ESC Cardiovascular Round Table

ESC European Society of Cardiology

From Drug Design to Long-Term Care
Making Safety Sustainable

Valentina Guarneri, MD, PhD

Department of Surgery, Oncology and Gastroenterology – University of Padova, Italy

Oncology 2 Unit – Istituto Oncologico Veneto – IRCCS, Padova, italy

Introduction

- Over the past two decades, many **cancers have evolved into “chronic” or potentially curable diseases**
- Improved survival has **unmasked cumulative and late-onset** toxicities
- Cardiotoxicity is **no longer a rare adverse event**, but a systemic consequence of effective cancer therapies
- Cardiovascular risk is **not static**, it evolves with treatment sequencing, aging, and comorbidities.
- **Survivorship** now represents a critical phase of cancer care, not a post-treatment afterthought

Long-term care in the evolving oncological lansdscape: today's agenda

- The population of cancer patients is evolving
- From drug design....
- ...to long-term care

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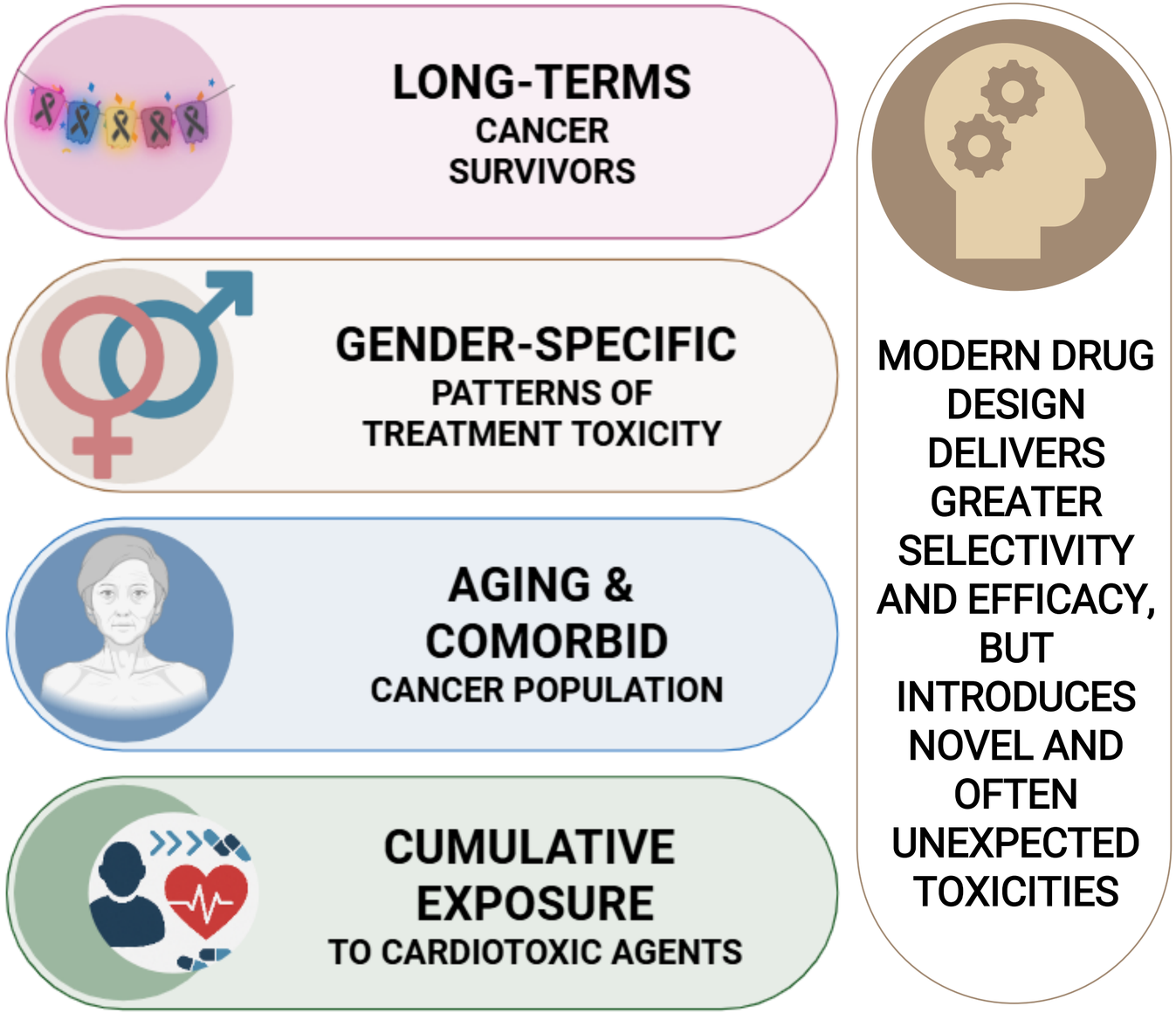
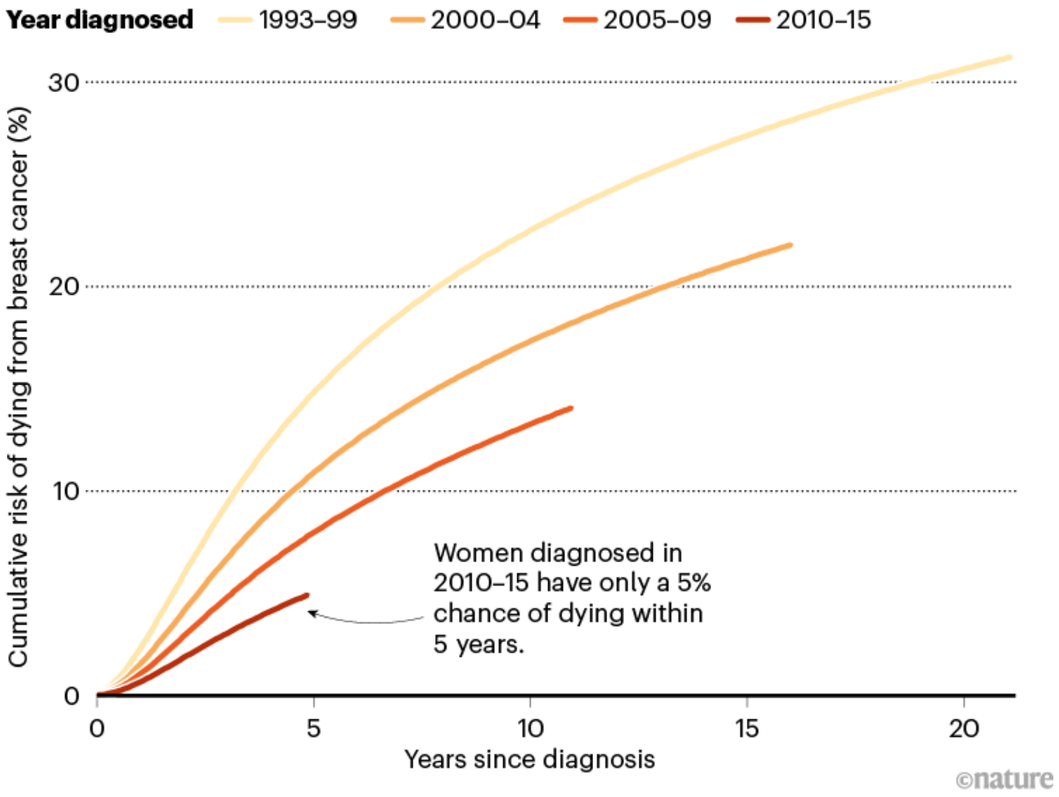
The population of cancer patients is evolving

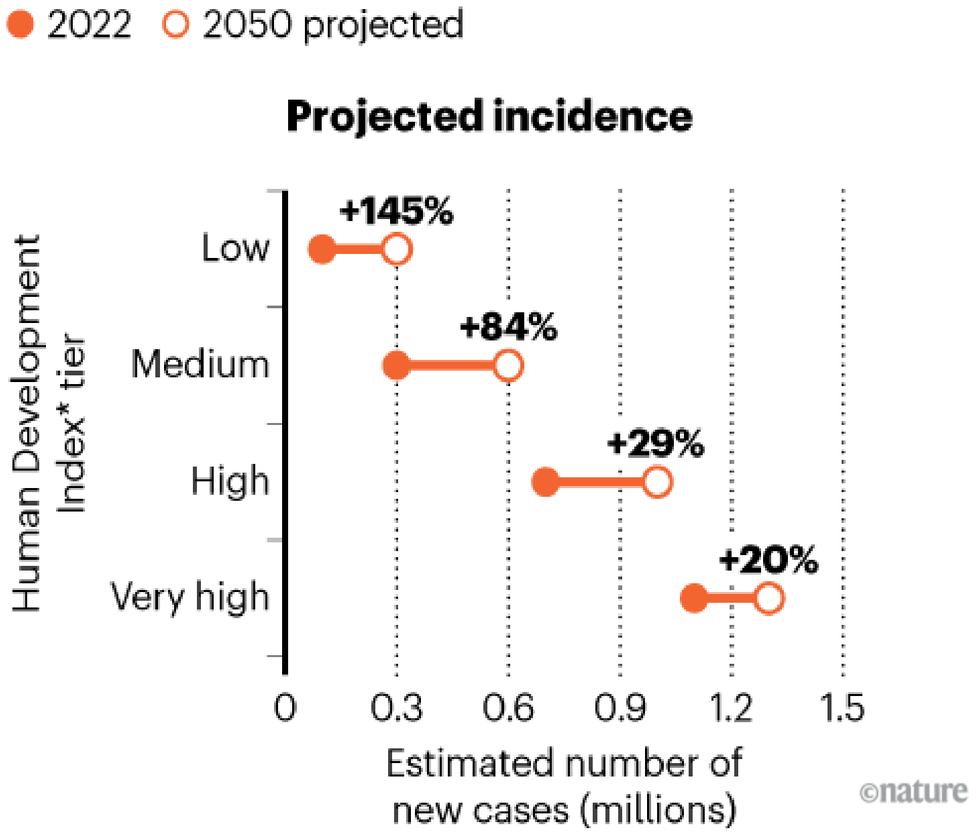


adapted and modified from Guarneri V, ESMO Congress 2025

Long-term survivorship: a growing clinical reality

the paradigmatic example of breast cancer





These survival gains are expected to markedly increase the prevalence of long-term breast cancer survivors over the coming decades

Adapted from Kim et al, Nature Medicine 2025 and from Taylor et al, BMJ 2023

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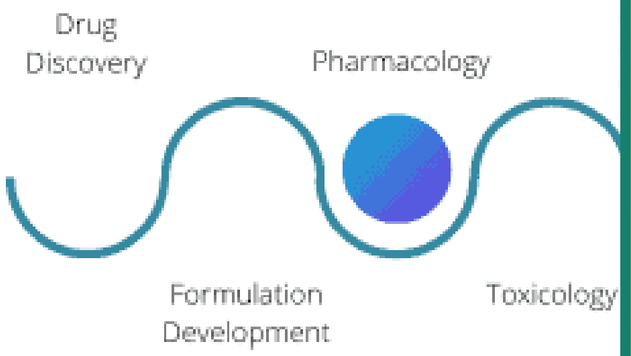
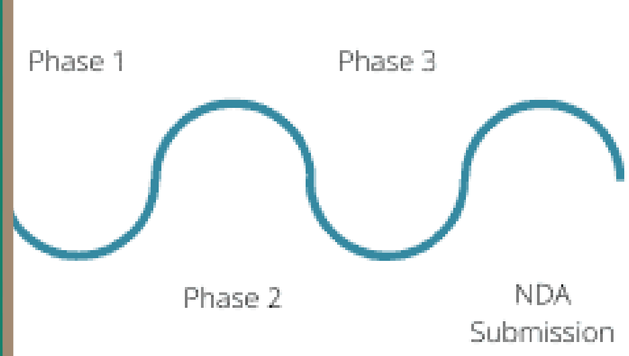
From drug design...

Preclinical



In preclinical studies, the nature and incidence of the range of potential **cardiovascular toxicities may either not be predictable or recognized.**

Clinical



Pivotal clinical trials may **exclude patients at heightened cardiovascular risk*** and typically are **not representative of the broader "real-world" population**

Cardiotoxicity may only become apparent when the drugs are used clinically, and potentially exacerbated by pre-existing cardiovascular risk factors and disease.

The primary focus of most oncology therapeutic trials is anticancer efficacy.

WHY IT MATTERS?
Underestimating cardiotoxicity does not just affect individual patients, it shifts the burden to survivorship care, increasing long-term cardiovascular morbidity and healthcare costs.

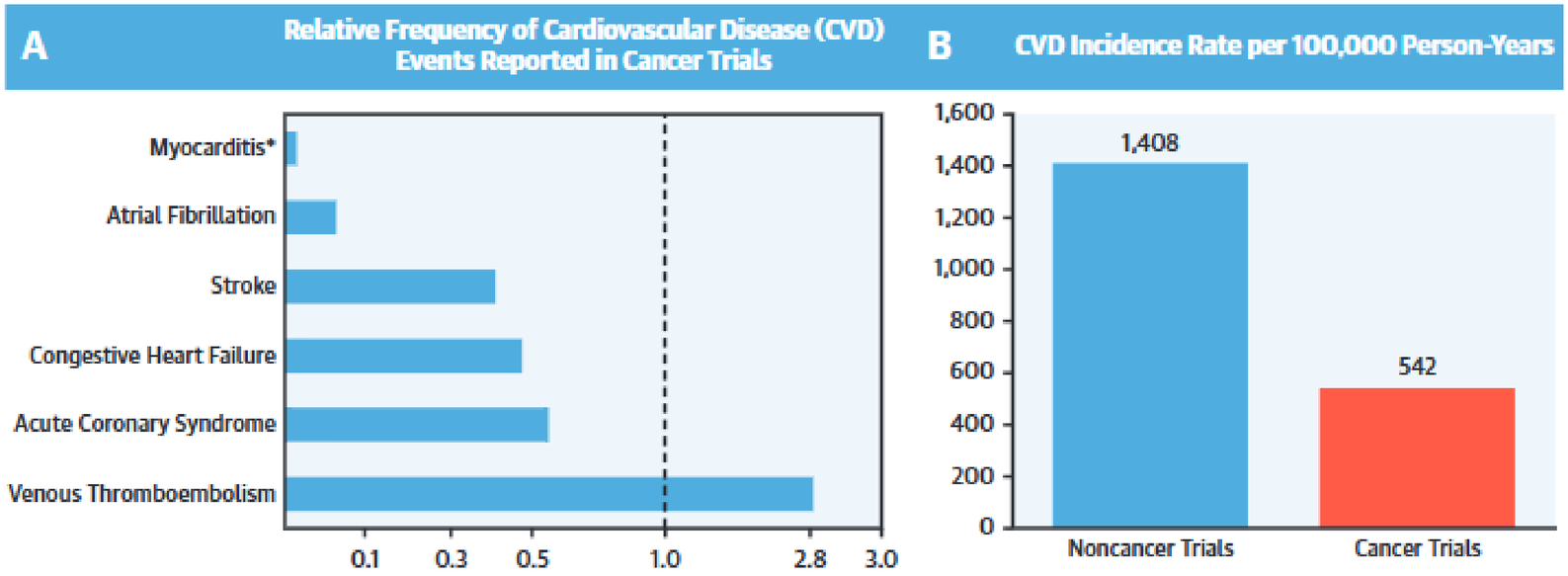
*FDA comprehensive review of eligibility criteria for commercial investigational new drug clinical trial applications submitted to FDA in 2015: 73% of trial protocols excluded patients with cardiovascular disease or increased cardiovascular risk

Bonaca et al, JACC Cardiooncology 2025; Jin et al, JCO 2017

From drug design...

Systematic evaluation of CV events reported in late-phase clinical trials supporting FDA approval of anticancer drugs:

- Major and non-major CV events were compared with background population risk
- Overall, **CV events were reported** in a substantial proportion of trials, but **at rates lower than those observed in comparable non-cancer populations**.



Bonsu, J.M. et al. J Am Coll Cardiol. 2020;75(6):620–8.

Bonsu et al, JACC 2020; Bishopric et al, JACC 2020

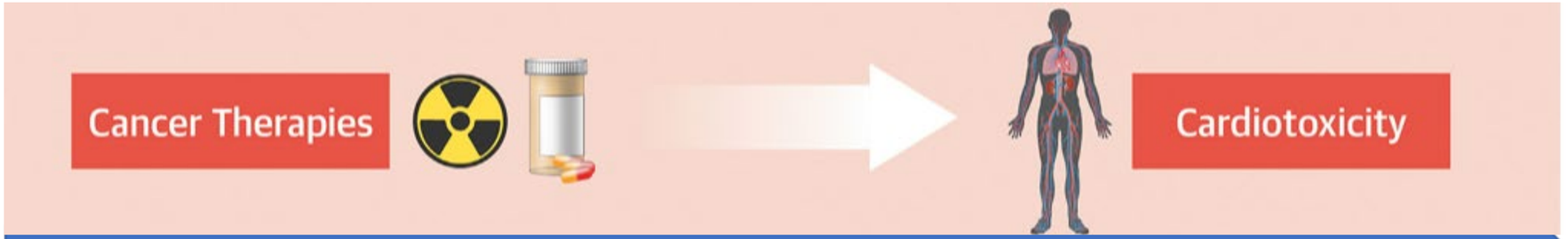
From drug design...

- **Pivotal oncology trials systematically underrepresent** patients at higher cardiovascular risk, due to both explicit exclusion criteria and implicit selection biases.
- Trial populations therefore **fail to reflect the cardiovascular risk profile of real-world cancer patients**, leading to underestimation of cardiotoxicity.
- This **limitation is particularly relevant in the era of novel targeted and immune-based therapies**, whose cardiovascular effects may be severe, delayed, and incompletely characterized.
- **Trials and post-marketing reports**, as currently designed, are **insufficient to capture** true cardiovascular risk, particularly subclinical and long-term toxicity.

Bonsu et al, JACC 2020; Bishopric et al, JACC 2020

From drug design...

proposed framework for cardiooncology-oriented trial desing



Conceptualization / design	Protocol / eCRF development	Trial conduct	Analysis
• Assessment of cardiovascular risk profile related to drug, background therapy, population • Multidisciplinary input with regard to strategy for CV event collection • Systematic approach consistent with strategy across development program	• Baseline characterization in eCRF (clinical characteristics, etc.) • Baseline & follow up biomarker characterization (e.g. blood, imaging) • Include IC-OS definitions of CV events in protocol appendix for consideration in safety reporting • Inclusion of specific event pages for safety events of special interest / trigger pages for adjudication • If adjudication planned, development of charter, adjudication system, data flows, processes for dossier collection / redaction	• Enhanced site training with regard to safety reporting including updating events for final diagnosis vs. initial signs/symptoms unless the later are prevailing & no diagnosis is known. • Individualized site plan regarding local specialist evaluation of CV events • Medical monitoring processes to query safety events to final diagnosis (rather than signs/symptoms/ lab results when appropriate) • Data management and medical monitoring processes to ascertain / trigger potential events for clarification • Event adjudication where applicable	• Prespecified analysis of safety event categories and approach to non-specific signs/symptoms or test results • Prespecified analyses of outcomes designed in context of drug mechanism, disease state, and population • Analyses including uniform data collection of pooled data / meta-analyzed across multiple studies • Analyses designed to account for both investigator reported data using established safety conventions as well as partial or fully adjudicated outcomes

Modified from Bonaca et al, JACC Cardiooncology 2025

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...to long-term care

what's missing and what we need next

Sustainable cardio-oncology safety

relies on three pillars:

SCIENTIFIC, CLINICAL, and SYSTEM-level

...to long-term care

what's missing and what we need next

Beyond standard cardiovascular biomarkers (e.g. cTn, NP), several **biomarkers are currently under investigation for the assessment of "personalized" cardiotoxicity**

Several **AI-based models** are emerging as promising tools **to enhance precision medicine in cardio-oncology** (risk-prediction, radiomics, AI-based drug discovery and development)

Therapeutic innovation in oncology is challenging established cardio-oncology algorithms and **calls for integrated and coordinated risk management**.

Effective cardio-oncology increasingly depends on **structured, multidisciplinary networks that support** shared decision-making and long-term CV surveillance

Robust, multicenter real-world data are essential to capture cumulative, competing and delayed CV risks across a patient's life-course →reliable&clinically meaningful cardio-oncology practice

Lyon AR et al, ESC guidelines; Guo AJ et al, World J Clin Oncol 2024; Li S and Tajiri K et al, Intern Med 2021; Finke D et al, Cancers 2021; Grabie N et al, Circulation 2007; Zhu H et al, Circulation 2022; Khera R et al, Circulation: Genomic and Precision Medicine 2025 ; Herrmann J, et al. European Heart Journal 2022, adapted from Guarneri V, ESMO Congress 2025

Making Safety Sustainable: A Shared Responsibility

- Cancer survivors are no longer “ex-oncology” patients, but represent a distinct clinical population with specific long-term needs.
- Within this perspective, long-term safety cannot be owned by cardiology alone, nor confined to cardiovascular assessment in isolation.
- It cannot be considered solely an oncology responsibility, despite being driven by increasingly complex therapeutic innovation.
- Nor can safety be addressed only through regulatory frameworks or trial-based requirements.
- **Rather, long-term safety represents a shared, cross-disciplinary responsibility, accompanying patients throughout their entire life-course.**

Making safety sustainable means shifting from reactive cardiotoxicity management to proactive, predictive and personalized cardio-oncology

Can we de-escalate CT in HER2+? Risk-adapted allocation

nature reviews clinical oncology

Gaining ground in personalized breast cancer therapy: lesson learned from PHERGain

Maria Vittoria Dieci & Valentina Guarneri

De-escalation of treatment for HER2$^+$ breast cancer is a priority, given the increase in cure rates owing in part to improved HER2-targeted therapies. In this regard, the neoadjuvant approach provides the ideal platform to test

We need to prioritize research on treatment de-escalation over the pursuit of incremental add-on therapies

HER2 blockade as a method of selecting patients who are most likely to benefit from chemotherapy-free neoadjuvant therapy.

Nature Reviews Clinical Oncology 21, 643–644 (2024)