Case Report

Balancing anticancer therapy efficacy and safety in advanced hepatocellular carcinoma: a case report

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Background: Hepatocellular carcinoma (HCC) is a significant health problem associated with several risk factors, increasingly driven by non-alcoholic steatohepatitis and metabolic syndrome. This association poses a challenge for the primary treatments of HCC, which may include immune checkpoint inhibitors and vascular endothelial growth factor inhibitors, due to their potential cardiotoxic effect. Therefore, it is imperative to balance the therapeutic effects of these agents with their potential cardiovascular adverse events.

Case Description: We describe the case of a man in his seventies with advanced HCC and significant cardiovascular comorbidities who was treated with atezolizumab and bevacizumab. Despite achieving a clinical and radiologic complete response, the patient experienced a deterioration in cardiac function after 16 months, necessitating the discontinuation of bevacizumab. The patient continued to respond well to atezolizumab, but unfortunately, he passed away due to a cardiac event after 4 years of follow-up.

Conclusions: Careful risk stratification and optimization of modifiable risk factors is of uttermost importance in management of HCC. Close monitoring, comprehensive patient management in a cardio-oncology clinic is also vital, particularly for patients at high risk of developing cardiovascular adverse events. The delicate balance between the efficacy of cancer treatments and their potential cardiotoxicity is one of the principal determinants of outcomes of patients diagnosed with HCC.

Keywords: Case report; cardiovascular toxicity; atezolizumab; bevacizumab; cardio-oncology

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Introduction

Hepatocellular carcinoma (HCC) is the most common liver malignancy (1). It ranks as the sixth most common cancer and the third leading cause of cancer-related mortality worldwide (2). HCC is closely related to chronic liver disease and liver cirrhosis which can be due to viral and non-viral causes including metabolic-associated steatohepatitis (MASH) and metabolic syndrome (1); conditions that have been linked to increased cardiovascular risks and liver-related mortality (3).

Advanced stage HCC necessitates systemic therapies. These include tyrosine kinase inhibitors (TKIs) monotherapies with sorafenib or lenvatinib, combination

therapies of vascular endothelial growth factor inhibitors (VEGFis) with immune checkpoint inhibitors (ICIs) with atezolizumab plus bevacizumab or cabozantinib, single agent VEGFi with ramucirumab, or dual ICI therapies with durvalumab and tremelimumab, or ipilimumab and nivolumab (1,4,5).

However, it is crucial to note that both VEGFi and ICI are classified as potentially cardiotoxic drugs (6). This emphasizes the critical need for preventive measures and close monitoring, especially in patients with cardiac comorbidities and metabolic syndrome. The management of these patients should be tailored to their individual risk profiles, balancing the potential benefits of treatment against the risk of cardiotoxicity. We present this case in accordance with the CARE reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-359/rc).

Case presentation

We present the case of a man in his seventies, treated at the American University of Beirut Medical Center, with known poorly controlled hypertension and diabetes mellitus type 2 and severe obesity (body mass index of 47 kg/m^2). The patient presented complaining of dyspnea on exertion, orthopnea, and decreased ambulation. His medical history also included peripheral artery disease, venous thromboembolism, stroke, and coronary artery disease treated with coronary artery bypass grafting (CABG) 3 years earlier. Patient experienced an acute heart failure due to triple vessel disease with a left ventricular ejection fraction (LVEF) of 20–25% which improved after CABG to 40–44%. His preoperative electrocardiogram showed a right bunch bundle block, ventricular extrasystoles, and T wave inversion in anterior leads. For treatment of cardiovascular comorbidities, the patient was receiving clopidogrel, bisoprolol, ramipril, and furosemide. The patient reported no significant alcohol intake and no family history of malignancy or sudden death.

On presentation, and part of the respiratory symptoms workup, a transthoracic echocardiography showed a mobile hyperechoic thrombus-like structure extending from the origin of the inferior vena cava and protruding into the right ventricle in diastole and global longitudinal strain (GLS) of –10.7% indicating that the patient was at an increased risk of cardiac toxicity from antineoplastic agents (7).

The patient was started on therapeutic anticoagulation for a presumed diagnosis of atrial thrombus. Computed tomography (CT) scan angiography was done for further assessment of the atrial mass which showed hypodense structure within the right atrium and a left hepatic lobe heterogeneous mass, in addition to multiple lung nodules. For further characterization of the liver mass, a magnetic resonance imaging (MRI) of the abdomen was done and demonstrated a 16-cm progressively enhancing liver mass in the left and caudate lobes, extending to segment VIII at the dome, narrowing the left portal and middle hepatic veins, occluding the left hepatic vein, and abutting the left and right hepatic arteries, in addition to prominent portacaval lymph nodes. A CT-guided biopsy of the liver mass demonstrated poorly differentiated HCC, with tumor tissue exhibiting diffuse and strong positivity for glypican-3, and no expression for HepPar-1, CK7, and TTF1. In summary, the patient was found to have a liver mass consistent with HCC, extending to the right atrium in addition to prominent portahepatic lymph nodes and lung nodules which makes the patient's Barcelona Clinic Liver Cancer stage C (BCLC-C) (8,9).

In anticipation of initiating systemic treatment with atezolizumab plus bevacizumab based on the

Highlight box

Key findings

- The combination of atezolizumab and bevacizumab for the treatment of a patient with hepatocellular carcinoma (HCC) and cardiovascular comorbidities led to complete radiological response but was associated with decrease in left ventricular ejection fraction necessitating discontinuation of bevacizumab. The patient maintained the good response on atezolizumab monotherapy until he passed away due to a presumed cardiac event.

What is known and what is new?

- Treatment of HCC may include the use of vascular endothelial growth factors inhibitors and immune checkpoint inhibitors (ICIs) which carry substantial risks of cardiotoxicity, especially in patients with pre-existing cardiovascular conditions.
- The patient maintained a good response on atezolizumab monotherapy. Patient later passed away for presumed cardiovascular event. Patient's death may be due to accelerated atherosclerosis secondary to ICIs which is shown only in pre-clinical models.

What is the implication, and what should change now?

- A thorough cardiovascular risk assessments and multidisciplinary management in HCC patients is critically needed. Personalized treatment strategies, with a focus on minimizing cardiotoxic risks, should be prioritized. Additionally, further research is necessary to explore the clinical relevance of accelerated atherosclerosis associated with ICIs.

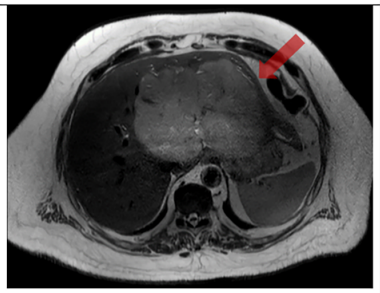
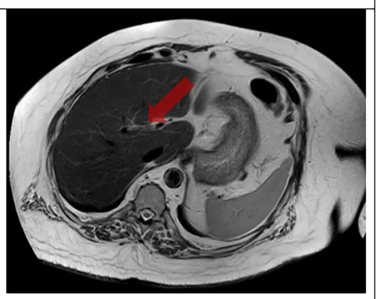
Time	At diagnosis	After 5 cycles	After 51 cycles
Liver lesion on MRI			
Tumor size	15.7 cm × 11.3 cm × 9.1 cm	7.0 cm × 4.6 cm × 3.3 cm	No suspicious hepatic lesion

Figure 1 Sequential MRI of the abdomen demonstrating reduction in hepatocellular carcinoma tumor size during treatment. Red arrow indicates the location of the tumor. The length of each cycle is 21 days. MRI, magnetic resonance imaging.

IMbrave150 clinical trial (10), the patient underwent an esophagogastroduodenoscopy to rule out esophageal varices. Furthermore, since the findings of echocardiography were in favor of a tumor thrombus rather than thrombosis, the previously prescribed anticoagulants were discontinued. After initiation of cancer systemic therapy with atezolizumab and bevacizumab, both given every 21 days, serial imaging demonstrated good response to treatment as per the Response Evaluation Criteria in Solid Tumors (RECIST) criteria (*Figure 1*) (11,12). Alpha-fetoprotein (AFP) decreased from 346.9 to 11.8 IU/mL after the first cycle of atezolizumab and bevacizumab and further decreased to 1.8 IU/mL after the fifth cycle and remained in that range (the trend of AFP is illustrated in Figure S1).

A year and a half later, the patient reported exertional dyspnea, with a drop in the LVEF on echocardiography to 35–39% (GLS: −12.1%). Since bevacizumab is known to cause cardiac dysfunction, and in the absence of any other explanation for the drop in LVEF, the decision was to discontinue the medication. The patient did not complain of any other symptom and did not follow up with his cardiologic, ultimately no other interventions were made. After completing 22 cycles of combination therapy with atezolizumab and bevacizumab, the patient continued on atezolizumab as monotherapy, despite the lack of the proof of evidence of efficacy.

With the discontinuation of bevacizumab and no other interventions, a follow-up echocardiography 5 months later showed an improvement of LVEF to 45–49%. With this improvement, bevacizumab was reintroduced for 2 cycles, but was ultimately discontinued due to the persistence of heart failure symptoms.

With continuation of single agent atezolizumab, tumor continued to show evident response. Three years later, patient passed away in sleep due to a presumed cardiovascular event resulting in cardiopulmonary arrest. All procedures performed in this study were in accordance with the ethical standards of the institutional research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent for publication of this case report and accompanying images was not obtained from the patient or the relatives after all possible attempts were made.

Discussion

Our case herein provides special insights into the critical role of cardiac interactions with modern oncologic therapies for patients with HCC, particularly those with a high risk of cardiovascular toxicity.

The patient under discussion was considered at a very high risk for VEGFi-related cardiotoxicity, given his history of arterial vascular disease and heart failure, which are both very high-risk factors, as well as other cardiotoxicity risk factors related to VEGFi (13). These factors are summarized in Table S1. He also experienced a drop in ejection fraction from 40–44% to 35–39% within 18 months while receiving bevacizumab, with consistently low GLS values since diagnosis. Cardiac deterioration coincided with treatment with bevacizumab, which was

eventually suspended.

The cardiovascular side effects vary with the cancer medication class, with some differences seen within the same class, some drugs being more cardiotoxic than others (*Table 1*). Each of atezolizumab and bevacizumab, which the patient was receiving, have a distinct cardiotoxicity profile. Bevacizumab is more likely to cause hypertension, arterial and venous thromboembolism, heart failure, myocardial infarction, and hemorrhage-related clinical events, while atezolizumab is more associated with immune-related side effects such as myocarditis (potentially fatal), pericarditis, vasculitis, and respiratory failure (22). Additionally, immune check point inhibitors cause accelerated atherosclerosis. In preclinical models, immune checkpoint proteins inhibit the progression of atherosclerosis (24), while ICIs cause activation of T-lymphocytes which leads to endothelial inflammation and dysfunction, and eventually causing microvascular disease which manifests as ischemic stroke, myocardial infarction or peripheral arterial disease (25,26). Management of ICI-associated atherosclerosis is currently being investigated and several medications including statins and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors are currently undergoing trials (26). Despite the overall decrease in the use of CABG, however, in patients with malignancy specifically, there is an increase (27). Furthermore, our patient previously underwent coronary artery bypass using vein grafts. To date, there are no clinical trials to evaluate the effects of ICIs in patients with vein grafts, however preclinical data indicate the role of inflammation and immunomodulation in vein graft failure (28).

According to the European Society of Cardiology (ESC) guidelines, a patient who suffers from symptomatic or asymptomatic cardiac dysfunction during cancer treatment often continue to experience early survivorship complications (<5 years after cancer therapy). GLS is used to predict subclinical cardiac dysfunction in patients receiving antineoplastic agents before the development of clinical symptoms. A normal GLS mean ranges from –18.8% to –22.7% (29). A decrease in GLS (absolute value) by 15% is indicative of subclinical ventricular dysfunction (7,29). The leading cause of cardiac death in patients taking the combination atezolizumab and bevacizumab is a thromboembolic event (22), which may be attributed to patient-related factors (age, obesity, cardiovascular comorbidities), cancer itself, and cancer treatment. Atezolizumab monotherapy can lead to an increased risk of mortality by respiratory failure compared to bevacizumab monotherapy or the combination of atezolizumab with bevacizumab. Therefore, it is important to tailor cancer treatment to maximize the potential benefit while reducing concomitant risk, and if appropriate, to give less cardiotoxic cancer treatment regimens.

Upon initiation of any potentially cardiotoxic drug, patients should be stratified as per their baseline risk of cardiotoxicity. The Heart Failure Association of the European Society of Cardiology cardio-oncology study group, in collaboration with the International Cardio-Oncology Society (HFA-ICOS), developed tools to stratify oncology patients into different risk categories (low risk, medium risk, high risk, and very high risk) based on the planned therapy and patient-related factors contributing to cardiovascular risk (13). These tools cover seven classes of cardiotoxic cancer treatments, allowing for a personalized approach to surveillance and management.

These baseline risk categories guide prevention and surveillance strategies. The ESC cardio-oncology guidelines of 2022 offer recommendations on cardiac surveillance to prevent cancer treatment-related cardiovascular toxicities (6). This includes clinical cardiovascular assessment (physical examination, blood pressure monitoring, lipids, glycosylated hemoglobin HbA1c, etc.), electrocardiography, echocardiography assessing the LVEF and, if possible, the GLS, and biomarkers (cardiac troponin, brain natriuretic peptide) at baseline and regularly during the disease course based on the treatment given and patient's risk level (*Table 2*). Patients with elevated cardiovascular risk require optimization of modifiable risk factors and close monitoring with cardiac imaging, serial electrocardiograms, and sequential biomarker assessment to predict and have early detection of cardiotoxicity.

With the increasing global prevalence of non-viral causes of HCC, such as MASH, and given that an elevated body mass index has been associated with a greater risk of thrombosis with the use of bevacizumab, careful patient selection is of critical importance (30,31). For patients at an increased risk of thrombosis, regimens that do not include anti-vascular endothelial growth factor (VEGF) therapies should be considered. The combination of durvalumab and tremelimumab is currently approved for first-line treatment of advanced HCC, but it is worth noting that the HIMALAYA trial was not published when our patient was initially diagnosed and initiated therapy (20).

Of note, the patient maintained a good response to atezolizumab monotherapy despite discontinuing bevacizumab. Although the estimated half-life of bevacizumab is around 20 days (with a range from 11 to

Table 1 Cardiovascular toxicities of first and second-line treatment modalities for hepatocellular carcinoma (6)

Category	Drug name	Monotherapy or bitherapy (name of trial)	Cardiovascular toxicities
VEGFi—monoclonal antibodies	Bevacizumab	In combination with atezolizumab—1st line (IMbrave150) (10)	HTN, VTE: +++; HF, ATE: ++; MI: +/–
	Ramucirumab	Monotherapy—2nd line (REACH-2) (14)	HTN: +++; ATE: ++; MI: +/–
VEGFi—TKI targeting VEGF receptors	Sorafenib	Monotherapy—1st line (SHARP) (15)	HTN: +++; HF, MI: ++; ↑ QTc: +/–
	Lenvatinib	Monotherapy—1st line (REFLECT) (16)	HTN: +++; HF, ↑ QTc, ATE, MI: ++
	Regorafenib	Monotherapy—2nd line (RESORCE) (17)	HTN: +++; HF, ATE, MI: +
	Cabozantinib	Monotherapy—2nd line (CELESTIAL) (18)	HTN: +++; ↑ QTc, VTE, ATE: ++; HF, MI: +
		In combination with atezolizumab—2nd line (COSMIC-312) (19)	
Immune checkpoint Inhibitors	Atezolizumab	In combination with bevacizumab—1st line (IMbrave150) (10)	Myocarditis, arrhythmia (Afib, VT/SVT): + to ++ (frequency 0.2–2%, but both can be fatal); pericarditis, HF, vasculitis: +; VTE, MI, Takotsubo: +/–; ICI cardiotoxicity increase, with dual ICI or in combination with other cardiotoxic agent
		In combination with cabozantinib—2nd line (COSMIC-312) (19)	
	Durvalumab	Monotherapy—1st line (HIMALAYA) (20)	
		In combination with tremelimumab—1st line (HIMALAYA) (20)	
	Tremelimumab	In combination with durvalumab—1st line (HIMALAYA) (20)	
	Pembrolizumab	Monotherapy—2nd line (KEYNOTE-224) (21)	
	Nivolumab	In combination with ipilimumab—2nd line (CheckMate-040) (22)	
	Ipilimumab	In combination with nivolumab—2nd line (CheckMate-040) (23)	

+++, very common, incidence ≥10%; ++, common, incidence 1–10%; +, uncommon, incidence 0.1–<1%; +/–, rare, incidence <0.1%. ↑: prolongation. VEGFi, vascular endothelial growth factor inhibitor; HTN, hypertension; VTE, venous thromboembolism; HF, heart failure; ATE, arterial thromboembolism; MI, myocardial infarction; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor; QTc, corrected QT interval; Afib, atrial fibrillation; VT, ventricular tachyarrhythmia; SVT, supraventricular tachyarrhythmia; ICI, immune checkpoint inhibitor.

50 days) (32), the patient's response to atezolizumab as single agent was sustained until his death 6 months after the last administered dose of bevacizumab. This observation highlights the importance of treatment regimens devoid of anti-VEGF (which consist of single agent ICI or double ICI) especially in patients with cardiovascular risk factors (5,20,33). To date, no study has investigated atezolizumab as monotherapy.

ICI cardiotoxicity increases when given as dual ICI therapy or when combined with another cardiotoxic agent like VEGFi (34,35). Therefore, it would be prudent to further assess the responses on ICI monotherapies. Moreover, only a few studies have evaluated predictive biomarkers for ICI in HCC, including programmed death-ligand 1 (PD-L1) expression, immune-related gene signatures, tumor mutational burden, and platelet-lymphocyte ratio (36). This area merits further investigation to identify patients who would benefit most from immunotherapy.

This study serves as a real-world example of a patient diagnosed with HCC. It emphasizes the importance of early recognition and follow up of cardiovascular adverse events that are associated with the treatment, in a population that likely has a baseline of cardiovascular comorbidities at diagnosis. It also asserts the importance of individualized approach to treatment and the need for multidisciplinary care. Furthermore, it shows the potential benefit of single agent immunotherapy for treatment of HCC. Its limitation lies in being based on a single case of a patient with metabolic syndrome and MASH, resulting in inability of generalizability to include patients with HCC due to other etiologies such as viral hepatitis. Additionally, its retrospective nature along with being based on a single study, leads to a lack of statistical power and insufficiency to establish causality.

Conclusions

This case highlights the critical importance of cardiovascular risk assessment in HCC patients before initiating cancer

Table 2 ESC guidelines on cardiovascular surveillance for patients undergoing VEGFi or ICI treatment, based on risk stratification (6)

Cardiac assessment modality	VEGFi		ICI	
	Baseline	Follow-up	Baseline	Follow-up
CV assessment				
Low risk	BP monitoring at every clinical visit [I-C]. Daily home monitoring of BP: 1st cycle, when increasing antineoplastic therapy dose, every 2–3 weeks thereafter [I-C]		Yes [I-B]	Every 3 cycles (until treatment completion) [I-C]→every 6–12 months [IIb-C]
Moderate risk			–	–
High risk			Yes [I-B]	Every 3 cycles (until treatment completion) [I-C]→every 6–12 months [I-C]
ECG				
Low risk	Yes [I-C]	–	Yes [I-B]	C2, C3, C4, every 3 cycles [IIa-B]→every 6–12 months [IIb-C]
Moderate risk	Yes [I-C]	Monthly first 3 months [I-C]→every 3–6 months [I-C]	–	–
High risk	Yes [I-C]	Monthly first 3 months [I-C]→every 3–6 months [I-C]	Yes [I-B]	C2, C3, C4, every 3 cycles [IIa-B]→every 6–12 months [I-C]
TTE				
Low risk	Yes [IIa-C]	–	Yes [IIb-C]	–
Moderate risk	Yes [IIa-C]	Every 4 months for 1 year [IIb-C] →every 6–12 months [IIa-C]	–	–
High risk	Yes [I-C]	Every 3 months for 1 year [IIa-C] →every 6–12 months [IIa-C]	Yes [I-B]	–
cTn				
Low risk	–	–	Yes [I-B]	C2, C3, C4, every 3 cycles [IIa-B]
Moderate risk	–	–	–	–
High risk	–	–	Yes [I-B]	C2, C3, C4, every 3 cycles [IIa-B]
NP				
Low risk	–	–	Yes [I-B]	Every 6–12 months [IIb-C]
Moderate risk	Yes [IIb-C]	Every 4 months for 1 year [IIb-C]	–	–
High risk	Yes [IIa-C]	Every 4 weeks→every 3 months for 1 year [IIa-C]	Yes [I-B]	Every 6–12 months [I-C]

The cycle length differs according to the agents being used. I: class I; IIa: class IIa; IIb: class IIb; B: level B; C: level C. ESC, European Society of Cardiology; VEGFi, vascular endothelial growth factor inhibitor; ICI, immune checkpoint inhibitor; CV, cardiovascular; BP, blood pressure; ECG, electrocardiography; C2, cycle 2; C3, cycle 3; C4, cycle 4; TTE, transthoracic echocardiography; cTn, cardiac troponin; NP, natriuretic peptide.

treatment and vigilant cardiovascular monitoring within a multidisciplinary cardio-oncology setting during the disease course, especially for high-risk patients. It also emphasizes the necessity of balancing the effectiveness of cancer treatment with its potential cardiotoxicity. Furthermore, this study encourages additional research into the efficacy of ICI monotherapy and the identification of predictive biomarkers for ICI to tailor treatment strategies for patients with HCC, enhancing their clinical outcomes.

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Footnote

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Peer Review File: Available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-359/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-359/coif). P.S. reports that he is the owner of Ladprao General Hospital with stock less than 5%. J.S. reports receiving consulting fee from Paige AI and having professional activities in Paige AI. G.K.A.A. reports receiving research grant support from Agenus, Arcus, Astra Zeneca, BioNtech, BMS, Elicio, Genentech/Roche, Helsinn, Parker Institute, Pertzye, Puma, QED, Servier, and Yiviva, and consulting support from Abbvie, Alligator Astra Zeneca, Autem, Berry Genomics, BioNtech, Boehringer Ingelheim, BMS, Eisai, Exelixis, Genentech/Roche, Incyte, Ipsen, J-Pharma, Merck, Merus, Neogene, Novartis, Servier, Tango, Tempus, Vector, and Yiviva. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent for publication of this case report and accompanying images was not obtained from the patient or the relatives after all possible attempts were made.

References

1. Vogel A, Meyer T, Sapisochin G, et al. Hepatocellular carcinoma. Lancet 2022;400:1345-62.
2. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin 2021;71:209-49.
3. Konyn P, Ahmed A, Kim D. Causes and risk profiles of mortality among individuals with nonalcoholic fatty liver disease. Clin Mol Hepatol 2023;29:S43-57.
4. National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology: Hepatocellular Carcinoma. Version 2. 2023.
5. Galle PR, Decaens T, Kudo M, et al. Nivolumab (NIVO) plus ipilimumab (IPI) vs lenvatinib (LEN) or sorafenib (SOR) as first-line treatment for unresectable hepatocellular carcinoma (uHCC): First results from CheckMate 9DW. J Clin Oncol 2024;42:abstr LBA4008.
6. Lyon AR, López-Fernández T, Couch LS, et al. 2022 ESC Guidelines on cardio-oncology developed in collaboration with the European Hematology Association (EHA), the European Society for Therapeutic Radiology and Oncology (ESTRO) and the International Cardio-Oncology Society (IC-OS). Eur Heart J 2022;43:4229-361.
7. Oikonomou EK, Kokkinidis DG, Kampaktsis PN, et al. Assessment of Prognostic Value of Left Ventricular Global Longitudinal Strain for Early Prediction of Chemotherapy-Induced Cardiotoxicity: A Systematic Review and Meta-analysis. JAMA Cardiol 2019;4:1007-18.
8. Amin MB, Greene FL, Edge SB, et al. The Eighth Edition AJCC Cancer Staging Manual: Continuing to build a bridge from a population-based to a more "personalized" approach to cancer staging. CA Cancer J Clin 2017;67:93-9.
9. Llovet JM, Brú C, Bruix J. Prognosis of hepatocellular carcinoma: the BCLC staging classification. Semin Liver Dis 1999;19:329-38.
10. Finn RS, Qin S, Ikeda M, et al. Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma. N Engl J Med 2020;382:1894-905.

11. Lencioni R, Llovet JM. Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. Semin Liver Dis 2010;30:52-60.
12. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228-47.
13. Lyon AR, Dent S, Stanway S, et al. Baseline cardiovascular risk assessment in cancer patients scheduled to receive cardiotoxic cancer therapies: a position statement and new risk assessment tools from the Cardio-Oncology Study Group of the Heart Failure Association of the European Society of Cardiology in collaboration with the International Cardio-Oncology Society. Eur J Heart Fail 2020;22:1945-60.
14. Zhu AX, Kang YK, Yen CJ, et al. Ramucirumab after sorafenib in patients with advanced hepatocellular carcinoma and increased α-fetoprotein concentrations (REACH-2): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol 2019;20:282-96.
15. Llovet JM, Ricci S, Mazzaferro V, et al. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 2008;359:378-90.
16. Kudo M, Finn RS, Qin S, et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. Lancet 2018;391:1163-73.
17. Bruix J, Qin S, Merle P, et al. Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 2017;389:56-66.
18. Abou-Alfa GK, Meyer T, Cheng AL, et al. Cabozantinib in Patients with Advanced and Progressing Hepatocellular Carcinoma. N Engl J Med 2018;379:54-63.
19. Kelley RK, Rimassa L, Cheng AL, et al. Cabozantinib plus atezolizumab versus sorafenib for advanced hepatocellular carcinoma (COSMIC-312): a multicentre, open-label, randomised, phase 3 trial. Lancet Oncol 2022;23:995-1008.
20. Abou-Alfa GK, Lau G, Kudo M, et al. Tremelimumab plus Durvalumab in Unresectable Hepatocellular Carcinoma. NEJM Evid 2022;1:EVIDoa2100070.
21. Zhu AX, Finn RS, Edeline J, et al. Pembrolizumab in patients with advanced hepatocellular carcinoma previously treated with sorafenib (KEYNOTE-224): a non-randomised, open-label phase 2 trial. Lancet Oncol 2018;19:940-52.
22. Niimura T, Goda M, Miyata K, et al. Evaluation of cardiovascular toxicity of the atezolizumab and bevacizumab combination. Front Drug Saf Regul 2023;3:1213771.
23. Yau T, Kang YK, Kim TY, et al. Efficacy and Safety of Nivolumab Plus Ipilimumab in Patients With Advanced Hepatocellular Carcinoma Previously Treated With Sorafenib: The CheckMate 040 Randomized Clinical Trial. JAMA Oncol 2020;6:e204564.
24. Piras L, Zuccanti M, Russo P, et al. Association between Immune Checkpoint Inhibitors and Atherosclerotic Cardiovascular Disease Risk: Another Brick in the Wall. Int J Mol Sci 2024;25:2502.
25. Inno A, Chiampan A, Lanzoni L, et al. Immune Checkpoint Inhibitors and Atherosclerotic Vascular Events in Cancer Patients. Front Cardiovasc Med 2021;8:652186.
26. Jo W, Won T, Daoud A, et al. Immune checkpoint inhibitors associated cardiovascular immune-related adverse events. Front Immunol 2024;15:1340373.
27. Guha A, Dey AK, Kalra A, et al. Coronary Artery Bypass Grafting in Cancer Patients: Prevalence and Outcomes in the United States. Mayo Clin Proc 2020;95:1865-76.
28. Baganha F, de Jong A, Jukema JW, et al. The Role of Immunomodulation in Vein Graft Remodeling and Failure. J Cardiovasc Transl Res 2021;14:100-9.
29. Plana JC, Galderisi M, Barac A, et al. Expert consensus for multimodality imaging evaluation of adult patients during and after cancer therapy: a report from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr 2014;27:911-39.
30. Toh MR, Wong EYT, Wong SH, et al. Global Epidemiology and Genetics of Hepatocellular Carcinoma. Gastroenterology 2023;164:766-82.
31. Vithayathil M, D'Alessio A, Fulgenzi CAM, et al. Impact of body mass index in patients receiving atezolizumab plus bevacizumab for hepatocellular carcinoma. Hepatol Int 2023;17:904-14.
32. Lu JF, Bruno R, Eppler S, et al. Clinical pharmacokinetics of bevacizumab in patients with solid tumors. Cancer Chemother Pharmacol 2008;62:779-86.
33. Qin S, Kudo M, Meyer T, et al. Tislelizumab vs Sorafenib as First-Line Treatment for Unresectable Hepatocellular Carcinoma: A Phase 3 Randomized Clinical Trial. JAMA Oncol 2023;9:1651-9.
34. Inno A, Veccia A, Madonia G, et al. Risk of cardiovascular toxicity with combination of immune-checkpoint inhibitors and angiogenesis inhibitors: a meta-analysis.

Front Cardiovasc Med 2024;11:1309100.
35. Rubio-Infante N, Ramírez-Flores YA, Castillo EC, et al. Cardiotoxicity associated with immune checkpoint inhibitor therapy: a meta-analysis. Eur J Heart Fail 2021;23:1739-47.
36. Ji JH, Ha SY, Lee D, et al. Predictive Biomarkers for Immune-Checkpoint Inhibitor Treatment Response in Patients with Hepatocellular Carcinoma. Int J Mol Sci 2023;24:7640.

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