Curriculum Vitae

Nama : Dr. Anna Mira Lubis, SpPD KHOM

Possition : - Medical staff of Hematology-Medical Oncology Division, Internal Medicine Dept, Universitas Indonesia

- Deputy head of Cytogenetic Lab, Cipto Mangunkusumo Hospital

Education

- Medical Doctor, Universitas Indonesia, 2002
- Specialist in Internal Medicine, Universitas Indonesia, 2008
- Consultant on Hematology – Medical Oncology, Universitas Indonesia, 2016

The 3rd Indonesian Symposium on Heart Failure and Cardiometabolic Disease 2023

Defining Cardiotoxicity of Cancer Therapies

Anna Mira Lubis
Division of Hematology and Medical Oncology
Dept. of Internal Medicine FMUI-RSCM

Disclosure

- No conflict of interests
- I am medical oncologyst

Outline

- Cancer global burden
- Cardiotoxicity in cancer treatment
- Defining CTRCD
- CTRCD risk assessment
- Screening and monitoring recommendation in cancer treatment
- Take home points

Female 43 yo

Des 31 st 2021

- Lump in the right breast.
- BUS & mammography : possible malignancy

* Family breast cancer + (mother)

* Fit no comorbidities

Jan 2022

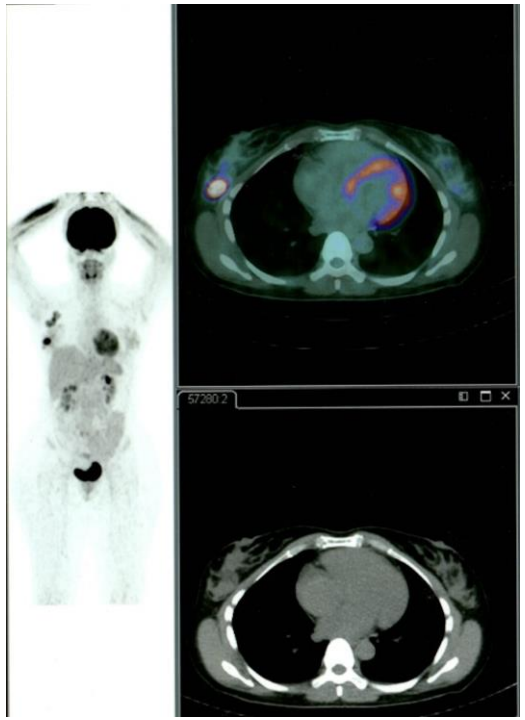
- MBC (bone and perihepatic LN) her-2 enriched of the right breast
- 6 cycles of TCHP

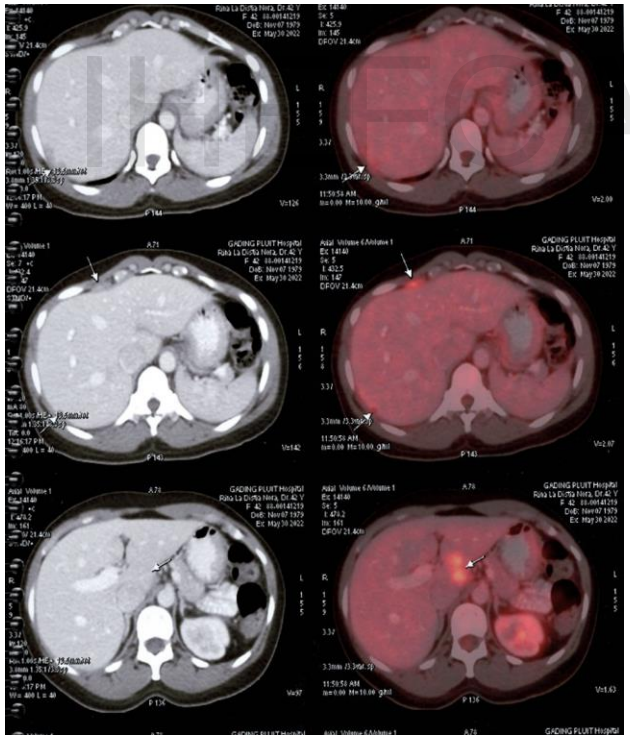
June 2022

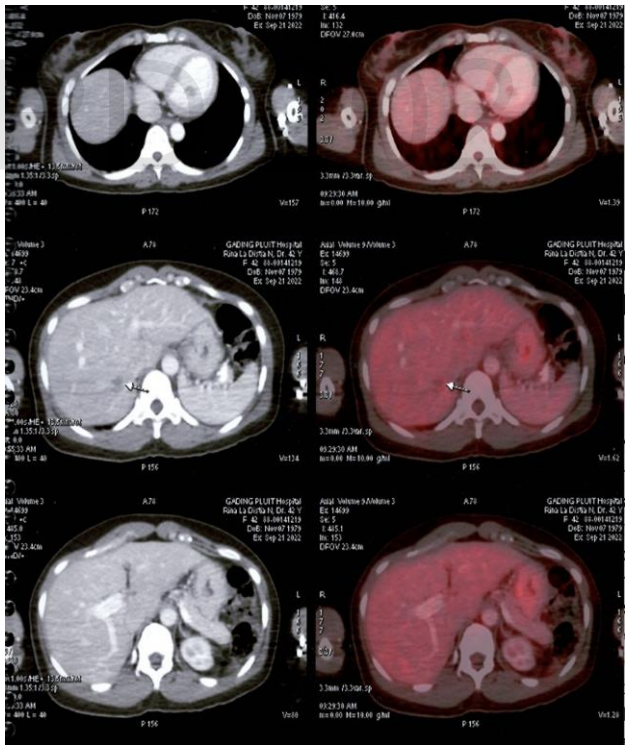
- TDM-1 due to disease progression

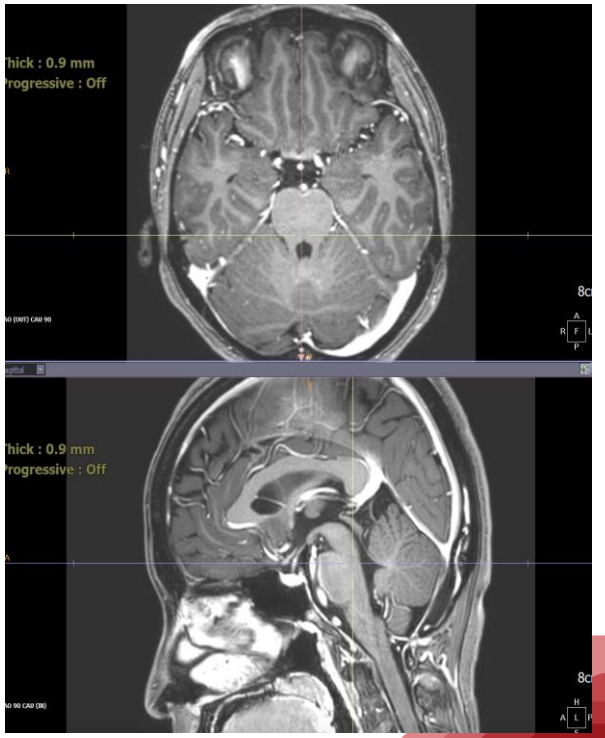
Jan 2023

TDX-d due to LMD

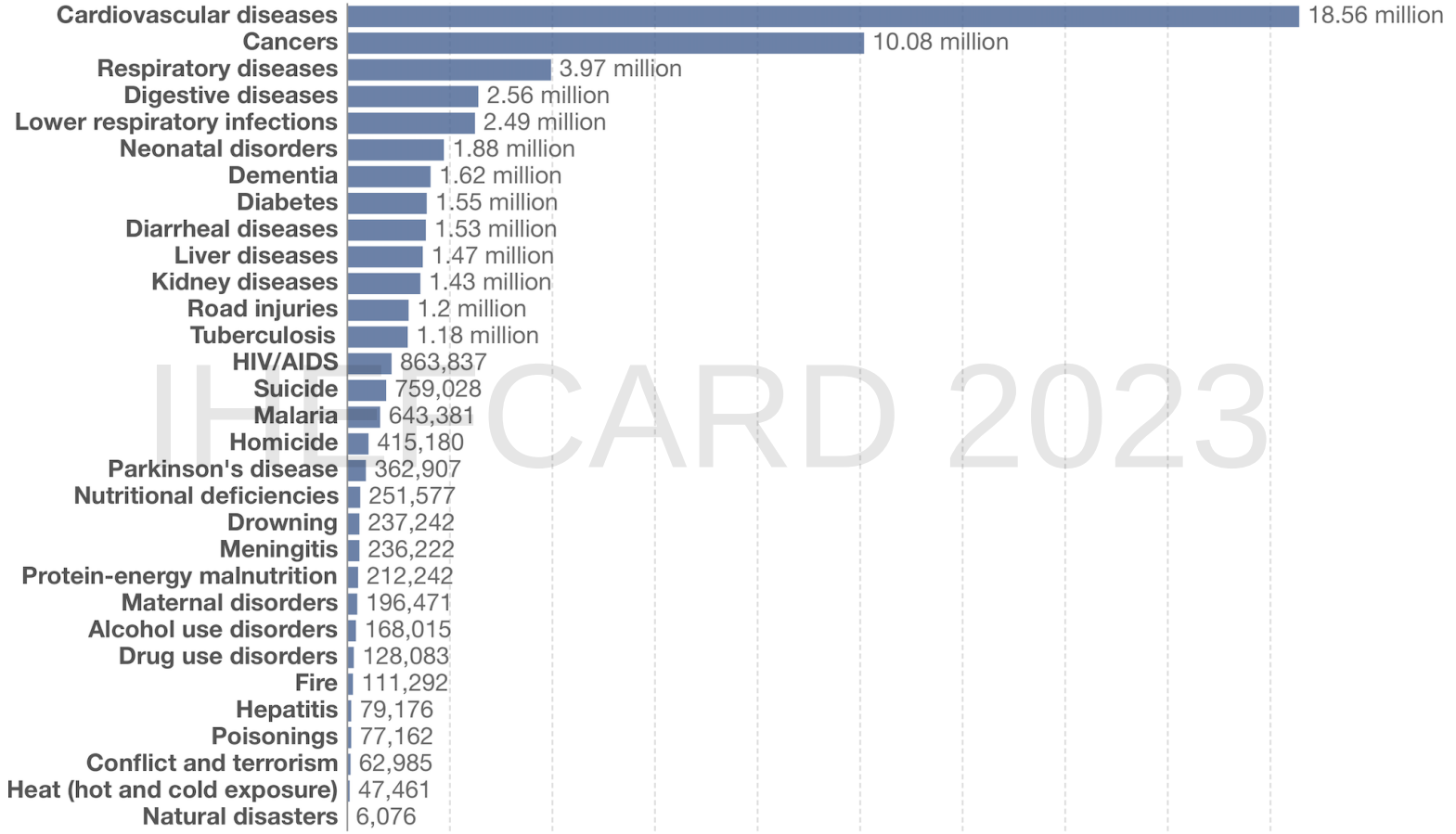








Cancer is one of leading cause of death

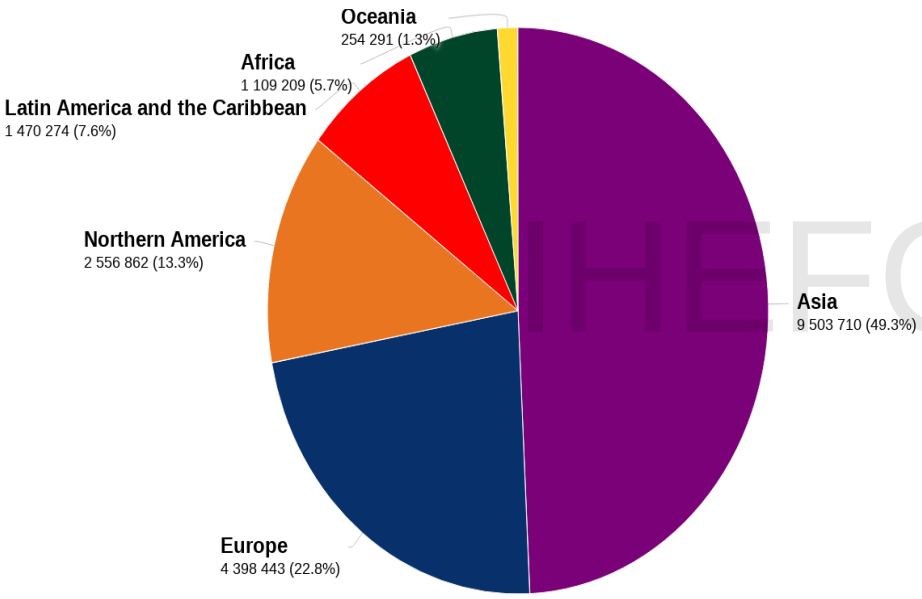


Every sixth death in the world is due to cancer. The worls is making progress against this disease

Max Roser and Hannah Ritchie (2019) - "Cancer". Published online at OurWorldInData.org. Retrieved from: 'https://ourworldindata.org/cancer' [Online Resource]

Cancer global burden

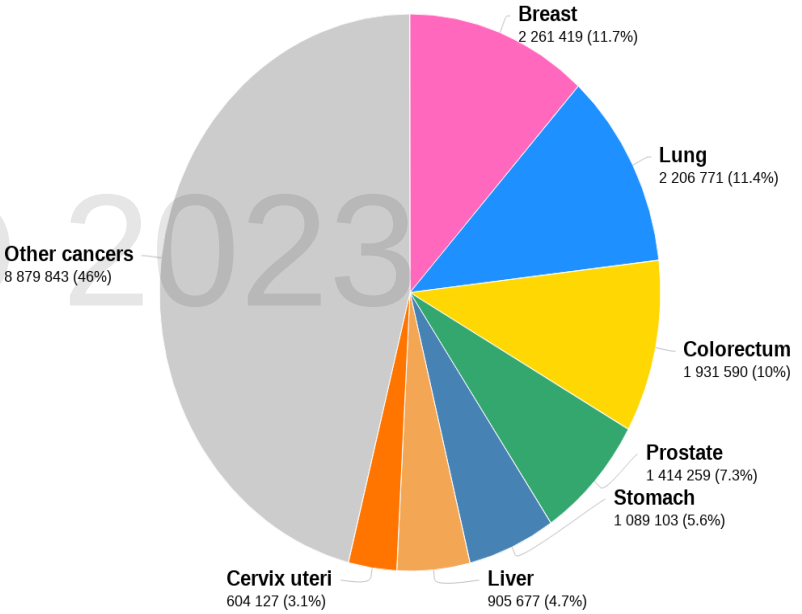
Estimated number of new cases in 2020, all cancers, both sexes, all ages



Total : 19 292 789

Data source: Globocan 2020
Graph production: Global Cancer Observatory (http://gco.iarc.fr)

Estimated number of new cases in 2020, World, both sexes, all ages

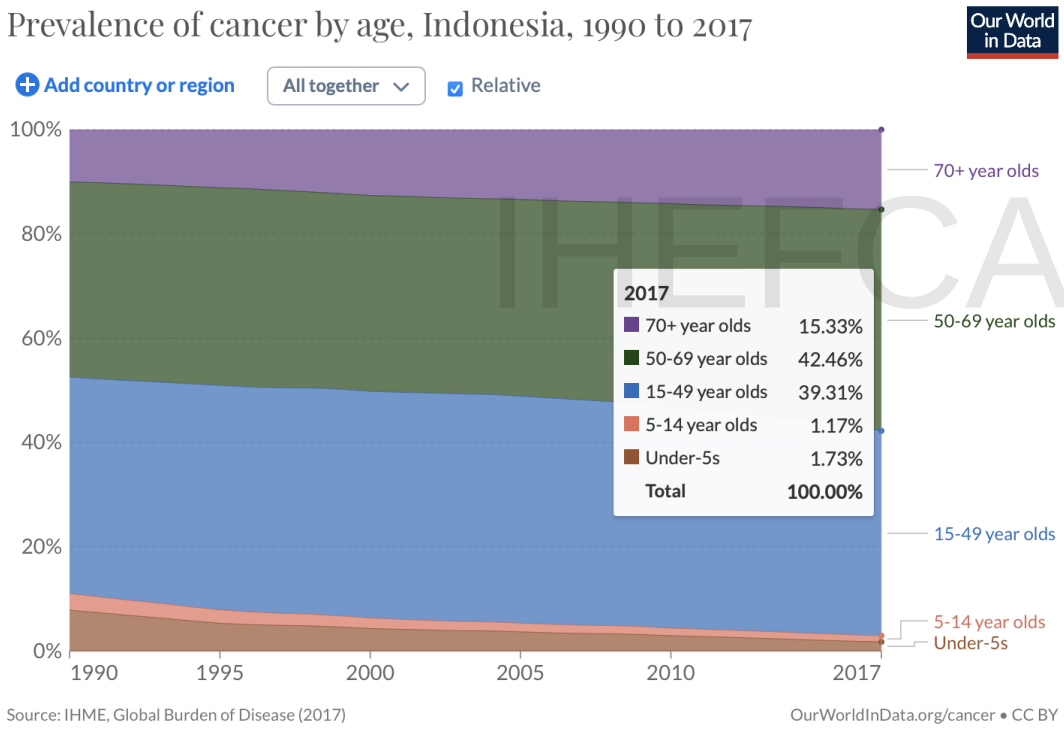


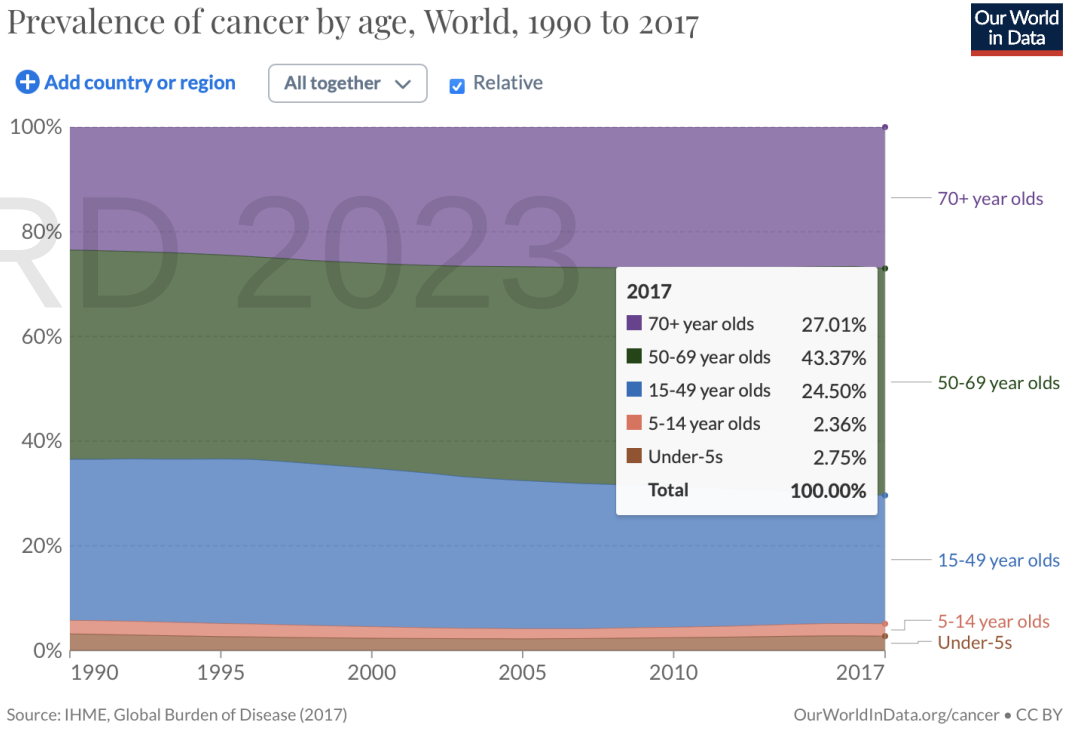
Total : 19 292 789

Data source: Globocan 2020
Graph production: Global Cancer Observatory (http://gco.iarc.fr)

GLOBOCAN 2020

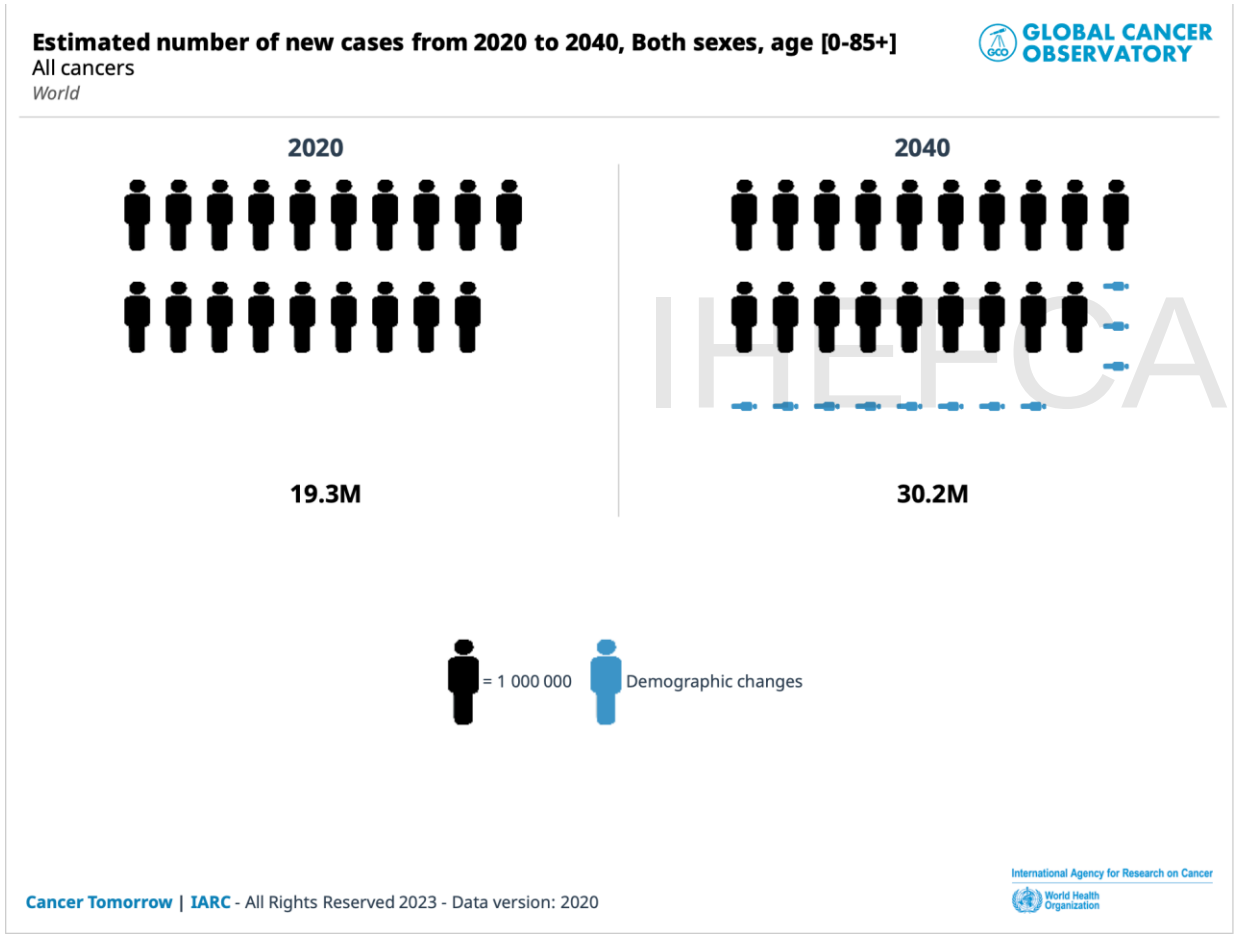
The majority of cancers occur in older populations. Approximately 60-70% occur in aged > 50 → comorbidities!

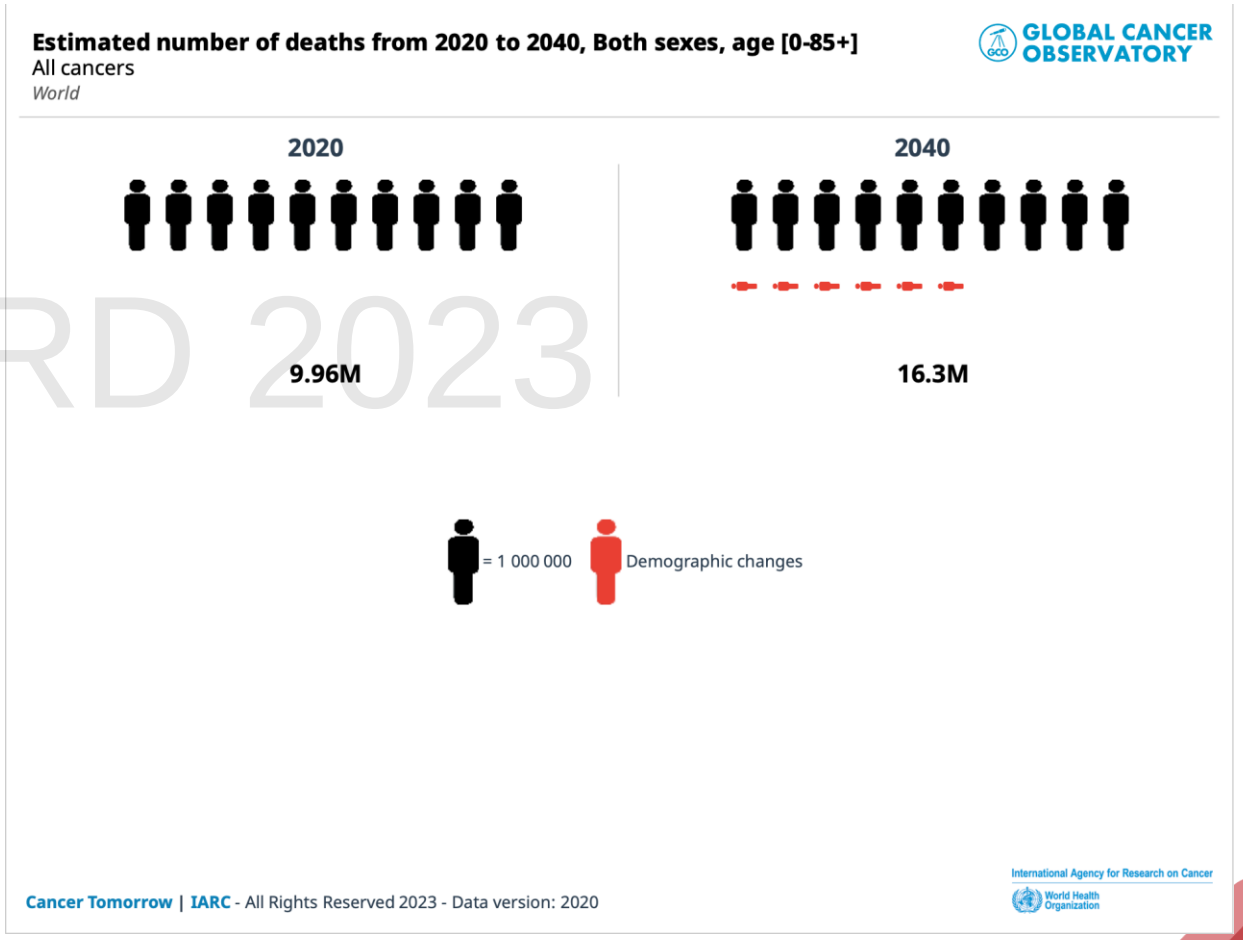




Max Roser and Hannah Ritchie (2019) - "Cancer". Published online at OurWorldInData.org. Retrieved from: 'https://ourworldindata.org/cancer' [Online Resource]

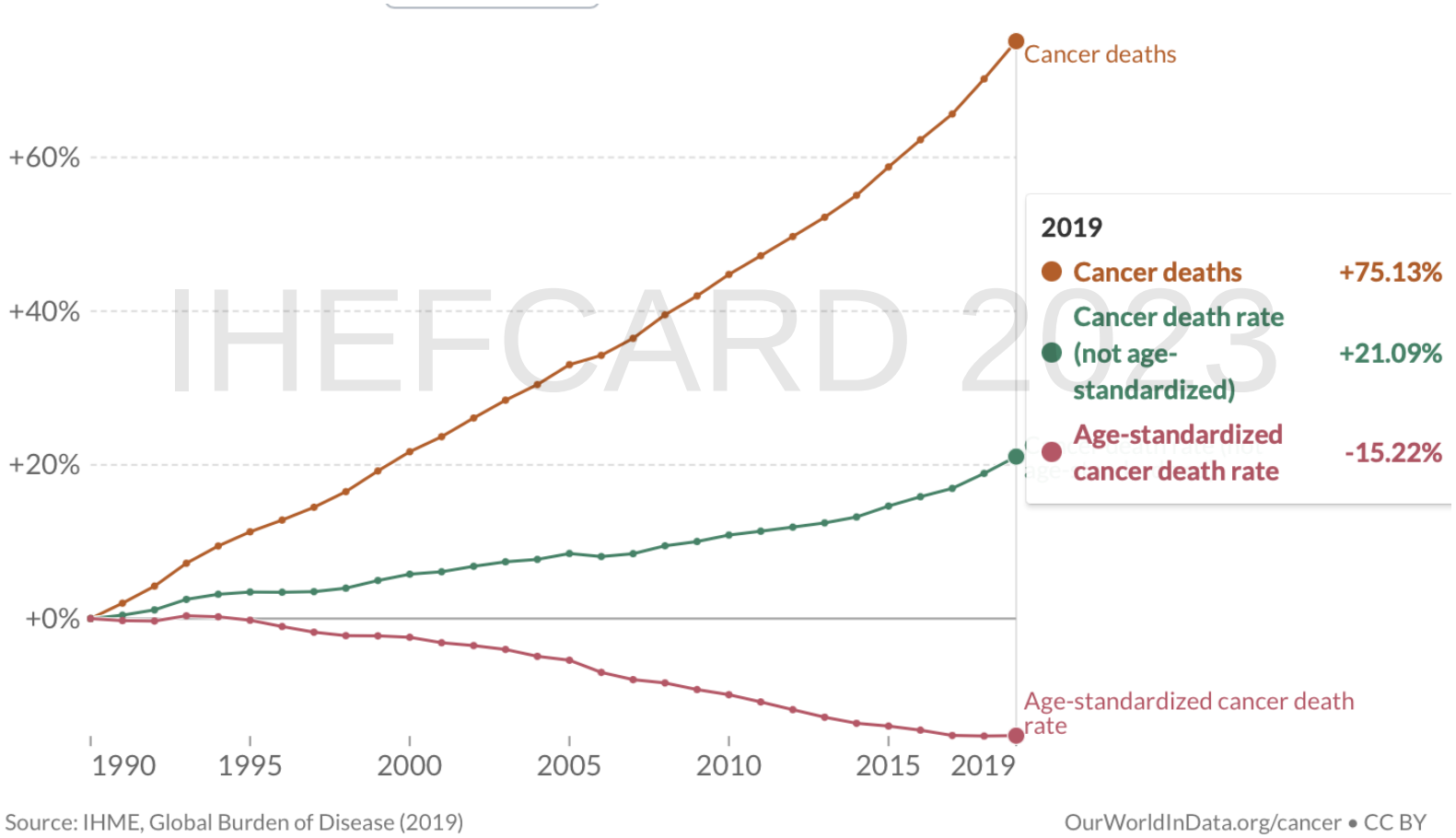
Cancer tomorrow





GLOBOCAN 2020

Is the world making progress against cancer?



Max Roser and Hannah Ritchie (2019) - "Cancer". Published online at OurWorldInData.org. Retrieved from: 'https://ourworldindata.org/cancer' [Online Resource]

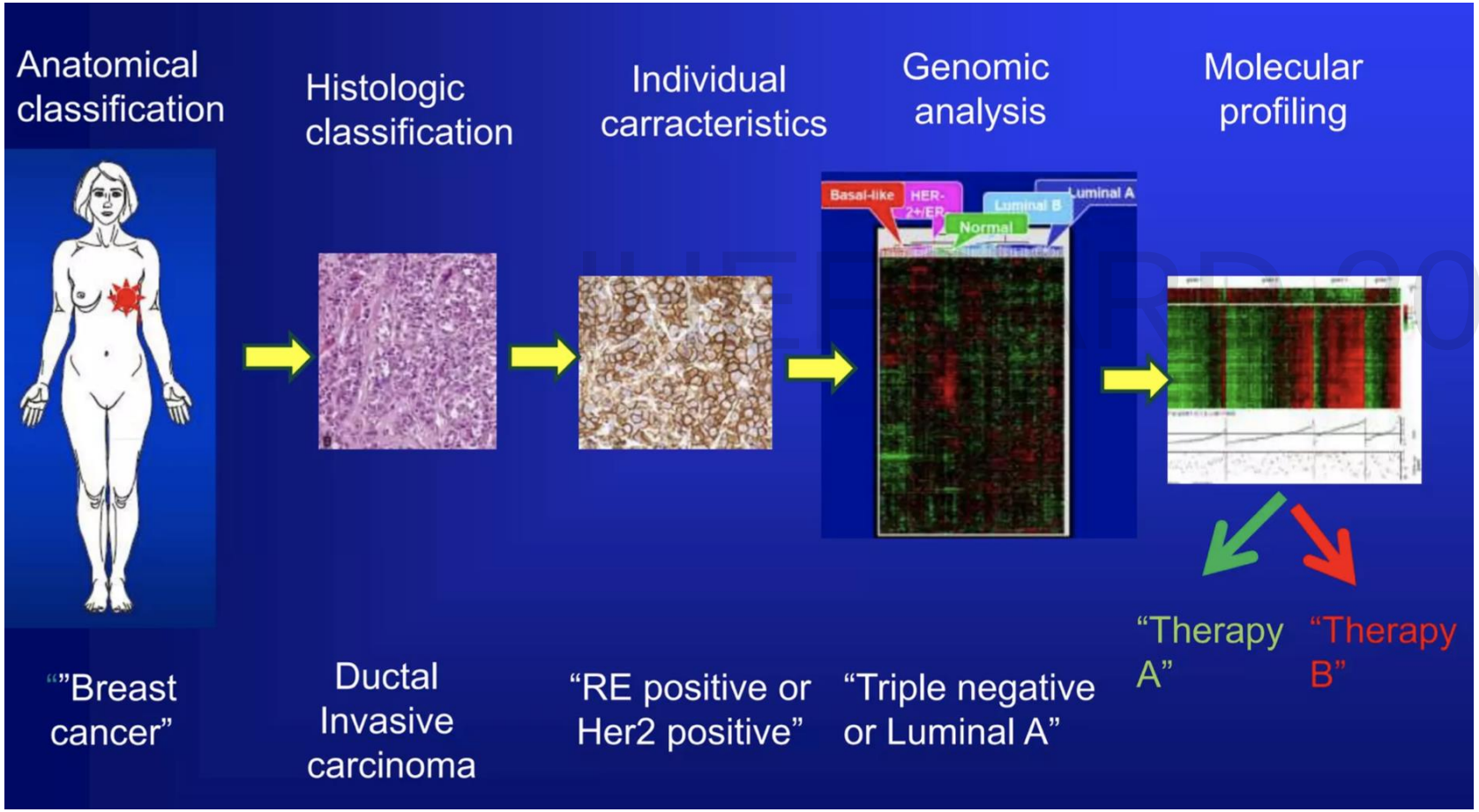
Cancer treatment modalities

SURGERY

RADIATION & CHEMORADIATION

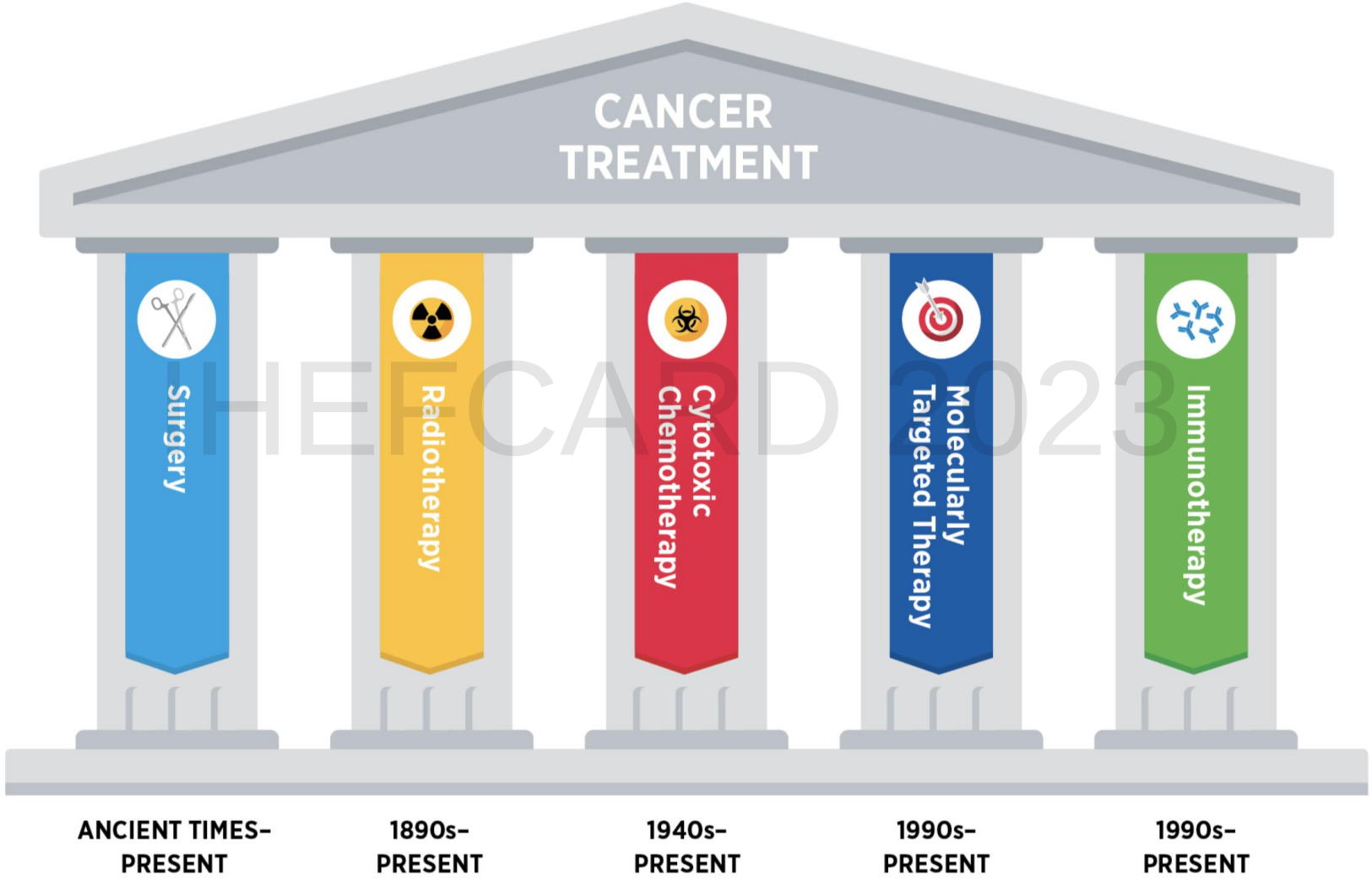
SYSTEMIC THERAPY

Evolution of Classification in Oncology : towards precision therapy

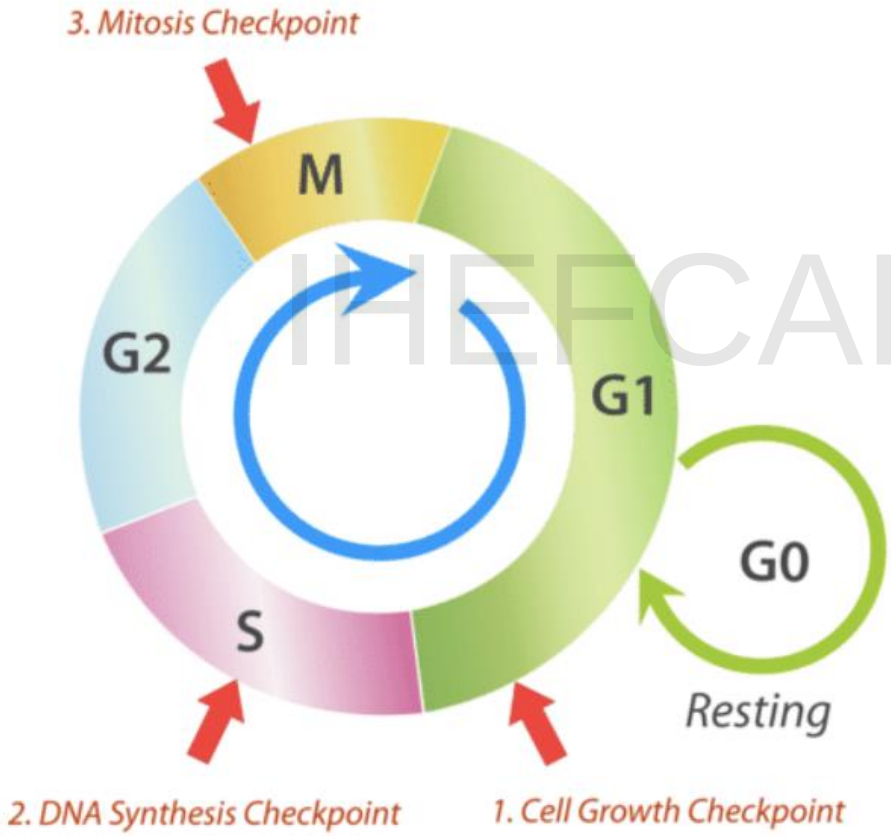


- Chemotherapy
- Hormonal Therapy
- Targeted therapy
- Immunotherapy

The pillars of cancer care



Cell cycle and cancer



1. Cell Growth Checkpoint

- Occurs toward the end of growth phase 1 (G1).
- Checks whether the cell is big enough and has made the proper proteins for the synthesis phase.
- If not, the cell goes through a resting period (G0) until it is ready to divide.

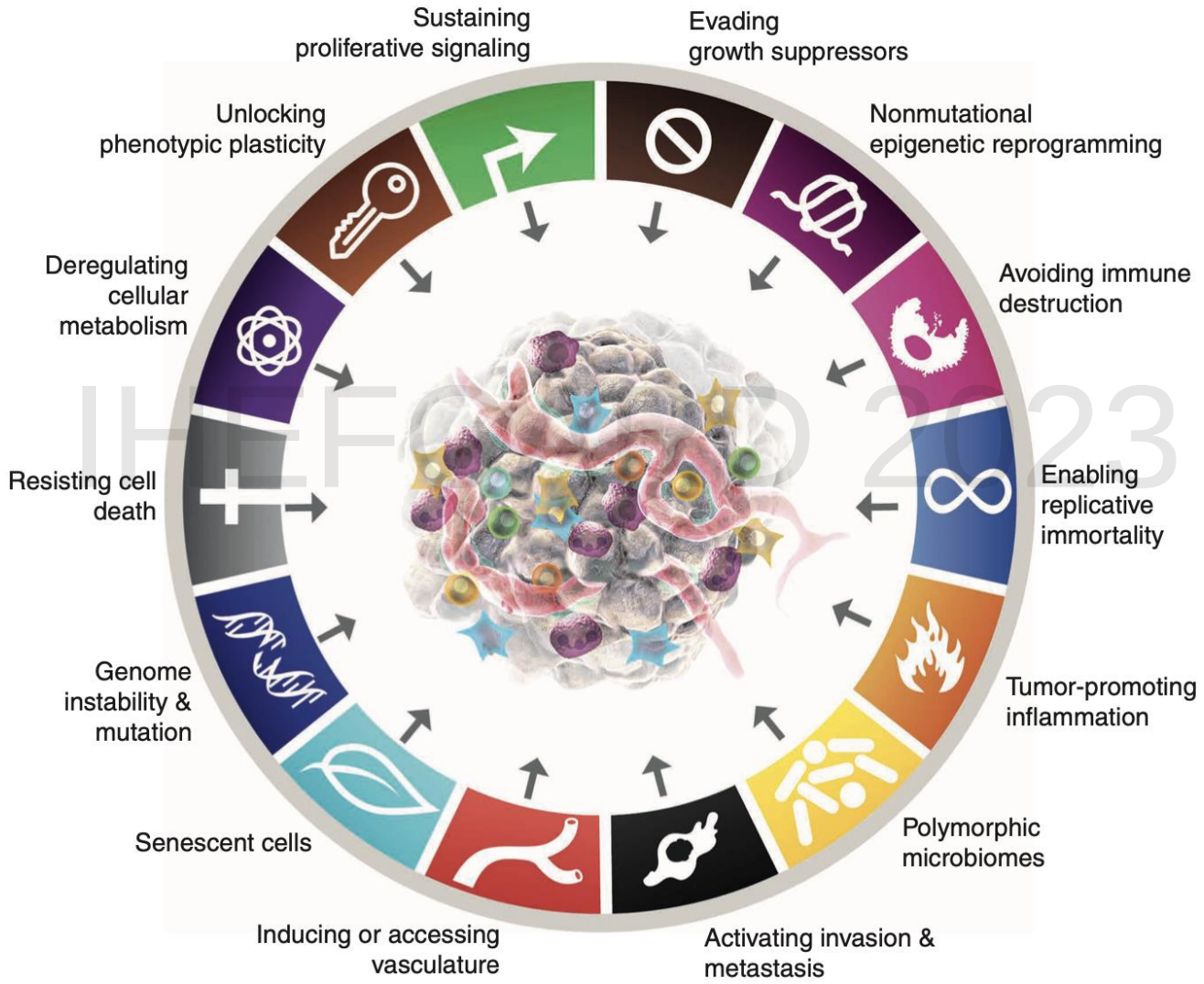
2. DNA Synthesis Checkpoint

- Occurs during the synthesis phase (S).
- Checks whether DNA has been replicated correctly.
- If so, the cell continues on to mitosis (M).

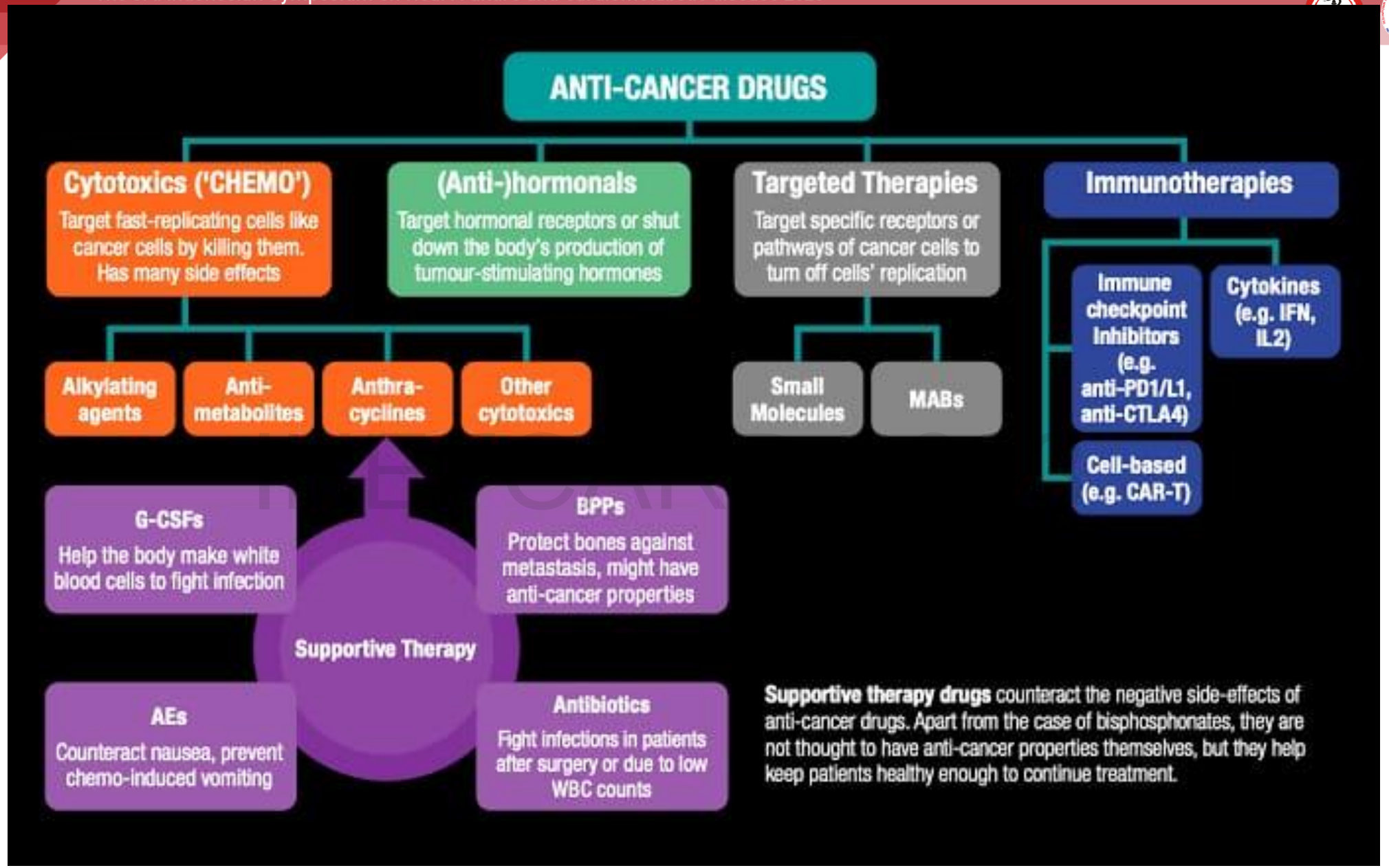
3. Mitosis Checkpoint

- Occurs during the mitosis phase (M).
- Checks whether mitosis is complete.
- If so, the cell divides, and the cycle repeats.

New dimension hallmarks of cancer



Hanahan D. Cancer Discovery. AACR. 2022



Oncology: The Disease, Dynamics & Challenges of Global Market Research.2021

Antineoplastic agents

CCS

- Active in a particular phase of cell cycle
- Only proliferating cells are killed
- Scheduled dependent (duration and timing rather dan dose)

CCNS

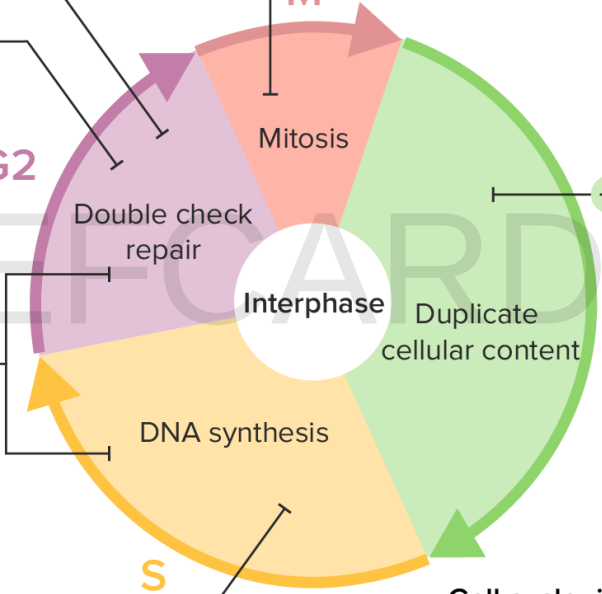
- Cytotoxic effect exerted irrespective of cell cycle state
- Both proliferating and non proliferating cells are killed
- Single dose has same effect as repeated fractions totalling the same amount
- Dose dependent

Cytotoxics drugs

Microtubule inhibitors
- Taxanes
- Vinca alkaloids

Bortezomib

Bleomycin



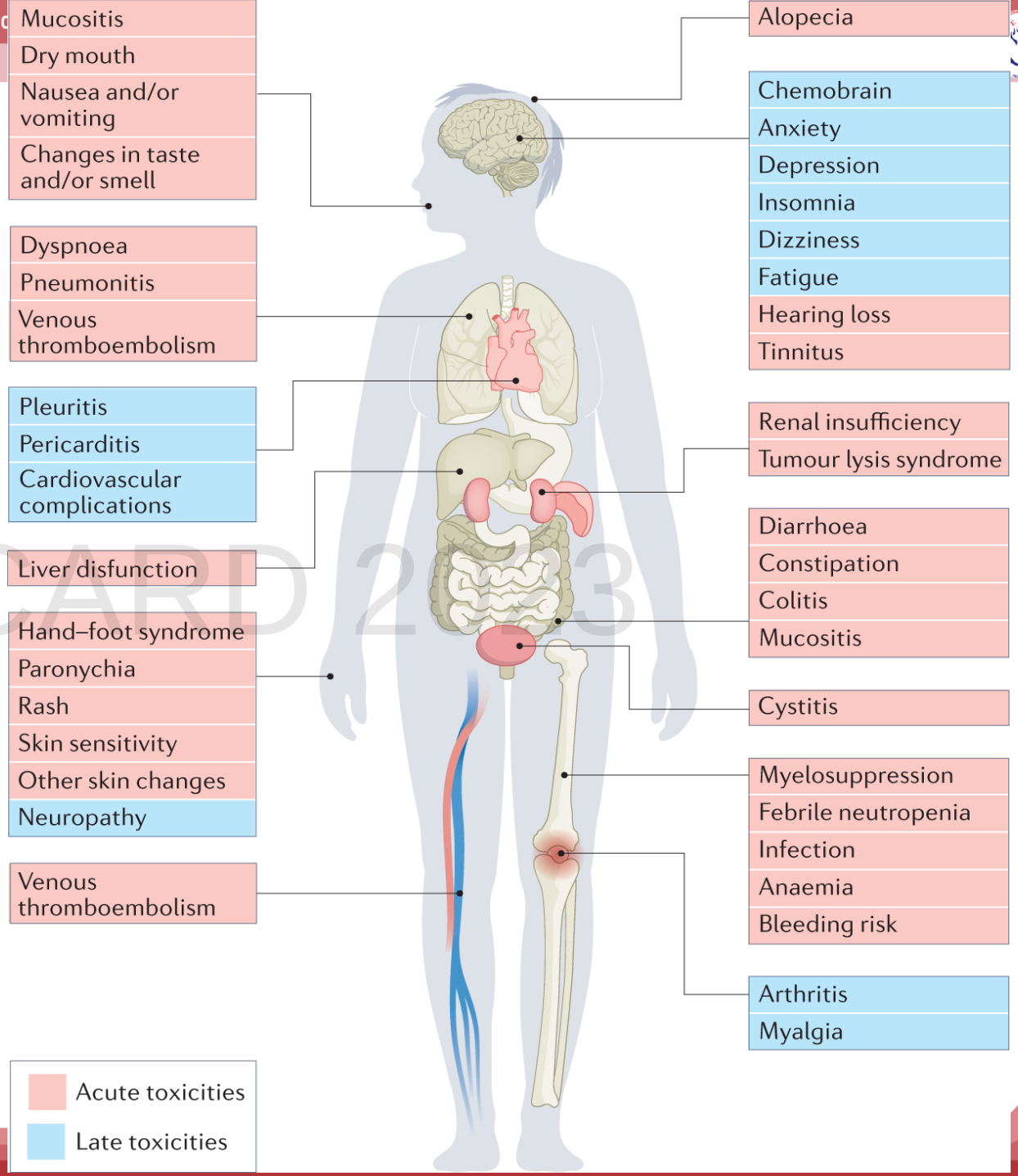
Dactinomycin

Topoisomerase inhibitors
- Etoposide
- Teniposide
- Irinotecan
- Topotecan

Antimetabolites
- Cladribine
- Cytarabine
- 5-fluorouracil
- Hydroxyurea
- Methotrexate
- Pentostatin
- Thiopurines

Cell cycle–independent drugs
- Anthracyclines
- Antitumor antibiotics
- Alkylating agents:
  - Nitrogen mustards
  - Nitrosoureas
  - Alkyl sulfonates
  - Triazenes
  - Ethyleneimines and methylmelamines
  - Platinum compounds

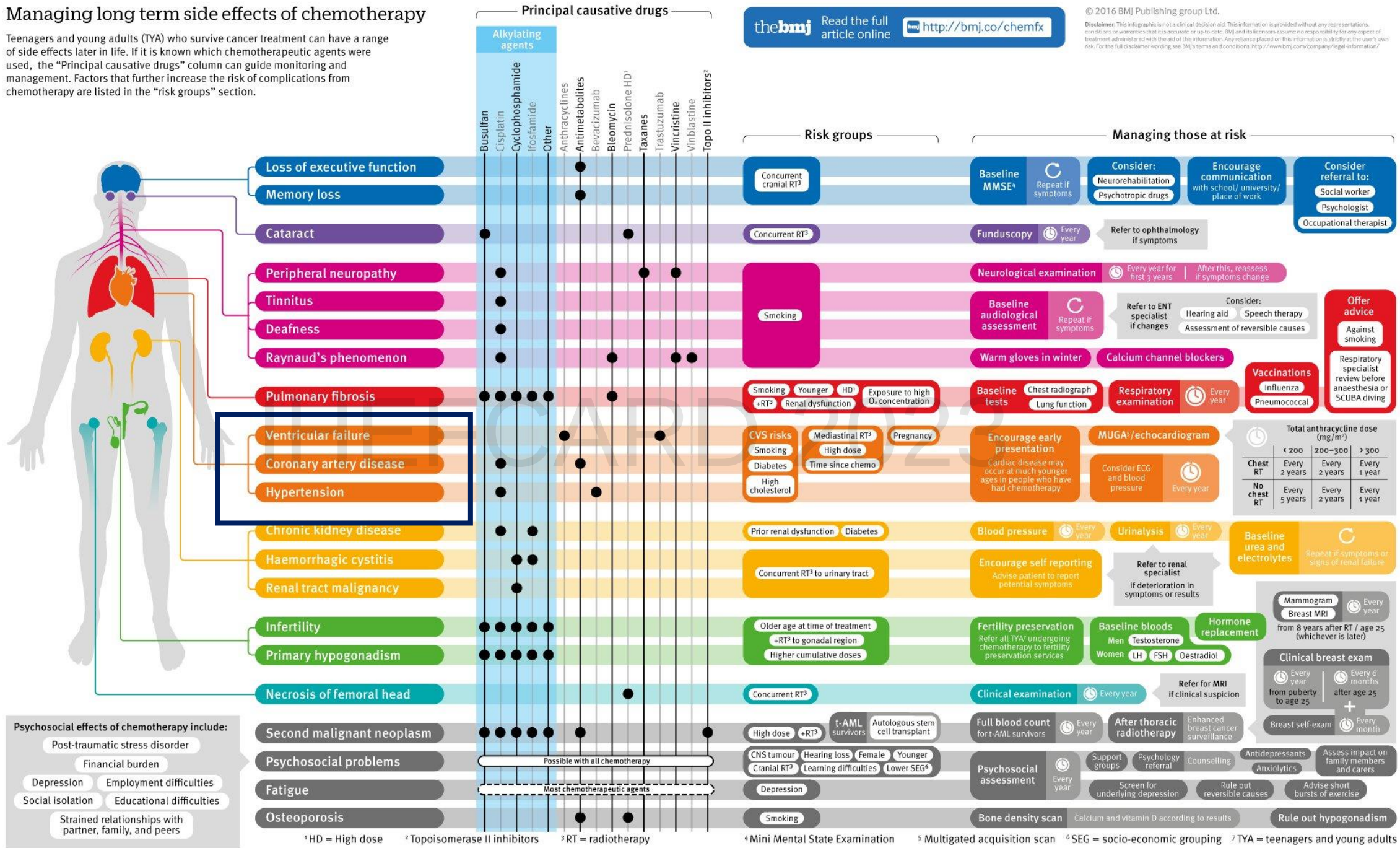
Chemotherapy Adverse events



Kuderer NM. et al. Nat Rev Oncol. 2022

Managing long term side effects of chemotherapy

Teenagers and young adults (TYA) who survive cancer treatment can have a range of side effects later in life. If it is known which chemotherapeutic agents were used, the "Principal causative drugs" column can guide monitoring and management. Factors that further increase the risk of complications from chemotherapy are listed in the "risk groups" section.



thebmj Read the full article online http://bmj.co/chemfx

[1] HD = High dose [2] Topoisomerase II inhibitors [3] RT = radiotherapy [4] Mini Mental State Examination [5] Multigated acquisition scan [6] SEG = socio-economic grouping [7] TYA = teenagers and young adults

BMJ, 2016.

CARDIOTOXICITY IN CANCER CARE →WHY IT'S IMPORTANT?

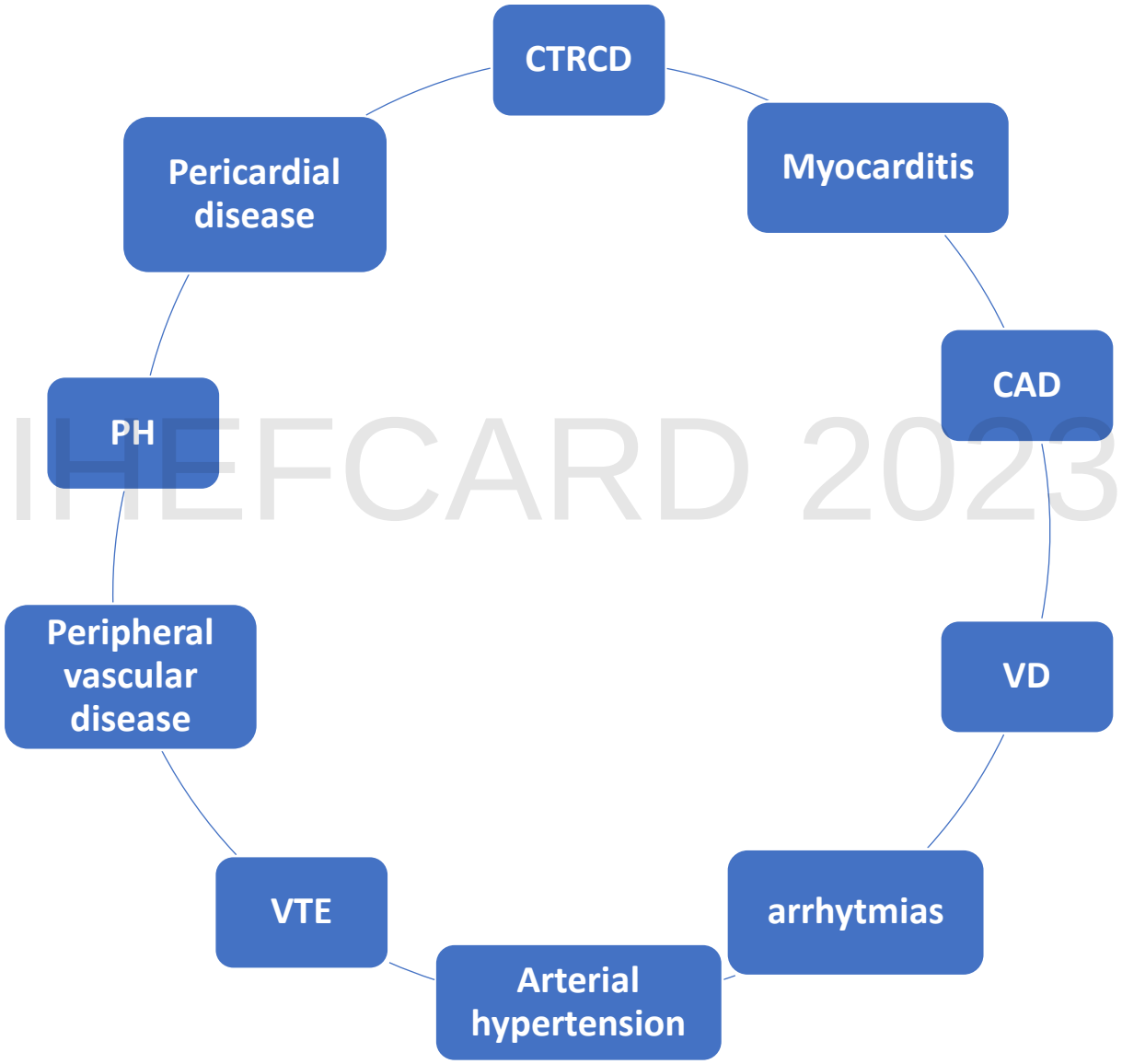
- Advances in early detection and ca Th/ have improved pts survival, with adverse event consequences by different mechanism
- Increase risk of cardiac toxicities → QoL and treatment interruption (ca prognosis)
- Individual treatment approach for optimal treatments, reduced toxicities →patient, cancer, treatment options

CARDIOTOXICITY CLASSIFICATION

TYPE 1	**Irreversible myocardial damage, dose dependent , cellular apoptosis/necrosis (ie anthracyclines)**
TYPE 2	Reversible myocardial damage, dose independent, cellular dysfunction (ie trastuzumab)
TYPE 3	Coronary disease related such as radiation exposure and spasm (ie radiation therapy and 5-FU, platinum)
TYPE 4	Miscellaneous related to myocarditis or takotsubo's cardiomyopathy (ie 5-FU , ICI, and TKIs)
TYPE 5	Indirect which are secondary to conduction abnormalities, arrhythmias, and hypertension (ie ibrutinib, fluorouracil, TKI, ALK inh, taxan, and platinum-based therapy)

Perez I E, et al. Clin Med Insight: cardiology .2019

Spectrum of CTR-CVT

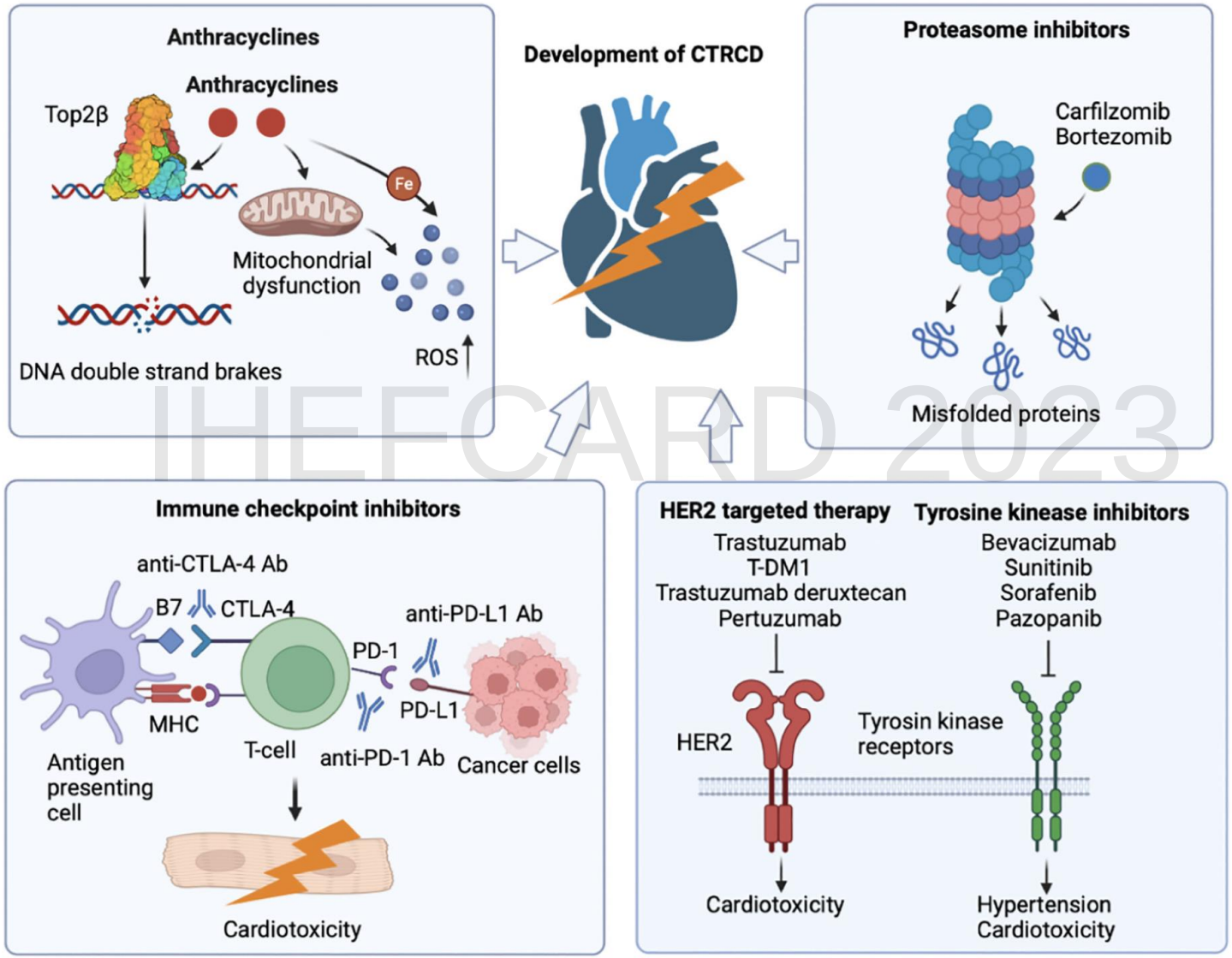


Cardiotoxicity of common cancer therapies

	LVSD	HTN	Angina	ACS	Takotsubo	Stroke	PAD	PHTN	DVT/ PE
Anthracyclines	X								
5-FU	X		X	X	X				
Gemcitabine			X	X					
Paclitaxel		X	X	X					X
Cisplatin		X	X	X		X	X		
Bleomycin			X	X		X		X	
Vincristine		X	X	X					
Cyclophos-phamide	X		X					X	
mTOR inhibitors		X	X						X
Carfilzomib	X	X		X				X	
Bevacizumab	X	X	X	X	X	X			X
Sunitinib	X	X	X	X	X	X			X
Nilotinib			X	X		X	X		X
Dasatanib	X							X	
Thalidomide									X
Rituximab		X	X	X	X				

Chung R, et al. Open Heart 2018;**5**:e000774.

CTRCD mechanisms



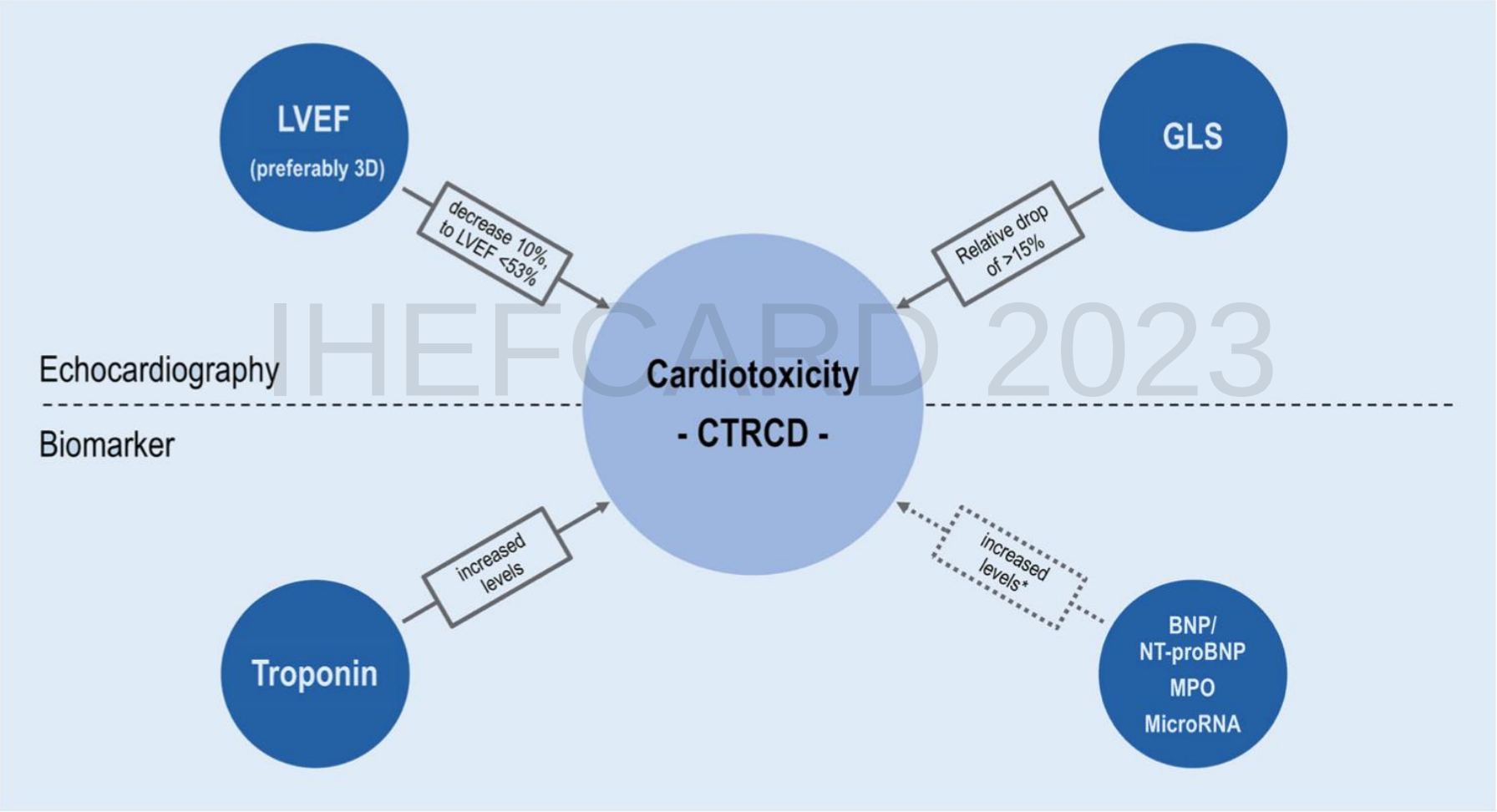
Oikawa M, eta al. Journal of Cardiology 81 (2023) 253–259

DEFINITIONS FOR CTRCD

	DEFINITIONS
The American Society of Echocardiography (ASE) and the European Association of cardiovascular Imaging (EACVI)	1. ⩾10% decline in LVEF to a final value less than 53% confirmed on subsequent imaging performed 2 to 3weeks after the initial measurement. 2.>15%relative decline in GLS compared with baseline strain.
US Food and Drug Administration (FDA)	Doxorubicin-mediated cardiotoxicity was defined as either: 1. ⩾20% absolute decline in LVEF. 2. ⩾10% decrease in LVEF to less than the lower limit of normal or absolute value of less than 45%.
Cardiac review and evaluation committee in trastuzumab trials	1. ⩾10% decline in the absence of symptoms. 2. ⩾5% decrease in symptomatic patients to a final LVEF of less than 55%.
Herceptin Adjuvant (HERA) trial	1. LVEF decline by at least 10% from baseline to a value of <50% was considered a significant LVEF decrease.
The National Cancer Institute (NCI)	Proposes the Common Terminology Criteria for Adverse Events (CTCAE) that define left ventricular dysfunction and HF based on severity into grades 1 to 5. 1. Grade 1 is asymptomatic elevations in biomarkers or abnormalities on imaging. 2. Grades 2 and 3 consist of symptoms with mild and moderate exertion. 3. Grade 4 includes severe, life-threatening symptoms requiring hemodynamic support. 4. Grade 5 involves death.

Perez I E, et al. Clin Med Insight: cardiology .2019

Different markers indicating cardiotoxicity



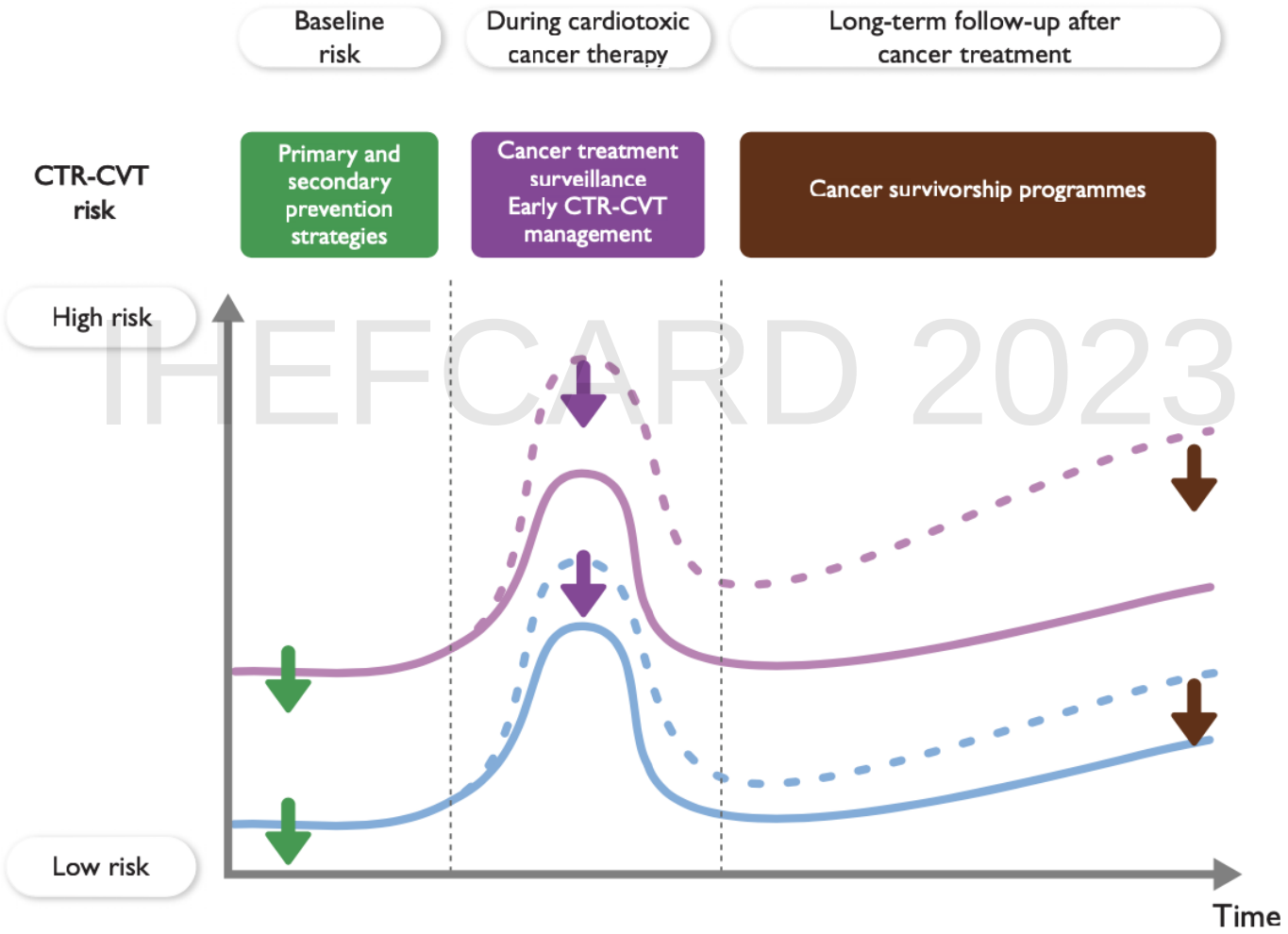
Berliner D et al. Springer Nature.2020

CTRCD clinical severity

SYMPTOMATIC CTRCD (HF)	**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
SYMPTOMATIC 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 biomarkersc
	Mild	LVEF ≥ 50% AND new relative decline in GLS by .15% from baseline AND/OR new rise in cardiac biomarkersc

Lyon A R, et al. European Heart Journal (2022) 43, 4229–4361

Dynamics of CV toxicity risk in can patients over



Lyon A R, et al. European Heart Journal (2022) 43, 4229–4361

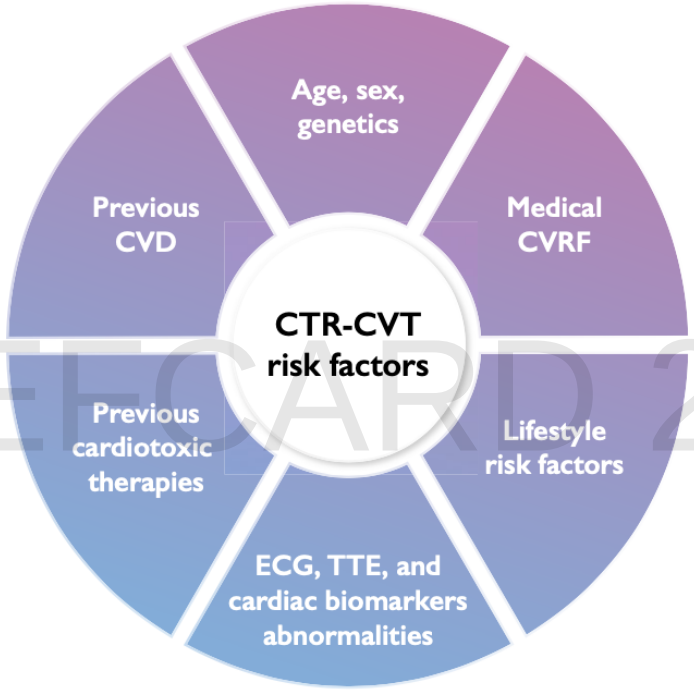
CARDIOTOXICITY RISK SCORES (CRS)

Patient-related risk actors	HTN, CAD/PAD, heart failure, diabetes, age<15 or >65years, female sex, anthracycline exposure, and chest radiation.
Chemotherapy- related risk factors	❖ High (risk score of 4): anthracyclines, trastuzumab, cyclophosphamide, ifosfamide, and clofarabine ❖ Moderate (risk score of 2): docetaxel, pertuzumab, sorafenib, and sunitinib ❖ Low (risk score of 1): imatinib, lapatinib, bevacizumab, and dasatinib ❖ Rare (risk score of 0): rituximab, etoposide, and thalidomide
overall risk for CRS (number of patient-related risk factors plus chemotherapy-related risk factors)	Very high: CRS>6 High: CRS 5 to 6 Moderate: CRS 3 to 4 Low: CRS 1 to 2 Very low: CRS 0

Perez I E, et al. Clin Med Insight: cardiology .2019

Baseline CV toxicity risk assessment

Baseline CV toxicity risk assessment checklist



Clinical assessment

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

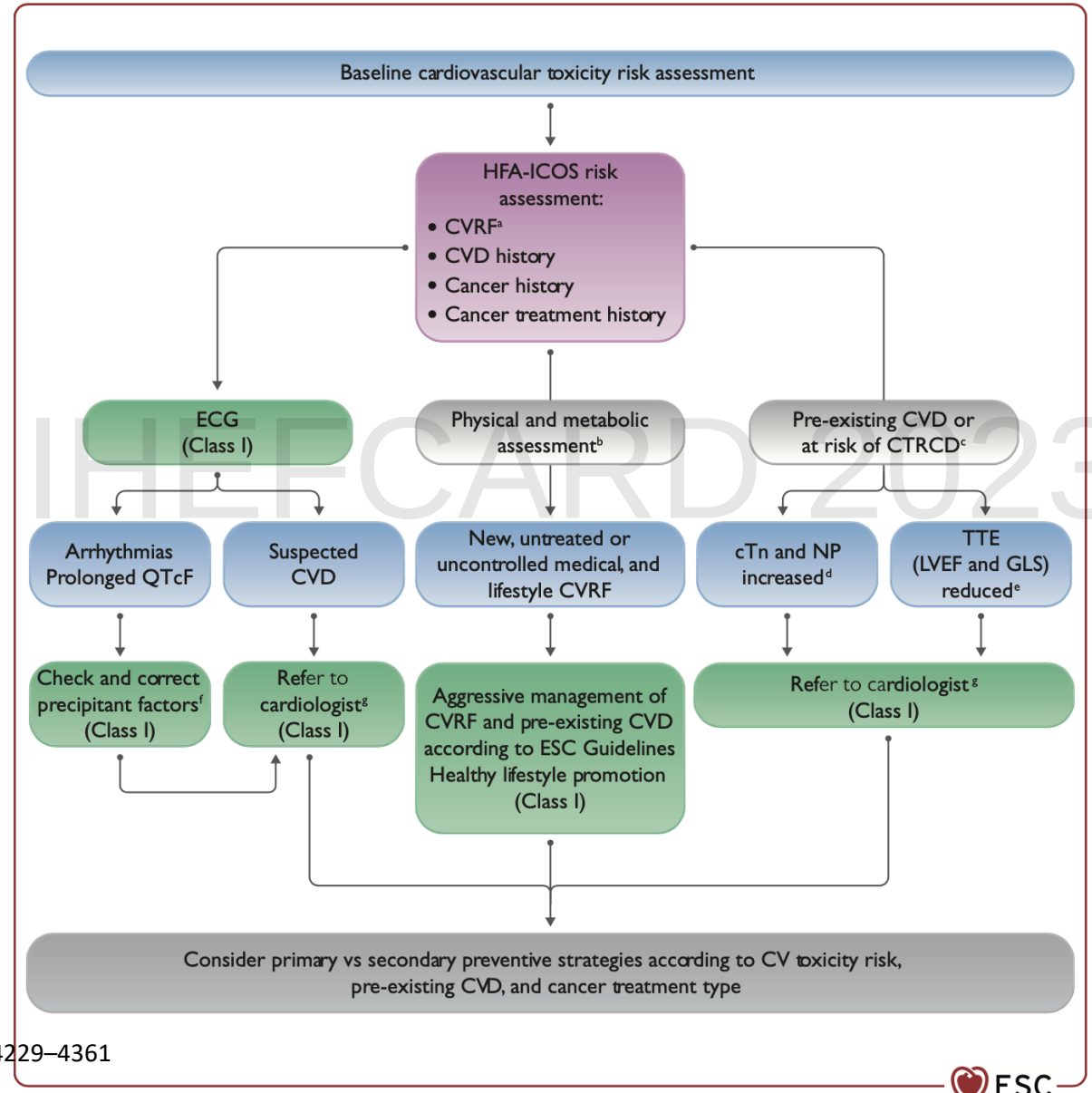
Complementary tests

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

INDIVIDUALIZED CV RISK!!

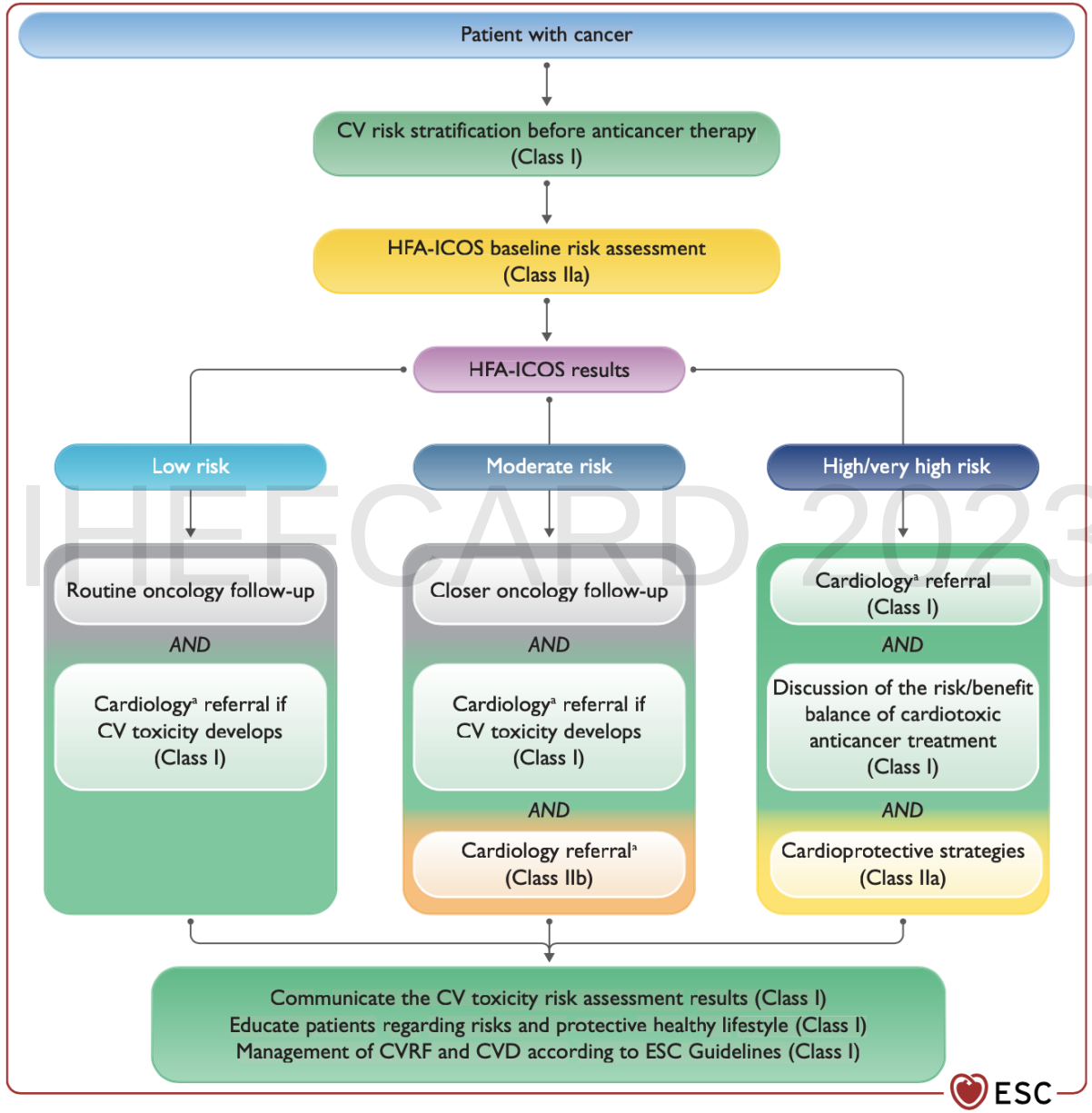
Lyon A R, et al. European Heart Journal (2022) 43, 4229–4361

Baseline cardiovascular toxicity risk assessment before anticancer therapy.



Lyon A R, et al. European Heart Journal (2022) 43, 4229–4361

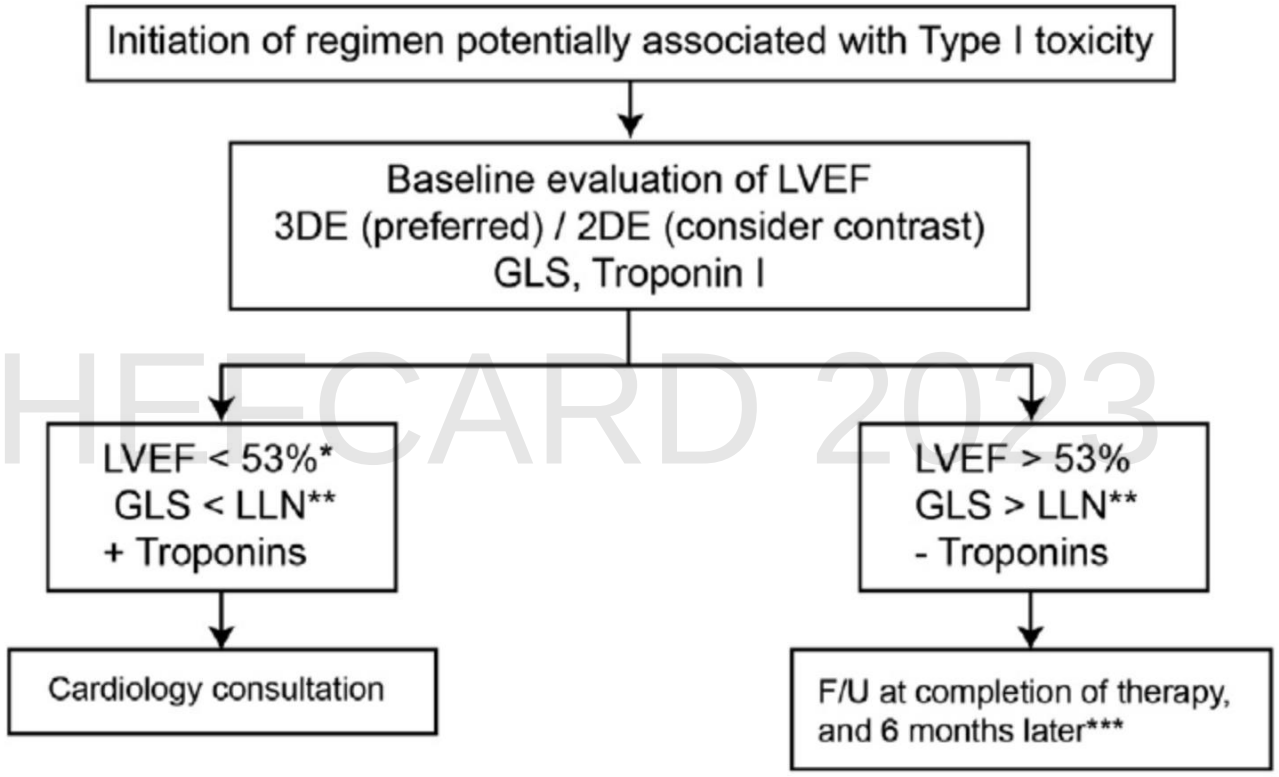
General cardio-oncology approach after Heart Failure



Lyon A R, et al. European Heart Journal (2022) 43, 4229–4361

Lyon A R, et al. European Heart Journal (2022) 43, 4229–4361

Baseline assessment and monitoring



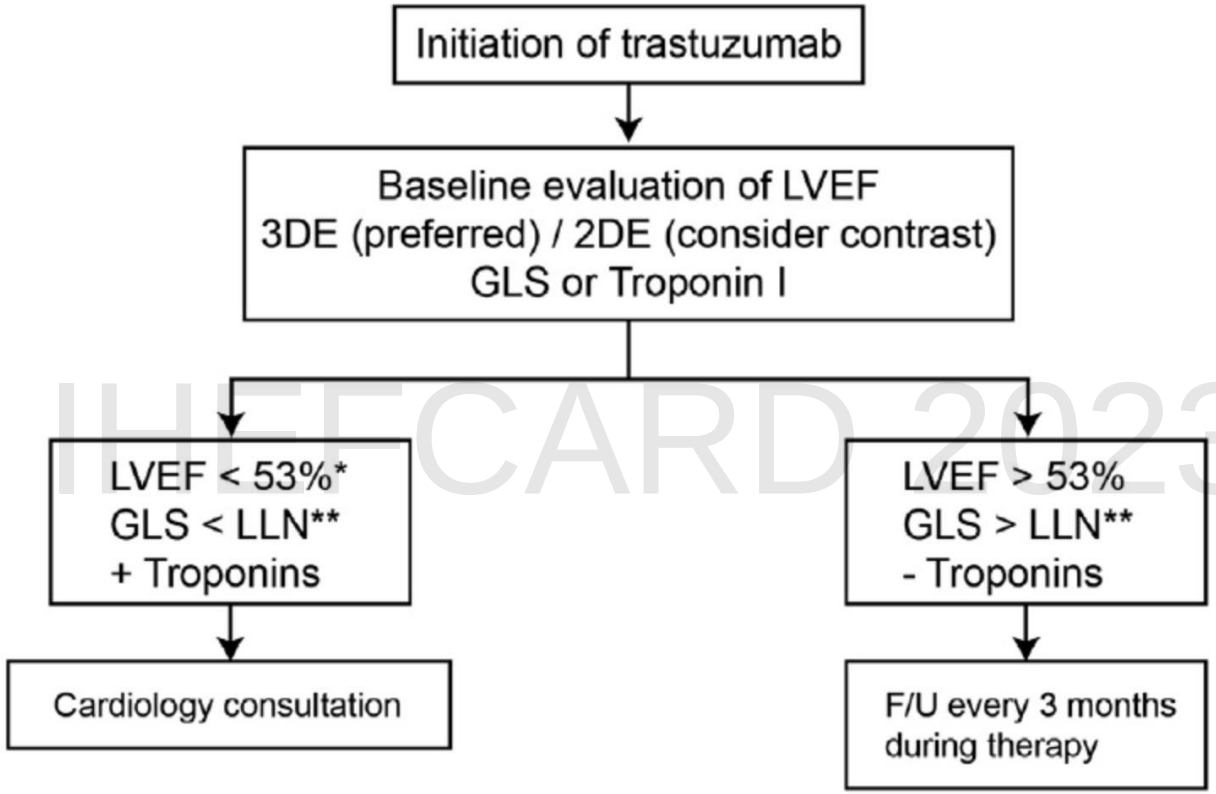
* Consider confirmation with CMR.

** LLN = Lower limit of normal. Please refer to Table 5 for normal GLS values based on vendor, gender and age.

*** If the dose is higher than 240 mg/m² (or its equivalent), recommend measurement of LVEF, GLS and troponin prior to each additional 50 mg/m².

Soesanto A. Indonesian society of echocardiography.2020

Baseline assessment and monitoring



* Consider confirmation with CMR.
** LLN = Lower limit of normal. Please refer to Table 5 for normal GLS values based on vendor, gender and age.

Soesanto A. Indonesian society of echocardiography.2020

Recommendations for a general approach to cardiovascular toxicity risk categorization

Recommendations	Class	Level
CV toxicity risk stratification **before starting potentially cardiotoxic anticancer therapy** is recommended in all patients with cancer	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	IIa	C
It is recommended that patients categorized to be at **low CV toxicity risk should proceed to anticancer therapy without delay**	I	C

Lyon A R, et al. European Heart Journal (2022) 43, 4229–4361

Recommendations for a general approach to cardiovascular toxicity risk categorization

Recommendations	Class	Level
In patients categorized at **moderate CV toxicity risk, cardiology referral may be considered**	IIb	C
Cardiology referral is recommended in **high-risk and very high-risk patients** before anticancer therapy	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 is recommended for patients with cancer and **pre-existing CVD or abnormal findings at baseline CV toxicity risk assessment** who require potentially cardiotoxic anticancer therapy	I	C

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Recommendations for electrocardiogram baseline assessment

Recommendations	Class	Level
An **ECG is recommended in all patients starting cancer** therapy as part of their baseline CV risk assessment	I	C
In patients with an abnormal baseline ECG, referral to cardiologist is recommended	I	C

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Recommendations for cardiac biomarker assessment prior to potentially cardiotoxic therapies

Recommendations	Class	Level
Baseline measurement of **NP and/or cTn** is recommended in **all patients with cancer at risk of CTRCD if these biomarkes are going to be measured during treatment to detect CTRCD**	I	C

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Recommendations for cardiac imaging modalities in patients with cancer

Recommendations	Class	Level
General		
Echocardiography is recommended as the first-line modality for the assessment of cardiac function in patients with cancer	I	C
3D echocardiography is recommended as the preferred echocardiographic modality to measure LVEF	I	B
GLS is recommended in all patients with cancer having echocardiography, if **available**	I	C
CMR should be considered for the assessment of cardiac function when echocardiography is unavailable or non diagnostic	IIa	C
MUGA may be considered when TTE is not diagnostic and CMR is not available	IIb	C
Baseline cardiac imaging prior to potentially cardiotoxic therapies		
Baseline comprehensive TTE is recommended in all patients with cancer at high risk and very high risk of CV toxicity before starting anticancer therapy	I	C

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ADVERSE EVENT MONITORING

	ECHO	TROP-I	NT PRO-BNP
Jan 18 2022	LVEF 76% (GLS 20%)		
Feb 2 2022	LVEF 71% (GLS 22%)	0.3 PG/ML	< 60 PG/ML
April 6 2022	LVEF 69% (GLS 20%		
Des 9 2022	LVEF 69% (GLS 21%	< 3.2 PG/ML	< 50 PG/ML
April 22rd 2023	LVEF 65% (GLS 20%)	< 3.2 PG/ML	78 PG/ML

Take home points

- The rapid progress of cancer treatment has changed its prognosis and survival with multiple adverse events
- Cardiac risk assessment is crucial throughout cancer therapy
- Awareness, risk stratification, prevention, early detection, management of CV toxicities are important --> tailored treatment & surveillance
- Cardiac function should be screened at baseline as well as during treatment, and appropriate measures should be taken to manage the toxicities
- close collaboration between oncologists and cardiologists is becoming more and more important→ MDT