Arrhythmias and QTc prolongation. It is recognized that societal consensus documents and guidelines (e.g. by the American College of Cardiology, the American Heart Association and the European Society of Cardiology) have already defined cardiac adverse events encountered in the general population; this writing group specifically focused on those adverse CV events uniquely encountered during cancer therapy.

1. Cardiac Dysfunction/Heart Failure

What constitutes cardiac (or myocardial) dysfunction as a cardiovascular toxicity?

Cancer therapy can adversely impact cardiac structure and/or function, emerging as asymptomatic cardiac dysfunction or symptomatic heart failure (HF), collectively termed Cancer Treatment Related Cardiac Dysfunction (CTRCD).

Which cancer therapeutics are associated with cardiomyopathy and heart failure?

CTRCD has been described in association with many cancer therapies including conventional chemotherapeutics (anthracyclines) and different classes of targeted therapies (HER2-targeted agents, certain small molecule kinase inhibitors, and specific proteasome inhibitors). The incidence and details of CTRCD associated with specific cancer therapeutics has been described extensively elsewhere.[6-9] For the purposes of this document, a summary of agents, for which a direct causative association with CTRCD has been described in clinical trials, is presented in **Supplemental Table 1**.

It is important to note that routine baseline left ventricular ejection fraction (LVEF) assessment and/or monitoring of cardiac function is recommended by the package insert/drug label for only a few subgroups of therapies/agents, while for all others only symptom-based surveillance is recommended. In clinical practice, the lack of a baseline LVEF can pose a challenge when evaluating the likelihood of true CTRCD. Additionally, the multitargeted nature of many cancer therapeutics means that other CV toxicities may be present, especially ischemia and thromboembolism, which may complicate and contribute to the development of HF.

Which cardiac dysfunction definitions have been used in cancer patients?

The definition of cardiac dysfunction associated with chemotherapy and other cancer treatments has evolved over the years from recognition of clinical HF to declines in cardiac function, elevation of cardiac biomarkers, or even histological evidence of cardiac injury on endocardial biopsies, especially with anthracycline use.[10-14] The first step towards a set of established criteria for asymptomatic and symptomatic cardiac dysfunction was taken after the emergence of an unexpected incidence of HF events associated with trastuzumab (a monoclonal antibody to HER2 receptor), confirmed by a post-hoc investigation by the independent Cardiac Review and Evaluation Committee (CREC). [15, 16] These criteria were incorporated in subsequent clinical trials and, ultimately, into regulatory package inserts and professional society guidelines for monitoring of cardiac function during trastuzumab-based therapy.[16] Subsequently, many professional groups developed modifications of the CREC definitions to define CTRCD, albeit with some notable differences (**Table 1**). In the most recent version of Common Terminology Criteria for Adverse Events (CTCAE), CTRCD can be reported as LVEF change, systolic dysfunction and/or HF events with unique severity grading within each category. These categories overlap with each other and are not aligned with standard terminology used in HF and cardiology guidelines, thus making them difficult to apply in a practical, multidisciplinary care model. Apart from these developments, investigators have used their own, independent definitions of CTRCD in research reports, impeding limiting efforts to compare study findings directly and to generate an evidence base for clinical practice. Thus, there is an urgent need to harmonize the multiple classification systems in the discipline of CO.

How is this definition of CTRCD different or improved?

The challenges of reconciling multiple classification systems are not unique to CO, where differences reflect growth and evolution of science (including preferences for terms such as HF over CHF, or the need for a universal definition of myocardial infarction), sophistication of cardiac imaging techniques, and numerous new targeted cancer therapeutics. In this document, we aim to harmonize previous and currently used definitions of cardiac dysfunction in CO practice and research with a contemporary approach to HF put forward by professional cardiovascular societies. Under the umbrella of CTRCD, we make the critical distinction between symptomatic HF and asymptomatic CTRCD and define the criteria for severity assessment in both categories, analogous to the CTCAE system (**Figure 2**). By utilizing this approach, the proposed definitions are applicable to CO clinical practice as well as clinical research in oncology treatment, registries, and clinical trials. The diagnosis of CTRCD includes a comprehensive evaluation of clinical symptoms, signs, cardiac imaging and cardiac biomarkers, in the context of exposure to potentially cardiotoxic agents.

What defines symptomatic CTRCD?

Symptomatic CTRCD is characterized by a HF syndrome including typical symptoms with signs of volume overload and/or inadequate perfusion, that are caused by structural and/or functional abnormalities of the heart consistent with AHA/ACC Stage C/D (**Supplemental Table 2**). However, these symptoms can be non-specific and therefore, in a patient presenting with symptoms of HF, a careful history and physical examination, accompanied by appropriate diagnostic tests, should be performed to differentiate between cardiac and non-cardiac disorders.

As such, the history should focus on potential cardiotoxic exposures and pre-existing CV risk factors or conditions placing the patient at risk for HF. Symptoms and signs should be assessed with particular attention to volume overload. However, rarely patients can present with signs of hypoperfusion in the absence of congestion. Symptoms of HF correlate with survival and even patients with mild symptoms are at increased risk of hospitalization and death.[17] These principles are especially pertinent in patients with cancer, in whom many of these symptoms could result from cancer therapy. A combination of signs, symptoms and objective findings has been utilized in the PROTECT (Prospective Observation of Cardiac Safety With Proteasome Inhibitor) study to diagnose HF in a cancer population undergoing cancer therapy and was noted to correlate with worse overall outcomes.[18]

Measurement of natriuretic peptides (NPs) (B-type natriuretic peptide, NTpro-BNP) can help establish or exclude the diagnosis of symptomatic HF [19, 20] and cut-off values, BNP < 100 pg/ml or NT-proBNP < 300 pg/ml, have been proposed to exclude HF in the acute setting.[21] In the subacute setting, lower values may be more appropriate with BNP < 35 pg/ml or NT-proBNP < 125 pg/ml having a negative predictive value of 93-97% for symptomatic HF.[22] NP levels, especially NT-proBNP, increase with age and declining renal function and decrease with obesity (body mass index >30 kg/m2), and all values should ideally be compared to a pre-treatment baseline in order to confirm new findings. Troponin elevation above the 99th percentile cutoff for the specific assay used can serve a supportive role as a biomarker indicating cardiac injury.[23-26] Isolated elevations of these biomarkers without imaging parameters indicating abnormalities may be considered as biochemical evidence of cardiotoxicity. Decisions regarding cancer treatment continuation versus discontinuation should not be based on biomarker abnormalities alone. The same applies to imaging studies other than substantial LVEF changes.

Cardiac imaging, typically with an echocardiogram (Echo), should be performed to define LVEF as well as chamber sizes, diastolic filling parameters and, preferably, global longitudinal strain (GLS).[27] We used the *intensity of therapy needed to resolve symptoms as a method for classifying the severity of symptomatic HF* (**Table 1**). This combines and builds on the CTCAE v 5.0 categories of LV systolic dysfunction and HF. [28]

What defines asymptomatic CTRCD?

Asymptomatic CTRCD is much more common during cancer therapy than symptomatic HF. Its identification is often based on threshold changes of LVEF on screening Echo during cancer treatment or as an incidental finding during survivorship surveillance. There have been multiple cutoffs of LVEF changes attempting to describe CTRCD, and there is uncertainty regarding which of these criteria is most prognostically relevant. A fall in LVEF to <50% appears to be prognostically important and can affect continuation of cancer therapy as well as cancer prognosis.[29-32] More importantly, a reduction in LVEF to <50% followed by persistent LVEF decline, or lack of recovery, despite optimal HF treatment, is associated with subsequent risk of major adverse CV events.[29, 30] This phenomenon is more common with anthracycline therapy, but has been observed with other cancer therapies as well.[33] Therefore, identification and treatment of asymptomatic CTRCD remains important. In addition to accurate LVEF assessment, the cardiac imaging technique needs to reliably detect a significant change in LVEF from baseline, as LVEF reduction is part of the CTRCD definitions in both asymptomatic and symptomatic populations (**Table 1**). The LVEF decline of >10% has been the most commonly accepted threshold value; however, it is important to emphasize that test-retest validity of the chosen imaging technique should be established and confirmed for each laboratory prior to being

able to reliably diagnose CTRCD. [34, 35] Given these recognized challenges with the serial LVEF measurements, more sensitive methods to detect and confirm cardiac dysfunction should be considered, including GLS and serum cardiac biomarkers (e.g. troponins and NPs).

GLS is a measure of myocardial deformation that is a surrogate measure of myocardial function, and a reduction of GLS (less negative) is a marker of myocardial dysfunction. This tool can detect changes in myocardial function prior to a significant threshold change in LVEF. [36]As the calculation of GLS varies between vendors of Echo machines and analytical equipment and software, it is recommended to use the same system to be able to accurately compare values over time. [27] Much of the literature on the use of GLS applies classically to patients with breast cancer receiving anthracyclines and/or trastuzumab therapy, thought data in patients on immune checkpoint inhibitor therapy are emerging. [37] Two studies have demonstrated significant concurrent association between temporal changes in GLS and LVEF.[38, 39] Therefore a change in GLS can be used as an arbiter of whether a true change in LVEF has occurred (**Table 1**). Conceptullay, however, the value of GLS is greatest in the absence of a significant change in LVEF. In this scenario, a change in GLS > 15% relative to baseline has been suggested as the threshold to identify subclinical cardiomyopathy.[27] Other thresholds have been considered, and the recently published SUCCOUR trial used a 12% relative change in GLS as a cuoff for the initiation of cardioprotective therapy. [40] Similar to GLS, an increase in troponin and NP levels have also been considered to have utility for the early detection of cardiotoxicity, and in some cases a prognostic value especially in the context of exposure to anthracyclines and HER2-targeted therapy or proteasome inhibitors.[18, 41, 42]

Considering these findings, asymptomatic CTRCD is graded on the basis of LVEF change and includes measures of GLS and/or biomarkers to help further determine severity

(**Table 1**). A reduction in LVEF to <40% indicates severe asymptomatic CTRCD, with recent data suggesting an association with poor prognosis in multiple cancers and treatment regimens.[43] Moderate asymptomatic CTRCD requires (i) a fall in LVEF into a clearly abnormal range (40-49%) with a change in LVEF beyond the described variability of the most commonly used echo based 2D-LVEF measurements (i.e. 10%), or (ii) a smaller change in LVEF but with a concomitant significant fall in GLS and/or new rise in cardiac biomarkers. Mild asymptomatic CTRCD is defined as preserved LVEF (i.e., LVEF ≥ 50%) with >15% reduction in GLS with or without concomitant increase in troponin or NPs.

2. Myocarditis

What constitutes myocarditis as a cardiovascular toxicity?

Myocarditis is an inflammatory disease of heart muscle cells. In cancer patients, most commonly myocarditis can be seen as a result of direct toxicity or as an immune-mediated event.[44]

Which cancer therapies have been associated with myocarditis?

Both traditional cytotoxic cancer therapies (e.g. doxorubicin, fluorouracil, and cyclophosphamide), radiation therapy, and immune checkpoint inhibitors (ICI) have been associated with the development of myocarditis.[6, 45]

Which myocarditis definitions have been used in cancer patients?

Historically, CTCAE has served as a reference for adverse events coding in cancer patients (**Table 2**). A specific set of criteria for adjudicating myocarditis in clinical trials with cancer therapeutics was forwarded by Bonaca et al. in 2019 (**Table 2**).

How is this definition of myocarditis different or improved?

The CTCAE definition and grading system is rather generic and lacks specific criteria for diagnosis. While specific criteria and a grading system of possible, proable, and definite myocarditis were provided by Bonaca et al., the goal of their definition was to facilitate identification and ascertainment of cases of myocarditis in clinical trials. As specifically stated, it their definition was not intended for clinical use. This is, however, very much the goal of the definition outlined herein, which may also be used in clinical trials to align clinical practice and research. The current definition furthermore takes into consideration additional data on ICI myocarditis that have become avaikable since the publication of the document by Bonaca et al. (including the utility and limitations of ECG, various imaging modalities and treatment implications). [46-48]

In distinction from prior definitions, the current definition is first of all binary: myocarditis is either present or absent, based on meeting major and/or minor criteria. In keeping with the concept of grading schemes, these were provided for severity, steroid refractory myocarditis and the degree recovery from myocarditis. These are crucial aspects for the management of myocarditis, includingdecisions on further antineoplastic therapies, especially if re-challenge with ICI therapy is being considered.

What defines ICI-mediated ICI myocarditis?

Consistent data have shown that myocarditis caused by an ICI is a T-cell mediated inflammatory disease of cardiac muscle cells leading to cell death. The mechanisms involved in the development of this T-cell mediated cardiac myocyte cell death are incompletely understood. Possible etiologies include the development of auto-antigens, allo-antigens or allergens. [49, 50] Lack of specificity in the clinical presentation, potential overlap with other cardiovascular and general medical conditions, and limited sensitivity and specificity of routine cardiovascular testing, make the diagnosis of ICI-associated myocarditis challenging.[37, 51, 52] Similar to prior criteria, we propose using a combination of clinical, electrocardiographic, cardiac biomarker, cardiovascular imaging (echocardiogram and cardiac MRI), and tissue pathology findings with some modifications based on recent data to increase the accuracy of the diagnosis (**Table 2, Supplemental Table 3)**. [53] We recognize that many of these tests can be abnormal in a variety of other conditions, emphasizing the importance of maintaining a broad differential in patients being evaluated for myocarditis.

Timely diagnosis of ICI myocarditis is critical since prompt initiation of immunosuppression can substantially improve cardiovascular outcomes.[52] Conversely, an incorrect diagnosis of myocarditis can lead to the discontinuation of a potentially effective cancer therapy and worsen cancer-related outcomes. We have therefore further classified myocarditis based on the severity of the clinical presentation (**Table 2**), as well as refractoriness to treatment with corticosteroids. We also define recovery from myocarditis with the intention that severity of the index presentation, the response to treatment and the degree of recovery may help guide further cancer therapy, especially if re-challenge with ICI therapy is being considered (**Table 2**).

While ICIs are currently the primary immune therapy associated with myocarditis, it is possible that other novel immunomodulatory agents may also cause myocarditis. Application of uniform diagnostic criteria to identify myocarditis in clinical trials of novel immunotherapies might enable us to better understand the incidence, severity and implications of myocarditis associated with a particular cancer therapy.[54-59]

3. Vascular toxicities

What constitutes vascular toxicity in the cancer patient?

Vascular toxicity is the induction or aggravation of vascular disease in the setting of cancer therapy.

Which cancer therapies have been associated with vascular toxicity?

This topic emerged with the introduction of 5-FU into cancer therapy regimens but has been noted with several other cancer drugs including: platinum drugs, cyclophosphamide, gemcitabine, bleomycin, vinca alkaloids, the immunomodulatory drugs interferon alpha 2B and lenalidomide, the proteasome inhibitor carfilzomib, and the mTOR inhibitor everolimus (**Supplemental Table 4**).[60] Vascular toxicities gained further interest with the introduction of targeted therapies, namely vascular endothelial growth factor (VEGF) signaling pathway inhibitors (VSPI), BCR-Abl tyrosine kinase inhibitors such as nilotinib and ponatinib, and the epidermal growth factor (EGF) receptor inhibitor erlotinib. [61, 62] Last but not least, vascular

toxicity can also be seen with radiation injury but do not emerge until sometime after completion of therapy.

Which vascular toxicity definitions have been used in cancer patients?

"Vascular toxicity" has been used as an umbrella term rather than a designated event or endpoint in clinical studies despite the common use of composite endpoints. The most commonly used composite endpoint in research studies in this area is arterial thromboembolism (ATE), variably defined, for instance, as a) any inpatient or outpatient diagnosis of myocardial infarction or ischemic stroke, or b) arterial thrombosis, cerebral infarct, cerebral ischemia, cerebrovascular accident, myocardial infarction, and myocardial ischemia, or c) angina pectoris, arterial thrombosis, cerebral infarct, cerebral ischemia, cerebrovascular accident, myocardial infarction, and myocardial ischemia.[63-65] The other terminology that has been used is arterial occlusive event (AOE), categorized based on a broad collection of >400 Medical Dictionary for Regulatory Activities preferred terms related to vascular ischemia or thrombosis. [66] Peripheral arterial occlusive disease (PAOD) is another term in the cardio-oncology literature, and an alternate term for peripheral arterial disease (PAD), also known as peripheral vascular disease (PVD) or lower extremity arterial disease.[67] The only standardized approach to the various aspects of vascular toxicity is found in the CTCAE catalogue, which has been used in clinical studies, especially trials in cancer patients (**Table 3**).

How is this definition of vascular toxicity different or improved?

As outlined, there is no standardized definition of vascular toxicity other than the approach provided by CTCAE. Even so, the CTCAE definitions do not necessarily match events taken into

account otherwise. For instance, the CTCAE Version 5 definition of arterial thromboembolism is that of "a disorder characterized by an occlusion of an arterial vessel by a blood clot that develops in an artery" and grading of severity starts with Grade 3 (urgent intervention indicated). ATE definitions used in clinical studies deviate from this by including presentations of ischemia not requiring urgent interventions or being life-threatening and may focus only on two arterial territories (coronary and cerebral) while the scope could be broader. Also, the origin of the thrombus may not always be the vasculature but would still qualify as an ATE if a thrombus embolized from cardiac chambers into an arterial territory. The definition proposed herein encourages the definition of the vascular disease entity and its mode of presentation using established societal criteria and guidelines (**Table 3**).

Which pathophysiological types of vascular toxicity have been noted?

As outlined, vascular toxicity has a broad spectrum of presentations, varying in type and by vascular bed involved. From a pathophysiological perspective, three main scenarios can be encountered that lead to luminal obstruction and reduction in blood flow with related sequelae: 1) altered vascular reactivity, 2) vascular thrombosis and 3) atherosclerosis.[60] A fourth one that can be seen is vasculitis, which may lead to all of the above (altered vasoreactivity, thrombosis, and/or structural obstruction).

What is the clinical presentation of vascular toxicity?

Vascular toxicity can be clinically silent (asymptomatic) or apparent (symptomatic). Asymptomatic vascular toxicity is detected by testing modalities and, while of interest for research studies, it is also important clinically, especially for the early recognition and prevention

of symptomatic disease and complications. For instance, recognition of progressive narrowing of the peripheral arteries by a decline in ankle brachial indices (ABI) over time in a patient with chronic myelogenous leukemia on nilotinib may prevent progression to the point of critical limb ischemia, which can result in gangrene and amputation. [62] Conversely, presentation with claudication or critical limb ischemia may lead to the detection of peripheral arterial disease which was not present before the start of cancer therapy, and thus might have been provoked by it.

In cases of suspected vascular toxicity, in addition to documenting a change from baseline, it is important to establish the likelihood of an association with the cancer therapy based on current knowledge (definite, probable, possible, unlikely), akin to the adverse event adjudication process in clinical trials. At times, and especially with new drugs, the appropriate association may not have been previously noted; recognition and reporting of potential toxicities is therefore extremely important.

Asymptomatic vascular changes

These reflect disease processes recognized by changes in diagnostic testing parameters beyond what can be expected based on analytical and biological variability. In addition to recognizing significant changes, taking common thresholds for abnormality into account is important for aligning with common practice standards and guidelines. The margin or reserve from the threshold of abnormality for vascular structure or function is reduced in patients with underlying cardiovascular disease and/or risk factors (**Table 3**).[68-75]

Symptomatic presentations

These are defined by societal guidelines as it is common clinical practice (**Table 3**). [76-86] Conventional terms such as peripheral arterial disease should be used in lieu of non-conventional terms such as POAD. Furthermore, it is recommended avoiding the use of combination and overlap terms such as ATEs. Instead, the specific component should be reported in keeping with standard definitions.

4. Hypertension

What constitutes hypertension as a cardiovascular toxicity?

An increase in systolic and/or diastolic blood pressure after initiation of cancer therapy, without any other contributing changes, constitutes an adverse effect which can be of various grading. Distinct from chronic hypertension, which can be present in the cancer patient and has been generally associated with an increased risk of cardiovascular events, less is known about the effects of short-term increases in blood pressure (BP) in patients with cancer. [87-91]

Which cancer therapies are associated with hypertension?

Several cancer therapies have been associated with hypertension and in particular newer targeted agents such as VSPIs. Other agents include the proteasome inhibitor carfilzomib, mTOR inhibitors, and tyrosine kinase inhibitors of BRAF, MEK, and BTK (**Supplemental Table 5**). Patients receiving VSPIs can develop hypertension within days of starting therapy and there is potential for life-threatening complications.[92-96] Of note, different agents may have variable hypertensive effects and there is remarkable inter-individual variation. Uncontrolled

hypertension is associated with diverse cardiac and non-cardiac complications. [97-99] Hypertension is a potent risk factor for cardiotoxicity and cardiovascular events in patients with cancer, both during cancer therapy and after its completion. Therefore, defining diagnostic and therapeutic thresholds is particularly important.

Which hypertension definitions have been used in cancer patients?

Multiple definitions and grading schemes exist for hypertension that have come out by groups such as American College of Cardiology/American Heart Association, European Society of Cardiology, and International Society of Hypertension **(Table 4**). However, none of them specifically address hypertension in the cancer patient.

How is this definition of hypertension different or improved?

Hypertension in the cancer patient presents a unique situation in which hypertension may be temporary and due to treatment, but with more abrupt onset that can lead to end organ damage and other complications. Uncontrolled hypertension may also lead to the holding of cancer treatment, which can have significant implications on the oncologic aspect of a patient's care. Thus, our definition and perspective of hypertension, as outlined in **Table 4**, was created with these considerations in mind.

What defines hypertension in the cancer patient?

The inaccuracy of BP measurements in the office setting has led to the recommendation for out-of-office BP measurements (ambulatory [ABPM] and home BP monitoring) to confirm a diagnosis of hypertension (**Table 4**).[100] Home BP monitoring should be adopted by all patients

with cancer receiving therapy known to cause or worsen hypertension.[91] In those with elevated BP, it remains important to rule out reversible causes such as obstructive sleep apnea, pain, and emotional stressors.

The diagnostic threshold for hypertension in patients with malignancy before or after cancer therapy is >130/80 mmHg (**Table 4**).[88] This is also the BP treatment threshold for patients during cancer treatment with pre-existing cardiovascular disease (CVD), proteinuric renal disease or diabetes. [88] In other patients during cancer treatment, the threshold for initiation of antihypertensive therapy can be extended to 140/90 mmHg. If the BP is > 180 mmHg systolic or 110 mmHg diastolic, the competing cancer and cardiovascular risks should be evaluated, and any cancer therapy associated with hypertension should be deferred or temporarily withheld until the BP is controlled to values below 160 mmHg systolic and 100 mmHg diastolic. The same holds true for an emergency hypertensive response, defined as the development of hypertension associated with signs or symptoms of end-organ injury including hypertensive encephalopathy, posterior reversible encephalopathy syndrome (PRES), papilledema, stroke, myocardial infarction, acutely decompensated heart failure, aortic dissection, and acute kidney injury. These need to be managed, along with BP control, before cancer therapy can resume after proper risk/benefit discussion. Patients with greater BP variability and/or an exaggerated response such as an absolute increase in systolic BP >20 mmHg and/or mean arterial BP >15 mmHg from baseline need particular attention as high BP may be reached precipitously and with clinical consequences.

5. Arrhythmias and QTc Prolongation

What constitutes QTc prolongation as a cardiovascular toxicity?

The full scope of abnormalities in cardiac electrophysiology can be seen in patients with cancer.[6, 101] These may be related to cancer therapy, underlying predisposition/risk, or both. While atrial fibrillation occurs commonly in this population, its definition as well as the definition of other supraventricular and ventricular arrhythmias does not differ from those applied to the general population. As such, they will not be discussed in this document. QTc prolongation which is a lengthening of the cardiac repolarization interval is of particular importance due to the risk of sudden cardiac death and its direct relation to cancer therapy and related treatments (anti-emetics, etc.). There is substantial variability in the literature regarding significant QT interval changes. No standardized definitions and recommendations exist, and cancer care providers are referred to the individual drug labels.[102] The goal of this section is to provide a harmonized definition of QT prolongation in the cancer patient population.[103]

Which cancer therapies are associated with QTc prolongation and the risk of sudden cardiac death?

Several cancer therapies have been recognized to cause QTc prolongation including arsenic trioxide, HDAC inhibitors, tyrosine kinase inhibitors (esp. vandetanib, vemurafenib, ceritinib, gilteritinib, trametinib, and those targeting Bcr-Abl and the VEGF signaling pathway) and CDK 4-6 inhibitors (ribociclib) (**Supplemental Table 6**). [6, 104, 105]

Which arrhythmia definitions have been used in cancer patients?

The CTCAE criteria have been used to define degrees of QT prolongation in clinical trials (**Table 5**). **Grade 1** prolongation is an average QTc 450 - 480 ms; **Grade 2** is an average QTc 481 - 500 ms; and **Grade 3** is an average QTc ≥ 501 ms or 60 ms change from baseline however these are not uniformly incorporated into routine clinical practice decision making.

How is this definition of arrhythmia different or improved?

While the CTCAE criteria provide grades of QT interval prolongation, they do not provide any guidance regarding management, specifically as it relates to withholding or dose reduction of cancer therapies. As such, each pharmaceutical manufacturer provides different recommendations and guidance. Our definition of significant QT interval prolongation is based on epidemiologic data demonstrating increased risk of arrhythnias and can be applied universally to all cancer therapies which will significantly improve and simplify care delivery (**Table 5**).

What defines QTc prolongation in the cancer patient?

QT interval assessment can be challenging, especially in the setting of arrhythmia, conduction delays due to bundle branch block or pacing, and abnormal T wave morphologies. Due to variations in the absolute QT interval with heart rate fluctuations, several correction formulae have been developed to standardize these measurements. [102, 105, 106] In the oncology setting, we recommend using the Fridericia formula $QT_c = QT \times RR^{-1/3}$ as this is relatively easy to calculate and has demonstrated less error than other correction methods such as Bazett at both tachy- and bradycardic heart rates. [102, 105-107] ECG machines provide an automated QT measurement; however, these systems are generally defaulted to the Bazett algorithm. We recommend re-programming machines being used for cancer patients to provide corrected QT measurements

using the Fridericia formula. While it is acceptable to use the automated QT values reported on the ECG tracing in most circumstances, any value that is abnormal or concerning should be manually evaluated by a cardiologist and/or electrophysiologist with cardio-oncology expertise. This is particularly true for patients with ventricular pacing or bundle branch blocks as the associated QRS prolongation must be accounted for when assessing the QT interval.

In the general population, the upper 99% limit of normal for QT interval is 470 ms for males and 480 ms for females.[107] Other cutoffs for a normal QTc interval, however, have been used, i.e. 450 ms for males and 470 ms for females. In general, the risk of malignant arrhythmias is considered to increase with QTc intervals in excess of 500 ms or an increase by more than 60 ms from baseline, although this may not always apply to cancer patients. [103] The exact frequency of malignant arrhythmias in clinical practice is not precisely defined, ranging from well under 1% to nearly 5% with tyrosine kinase inhibitors. [103, 104] The differences may be explained by the number of factors that can affect the QT interval and arrhythmogenic risk including cancer drugs, concomitant medications (i.e. antibiotics, psychiatric medications) and electrolyte abnormalities and comorbidities contributing to these, as well as underlying cardiovascular disease.

In general, if the corrected QT interval is less than 500 ms, the risk of torsade de pointes is exceedingly low.[108] As such, we recommend considering a change in cancer therapy only when the corrected QT interval is greater than 500 ms. Moreover, changes in the QT interval of more than 60 ms from baseline are clinically insignificant if the QT remains less than 500 ms and should not routinely affect treatment decisions. It is important to remember that the QT interval is not stagnant and should be re-assessed if the clinical status (e.g. electrolyte disturbances) of the patient changes or dose changes have been applied (**Figure 3**).

Summary

The current document reflects a harmonizing review of the current landscape in cardiovascular toxicities and the definitions used to define these. This consensus effort aims to provide a structure for definitions of cardiovascular toxicity in the clinic and for future research. It will be important to link the definitions outlined herein to outcomes in clinical practice and cardiovascular endpoints in clinical trials. It should facilitate communication across various disciplines to improve clinical outcomes for cancer patients with cardiovascular diseases.

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Figure legends

Central illustration. Outline of the five focus areas of cardiovascular toxicities covered in this universal definition document.

Figure 1. Pubmed entries over time for case reports, clinical, observational, or multicenter studies, and randomized controlled clinical trials based on the following search terms: cardiotoxicity OR cardiac dysfunction OR cardiomyopathy OR heart failure AND cancer, myocarditis AND cancer, vascular toxicity OR atherosclerosis OR thrombosis OR vasospasm AND cancer, hypertension AND cancer, pericarditis OR pericardial disease AND cancer, valvular heart disease AND cancer.

Figure 2. Diagnostic Algorithm for Cancer Therapy Related Cardiac Dysfunction (CTRCD)

Figure 3. Overview of the approach to QTc prolongation in cancer patients.

Table 1: Definitions for Cancer Treatment Related Cardiac Dysfunction

Cardiac Review and Evaluation Committee, Definition of Chemotherapy-induced Cardiotoxicity[16]	Any one of the following: 1) reduction of LVEF, either global or specific in the interventricular septum; 2) symptoms of congestive heart failure 3) signs associated with heart failure (HF), such as S3 gallop, tachycardia, or both 4) reduction in LVEF from baseline ≥ to 5% to <55% in the presence of signs or symptoms of HF, or a reduction in LVEF ≥10% to <55% without signs or symptoms of HF			
NYHA Classification	**Class I** No symptoms.	**Class II** Mild symptoms and slight limitation during ordinary activity	**Class III** Marked limitation due to symptoms, even with less than ordinary activity.	**Class IV** Symptoms at rest.
ACCF/AHA Stages of HF	**Stage A** At high risk for HF but without structural disease or symptoms of HF.	**Stage B** Structural heart disease but without signs or symptoms of HF.	**Stage C** Structural heart disease with prior or current symptoms of HF.	**Stage D** Refractory HF requiring specialized interventions.
CTCAE v5.0 Ejection Fraction Decreased*		**Grade 2** Resting ejection fraction (EF) 50-40%; 10-19% drop from baseline	**Grade 3** Resting ejection fraction (EF) 39-20%; >= 20% drop from baseline	**Grade 4** Resting ejection fraction (EF) < 20%
CTCAE v5.0 LV Systolic Dysfunction*		**Grade 3** Symptomatic due to drop in ejection fraction responsive to intervention		**Grade 4** Refractory or poorly controlled heart failure due to drop in ejection fraction; intervention such as ventricular assist device, intravenous vasopressor support, or heart transplant indicated
CTCAE v5 Heart Failure*	**Grade 1** Asymptomatic with laboratory (e.g., BNP [B-Natriuretic Peptide]) or cardiac imaging abnormalities	**Grade 2** Symptoms with moderate activity or exertion	**Grade 3** Symptoms at rest or with minimal activity or exertion; hospitalization; new onset of symptoms	**Grade 4** Life–threatening consequences; urgent intervention indicated (e.g., continuous IV therapy or mechanical hemodynamic support)
Package Insert Guidelines to Hold Cancer Therapy Due to LV Dysfunction	**Trastuzumab** ≥16 % absolute decrease in LVEF or ≥ 10 % drop to below institutional limits of normal		**Pertuzumab** ≥ 10 % drop in LVEF to < 50% for early breast cancer, ≥ 10 % drop in LVEF to 40-45% for metastatic breast cancer, or drop to less than 40%	

2014 Echo Guidelines for Subclinical LV Dysfunction[27]	**Subclinical LV dysfunction** > 15% relative drop in GLS from baseline		**CRTCD** Drop in LVEF of > 10 percentage points to a level < 53%. Should be confiurmed by repeat testing.	
2016 ESC Position Statement	**Mild (Asymptomatic)** LVEF < 50% or LVEF reduction > 10% from baseline, should be repeated within 3-4 weeks		**Moderate (Symptomatic from HF)** LVEF <50%	
2017 ASCO Guideline	Cardiotoxicity not specifically defined			
2020 ESMO Guideline	**Mild (Asymptomatic)** LVEF > 15% from baseline if LVEF >50%	**All Cancer Therapy**	**Moderate** Symptomatic HF regardless of LVEF	**Severe** LVEF < 40%
		Anthracycline or Trastuzumab Related	**Moderate** LVEF ≥10% from baseline, or Any drop of LVEF to <50% but ≥40%	
ICOS 2021 Universal Definition				
Asymptomatic CTRCD (with or without additional biomarkers)	**Mild** New LVEF reduction to ≥50% AND new fall in GLS by >15% +/- new rise in cardiac biomarkers§	**Moderate** New LVEF reduction to >10% and to 40-49% New LVEF reduction by <10% and to 40-49% AND new fall in GLS by >15% +/- new rise in cardiac biomarkers§	**Severe** New LVEF reduction to <40%	
Symptomatic CTRCD (with LVEF and supportive diagnostic biomarkers)	**Mild** Mild HF symptoms, no intensification of therapy required	**Moderate** Need for Outpatient intensification of diuretic and HF therapy	**Severe** HF Hospitalization	**Very Severe** Requiring inotropic support, mechanical circulatory support or consideration for transplantation

ACCF=American College of Cardiology Foundation. AHA = American Heart Association. ASE = American Society of Echocardiography. CTCAE = Common Terminology Criteria for Adverse Events. CTRCD = Cancer-therapeutics Related Cardiac Dysfunction. HF = Heart Failure. GLS = Global Longitudinal Strain. LVEF = Left ventricular ejection fraction. NYHA: New York Heart Association.

*Oncology trial investigators can choose to classify a given event under “ejection fraction decreased,” “LV systolic dysfunction,” or “Heart Failure” with associated grades if they decide the adverse effect is related to the intervention. This contributes to difficulty in comparing results of trials and effects of cancer therapies. Grade 1 – Grade 4 (mild to severe). Death = Grade 5. No Grade 5 for “ejection fraction decreased.”
§Cardiac troponin I/T>99th percentile, BNP ≥ 35 pg/ml, NT-proBNP≥125 pg/mL

Table 2. Definitions for Immune Checkpoint Inhibitor Associated Myocarditis

CTCAE v5.0 Definition		
A disorder characterized by inflammation of the muscle tissue of the heart.		
Grade 2 Symptoms with moderate activity or exertion	**Grade 3** Severe with symptoms at rest or with minimal activity or exertion; intervention indicated; new onset of symptoms	**Grade 4** Life-threatening consequences; urgent intervention indicated (e.g., continuous IV therapy or mechanical hemodynamic support)
Bonaca et al. Definition		
Definitive	• Pathology OR • Diagnostic CMR + syndrome +biomarker or ECG OR • Echo WMA + syndrome + biomarker + ECG + negative angiography	
Probable	• Diagnostic CMR (no syndrome, ECG, biomarker) OR • Suggestive CMR with either syndrome, ECG or biomarker OR • Echo WMA and syndrome (with either biomarker or ECG) OR Syndrome with PET scan evidence and no alternative diagnosis	
Possible	• Suggestive CMR with no syndrome, ECG or biomarker OR Echo WMA with syndrome or ECG only OR Elevated biomarker with syndrome or ECG and no alternative diagnosis	
ICOS 2021 Universal Definition		
• Either 1 major or 3 minor criteria		
• If 2 minor criteria are present and consist of any two of the following: Newly elevated troponin, reduced LVEF and/or suggestive cardiac MRI, it may be adequate to make a diagnosis especially after exclusion of other potential etiologies		

Major Criteria[§]

- Pathology
- Syndrome + elevated cTn + diagnostic cardiac MRI
- Syndrome + elevated cTn + new reduction in LVEF[*#]
- Newly elevated cTn + diagnostic cardiac MRI
- Ventricular arrhythmia and/or high-grade conduction system disease + elevated cTn[*#]
- Cardiogenic shock with newly reduced ejection fraction + elevated cTn[*#]

Minor Criteria

- Syndrome
- New ECG changes (e.g. new RBBB, new LBBB, new bifascicular block, new complete heart block)
- Elevated troponin*
- Reduced LVEF*± pericardial effusion*
- Immune mediated myositis, myopathy, or myasthenia gravis
- Suggestive cardiac MRI (non-diagnostic)

Both troponin I and troponin T can be used, however, troponin T may be falsely elevated in those with concomitant myositis.
*After reasonable exclusion of other potential etiologies.
[#] Confirm with CMR or EMB if feasible.
[§] In a patient that is clinically unwell, treatment with immunosuppression should be promptly initiated while awaiting further confirmatory testing.

Modifiers	
Severity of Myocarditis	
Severe	Hemodynamic instability, heart failure requiring non-invasive or invasive ventilation, complete or high-grade heart block, and/or significant ventricular arrhythmia
Non-Severe (clinically significant)	Symptomatic but hemodynamically and electrically stable, may have reduced LVEF, no features of severe disease
Smoldering (sub-clinical)	Incidentally diagnosed myocarditis without any clinical signs or symptoms

Steroid Refractory	Non-resolving or worsening myocarditis (clinical worsening or persistent troponin elevation after exclusion of other etiologies) despite 1000 mg of methylprednisolone. .
Recovery from Myocarditis	
Complete Recovery	Patients with complete resolution of acute symptoms, normalization of biomarkers and recovery of LVEF after discontinuation of immunosuppression are considered to have achieved complete recovery. CMR may still show LGE or elevated T1 due to fibrosis but any suggestion of acute edema should be absent.
Recovering	Ongoing improvement in patient clinical symptoms, signs, biomarkers and imaging parameters, but not yet normalized, while on tapering doses of immunosuppression.
Refractory/ Incomplete Recovery	1. An increase in symptoms or biomarkers of myocarditis or an inability to taper immunosuppression without a clinical or biomarker flare. 2. Patients with persistent LV dysfunction despite resolution of acute symptoms with immunosuppression.

Table 3. Definitions for vascular toxicities with cancer therapies

CTCAE Version 5		
Event	Definition	Grades
Arterial injury	A finding of damage to an artery.	Grade 1: Asymptomatic diagnostic finding; intervention not indicated Grade 2: Symptomatic; repair or revision not indicated Grade 3: Severe symptoms; limiting self care ADL; repair or revision indicated Grade 4: Life-threatening consequences; evidence of end organ damage; urgent operative intervention indicated
Arterial thromboembolism	A disorder characterized by occlusion of an arterial vessel by a blood clot that develops in an artery.	Grade 3: urgent intervention indicated Grade 4: life-threatening consequences, hemodynamic or neurologic instability; organ damage; loss of extremity(ies)
Chest pain (cardiac)	A disorder characterized by substernal discomfort due to insufficient myocardial oxygenation e.g., angina pectoris.	Grade 1: Mild pain Grade 2: Moderate pain; pain on exertion; limiting instrumental ADL; hemodynamically stable Grade 3: Pain at rest; limiting self care ADL; cardiac catheterization; new onset cardiac chest pain; unstable angina
Cerebrovascular ischemia	A disorder characterized by a decrease or absence of blood supply to the brain caused by obstruction (thrombosis or embolism) of an artery resulting in neurological damage.	Grade 1:Asymptomatic; clinical or diagnostic observations only; intervention not indicated Grade 2: Moderate symptoms
Myocardial infarction	A disorder characterized by gross necrosis of the myocardium; this is due to an interruption of blood supply to the area.	Grade 2: Symptoms with moderate activity or exertion Grade 3: Severe with symptoms at rest or with minimal activity or exertion; intervention indicated; new onset of symptoms Garde 4: Life-threatening consequences; urgent intervention indicated (e.g., continuous IV therapy or mechanical hemodynamic support)
Peripheral ischemia	A disorder characterized by impaired circulation to an extremity.	Grade 2: Brief (<24 hrs) episode of ischemia managed medically and without permanent deficit Grade 3: Prolonged (>=24 hrs) or recurring symptoms and/or invasive intervention indicated

		Grade 4: Life-threatening consequences; evidence of end organ damage; urgent operative intervention indicated
Stroke	A disorder characterized by a decrease or absence of blood supply to the brain caused by obstruction (thrombosis or embolism) of an artery resulting in neurological damage.	Grade 1: Incidental radiographic findings only Grade 2: Mild to moderate neurologic deficit; limiting instrumental ADL Grade 3: Severe neurologic deficit; limiting self care ADL; hospitalization Grade 4: Life-threatening consequences; urgent intervention indicated
Thromboembolic event	A disorder characterized by occlusion of a vessel by a thrombus that has migrated from a distal site via the blood stream.	Grade 1: Medical intervention not indicated (e.g., superficial thrombosis) Grade 2: Medical intervention indicated Grade 3: Urgent medical intervention indicated (e.g., pulmonary embolism or intracardiac thrombus) Grade 4: Life-threatening consequences with hemodynamic or neurologic instability
Transient ischemic attack	A disorder characterized by a brief attack (less than 24 hours) of cerebral dysfunction of vascular origin, with no persistent neurological deficit.	Grade 1:Mild neurologic deficit with or without imaging confirmation Grade 2: Moderate neurologic deficit with or without imaging confirmation
Vasculitis	A disorder characterized by inflammation involving the wall of a vessel.	Grade 1: Asymptomatic, intervention not indicated Garde 2: Moderate symptoms, medical intervention indicated Grade 3: Severe symptoms, medical intervention indicated (e.g., steroids) Grade 4: Life-threatening consequences; evidence of peripheral or visceral ischemia; urgent intervention indicated
Vascular disorder		Grade 1: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self care ADL Grade 4: Life-threatening consequences; urgent intervention indicated
Venous injury	A finding of damage to a vein	Grade 1: Asymptomatic diagnostic finding; intervention not indicated

	Grade 2: Symptomatic (e.g., claudication); repair or revision not indicated Grade 3: Severe symptoms; limiting self care ADL; repair or revision indicated Grade 4: Life-threatening consequences; evidence of end organ damage; urgent operative intervention indicated
ICOS 2021 Universal Definition	
Asymptomatic vascular toxicity	
Abnormal vasoreactivity	Peripheral: New flow-mediated dilation of the brachial artery (FMD) < 7.1% or reactive hyperemia index (RHI) <2 on Endo-PAT, or Change in FMD or RHI by >50% from baseline [68] [69] [70] [71]
	Coronary epicardial: New coronary vasoconstriction (reduction in coronary artery diameter) in response to acetylcholine infusion.[109]
	Coronary microvascular: New <50% increase in coronary blood flow in response to acetylcholine infusion, or a coronary flow velocity reserve <2 in response to adenosine.[75]
Thrombosis	Venous thrombosis: New characteristic features on Duplex ultrasound, contrast CT, or venogram
	Arterial thrombosis: New characteristic features on ultrasound or angiogram, or OCT
Atherosclerosis	Peripheral arterial disease: New ABI value ≤ 0.9 is considered abnormal, with 0.7-0.9 being mildly reduced, 0.4-0.69 moderately reduced, and <0.4 severely reduced; ABI value >1.3 is suggestive of non-compressible vessels, or Change from baseline by -0.15 [73]
	Carotid artery disease: New Intima media thickness (IMT) >0.9 mm or plaque on carotid ultrasound, or Change in IMT >0.04/year from baseline [72]
	Coronary artery disease: New coronary artery stenosis >50% on coronary CT angiography or >70% on coronary angiogram, or newly abnormal ECG, nuclear or echo stress test [74]
Symptomatic vascular toxicity	
Raynaud's phenomenon	Meeting the diagnostic criteria of an international consensus panel of recurrent episodes bilateral blanching or tricolor change of the fingers. [76] [77]
Peripheral arterial disease	2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in collaboration with the European Society for Vascular Surgery (ESVS) [85]

Vasospastic angina	2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes: The Task Force for the diagnosis and management of chronic coronary syndromes of the European Society of Cardiology (ESC) [83]
Microvascular angina	2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes: The Task Force for the diagnosis and management of chronic coronary syndromes of the European Society of Cardiology (ESC) [83]
Chronic coronary syndromes	2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes: The Task Force for the diagnosis and management of chronic coronary syndromes of the European Society of Cardiology (ESC) [83]
Acute coronary syndromes	2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction[79] 2014 AHA/ACC Guideline for the Management of Patients With Non–ST-Elevation Acute Coronary Syndromes[80] 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation[81] 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation [82]
Myocardial infarction	4th Universal Definition of MI [78]
Stroke	2018 AHA/ASA Guidelines for the Early Management of Patients With Acute Ischemic Stroke[110] An Updated Definition of Stroke for the 21st Century Stroke: [84]
Transient ischemic attack	2018 AHA/ASA Guidelines for the Early Management of Patients With Acute Ischemic Stroke[110] An Updated Definition of Stroke for the 21st Century Stroke: [84]

Table 4. Definition of hypertension in cancer patients

CTCAE Version 5 [28]	ACC/AHA 2017 [88]	ESC 2018 [111]	ISH 2020 [112]	ICOS 2021 Universal Definition**
	Normal SBP <120 mmHg and DBP <80 mmHg	**Optimal** SBP <120 mmHg and DBP <80 mmHg	**Normal** SBP <130 mmHg and DBP <85 mmHg	**Normal** SBP ≤130 mmHg and DBP ≤80 mmHg
Grade 1 SBP 120 to 139 mmHg or DBP 80 to 89 mmHg	**Elevated** SBP 120–129 mmHg and/or DBP <80 mmHg	**Normal** SBP 120–129 mmHg and/or DBP 80–84 mmHg		**Treatment threshold for HTN Before, During, and Off therapy/Cancer Survivors:** **CVD or ASCVD risk ≥ 10%:** ≥130 mmHg systolic and/or ≥80 mmHg diastolic **Otherwise:** ≥140 mmHg systolic and/or ≥90 mmHg diastolic
	Stage 1 SBP 130–139 mmHg and/or DBP 80–89 mmHg Initiate pharmacologic therapy if ASCVD is present or 10-year ASCVD risk ≥10 %	**High normal** SBP 130–139 mmHg and/or DBP 85–89 mmHg BP drug treatment may be considered if the CV risk is very high, or established CVD, especially CAD	**High normal** SBP 130-139 mmHg and/or DBP 85-89 mmHg	
Grade 2 SBP 140–159 mmHg or DBP 90–99 mmHg if previously WNL; Change in baseline medical intervention indicated; recurrent or persistent (≥24	**Stage 2** SBP ≥140 mmHg and/or DBP ≥90 mmHg BP drugs targeting <130/80 mmHg	**Grade 1** SBP 140–159 mmHg and/or DBP 90–99 mmHg BP drugs target <140/90 as first objective, if well tolerated, further target is	**Grade 1** SBP 140-159 mmHg and/or DBP 90-99 mmHg Immediate drug treatment in high-risk patients or those with	

hours); symptomatic DBP increase by >20 mmHg or to >140/90 mmHg; monotherapy indicated initiated		<130/80 mmHg but not <120 SBP mmHg In older >65 years, target SBP 130–140 mmHg, and DBP <80 mmHg, initiate with two-drug combination	CVD, CKD, DM, or HMOD; Target BP reduction by at least 20/10 mmHg, ideally to <140/90 mmHg; Optimal targets: <65 years: 120-130/70-79mmHg ≥65 years: <140/90 mmHg	
Grade 3 SBP ≥160 mmHg or DBP ≥100 mmHg; medical intervention indicated; more than one drug or more intensive therapy than previously used indicated		**Grade 2** SBP 160–179 mmHg and/or DBP 100–109 mmHg	**Grade 2** SBP ≥160 mmHg and/or DBP ≥100 Immediate drug treatment in all patients	**Cancer therapy holding threshold:** ≥180 mmHg systolic and/or ≥110 mmHg diastolic
Grade 4 Life-threatening consequences (e.g. malignant HTN, transient or permanent neurologic deficit, hypertensive crisis); urgent intervention needed	**Hypertensive crisis** SBP ≥180 mmHg and/or DBP ≥120 mmHg Immediate initiation of BP drugs	**Grade 3** SBP ≥180 mmHg and/or DBP ≥110	**Criteria for hypertension**: Office BP: ≥140 mmHg +/- ≥90 mmHg ABPM: 24-h average: ≥130 mmHg +/- ≥90 mmHg Day average: ≥135 mmHg +/- ≥85 mmHg	**Exaggerated hypertensive response:** Systolic BP increase >20 mmHg or mean arterial BP increase >15 mmHg **Hypertensive emergency response:**

			Night average: ≥120 mmHg +/- ≥70 mmHg HBPM: ≥135 mmHg +/- ≥85 mmHg	BP elevation with signs and symptoms of end organ damage

ACC, American College of Cardiology; AHA, American Heart Association; ASCVD, atherosclerotic cardiovascular disease; BP, Blood pressure; CAD, coronary artery disease; CKD, chronic kidney disease; CTCAE, Common Terminology Criteria for Adverse Events; CV, cardiovascular; CVD, cardiovascular disease; DBP, diastolic blood pressure; DM, diabetes mellitus; ESC, European Society of Cardiology; HTN, hypertension; ICOS, International Cardio-Oncology Society; ISH, International Society of Hypertension; SBP systolic blood pressure.
*Guidelines for non-cancer patients, not specifically receiving agents causing HTN
**Definition of hypertension aspect in the cancer patient

These values are based on office blood pressure measurement; home blood pressure measurement cutoffs are 5 mmHg points lower.

Table 5. Definition of QTc prologation with cancer therapies

CTCAE v5.0	ICOS 2021
Grade 1: Average QTc 450-480ms	QTcF < 480ms – continue current treatment
Grade 2: Average QTc 481-500ms	QTcF 480-500ms – proceed with caution; minimize other QT prolonging medications, replete electrolytes
Grade 3: Average QTc ≥501 ms; >60 ms change from baseline	QTcF >500ms – stop treatment and evaluate. May requiredose reduction or alternative therapy
Grade 4: Torsade de pointes; polymorphic ventricular tachycardia; signs/symptoms of serious arrhythmia	

Supplemental Table 1. Cancer Therapeutics Associated with CTRCD

Class of Therapy	Example drugs	Regulatory Recommendations for Cardiac Function Monitoring*
Anthracyclines	Doxorubicin, daunorubicin, epirubicin, idarubicin, mitoxantrone	Routine baseline LVEF assessment with repeated assessment after achieving higher cumulative dose
HER2 targeted agents	Trastuzumab, pertuzumab, T-DM1, lapatinib, tucatinib	Routine baseline LVEF assessment with repeated assessment during treatment
MEK inhibitors/*BRAF inhibitors	Trametinib, cobimetinib, binimetinib/	Routine baseline LVEF assessment with repeated assessment during treatment
Proteasome inhibitors	Bortezomib, carfilzomib	Monitoring for symptoms of heart failure and other CV adverse effects including ischemic and thromboembolic events.
Multitargeted kinase inhibitors	Sunitinib, sorafenib, axitinib, pazopanib, ponatinib, vandetanib	Monitoring for symptoms of heart failure and other CV adverse effects including hypertension and ischemic and thromboembolic events.
EGFR inhibitor	Osimertinib	Routine baseline LVEF assessment with repeated assessment during treatment
Immune checkpoint inhibitors	nivolumab, ipilimumab, pembrolizumab, atezolizumab, durvalumab	Monitoring for symptoms of immune-related adverse effects, of which myocarditis may present with signs and symptoms of heart failure

LVEF: left ventricular ejection fraction, MEK: mitogen-activated protein kinase kinase, EGFR: epidermal growth factor receptor

* Summarized are overall recommendations, for specific guidance reader is directed to the individual drug-label; refers to FDA package insert

Supplemental Table 2. Signs and Symptoms of Symptomatic Heart Failure (adapted from ESC and ACC/AHA HF Guidelines[19, 20]

	Congestion	**Inadequate Perfusion**
Symptoms	Dyspnea, orthopnea, paroxysmal nocturnal dyspnea, lower extremity edema, nocturnal cough, bendopnea, abdominal bloating, early satiety.	Exertional intolerance, fatigue, difficulty concentrating/confusion
Signs	Jugular venous distention, hepatojugular reflux, laterally displaced and broadened apical impulse, audible S3, loud P2, square wave blood pressure response to the Valsalva maneuver, rales, peripheral edema, hepatomegaly, ascites.	Tachycardia, narrow pulse pressure, cold proximal extremities, oliguria.

Supplemental Table 3: Clinical Presentation and Diagnostic Testing for Immune Checkpoint Inhibitor Associated Myocarditis

Clinical Syndrome*	
Symptoms	Fatigue, myalgias, chest pain, shortness of breath, orthopnea, lower extremity edema, palpitations, lightheadedness/dizziness, syncope, muscle weakness.
Chronology	Typically occurs early in the treatment course (median reported time is 30–65 days after the first dose of ICI therapy). However, it may occur at any time [49, 54].
Other irAEs	Myositis, myopathy, and myasthenia gravis have been reported concomitantly in patients with ICI-associated myocarditis [55, 56]. Myocarditis should be excluded in patients with myositis, myopathy or myasthenia gravis.
Electrocardiogram	While ECG abnormalities are reported in most cases, a normal ECG does not rule out ICI-associated myocarditis. Most often, the findings are nonspecific and may include sinus tachycardia, QRS prolongation, conduction abnormalities, focal or diffuse T-wave inversion, abnormal Q waves, atrial and ventricular arrhythmias, and focal or diffuse ST changes can be seen [49, 50].
Biomarkers	
Cardiac Troponin	cTn can be used as a diagnostic and prognostic tool. An increase in cTn (>99% UNL) is reported in most cases [49]. Elevated cTn is highly sensitive but non-specific for ICI-associated myocarditis. While very uncommon, a normal cTn level does not rule out myocarditis. [50]. It is important to rule out other etiologies of cTn elevation. As compared to troponin T, an increase in troponin I is more specific for myocardial injury as troponin T can be non-specifically elevated in myositis. Hence, troponin I is

	preferred in patients with a suspicion of, or confirmed myositis.
Creatinine Kinase (CK)	CK and CK-MB isoform may be elevated in patients with myocarditis. However, these are less specific than cardiac troponin and hence when available, cTn is the preferred test. When not available, CK-MB is a reasonable alternative.
BNP or NT-pro BNP	Natriuretic peptides can be elevated, especially in patients with volume overload/heart failure. While natriuretic peptides can be helpful in evaluating patients with symptoms of unclear etiology and can aid in the diagnosis of ICI-associated myocarditis in the appropriate clinical setting, they lack sensitivity and specificity for ICI-associated myocarditis, and hence are not used to confirm or deny the diagnosis. Like cTn, BNP/NT-pro-BNP elevation may also be of prognostic value.
C-Reactive Protein (CRP)	CRP is a marker of acute inflammation. While it can be elevated in patients with ICI-associated myocarditis, particularly if other irAE (e.g. myositis) are also present. However, CRP lacks sensitivity and specificity for the diagnosis.
Cardiovascular Imaging	
Echocardiogram	Echocardiography may show normal or reduced LV systolic function, regional wall motion abnormalities and/or a pericardial effusion. Less frequently, increased wall thickness secondary to edema may be noted [49, 50]. While it is an appropriate test for initial assessment, it does not provide tissue characterization and lacks the ability to detect subtle myocardial abnormalities. Furthermore, a normal LVEF does not exclude ICI myocarditis [49]. Decreased GLS is a predictor for future adverse cardiac events in patients with ICI-associated myocarditis, presenting with either preserved or reduced LVEF [37], and

	should be considered where available in the assessment of patients.
Cardiac MRI (CMR)	If feasible, CMR is highly sensitive and specific and is the primary imaging tool for diagnosis in suspected cases of myocarditis. Myocardial hyperemia, edema and/or fibrosis caused by myocarditis can be detected by applying T1-weighted and T2-weighted sequences [57]. Active myocardial inflammation may be diagnosed based on at least one T2-based criterion, with at least one T1-based criterion. Having both a positive T2-based marker and a T1-based marker increases the specificity for diagnosing acute myocardial inflammation; having only one may support a diagnosis of acute myocardial inflammation in the appropriate clinical scenario. (updated Lake Louise criteria [58]: 1. T2-based criterion: regional or global increase of native T2, or T2 signal intensity. 2. T1-based criterion: regional or global increase of native T1, or regional or global increase in the ECV, or presence of LGE. 3. Supportive criteria: Pericarditis and/or regional or global LV systolic dysfunction)
Coronary CT angiogram (CCTA)	CCTA is not useful for making the diagnosis of myocarditis. However, it can be very useful to rule out underlying obstructive coronary artery disease which may mimic myocarditis.
Pathology	
	Endomyocardial biopsy is considered the gold standard for diagnosis but can be falsely negative because of patchy involvement of the myocardium. Given its invasive nature and

	associated potential complications, it is not considered a first-line investigation unless the patient is hemodynamically unstable [50]. EMB is typically reserved for cases with high clinical suspicion and an otherwise negative non-invasive evaluation. Myocardial tissue is evaluated using the Dallas criteria, which require 2 main components on histology [59]: 1. inflammatory infiltrate and 2. myocardial necrosis The presence of myocardial necrosis is required to make the diagnosis of myocarditis. When an inflammatory infiltrate is present without myocardial necrosis on an EMB then a diagnosis of borderline myocarditis is made [113]. The inflammatory infiltrate can be global, focal or confluent. A T-cell predominant lymphocytic infiltrate is the most common histologic finding. Immunohistochemical staining has typically shown predominantly CD8+ T cells interspersed with CD4+ T-cells and macrophages [55]. T-cell clonality in the myocardium is similar to T-cell clones in the tumor [55]. In addition, upregulation and positive staining for PD-L1 in can also be found in myocardial tissue. Pre-procedural localization of inflammatory changes by CMR may reduce sampling error.
Exclusion of other diagnoses	
	Acute coronary syndrome, type II myocardial infarction, stress-induced cardiomyopathy, tachyarrhythmia mediated cardiomyopathy, other chemotherapy-associated cardiotoxicity, viral myocarditis,

	giant cell myocarditis, other forms of inflammatory cardiomyopathy such as cardiac sarcoidosis, etc.

* Clinical syndrome may have any combination of symptoms in an appropriate chronology with or without associated other immune-related adverse events (irAEs)

Supplemental Table 4. Spectrum of vascular toxicities with chemotherapeutics (adapted from [60])

	Most common use	Raynaud's	Angina	AMI	Stroke	PAD	DVT/PE
Antimetabolites							
5-Fluorouracil	Colorectal cancer, esophageal cancer, gastric cancer, hepatobiliary cancer, pancreatic cancer	ND	ND	ND	ND		
Capecitabine	As above, and ovarian, fallopian peritoneal cancer	+	++	++	+		+
Gemcitabine	Small and non-small cell lung cancer, genitourinary, head and neck cancer, lymphoma, mesothelioma	+	+	+			
Anti-microtubule agents							
Paclitaxel	breast cancer, small and non-small cell lung cancer, genitourinary, head and neck cancer		+	+			+
Alkylating agents							
Cisplatin	Small and non-small cell lung cancer, genitourinary, head and neck cancer, lymphoma, mesothelioma	+	++	++	+	+	
Cyclophosphamide	Leukemia, breast cancer, Hodgkin's and non-Hodgkin's lymphoma		+	+			

Antitumor antibiotics							
Bleomycin	Hodgkin’s lymphoma, testicular cancer, ovarian germ cell cancer	+	+	+	+		
Vinca alkaloids							
Vincristine	Acute lymphocytic leukemia, Hodgkin and Non-Hodgkin lymphoma, Ewing sarcoma	ND	ND	ND			
mTOR inhibitors							
Everolimus	Breast cancer, neuroendocrine tumors, renal cell cancer		++	+			++
Temsirolimus	Renal cell cancer		+++				++
Proteasome inhibitors							
Bortezomib	Multiple myeloma, mantle cell lymphoma, T-cell lymphoma, follicular lymphoma, systemic light chain amyloidosis, Waldenstrom's			ND	ND		ND
Carfilzomib	Multiple myeloma, Waldenstrom's		+++	+++			
Monoclonal antibodies (by target)							
Anti-VEGF/KDR							
Bevacizumab	Glioblastoma, metastatic colorectal cancer		++	++	++		+++

	non-small (non-squamous) cell lung						
Ramucirumab	Metastatic non-small cell lung, metastatic gastric, metastatic colorectal cancer			++	++		
Anti-CD20							
Rituximab	Burkitt lymphoma, chronic lymphocytic leukemia, Hodgkin's and non-Hodgkin's lymphoma, Waldenstrom's		+	+			
VEGF-receptor fusion molecules							
Aflibercept	Metastatic colorectal cancer			++	++		++
Kinase inhibitors (by target)							
VEGF							
Axitinib	Renal cell carcinoma, thyroid cancer		+	++	+		++
Sorafenib	Hepatocellular cancer, renal cell cancer, thyroid cancer, angiosarcoma, GIST		+	++	+		+
Sunitinib	Gastrointestinal stromal tumor (GIST), pancreatic neuroendocrine tumors, renal cell cancer, soft tissue sarcoma, thyroid cancer		+++	+	+		++
Pazopanib	Renal cell carcinoma, soft tissue carcinoma, thyroid cancer		+++	++	+		++

Regorafenib	Colorectal cancer, GIST, hepatocellular carcinoma		+	+			++
Cabozantinib	Renal cell cancer, thyroid cancer, hepatocellular carcinoma			++	++		++
Vandetanib	Thyroid cancer				+		++
Lenvatinib	Renal cell cancer, thyroid cancer, hepatocellular carcinoma			++			++
Bcr-Abl							
Nilotinib	Philadelphia chromosome positive acute lymphocytic leukemia and chronic myeloid leukemia, GIST		++	+	++	+++	ND
Ponatinib	Philadelphia chromosome positive acute lymphocytic leukemia and chronic myeloid leukemi		+++	+++	++	++	++
Dasatinib	Philadelphia chromosome positive acute lymphocytic leukemia and chronic myelogenous leukemia, GIST		++				<1%
Alk							
Alectinib	Non-small cell lung cancer						+
Crizotinib	Non-small cell lung cancer						++
EGFR							
Erlotinib	Non-small cell lung cancer, pancreatic cancer		+++	++ (with gemcitabine)	++ (with gemcitabine)		+++ (with gemcitabine)

Dacomitinib	Non-small cell lung cancer		++				
B-raf							
Dabrafenib	Melanoma, non-small cell lung cancer, thyroid cancer						+
c-Met							
Crizotinib	Non-small cell lung cancer						++
Cabozantinib	Hepatocellular carcinoma, renal cell carcinoma, thyroid cancer			+	+		++
MEK							
Trametinib	Melanoma, non-small cell lung cancer, thyroid cancer						++ (combination with BRAF inhibitor)
Binimetinib	Melanoma						++ (combination with BRAF inhibitor)
Miscellaneous drugs							
Interferon-alpha 2B	Hairy cell leukemia, lymphoma, malignant melanoma, Kaposi sarcoma	++	+++	++	++	++	++
Thalidomide	multiple myeloma, systemic light chain amyloidosis, Waldenstrom's						+++
Lenalidomide	chronic lymphocytic leukemia, diffuse large B-cell		++	++	++		+++

	lymphoma,mantle cell lymphoma, multiple myeloma, myelodysplastic syndrome						
Radiation therapy							
Radiation therapy			ND	ND	ND	ND	

+ = uncommon (<1%), ++ = common (1-10%), +++ = very common (>10%),
AMI = acute myocardial infarction, DVT = deep vein thrombosis, HTN = hypertension, ND = frequency not defined,
PAD = peripheral arterial disease, PE = pulmonary embolism, VEGF = vascular endothelial growth factor.

Supplemental Table 5. Cancer therapeutics associated with the development of hypertension (adapted from [60])

Drug	Most common use	HTN Frequency
mTOR inhibitors		
Everolimus	Breast cancer, neuroendocrine tumors, renal cell cancer	+++
Temsirolimus	Renal cell cancer	
Proteasome inhibitors		
Carfilzomib	Multiple myeloma, Waldenstrom's	+++
Monoclonal antibodies		
Bevacizumab	Glioblastoma Persistent/recurrent/metastatic cervical cancer, Metastatic colorectal cancer, non-small (nonsquamous) cell lung	+++
Ramucirumab	Metastatic non-small cell lung, metastatic gastric, metastatic colorectal cancer	+++
Rituximab	Burkitt lymphoma, chronic lymphocytic leukemia (CLL), CNS lymphoma, Hodgkin lymphoma, non-Hodgkin lymphoma, Waldenstrom's	+++
VEGF-receptor fusion molecules		
Aflibercept	Metastatic colorectal cancer	+++
Tyrosine kinase inhibitors		
Axitinib	Renal cell carcinoma, thyroid cancer	+++
Sorafenib	Hepatocellular cancer, renal cell cancer, thyroid cancer, angiosarcoma, gastrointestinal stromal tumor (GIST)	+++
Sunitinib	GIST, pancreatic neuroendocrine tumors, renal cell cancer, soft tissue sarcoma, thyroid cancer	+++
Pazopanib	Renal cell carcinoma, soft tissue carcinoma, thyroid cancer	+++
Regorafenib	Colorectal cancer, GIST, hepatocellular carcinoma	+++
Cabozantinib	Renal cell cancer, thyroid cancer, hepatocellular carcinoma	+++
Vandetanib	Thyroid cancer	+++

Ponatinib	Philadelphia chromosome positive acute lymphocytic leukemia and chronic myeloid leukemiab	+++
Dabrafenib	Melanoma, non-small cell lung cancer, thyroid cancer	+++
Trametinib	Melanoma, non-small cell lung cancer, thyroid cancer	+++
Anti-Hormonal		
Abiraterone	Prostate cancer	+++
Enzalutamide	Prostate cancer	+++
Aromatase Inhibitors	Breast Cancer	++
Tyrosine kinase inhibitors		
Ibrutinib	CLL, mantle cell lymphoma, Waldenstom's macroglobulinema, graft versus host disease	++
Nilotinib	Philadelphia chromosome positive acute lymphocytic leukemia and chronic myeloid leukemia, GIST	++
Binimetinib	Melanoma	++
Miscellaneous drugs		
Interferon-alpha 2B	Hairy cell leukemia, lymphoma, malignant melanoma, Kaposi sarcoma	++
Lenalidomide	Chronic lymphocytic leukemia, diffuse large B-cell lymphoma,mantle cell lymphoma, multiple myeloma, myelodysplastic syndrome	++
Antimetabolites		
Capecitabine	Colorectal cancer, esophageal cancer, gastric cancer, hepatobiliary cancer, pancreatic, ovarian, fallopian	+
Anti-microtubule agents		
Paclitaxel	breast cancer, small and non-small cell lung cancer, genitourinary, head and neck cancer	+
Alkylating agents		
Cisplatin	Small and non-small cell lung cancer, genitourinary, head and neck cancer, lymphoma, mesothelioma	+

+ = uncommon (<1%), ++ = common (1-10%), +++ = very common (>10%)

Supplemental Table 6. Types of arrhythmia reported with the use of cancer therapeutics (adapted from [6])

Therapy class	Agent name (target)	AF	SVT	Bradycardia	AV block	QTc prolongation	TdP	VT/VF	SCD
Miscellaneous	Arsenic trioxide	++	++	–	+	+++	++	–	+
Alkylating agents	Anthracyclines; acute	x	–	x	x	x	–	x	
	Busulfan	x	x	–	x	–	–	–	x
	Cyclophosphamide	x	–	–	x	x	–	x	–
	Ifosfamide	x	–	x	–	–	–	x	x
	Melphalan	x	x	–	–	–	–	x	
Antimetabolites	5-Fluorouracil	x		x	x	x	–	x	x
	Capecitabine	++	–	++	–	+	–	–	+
	Clofarabine	x	x	x	–	–	–	–	–
	Cytarabine	x		x	–	–	–	–	–
	Gemcitabine	+	+	–	–	–	–	–	–
Microtubule-binding agents	Paclitaxel	+	+	++	+	–	–	+	–
Platinum drugs	Cisplatin	+	+	+	+	–	–	+	–
Immunomodulatory drugs	Lenalidomide	x	x	x	–	–	–	–	–
	Thalidomide	+		+	–	–	–	–	–
Proteasome inhibitors	Bortezomib	x	–	x	x	x	x	x	x
	Carfilzomib	x	x	x	x	–	–	–	x
HDAC inhibitors	Romidepsin	+	++	–	–	++	+	++	+
	Panobinostat	–	–	–	–	++	–	–	–
	Vorinostat	–	–	–	–	++	–	–	–
CDK4/CDK6 inhibitors	Ribociclib	–	–	–	–	++	–	–	–
mTOR inhibitors	Everolimus	++	–	–	–	–	–	–	–
Monoclonal antibodies	Alemtuzumab (anti-CD52)	++	–	++	–	–	–	+	+

	Cetuximab (anti-EGFR/HER1)	+		+	–	–	–	+	+
	Necitumumab (anti-EGFR/HER1)	–	+	–	–	–	–	–	++
	Pertuzumab (anti-EGFR/HER1)	+	+	+	–	–	–	+	+
	Rituximab (anti-CD20)	+	+	+	+	+	+	+	+
	Trastuzumab (anti-HER2/ERBB2)	++	++	+	–	–	–	+	–
Multi-targeted kinase inhibitors	Osimertinib (EGFR/HER1)	–	–	–	–	++	–	–	–
	Lapatinib (HER2/ERBB2)	+	+	–	–	+	–	–	–
	Lenvatinib (VEGFR)	–	–	–	–	++	–	–	–
	Pazopanib (VEGFR)	–	–	+++	–	++	–	–	–
	Sorafenib (VEGFR)	+	–	+	+	+	+	–	–
	Sunitinib (VEGFR)	–	–	+	–	+	+	–	–
	Vandetanib (VEGFR)	–	–	–	–	+++	–	+	+
	Bosutinib (BCR–ABL1)	–	–	+	–	++	–	–	–
	Dasatinib (BCR–ABL1)	+	+	–	–	+	–	+	+
	Imatinib (BCR–ABL1)	+	+	–	–	–	–	–	–
	Nilotinib (BCR–ABL1)	++		++	++	++	–	–	+
	Ponatinib (BCR–ABL1)	++	+	+	+	+	–	+	
	Ibrutinib (BTK)	+++	–	–	–	–	–	+	+
	Alectinib (ALK)	–	–	+++	–	+	–	–	–
	Ceritinib (ALK)	–	–	+	–	++	–	–	–
	Crizotinib (ALK)	–	–	+++	–	+	–	–	–
	Brigatinib (ALK)	–	–	++	–	–	–	–	–
	Lorlatinib (ALK)	–	–	–	+	–	–	–	–
	Encorafenib (BRAF)	–	–	–	–	+	–	–	–

	Vemurafenib (BRAF)	++		+	–	+++	+	–	–
	Gilteritinib (FTL3)	–	–	–	–	++	–	–	–
	Trametinib (MEK)	–	–	++	–	++	–	–	–
	Ruxolitinib (JAK)	–	–	+	–	+	–	–	–
Immune checkpoint inhibitors	Ipilimumab (anti-CTLA4)	+	–	+	+	–	–	+	+
	Nivolilumab (anti-PD1)	+	–	+	+	–	–	+	+
	Pembrolizumab (anti-PD1)	+	–	+	+	–	–	+	+

Frequency not always defined for the individual entities, but when available: +, uncommon (<1%); ++, common (1–10%); +++, very common (>10%); x, frequency not defined. AF, atrial fibrillation; CTLA4, cytotoxic T lymphocyte antigen 4; HDAC, histone deacetylase; JAK, Janus kinase; mTOR, mechanistic target of rapamycin; NA, not applicable; PD1, programmed cell death protein 1; SCD, sudden cardiac death; SVT, supraventricular tachycardia; TdP, torsades de pointes, VEGFR = vascular endothelial growth factor receptor