Next-Generation Targeted Therapies: Opportunities and Emerging Risks

Valentina Guarneri, MD, PhD

Department of Surgery, Oncology and Gastroenterology – University of Padova, Italy
Oncology 2 Unit – Istituto Oncologico Veneto – IRCCS, Padova, italy

Declaration of Interest

Personal fees for advisory board membership for AstraZeneca, Daiichi Sankyo, Eli Lilly, Exact Sciences, Menarini Stemline, MSD, Novartis, Pfizer, Roche, Gilead

Personal fees as an invited speaker for AstraZeneca, Daiichi Sankyo, Eli Lilly, Pfizer, Exact Sciences, Gilead, Menarini Stemline, Novartis, Roche, Abbvie

Introduction

- Heart disease and cancer are the major causes of morbidity and mortality worldwide
- Advances in systemic cancer therapies as well as the new targeted therapies have dramatically altered cancer prognosis
- Anticancer therapies can cause a wide spectrum of short- and long-term cardiotoxic effects
- New targeted therapies can have unintended impacts on the CV system, and introduced unexpected CV complications beyond congestive heart failure

Where do we come from?

The Trastuzumab paradigm

Long-Term Cardiac Tolerability of Trastuzumab in Metastatic Breast Cancer: The M.D. Anderson Cancer Center Experience

Valentina Guarneri, Daniel J. Lenihan, Vicente Valero, Jean-Bernard Durand, Kristine Broglio, Kenneth R. Hess, Laura Boehnke Michaud, Ana M. Gonzalez-Angulo, Gabriel N. Hortobagyi, and Francisco J. Esteva

VOLUME 24 · NUMBER 25 · SEPTEMBER 1 2006

JOURNAL OF CLINICAL ONCOLOGY

EDITORIAL

Heart of Darkness: The Downside of Trastuzumab

Daniel F. Hayes, *Breast Oncology Program, University of Michigan Comprehensive Cancer Center, Ann Arbor, MI*
Michael H. Picard, *Cardiac Ultrasound Laboratory, Cardiology Division, Massachusetts General Hospital and Harvard Medical School, Boston, MA*

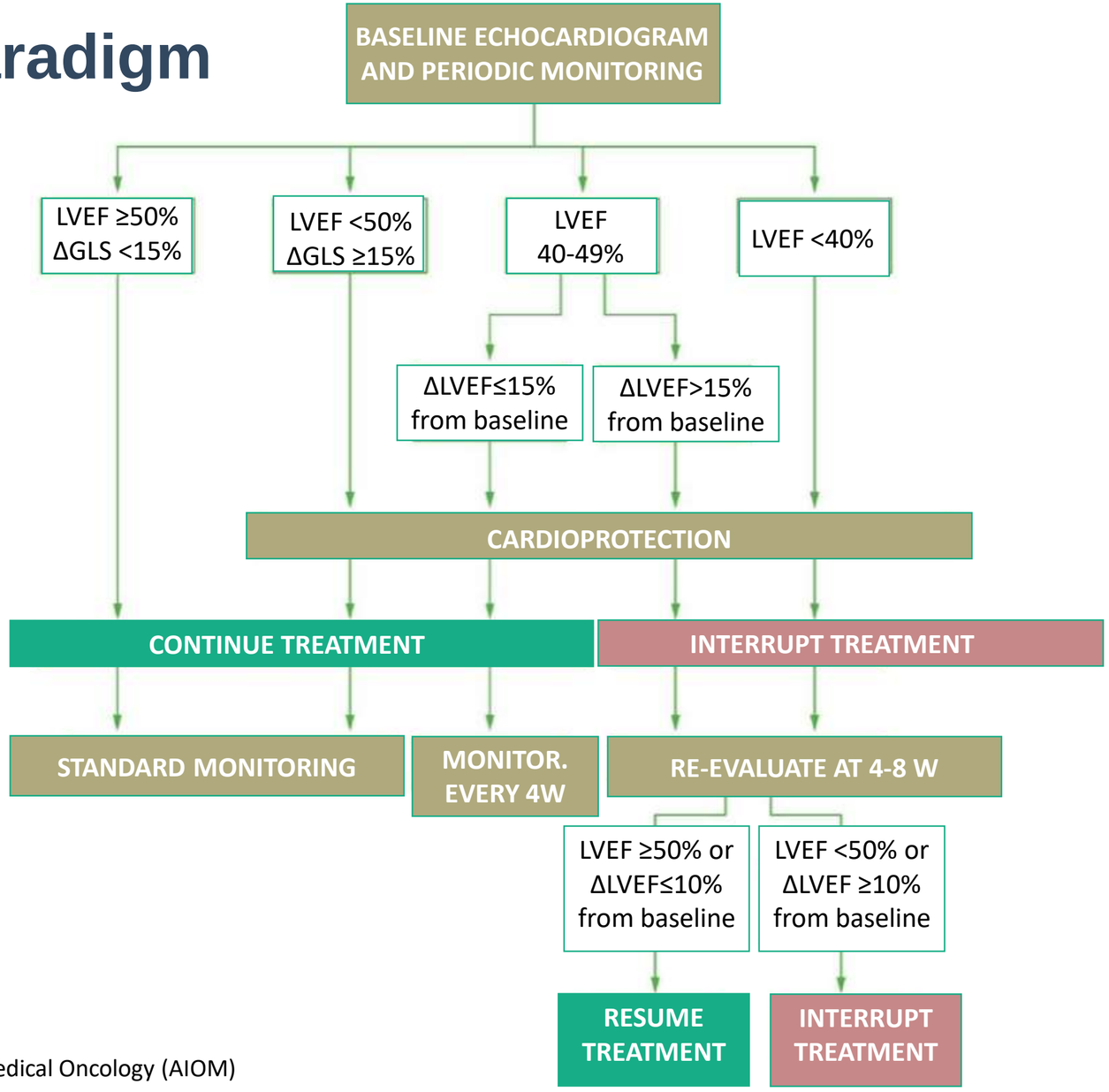
In most trials,
significant asymptomatic LVEF decline
was defined as an **absolute decrease in LVEF of ≥ 10% to below the lower limit of normal or ≥ 16% from baseline value.**

Trastuzumab was stopped temporarily or permanently as indicated on the basis of adequate or insufficient recovery, respectively.

Where do we come from?

The Trastuzumab paradigm

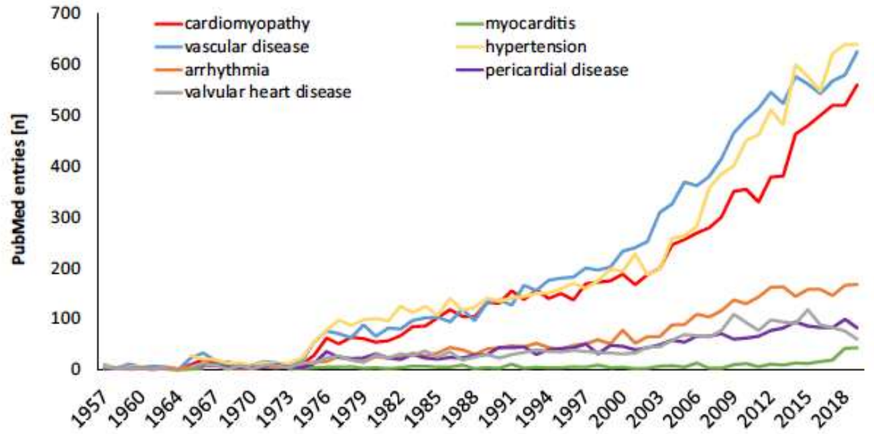
With the evolution of cardio-oncology and the integration of cardioprotective strategies into our monitoring algorithms, we are now able to 'rescue' a proportion of patients who in the past would have permanently discontinued trastuzumab, allowing them instead to resume and successfully complete treatment

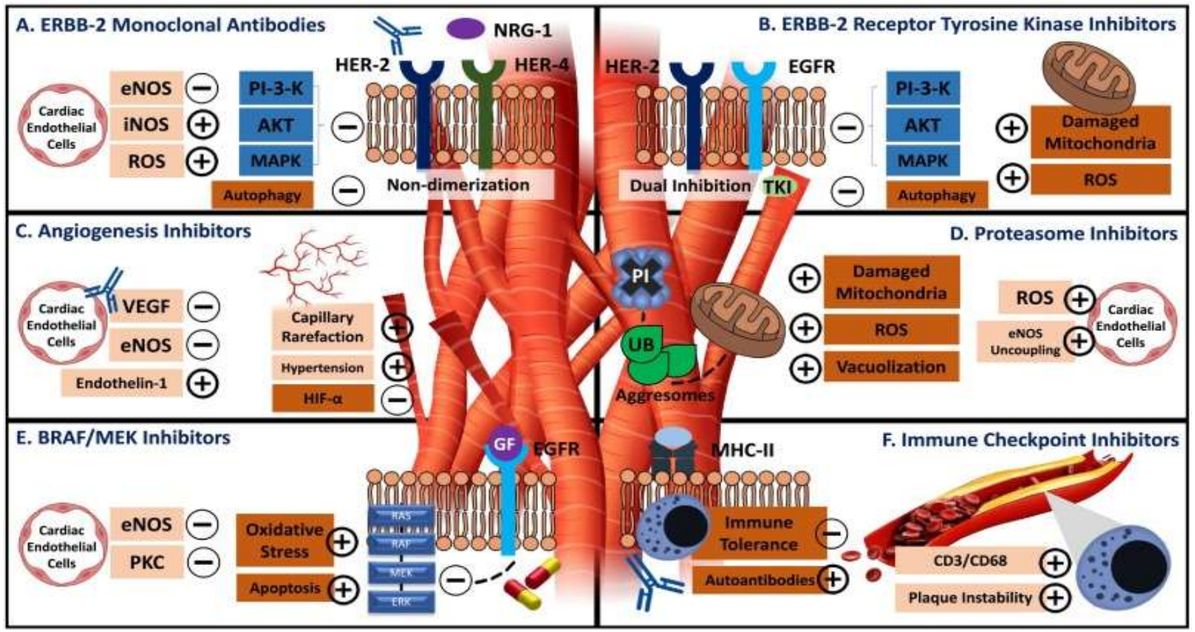


Adapted from Italian Guidelines on Cardio-Oncology – Italian Association of Medical Oncology (AIOM)

The Cardio-Oncology Discipline and the definition of cardiovascular toxicity of cancer therapy

- In the past 20 years, increased recognition of short- and long-term cardiovascular side effects, as a result of increased awareness and attention to this toxicity, as well as the increased exposure of a growing number of patients to potentially toxic therapies
- The discipline of Cardio-Oncology has emerged to prevent, mitigate, and manage CV diseases and complications in cancer patients in addition to providing assistance in balancing the risks and benefits of cancer therapy
- A uniform understanding and agreement regarding what constitutes a CV toxicity represent a critical element of such efforts, for both clinical practice and research endeavours
- Coordinated effort from international scientific societies to develop guidelines for prevention and management of CV side effects of anticancer therapy





Lyon R, et al. Eur Heart Journal 2022;
Curigliano G, et al. Ann Oncol 2020; Herrmann J, et al. European Heart Journal (2022) 43, 280–299, Kreidieh and McQuade, American Heart Journal Plus: Cardiology Research and Practice 2024

Cardiovascular side effects of new targeted agents: today’s agenda

- Immune checkpoint inhibitors (ICI): dealing with the host
- “Old” drugs-new role: the shift towards adjuvant treatment of early stages
- Old targets-new drugs: the advent of Antibody Drug Conjugates

Cardiovascular side effects of new targeted agents: today’s agenda

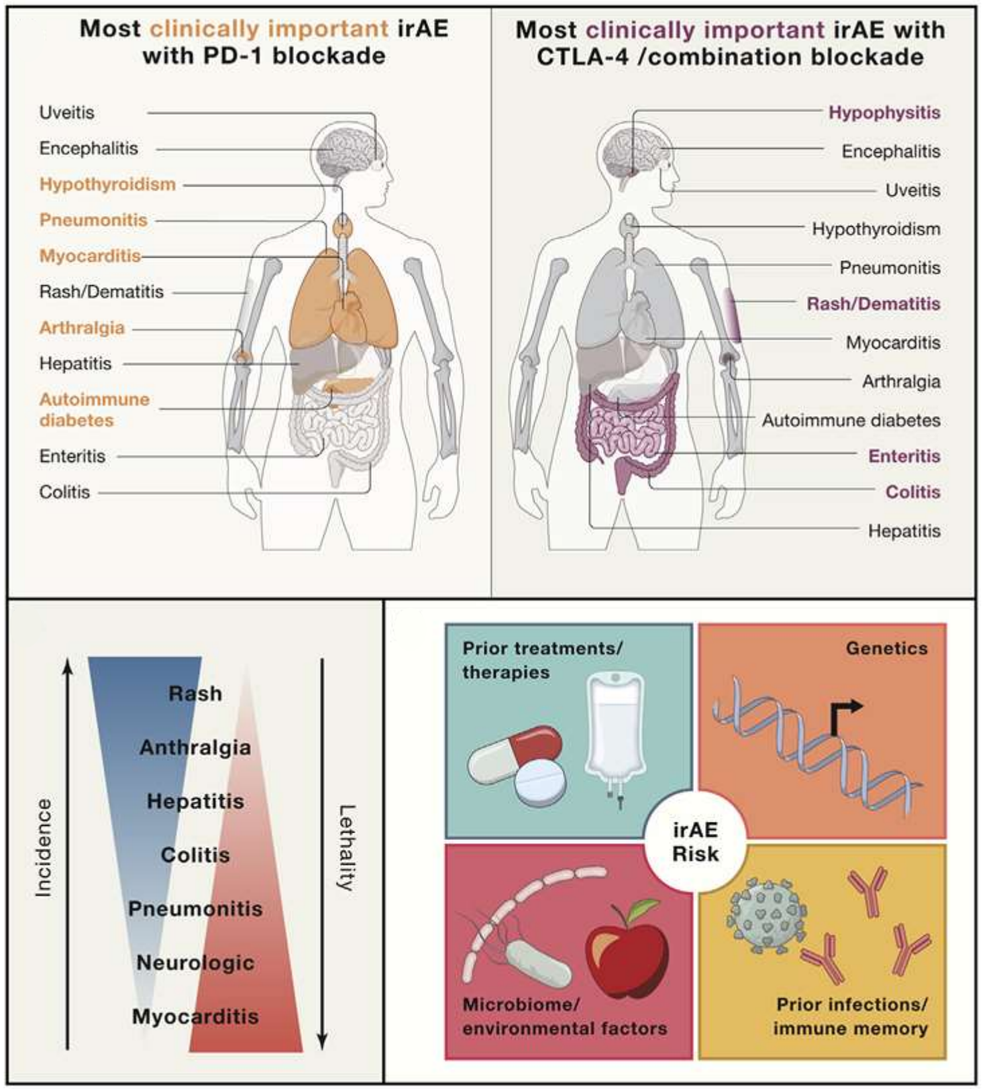
- Immune checkpoint inhibitors (ICI): dealing with the host
- “Old” drugs-new role: the shift towards adjuvant treatment of early stages
- Old targets-new drugs: the advent of Antibody Drug Conjugates

Immune checkpoint inhibitors (ICI)

Dealing with the host

- **Immunotherapy has now become an integral component of therapeutic algorithms** for the majority of solid tumors.
  - It has significantly improved progression-free survival and overall survival in the metastatic setting.
  - In the early disease setting, it has also led to meaningful gains in disease-free survival and even OS, contributing to a modification of the natural history of several cancers.

- These advances, however, have introduced **new toxicity profiles, including clinically relevant cardiac toxicities**.
  - from subclinical disease with asymptomatic cardiac biomarker elevation, fatigue, and general malaise to chest pain, dyspnea, palpitations, multiorgan failure, cardiogenic shock, and cardiac arrest *(often secondary to myocarditis)*

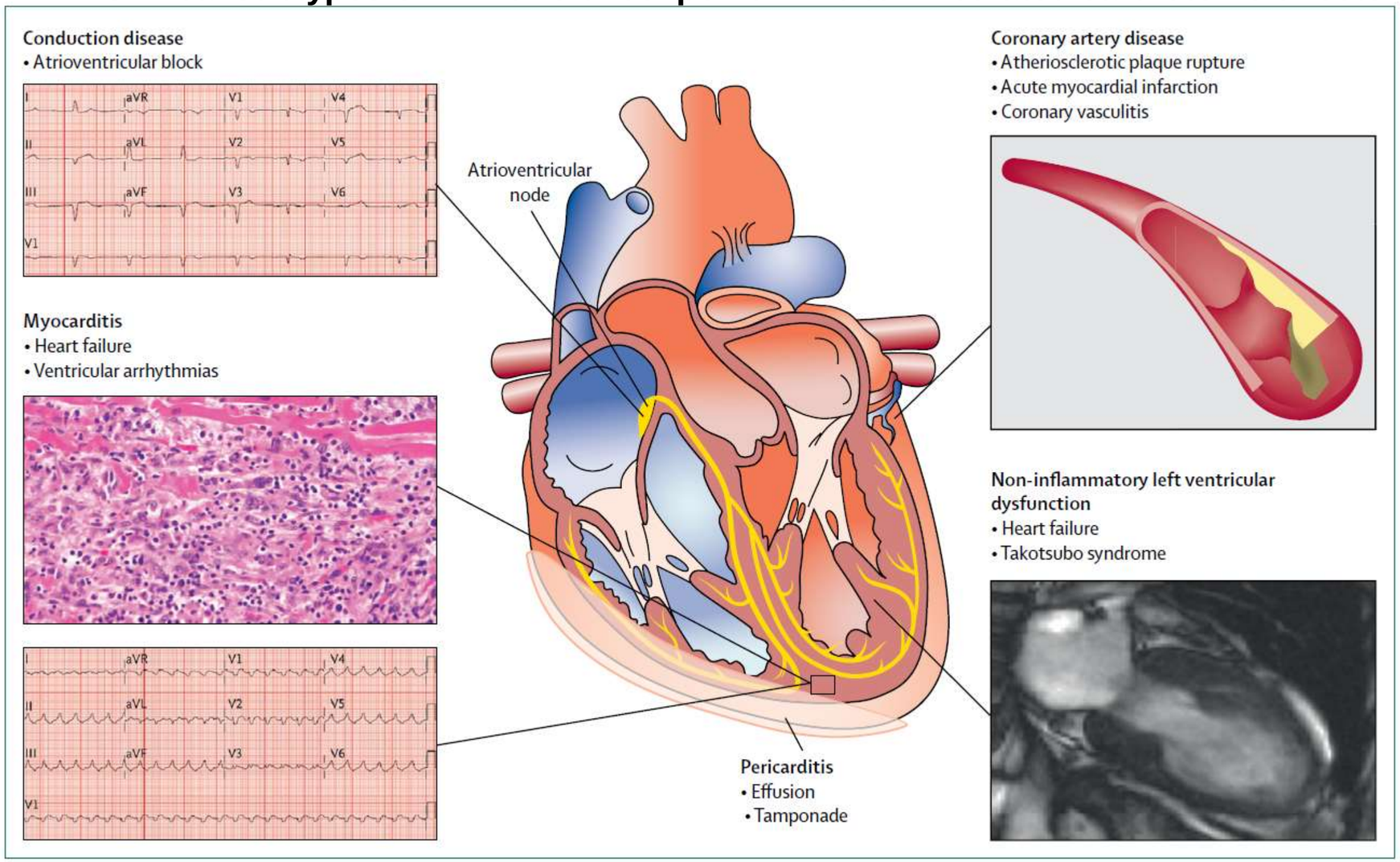


Dougan M et al, Cell 2021

Cardiotoxicity of ICI

Well-known risk

Clinical subtypes of immune checkpoint inhibitor-mediated cardiotoxic effects

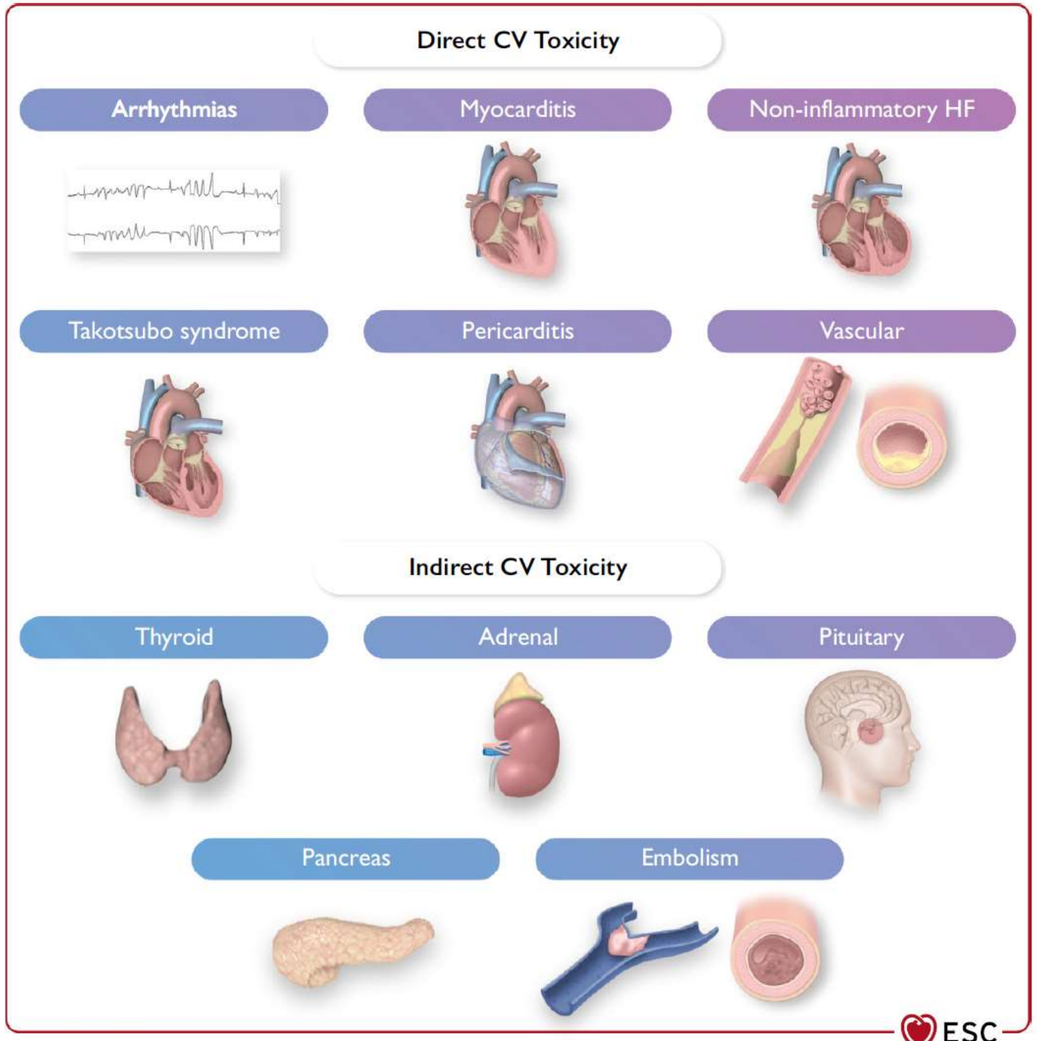


Lyon AR et al, Lancet Oncol 2018,
Guarneri V, ESMO Congress 2025

Cardiotoxicity of ICI

Well-known risk

immune checkpoint inhibitor-mediated cardiotoxic effects



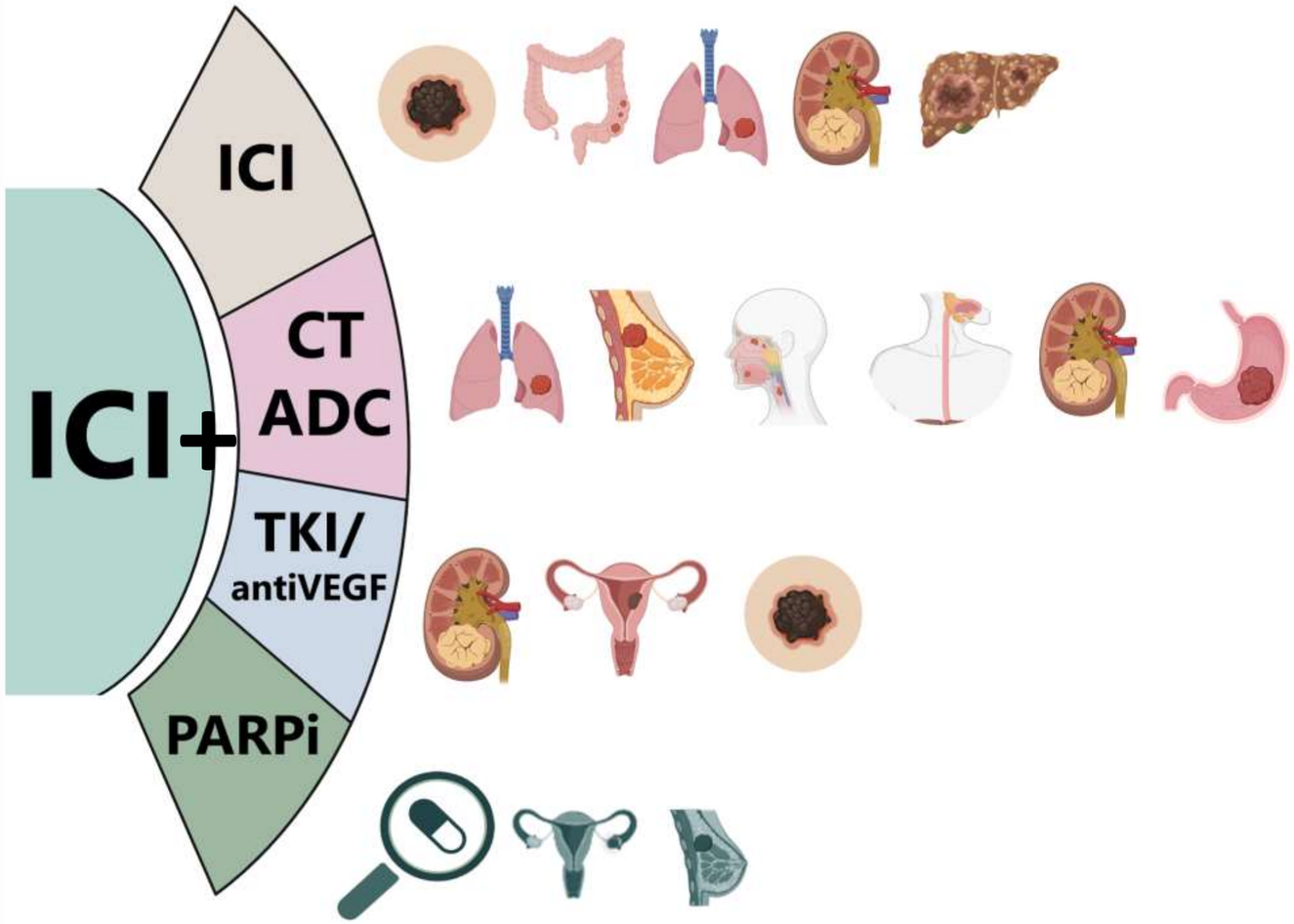
Cardiotoxicity	Incidence*
Myocarditis	0.09%-2.4%
Pericarditis	<1%-2%
Pericardial effusion	2%
Cardiac Arrhytmia	4%
Myocardial Infarction	<1%-2%
Heart failure	0.4%
Takotsubo cardiomiopathy	Rarely reported
Cardiac arrest	Rarely reported

*varies according to the molecule used and the method of treatment (mono-combo)

Lyon R, et al. European Heart Journal 2022, Guarneri V ESMO Congress 2025

Cardiotoxicity of ICI + …

Emerging combinations



SYNERGISTIC CARDIOTOXICITY

ICI causes myocardial injury

Myocardial injury amplified by the concomitant or subsequent use of a cancer therapy
targeting a survival pathway expressed in both cancer cells and cardiomyocytes

and so on...

Guarneri, ESMO Congress 2025

Cardiovascular side effects of new targeted agents: today’s agenda

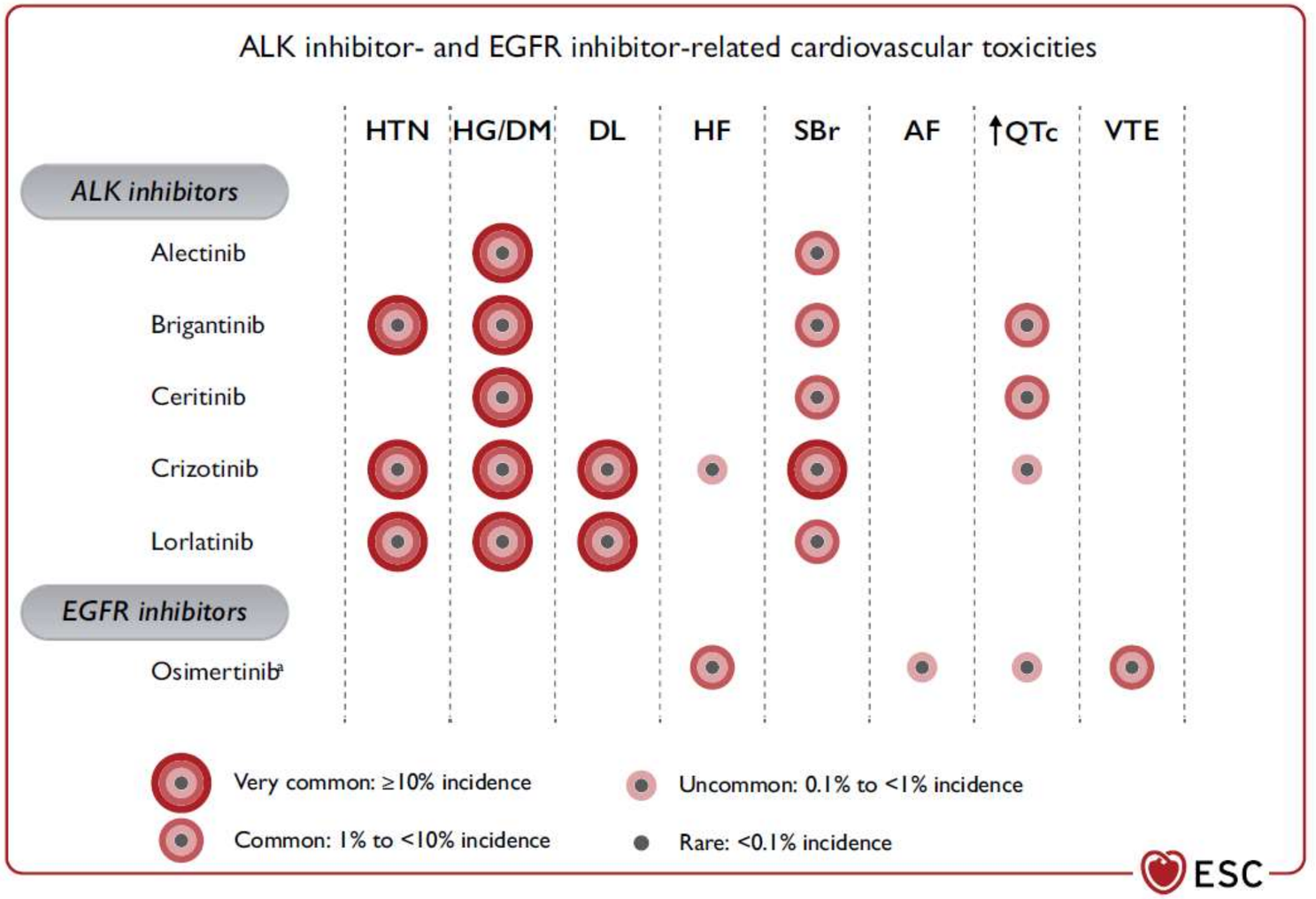
- Immune checkpoint inhibitors (ICI): dealing with the host
- “Old” drugs-new role: the shift towards adjuvant treatment of early stages
- Old targets-new drugs: the advent of Antibody Drug Conjugates

From metastatic to curative setting: new responsibilities

Moving targeted therapies into the curative setting amplifies challenges in risk-benefit assessment, demanding more robust long-term safety monitoring and surveillance protocols.

- Higher expectations of cure may translate into a lower tolerance for long-term toxicity
- Late, cumulative, and off-target effects become clinically meaningful
- Risk–benefit assessment differs fundamentally from the metastatic setting
- Structured, long-term surveillance strategies are required

ALK and EGFR inhibitors



Lyon R, et al. European Heart Journal 2022

Cyclin dependent kinase (CDK) 4/6 inhibitors

Recommendations	Class[a]	Level[b]
QTc[c,d] monitoring is recommended at baseline and 14 and 28 days in all patients with cancer receiving ribociclib.[361,365,367,368]	I	A
QTc[c,d] monitoring is recommended in patients treated with ribociclib with any dose increase.[361,365,367,368]	I	B
QTc[c] monitoring should be considered in patients treated with palbociclib or abemaciclib who have a baseline QTc above the normal range[c] or other conditions that may prolong the QTc interval.[e]	IIa	C

Lyon R, et al. European Heart Journal 2022

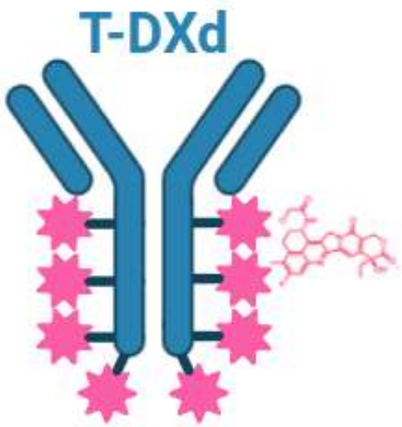
Cardiovascular side effects of new targeted agents: today’s agenda

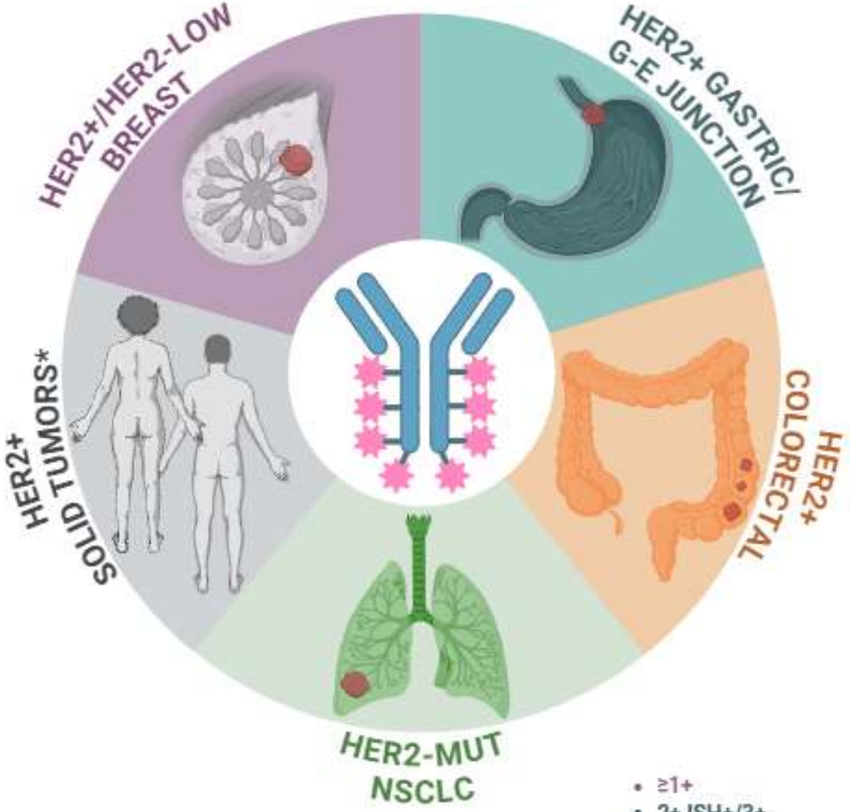
- Immune checkpoint inhibitors (ICI): dealing with the host
- “Old” drugs-new role: the shift towards adjuvant treatment of early stages
- Old targets-new drugs: the advent of Antibody Drug Conjugates

Antibody-drug Conjugates (ADCs)

Antibody-drug conjugates (ADC) have revolutionized the concept of chemotherapy in oncology by combining the cytotoxic effect of chemotherapy with a targeted mechanism of action.

- **A key question is whether this dual nature may influence cardiotoxicity, particularly when the ADC target is HER2**





5.4 mg/mq (n=1449)	LVEF decrease 3.9%
6.4 mg/mq (n=669)	LVEF decrease 1.6%

*agnostic FDA indication

Hamilton E et al, CCR 2024; Levy BP et al, ASCO 2025; Guarneri V ESC Congress 2024, Guarneri V, ESMO Congress 2025

Take home messages

- Therapeutic innovation has transformed cancer outcomes while redefining cardiovascular risk
- New targeted and immune-based therapies introduce complex and delayed cardiotoxicities
- The curative setting requires a different risk-benefit paradigm and long-term surveillance
- Clinical trials alone are insufficient to capture the true cardiovascular risk of contemporary oncology treatments *(...stay tuned...)*
- Integrated cardio-oncology services and real-world data are essential to safely translate therapeutic innovation into long-term patient benefit