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CARDIONCOLOGIA: UPDATE 2022. Parte II

TERAPIA CON CHECK- POINT INIBITORI E CAR-T: LE COSE ESSENZIALI CHE UN CARDIOLOGO DEVE SAPERE

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outline

- Immune checkpoint inhibitors: what, who, how (mechanisms of cardiovascular toxicity)
- CAR-T cell: what, who, how (mechanisms of cardiovascular toxicity)
- Cardiovascular management according to the latest ESC/EHA/ESTRO/IC-OS guidelines on cardio-oncology

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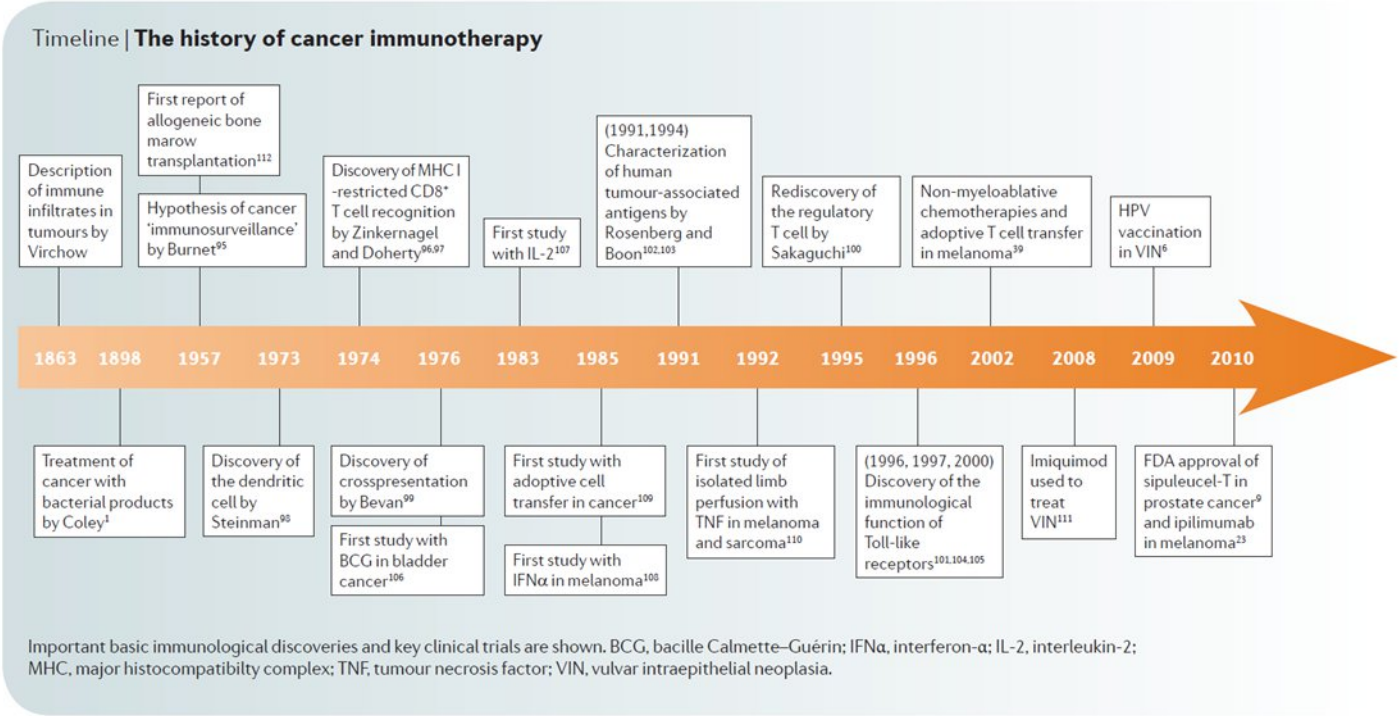

Lesterhuis WJ, et al. *Nat Rev Drug Discov* 2011

Discovery of cancer therapy by inhibition of negative immune regulation

Nobel Prizes & Laureates | Nomination | Alfred Nobel | News & insights | Events | Educational

Medicine | The Nobel Prize in Physiology or Medicine 2018 | Summary

The Nobel Prize in Physiology or Medicine 2018

James P. Allison
Tasuku Honjo

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The Nobel Prize in Physiology or Medicine 2018

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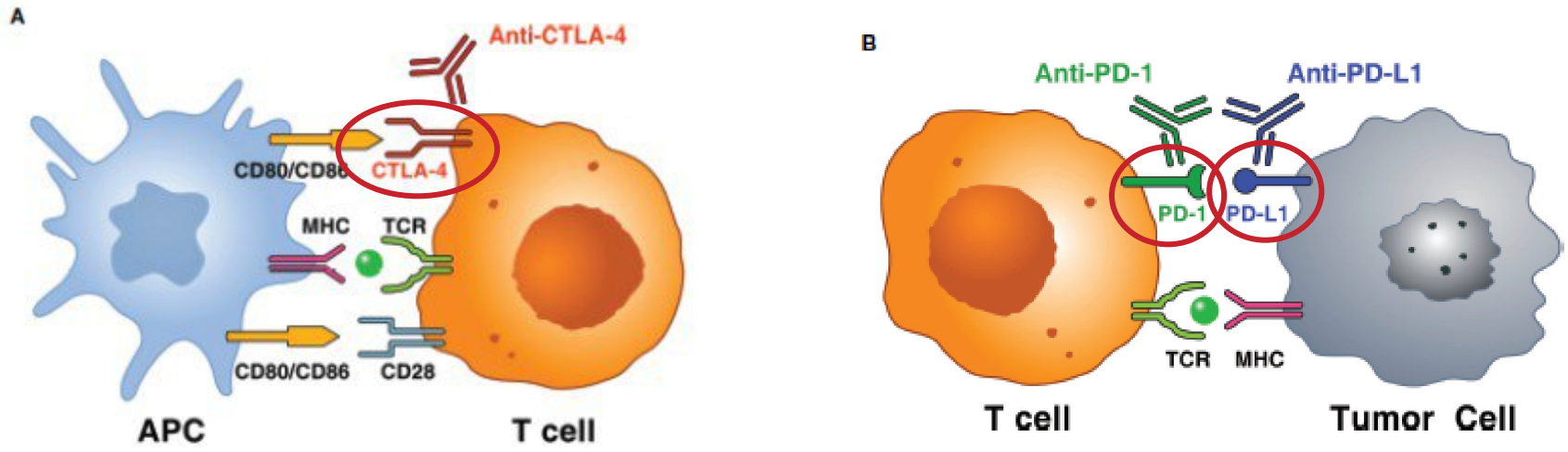
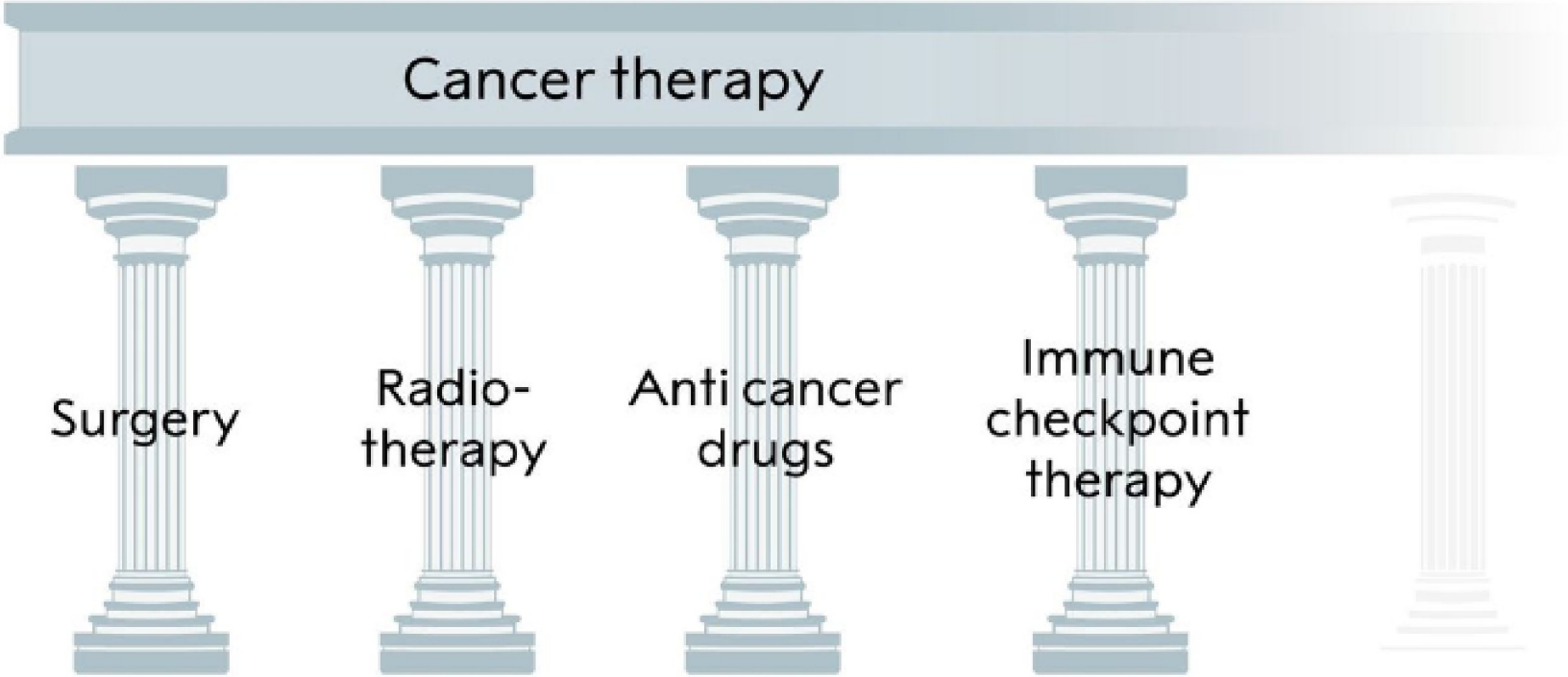
Immune mechanisms of immune checkpoints and immune checkpoint inhibitors



Poto R, et al. *Front Immunol* 2022

Molecular target	Indication according to FDA label



FDA=US Food and Drug Administration.

Lyon AR, et al. Lancet Oncol 2018

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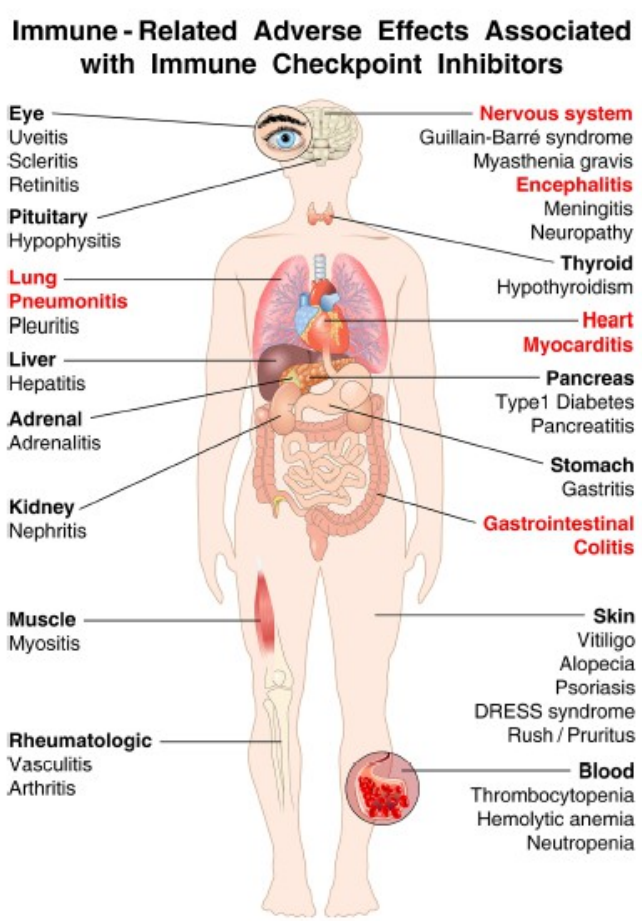
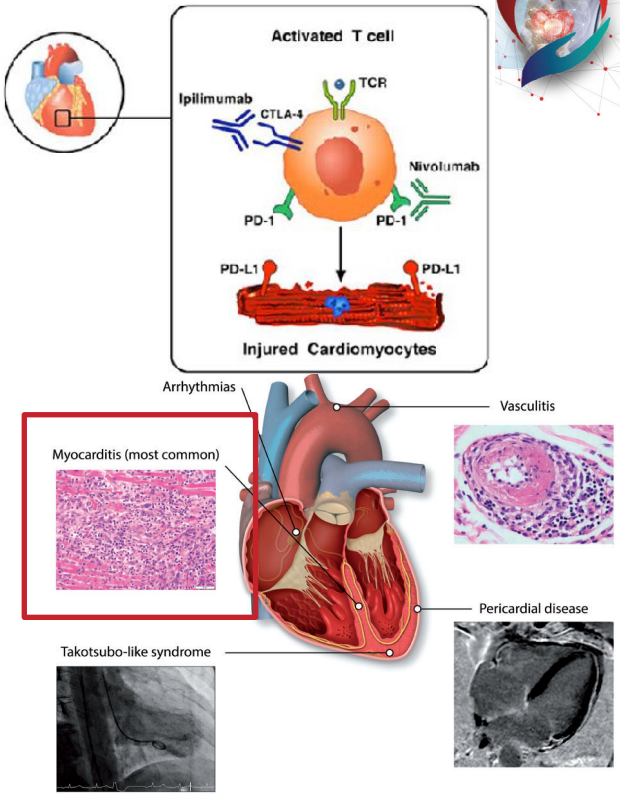
	Anti CTLA-4	Anti PDL-1/PD-1
Skin	43-45%	34%
Digestive system	32-54%	5-10%
Endocrine system	5-10%	5-10%
Pneumonia		2-4%
Nephritis	2-5%	
Neurologic toxicity	1-12%	
Myocarditis	1.14%	





Hu JR, et al. *Cardiovasc Res* 2019
Varricchi G, et al. *Circulation* 2017
Poto R, et al. *Front Immunol* 2022

ICI myocarditis (either pathohistological diagnosis or clinical diagnosis)	
Pathohistological diagnosis (EMB)	Multifocal inflammatory cell infiltrates with overt cardiomyocyte loss by light microscopy
Clinical diagnosis[d]	**cTn elevation** (new or significant change from baseline)[e] **with 1 major criterion or 2 minor criteria,** after exclusion of ACS and acute infectious myocarditis based on clinical suspicion[f]
	Major criterion: • CMR diagnostic for acute myocarditis (modified Lake Louise criteria)[g]
	Minor criteria: • Clinical syndrome (including any one of the following: fatigue, myalgias, chest pain, diplopia, ptosis, shortness of breath, orthopnoea, lower-extremity oedema, palpitations, light-headedness/dizziness, syncope, muscle weakness, cardiogenic shock) • Ventricular arrhythmia (including cardiac arrest) and/or new conduction system disease • Decline in LV systolic function, with or without regional wall motion abnormalities in a non-Takotsubo pattern • Other immune-related adverse events, particularly myositis, myopathy, myasthenia gravis • Suggestive CMR[h]
Severity of myocarditis	• **Fulminant:** Haemodynamic instability, HF requiring non-invasive or invasive ventilation, complete or high-grade heart block, and/or significant ventricular arrhythmia • **Non-fulminant:** including symptomatic but haemodynamically and electrically stable patients and incidental cases diagnosed at the same time as other immuno-related adverse events. Patients may have reduced LVEF but no features of severe disease • **Steroid refractory**: non-resolving or worsening myocarditis (clinical worsening or persistent troponin elevation after exclusion of other aetiologies) despite high-dose methylprednisolone
Recovery from myocarditis	• **Complete recovery**: Patients with complete resolution of acute symptoms, normalization of biomarkers, and recovery of LVEF after discontinuation of immunosuppression. CMR may still show LGE or elevated T1 due to fibrosis, but any suggestion of acute oedema should be absent • **Recovering**: Ongoing improvement in patient clinical symptoms, signs, biomarkers, and imaging parameters, but not yet normalized, while on tapering doses of immunosuppression

Lyon AR, Lopez-Fernandez T, et al. *Eur Heart J* 2022

Table 1 Cancer therapy classes identified for cardiovascular baseline risk assessment and associated cardiovascular toxicity

Cancer treatment class	Cancer indication	Treatment-related CV toxicity
		Hypertension
Immune checkpoint inhibitors:	Melanoma (metastatic and adjuvant)	Myocarditis including fulminant myocarditis
anti-programmed cell death 1 inhibitors (nivolumab, pembrolizumab)	Metastatic renal cancer, non-small cell lung cancer, small cell lung cancer, refractory Hodgkin's lymphoma, metastatic triple negative breast cancer, metastatic urothelial cancer, liver cancer, MMR-deficient cancer	Pericarditis
		Non-inflammatory heart failure
		Ventricular arrhythmias
anti-cytotoxic T-lymphocyte-associated protein 4 inhibitor (ipilimumab)		AV block
anti-programmed death-ligand 1 inhibitors (avelumab, atezolizumab, durvalumab)		Acute coronary syndromes including atherosclerotic plaque rupture and vasculitis

Lyon AR, Lopez-Fernandez T, et al. *Eur Heart J* 2022

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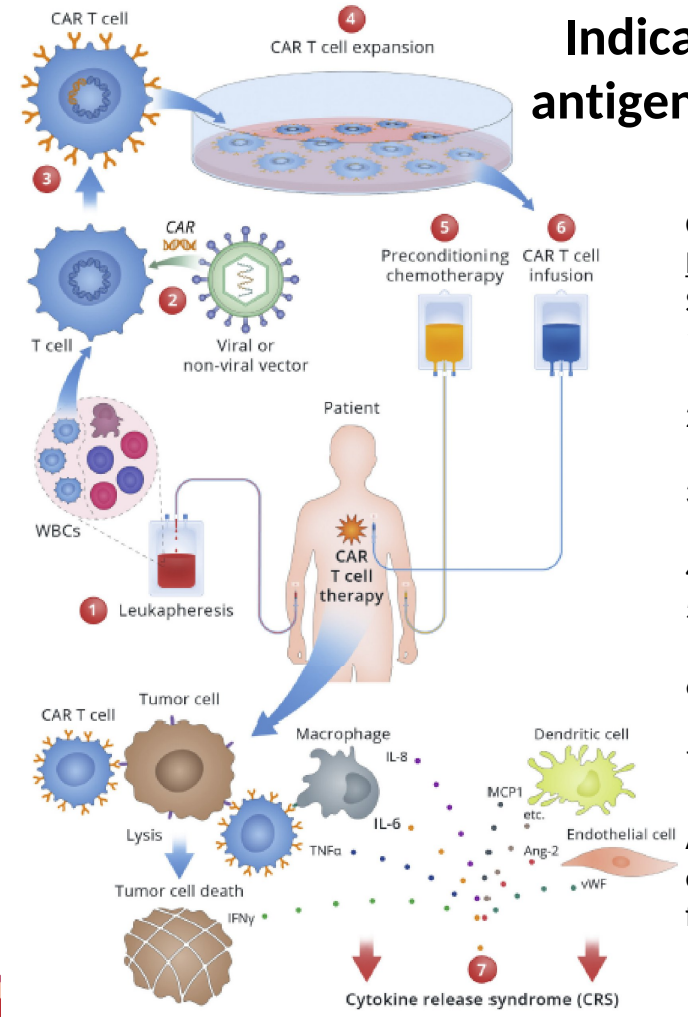
Indication and stepwise mechanism of chimeric antigen receptor (CAR) T-cell therapy and cytokine release syndrome (CRS)



CAR-T therapy is used for the treatment of acute lymphocytic leukaemia and aggressive B-cell lymphomas.

Stepwise mechanism of action:

1. White blood cells (WBC) are drawn from the patient via leukapheresis. T cells are then separated in the lab.
2. T cells are genetically modified or “engineered” with viral or nonviral vector inserting a gene encoding a CAR into the T cells.
3. Engineered T cells, now known as CAR T cells, can recognize and attach to the specific antigen on the cancer cells.
4. CAR T cells are grown and multiplied in the bioreactor to create millions of copies.
5. Before the CAR T cells are administered, the patient receives pre-conditioning chemotherapy to lower the cell count to allow space for the incoming CAR T cells.
6. CAR T cells are infused back into the patient’s blood where they proliferate, detect, and destroy the tumor cells.
7. CRS occurs as a result of the supraphysiologic levels of inflammatory cytokines released by the activated CAR T cells and other immune cells such as macrophages.

Ang-2 = angiopoietin 2; IL = interleukin; IFN-g = interferon gamma; MCP1 = monocyte chemoattractant protein 1; TNF-a = tumor necrosis factor alpha; vWF = von Willebrand factor

Ganatra S, et al. *J Am Coll Cardiol* 2019

CAR-T cell therapy-related cytokine release syndrome (CRS)

TABLE 1 Clinical Manifestation of CRS-Related Toxicities

Organ System	Manifestation
Constitutional	Fever, malaise, fatigue, anorexia, arthralgias
Cardiovascular	Tachycardia, widened pulse pressure, hypotension or shock or both, arrhythmias, pulmonary edema, decreased LV ejection fraction, troponinemia, QT prolongation
Renal	Acute kidney injury, tumor lysis syndrome
Pulmonary	Hypoxia, pulmonary edema
Hepatic	Transaminitis
Hematologic	Anemia, thrombocytopenia, coagulopathy

Some of the toxicities may in part be attributed to the lymphodepletion regimen used prior to chimeric antigen receptor T-cell infusion and to acute volume changes.
CRS = cytokine release syndrome; LV = left ventricle.

TABLE 2 Incidence of CRS and CV Complications in Pivotal Trials

Clinical Trial (Ref. #)	Type of Cancer	Type of CAR T-Cell Therapy	CRS (%)	MI	Cardiac Arrest	Cardiac Failure	Death Due to CRS
JULIET (12)	Relapsed or refractory diffuse large B-cell lymphoma	Tisagenlecleucel	64/111 (58.0)	None	None	No report	None
ELIANA (10)	Relapsed or refractory B-cell lymphoblastic leukemia	Tisagenlecleucel	58/75 (77.0)	None	3 (4.0)	2 (2.7)	None
ZUMA-1 (11)	Refractory large B-cell lymphoma	Axicabtagene ciloleucel	94/101 (93.0)	None	1 (1.0)	No report	1 (1.0); same patient as cardiac arrest

Values are n/N (%) or n patients (%).
CAR = chimeric antigen receptor; CRS = cytokine release syndrome; CV = cardiovascular; ELIANA = Determine Efficacy and Safety of CTL019 in Pediatric Patients With Relapsed and Refractory B-Cell ALL and High Risk B-Cell ALL at First Relapse: Determine Feasibility and Safety of CTL019 Therapy in Pediatric Patients With High-Risk B-Cell ALL That Relapsed <6 Months Post All-HSCT; JULIET = Study of Efficacy and Safety of CTL019 in Adult DLBCL Patients; MI = myocardial infarction; ZUMA-1 = Safety and Efficacy of KTE-C19 in Adults With Refractory Aggressive Non-Hodgkin Lymphoma.

Ganatra S, et al. *J Am Coll Cardiol* 2019

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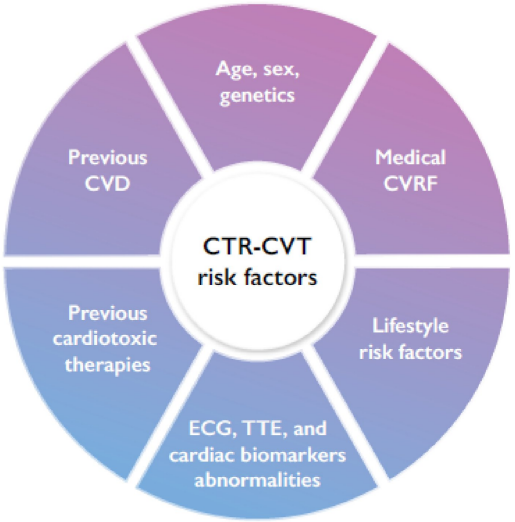
ESC European Society of Cardiology
European Heart Journal (2022) 00, 1–133
https://doi.org/10.1093/eurheartj/ehac244

ESC GUIDELINES

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)

Developed by the task force on cardio-oncology of the European Society of Cardiology (ESC)

Baseline CV toxicity risk assessment checklist



Clinical assessment

- Cancer treatment history
- CV history
- CVRF
- Physical examination
- Vital signs measurement[a]

Complementary tests

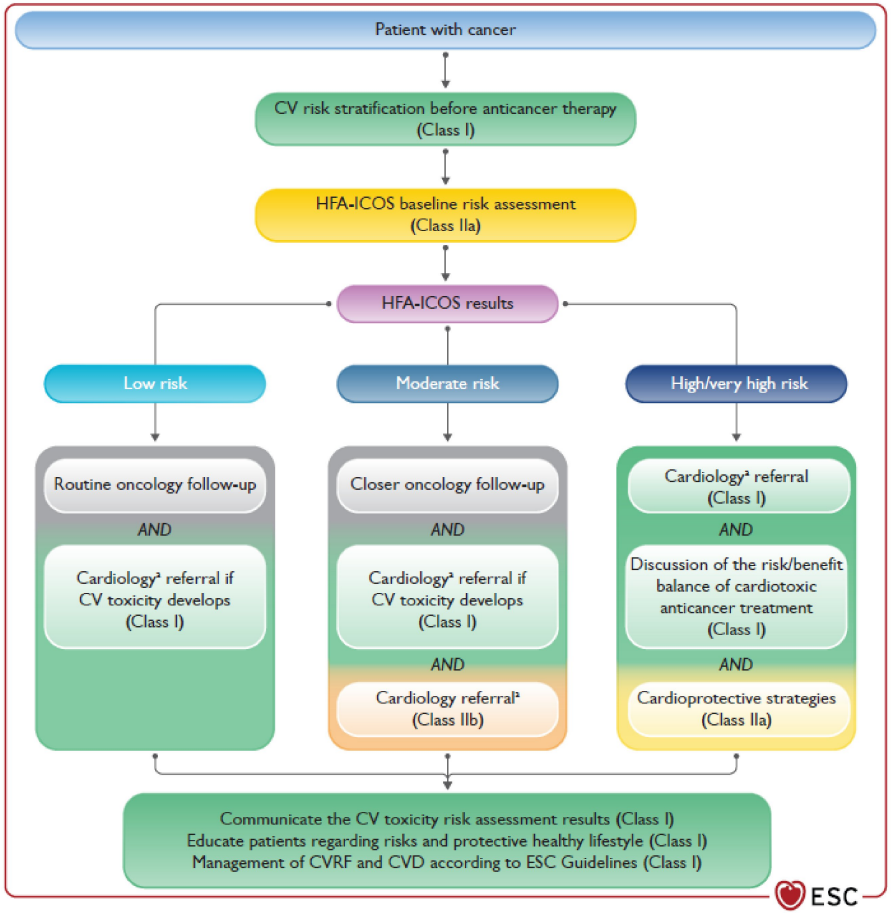
- BNP or NT-proBNP[b]
- cTn[b]
- ECG
- Fasting plasma glucose / HbA1c
- Kidney function / eGFR
- Lipid profile
- TTE[c]

ESC

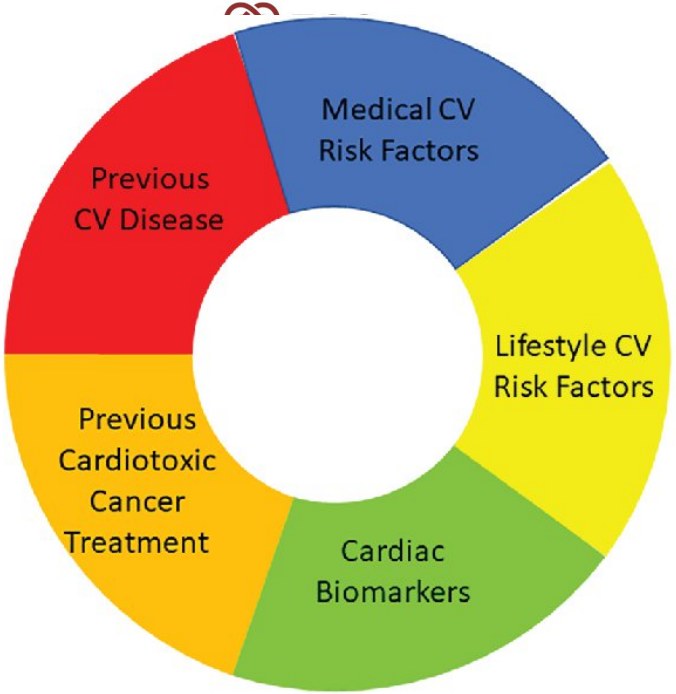
Recommendation Table 1 — Recommendations for a general approach to cardiovascular toxicity risk categorization

Recommendations	Class[a]	Level[b]
CV toxicity risk stratification[c] before starting potentially cardiotoxic anticancer therapy is recommended in all patients with cancer.[12,14,19,21,25,28,31]	I	B
Communicating the results of the CV toxicity risk assessment to the patient and other appropriate healthcare professionals is recommended.	I	C
The use of HFA-ICOS risk assessment should be considered to stratify CV toxicity risk in patients with cancer scheduled to receive cardiotoxic anticancer therapy.[12]	IIa	C
It is recommended that patients categorized to be at low CV toxicity risk should proceed to anticancer therapy without delay.	I	C
In patients categorized at moderate CV toxicity risk, cardiology referral[d] may be considered.[e]	IIb	C
Cardiology referral[d] is recommended in high-risk and very high-risk patients before anticancer therapy.[f]	I	C
Discussion of the risk/benefit balance of cardiotoxic anticancer treatment in high- and very high-risk patients in a multidisciplinary approach prior to starting treatment is recommended.	I	C
Cardiology referral[d] is recommended for patients with cancer and pre-existing CVD or abnormal findings at baseline CV toxicity risk assessment[g] who require potentially cardiotoxic anticancer therapy.	I	C

Lyon AR, Lopez-Fernandez T, et al. *Eur Heart J* 2022



Lyon AR, Lopez-Fernandez T, et al. *Eur Heart J* 2022



Baseline CV Risk Assessment Checklist

Cardiac history
Cancer treatment history
CV risk factors

Blood pressure
HbA1c
Cholesterol profile

Cardiac troponin*
BNP or NT-proBNP*

ECG

Echocardiogram

Panel 1: Potential risk factors for immune checkpoint inhibitor-related cardiotoxic effects

Treatment-related factors
- Dual immunotherapy (eg, ipilimumab and nivolumab)
- Combined immunotherapy and other cardiotoxic cancer therapy (eg, VEGF tyrosine kinase inhibitors)

Concurrent immune-related toxic effects
- Immune checkpoint inhibitor-related skeletal myositis

Previous cardiovascular disease with myocardial injury
- Myocardial infarction
- Heart failure
- Myocarditis
- Previous anthracycline chemotherapy
- Previous cancer therapy-induced left ventricular dysfunction

Previous autoimmune disease
- Systemic lupus erythematosus
- Rheumatoid arthritis
- Sarcoidosis
- Dressler's syndrome

Tumour-related factors
- Cardiac antigens expressed in tumour
- Cardiac T-cell clones

Genetic factors
- Unknown

Lyon AR, et al. *Lancet Oncol* 2018
Lyon AR, et al. *Eur J Heart Fail* 2020

Table 2

Distribution of LVD and other CV events according to HFA/ICOS risk allocation.

	LVD	Other CV events	All CV events
Anthracyclines (n = 202)	0	4[§] (2%)	4 (2%)
Low risk (n = 103)	0	0	0
Medium risk (n = 86)	0	2 (2%)	2 (2%)
High & very-high risk (n = 13)	0	2 (15%)	2 (15%)
Anti-HER2 drugs (n = 171)	16 (9%)	5[§§] (3%)	21 (12%)
Low risk (n = 47)	2 (4%)	1 (2%)	3 (6%)
Medium risk (n = 99)	11 (11%)	3 (3%)	14 (14%)
High & very-high risk (n = 25)	3 (12%)	1 (4%)	4 (16%)

[§] Other CV events included: 2 pulmonary embolisms; 1 case of uncontrolled arterial hypertension; 1 case of heart failure with a preserved ejection fraction in a patient with arterial hypertension and LVH.

[§§] These included: 1 cardiac tamponade; 1 fatal ischeamic stroke; 1 case of symptomatic ectopic ventricular beats; 2 cases of uncontrolled arterial hypertension.

Tini G, et al. *Int J Cardiol* 2022

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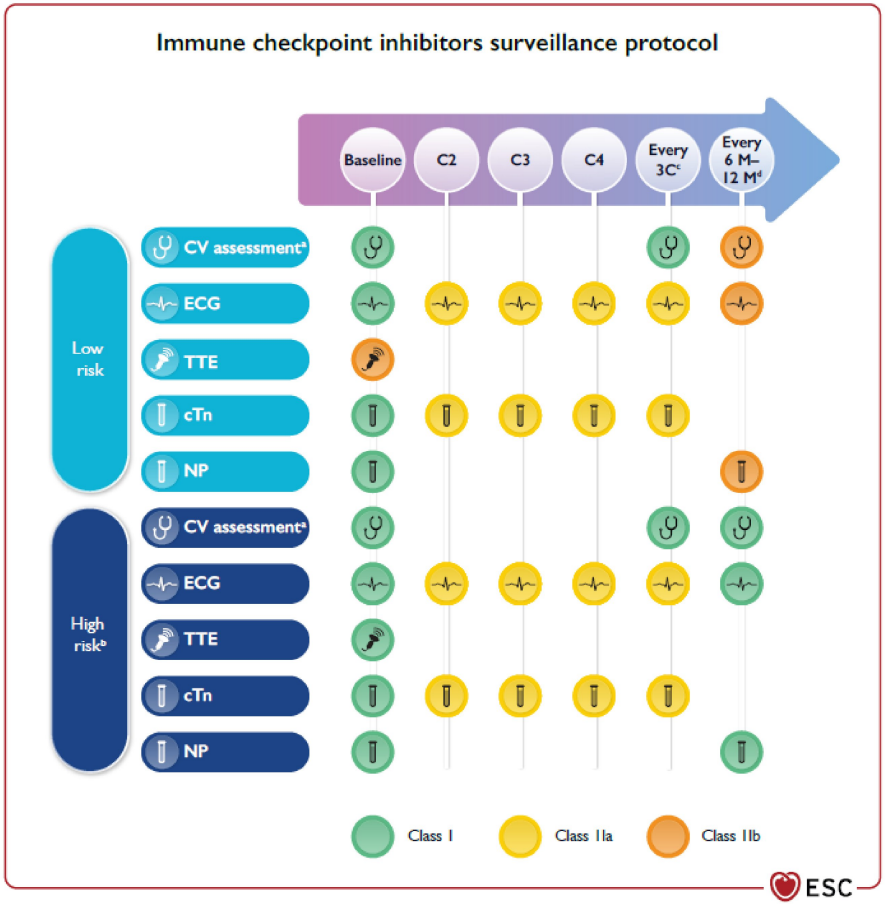


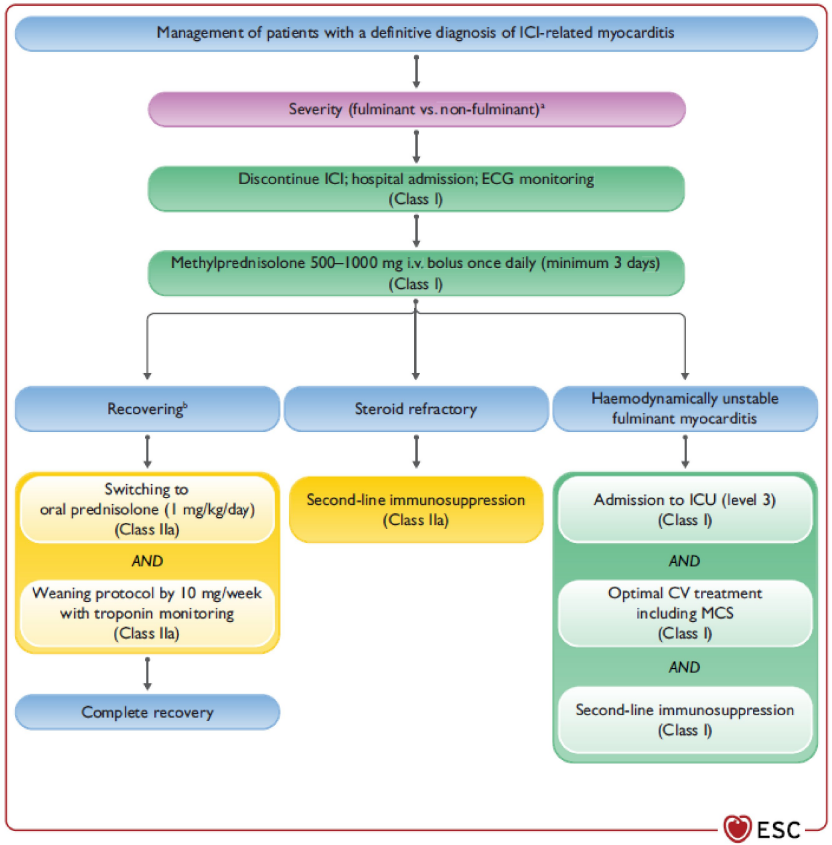
Recommendation Table 15 — Recommendations for baseline risk assessment and monitoring during immunotherapy

Recommendations	Class[a]	Level[b]
ECG, NP, and cTn measurements are recommended in all patients before starting ICI therapy.[333]	I	B
Baseline echocardiography is recommended in high-risk patients[c] before starting ICI therapy.[333]	I	B
Baseline echocardiography may be considered in all patients before starting ICI therapy.	IIb	C
Serial ECG and cTn measurements should be		

High risk:

- Dual ICI
- combination ICI-cardiotoxic therapy
- ICI-related non-CV events
- prior cancer therapy-related cardiac dysfunction
- Any cardiovascular disease

Lyon AR, Lopez-Fernandez T, et al. *Eur Heart J* 2022



Lyon AR, Lopez-Fernandez T, et al. *Eur Heart J* 2022

Recommendation Table 20 — Recommendations for baseline risk assessment and monitoring in patients receiving chimeric antigen receptor T cell and tumour-infiltrating lymphocytes therapies

Recommendations	Class[a]	Level[b]
Baseline ECG, NP, and cTn are recommended in all patients with cancer before starting CAR-T and TIL therapies.[388]	I	C
A baseline echocardiography is recommended in patients with pre-existing CVD before starting CAR-T and TIL therapies.[388]	I	C
A baseline echocardiography should be considered before starting CAR-T and TIL therapies.[388]	IIa	C
Measurement of NP, cTn, and echocardiography are recommended in patients who develop CRS of ASTCT ≥ 2.[c,378,388]	I	C

ASTCT, American Society for Transplantation and Cellular Therapy; CAR-T, chimeric antigen receptor T cell; CRS, cytokine release syndrome; cTn, cardiac troponin; CVD, cardiovascular disease; ECG, electrocardiogram; NP, natriuretic peptides; TIL, tumour-infiltrating lymphocytes.

[a]Class of recommendation.

[b]Level of evidence.

[c]Determine CRS grade according to ASTCT grading: Grade 1: fever; Grade 2: fever AND hypotension not requiring vasopressors AND/OR hypoxia requiring low-flow nasal oxygen; Grade 3: fever AND hypotension requiring one vasopressor ± vasopressin AND/OR hypoxia requiring high-flow nasal cannula or facemask or non-rebreather mask or Venturi mask; Grade 4: fever AND hypotension requiring multiple vasopressors, not including vasopressin AND/OR hypoxia requiring positive airway pressure.

Lyon AR, Lopez-Fernandez T, et al. *Eur Heart J* 2022

Cardiovascular preventative and supportive care interventions for CAR-T cell therapy

Pre T-Cell Infusion
Comprehensive assessment that includes a detailed CV history and physical examination including estimation of exercise tolerance, screening for CV disease risk factors (hypertension, diabetes, hyperlipidemia, obesity, smoking), and baseline 12-lead ECG, analogous to assessment prior to cardiotoxic treatment. Cardio-oncology consult for further evaluation and risk stratification as per Figure 1.
Baseline echocardiogram to evaluate cardiac structure and function especially in older patients, those with impaired exercise tolerance, known structural heart disease, abnormal baseline ECG, suggestive symptoms, or multiple CV risk factors.
Consider evaluation for ischemia in patients with poor exercise tolerance or any exertional symptoms.
Consider tapering antihypertensive medications prior to infusion.

During Therapy
Continue low-dose aspirin in patients with known coronary artery disease or percutaneous coronary intervention or both until platelets <30,000 (35).
Monitor vital signs every 4 h with attention to fevers, hypotension, and tachycardia; every 2 h in patients with fever and tachycardia. Telemetry monitoring for patients found to have persistent tachycardia or arrhythmia.
Maintenance of adequate hydration. Initiate replacement IV fluids for patients with poor oral intake or high insensible losses to maintain euvolemia.
Initiate volume resuscitation with IV fluid for sustained hypotension.
Consider intensive care monitoring if hypotension recurs after first fluid bolus or HR persistently >125 beats/min.
ECG, troponin, and echocardiogram for persistent hypotension not responsive to IV fluid boluses. Consider intensive care unit transfer for hemodynamic management.
Initiate vasopressor support if BP unresponsive to first fluid resuscitation. Discuss with CAR-T team regarding the use of tocilizumab.
Consider invasive hemodynamic monitoring for patients with shock who have reduced LV systolic function or refractory to low-dose vasopressor or both.

Ganatra S, et al. *J Am Coll Cardiol* 2019

Summary

- Both ICI and CAR-T have drastically improved cancer patients' survival, but are burden by different type of cardiovascular toxicities
- ICIs toxicity is tightly connected to their mechanism of action
- ICIs might cause severe myocarditis, fatal in almost 50% of cases
- CAR-T can cause a cytokine related syndrome that may affect the cardiovascular system
- Cardiovascular baseline assessment and strict cardiovascular follow-up according to a risk stratification tool (HFA-ICOS) are pivotal in such context

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ORIGINAL ARTICLE

Impact of a cardio-oncology unit on prevention of cardiovascular events in cancer patients

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Cuomo A, Mercurio V, et al. *ESC Heart Fail* 2022