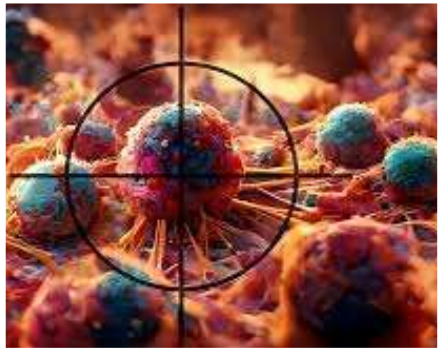

Cardiotoxicity of HER2 Targeted Therapy

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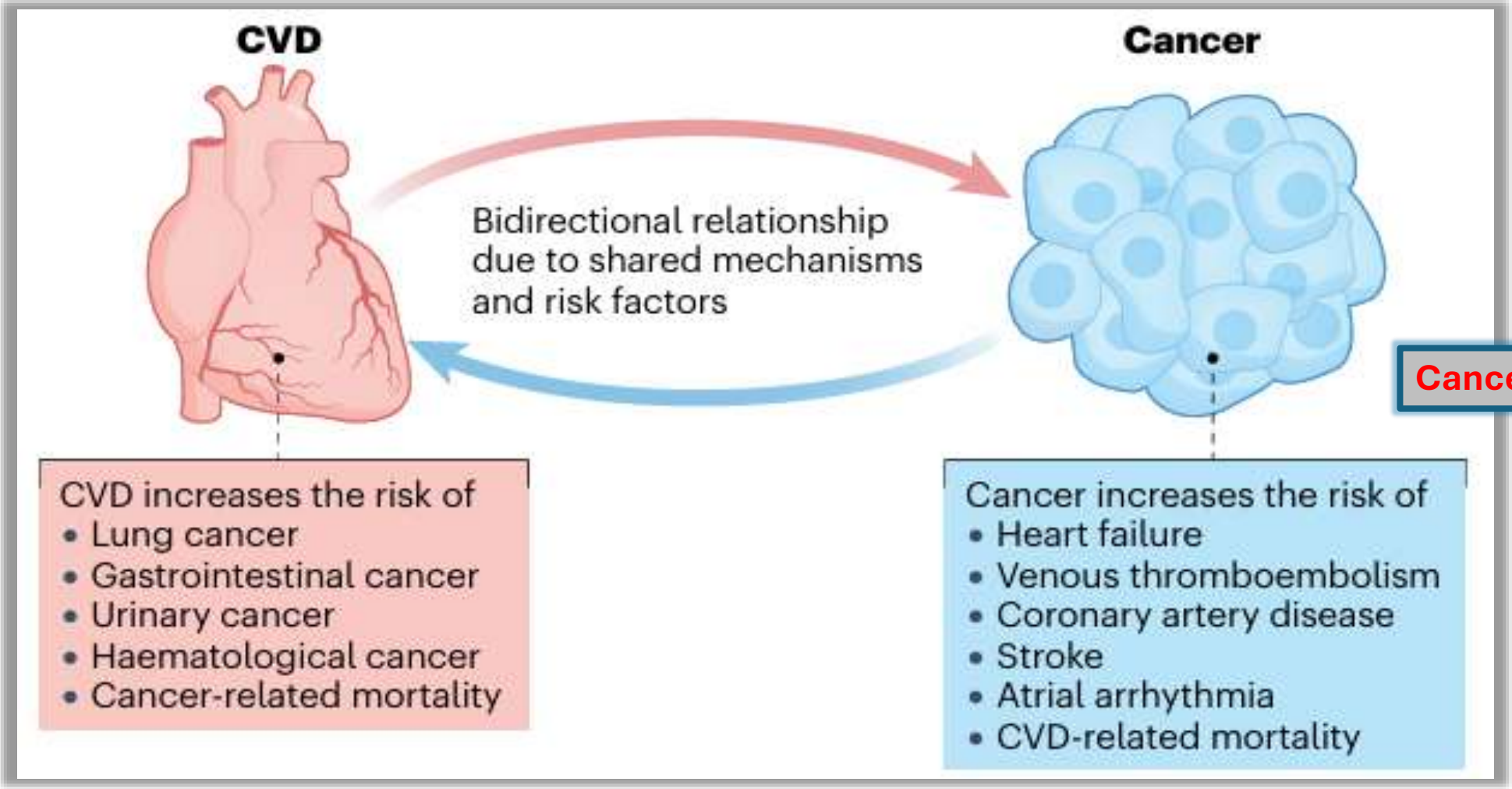
Disclosure

- No Conflict of Interest

Outline

- Cancer , cancer therapy and the Heart
- Cardio-Oncology as a subspeciality
- HER 2 Targeted therapy
- HER 2 Targeted therapy Cardiotoxicity
- Evaluation, monitoring and management
- Take home messages

The Bidirectional Relationship Between CVD and Cancer



Nature Reviews Cardiology | Volume 21 | September 2024 | 617–631

Cancer Therapy Evolution

30-yrs ago

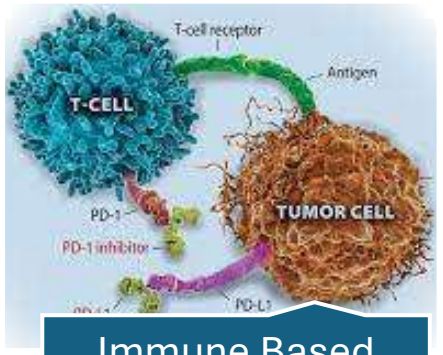
Cytotoxic Chemotherapy

Radiation Therapy

Surgical Resection

Currently

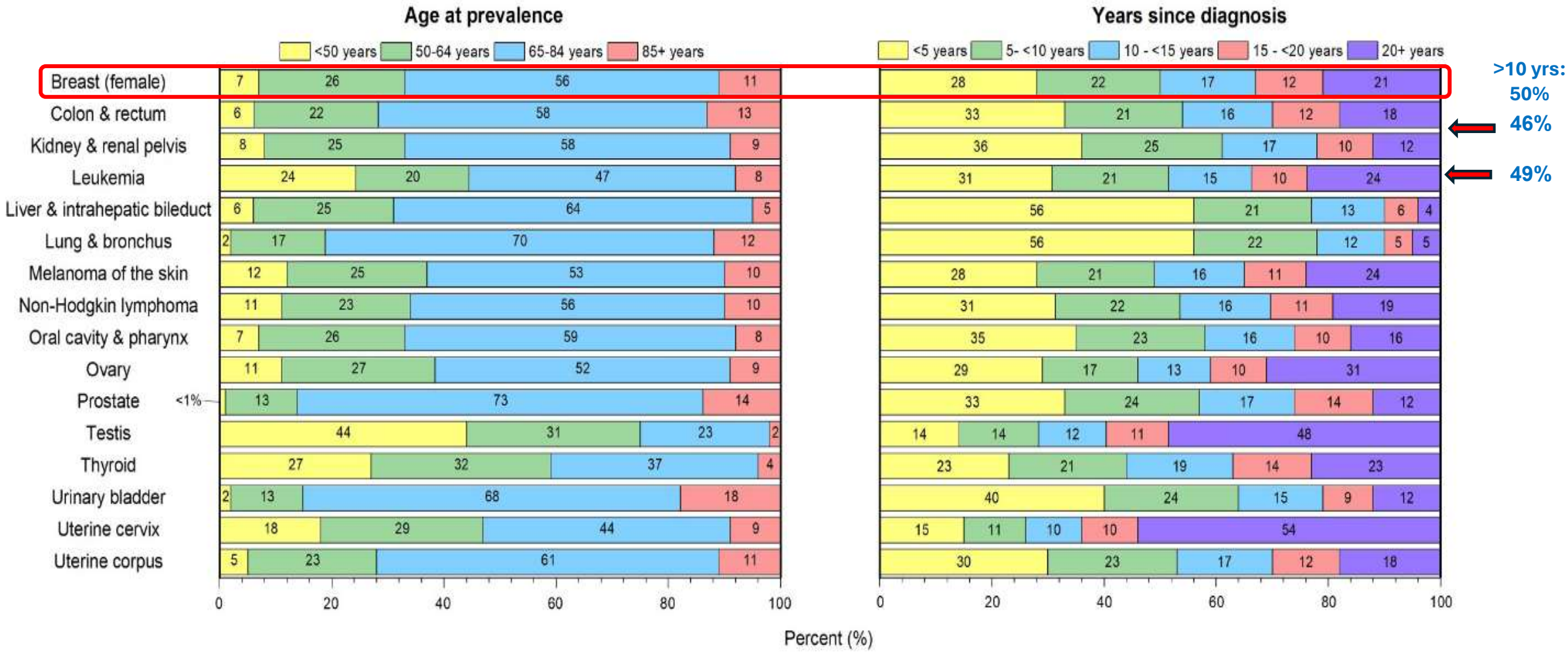
Targeted Therapy



Immune Based Therapy

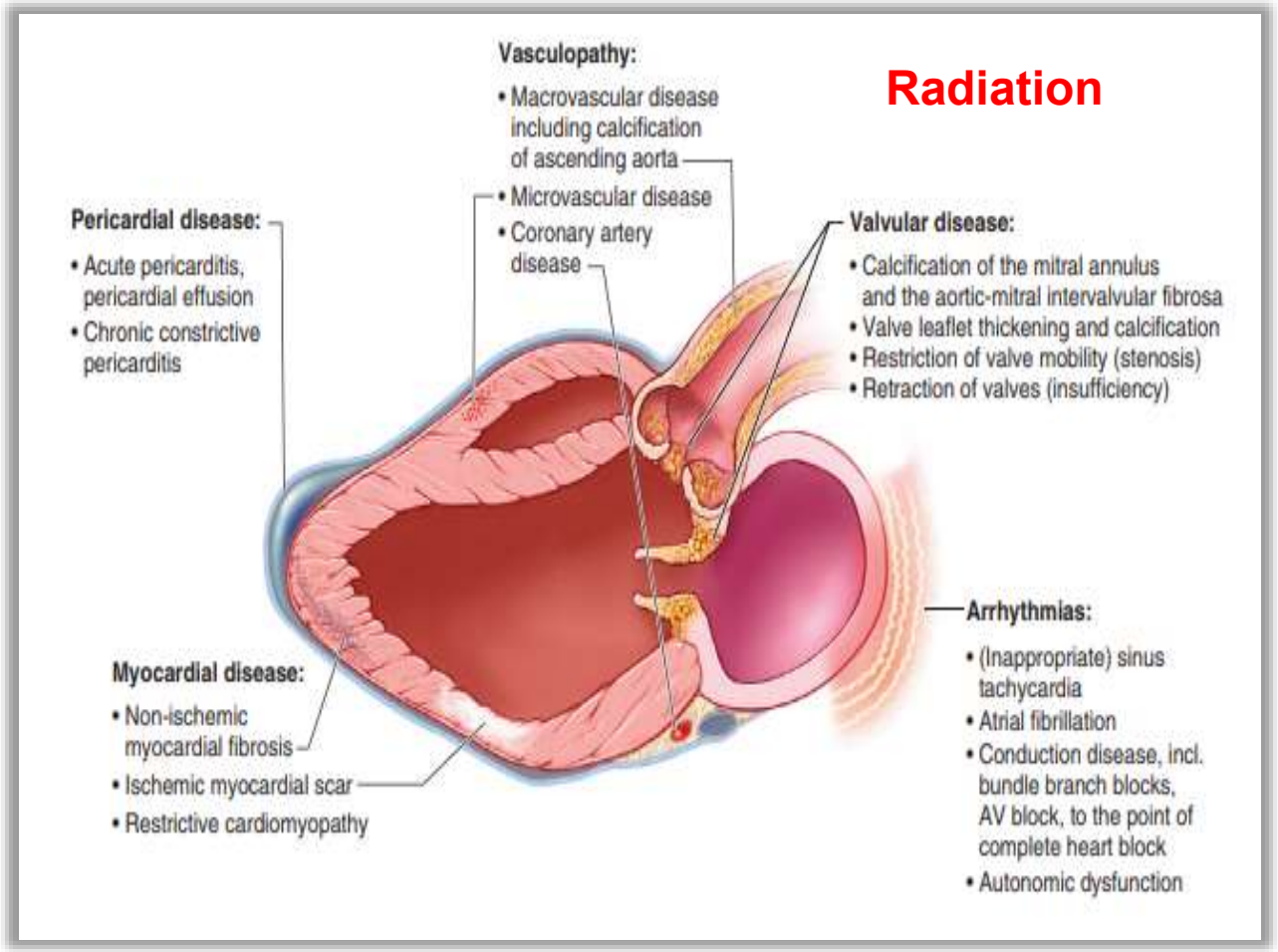
Transformed the practice radically

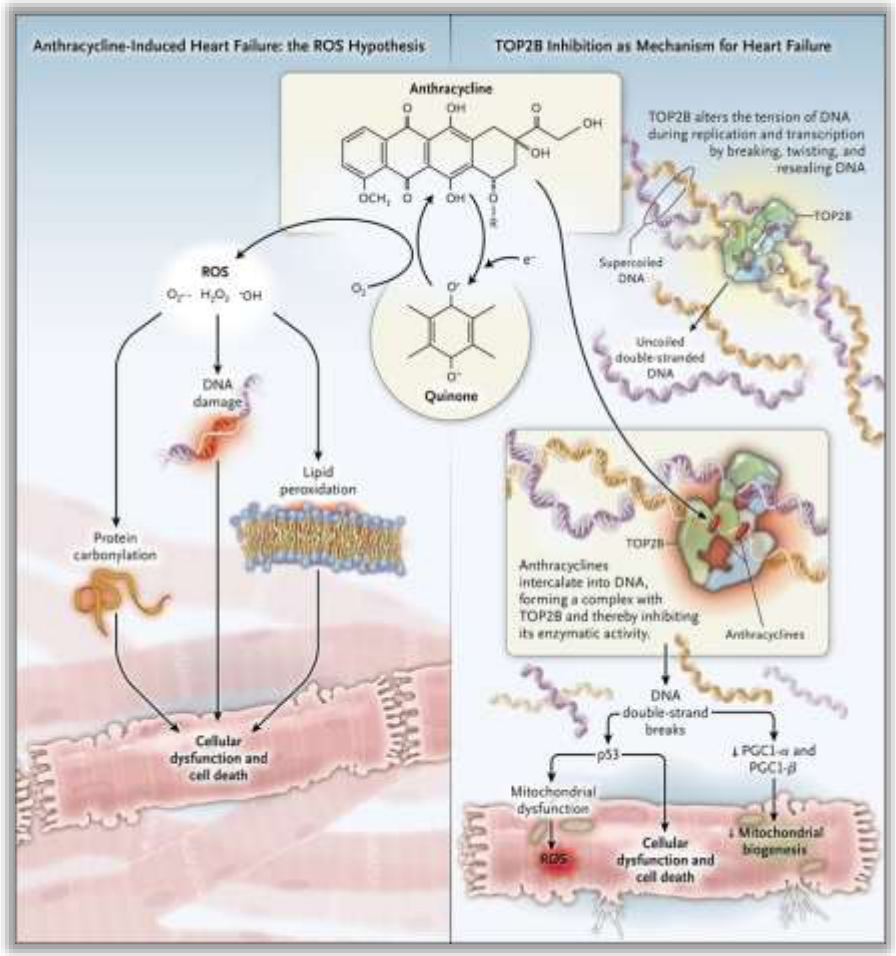
Distribution (%) of survivors of selected cancers in the United States as of January 1, 2025 by age at prevalence and years since diagnosis



CA Cancer J Clin. 2025;75:308–340

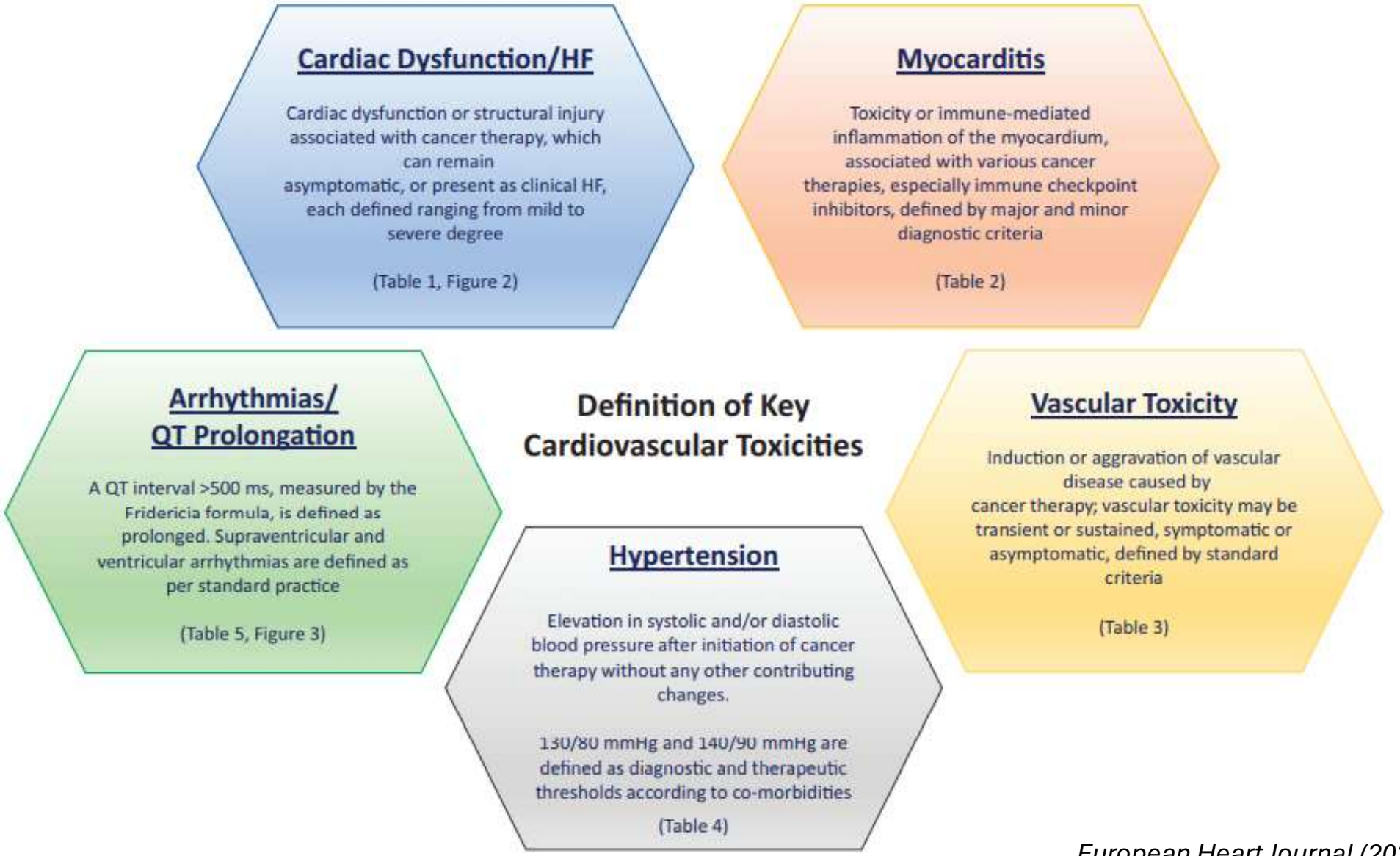
Historically: Radiation Therapy & Anthracycline Cardiotoxicities





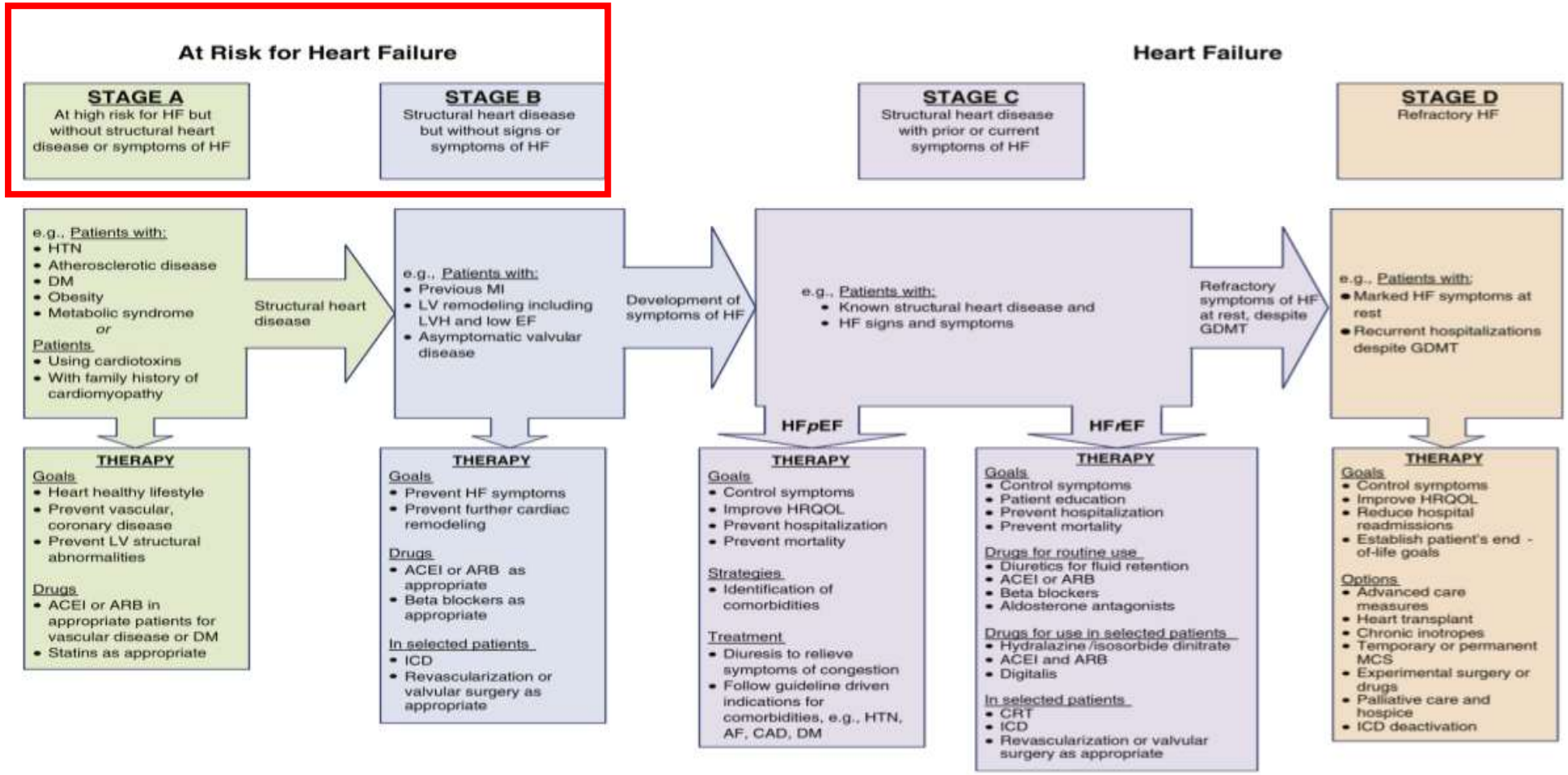
JACC CO 2019

IC-OS Cardiotoxicity Definition



European Heart Journal (2022) 43, 280–299

Cancer (Chemotherapy /Radiotherapy) Should be considered as a Novel Cardiovascular Risk Factor



ACC 2013 HF Guidelines
EHFJ 2021

Cardio-Oncology:

A New Era in Cardiology

Cardio-Oncology : The 5 Key Elements

- **Risk Stratification**
- **Early diagnosis**
- **Prevention**
- **Treatment**
- **Long-term surveillance**

"The cured cancer patient of <u>Today</u> does not want to become the cardiac patient of <u>Tomorrow</u>"

The four main goals of the cardio-Oncologist are:

- ✓ **to avoid the possibility that cancer therapy could induce cardiac disease**
- ✓ **To avoid cardiotoxicity from interrupting cancer therapy**
- ✓ **to avoid the possibility that pre-existent cardiac disease be a barrier and lead to a reduction of therapeutic opportunities for the patient**
- ✓ **Follow up patients at risk of cardiotoxicity post cancer therapy**

H. Skouri 2025

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

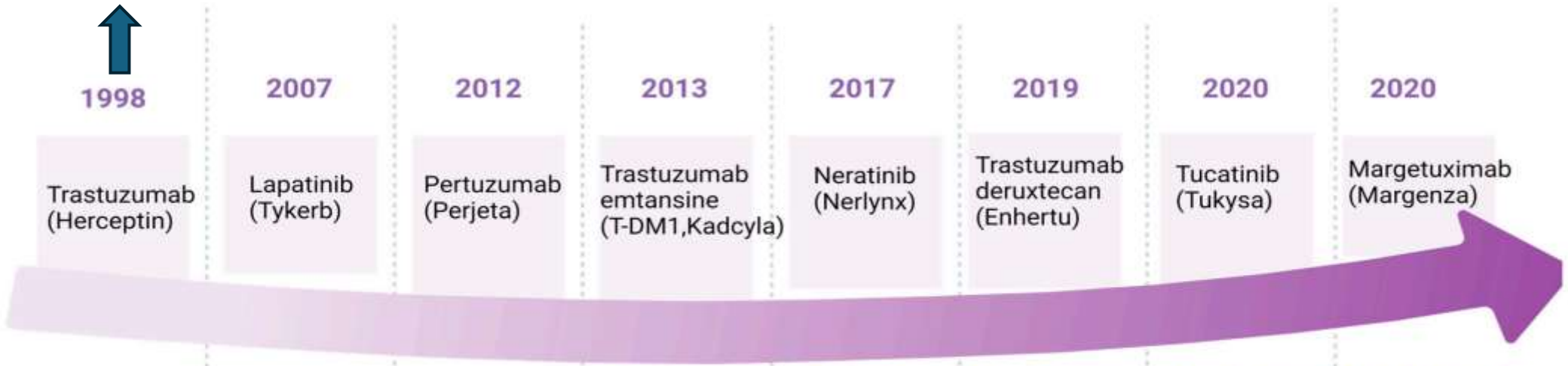
Cancer treatment class	Cancer indication	Treatment-related CV toxicity
Anthracycline chemotherapy (doxorubicin, epirubicin, daunorubicin, idarubicin)	Breast cancer, lymphoma, acute leukaemia, sarcoma	Heart failure Asymptomatic LVSD Atrial and ventricular arrhythmias
HER2-targeted therapies (trastuzumab, pertuzumab, trastuzumab emtansine (T-DM1), lapatinib, neratinib, tucatinib)	HER2+ breast cancer HER2+ gastric cancer	Heart failure Asymptomatic LVSD Hypertension
VEGF inhibitors TKIs (sunitinib, pazopanib, sorafenib, axitinib, tivozanib, cabozantinib, regorafenib, lenvatinib, vandetinib) and antibodies (bevacizumab, ramucirumab)	VEGF TKIs: renal cancer, hepatocellular cancer, thyroid cancer, colon cancer, sarcoma, GIST Antibodies: breast cancer, ovarian cancer, gastric cancer, gastro-oesophageal cancer, colon cancer	Hypertension Heart failure Asymptomatic LVSD Myocardial ischaemia and infarction QTc prolongation
Multi-targeted kinase inhibitors: second and third generation BCR-ABL TKIs (ponatinib, nilotinib, dasatinib, bosutinib)	Chronic myeloid leukaemia	Arterial thrombosis (myocardial infarction, stroke and PAOD[a]) Venous thromboembolism Hypertension Heart failure and asymptomatic LVSD Atherosclerosis[b] QTc prolongation[b] Pulmonary hypertension[c]
Proteasome inhibitors (carfilzomib, bortezomib, ixazomib) **Immunomodulatory drugs** (lenalidomide, pomalidomide)	Multiple myeloma	Heart failure[d] Asymptomatic LVSD[d] Myocardial ischaemia and infarction Atrial and ventricular arrhythmias Venous thromboembolism Arterial thrombosis Hypertension
Combination RAF and MEK inhibitors (dabrafenib + trametinib, vemurafenib + cobimetinib, encorafenib + binimetinib)	Raf mutant melanoma	Heart failure and asymptomatic LVSD Hypertension QTc prolongation[e]
Androgen deprivation therapies **GnRH agonists** (goserelin, leuprorelin) **Antiandrogrens** (abiraterone)	Prostate cancer ER+ breast cancer[f]	Atherosclerosis Myocardial ischaemia and infarction Diabetes mellitus Hypertension
Immune checkpoint inhibitors: **anti-programmed cell death 1 inhibitors** (nivolumab, pembrolizumab) **anti-cytotoxic T-lymphocyte-associated protein 4 inhibitor** (ipilimumab) **anti-programmed death-ligand 1 inhibitors** (avelumab, atezolizumab, durvalumab)	Melanoma (metastatic and adjuvant) 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	Myocarditis including fulminant myocarditis Pericarditis Non-inflammatory heart failure Ventricular arrhythmias AV block Acute coronary syndromes including atherosclerotic plaque rupture and vasculitis

This is Why I became interested as a Heart Failure physician in Cardio-Oncolgy

European Journal of Heart Failure (2020)

Significantly improved survival rates in both early and advanced disease

Evolutions of HER2-based drugs



HER2-targeted therapies
(trastuzumab, pertuzumab, trastuzumab emtansine (T-DM1), lapatinib, neratinib, tucatinib)

HER2+ breast cancer
HER2+ gastric cancer

Heart failure
Asymptomatic LVSD
Hypertension

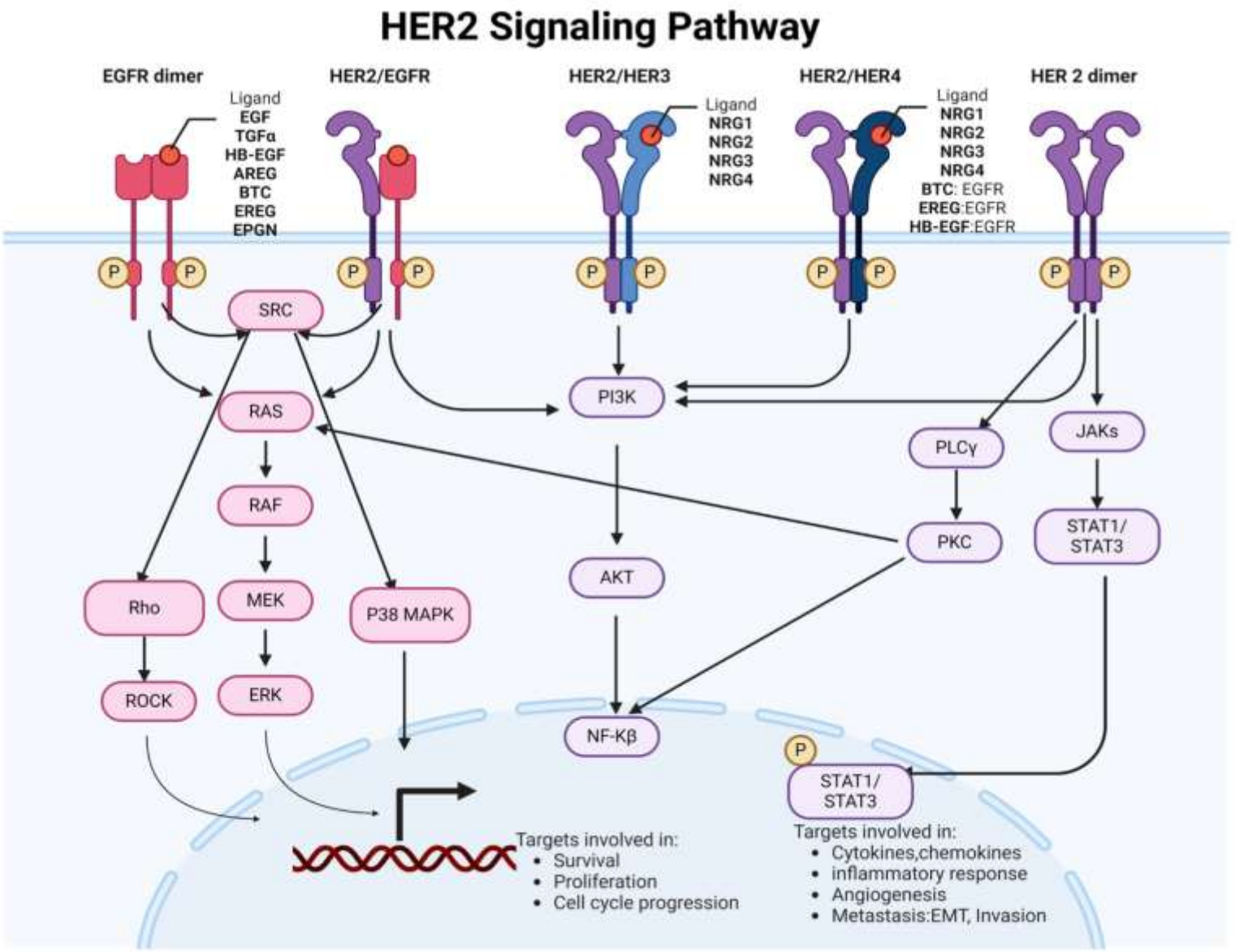
Approved HER2-targeted therapies for breast cancer

Drug (Generic)	Type	Mechanism of Action	Approved Indications	Key Trials
Trastuzumab	Monoclonal antibody	Binds HER2 extracellular domain	Early-stage, metastatic HER2+	HERA, NSABP B-31, N9831, BCIRG-006
Pertuzumab	Monoclonal antibody	Inhibits HER2 dimerization	Early-stage (node+), metastatic HER2+	APHINITY, CLEOPATRA
Margetuximab	Fc-engineered antibody	Enhances ADCC via Fc modification	Metastatic HER2+ (FDA only)	SOPHIA
T-DM1 (Ado-trastuzumab emtansine)	ADC	HER2 antibody linked to DM1 (microtubule inhibitor)	Residual disease post-NAT, metastatic HER2+	KATHERINE, EMILIA
T-DXd (Trastuzumab deruxtecan)	ADC	HER2 antibody linked to topoisomerase I inhibitor	Metastatic HER2+, HER2-low	DESTINY-Breast01–04
Lapatinib	Small molecule TKI	Dual EGFR/HER2 TKI (reversible)	Metastatic HER2+	EGF100151
Neratinib	Small molecule TKI	Irreversible pan-HER TKI	Extended adjuvant (HR+), metastatic HER2+	ExteNET, NALA
Tucatinib	Small molecule TKI	Selective HER2 TKI	Metastatic HER2+ (including brain mets)	HER2CLIMB

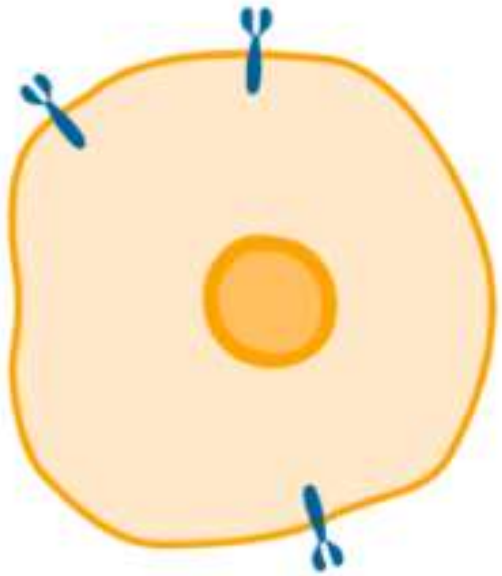
Expert Opinion Pharmacology 2025 (26):1855-1865

Function of HER2

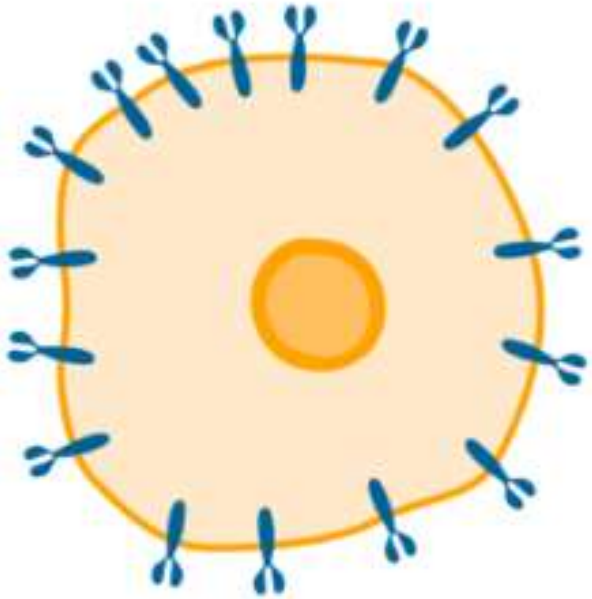
- HER2 is a receptor tyrosine kinase, a **transmembrane protein of cells that helps regulate cell growth and division**
- HER2 can **form homodimers or heterodimers with other EGFR family** members in ligand-dependent and-independent manners
- The formation of dimers—either homodimers or heterodimers—**is a key step in the activation of HER2 signaling pathways**
- In some cases, **HER2 is overexpressed** with too many copies of the HER2 gene, and, consequently, there is too much HER2 protein on the transmembrane of cancer cells
- The overexpression can lead to **uncontrolled cell growth and is associated with more aggressive forms of cancer**



What Happens in HER2 Positive Breast Cancer?



Normal
Breast Cell



HER2-positive
Breast Cancer Cell

Overexpression can occur:

1-Breast

2-Gastric

3-Lung

4-Colorectal

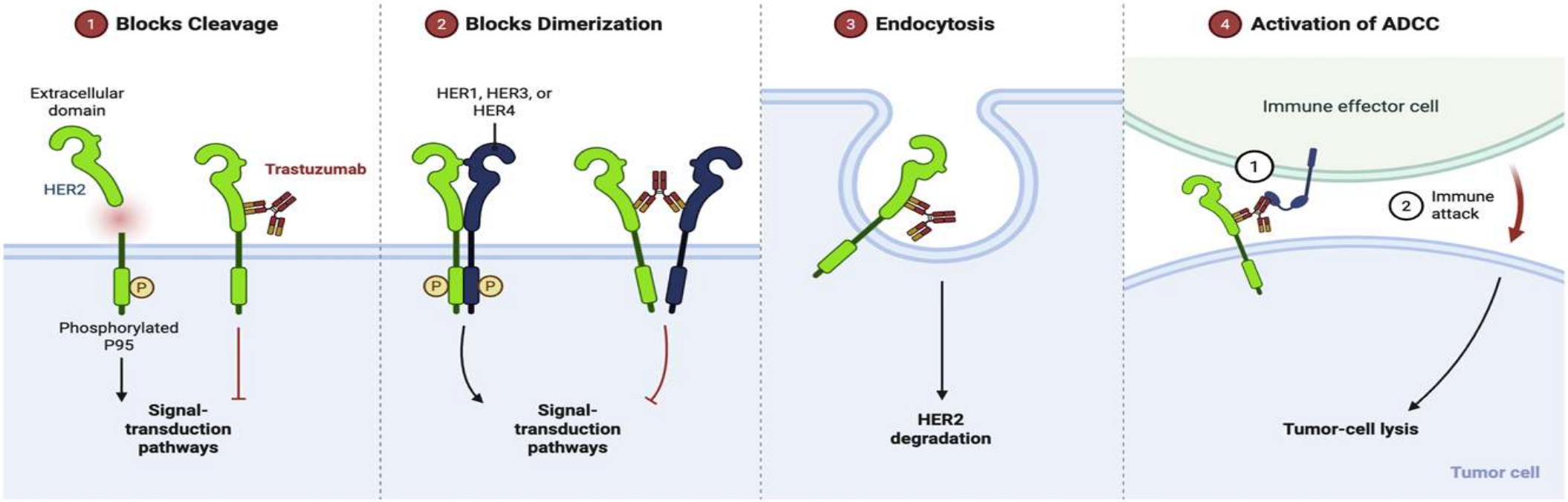
5-Ovarian

Aggressive disease and poor outcomes

HER2-Targeted therapies

- HER2-positive invasive BC in both: early and metastatic settings.
- Neoadjuvant and/or adjuvant settings
- Drugs currently approved are trastuzumab, pertuzumab, trastuzumab emtansine, and neratinib.
- In the metastatic setting :trastuzumab, pertuzumab, trastuzumab emtansine, tucatinib, and trastuzumab deruxtecan are currently approved (1st line –second line, >3rd line-Longer duration of exposure
- Trastuzumab can also be used in patients with HER2-overexpressing metastatic gastric adenocarcinomas in combination with platinum-based chemotherapy and either capecitabine or 5-fluorouracil (5-FU)

Mechanisms of Trastuzumab Action on HER2-positive Tumor Cells



Trastuzumab exerts various antitumor effects by targeting HER2 signaling:

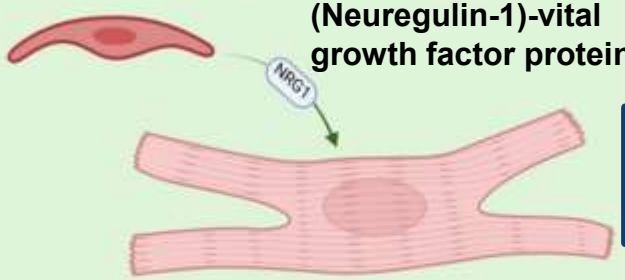
- **First, it blocks cleavage of the extracellular HER2 domain, preventing generation of the constitutively active phosphorylated P95 fragment that drives oncogenic signaling**
- **Second, it inhibits HER2 dimerization with other HER family receptors (HER1, HER3, HER4), thereby suppressing downstream signal transduction pathways**
- **Third, binding of trastuzumab promotes endocytosis and degradation of HER2, reducing receptor availability at the cell surface**
- **Finally, trastuzumab activates antibody-dependent cellular cytotoxicity (ADCC), in which immune effector cells recognize trastuzumab-coated HER2 receptors and mediate tumor cell lysis.**

Current Problems in Cardiology 50 (2025) 103168

Normal cardiac HER2 signaling

Endothelial cell releases **NRG-1**

(Neuregulin-1)-vital growth factor protein



- **NRG-1** activates **HER2/HER4** signaling in cardiomyocytes
- Downstream survival pathways: **PI3K/ AKT MAPK/ERK**
- Maintains mitochondrial integrity, calcium handling, stress adaptation, contractile reserve

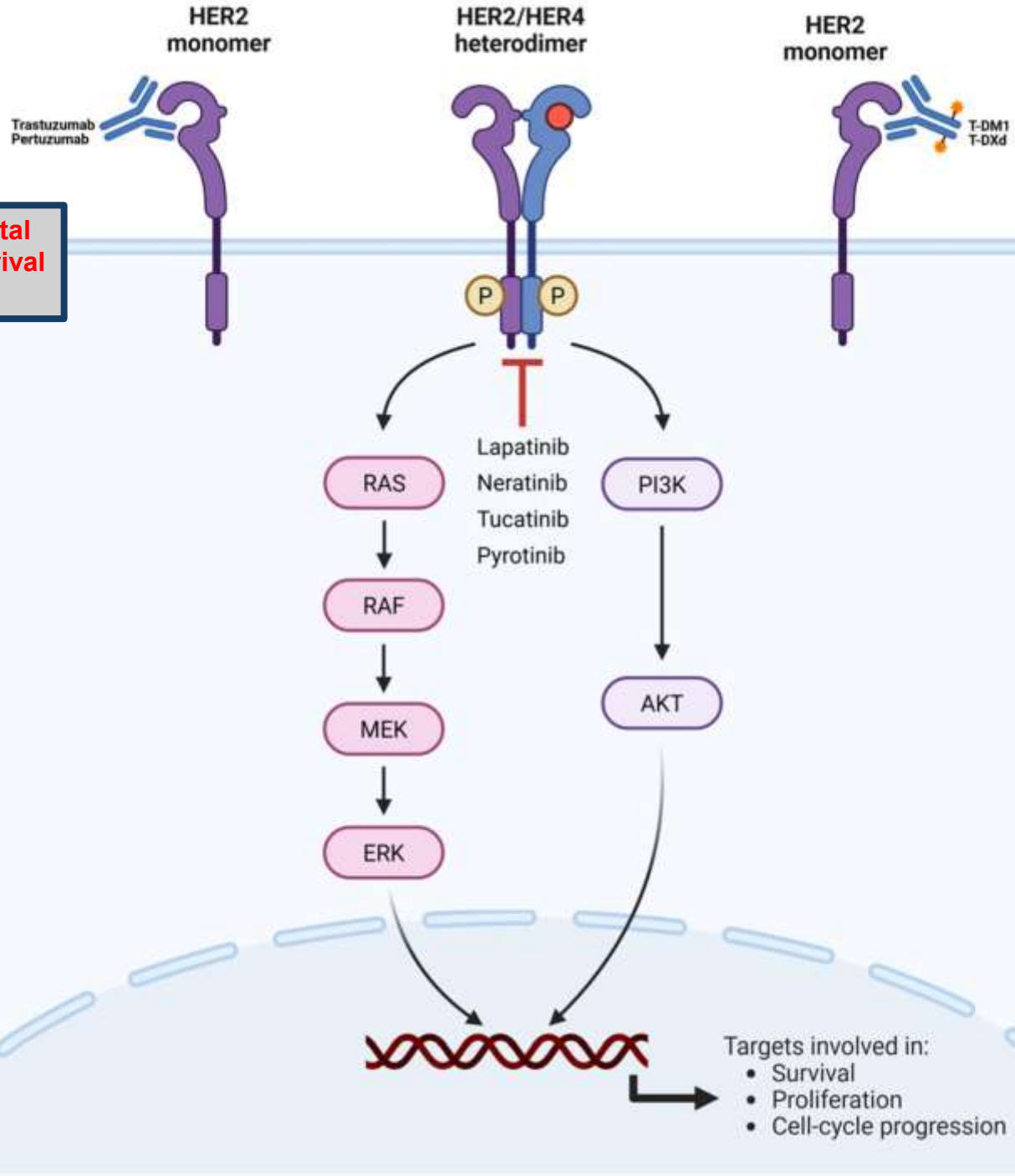
HER2 signaling plays a vital role in cardiomyocyte survival and stress adaptation

HER2 targeted therapy

Monoclonal antibodies: Trastuzumab, Pertuzumab

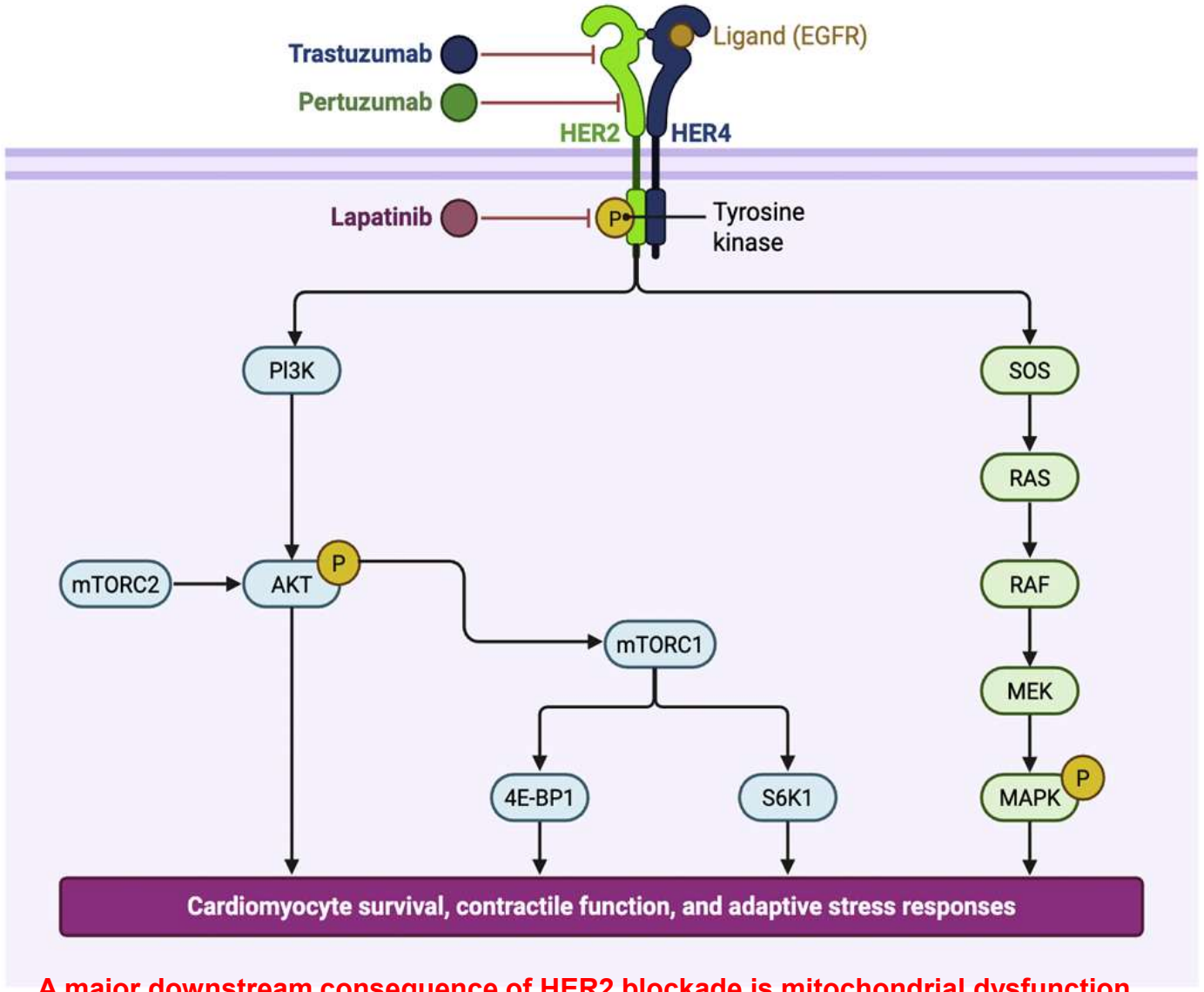
Drug Antibody Conjugates (ADCs): Trastuzumab emtansine (T-DM1), Trastuzumab deruxtecan (T-DXd)

Tyrosine Kinase Inhibitors: Lapatinib, Neratinib, Tucatinib, Pyrotinib



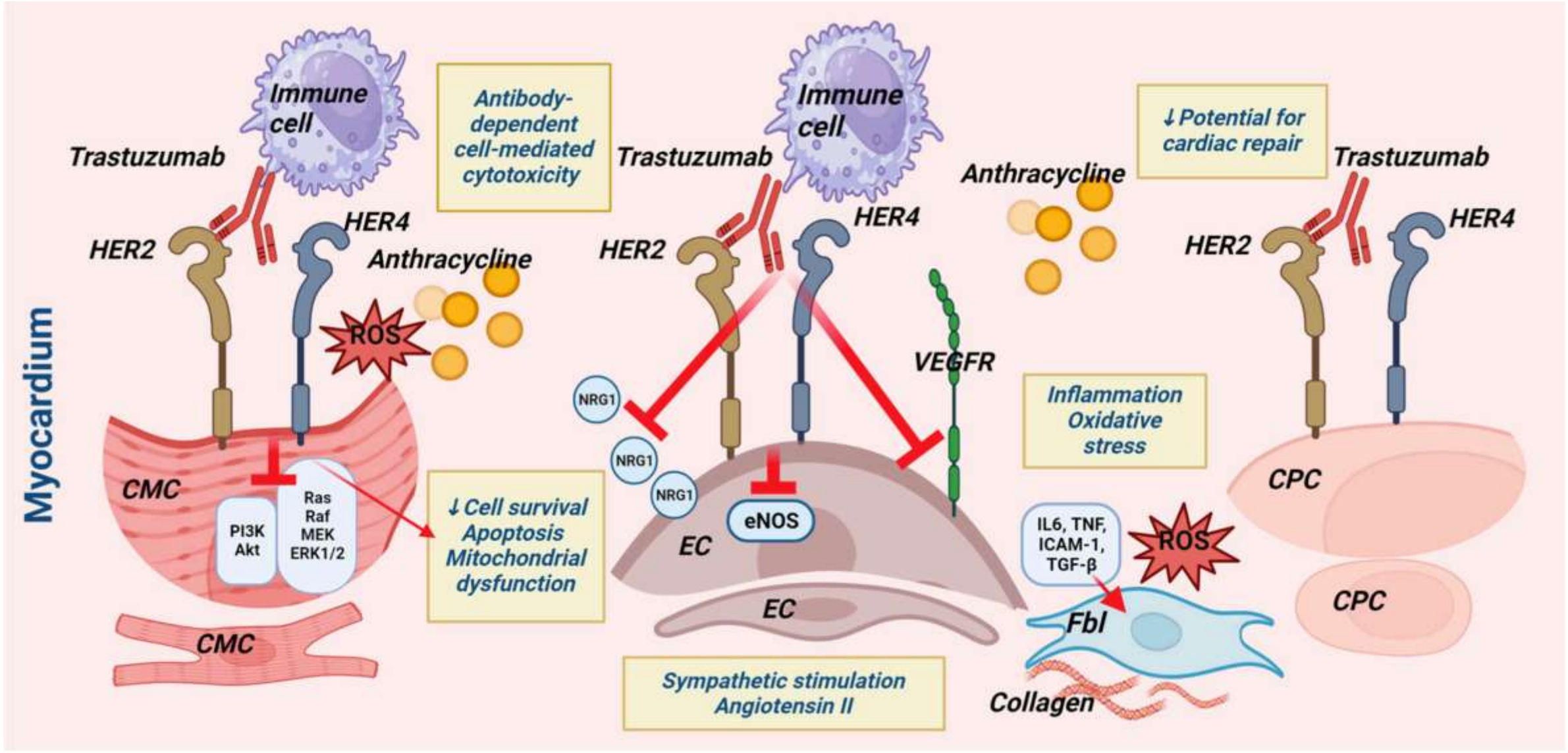
Mechanisms of HER2 blockade–induced cardiotoxicity

- fundamental role of HER2 signaling in **maintaining myocardial homeostasis**
- HER2 forms heterodimers with HER4 in response to neuregulin-1 (NRG-1), a growth factor secreted by cardiac endothelial cells
- dimerization activates key survival pathways, notably the phosphoinositide 3-kinase (PI3K)/Akt and mitogen-activated protein kinase (MAPK) cascades
- Inhibition of HER2 by targeted therapies disrupts these protective cascades
- Trastuzumab and pertuzumab block HER2 extracellular signaling and prevents HER2 dimerization, while lapatinib inhibits HER2 tyrosine kinase activity
- These interventions reduce downstream activation of AKT, mTORC1, and MAPK, impairing cardiomyocyte survival mechanisms and stress adaptation, thereby contributing to drug-induced cardiotoxicity



A major downstream consequence of HER2 blockade is mitochondrial dysfunction

Current Problems in Cardiology 50 (2025) 103168



- Interactions among various cell types that express HER2 receptors—cardiomyocytes, endothelial cells, and cardiac progenitor cells.
- Blocking the heterodimerization of HER2/HER4:inhibits downstream pro-survival pathways
- Immune cell activation, inflammation, reactive oxygen species generation, fibroblast stimulation, and collagen deposition in the extracellular matrix all play a role in myocardial injury.

J. Cardiovasc. Dev. Dis. 2023, 10, 489.

Most Common Cardiotoxicity:

- LV dysfunction
- Diastolic dysfunction
- HFrEF
- HFpEF
- RV dysfunction
- Arrhythmias??

Early studies on Trastuzumab:

- cardiac events :up to 27 % of patients receiving concomitant anthracyclines
- 16 % experiencing severe congestive heart failure
- most events are asymptomatic, reversible, and rarely lead to permanent discontinuation of therapy
- Novel agents such as antibody–drug conjugates (ADCs) demonstrate significantly lower rates of cardiotoxicity compared to traditional monoclonal antibodies

Trials & Observational Studies

- Incidence of Asymptomatic LV dysfunction is higher

- Incidence : Trastuzumab<ACT-TZ sequential< ACT+TZ concurrent

The mechanism of cardiac dysfunction differs fundamentally from the structural, dose-dependent cardiotoxicity seen with anthracyclines.

Instead of inducing myocyte necrosis, trastuzumab primarily causes "functional cardiotoxicity," characterized by reversible left ventricular (LV) systolic dysfunction without histologic evidence of myocyte death or fibrosis

Major HER2-targeted drugs and their cardiotoxicity profiles

Parameter	Trastuzumab	Pertuzumab	T-DM1 (Trastuzumab Emtansine)	T-DXd (Trastuzumab Deruxtecan)	Lapatinib	Neratinib
Drug Class	Monoclonal antibody	Monoclonal antibody	Antibody–drug conjugate (ADC)	Antibody–drug conjugate (ADC)	Tyrosine kinase inhibitor (TKI)	Tyrosine kinase inhibitor (TKI)
Mechanism of Action	Binds HER2 extracellular domain IV; blocks signaling; induces ADCC	Binds HER2 dimerization domain; prevents HER2–HER3 dimerization	Trastuzumab linked to DM1 (microtubule inhibitor) for targeted cytotoxicity	Trastuzumab linked to deruxtecan (topoisomerase I inhibitor)	Reversibly inhibits HER2 and EGFR intracellular kinase domains	Irreversibly inhibits HER1, HER2, and HER4 kinase domains
Pharmacokinetics (PK)	$t_{1/2} \approx 28$ days; IV route; nonlinear clearance	$t_{1/2} \approx 18$ days; IV route	$t_{1/2} \approx 4$ days; IV route	$t_{1/2} \approx 6$ days; IV route	Oral bioavailability ≈ 50 %; $t_{1/2} \approx 24$ hours; CYP3A4 metabolism	Oral bioavailability ≈ 35–40 %; $t_{1/2} \approx 14$ hours; CYP3A4 metabolism
Pharmacodynamics (PD)	HER2 inhibition reduces PI3K/Akt and MAPK survival signaling in cardiomyocytes	Similar to trastuzumab	Combines HER2 blockade with intracellular delivery of cytotoxic payload	HER2 blockade plus potent DNA damage via deruxtecan payload	Inhibits downstream signaling from HER2/EGFR, reducing cell proliferation	Broad HER family inhibition, including HER4; enhances pathway blockade
Recommended Dosing	8 mg/kg IV loading → 6 mg/kg IV q3w	840 mg IV loading → 420 mg IV q3w	3.6 mg/kg IV q3w	5.4 mg/kg IV q3w	1250 mg PO daily	240 mg PO daily
Cardiotoxicity Incidence	10–14 %	7–12 % (in combination with trastuzumab)	1–5 %	<2 %	<2 %	<1 %
Cardiotoxicity Pattern	Functional (reversible LV dysfunction)	Functional (reversible LV dysfunction)	Functional, mild	Functional, rare	Functional, rare	Functional, rare
Reversibility	Usually reversible with drug hold and HF therapy	Reversible	Reversible	Reversible	Reversible	Reversible
Key Risk Modifiers	Anthracycline use, age, baseline LVEF	Same as trastuzumab	Low risk even with cardiac comorbidities	Limited data on high-risk populations	Minimal; monitor in patients with baseline CVD	Minimal; monitor in high-risk patients

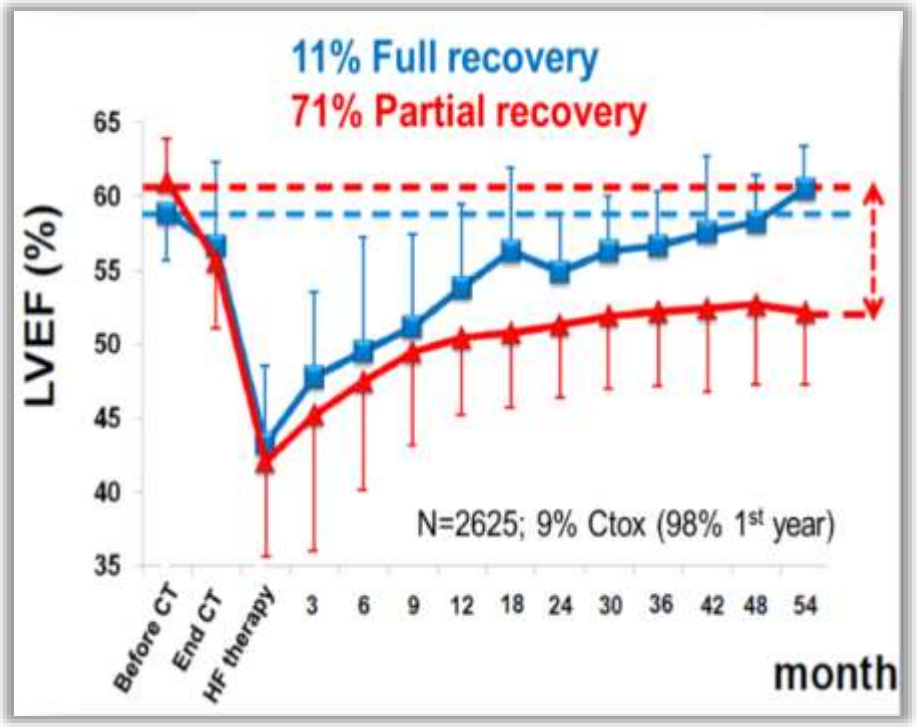
Baseline cardiovascular risk stratification proforma for HER2-targeted cancer therapies (trastuzumab, pertuzumab, T-DM1, lapatinib, neratinib)

Risk factor	Score	Level of evidence
Previous cardiovascular disease		
Heart failure or cardiomyopathy	Very high	C
Myocardial infarction or CABG	High	B
Stable angina	High	B
Severe valvular heart disease	High	C
Baseline LVEF <50%	High	C
Borderline LVEF 50–54%	Medium[2]	B
Arrhythmia[a]	Medium[2]	C
Cardiac biomarkers (where available)		
Elevated baseline troponin[b]	Medium[2]	B
Elevated baseline BNP or NT-proBNP[b]	Medium[2]	C
Demographic and cardiovascular risk factors		
Age ≥80 years	High	B
Age 65–79 years	Medium[2]	B
Hypertension[c]	Medium[1]	B
Diabetes mellitus[d]	Medium[1]	C
Chronic kidney disease[e]	Medium[1]	C
Current cancer treatment regimen		
Includes anthracycline before HER2-targeted therapy	Medium[1f]	B
Previous cardiotoxic cancer treatment		
Prior trastuzumab cardiotoxicity	Very high	C
Prior (remote) anthracycline exposure[g]	Medium[2]	B
Prior radiotherapy to left chest or mediastinum	Medium[2]	C
Lifestyle risk factors		
Current smoker or significant smoking history	Medium[1]	C
Obesity (BMI >30 kg/m^2)	Medium[1]	C
Risk level		

European Journal of Heart Failure (2020)

The Role of LVEF in Cardio-Oncology

- LVEF measurement **is essentially a relatively insensitive tool** for detecting cardiotoxicity at an early stage, mainly because no considerable change in LVEF occurs until a critical amount of myocardial damage has taken place, and the damage only comes to the forefront after compensatory mechanisms are exhausted.



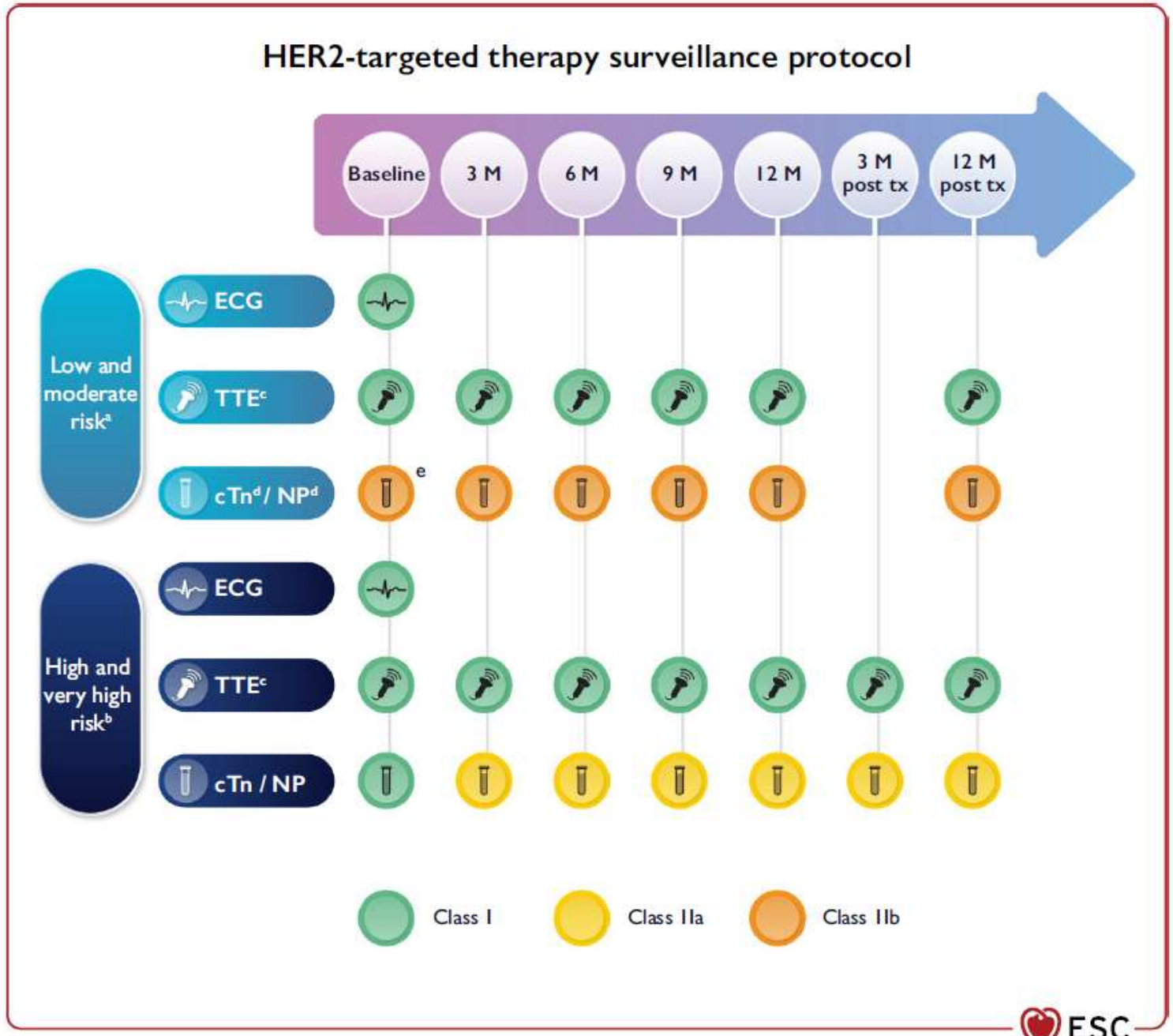
- The diagnosis of cardiotoxicity, based on evidence of a decrease in LVEF, **precludes** any chance of

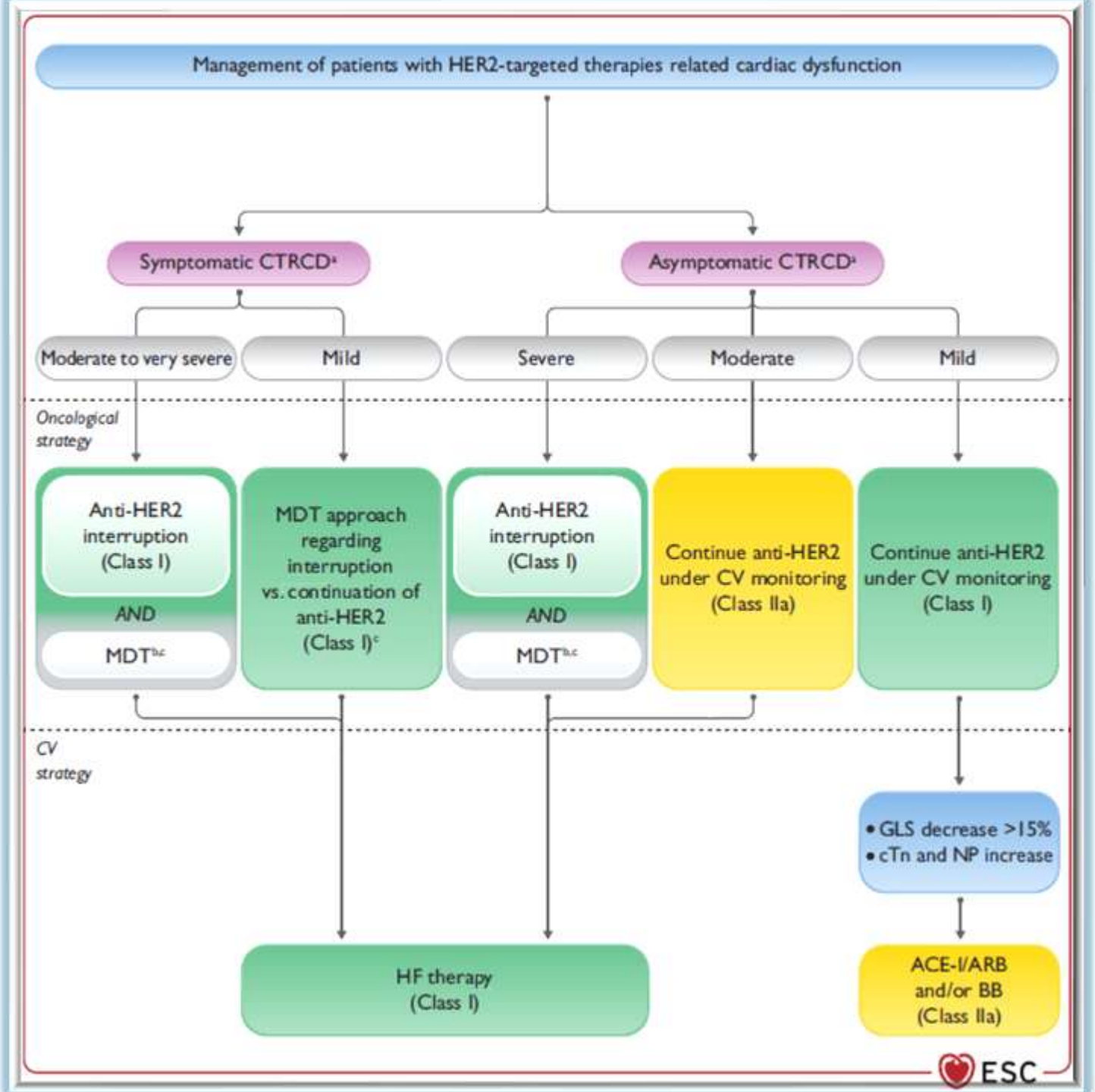
- *A normal LVEF does not exclude the possibility of later cardiac deterioration*

Definition of Chemotherapy Related Cardiotoxicity

CTRCD		
Symptomatic CTRCD (HF)[a,b]	Very severe	HF requiring inotropic support, mechanical circulatory support, or consideration of transplantation
	Severe	HF hospitalization
	Moderate	Need for outpatient intensification of diuretic and HF therapy
	Mild	Mild HF symptoms, no intensification of therapy required
Asymptomatic CTRCD	Severe	New LVEF reduction to <40%
	Moderate	New LVEF reduction by ≥10 percentage points to an LVEF of 40–49% *OR* New LVEF reduction by <10 percentage points to an LVEF of 40–49% AND either new relative decline in GLS by >15% from baseline OR new rise in cardiac biomarkers[c]
	Mild	LVEF ≥ **50%** AND new relative decline in GLS by >15% from baseline AND/OR new rise in cardiac biomarkers[c]

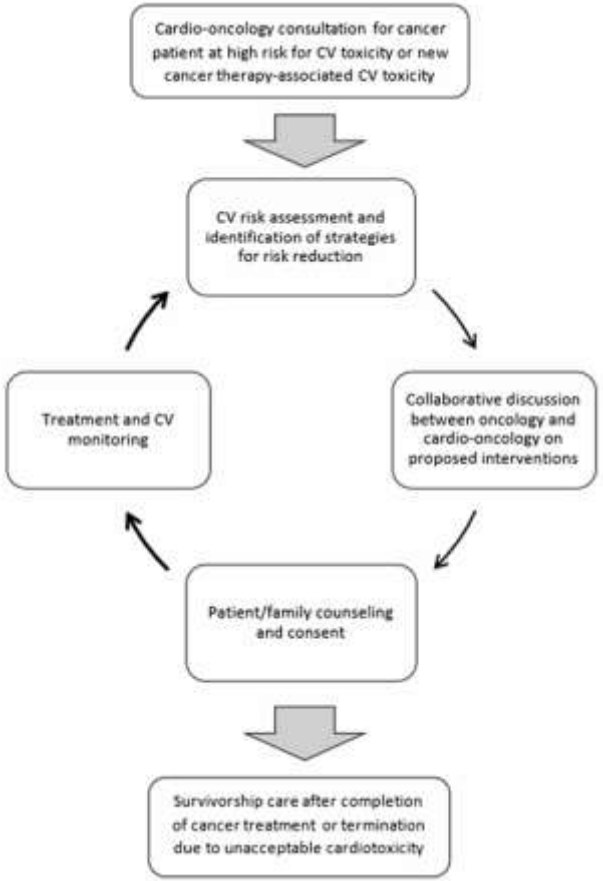
ESC C-O Guidelines 2022

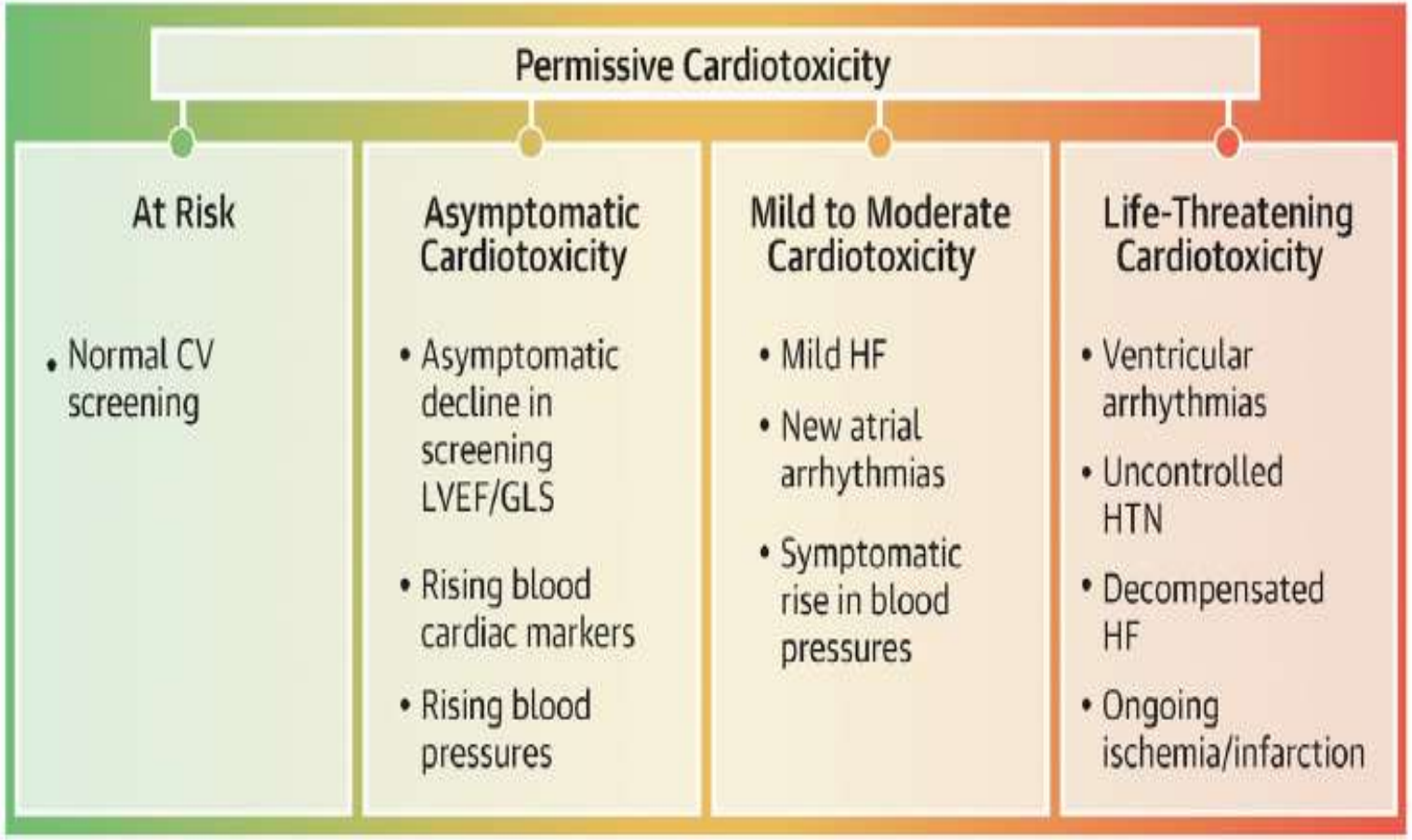

HER2-targeted therapy surveillance protocol
Baseline
3 M
6 M
9 M
12 M
3 M post tx
12 M post tx
Low and moderate risk[a]
ECG
TTE[c]
cTn[d] / NP[d]
e
High and very high risk[b]
ECG
TTE[c]
cTn / NP
Class I
Class IIa
Class IIb
ESC


Management of patients with HER2-targeted therapies related cardiac dysfunction
Symptomatic CTRCD[a]
Asymptomatic CTRCD[a]
Moderate to very severe
Mild
Severe
Moderate
Mild
Oncological strategy
Anti-HER2 interruption (Class I)
AND
MDT[b,c]
MDT approach regarding interruption vs. continuation of anti-HER2 (Class I)[c]
Anti-HER2 interruption (Class I)
AND
MDT[b,c]
Continue anti-HER2 under CV monitoring (Class IIa)
Continue anti-HER2 under CV monitoring (Class I)
CV strategy
• GLS decrease >15%
• cTn and NP increase
HF therapy (Class I)
ACE-I/ARB and/or BB (Class IIa)
ESC

The Spectrum of Permissive Cardiotoxicity: From "At Risk" Through Life-Threatening Cardiotoxicity

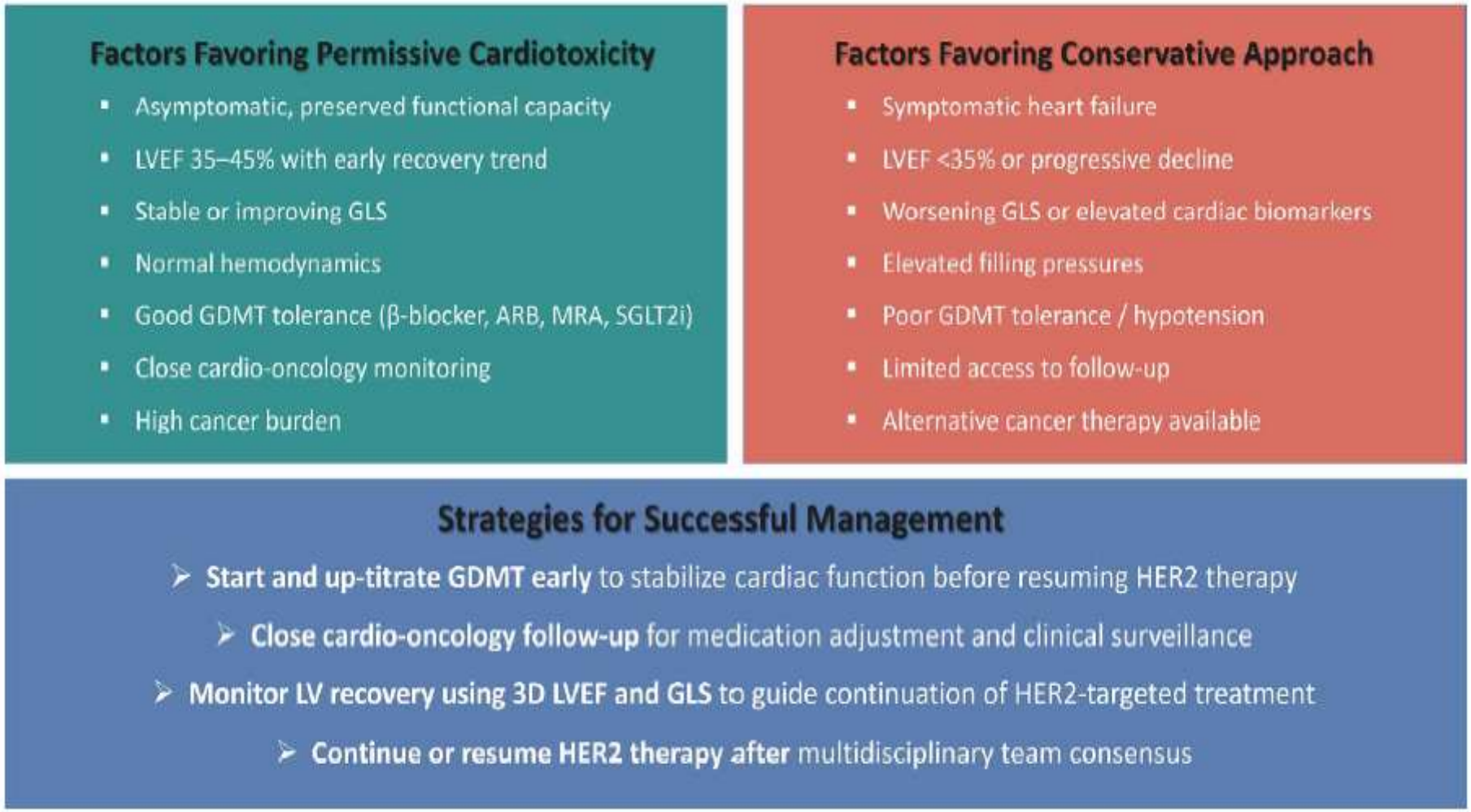
"Should this therapy be discontinued?" vs. "How can this therapy be continued?"





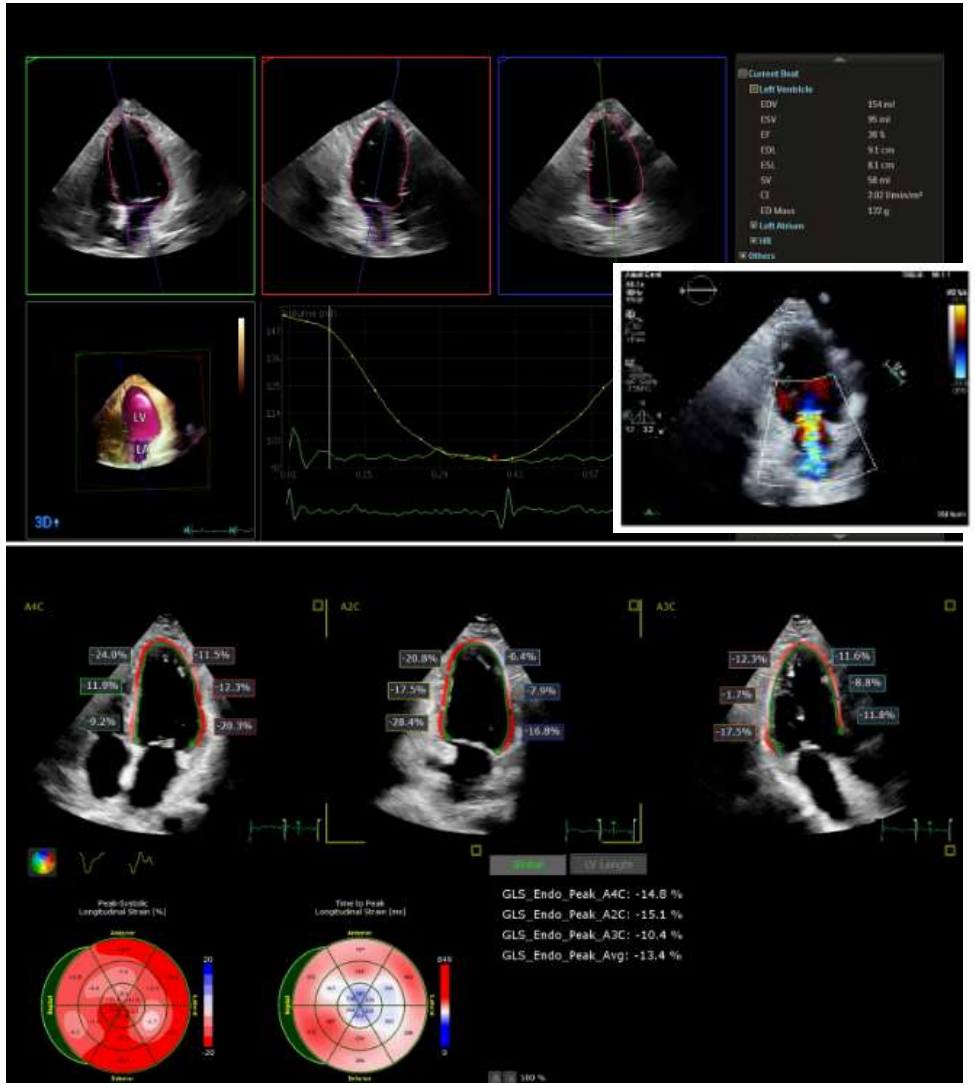
Porter C, et al. J Am Coll Cardiol CardioOnc. 2022;4(3):302-312.

Permissive Cardiotoxicity in HER2+ Breast Cancer

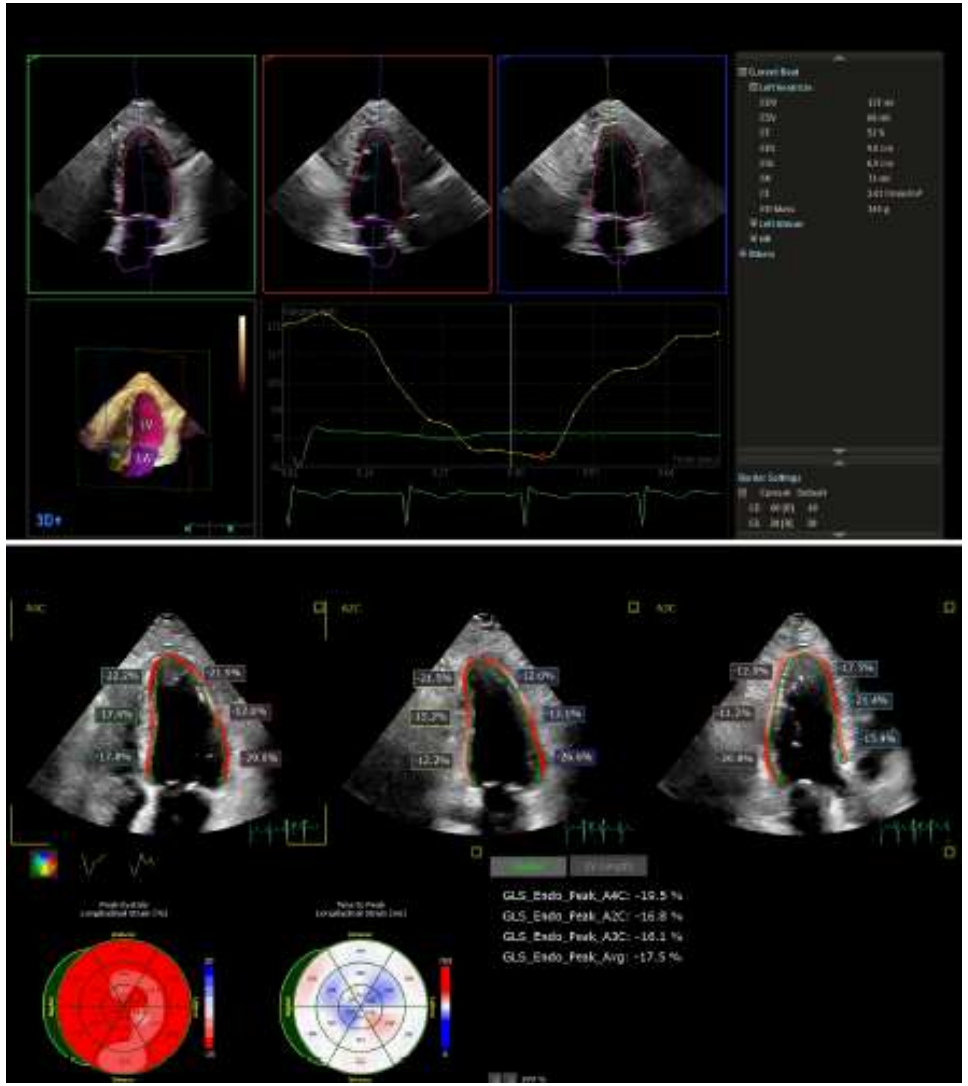


JACC Case Rep. 2026;31:106555

During Trastuzumab Treatment



HF Therapy+ continueTrastuzumab



J Am Coll Cardiol CardioOnc 2022;4:302–312

Selected Novel HER2-targeted therapies in Development

Drug Name	Class	Target(s)/Mechanism of Action:	Current Stage of Development	Relevant Clinical Trials	Noteworthy Findings/Potential Advantages
Zanidatamab	Bispecific Antibody	HER2 (two distinct epitopes)	Phase 2	NCT01042379	Greater antitumor activity than trastuzumab + pertuzumab preclinically
KN026	Bispecific Antibody	HER2 (based on trastuzumab and pertuzumab)	Phase 2	NCT05838066 NCT04881929 NCT06747338	Comparable efficacy to trastuzumab + pertuzumab in MBC
Inetetamab	Monoclonal Antibody	HER2 (enhanced ADCC)	Approved (China), Phase 2/3	NCT04681911 NCT04681287 NCT06641544	Potential in combination with PD-1 inhibitors, pyrotinib, pertuzumab
Trastuzumab Duocarmazine (SYD985)	ADC	HER2+duocarmycin payload	Phase 3	NCT01042379	Promising efficacy in HER2-positive and HER2-low BC
ARX788	ADC	HER2+proprietary payload	Phase 2	NCT01042379 NCT06578286	Activity in HER2-positive, HER2-low, and T-DM1-resistant models
Disitamab Vedotin (RC48)	ADC	HER2+MMAE payload	Approved (China), Phase 2	NCT06278870	Good performance in HER2-positive and HER2-low preclinical models and clinical trials
Pyrotinib	TKI	Irreversible pan-HER (EGFR, HER2, HER4)	Approved (China), Phase 3	NCT06832904 NCT06475443	Promising antitumor activity, including in brain metastases
Poziotinib	TKI	Irreversible pan-HER	Phase 2	NCT04172597 NCT03429101	Antitumor activity in heavily pretreated HER2-positive MBC and HER2 exon 20 mutant NSCLC
Mobocertinib	TKI	Selective HER2 (exon 20 insertions)	Approved (NSCLC), Phase 1/2 (Breast Cancer)	NCT05241873 NCT04129502	Potential efficacy in HER2-mutant solid tumors, including breast cancer

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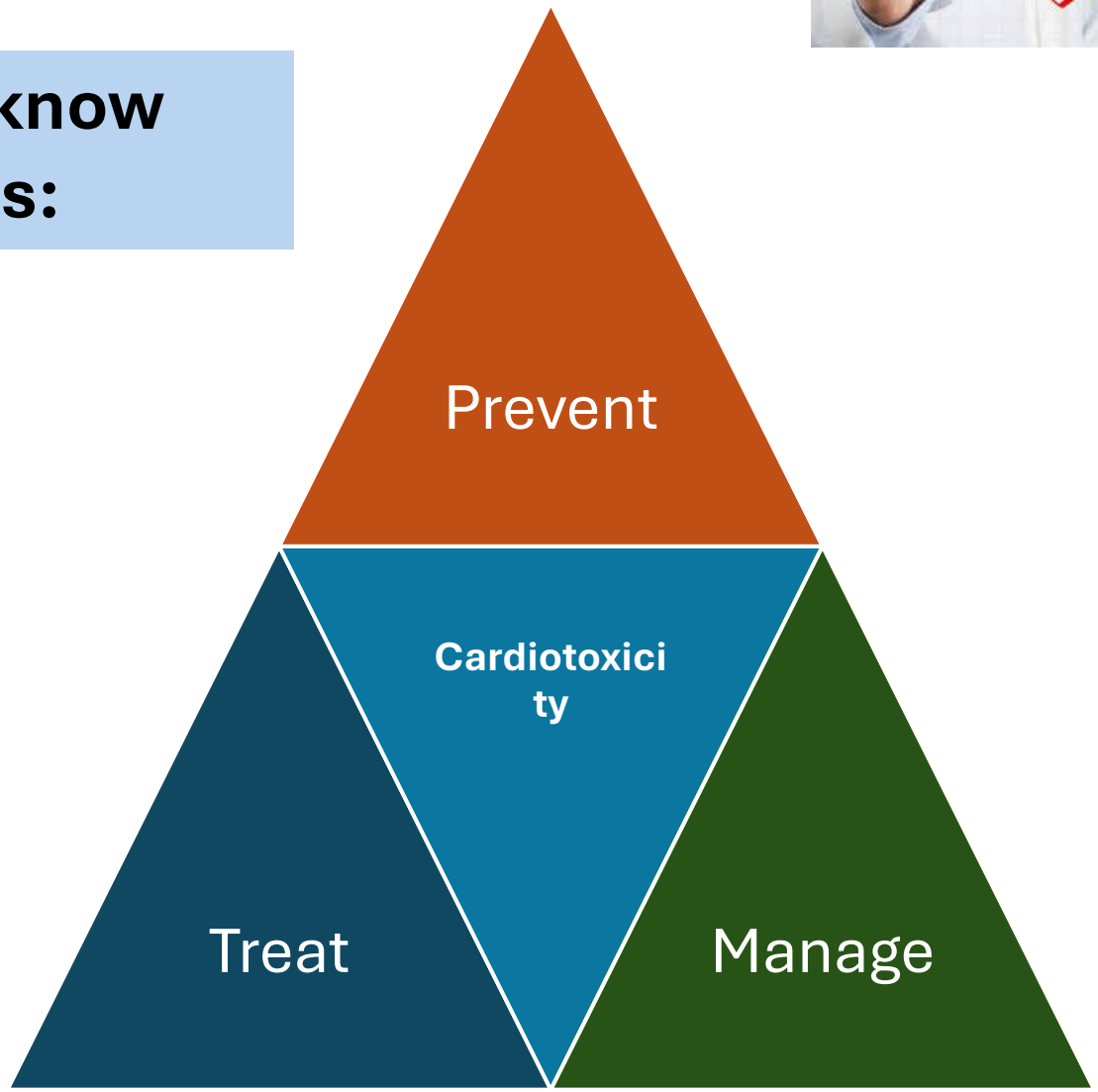
Take Home Message

Three Tasks A Cardiologist Should know when Encountering Cancer Patients:

- **Prevention (risk stratification-Early detection and continuous monitoring)**
- **Treatment (too late-try NOT to reach this stage)**
- **Manage during anticancer therapy (Exacerbation of existing HF, ACS,…)**



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