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## Cardio-Oncology Care in the Era of the Coronavirus Disease 2019 (COVID-19) Pandemic: An International Cardio-Oncology Society (ICOS) Statement

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### Abstract

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The severe acute respiratory syndrome coronavirus 2 (SARS–CoV-2) has given rise to a pandemic of unprecedented proportions in the modern era because of its highly contagious nature and impact on human health and society: coronavirus disease 2019 (COVID-19). Patients with cardiovascular (CV) risk factors and established CV disease (CVD) are among those initially identified at the highest risk for serious complications, including death. Subsequent studies have pointed out that patients with cancer are also at high risk for a critical disease course. Therefore, the most vulnerable patients are seemingly those with both cancer and CVD, and a careful, unified approach in the evaluation and management of this patient population is especially needed in times of the COVID-19 pandemic. This review provides an overview of the unique implications of the viral outbreak for the field of cardiooncology and outlines key modifications in the approach to this ever-increasing patient population. These modifications include a shift toward greater utilization of cardiac biomarkers and a more focused CV imaging approach in the broader context of modifications to typical practice pathways. The goal of this strategic adjustment is to minimize the risk of SARS–CoV-2 infection (or other future viral outbreaks) while not becoming negligent of CVD and its important impact on the overall outcomes of patients who are being treated for cancer.

### Keywords

best practice; cancer; cardiac safety; cardio-oncology; coronavirus disease 2019 (COVID-19); pandemic; recommendations; virus

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### Introduction

On December 31, 2019, Chinese officials informed the World Health Organization of a cluster of cases of pneumonia in Wuhan, central China, related to a novel coronavirus (2019-nCoV, later designated severe acute respiratory syndrome coronavirus 2 [SARS–CoV-2]).<sup>1</sup> The viral outbreak has been marked by the rapidity of spread to pandemic proportions (coronavirus disease 2019 [COVID-19]) and the spectrum of presentations from asymptomatic supercarrier status to life-threatening respiratory failure.<sup>1,2</sup> Individuals with SARS–CoV-2 at highest risk for morbidity and mortality include the elderly, those with cardiovascular (CV) risk factors and established CV disease (CVD), and those with cancer.<sup>3–8</sup> Accordingly, patients with both cancer and CVD are likely to be at highest risk to experience morbidity and mortality from SARS–CoV-2. The purpose of this review from the International Cardio-Oncology Society ([www.IC-OS.org](http://www.IC-OS.org)) is to address and provide general guidance for the assurance of cardiac safety among patients with cancer that can be practically useful for oncologists, hematologists, and cardiologists during and after this COVID-19 pandemic. Importantly, the need for such guidance is underscored by the projection that COVID-19 will remain a legitimate concern for health care systems and the practice of medicine for the foreseeable future. The expected timeline for the development of an effective vaccine is unknown, and reports are surfacing that there may be a relatively short-lasting immunity among patients who have had the SARS–CoV-2 infection (compared with other viral illnesses).<sup>9</sup>

Therefore, this review is appropriate not only for immediate utilization but also for the new reality that this pandemic has created: cardio-oncology (C-O) care in the era of COVID-19 (Fig. 1). As a disclaimer, as the evidence base in this area is rapidly evolving, a complete understanding is still in its early stages, and many specific aspects still need to be conclusively defined.

## Impact of COVID-19 on the CV System

CV injury and dysfunction are leading causes of death and disability among patients with SARS-CoV-2. For example, Guo et al demonstrated that 27.8% of patients with SARS-CoV-2 had myocardial injury (defined by an elevation in troponin), 20% had arrhythmias, and 16% needed hemodynamic support.<sup>10</sup> Importantly, cardiac troponin elevations indicate worse outcomes; for instance, a >60% mortality rate among patients with CVD.<sup>2</sup> Interestingly, elevated cardiac troponin levels are correlate with high C-reactive protein levels and an exaggerated inflammatory response, perhaps similar to that seen after chimeric antigen receptor-T cell (CAR-T) therapy.<sup>11</sup> This exaggerated inflammatory response/cytokine storm is postulated to be one of the primary mechanisms leading to cardiac injury and dysfunction. However, there are multiple potential mechanisms for cardiac injury with COVID-19 beyond an exaggerated inflammatory response, including acute coronary syndrome, microvascular dysfunction, thrombosis, and even myocarditis. It is interesting to note that the cellular receptor for viral entry into the human body is the angiotensin-converting enzyme-2 receptor (ACE2), which is expressed on lung epithelial cells (type 2 pneumocytes) as well as vascular endothelial cells, pericytes, cardiomyocytes, and macrophages. Accordingly, SARS-CoV-2 may be viewed not only as a respiratory virus but also as a CV virus, which can result in both severe acute lung injury and severe CV injury.<sup>12-17</sup> Indeed, several autopsy-based studies have now conclusively reported arterial and venous thrombosis, including pulmonary thrombosis and infarction, in addition to acute lung injury.<sup>18-20</sup>

These prominent thrombotic aspects are a distinguishing feature of SARS-CoV-2. The mechanisms are not fully detailed but may relate to the inflammatory response and endothelial injury. From the initial reports, there appears to be a link between markers of inflammation (interleukin-6 [IL-6]), myocardial injury (troponin), and thrombosis/fibrinolysis (D-dimer) for identifying patients who are suffering important CV consequences.<sup>4</sup> In fact, a D-dimer level >1 $\mu$ g/mL was the only biomarker independently and most potently predictive of mortality in one of the first studies on patients hospitalized with COVID-19.<sup>4</sup> The value of D-Dimer levels in this regard has subsequently been confirmed in other studies.<sup>21</sup>

## Impact of COVID-19 on Patients With Cancer

While the course of COVID-19 in patients with cancer continues to be defined, current data suggest that patients with cancer are at higher risk of acquiring the infection and experiencing a more severe course and higher mortality.<sup>6,22,23</sup> Indeed, various factors might influence susceptibility to COVID-19 among patients with cancer, including the type and stage of cancer, its location, the immunosuppressive effects of the therapeutic choices, the

degree of bone marrow suppression, the frequent visits to the health care system, and the prevalence of COVID-19 in the region.

An overview of studies on patients with cancer who had COVID-19 published in the first one-half of 2020 is provided in Table 1.<sup>6,24–31</sup> The majority of these studies confirm the notion that patients with cancer have a more severe course of COVID-19 and are also at a higher mortality risk. Increasing age has been the most consistent predictor of poor outcomes in these patients, followed by male sex. The presence of comorbidities, in particular CVD, have been identified as risk factors for a more severe and even fatal course of COVID-19. No particular cancer type has been identified to pose the highest risk, although lung cancer and hematologic malignancies have been discussed. Patients with active, progressive, and metastatic cancer seem to be more vulnerable to poor outcomes. No specific type of cancer therapy has been identified to pose a risk for a complicated or fatal course of COVID-19.

Interestingly, calls to prepare for the care of patients with cancer in times of a pandemic were issued over a decade ago and were updated more recently.<sup>32</sup> These include preparation for a change in the delivery of cancer care, including type, timing, and setting. Such an approach may shift away from surgery, radiation therapy, and conventional infusion chemotherapy toward therapies that can be given as a tablet or injection. More recently, specific recommendations for the care of patients with cancer in times of COVID-19 have emerged. A key concept is the designation of patients with cancer as high-risk or low-risk for disease progression without cancer therapy and thus at high need or low need for urgent treatment.<sup>33,34</sup> This concept of prioritization is depicted in Figure 2.

## Impact of COVID-19 on the Patient With Cancer and CV Disease

Contemporary cancer therapy has expanded beyond traditional chemotherapeutics, radiation therapy, and surgery to include targeted therapies as well as immunotherapy, resulting in a range of potential CV toxicities that require more complex CV monitoring.<sup>11,35–37</sup> Specific cancer therapies are associated with worsening CV risk factors, such as hypertension and dyslipidemia, as well as the development of CVD, including heart failure, reduced left ventricular ejection fraction (LVEF), accelerated coronary artery disease, myocardial infarction, increased thrombosis, and (uncommonly) myocarditis. Patients with cancer or those who have been previously treated may be immunocompromised and have increased susceptibility to SARS-CoV-2; however, more than half of the patients reported previously from Wuhan who had cancer were survivors and were not necessarily undergoing active therapy. This suggests that the adverse outcomes in patients with cancer may relate, in part, to a reduced cardiopulmonary reserve or the presence of CVD. Importantly, in terms of acute CVD related to cancer therapy, it remains to be seen whether patients exposed to potentially cardiotoxic cancer therapies are at an even higher risk with COVID-19. Indeed, the CV effects of certain cancer therapies may be unmasked or heightened by the current pandemic, especially when newer cancer therapy has the potential to cause endothelial damage and reduce CV reserve.<sup>38</sup> For this very reason, a multidisciplinary C-O approach is needed for patients with cancer during COVID-19.

The central conundrum for C-O care in the era of COVID-19 is how to deliver optimal care with fewer resources and at the lowest (possible) risk. Important questions include the following: 1) Which patients need attention, and by what means? 2) Is there a need to modify published algorithms and protocols? 3) Should there be a switch from CV imaging to serum biomarkers? 4) Which innovative approaches for remote monitoring can be quickly and effectively used? The answers to many of these questions may vary, depending on the local impact of COVID-19 or any other pandemic at the time, and these questions should be approached with vibrant and ongoing communication between oncology, hematology, and C-O providers alike. In fact, it is advisable that the directors of C-O clinics and service lines be proactive in approaching and working out potential new workflows completely integrated with the cancer team (Figs. 2 and 3). Some of these newly developed strategies in response to a pandemic can be found in other areas of cardiology, such as the care of patients with acute coronary syndrome and stroke, the need for cardioversion, and imaging.<sup>16,39-41</sup> It is important to emphasize that postponing or neglecting any appropriate care because of the COVID-19 pandemic is as detrimental as not considering potential exposures to COVID-19 and its impact on the patient and the health care system.

## General Recommendations

One of the key traits of SARS-CoV-2 is the high level of contagiousness.<sup>42-44</sup> The primary route of transmission from person to person is via droplets generated by a cough or sneeze of an infected person. These droplets are propelled through the air, often several meters, and can deposit on the mucous membranes of the mouth, nose, or eyes of individuals nearby. The virus also can spread when a person touches a surface or object contaminated with infectious droplets and then touches his or her mouth, nose, or eye(s). Of note, the virus can survive outside the body for several days, including on common surfaces (cardboard for 24 hours, stainless steel for 48 hours, and plastic for 72 hours).<sup>45</sup> Of particular concern is the fact that infected individuals may maintain high viral loads in the upper respiratory tract without any symptoms, leading to asymptomatic viral shedding and transmission. In the medical setting, the risk of viral transmission is particularly high when aerosol-generating procedures are pursued, including nebulizer treatment, highflow oxygen, bronchoscopy, open tracheal suctioning, intubation, extubation, noninvasive positive-pressure ventilation, endoscopy, and transesophageal echocardiography.

A systematic review and meta-analysis concluded that face masks are the most effective measure of protection.<sup>46</sup> Health care systems thus should adopt a universal face mask policy with an increased level of respiratory protection for health care personnel in high-risk exposure scenarios. Other measures include eye protection. Physical distancing may be difficult in the office setting, especially in the examination room, but any degree of one meter or more is helpful.<sup>46</sup> Along these lines, the indications for close contact, as required for physical examination and certain clinical studies, need to be carefully considered. Hand hygiene, especially hand washing before and after seeing and examining a patient, is key. Soap is highly effective, although evaporating disinfectant dispenser bottles are very convenient.<sup>47,48</sup> Universal gloving, as needed (eg, for neutropenic patients), should include only new gloves used once per patient.

## Recommendation

1. Patients with cancer should be shielded as much as possible from infection risks, including those from SARS–CoV-19, by proper hygiene standards in the health care system, such as proper hand washing, cleaning of examination rooms, and cleaning of instruments for clinical examination.
2. Universal face masking is recommended, especially during periods of high virus spread and/or risk, as with any community exposure to a viral pandemic such as COVID-19.
3. Depending on clinical exposure risk, personal protection equipment (PPE) for health care personnel needs to be maximized, including N95 masks, eye protection, gowns, and gloves.
4. Physical distancing is recommended at all times, including limiting close contacts, such as those needed for physical examination and clinical testing, including echocardiography (Echo).

## Specific Recommendations

### Strategies to Optimize CV Care of Patients With Cancer During a Pandemic

When cardiology input is needed in the care of a patient with cancer, the first consideration should be appropriate triage based on clinical acuity and practice environment (Fig. 2). Patients with CV emergencies still need to be treated as such, with the right protective precautions and resultant workflow modifications (Fig. 3). On the other end of the spectrum, those with routine care needs can be rescheduled or followed using non-face-to-face (virtual) formats. Telehealth (including video consultations) might be the ideal tool to connect physicians and other health care professionals with patients in this setting. The advantages and disadvantages of the various consultations types are summarized in Table 2.

### Recommendation

1. During periods of high virus spread and/or risk, C-O consultation before, during, or after cancer therapy should be performed virtually if clinically feasible; in-person consultation should be limited to emergencies for which physical examination is essential in determining clinical management.

### Cardiovascular Surveillance

Cardiac imaging plays an important role in treatment decisions for C-O patients and, as a result, at least 2 groups, the European Association of Cardiovascular Imaging and the American Society of Echocardiography, have produced recommendations on precautions, indications, prioritization, and protection for patients and health care personnel during the time of the COVID-19 pandemic (key points are highlighted in Table 3).<sup>41,49</sup> A key aspect to consider is not only the frequency of imaging but also the type and duration. Echo involves much closer and longer patient-staff contact than cardiac magnetic resonance imaging, nuclear scans, computed tomographic angiography, or coronary computed tomographic angiography. To decrease exposure time and risk, many imaging centers have incorporated

abbreviated protocols to decrease the duration of Echo scanning: the focused cardiac ultrasound study. For instance, if the only interest is in cardiac function or LVEF, this can commonly be obtained in 5 minutes, even when both right and left ventricular function are assessed, which is recommended in the context of COVID-19.<sup>50</sup> A summary of the advantages and disadvantages of the various cardiac imaging techniques is provided in Table 4.<sup>51</sup>

Previous algorithms on the cardiac safety and monitoring of patients with cancer who are exposed to potentially cardiotoxic medications have varied greatly, but a contemporary and comprehensive consensus has recently been published by the European Society of Medical Oncology (ESMO).<sup>35</sup> The American Society of Clinical Oncology (ASCO) had previously published a guideline that was focused specifically on cardiac dysfunction in survivors of cancer therapy, particularly those treated with anthracyclines and trastuzumab.<sup>52</sup> During the current COVID-19 pandemic, the requirement for *social distancing* has broad impact within medical care to the degree that virtual and/or telemedicine visits are emphasized. In previous ESMO recommendations, a cardiac serum biomarker approach using troponin I was considered a valid alternative to echocardiographic imaging during anthracycline-based therapy.<sup>53</sup> This strategy is certainly appealing in principle, but efforts to validate this approach in a broad range of patients receiving treatment for cancer has varied significantly based on malignancy and type of cancer therapy.<sup>54,55</sup> In addition, the length and timing of the screening is important, as outlined for natriuretic peptides (NPs), ie, B-type NP (BNP) and N-terminal pro-BNP (NT-proBNP), which have been successfully used in patients with multiple myeloma (MM) undergoing treatment with carfilzomib.<sup>56</sup> For cardiotoxicity surveillance measures, serum biomarker measurements would appear to provide a safe and cost-effective alternative to cardiac imaging, considering the potential exposure risks of patients and health care providers to SARS-CoV-19 (Fig. 4). Serial cardiac biomarker assessments allow for the recognition of trends over time and reassurance when no change is noted. Even more, taking the high negative predictive value into consideration, patients with values below the institutional laboratory cutoff for BNP, NT-proBNP, and cardiac troponin assays (below the 99th percentile) would be expected to present a rather low-risk constellation. Thus a cardiac biomarker-based surveillance approach holds merit, particularly to identify those patients who are not expected to benefit from cardiac imaging to such a degree that justifies the potential risk of SARS-CoV-19 exposure. The section below is based on the current ESMO consensus document with updated modifications that are in line with alterations in medical care necessitated by the current and any possible future pandemics (Table 5).<sup>27</sup>

### Recommendations

1. All cardiac imaging should be reduced in frequency to that which is critical and necessary for clinical decision making.
2. When performed, the cardiac imaging technique that addresses the clinical question in the most effective and efficient manner should be used, decreasing exposure time and risk as much as possible; modified, focused cardiac imaging protocols (eg, focused cardiac ultrasound study) are encouraged, especially for Echo.

3. A cardiac biomarker-based approach, using cardiac troponins and/or NPs, in combination with accurate symptom assessment should allow adequate monitoring of cardiac safety to avoid unnecessary cardiac imaging.

### Anthracycline-Based Therapy

Baseline (pretherapy) assessment of cardiac function in an asymptomatic patient rarely leads to withholding of cancer therapy. However, the baseline LVEF evaluation does serve the important purpose of a point of reference in the event of evolving cardiac dysfunction/heart failure and to establish a causal association with cancer therapy. This is particularly true in patients considered at high risk for cardiotoxicity. According to ASCO practice guidelines, this includes 3 groups of patients: 1) those receiving either 250 mg/m<sup>2</sup> of doxorubicin (or its equivalent), or radiation therapy 30 grays in which the heart is in the treatment field, or any dose combination of anthracycline and chest radiation therapy; 2) those receiving sequential anthracycline and trastuzumab therapy; and 3) those receiving anthracycline or trastuzumab therapy who are either aged 60 years or have 2 CV risk factors, or an LVEF 55%, or a history of myocardial infarction, or moderate or greater valvular heart disease.<sup>52</sup> To document evidence of substantial clinical cardiotoxicity, early recognition of a decline in LVEF to <50%, even if asymptomatic (American College of Cardiology/American Heart Association stage B heart failure), is important in terms of timely initiation of cardioprotective therapy as well as overall prognosis.<sup>57,58</sup> As such, current consensus guidelines support cardiac follow-up evaluations 6 to 12 months in high risk patients, especially after full completion of anthracycline-based cancer therapy.<sup>52</sup> In the COVID era, this practice should remain although the timing of surveillance imaging may vary based on availability and safety.

Some data indicate that a persistent increase in cardiac biomarkers, including cardiac troponin and NPs, measured repeatedly during (cardiac troponins in particular) and after (NPs) anthracycline administration, is associated with a subsequent decline in cardiac function over time and thus may serve as a gatekeeper.<sup>55,59</sup> Subject to further studies, cardiac biomarkers drawn during routine laboratory assessments in the context of oncology/hematology care may help risk-stratify patients with a more urgent need for cardiac imaging.

### Recommendation

1. Routine *precancer therapy* cardiac function assessment should continue to be performed in individuals at high risk (eg, ASCO guidelines for high risk,<sup>52</sup> prior CVD, symptoms of cardiac dysfunction), whereas routine assessment of cardiac function (although recommendable) could be deferred otherwise.
2. Routine *postanthracycline therapy* imaging should still be considered in those with heart failure symptoms, prior CVD, multiple CV risk factors, and persistent elevation in serum cardiac biomarkers or if there is a need to continue anthracycline therapy with doses exceeding 250 mg/m<sup>2</sup> of doxorubicin (or its equivalent). For cancer survivors beyond the acute period, all routine cardiac surveillance should be postponed unless patients have a history of or express new signs and symptoms of heart failure.



## Human Epidermal Receptor-2–Directed Therapy

Similar to anthracyclines, trastuzumab (and other human epidermal growth factor receptor 2 [HER2]-based therapies, such as pertuzumab) carry a black-box warning for cardiotoxicity, and LVEF assessment is recommended before and during every 3 months therapy in all settings, ie, neoadjuvant, adjuvant, and metastatic, per the package insert. The role of cardiac biomarkers as substitutes for cardiac function imaging has not been well defined in patients with breast cancer undergoing HER2-directed therapy. Cardiac troponin elevations related to HER2-directed therapy are most commonly noted early after anthracycline exposure.<sup>60</sup> The absence of troponin elevation makes irreversible LVEF declines very unlikely but cannot exclude the possibility that reductions in LVEF may occur. The published literature on NPs in patients with breast cancer actively undergoing trastuzumab therapy is not robust enough to endorse its complete substitution for cardiac imaging surveillance during standard care.<sup>35,62–74</sup> However, there is substantial experience that serial use of either BNP or NT-proBNP can allow for adequate cardiac safety assessment during this time.<sup>66</sup> As stated previously, there is evidence in the general population that NPs have high negative predictive value for excluding heart failure, and assessing NPs in an asymptomatic patient may allow deferring any cardiac imaging in a high-risk COVID-19 environment.<sup>61,66</sup>

### Recommendation

1. Routine *pretherapy* cardiac function assessment should continue to be performed in individuals at high risk (eg, ASCO guidelines for high risk,<sup>52</sup> prior CVD, symptoms of cardiac dysfunction), whereas routine assessment of cardiac function (although recommendable) could be deferred otherwise.
2. *During therapy with HER-2–based treatment*, cardiac biomarkers may be useful to identify those patients who do not require cardiac imaging to establish cardiac safety. In patients at low CV risk who remain asymptomatic and have stable or normal cardiac biomarkers during monitoring, cardiac function imaging may be deferred.<sup>66,75</sup>

## Tyrosine Kinase Inhibitors Inhibiting the Vascular Endothelial Growth Factor Pathway

Consensus recommendations, such as the 2014 American Society of Echocardiography statement, outlined that, for various tyrosine kinase inhibitors (TKIs) associated with potential cardiotoxicity, a strategy for LVEF assessment should be undertaken.<sup>76</sup> For vascular endothelial growth factor signaling pathway inhibitors (VSPs), the primary issue is hypertension management.<sup>77,78</sup> The use of NPs has been proposed as a more relevant tool for identifying those at risk of CV events with VSP inhibitor-based therapy.<sup>79,80</sup> In times of a viral pandemic, home-based (remote care, including telemedicine) approaches are preferred to obtain vital signs, especially serial (up to daily) blood pressure measurements in any patient on VSP-based TKIs and to focus attention on the medical management of hypertension.

### Recommendation

1. For patients receiving VSP inhibitors, serial (daily) home blood pressure monitoring is paramount, and the periodic use of NPs can effectively screen for

those patients at risk for the development of heart failure. Routine cardiac function imaging is not recommended.

### Proteasome Inhibitors

Carfilzomib, an irreversible inhibitor of the proteasome, is a drug with a notable risk of cardiotoxicity, especially in patients with relapsed MM.<sup>56,81</sup> Interestingly, echocardiography (LVEF) is not of high value, and risk-benefit analysis does not support its use in the COVID-19 era for screening.<sup>56,81</sup> In contrast, there is demonstrated value in the measurement of NPs, even as early as mid-first cycle.<sup>56</sup> CVD is highly prevalent in the MM population and is associated with adverse events that affect long-term outcomes, including those after a stem cell transplantation.<sup>82</sup> Patients with amyloidosis (light-chain disease [AL]) with or without MM are commonly treated with bortezomib, ixazomib, and (less commonly) carfilzomib, and these patients frequently have complex CVD as well as multiple CV complications during therapy.<sup>83</sup> The use of cardiac biomarkers is essential in the AL amyloidosis population, and these cardiac biomarkers are used to stage and prognosticate in this disease.<sup>84</sup> As a result of the high prevalence of CVD in patients with MM and AL amyloidosis, these patients are considered high-risk for the development of cardiac adverse events. Furthermore, cardiac biomarkers are an essential and proven tool for assessing cardiac safety during treatment in these patients, whereas cardiac imaging is not apparently useful.

### Recommendation

1. Cardiac biomarker assessments before and during cancer treatment are essential components of ensuring cardiac safety in patients with MM and AL amyloidosis. The utility of cardiac imaging for early detection of CV adverse events with ongoing cancer treatment in these patients is not established or recommended.

### Immune Checkpoint Inhibitors

The use of immune checkpoint inhibitors (ICIs) has expanded significantly but may be associated with immune-related adverse events (irAEs). Although one of the least common irAEs, myocarditis with an ICI is one of the most fatal.<sup>37,85</sup> Different degrees (high-level and lowlevel) of lymphohistiocytic myocardial inflammation can be seen, and the exact mechanisms of this presentation are not yet defined.<sup>86</sup> Confirmation of the diagnosis can be challenging because neither magnetic resonance imaging nor endomyocardial biopsy is sufficiently sensitive, and a diagnosis is often made based on the overall clinical picture (in keeping with proposed consensus definitions).<sup>37,87,88</sup> As SARS-CoV-2 can directly infect the myocardium, with a resultant inflammatory response, SARS-CoV-2 should be considered in the differential diagnosis of a patient with concern for ICI-associated myocarditis.<sup>13,14</sup> There are no data to suggest caution for the continued use of ICIs during this COVID-19 pandemic, especially considering the dramatic cancer responses and overall safety profiles that have been reported with these therapies in previously recalcitrant cancer conditions.<sup>89,90</sup> Persistent viral infections or excessive viral antigen load may cause T-cell exhaustion, with increased expression of PD-1 and PD-L1. In this setting, the effect of ICI directed against PD-1/PD-L1 is unknown. However, in contradistinction, supporting the immune response with a CTLA-4 agonist has been shown to be helpful in other models of

acute infection. Although various CV adverse events have been reported with ICI therapy, including serious rhythm issues, the optimal strategy for monitoring cardiac safety before, during, and after ICI therapy for cancer has not been standardized or recommended.<sup>37,38,91</sup> Serial electrocardiography (ECG) and cardiac troponin and/or NP levels have been considered, but the value is unclear.<sup>37,92</sup> A complete baseline assessment, including biomarkers and an ECG, would be prudent given the range of potential CV adverse events, but it is unclear whether an assessment of LVEF is necessary or helpful.

### Recommendation

1. In patients about to receive ICI therapy for cancer, baseline assessment for CVD, including cardiac biomarkers and ECG, should be completed as well as SARS–CoV-2 status. The need or value of cardiac imaging before initiating ICI therapy is not established. The optimal protocol for monitoring cardiac safety during treatment with ICIs is unknown at present. Serious cardiac adverse events related to ICI therapy have been reported, and any suspicious symptoms or clinical findings of CV toxicity should be aggressively investigated. SARS–CoV-2 has been noted to cause myocarditis, which needs to be differentiated from ICI myocarditis in patients on ICI therapy.

### CAR-T and Bispecific T-Cell–Engager Therapy

Adoptive immunotherapy for cancer may result in a systemic inflammatory response of varying severity, referred to as the cytokine release syndrome (CRS).<sup>93</sup> This has been associated with neurotoxicity and CV toxicity.<sup>11,94</sup> The value of cardiac imaging at baseline before therapy or during the monitoring phase after treatment is still quite uncertain. The measurement of cardiac biomarkers has been identified as a useful strategy for ensuring cardiac safety, although the experience remains quite limited in general.<sup>11</sup> In the current COVID-19 pandemic, the virus itself can lead to a severe and overwhelming CRS, thus treatment with these cancer therapies may likely lead to added CV risk for CRS. Interestingly, IL-6 antagonists, typically used to treat CAR-T therapy-associated CRS, are also currently being tested in severely ill patients with COVID-19 who display an overwhelming inflammatory response that is a harbinger of poor outcomes.<sup>95</sup> Recently, the Society for Immunotherapy in Cancer proposed that efforts should be made to maximize the availability of anti-IL-6 agents, including tocilizumab and sarilumab, for use on a compassionate basis to critically ill, hospitalized, COVID-19–infected patients.<sup>96</sup>

### Recommendation

1. In patients receiving CAR-T or bispecific T-cell–engager therapy, it is recommended to screen for active COVID-19 infection before initiation of treatment. A low threshold for the use of an anti-IL-6 agent, such as tocilizumab, should be considered in patients who develop CRS in the current pandemic, given the potential for unrecognized coinfection with SARS–CoV-2.
2. Patients on active cancer therapy that is compromising the immune system should receive maximal precautions and protection against SARS–CoV-2 exposure.

## Cancer Therapies With Vascular Toxicity

SARS-CoV-2 uses the ACE2 receptor for cellular entry, which may explain why certain organs are preferentially affected in COVID-19.<sup>97</sup> ACE2 is expressed on lung alveolar epithelial cells and enterocytes of the small intestine as well as on the arterial and venous endothelium.<sup>97</sup> As outlined above, patients with preexisting CVD and/or CV risk factors are at the highest risk of experiencing a more severe course with COVID-19, and it is hypothesized that this may be related to reduced endothelial reserve. Along these lines, several cancer therapies, including chemotherapies (eg, cisplatin, cyclophosphamide), targeted therapies (eg, VSP inhibitors), immune therapies (eg, ICIs), and radiation therapy, can activate and injure the endothelium.<sup>98</sup> Although this vascular injury may often go unnoticed in clinical practice, it may become more evident in the setting of a potent endothelial stressor such as COVID-19. Indeed, viral infection of endothelial cells has been observed, and the vascular injury is considered to contribute to several complicating manifestations of COVID-19.<sup>99</sup> Recent data suggest that statin therapy may be an important adjunct for minimizing the major adverse vascular effects and inflammation that appears to be critically important during COVID-19.<sup>100</sup> It is unknown whether aspirin is a beneficial or harmful adjunctive therapy unless otherwise indicated for patients presenting with classic acute myocardial infarction, stroke, or acute limb ischemia, as per standard practice guidelines. Trials are currently ongoing to address the thrombotic aspects of COVID-19, which include microthrombi in various organs, and the merit of anticoagulation strategies.

### Recommendation

1. In patients with cancer who present with acute vascular events, such as acute myocardial infarction or stroke, the possibility of an infection with SARS-CoV-2 should be considered. This is especially important for patients who are being considered for invasive procedures. Myopericarditis is an important condition that should be considered in patients with SARS-CoV-2 and can mimic even ST-segment elevation myocardial infarction.
2. Statins should be continued in patients already on therapy and should be considered in patients undergoing therapies with potential CV toxicity.

## Radiation Therapy

Patients who received prior chest radiation, especially those treated >2 decades ago, are at particular risk for radiation-induced heart and lung disease and represent a patient population expected to have a significantly reduced reserve should they develop COVID-19. For patients who received radiation therapy in the more recent era, the risk is likely lower. For those who are currently undergoing or are planned to undergo radiation therapy, acute injury and inflammation may pose a risk. Furthermore, it is recommended that, once radiation therapy is started, the full course of treatment should be completed.<sup>33</sup>

### Recommendation

1. In patients receiving active radiation therapy, clinicians should be aware that symptoms related to radiation-induced pneumonitis may mimic symptoms of COVID-19.

2. Patients who have received prior radiation therapy may have a reduced cardiopulmonary reserve and may be especially susceptible to a complicated course of COVID-19; strict safety measures should be in place for these patients.

### **Use of ACE Inhibitors/Angiotensin Receptor Blockers During COVID-19**

ACE2 is a coreceptor for SARS-CoV-2, thus there has been a debate regarding the safety of ACE inhibitors (ACE-Is) and angiotensin 2 receptor blockers (ARBs) during the COVID pandemic.<sup>101,102</sup> A higher proportion of patients with adverse outcomes had hypertension and diabetes, and it has been speculated that ACE2 levels are upregulated in these patients, putting them at greater risk. One hypothesis is that ACE2 upregulation may be related to the pathogenesis of these CV risk factors or to other related comorbidities, such as obesity.<sup>103–105</sup> Alternatively, treatment of hypertension and diabetes with ACE-Is and ARBs may increase ACE2 expression, thus increasing the risk of viral entry and propagation.<sup>106</sup> However, in animal models, SARS-CoV infection led to reduced ACE2 expression and acute lung injury that was rescued by blocking the renin-angiotensin-aldosterone pathway. Clinical trials are ongoing that testing whether losartan, an ARB, is protective in COVID-19.<sup>107</sup> Furthermore, ACE-Is and ARBs have established efficacy for the treatment of cardiomyopathy and heart failure, even in patients with cancer, and should be a preferred agent when used for cardioprotection in patients receiving cardiotoxic therapies. Current statements by CV societies ([acc.org/latest-in-cardiology/articles/2020/03/17/08/59/hfsa-acc-aha-statementaddresses-concerns-re-using-raas-antagonists-in-covid-19](https://www.acc.org/latest-in-cardiology/articles/2020/03/17/08/59/hfsa-acc-aha-statementaddresses-concerns-re-using-raas-antagonists-in-covid-19) and [escardio.org/Councils/Council-on-Hypertension\(CHT\)/News/position-statement-of-the-esc-council-onhypertension-on-ace-inhibitors-and-ang](https://www.escardio.org/Councils/Council-on-Hypertension(CHT)/News/position-statement-of-the-esc-council-onhypertension-on-ace-inhibitors-and-ang)) do not indicate that there are adequate data to recommend stopping or withholding these therapies in patients with cancer who have established indications for their use.<sup>108</sup> This view is supported by the observation that clinical outcomes did not differ between patients with a history of hypertension who were hospitalized for COVID-19 in Wuhan, China, and were treated either with an ACE-I/ARB or with an alternative antihypertensive regimen.<sup>10,109</sup>

### **Recommendation**

1. ACE-Is and ARBs should be continued in patients with cancer who are receiving them for established indications during the COVID-19 pandemic.
2. ACE-Is and ARBs, the  $\beta$ -blocker carvedilol, and statins should continue to be appropriate strategies for cardioprotection while patients are receiving cancer therapy during the COVID-19 pandemic.

### **Cancer Therapies With Arrhythmic and QT-Prolonging Potential**

Malignant ventricular arrhythmias have been recognized in patients with COVID-19 infection and lead to many management challenges.<sup>40</sup> Moreover, various investigational treatments for COVID-19, including hydroxychloroquine and azithromycin, are associated with significant QT prolongation, which can increase the likelihood of ventricular tachyarrhythmia, particularly torsades de pointes. On the basis of these considerations and emerging data, the US Food and Drug Administration determined that the benefits of chloroquine and hydroxychloroquine no longer outweigh their potential risks within the

anticipated framework of use, and they revoked the emergency use authorization for these medications on June 15, 2020. It should be added that the arrhythmic risk of these medications is likely increased in patients receiving active cancer therapy because many targeted agents may have an effect on the QT interval during treatment. For example, cancer therapeutics that are known to have important effects on the QT interval include arsenic trioxide, certain TKIs (vandetanib, nilotinib, vemurafenib), as well as ribociclib (Table 6). In addition, other risk factors during cancer therapy, such as nausea and diarrhea, may further exacerbate any changes in the QT interval as a result of hypomagnesemia or hypokalemia. In patients with QT prolongation who are receiving cancer therapeutics (ie, QTc  $\geq$  500 msec or QT  $>$ 60 msec from baseline), caution should be exercised when initiating COVID-19 therapies that may have an important effect on the QT interval. Moreover, electrolytes should be continually repleted, and any other nonessential QT-prolonging medications should be discontinued. In patients with significant QT prolongation ( $>$ 500 msec) in whom both cancer-related and COVID-19-related therapies are considered essential and cannot be altered, additional protective measures may be considered, including topical patch monitors and/or external wearable defibrillators, especially if the patient is treated in the outpatient setting.<sup>110</sup>

QT interval and arrhythmia monitoring strategies are constantly evolving. Recent publications provide helpful guidance in monitoring for the risk of ventricular arrhythmia caused by hydroxychloroquine-azithromycin treatment for COVID-19.<sup>111,112</sup> Although a standard 12-lead ECG is the most accurate way to assess the QT interval and cardiac arrhythmias, resource utilization and management are important considerations in the setting of COVID-19. Acquisition of a 12-lead ECG requires both personnel and equipment exposure. As such, the number of requested ECGs should be limited, and only a small number of technicians and ECG machines should be designated for patients with COVID-19 to limit exposure. For inpatients, telemetry monitoring may be considered for those deemed high risk based on a validated risk score for drug-associated QT interval prolongation.<sup>113</sup> There is also a need for alternative tools for QT monitoring considering the tremendous cost and resource utilization required for currently recommended QT interval monitoring with serial 12-lead ECGs, typically in triplicate.<sup>114</sup> For example, many wearable devices and other digital technology, such as the Apple Inc smartwatch, can provide single-lead ECG data with excellent fidelity. The KardiaMobile-6L, developed by AliveCor for atrial fibrillation detection, just received emergency clearance from the US Food and Drug Administration for use as a device for QT interval monitoring of patients with COVID-19. This tool and the BodyGuardian Heart (Preventice Solutions) may be very important devices to ensure cardiac safety and also to maintain the currently required social distancing mandates.<sup>110</sup>

### Recommendation

1. All patients with cancer who are being initiated on therapies associated with QT interval prolongation require a baseline 12-lead ECG. Any subsequent monitoring that is necessary can be accurately and safely performed with topical devices that allow monitoring of arrhythmias and QT interval prolongation.

Nonessential medications should be eliminated, and electrolytes should be fastidiously replaced if those issues are present.

### **Cancer Therapies With Risk of Thromboembolism**

The characteristics of cancer disease, the type of anticancer therapy, and coexisting diseases, including CVD, are important risk factors for venous thromboembolism.<sup>115</sup> Pulmonary embolism remains a leading cause of mortality in clinical oncology. SARS-CoV-2 appears to be an additional risk factor for thromboembolic complications (including arterial microthrombi), and D-dimer ( $>1 \mu\text{g/mL}$ ) is one of the most important predictors for fatal outcomes.<sup>116–120</sup> Inflammation, endothelial activation, and injury are the most likely mechanisms. The clinical difficulty is that pulmonary embolism, pulmonary infarction, and SARS-CoV-2 may have the same symptoms—shortness of breath, cough, and even fever—and they can coexist.<sup>17</sup>

### **Recommendations**

1. In C-O patients with confirmed SARS-CoV-2 who are immobilized in bed, primary antithrombotic prophylaxis should be used.
2. In C-O patients with dyspnea, cough, and fever, diagnostics for the exclusion of SARS-CoV-2 and pulmonary embolism should be performed.
3. In patients with cancer who have confirmed pulmonary embolism, SARS-CoV-2 should be excluded.
4. In patients with cancer who have pneumonia and confirmed SARS-CoV-2, evaluation by computed tomography should include an assessment for pulmonary embolism.
5. Low-molecular-weight heparins appear to be the first choice for antithrombotic treatment; new oral anticoagulants may be considered if there are not important drugdrug interactions with other planned treatments.

### **Concluding Statements**

In a matter of a few months, COVID-19 has had an unimaginable impact on human lives and local, national, and global economies. The pace and number of studies in this area have been unprecedented, and so has the rapidly evolving knowledge base. Specific recommendations for clinical practice will continue to evolve in the weeks and months to come. The current general observations emphasize that patients with CVD and/or cancer are among the highest risk groups for poor outcomes, especially if they contract SARS-CoV-2. Proper awareness and strategies need to be in place to manage these patients optimally and thoughtfully to ensure a safe environment. Patients who are being treated for cancer represent a complex and fragile population. The management of their comorbidities, and of CVD in particular, becomes an absolute priority, especially during COVID-19. As a result of this pandemic, the need for a proactive and integrated approach to C-O care has never been more important than it is today. It is the intent of this consensus document to provide a meaningful structure to achieve a truly integrated and safe approach for the benefit of our patients.

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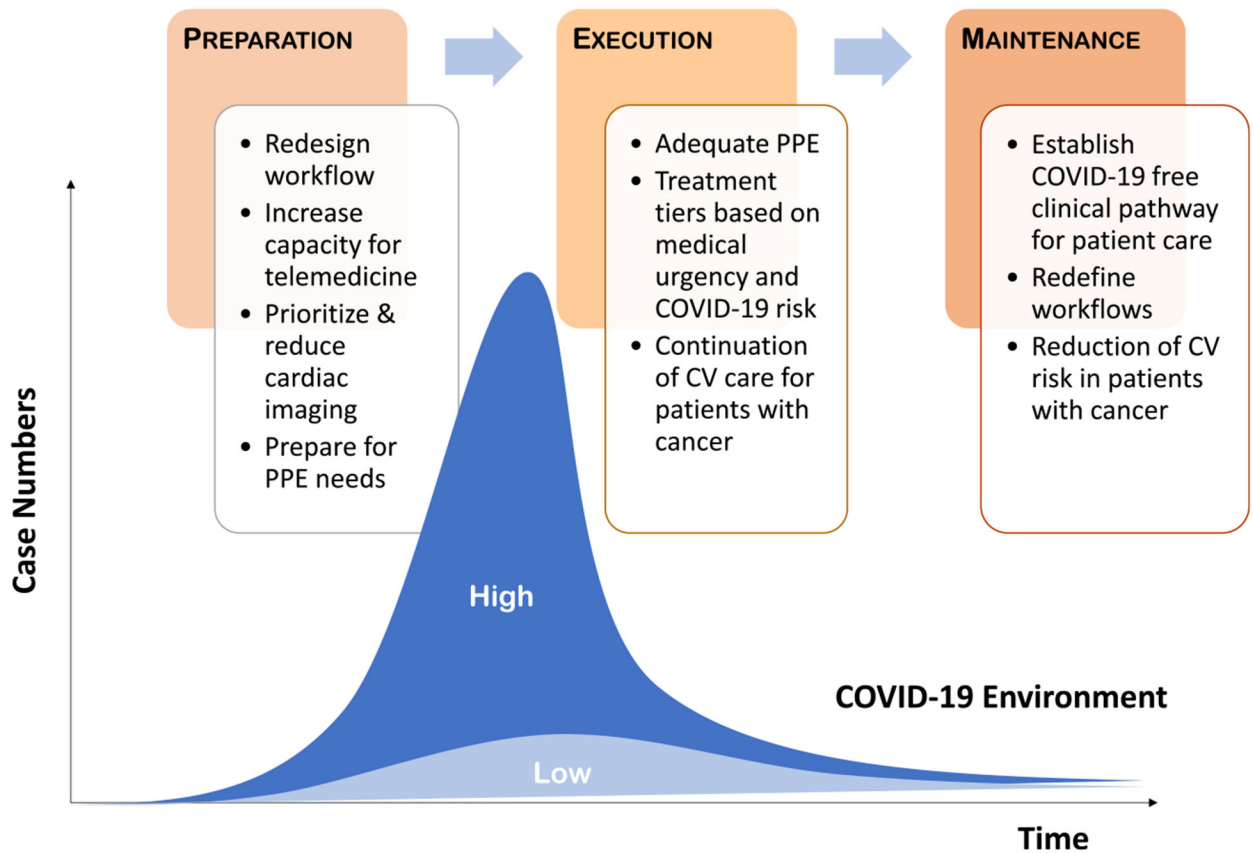
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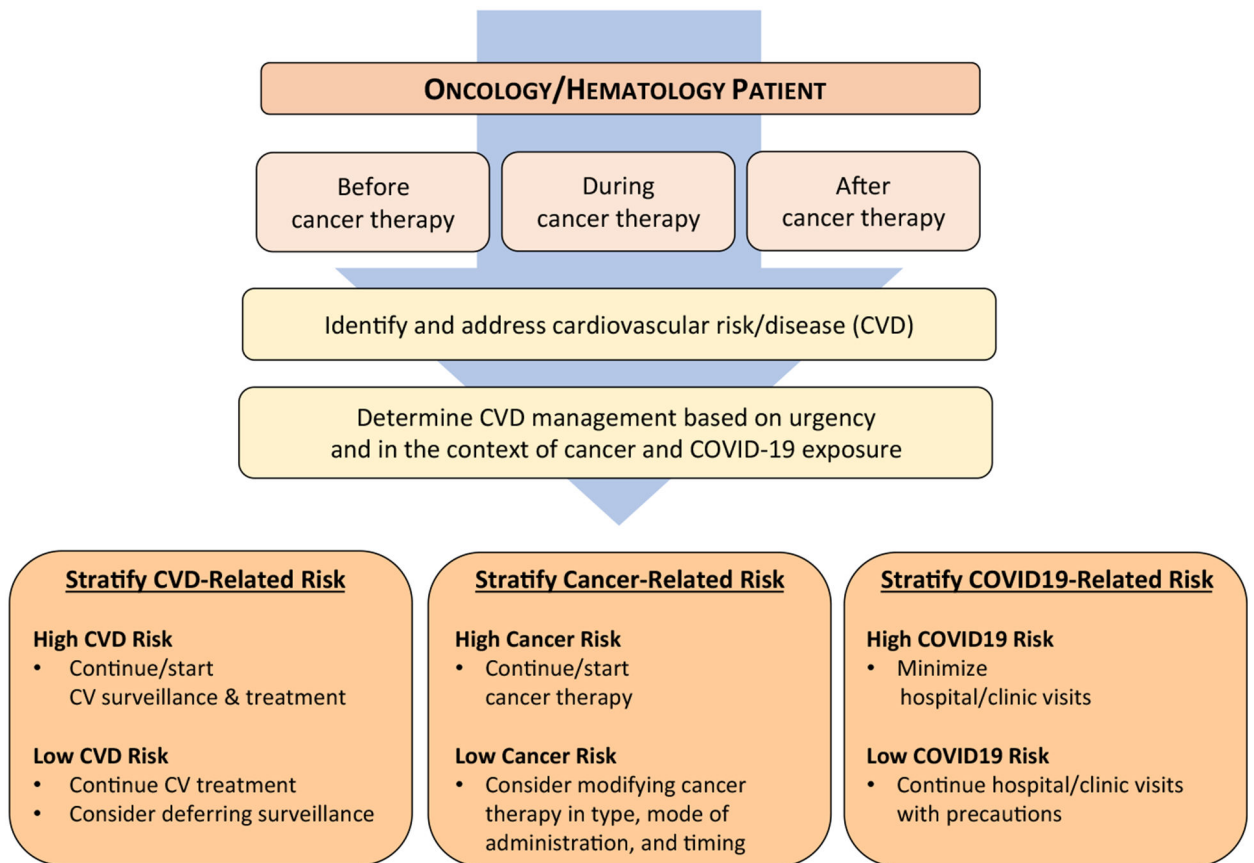
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**FIGURE 1.**

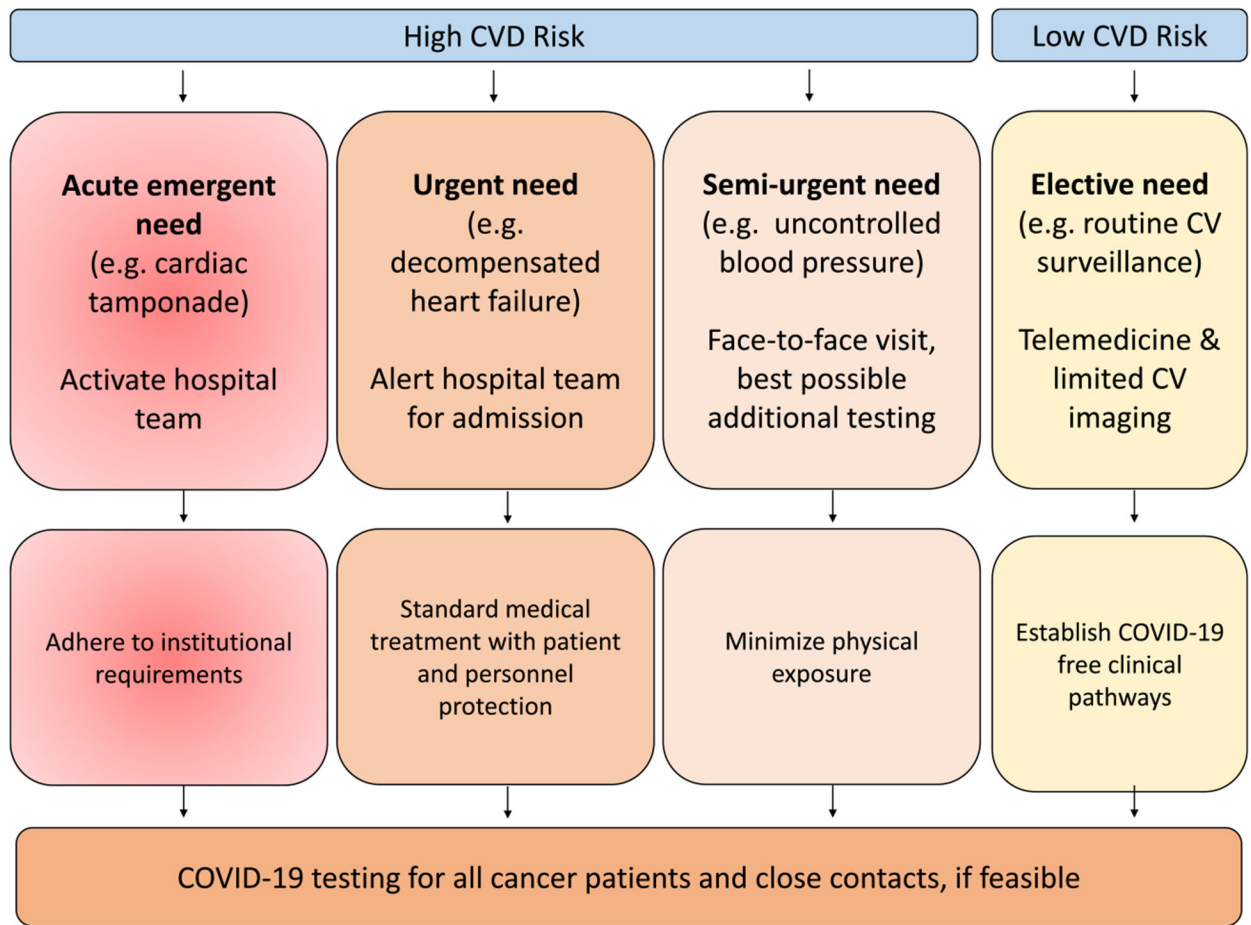
Cardio-Oncology Care in the Era of Coronavirus Disease 2019 (COVID-19). This is an overview of the changes in medical practice for patients with cancer in the setting of a viral pandemic such as COVID-19. These include proper preparation, execution of modified workflows, and maintenance of excellent care. Some modified practices evolving before and during peak times of a pandemic will likely remain in place to address persistent residual risk and resurges and/or those recognized to contribute to practice optimization in general. CV indicates cardiovascular; PPE, personal protection equipment.



**FIGURE 2.**

Workflow Outline for Cardio-Oncology in Times of a Viral Pandemic. Initial triage should take cardiovascular (CV) disease (CVD) acuity into consideration as well as the broader scope of the patient’s cancer care and the specific viral pandemic practice environment. COVID-19 indicates coronavirus disease 2019.





**FIGURE 3.** Outline of High-Risk and Low-Risk Cardiovascular (CV) Conditions. All cases should be addressed on an individual basis. The type of clinical encounter is driven by the clinical presentation. Coronavirus disease 2019 (COVID-19) screening should be obtained for any patient to be seen in person and, ideally, for all patients proceeding with cancer therapy. Repeat and serial testing might be required. CVD indicates cardiovascular disease.

	Normal NP*	Abnormal NP*
Normal Troponin*	<p><b>Asymptomatic<sup>φ</sup>:</b></p> <ol style="list-style-type: none"> <li>1. Continue CV monitoring based on established guidelines</li> <li>2. If the patient is receiving high risk cancer therapy<sup>‡</sup> or has high CV risk, consider measuring biomarkers at the time of cancer safety labs</li> </ol> <p><b>Symptomatic<sup>φ</sup>:</b></p> <ol style="list-style-type: none"> <li>1. Search for non-cardiac causes of patient’s symptoms</li> </ol>	<p><b>Asymptomatic<sup>φ</sup>:</b></p> <ol style="list-style-type: none"> <li>1. If the patient is receiving high risk cancer therapy<sup>‡</sup> or has high CV risk, consider repeating both biomarkers in 1-2 weeks.</li> <li>2. If either biomarker is then abnormal, cardiac imaging and Cardio-Oncology<sup>#</sup> consult are recommended.</li> </ol> <p><b>Symptomatic<sup>φ</sup>:</b></p> <ol style="list-style-type: none"> <li>1. Cardio-Oncology consult is recommended<sup>#</sup>.</li> <li>2. Consider cardiac imaging</li> </ol>
Abnormal Troponin*	<ol style="list-style-type: none"> <li>1. Consider cardio-protective therapy<sup>β</sup></li> <li>2. Repeat both biomarkers before the next cycle and if these are normal , continue observation</li> <li>3. If either repeat biomarker is abnormal, cardiac imaging and Cardio-Oncology consult are recommended<sup>#</sup>.</li> </ol>	<ol style="list-style-type: none"> <li>1. Cardio-Oncology consult is recommended<sup>#</sup>.</li> <li>2. Consider cardiac imaging appropriate to cancer therapy</li> <li>3. Multidisciplinary risk-benefit assessment of continuing current cancer therapy is highly recommended.</li> <li>4. Start/modify cardio-protective therapy<sup>β</sup></li> </ol>

**FIGURE 4.**

Action Grid for Cardiac Biomarker Profile. This is an outline of recommendations based on the constellation of troponin and natriuretic peptide values and within the context of the clinical presentation. CV indicates cardiovascular. \*NP indicates natriuretic peptides (B-type natriuretic peptide [BNP] and N-terminal pro-BNP [NT-proBNP]); troponin, troponin I or troponin T (normal vs abnormal levels are based on the institutional reference range). <sup>φ</sup>Asymptomatic indicates the absence of symptoms of heart failure (HF) or acute coronary syndrome (ACS); symptomatic, symptoms of HF or ACS. <sup>#</sup>A consultation can happen in person or by telemedicine. Discussion should include initiation of cardioprotective therapy. <sup>‡</sup>High-risk cancer therapy is that known to be associated with HF or left ventricular dysfunction (LVD). <sup>β</sup>Cardioprotective therapy indicates that an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker and/or carvedilol with or without a statin (if the patient is receiving anthracycline-containing chemotherapy) is recommended.

**TABLE 1.** Studies on Coronavirus Disease 2019 (COVID-19) in Patients With Cancer (Status as of June 2020)

STUDY	COUNTRY	CANCER COHORT	NO.	COVID-19+	ICU	MV	MORTALITY	SEVERE	INDEPENDENT PREDICTORS
Liang 2020 <sup>6</sup>	5 Districts, China	17 Solid cancers, 1 lymphoma; 4 on active therapy	18 Patients with cancer and 1572 patients without cancer	1 % of patients with cancer vs 0.29% in general population			39% in patients with cancer vs 8% in general population ( <i>P</i> < .001)	For severe events: <ul style="list-style-type: none"> <li>Cancer (OR, 5.59; 95% CI, 1.8–16.2; <i>P</i> = .003)</li> <li>COPD (OR, 3.4; 95% CI, 1.4–8.4; <i>P</i> = .008)</li> <li>DM (OR, 2.2; 95% CI, 1.3–3.7; <i>P</i> = .002)</li> <li>HTN (OR, 1.9, 95% 1.2–2.9; <i>P</i> = .004)</li> <li>Age (OR, 1.1, 95% 1.0–1.1; <i>P</i> &lt; .001)</li> <li>Women (OR, 0.6, 95% 0.4–0.9; <i>P</i> = .02)</li> </ul>	
Zhang 2020 <sup>24</sup>	Hubei, China	Solid cancer only; 6 received anticancer therapy within 14 d (1 radiation, 5 drug)	28	2.2% of all admitted patients	21.4%	35.7%	53.6%	For severe events: <ul style="list-style-type: none"> <li>Anticancer therapy within 14 d (OR, 4.1; 95% CI, 1.1–15.3; <i>P</i> = .04)</li> <li>Patchy consolidation (OR, 5.4; 95% CI, 1.5–19.8; <i>P</i> = .01)</li> </ul>	
Dai 2020 <sup>25</sup>	Hubei, China	96 Solid cancers, 9 hematologic malignancies; 48 with cancer therapy within 40 d (8 surgery, 13 radiation therapy)	105 Patients with cancer; 536 matched patients without cancer	NA	19.05%	9.52%	11.43%	Death: <ul style="list-style-type: none"> <li>Age (OR, 30.1; <i>P</i> = .003)</li> <li>DM (OR, 2.99; <i>P</i> = .03)</li> </ul> Severe symptoms: <ul style="list-style-type: none"> <li>Cancer (OR, 1.99; <i>P</i> = .006)</li> <li>HTN (OR, 1.8; <i>P</i> = .02)</li> </ul> ICU: <ul style="list-style-type: none"> <li>Cancer (OR, 3.1; <i>P</i> = .001)</li> <li>Age (OR, 11.2; <i>P</i> = .008)</li> </ul> MV: <ul style="list-style-type: none"> <li>Cancer (OR, 2.7; <i>P</i> = .04)</li> </ul> For severe symptoms: <ul style="list-style-type: none"> <li>Cancer (HR 2.5; 95% CI, 1.7–3.8; <i>P</i> &lt; .01)</li> </ul>	

STUDY	COUNTRY	CANCER COHORT	NO.	COVID-19+	ICU	MV	MORTALITY	SEVERE	INDEPENDENT PREDICTORS
Yang 2020 <sup>26</sup>	Hubei, China	183 Solid tumors, 22 hematologic malignancies; 54 with cancer therapies in the 4 wk prior (31 chemotherapy, 12 targeted therapy, 4 immunotherapy, 9 radiation, 2 surgery)	205	NA	15%	10%	20%		<ul style="list-style-type: none"> <li>Hem. malignancy (HR 6.3; 95% CI, 2.7–14.9; <i>P</i>&lt;.01)</li> <li>Lung cancer (HR 2.6; 95% CI, 1.3–5.0; <i>P</i>&lt;.01)</li> <li>Met. cancer (HR 2.5; 95% CI, 1.2–5.1; <i>P</i>= .01)</li> <li>Immunotherapy (HR 4.8, 95% 1.7–13.5; <i>P</i>&lt;.01)</li> <li>Surgery (HR, 6.2; 95% CI, 2.4–15.8; <i>P</i>&lt;.01)</li> </ul>
Rogado 2020 <sup>27</sup>	Madrid, Spain	45 Solid cancers; 71.1% on active treatment	45	4.2% (vs 0.6% in the overall population)	0%		42.2% (vs 13.2% in the overall population)	64%	<p>Mortality:</p> <ul style="list-style-type: none"> <li>On chemotherapy (OR, 3.5; 95% CI, 1.2–10.6; <i>P</i>= .03)</li> <li>Men (OR, 3.9; 95% CI, 1.6–9.5; <i>P</i>= .003)</li> </ul> <p>Cancer type, stage, and time since diagnosis not predictive</p> <p>Mortality:</p> <ul style="list-style-type: none"> <li>Age (OR, 1.1; 95% CI, 1–1.1; <i>P</i>= .03)</li> </ul> <p>Cancer type, stage, and treatment not predictive</p>
Mehta 2020 <sup>28</sup>	New York City, USA	164 Solid cancers, 54 hem. malignancies; 92 with active cancer <1 y (49 on radiation therapy, 47 on drug therapy)	218 With cancer; 1090 age-matched and sex-matched controls	NA	10.5%	20.6%	28% (14% in control group)		<p>Mortality:</p> <ul style="list-style-type: none"> <li>Cancer (OR, 2.45; <i>P</i>&lt;.001)</li> </ul> <p>Disease characteristics significantly more common in patients with cancer who died: HTN, CAD, CHF, chronic lung disease</p>
Garassino 2020 <sup>29</sup>	USA, UK, Spain, Italy, France, Switzerland, China, Netherlands	Thoracic malignancies, 151 NSCLC, 29 SCLC, 8 thymomas, 2 carcinoids, 1 mesothelioma; 147 on therapy	200	NA	10%	6%	33%		<p>Mortality:</p> <ul style="list-style-type: none"> <li>Current or former smoker (OR, 3.2; 95% CI, 1.1–9.1)</li> </ul>
Kuderer2020 <sup>30</sup>	USA, Canada, Spain	758 Solid cancers, 204 hematologic malignancies; 366 with cancer therapy within 4 wk of COVID-19 diagnosis (160 cytotoxic therapy, 72 targeted	928	NA	14%	12%	13%	26%	<p>30-D mortality:</p> <ul style="list-style-type: none"> <li>Age per 10 y (OR, 1.8; 95% CI, 1.5–2.2)</li> <li>Men (OR, 1.6; 95% CI, 1.1–2.5)</li> <li>Former smoker (OR, 1.6; 95% CI, 1.0–2.5)</li> </ul>

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STUDY	COUNTRY	CANCER COHORT	NO.	COVID-19+	ICU	MV	MORTALITY	SEVERE	INDEPENDENT PREDICTORS
Lee 2020 <sup>31</sup>	UK	693 Solid tumors, 169 hematologic malignancies, 47 unspecified; 518 on cancer therapy within 4 wk of COVID-19 diagnosis (281 chemotherapy, 72 targeted therapy, 44 immunotherapy, 76 radiation, 29 surgery)	800	NA	7%	NA	28%	23% (critical, 22%)	<ul style="list-style-type: none"> <li>No. of comorbidities &gt;1 (OR, 3.6)</li> <li>Cancer not in remission, but stable (OR, 1.8; 95% CI, 1.1–3.0) or progressing (OR, 5.2; 95% CI, 2.8–9.8)</li> <li>ECOG status 2 (OR 3.9, 95% CI 2.1–7.2) ECOG status 3 (OR 5.7, 95% CI 2.8–11.5)</li> <li>Azithromycin + hydroxychloroquine (OR, 2.9; 95% CI, 1.8–4.8)</li> </ul> <p>No association with cancer type or therapy</p> <p>Mortality:</p> <ul style="list-style-type: none"> <li>Men (OR, 1.7; 95% CI, 1.2–2.3; <i>P</i> = .006)</li> <li>Age (OR, 9.4; 95% CI, 6.6–10.0; <i>P</i> &lt; .0001)</li> <li>CVD (OR, 2.3; 95% CI, 1.5–3.6; <i>P</i> = .002)</li> <li>HTN (OR, 1.95; 95% CI 1.4–2.8; <i>P</i> = .002)</li> </ul> <p>No association with cancer type, stage, or therapy</p>

Abbreviations: CAD, coronary artery disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disorder; CVC, cardiovascular disease; DM, diabetes mellitus; ECOG, Eastern Cooperative Oncology Group; Hem, malignancy, hematologic malignancy; HR, hazard ratio; HTN, hypertension; ICU, intensive care unit; Met, cancer, metastatic cancer; MV, mechanical ventilation; NA, not available; NSCLC, nonsmall cell lung cancer; OR, odds ratio; SCLC, small cell lung cancer.

**TABLE 2.**

Types of Cardio-Oncology Consultations

TYPE OF CONSULTATION	DESCRIPTION	ADVANTAGES AND DISADVANTAGES
E-consultation	Virtual chart review: Examine the past medical history, active problem list, ongoing cardiovascular concerns E-messaging: Maintain bidirectional communication between patients and providers, including report of symptoms, vital signs, laboratory test results	<p>Advantages:</p> <ul style="list-style-type: none"> <li>• Efficient way for providers to seek specialty opinion</li> <li>• Low logistic demand, depending on institutional resources</li> <li>• Feasible, easy to access</li> </ul> <p>Disadvantages:</p> <ul style="list-style-type: none"> <li>• Disproportional time commitment (and reimbursement)</li> <li>• Risk of incomplete coverage of the consultation reason</li> </ul>
Telephone consultation	Telephone appointment: Requires a dedicated time for a phone call with direct, real-time communication	<p>Advantages:</p> <ul style="list-style-type: none"> <li>• Efficient and direct communication</li> <li>• Flexible location</li> <li>• Low logistic demand</li> </ul> <p>Disadvantages:</p> <ul style="list-style-type: none"> <li>• Time commitment and reimbursement</li> <li>• No visual assessment of the patient</li> <li>• Inability to perform a physical examination</li> </ul>
Video consultation	Live streaming: Provides limited but direct visual communication between the patient and the provider	<p>Advantages:</p> <ul style="list-style-type: none"> <li>• Flexibility for patients and providers regarding location and scheduling</li> <li>• Personal visual contact</li> <li>• Direct overall assessment of patient's condition</li> <li>• Thorough medication reconciliation with visual confirmation</li> </ul> <p>Disadvantages:</p> <ul style="list-style-type: none"> <li>• More technology required</li> <li>• Inability to perform a complete physical examination</li> </ul>
Face-to-face consultation	Traditional appointment: Allows a direct interaction between the patient and provider, including ability to perform a physical examination	<p>Advantages:</p> <ul style="list-style-type: none"> <li>• Complete assessment of the patient</li> </ul> <p>Disadvantages:</p>

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TYPE OF CONSULTATION	DESCRIPTION	ADVANTAGES AND DISADVANTAGES
		• Potential exposure/transmission risk

Key Points With Regard to Cardiac Imaging in Response to Coronavirus Disease 2019 (COVID-19)

TABLE 3.

<p>General recommendations</p> <ul style="list-style-type: none"> <li>• Cardiac imaging should be performed if appropriate and only if it is likely to substantially change patient management</li> <li>• Use the imaging modality with the best capability to meet the request considering the safety of medical staff regarding exposure (avoid unnecessary repetitions)</li> <li>• Elective nonurgent and routine follow-up examinations may be postponed or cancelled</li> <li>• Because of the risk of widespread contamination from transportation of critically ill or high-risk patients, a portable machine should be brought to the patient</li> <li>• Prolonged duration of a cardiac imaging study will increase the likelihood of contamination</li> <li>• A focused cardiac ultrasound study is recommended to reduce the duration of exposure and reduce the risk of contamination; to minimize exposure risk and use of resources, point-of-care ultrasound may be an option at selected centers</li> </ul> <p>Specific considerations</p> <ul style="list-style-type: none"> <li>• Echocardiography should only be performed in patients with COVID-19 when there is a clear indication that this testing will alter management</li> <li>• The risk of contamination of equipment and personnel is very high during a transesophageal echocardiography; consider other alternatives</li> <li>• Chest computed tomography (CT) is frequently used to confirm COVID-19–related pneumonia and might provide possible synergies for cardiac imaging</li> <li>• Coronary CT angiography can be used to exclude or confirm an acute coronary syndrome in COVID-19 pneumonia, in which elevated troponins are common</li> </ul>
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Modified from: Skulstad H, Cosyns B, Popescu BA, et al. COVID-19 pandemic and cardiac imaging: EACVI recommendations on precautions, indications, prioritization, and protection for patients and healthcare personnel. *Eur Heart J Cardiovasc Imaging*. 2020; 21:592–598<sup>41</sup>; and Kirkpatrick JN, Mitchell C, Taub C, Kort S, Hung J, Swaminathan M. ASE statement on protection of patients and echocardiography service providers during the 2019 novel coronavirus outbreak. *J Am Coll Cardiol*. 2020; 75:3078–3084. 49



Strengths and Limitations of Different Imaging Modalities for Diagnosis and Monitoring of Cardiotoxicity<sup>a</sup>

TABLE 4.

IMAGING MODALITY	VOLUME/FUNCTION	TISSUE/MASS	MYOCARDITIS/INFLAMMATION	VALVE DISEASE	PERICARDIAL DISEASE	CORONARY DISEASE/ISCHEMIA	RADIATION EXPOSURE	REPRODUCIBILITY ACCURACY	COST	AVAILABILITY	BEDSIDE TEST OPTION	EXAMINATION TIME	VIRAL INFECTION RISK
0	+	+	0	+++	++	0	None	+	+	+++	+++	+ to +++	++
	+	+	0	+++	+	0	None	++	++	++	+++	+ to ++	+++
<sup>b</sup>	+++	+++ <sup>b</sup>	+++	++	+++	+++	None	+++	+++	++	0	++	+
<sup>c</sup>	++	+	+	0	++	++	+++	++	+	++	0	+	+
	+	+	0	+	++	+++ <sup>d</sup>	+ / ++	+++	++	++	0	+++	+

Abbreviations: 2D Echo, 2-dimensional echocardiography; CCTA, coronary computed tomography angiogram; CMR, cardiac magnetic resonance; TEE, transesophageal echocardiography. Scores are scored as follows: +++, excellent diagnostic accuracy or features/high cost; ++, intermediate diagnostic accuracy or features/intermediate cost; +, reasonable diagnostic accuracy or low cost; 0, unable to diagnose.

<sup>a</sup> The established gold standard. <sup>b</sup> Imaging modalities include single-photon emission computed tomography and multigated acquisition. <sup>c</sup> The only noninvasive test that provides anatomic information with regard to the presence of coronary disease, and it also allows for imaging of the lung parenchyma, which shows characteristic in coronavirus disease 2019 and in the pulmonary vasculature and aorta (triple rule out); furthermore, it can identify pericardial effusion.

<sup>d</sup> from: Seraphim A, Westwood M, Bhuvan AN, et al. Advanced imaging modalities to monitor for cardiotoxicity. *Curr Treat Options Oncol.* 2019; 20:73-51

Best Practices for the Prevention and Management of Cardiac Complications in Patients With Cancer in the Coronavirus Disease 2019 (COVID-19) Era

TABLE 5.

2020 ESMO CONSENSUS RECOMMENDATION	ICOS CONSENSUS RECOMMENDATION IN THE COVID-19 ERA
<p>1. General principles</p> <p>1.1. Screening for known CV risk factors in patients with cancer is recommended; treatment of identified CV risk factors according to current guidelines is recommended (LOE, I; GOR, A)</p> <p>1.2. Many types of cancer therapy, especially mediastinal and left-sided chest radiation and certain chemotherapy and targeted agents, can substantially affect the heart and vascular system, and it is recommended that CV safety be monitored (LOE, I; GOR, A)</p> <p>1.3. Close and early collaboration between cardiologists, oncologists, hematologists, and radiation oncologists is recommended to ensure lifelong CV health and to avoid unnecessary discontinuation of cancer therapy (LOE, III; GOR, C)</p> <p>2. Baseline CV risk assessments (precancer therapy)</p> <p>2.1. Routine use of cardiac biomarkers (cardiac troponins I or T [TnI or TnT] and B-type natriuretic peptide [BNP], or N-terminal pro-BNP [NT-pro-BNP]) for patients undergoing potentially cardiotoxic chemotherapy is not well established; however, for high-risk patients (with preexisting, significant CVD) and those receiving high doses of cardiotoxic chemotherapy such as an anthracycline, baseline measurement of such cardiac biomarkers should be considered (LOE, III; GOR, A)</p> <p>2.2. For patients with a cancer diagnosis that requires treatment with a potentially cardiotoxic treatment, a baseline electrocardiogram (ECG), including measurement of a heart rate-corrected QT interval (QTc), is recommended (LOE, I; GOR, A); QTc should be calculated by either of the 2 most standardized methods—Bazett or Fridericia—and the comparative measurements during treatment should all be done using the same method</p> <p>2.3. In patients scheduled to undergo cancer therapy associated with heart failure or left ventricular (LV) dysfunction, baseline evaluation of left ventricular ejection fraction (LVEF), with strain imaging when possible, and diastolic function according to accepted comprehensive imaging practice is recommended (LOE, I; GOR, A)</p> <p>3. Primary prevention therapy</p> <p>3.1. In patients with a normal LVEF scheduled to undergo cancer therapy with known cardiotoxic agents and risk factors for cardiac toxicity, prophylactic use of angiotensin-converting enzyme inhibitors (ACE-Is) or, alternatively, angiotensin receptor blockers (ARBs), and/or selected <math>\beta</math>-blockers (BBs) may be considered to reduce the risk of cardiotoxicity; dexrazoxane has been validated as a cardioprotectant in selected populations who are receiving anthracycline-based chemotherapy (LOE, II; GOR, B)</p> <p>3.2. Patients with evidence of hyperlipidemia may benefit from treatment during active cancer therapy, especially cardiotoxic chemotherapy (LOE, II; GOR, C)</p> <p>4. During cancer treatment: Cardiac safety surveillance</p> <p>4.1. The following general principles are recommended for medical imaging in patients with cancer at risk for cardiac complications particularly for the periodic assessment of LV systolic function:</p> <p>4.1.1. Highly reproducible, quantitative volumetric, nonirradiating imaging with quality control is recommended (quantitative 2-dimensional [2D] and 3-dimensional [3D] echocardiography, and cardiac MRI) (LOE, I; GOR, A)</p> <p>4.1.2. For each patient, the same imaging modality at the same facility is highly recommended for serial testing (LOE, I; GOR, A)</p> <p>4.1.3. LV global longitudinal strain (GLS) imaging may be considered, when available, for baseline and serial LV systolic function monitoring (LOE, III; GOR, C)</p>	<p>1.1. Continuing approval without change</p> <p>1.2. Continuing approval without change</p> <p>1.3. Continuing approval without change</p> <p>2.1. Continuing approval without change</p> <p>2.2. Continuing approval without change</p> <p>2.3. Transthoracic echocardiogram (with or without strain imaging) and cardiac MRI (with or without strain) are the recommended imaging modalities</p> <p>3.1. Continuing approval without change</p> <p>3.2. Continuing approval without change</p> <p>4.1. Continuing approval without change</p>

<p><b>2020 ESMO CONSENSUS RECOMMENDATION</b></p>	<p><b>ICOS CONSENSUS RECOMMENDATION IN THE COVID-19 ERA</b></p>
<p>4.2. Asymptomatic patients receiving anthracycline-based chemotherapy with no cardiac biomarker or imaging abnormalities should undergo surveillance for risk stratification and the early detection of cardiac toxicity</p> <p>4.2.1. Periodic (every 3–6 wk or before each cycle) measurement of TnI or TnT and BNP or NT-proBNP using the same institutional laboratory using an acceptable 99% upper limit of normal reference range as the threshold for abnormal (LOE, III; GOR, C)</p> <p>4.2.2. Reassessment of LVEF and GLS (when possible) following the general imaging principles is recommended after a cumulative dose of 250 mg/m<sup>2</sup> of doxorubicin or its equivalent anthracycline, after approximately each additional 100 mg/m<sup>2</sup> (or approximately 200 mg/m<sup>2</sup> of epirubicin) beyond 250 mg/m<sup>2</sup>, and at the end of therapy, even if the cumulative dose is &lt;400 mg/m<sup>2</sup> (LOE, I; GOR, A)</p> <p>4.3. Aligned to the current recommendations by the FDA for asymptomatic, nonmetastatic patients undergoing adjuvant trastuzumab treatment, routine surveillance, consisting of cardiac imaging every 3 mo, should be considered for the early detection of cardiac toxicity; however, the effectiveness of this strategy in patients at low CV risk with no evidence of early LV dysfunction has not been demonstrated (LOE, II; GOR, B)</p> <p>4.4. Cardiac biomarker assessment may be considered as a valuable tool for cardiac safety surveillance in patients receiving adjuvant anti-HER2–based treatment (LOE, III; GOR, C)</p> <p>4.5. Asymptomatic patients receiving anti-HER2–based treatment (trastuzumab, pertuzumab, T-DM1) for metastatic disease should have general surveillance for cardiac toxicity that may consist of periodic physical examination, cardiac biomarkers, and/or cardiac imaging (LOE, I; GOR, B)</p> <p>4.6. In patients receiving cancer therapeutics associated with a risk of systemic hypertension, especially anti-VEGF-based therapy, establishment of a baseline blood pressure measurement and serial blood pressure monitoring is recommended along with surveillance for the early detection of CV toxicity that may consist of periodic cardiac examination, cardiac biomarkers, and/or cardiac imaging (LOE, I; GOR, A)</p> <p>5. During cancer treatment: Asymptomatic, new laboratory abnormalities (or preclinical toxicity)</p> <p>5.1. In asymptomatic patients receiving treatment with anthracyclines who have an LVEF decrease of 10% from baseline to &lt;50% or decrease in LVEF to 40% but &lt;50%, the following evaluations are recommended (LOE, III; GOR, A):</p> <p>5.1.1. Cardiology consultation (preferably a cardio-oncology specialist)</p> <p>5.1.1.1. Cardiology consultation (preferably a cardio-oncology specialist)</p> <p>5.1.1.2. Consider initiation of cardioprotective treatment (ACE-I or ARB with or without BB, and perhaps a statin), if not already prescribed</p> <p>5.1.3. Consider measuring cardiac biomarkers (TnI or TnT and BNP or NT-proBNP) and perform a cardiac-focused physical examination after each dose of anthracycline</p>	<p>4.2. Measurement of cardiac biomarkers (TnI or TnT and BNP, or NT-proBNP) should be considered in conjunction with cancer treatment safety laboratories if obtained with each cycle of chemotherapy; if either cardiac biomarker (TnI or TnT and BNP or NT-proBNP) is abnormal at the assay-specific cutoff and/or the patient becomes symptomatic, reassessment of LVEF with or without GLS should be performed using either 2D or 3D echocardiography, or cardiac MRI</p> <p>4.3. In patients who remain asymptomatic and who have normal or less than a 50% increase in cardiac biomarkers during monitoring, cardiac imaging is not recommended</p> <p>4.4. Cardiac imaging should be performed only when patients become symptomatic or have abnormal cardiac biomarkers</p> <p>4.5. Continuing approval without change; the threshold to obtain cardiac imaging should be higher in the COVID-19 era, but continued surveillance for the detection of new symptoms or elevation of cardiac biomarkers is unchanged</p> <p>5.1. This recommendation remains the same, except for repeating LVEF with or without GLS after every other dose of anthracycline-based chemotherapy; it is recommended to monitor patients by checking cardiac biomarkers (TnI or TnT and BNP or NT-proBNP) every other cycle, and reassessing LV function with imaging only if either biomarker is abnormal or the patient develops heart failure symptoms. The determination for the presence of heart failure symptoms can be obtained by telemedicine</p>

2020 ESMO CONSENSUS RECOMMENDATION	ICOS CONSENSUS RECOMMENDATION IN THE COVID-19 ERA
<p>5.1.4. Repeat LVEF with or without GLS measurement after every other dose of anthracycline-based chemotherapy</p> <p>5.1.5. If further anthracycline therapy is planned, the benefit-risk assessment of continued anthracycline-based therapy as well as options of nonanthracycline regimens should be discussed, and there should be consideration for the use of dexrazoxane and/or liposomal doxorubicin</p> <p>5.2. In asymptomatic patients receiving treatment with trastuzumab who have an LVEF decrease of 10% from baseline to &lt;50% or have a decrease in LVEF to 40% but &lt;50%, the following evaluations are recommended (LOE, III; GOR, A):</p> <p>5.2.1. Cardiology consultation (preferably a cardio-oncology specialist)</p> <p>5.2.2. Consider initiation of cardioprotective treatment (ACE-I or ARB with or without BB), if not already prescribed</p> <p>5.2.3. Consider measuring cardiac biomarkers (TnI or TnT and BNP or NT-proBNP) at a suggested interval of every 4–6 wk and periodic cardiac-focused physical examination for ongoing monitoring of cardiac toxicity</p> <p>5.2.4. Repeat LVEF with or without GLS measurement within 3–6 wk after holding trastuzumab, and, if LVEF with or without GLS has normalized, trastuzumab therapy can be resumed</p> <p>5.3. In asymptomatic patients receiving treatment with any cardiotoxic cancer therapy who have a normal LVEF but a decrease in average GLS from baseline assessment ( 12% relative decrease or 5% absolute decrease), the following evaluation and treatment should be considered (LOE, III; GOR, B):</p> <p>5.3.1. Consider initiation of cardioprotective treatment (ACE-I or ARB with or without BB), if not already prescribed</p> <p>5.3.2. Repeat LVEF with or without GLS measurement every 3 mo, or sooner, if cardiac symptoms develop</p> <p>5.3.3. Consider measuring cardiac biomarkers (TnI or TnT and BNP or NT-proBNP) as needed based on the cancer treatment's risk of cardiac toxicity</p> <p>5.3.4. Life-saving cancer treatment should not (?) be altered solely based on changes in LV strain</p> <p>5.4. In asymptomatic patients undergoing treatment with cardiotoxic anticancer therapy and an have elevation in cardiac troponin, the following measures should be considered (LOE, III; GOR, O):</p> <p>5.4.1. Cardiology consultation, preferably a cardio-oncology specialist</p> <p>5.4.2. Consider LVEF and GLS assessment with echocardiography</p> <p>5.4.3. Appropriate evaluation to exclude ischemic heart disease as a comorbidity</p> <p>5.4.4. Consider initiation of cardioprotective treatments (ACE-Is, ARBs and/or BBs), if not already prescribed</p> <p>5.4.5. Consider initiation of dexrazoxane in patients undergoing anthracycline-based chemotherapy</p> <p>5.4.6. It is possible that anticancer therapy may be continued without interruption if only mild elevations in cardiac biomarkers occur without significant LV dysfunction</p> <p>6. During cancer treatment: Clinical cardiac dysfunction</p>	<p>5.2. If the baseline LVEF with or without GLS is within normal range and the patient is asymptomatic while on treatment with trastuzumab, cardiac biomarkers (TnI or TnT and BNP or NT-proBNP) can be measured every other cycle; cardiac imaging with either echocardiography or cardiac MRI is recommended only if any cardiac biomarker is abnormal or the patient develops heart failure symptoms</p> <p>5.3. Continuing approval without change</p> <p>5.3.2. Cardiac imaging should be performed in patients with abnormal cardiac biomarkers or in those who develop cardiac symptoms</p> <p>5.4. Continuing approval without change</p>

<p><b>2020 ESMO CONSENSUS RECOMMENDATION</b></p>	<p><b>ICOS CONSENSUS RECOMMENDATION IN THE COVID-19 ERA</b></p>
<p>6.1. In patients with an abnormal LVEF &lt;50% but ≥40%, medical therapy with an ACE-I (or ARB) and/or BB is recommended before starting potential cardiotoxic treatment (LOE, I; GOR, A)</p> <p>6.2. For those with an LVEF &lt;40%, anthracycline therapy, in particular, is not recommended unless there is no other effective alternative cancer treatment option (LOE, IV; GOR, A)</p> <p>6.3. For a patient receiving treatment with any cardiotoxic agent who presents with potentially cardiac-related but unexplained signs and symptoms, such as (but not limited to) sinus tachycardia, rapid weight gain, dyspnea, peripheral edema, or ascites, it is recommended to obtain a cardio-oncology consultation, reassess LVEF with or without GLS, and potentially measure cardiac biomarkers (LOE, III; GOR, A)</p> <p>6.4. For a patient receiving treatment with trastuzumab (or any HER2-targeted molecular therapy) who has signs and symptoms of heart failure, or for an asymptomatic patient with an LVEF &lt;40%, the same assessments as those for an LVEF ≥40% are recommended; in addition, trastuzumab (or any HER2-targeted molecular therapy) should be held until the cardiac status has stabilized, and a discussion regarding the risk/benefits of continuation should be held with the multidisciplinary team and the patient (LOE, I; GOR, A)</p> <p>6.5. For a patient in whom trastuzumab (or any HER2-targeted molecular therapy) has been interrupted, whose LVEF has increased to ≥40%, and/or whose signs and symptoms of heart failure have resolved, resumption of trastuzumab (or any HER2-targeted molecular therapy) should be considered, along with the following recommendations (LOE, III; GOR, B):</p> <p>6.5.1. Continued medical therapy for heart failure and ongoing cardiology care</p> <p>6.5.2. Periodic cardiac biomarker (BNP or NT-proBNP) assessment</p> <p>6.5.3. Periodic LVEF assessments during ongoing treatment</p> <p>6.6. For a patient in whom trastuzumab (or any HER2-targeted molecular therapy) has been interrupted, whose signs and symptoms of heart failure do not resolve, cardiac biomarker does not normalize, and/or LVEF remains &lt;40%, resumption of trastuzumab may be considered if no alternative therapeutic options exist; the risk-benefit assessment of prognosis from cancer versus heart failure should be discussed with the multidisciplinary team and the patient (LOE, IV; GOR, C)</p> <p>6.7. For a patient receiving treatment with sunitinib (or any other anti-VEGF based therapy) with signs and symptoms of heart failure, assessment of blood pressure control is recommended and measurement of LVEF and/or cardiac biomarkers should be considered; in addition, sunitinib (or any other anti-VEGF-based therapies) should be interrupted until the appropriateness of reinstating this therapy has been fully assessed (LOE, III; GOR, A)</p> <p>7. Survivors of cancer therapy (posttreatment)</p> <p>7.1. For asymptomatic patients who have been treated with cardiotoxic agents and have normal cardiac function, periodic screening for the development of new asymptomatic LV dysfunction with cardiac biomarkers and, potentially, cardiac imaging should be considered at 1-y and 2-y posttreatment, and periodic reassessment thereafter should be considered (LOE, III; GOR, B)</p> <p>7.2. For patients who developed asymptomatic LV dysfunction or heart failure because of trastuzumab (or any other HER2-targeted molecular therapy), anthracycline, or other cancer therapy, CV care, including medical treatment with ACE-I (or ARB) and/or BB and regular CV evaluation (eg, annually, if asymptomatic), should be continued indefinitely, regardless of improvement</p>	<p>6.1. Continuing approval without change</p> <p>6.2. Continuing approval without change</p> <p>6.3. It is recommended to obtain cardiac biomarkers and discuss with a cardio-oncologist if cardiac imaging is warranted</p> <p>6.4. It is recommended to obtain cardiac biomarkers and discuss with a cardio-oncologist if cardiac imaging is warranted</p> <p>6.5. Continuing approval without change</p> <p>6.5.2. Periodic cardiac biomarker (BNP or NT-proBNP) assessment should be performed at a frequency determined by the treating physician considering the patient's clinical presentation and risk of cardiac toxicity</p> <p>6.5.3. LVEF assessment is recommended only in the setting of an abnormal cardiac biomarker and/or worsening symptoms of heart failure</p> <p>6.6. Continuing approval without change</p> <p>6.7. It is first recommended to assess blood pressure control and cardiac biomarkers; if cardiac biomarkers are abnormal and/or symptoms of heart failure worsen despite achieving adequate blood pressure control, measurement of LVEF is then recommended; early involvement of a cardio-oncologist is strongly recommended to guide choice of antihypertensive therapy</p> <p>7.1. A thorough history, including assessment of CV risk factor control, should be performed along with cardiac biomarkers; these should then guide the decision about assessing LVEF with or without GLS; early consultation with a cardiologist or cardio-oncologist is strongly recommended; if prior imaging was significantly abnormal (ie, valvular or pericardial disease), the interval for reassessment should not be excessively delayed</p> <p>7.2. Decision about withdrawing any cardiac medications should first be discussed with the patient's cardio-oncologist</p>

2020 ESMO CONSENSUS RECOMMENDATION	ICOS CONSENSUS RECOMMENDATION IN THE COVID-19 ERA
<p>in LVFEF or symptoms; any decision to withdraw guideline-based medical therapy should only be done after a period of stability, no active cardiac risk factors, and no further active cancer therapy (LOE, II; GOR, B)</p>	
<p>7.3. For patients with a history of mediastinal or chest radiation, evaluation for coronary artery disease and myocardial ischemia as well as valvular heart disease is recommended, even if asymptomatic, starting at 5 y posttreatment and then at least every 3–5 y thereafter (LOE, I; GOR, A)</p>	<p>7.3. Any routine CV imaging should be postponed until COVID-19 restrictions are suspended as long as the patient is asymptomatic; symptom awareness, optimal CV risk factor management, and occasional cardiac biomarker assessment should continue at the recommended intervals</p>
<p>8. Immune checkpoint inhibitor-associated CV toxicity</p>	
<p>8.1. For patients who develop new CV symptoms or are incidentally noted to have any arrhythmia, conduction abnormality on ECG, or LVSD on echocardiogram while undergoing (or after recent completion) of immune checkpoint inhibitor (ICI) therapy, further appropriate work-up (ECG, troponin, BNP or NT-pro-BNP, C-reactive protein, viral titer, echocardiogram with GLS, cardiac MRI) for ICI-associated CV toxicity, particularly myocarditis and other common differential diagnoses, should be carried out promptly (LOE, IV; GOR, C)</p>	<p>8.1. Continuing approval without change</p>
<p>8.2. Endomyocardial biopsy for diagnosis should be considered if the diagnosis is highly suspected with otherwise negative work-up (LOE, IV; GOR, C)</p>	<p>8.2. Continuing approval without change</p>
<p>8.3. With either suspicion or confirmation of ICI-associated myocarditis, further therapy with ICIs should be withheld, and high-dose corticosteroids (methylprednisolone 1000 mg/d followed by oral prednisone 1 mg/kg/d) should be initiated promptly; corticosteroids should be continued until resolution of symptoms and normalization of troponin, LV systolic function, and conduction abnormalities (LOE, IV; GOR, C)</p>	<p>8.3. Continuing approval without change</p>
<p>8.4. For steroid-refractory or high-grade myocarditis with hemodynamic instability, other immunosuppressive therapies, such as anitihymocyte globulin, infliximab (except in patients with HF), mycophenolate mofetil, or abatacept, should be considered (LOE, IV; GOR, C)</p>	<p>8.4. Continuing approval without change</p>
<p>8.5. For patients with cardiomyopathy and/or HF, appropriate guideline-directed medical therapy and hemodynamic support should be provided as indicated (LOE, IV; GOR, C)</p>	<p>8.5. Continuing approval without change</p>
<p>8.6. For patients with atrial or ventricular tachyarrhythmia or heart block, appropriate medical and supportive care should be provided as indicated (LOE, IV; GOR, C)</p>	<p>8.6. Continuing approval without change</p>
<p>8.7. ICI therapy should be permanently discontinued with any clinical myocarditis; the decision regarding restarting ICI therapy in the absence of alternative available antineoplastic therapy needs to be individualized with multidisciplinary discussion considering the cancer status, response to prior therapy, severity of cardiotoxicity, regression of toxicity with immunosuppressive therapy, and patient preference after weighing the risks and benefits; if ICI therapy needs to be restarted, monotherapy with an anti-programmed cell death protein 1 (anti-PD-1) agent might be considered with very close surveillance for cardiotoxicity development (LOE, V; GOR, C)</p>	<p>8.7. Continuing approval without change</p>
<p>Level of evidence (LOE)</p> <ul style="list-style-type: none"> <li>• Evidence from at least one large randomized, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well conducted randomized trials without heterogeneity</li> <li>• Small randomized trials or large randomized trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity</li> <li>• Prospective cohort studies</li> <li>• Retrospective cohort studies or case-control studies</li> </ul> <p>Studies without control group, case reports, expert opinions</p>	

2020 ESMO CONSENSUS RECOMMENDATION	ICOS CONSENSUS RECOMMENDATION IN THE COVID-19 ERA
Grading of recommendation (GOR)	<p><b>A.</b> Strong evidence for efficacy with a substantial clinical benefit, strongly recommended</p> <p><b>B.</b> Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended</p> <p><b>C.</b> Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, etc), optional</p> <p><b>D.</b> Moderate evidence against efficacy or for adverse outcome, generally not recommended</p> <p><b>E.</b> Strong evidence against efficacy or for adverse outcome, never recommended</p>

Abbreviations: CV, cardiovascular; ESMO, European Society of Medical Oncology; FDA, US Food and Drug Administration; HF, heart failure; ICOS, International Cardio-Oncology Society; LVEF, left ventricular ejection fraction; LVSD, left ventricular systolic dysfunction; MRI, magnetic resonance imaging; T-DM1, trastuzumab emtansine. Modified from Rogado J, Obispo B, Pangua C, et al. Covid-19 transmission, outcome and associated risk factors in cancer patients at the first month of the pandemic in a Spanish hospital in Madrid. *Clin Transl Oncol*. Published online May 25, 2020.<sup>27</sup>

**TABLE 6.**

**Cardiovascular Adverse Effects From Cancer Therapies**

ANTICANCER AGENT	CANCER USE	IMPORTANT COMMON CV ADVERSE EFFECT
Anthracyclines		
Doxorubicin	Breast, sarcoma, lung, bladder, gastric, prostate, leukemia, lymphoma, others	Heart failure, cardiomyopathy, arrhythmia
Daunorubicin		
Epirubicin		
Idarubicin		
Mitoxantrone		
Alkylating agents		
Cisplatin	Lung, bladder, testicular, breast, esophageal, head and neck	Venous and arterial thromboembolism, hypertension
Melphalan	Multiple myeloma, ovarian, neuroblastoma	Arrhythmia
Antimetabolites		
Capecitabine	Breast, colon, gastric, pancreatic	Arterial (coronary) vasospasm, (myocardial) ischemia, Takotsubo
Fluorouracil		
Monoclonal antibodies		
Bevacizumab	Colorectal, cervical, glioblastoma, ovarian, renal, endometrial, sarcoma, breast	Hypertension, arterial and venous thromboembolism, bleeding
Rituximab	Lymphoma, leukemia	Hypotension (infusion reaction) Hypertension
Ofatumumab		
Alemtuzumab		
Pertuzumab	Breast, gastric, esophageal	Heart failure, cardiomyopathy
Trastuzumab		
Small-molecule tyrosine kinase inhibitors		
Axitinib	Renal	Hypertension
Cabozantinib	Thyroid, renal	Hypertension, arterial and venous thromboembolism
Cetuximab	Lung, pancreatic, colorectal	Arterial and venous thromboembolism
Crizotinib	Lung	Bradycardia, QT prolongation
Dabrafenib	Melanoma	QT prolongation
Dasatinib	Leukemia, gastrointestinal stromal tumor	QT prolongation, pleural effusion, pulmonary hypertension
Erlotinib	Lung, pancreatic, colorectal	Arterial and venous thromboembolism



ANTICANCER AGENT	CANCER USE	IMPORTANT COMMON CV ADVERSE EFFECT
Ibrutinib	Lymphoma	Atrial fibrillation, hypertension, bleeding
Imatinib	Leukemia, gastrointestinal stromal tumor, myelodysplastic syndrome, melanoma, mastocytosis, sarcoma	Edema
Osimertinib	Lung	Atrial fibrillation, heart failure, cardiomyopathy, QT prolongation
Pazopanib	Renal, sarcoma, thyroid	Hypertension, bradyarrhythmia, heart failure, cardiomyopathy
Ponatinib	Leukemia	Heart failure, cardiomyopathy, hypertension, ischemia, arterial and venous thromboembolism
Ramucirumab	Colorectal, gastric, lung	Hypertension
Regorafenib	Colorectal, gastrointestinal stromal tumor	Hypertension
Sorafenib	Hepatocellular, renal, thyroid	Hypertension, heart failure, cardiomyopathy, ischemia
Sunitinib	Renal, thyroid, sarcoma, gastrointestinal stromal tumor, pancreatic neuroendocrine tumor	Hypertension, heart failure, cardiomyopathy, arterial and venous thromboembolism
Trametinib	Melanoma	Heart failure, cardiomyopathy, bradyarrhythmia, QT prolongation, arterial and venous thromboembolism, hypertension
Vandetanib	Thyroid	Hypertension, QT prolongation
Vemurafenib	Melanoma	Hypertension, QT prolongation
Ziv-aflibercept	Colorectal	Hypertension
Immune checkpoint inhibitors	Melanoma, lung, kidney, bladder, head and neck, lymphoma	Myocarditis, arrhythmia/sudden cardiac death, cardiomyopathy, vasculitis, pericarditis
PD-1 inhibitors		
• Cemiplimab		
• Nivolumab		
• Pembrolizumab		
PD-L1 inhibitors		
• Atezolizumab		
• Avelumab		
• Durvalumab		
CTLA-4 inhibitor		
• Ipilimumab		
Proteasome inhibitors		
Bortezomib	Multiple myeloma, mantle cell lymphoma	Hypertension

ANTICANCER AGENT	CANCER USE	IMPORTANT COMMON CV ADVERSE EFFECT
Carfilzomib	Multiple myeloma	Hypertension, heart failure, cardiomyopathy, arterial and venous thromboembolism, acute coronary syndrome
mTOR inhibitors		
Everolimus	Breast, pancreas	Hypertension
Temsirolimus	Renal	Hypertension
Immunomodulatory drugs	Multiple myeloma	Venous thromboembolism
Lenalidomide		
Pomalidomide		
Thalidomide		
Histone deacetylase inhibitors	Lymphoma	QT prolongation
Belinostat		
Vorinostat		
Endocrine therapy		
Selective estrogen receptor modulators	Breast	Venous thromboembolism, QT prolongation
• Tamoxifen		
• Toremifene		
Aromatase inhibitors	Breast	Venous thromboembolism, hypertension, hyperlipidemia
• Anastrozole		
• Letrozole		
• Exemestane		
Antiandrogens	Prostate	Hypertension, hyperlipidemia, atherosclerosis
• Flutamide		
• Bicalutamide		
• Nilutamide		
CYP17 inhibitor	Prostate	Hypertension, myocardial infarction
• Abiraterone		
Chimeric antigen receptor T-cell therapy	B-cell acute lymphoblastic leukemia (refractory or relapse), large B-cell lymphoma (refractory or relapse)	Tachycardia, arrhythmia, hypotension, hypertension, heart failure, cytokine release syndrome
Axicabtagene ciloleucel		
Tisagenlecleucel		

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ANTICANCER AGENT	CANCER USE	IMPORTANT COMMON CV ADVERSE EFFECT
Miscellaneous		
Ribociclib	Breast	QT prolongation
Arsenic trioxide	Leukemia	QT prolongation
Tretinoin	Leukemia	Heart failure, cardiomyopathy