10° CONGRESSO NAZIONALE

CAMPUS Cuore

Quello che le Linee Guida Non Dicono

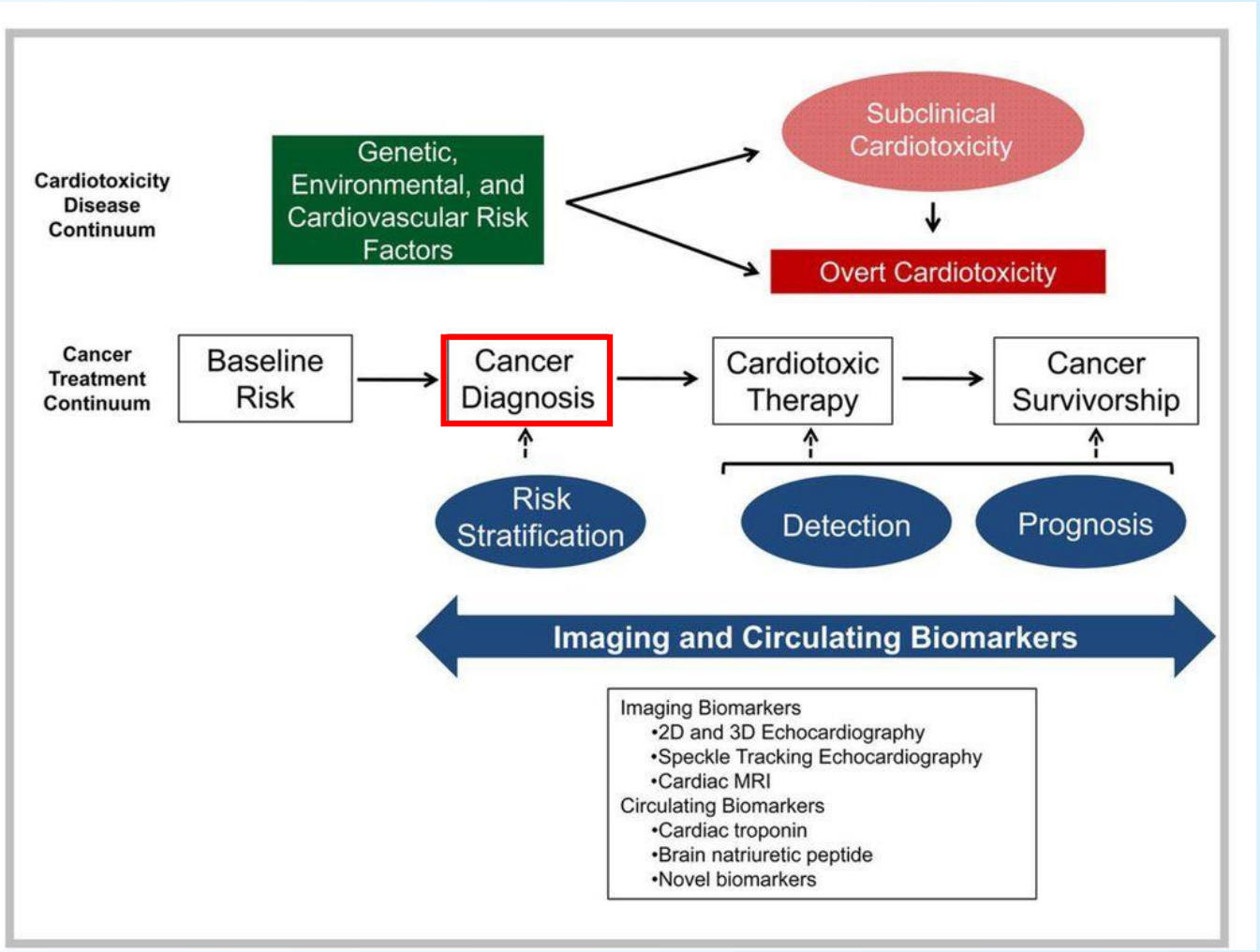
Napoli
Hotel Excelsior
14-15 aprile 2023

Caso clinico 5: cardiotossicità da chemioterapici

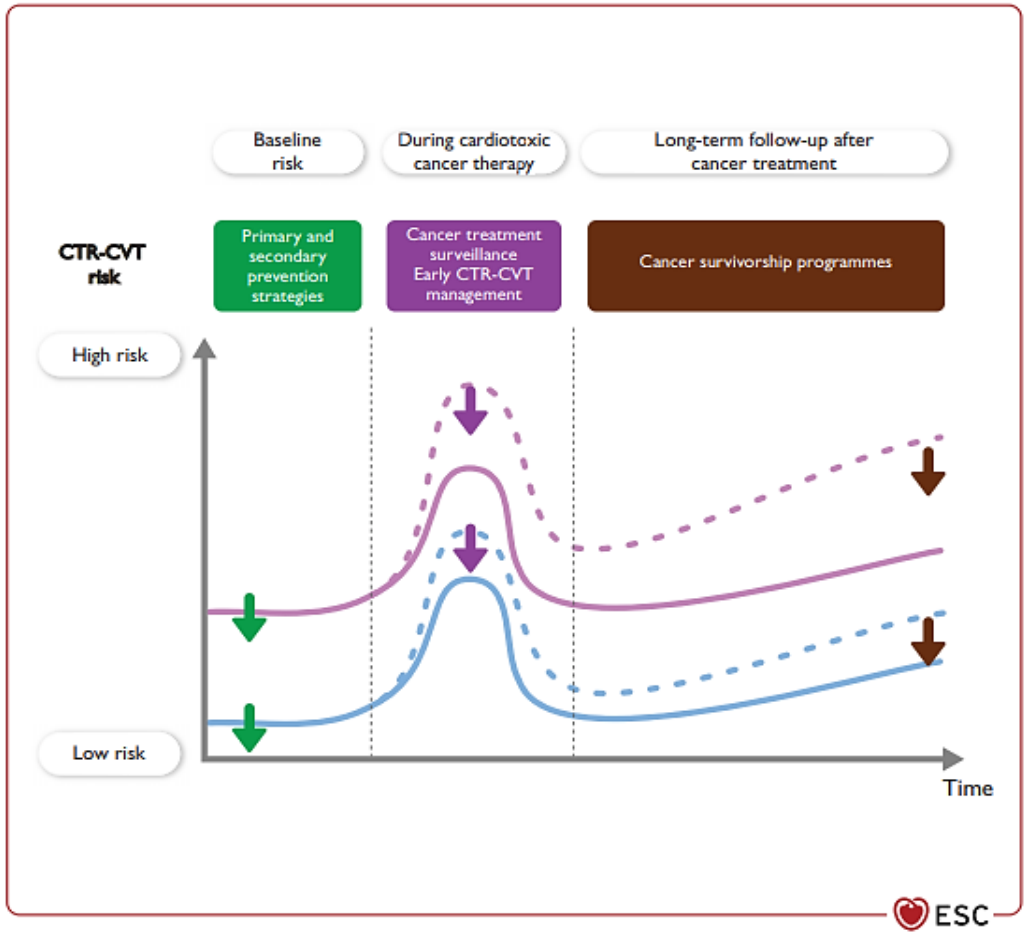
Dott.ssa Maria Prastaro

Cardiologia
Università degli Studi
di Napoli Federico II

Rischio di cardiotossicità: continuum….



CTR-CVT: cancer therapy related - cardiovascular toxicity



- Il rischio di cardiotossicità da terapia oncologica (CTR-CVT) è una ***variabile dinamica*** che cambia durante il percorso di cura
- E' influenzato da diverse condizioni tra cui l'età, la storia del cancro, pre-esistente rischio o malattia cardiovascolare (CVRF o CVD) e precedente terapia oncologica cardiotossica
- Il rischio CTR-CVT cambia durante e dopo il trattamento in base a tipo, dose, frequenza e durata del trattamento oncologico

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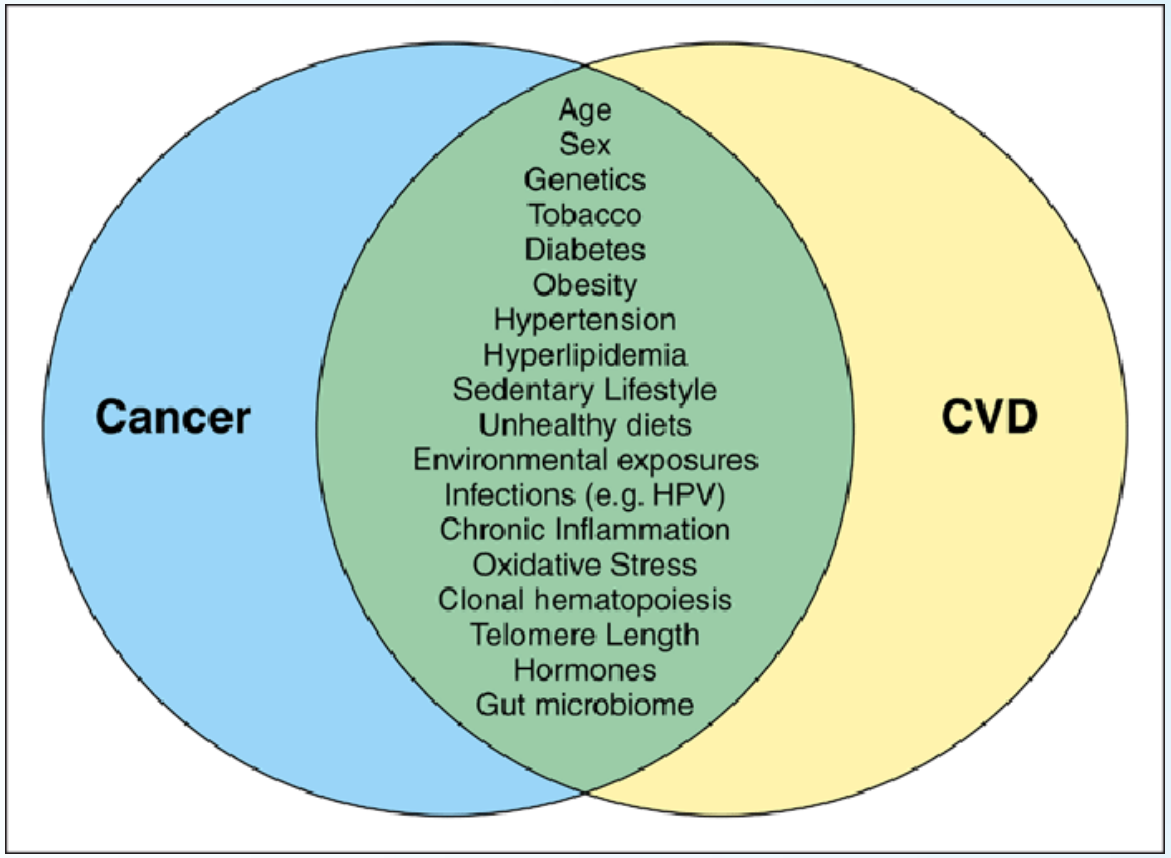
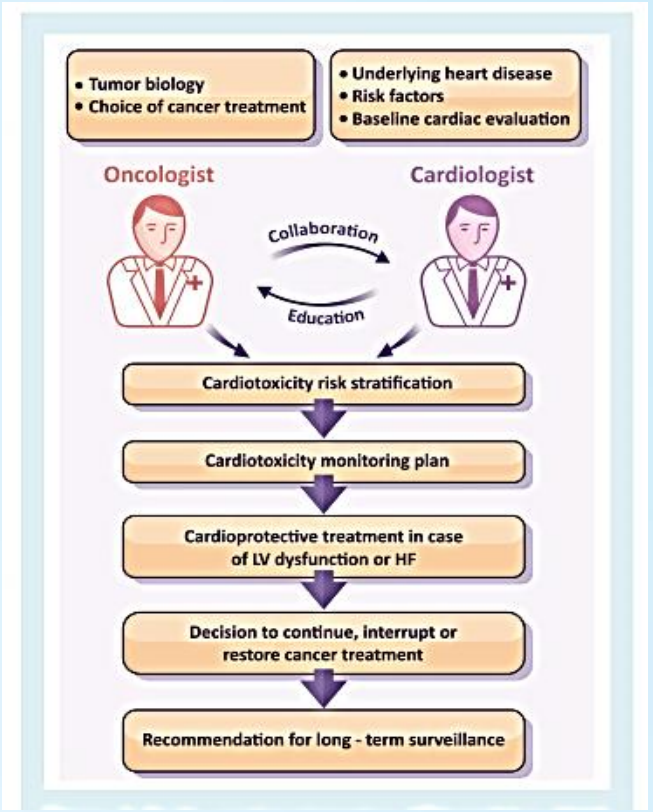
Le malattie cardiovascolari ed il cancro condividono fattori di rischio



Team Cardioncologico

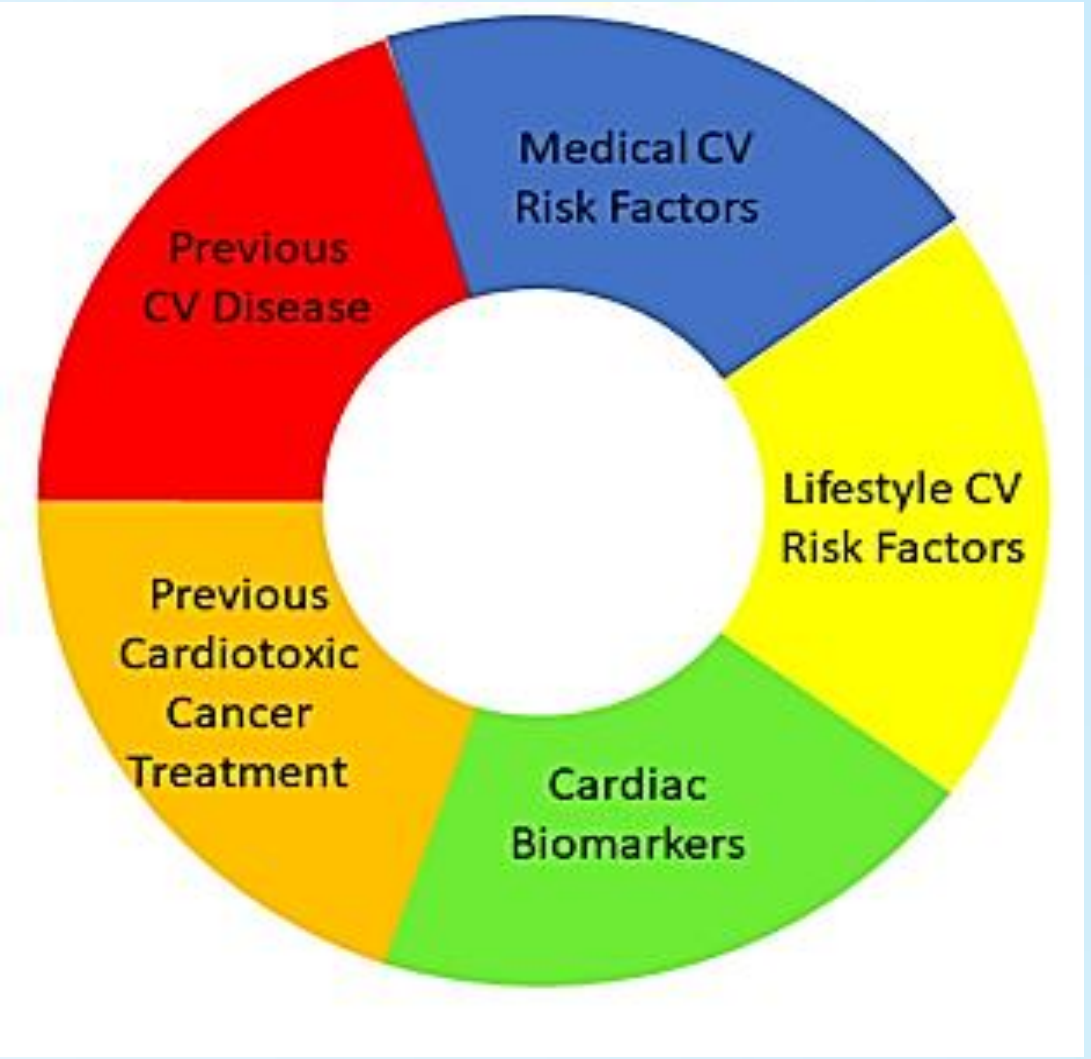


Correlati al trattamento antineoplastico:

- **tipo e dose di farmaco utilizzato**
- **precedente esposizione a trattamenti chemio o radioterapici**

Correlati al paziente:

- **fattori di rischio cardiovascolare** (età, fumo, familiarità, consumo di alcolici, ipertensione arteriosa, diabete, dislipidemia, obesità,sedentarietà, disfunzione renale)
- **malattie cardiovascolari preesistenti** (funzione cardiaca compromessa, malattia coronarica , valvulopatie di grado almeno moderato, cardiomiopatie, aritmie che necessitano di trattamento)



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)

Recommendation Table 1 for a general approach to cardiovascular toxicity risk categorization		
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
It is recommended that patients categorized as low CV toxicity risk should proceed with anticancer therapy without delay.	I	C
Cardiology referral is recommended in high-risk and very high-risk patients before anticancer therapy.	I	C

ESC European Society of Cardiology
European Heart Journal (2022) 00, 1–133
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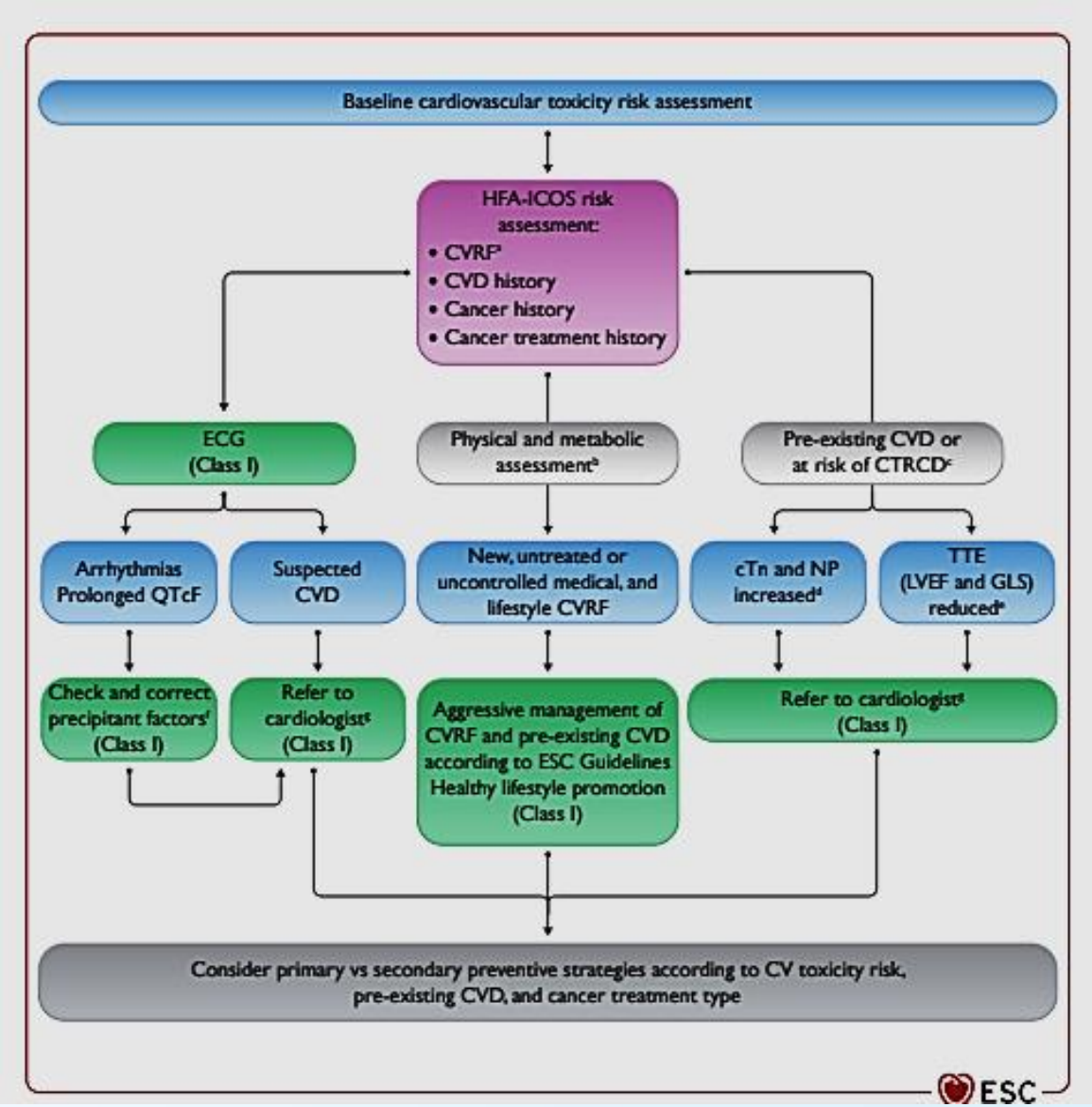
ESC GUIDELINES



Donna, 59 anni

Fattori di rischio cardiovascolare:

- *Ipercolesterolemia*
- *Ipertensione arteriosa*
- *Familiarità per eventi cardiovascolari*

Comorbidità:

- *Anemia Mediterranea*

Anamnesi cardiologica:

- *Fibrillazione atriale parossistica cardiovertita farmacologicamente (2019) in NAO*

TERAPIA DOMICILIARE

➢ PEPTAZOL 20 mg	1 cp/die
➢ CARDICOR 5 mg	1 cp/die
➢ ELIQUIS 5 mg	1 cp x 2/die
➢ ALMARYTM 100 mg	1 cp x 2/die
➢ TORVAST 20 mg	1 cp/die

ANAMNESI ONCOLOGICA

- *2020: diagnosi di K della mammella (ER: 5%; PgR: assente; HER-2: +)*

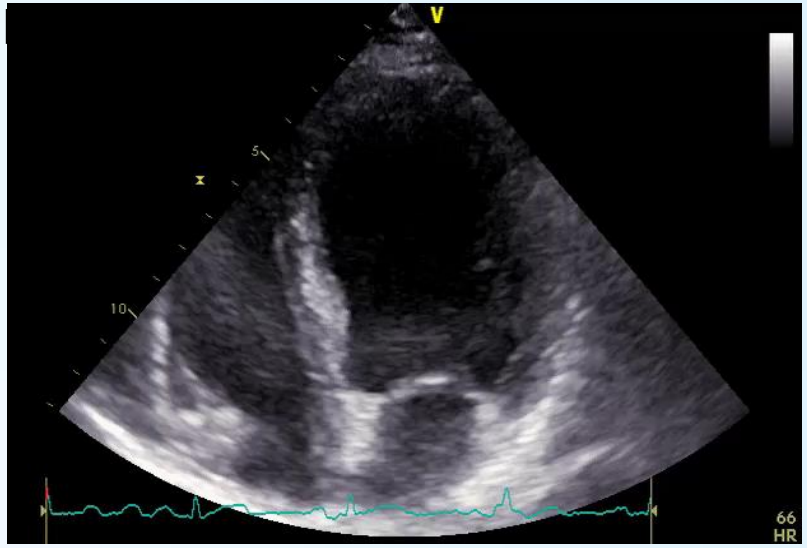
- *Terapia neoadiuvante con Taxano (12 cicli) e Trastuzumab-Pertuzumab (5 cicli), seguiti da Epirubicina-Ciclofosfamide (4 cicli)*

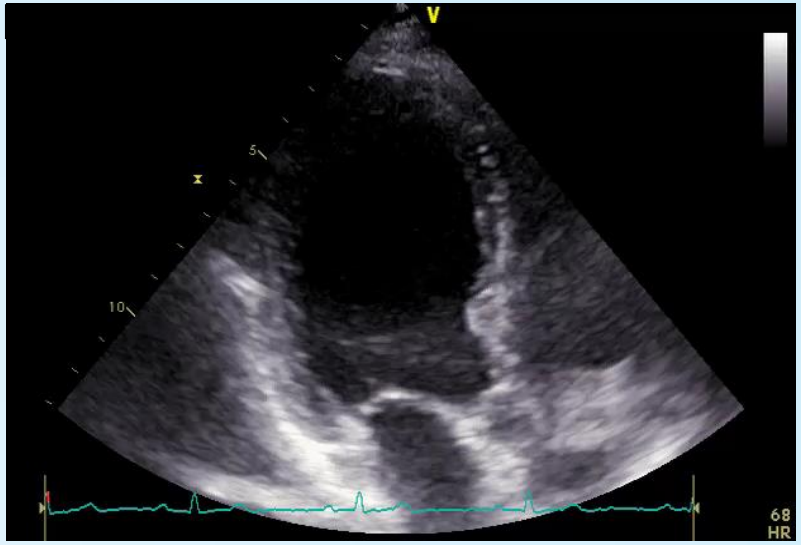
Recommendation Table 7 for baseline risk assessment and monitoring during anthracycline chemotherapy and in the first 12 months after therapy		
TTE		
Baseline echocardiography is recommended in all patients with cancer before anthracycline chemotherapy.	**I**	**B**
Recommendation Table 8 for baseline risk assessment and monitoring during HER2-targeted therapies and in the first 12 months after therapy		
TTE		
Baseline echocardiography is recommended before HER2-targeted therapies in all patients.	**I**	**B**

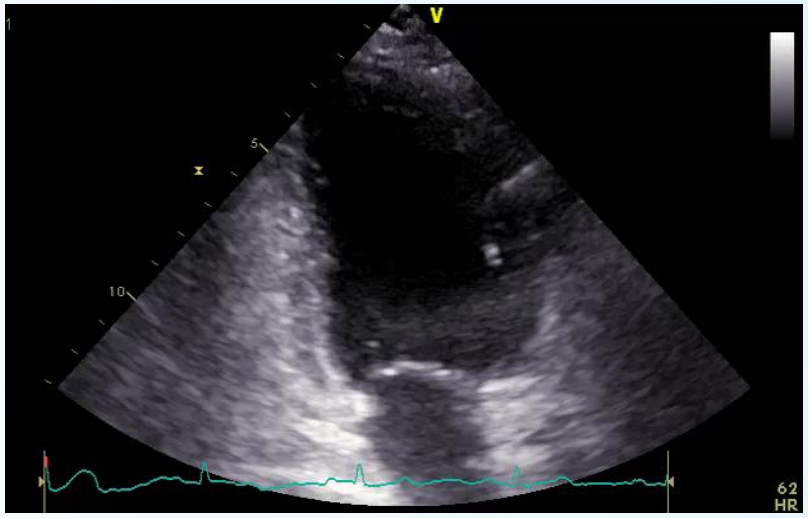
2020: eco Baseline

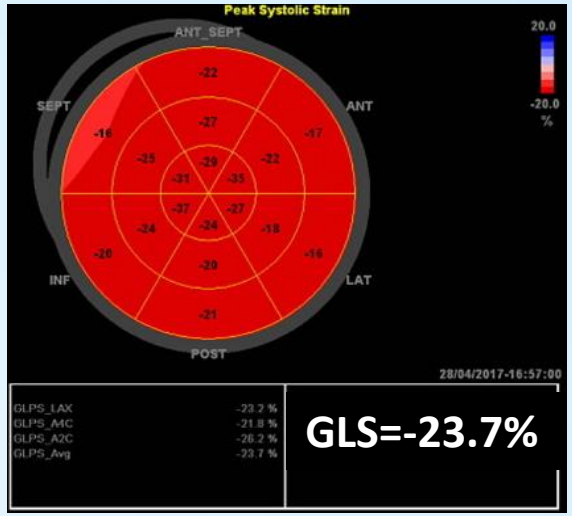
Nessuna sintomatologia CV

EF= 63%





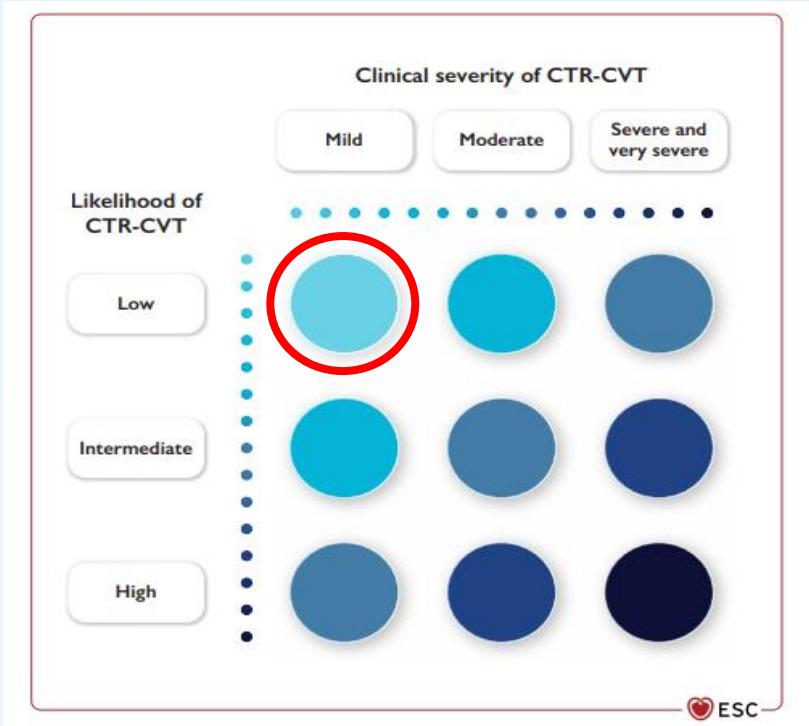




Heart Failure Association–International Cardio-Oncology Society baseline cardiovascular toxicity risk stratification

Table S2 Baseline cardiovascular toxicity risk assessment of patients treated with anthracycline chemotherapy

Risk factor	Score	Level of evidence
Previous CVD		
HF or cardiomyopathy	Very high	B
Severe VHD	High	C
MI or previous coronary revascularization (PCI or CABG)	High	C
Stable angina	High	C
Cardiac imaging		
Baseline LVEF < 50%	High	B
Borderline LVEF 50–54%	Medium2	C
Cardiac biomarkers (where available)		
Elevated baseline troponin[a]	Medium1	C
Elevated baseline BNP or NT-proBNP[a]	Medium1	C
Demographic and CVRF		
Age ≥ 80 years	High	B
Age 65–79 years	Medium2	B
Hypertension[b]	Medium1	B
DM[c]	Medium1	C
Chronic kidney disease[d]	Medium1	C
Previous cardiotoxic cancer treatment		
Previous anthracycline exposure	High	B
Prior RT to left chest or mediastinum	High	C
Previous non-anthracycline-based chemotherapy	Medium1	C
Lifestyle risk factors		
Current smoker or significant smoking history	Medium1	C
Obesity (BMI > 30 kg/m^2)	Medium1	C



- ***Low risk:*** no risk factors or one medium1 risk factor
- ***Medium risk***: medium risk factors with a total of 2–4 points
- ***High risk***: medium risk factors with a total of ≥5 points or any high-risk factor
- ***Very-high risk***: any very high-risk factor

Medium1 = 1 point
Medium2 = 2 points

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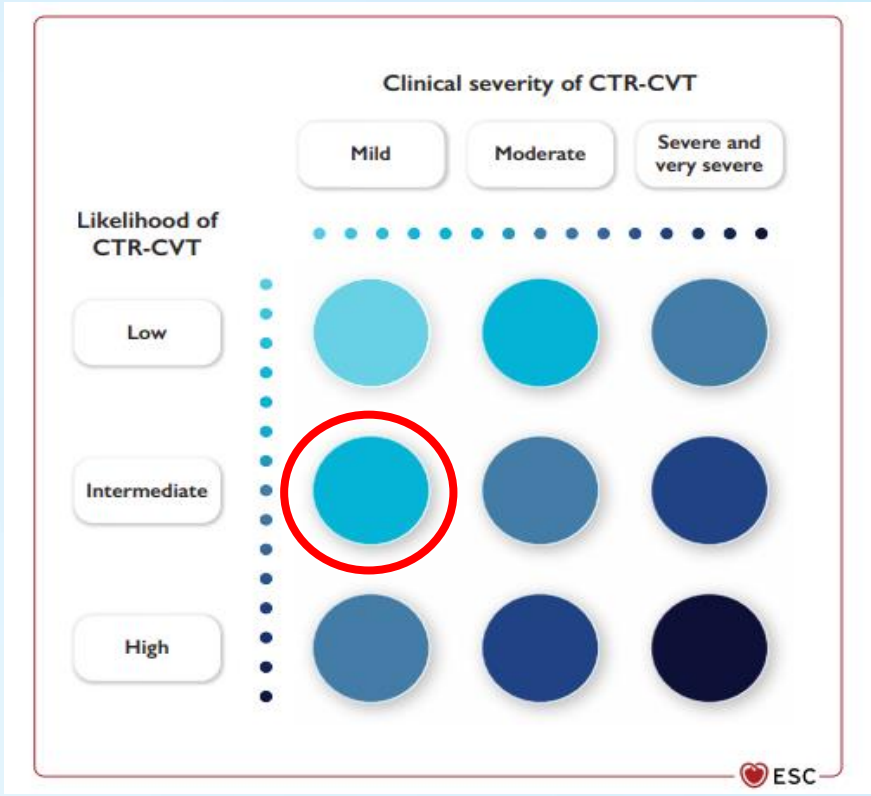
Table S3 Baseline cardiovascular toxicity risk assessment of patients treated with human epidermal factor 2-targeted therapies

Risk factor	Score	Level of evidence
Previous CVD		
HF or cardiomyopathy	Very high	C
MI or CABG	High	B
Stable angina	High	B
Severe VHD	High	C
Arrhythmia[a]	Medium2	C
Cardiac imaging		
Baseline LVEF < 50%	High	C
Borderline LVEF 50–54%	Medium2	B
Cardiac biomarkers (where available)		
Elevated baseline troponin[b]	Medium2	B
Elevated baseline BNP or NT-proBNP[b]	Medium2	C
Demographic and CVRF		
Age ≥ 80 years	High	B
Age 65–79 years	Medium2	B
Hypertension[c]	Medium1	B
DM[d]	Medium1	C
Chronic kidney disease[e]	Medium1	C
Current cancer treatment regimen		
Includes anthracycline before HER2-targeted therapy	Medium1[f]	B
Previous cardiotoxic cancer treatment		
Prior trastuzumab cardiotoxicity	Very high	C
Prior (remote) anthracycline exposure[g]	Medium2	B
Prior RT to left chest or mediastinum	Medium2	C
Lifestyle risk factors		
Current smoker or significant smoking history	Medium1	C
Obesity (BMI > 30 kg/m^2)	Medium1	C

FOLLOW-UP ONCOLOGICO: OTTOBRE 2021

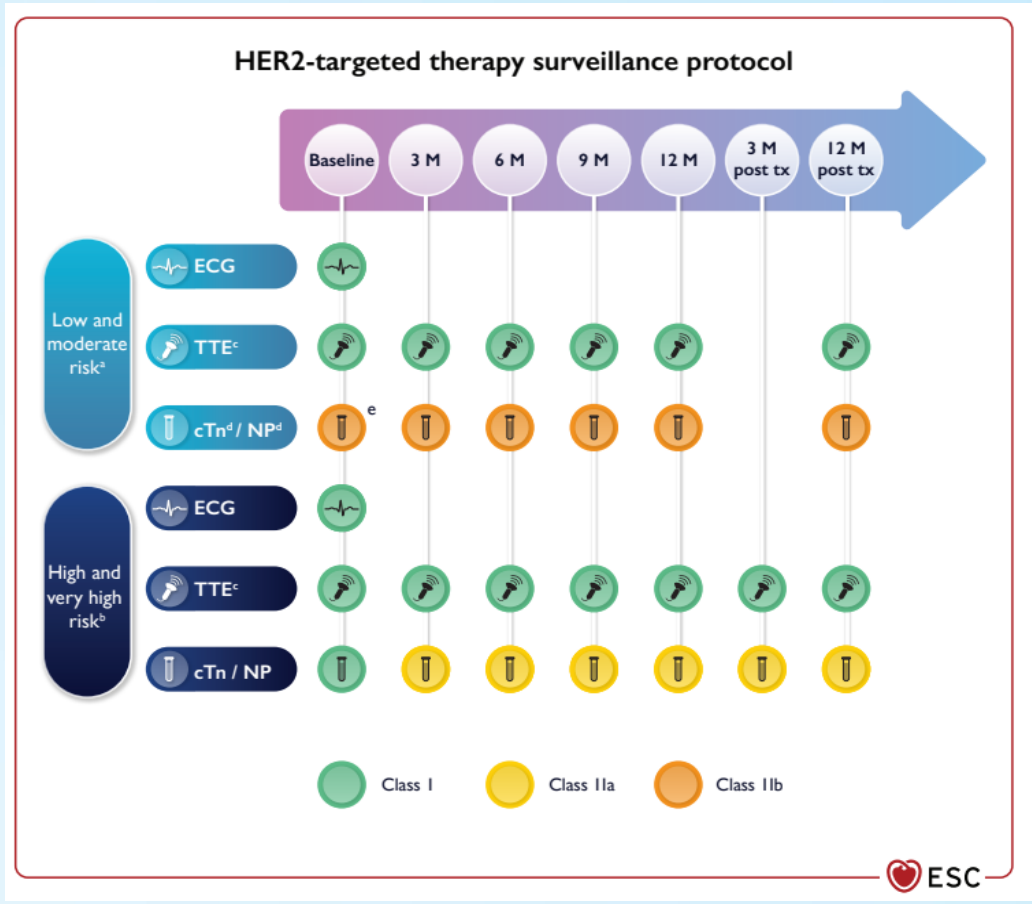
- *Febbraio 2021: quadrantectomia sinistra e successiva terapia adiuvante con anti-HER2 (Trastuzumab-Pertuzumab) + radioterapia*

Fattori correlati al trattamento antineoplastico	Fattori correlati al paziente
Basso rischio: Basse dosi di antracicline (es. doxorubicina <200 mg/m2, epirubicina <300 mg/m2), formulazioni liposomiali Trastuzumab senza antracicline	Età >18 e <50 anni
Rischio intermedio: Dosi moderate di antracicline (doxorubicina 200–400mg/m2 and epirubicina 300–600 mg/m2) Antracicline seguite da trastuzumab Inibitori delle tirosin-kinasi anti-VEGF Inibitori delle tirosin-kinasi anti Bcr-Abl di seconda e terza generazione Inibitori del proteosoma Immunocheckpoint inibitori in combinazione	Età compresa tra 50–64 anni 1–2 fattori di rischio cardiovascolare tra cui ipertensione dislipidemia, obesità, insulino resistenza, fumo
Rischio elevato : Utilizzo simultaneo di antracicline e trastuzumab Alte dosi di antracicline (doxorubicina ≥400 mg/m2 o epirubicina ≥600 mg/m2) Dosi modeste di antracicline più radioterapia del torace sinistro Elevati valori di troponina post-antracicline e prima della terapia anti-HER2 Alte dosi di radioterapia ≥30 Gy coinvolgente la regione cardiaca Trattamento con Inibitori delle tirosin-kinasi anti-VEGF dopo precedente terapia con antracicline	Età ≥65 anni >2 fattori di rischio cardiovascolare tra cui ipertensione, dislipidemia, obesità, fumo, diabete Patologia cardiaca concomitante: cardiopatia ischemica, arteriopata periferica, cardiomiopatia, valvulopatia severa, scompenso cardiaco Frazione di eizione ridotta o ai limiti inferiori 50–54%) prima del trattamento Precedente trattamenento antineoplastico



Sorveglianza durante chemioterapia con anti HER-2

Recommendation Table 8 for baseline risk assessment and monitoring during HER2-targeted therapies and in the first 12 months after therapy		
TTE		
Baseline echocardiography is recommended before HER2-targeted therapies in all patients.	I	B
In patients receiving neoadjuvant or adjuvant HER2-targeted therapies, echocardiography is recommended every 3 months and within 12 months after completing treatment.	I	B
In metastatic HER2+ disease, echocardiography is recommended every 3 months during the first year; if the patient remains asymptomatic without CV toxicity, then surveillance can be reduced to every 6 months during future treatment.	I	C
Cardiac biomarkers		
Baseline NP and cTn measurement are recommended in high- and very high-risk patients prior to anti-HER2-targeted therapies.	I	C



Lyon AR et al., ESC Scientific Document Group. 2022 ESC Guidelines on cardio-oncology Eur Heart J. 2022

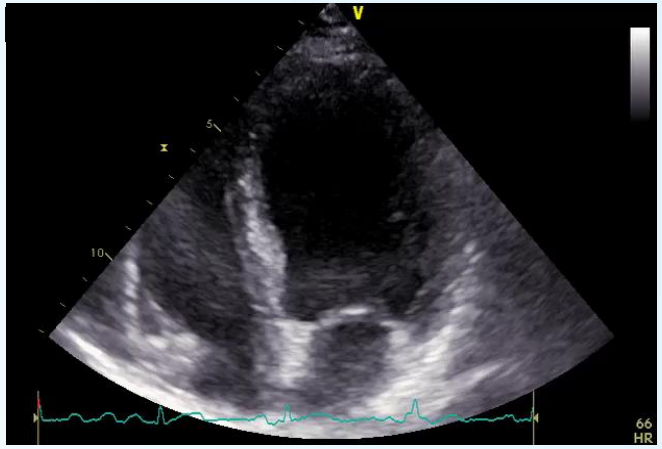
FOLLOW-UP ONCOLOGICO 9m: OTTOBRE 2021

Controlli cardiologici nel corso del follow-up esterni

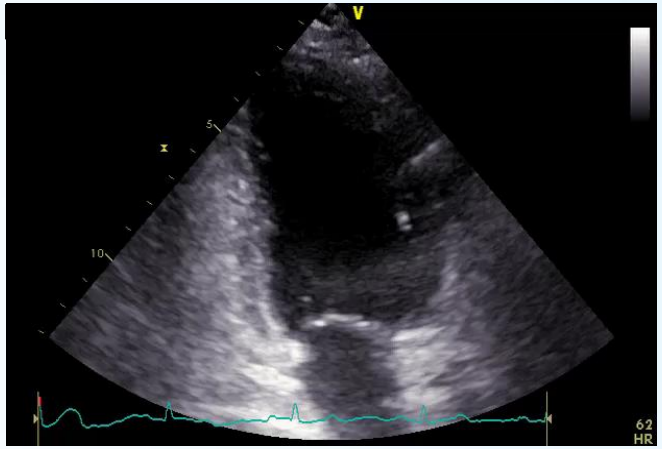
Per la comparsa di sintomatologia viene a visita di controllo presso il nostro servizio di cardioncologia, al XII ciclo di Trastuzumab-Pertuzumab

- *Nega angor, cardiopalmo e sincope. Riferisce astenia e dispnea per sforzi moderati.*
- *PA= 135/80, fc 90 bpm*
- *EOC: Toni puri,pause libere*
- *EOT: fini crepitii bibasali*
- *Hgb: 10,1 g/dl*

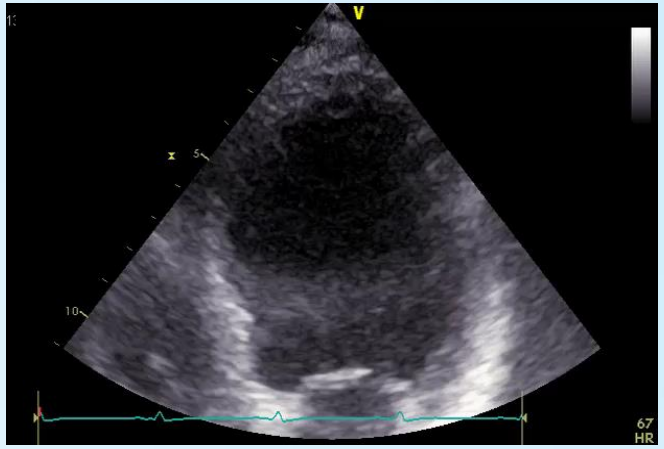
2020



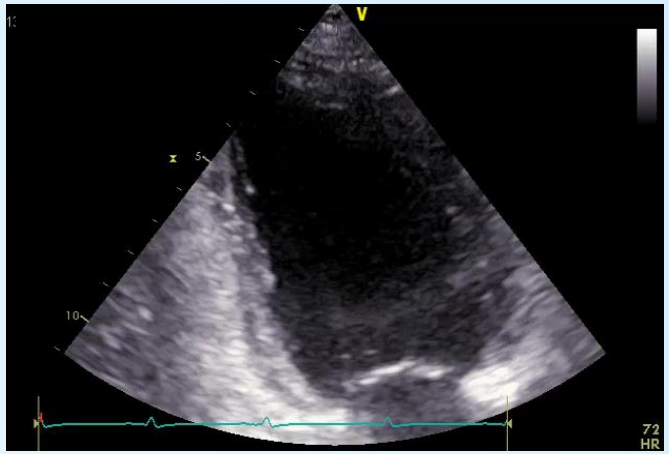
EF= 63%



2021

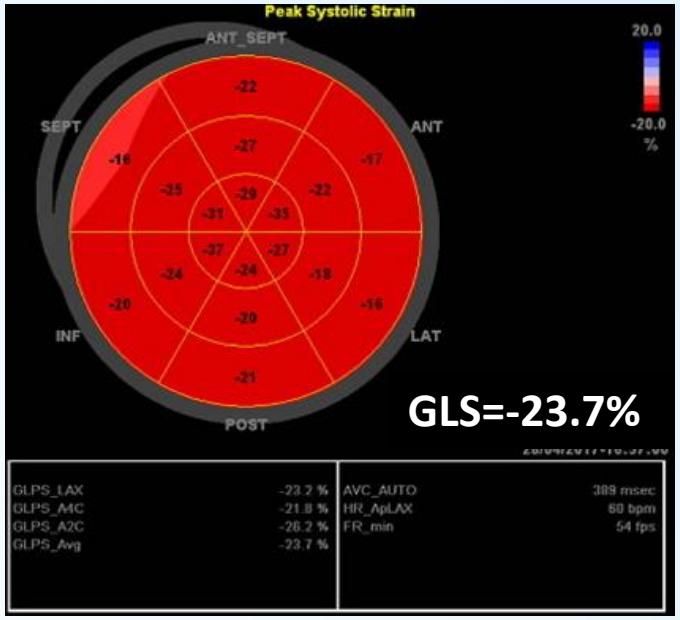


EF= 48%

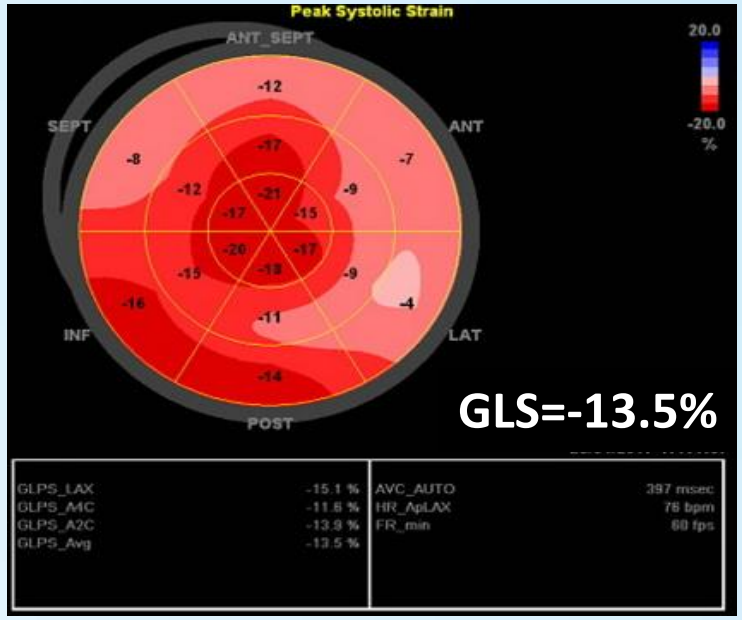


Drop out 23%

Baseline



12˚ ciclo di Trastuzumab



Drop out 43%

Table 3 Cancer therapy-related cardiovascular toxicity definitions

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]

Lyon AR et al., ESC Scientific Document Group. 2022 ESC Guidelines on cardio-oncology Eur Heart J. 2022

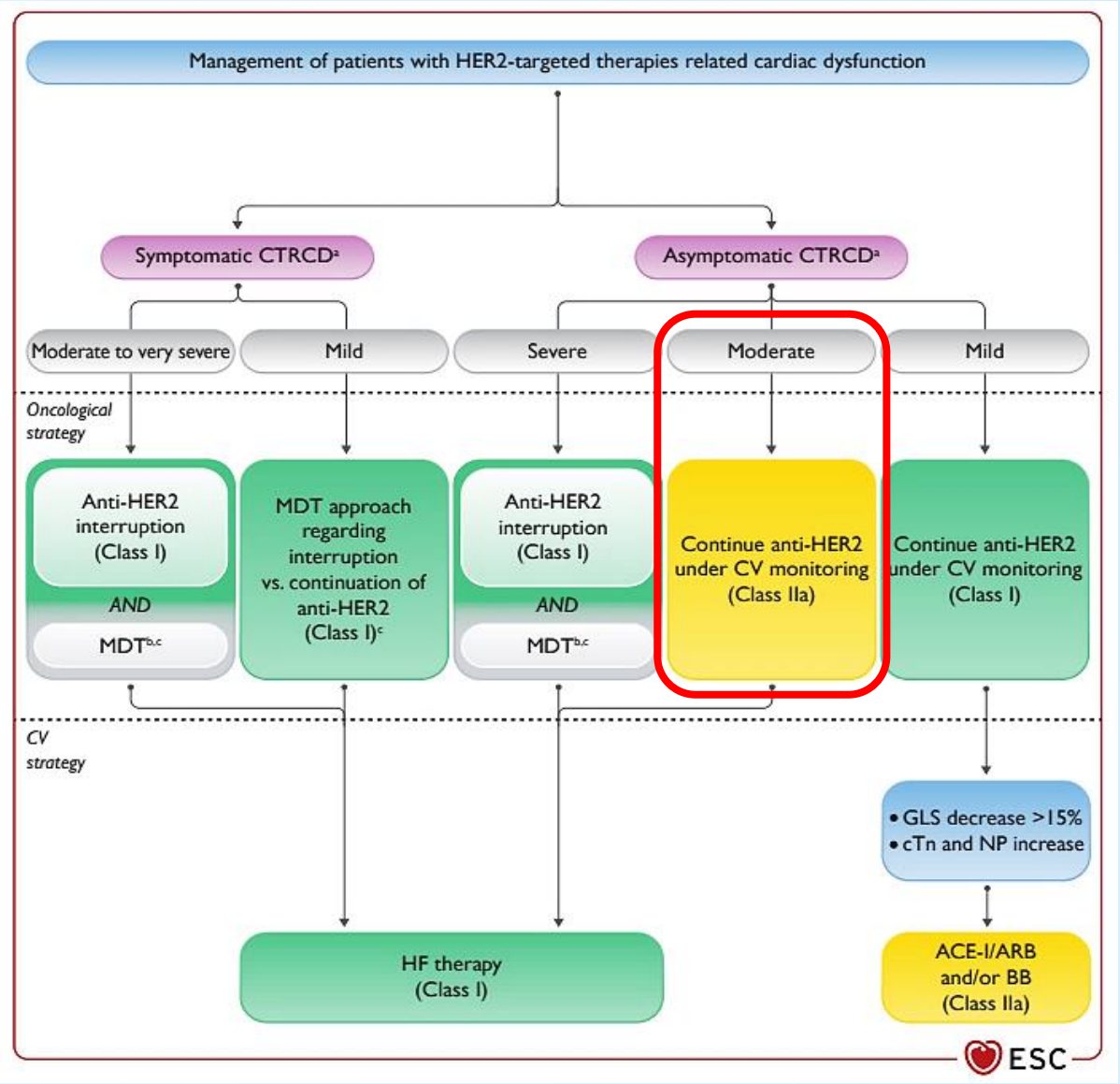
OTTOBRE 2021

➢ PEPTAZOL 20 mg	1 cp/die
➢ CARDICOR 5 mg	1 cp/die
➢ ELIQUIS 5 mg	1 cp x 2/die
➢ **AMIODARONE 200 mg**	**1 cp/die**
➢ ROSUMIBE 20 mg/10mg	1 cp/die
➢ **LASIX 25 mg**	**1 cp a gg alterni**
➢ **TRIATEC 10 mg**	**1 cp/die**
➢ **ALDACTONE 100 mg**	**1/2 cp/die**

Gestione disfunzione cardiaca da anti HER-2

Ottobre 2021

- ✓ ***Controllo ecocardiografico nel breve termine***

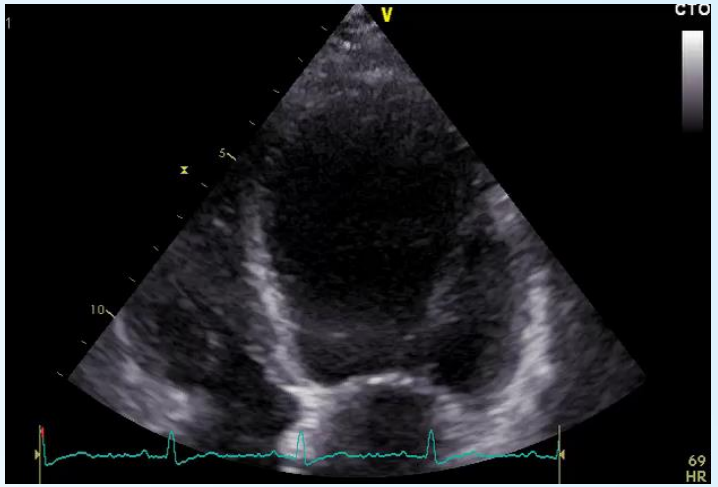


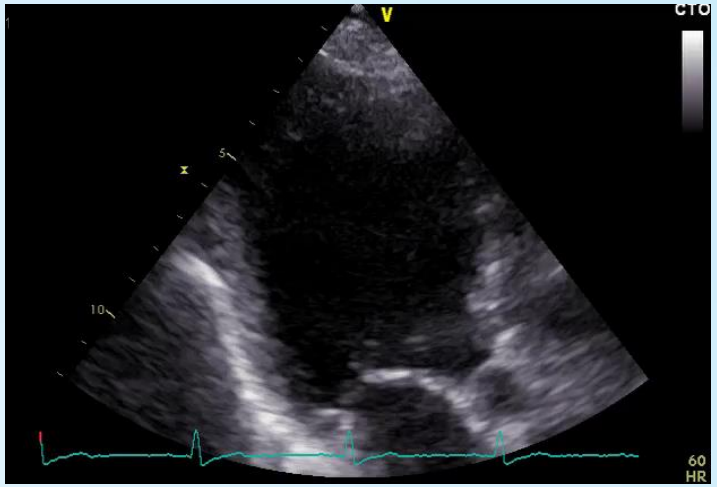
NOVEMBRE 2021

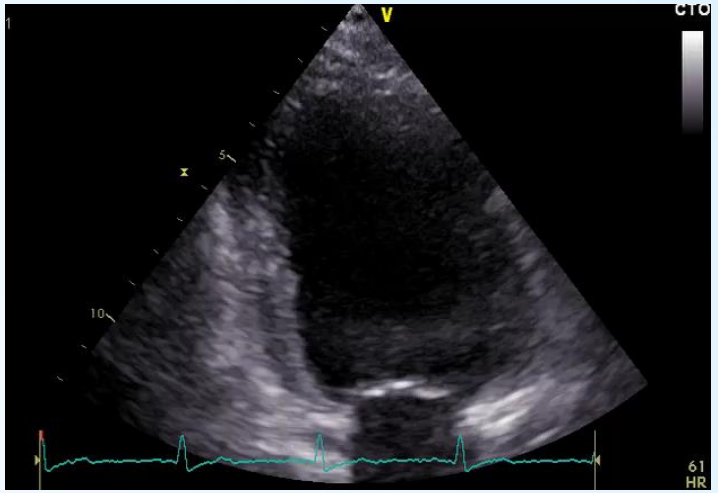
- *Persiste dispnea per sforzi moderati*
- *PA 130/80 mmHg,*
- *EOT fini crepitii basali bilaterali*
- *Hgb= 10,9 g/dl*
- *BNP=282 pg/dl*

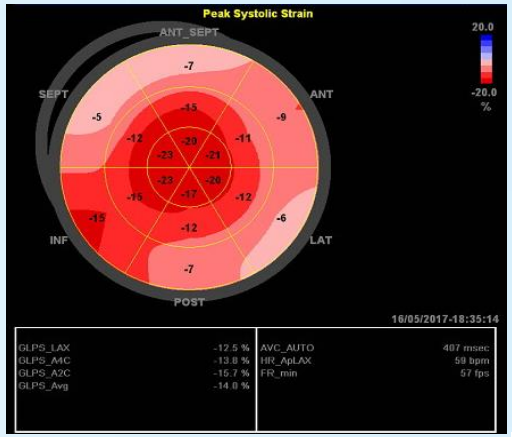
EF= 50%

Continua terapia in stretto follow-up clinico-strumentale





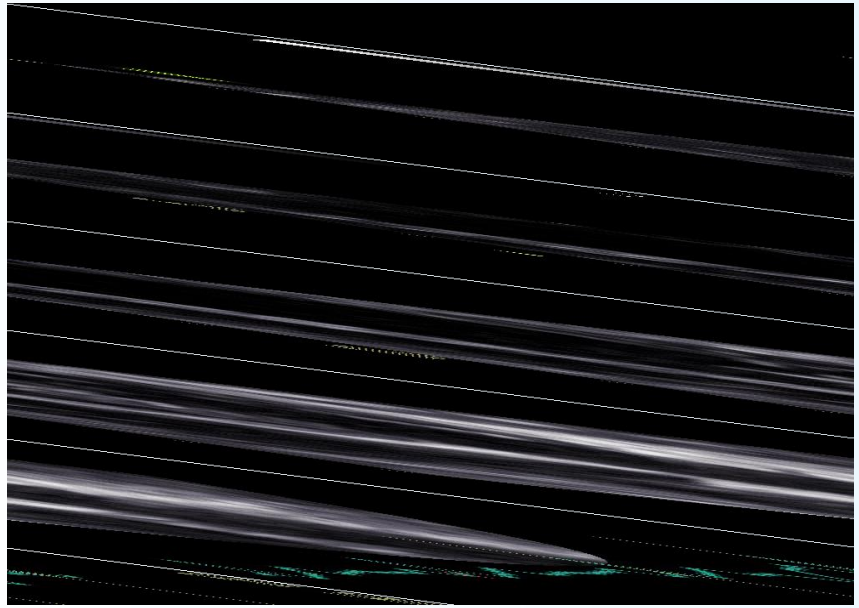
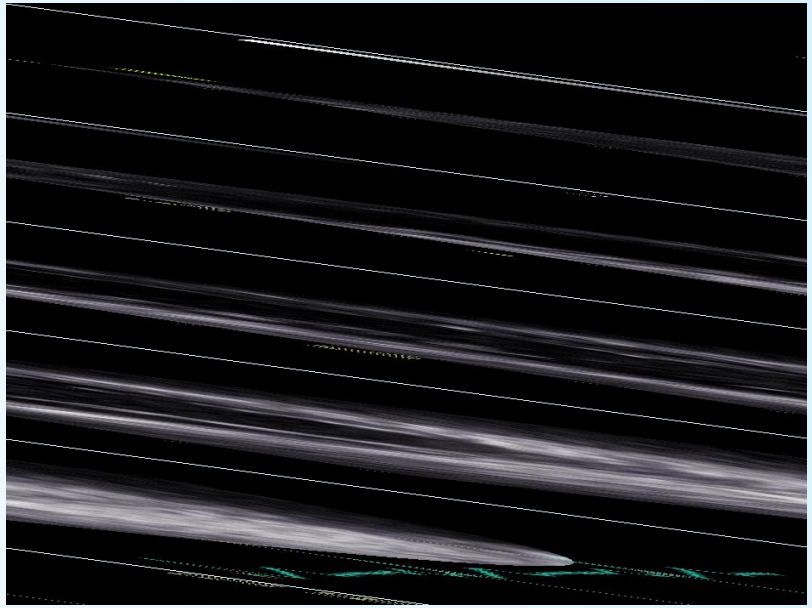
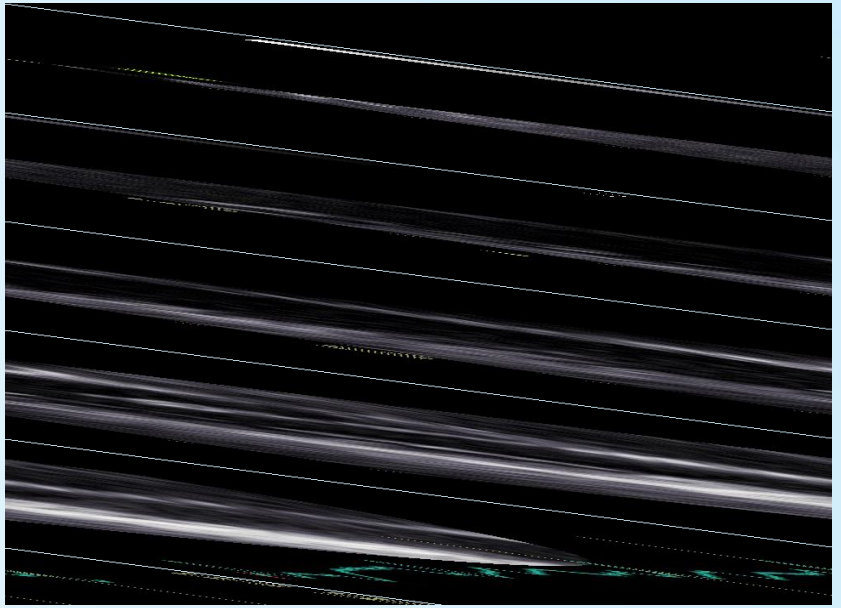




DICEMBRE 2021

- *Dispnea per sforzi lievi ed astenia*
- *PA 125/75 mmHg*
- *Hgb=10,5 g/dl*
- *BNP=884 pg/dl*

- ***EF 39%***

- ***Coro-TC: albero coronarico ateromasico ma esente da lesioni significative***

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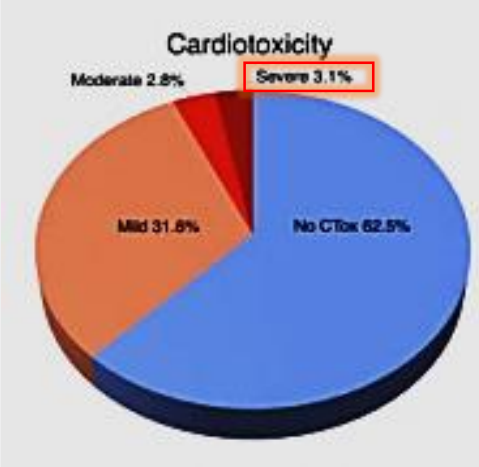


Lyon AR et al., ESC Scientific Document Group. 2022 ESC Guidelines on cardio-oncology Eur Heart J. 2022

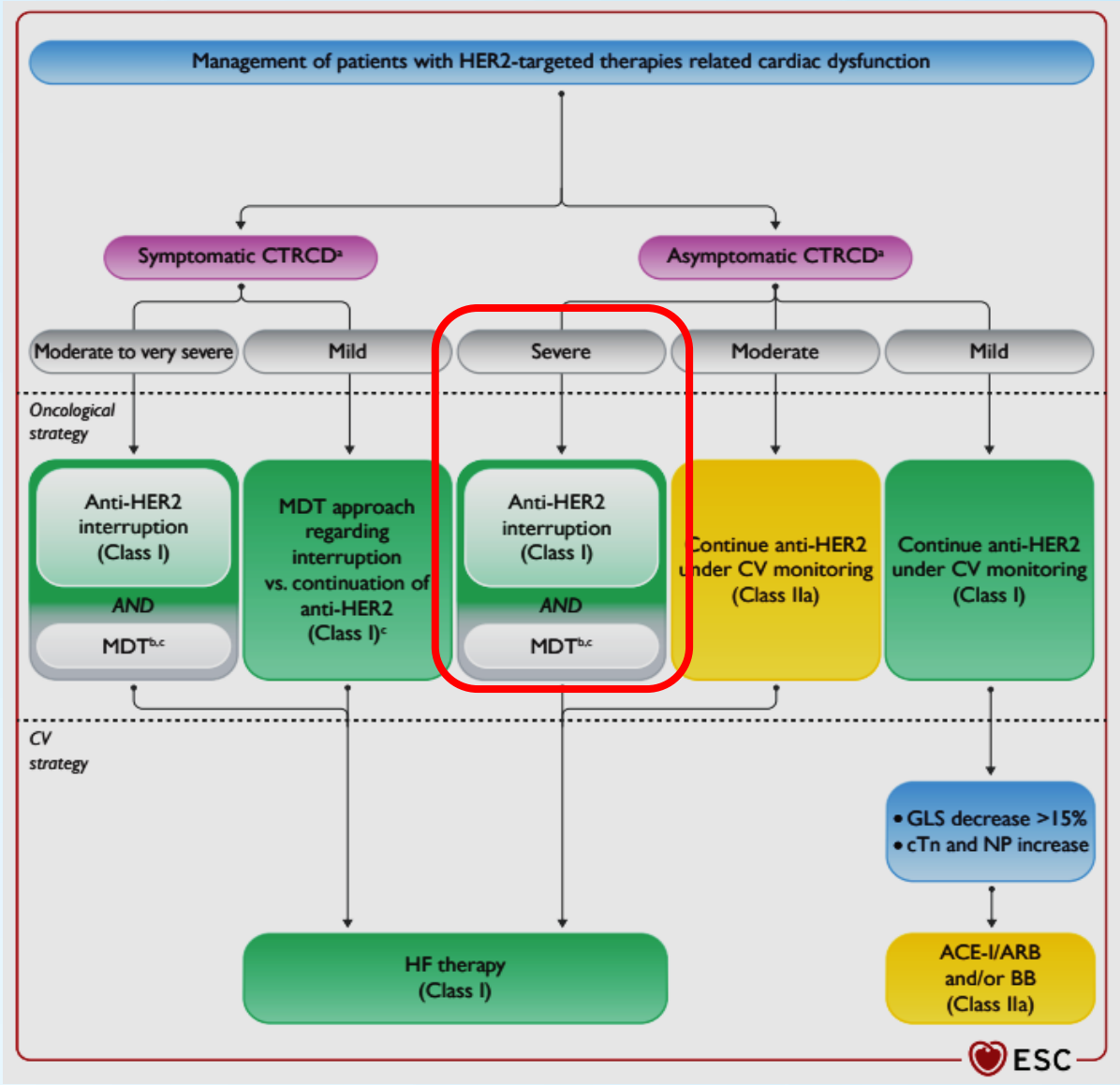
Tossicità da antineoplastici in relazione al timing

- **Acuta:** si manifesta immediatamente dopo la somministrazione del farmaco
- **Subacuta:** entro 2 settimane dal trattamento antineoplastico
- **Cronica a insorgenza precoce** (entro un anno)
- **Cronica a insorgenza tardiva** (oltre l'anno, mediamente dopo 7 anni dall'inizio del trattamento)

Gestione disfunzione cardiaca da anti HER-2

DICEMBRE 2021

STOP Chemioterapia



CARDIOTOSSICITA'
DA ANTI-HER-2

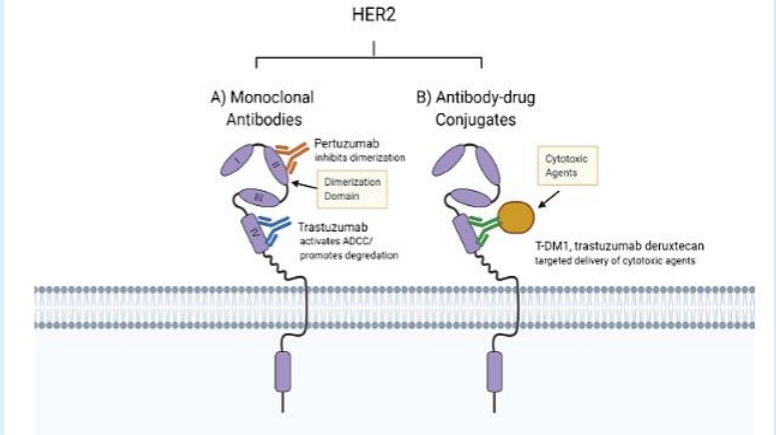
Classi di farmaci usate in chemioterapia: HER2-targeted therapies

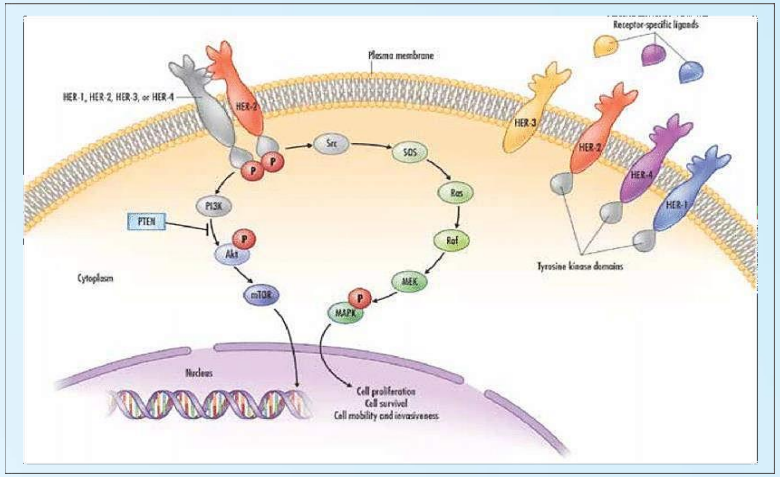
- Lo **human epidermal growth factor receptor 2 (HER2)** è un recettore di membrana del tipo tirosin-chinasico, che regola la crescita ed il differenziamento cellulare

- In circa il 15-20% dei carcinomi mammari (CM) HER 2 è iperespresso

- L'iperespressione di HER2 nel CM sembra conferire un fenotipo più aggressivo e, storicamente, correla con una prognosi sfavorevole e tassi di sopravvivenza libera da malattia e di sopravvivenza globale inferiori rispetto alle pazienti non esprimenti HER2

- La classe di farmaci anti-HER2 è costituita da anticorpi monoclonali (**trastuzumab e pertuzumab**), anticorpi monoclonali coniugati ad agente chemioterapico (**trastuzumab-emtansine)**





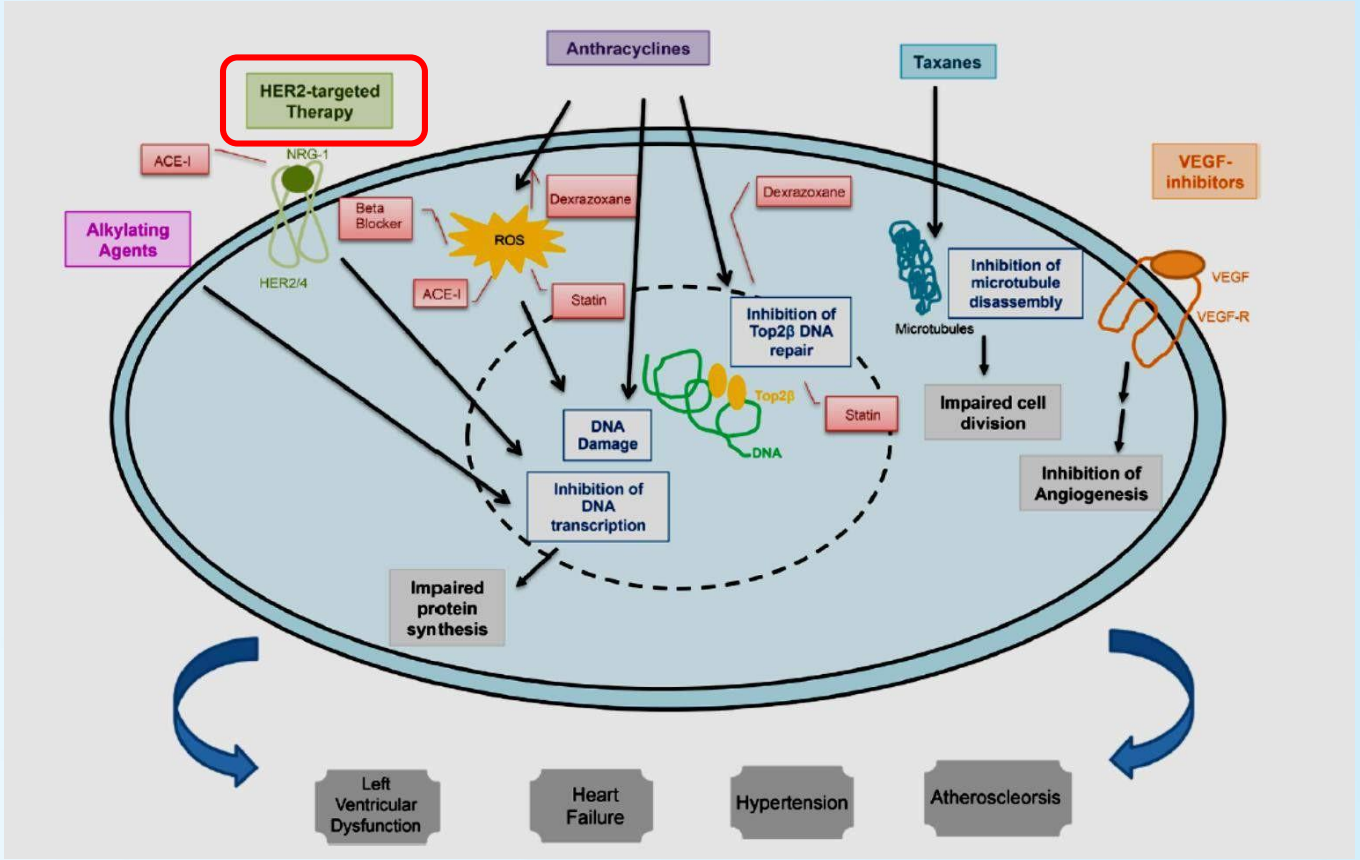
Danno cardiaco trattamento-correlato

Tipo I (agenti citotossici)

- danno miocardico ritenuto irreversibile
- correlato alla dose cumulativa (ad esempio antracicline)

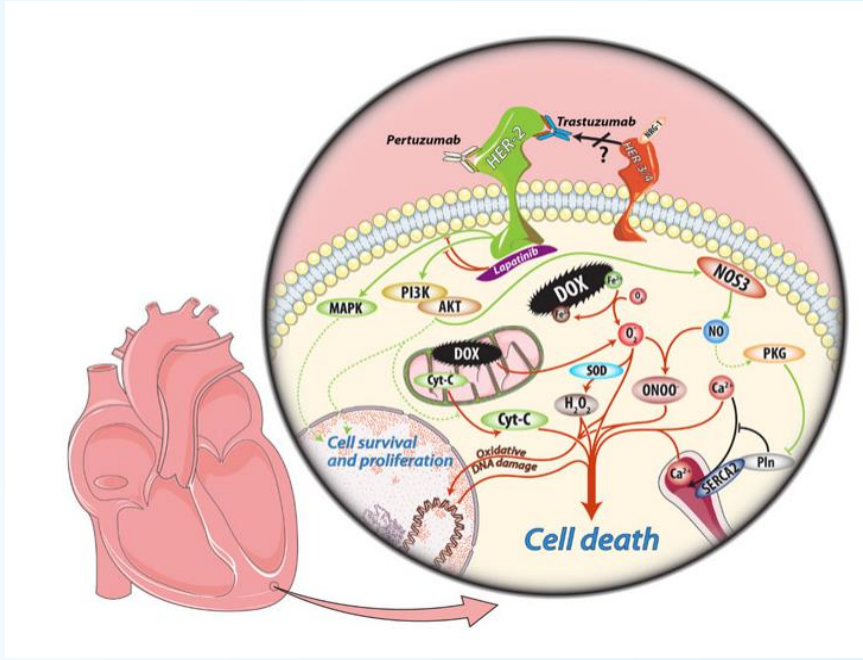
Tipo II (agenti a bersaglio molecolare)

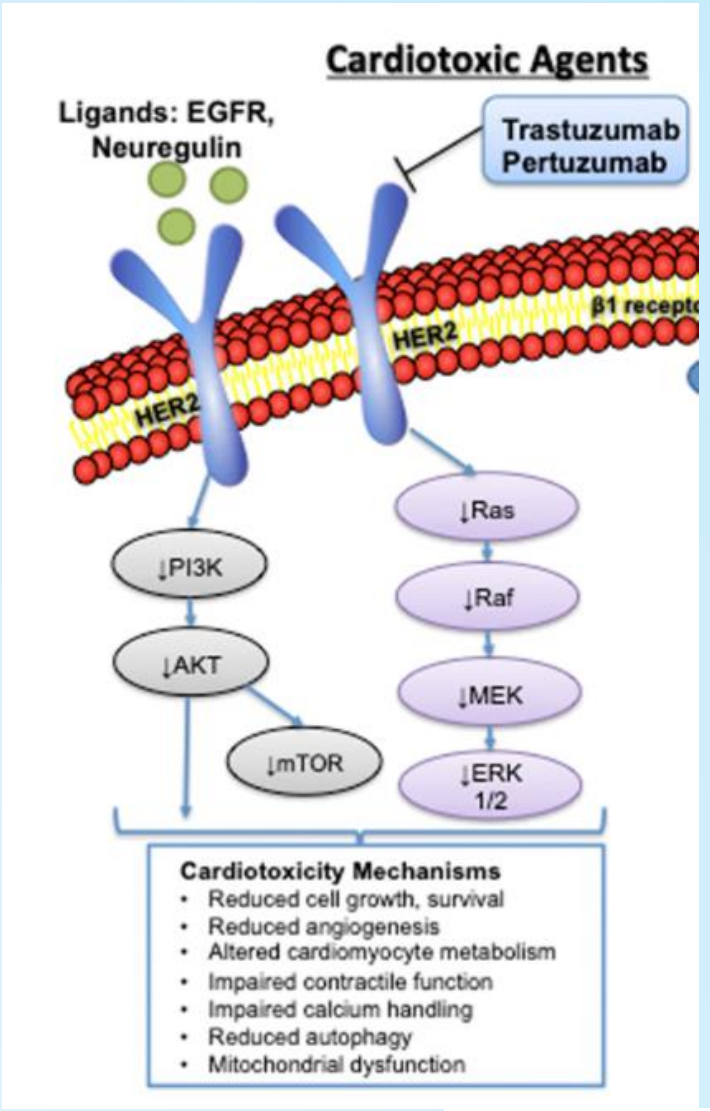
- ✓ eventi avversi si associano prevalentemente ad ipertensione arteriosa, aritmie cardiache e disfunzione ventricolare
- ✓ Non alterazioni morfostrutturali a carico dei cardiomiociti
- ✓ ***Il danno è solitamente reversibile***
- ✓ non sono correlati alla dose cumulativa di farmaco



- Il trattamento anti-HER-2 determina una inibizione della produzione di ATP e ossido nitrico signaling intracellulare che favorisce la sopravvivenza dei cardiomiociti
- Parallelamente, senza un adeguato controbilanciamento, i processi pro-apoptotici (danno mitocondriale ed un aumento della concentrazione intracellulare di calcio) possono facilitare la morte cellulare
- Non vi è effetto citotossico diretto
- L'effetto pro-apoptosico è reversibile con la sospensione del farmaco

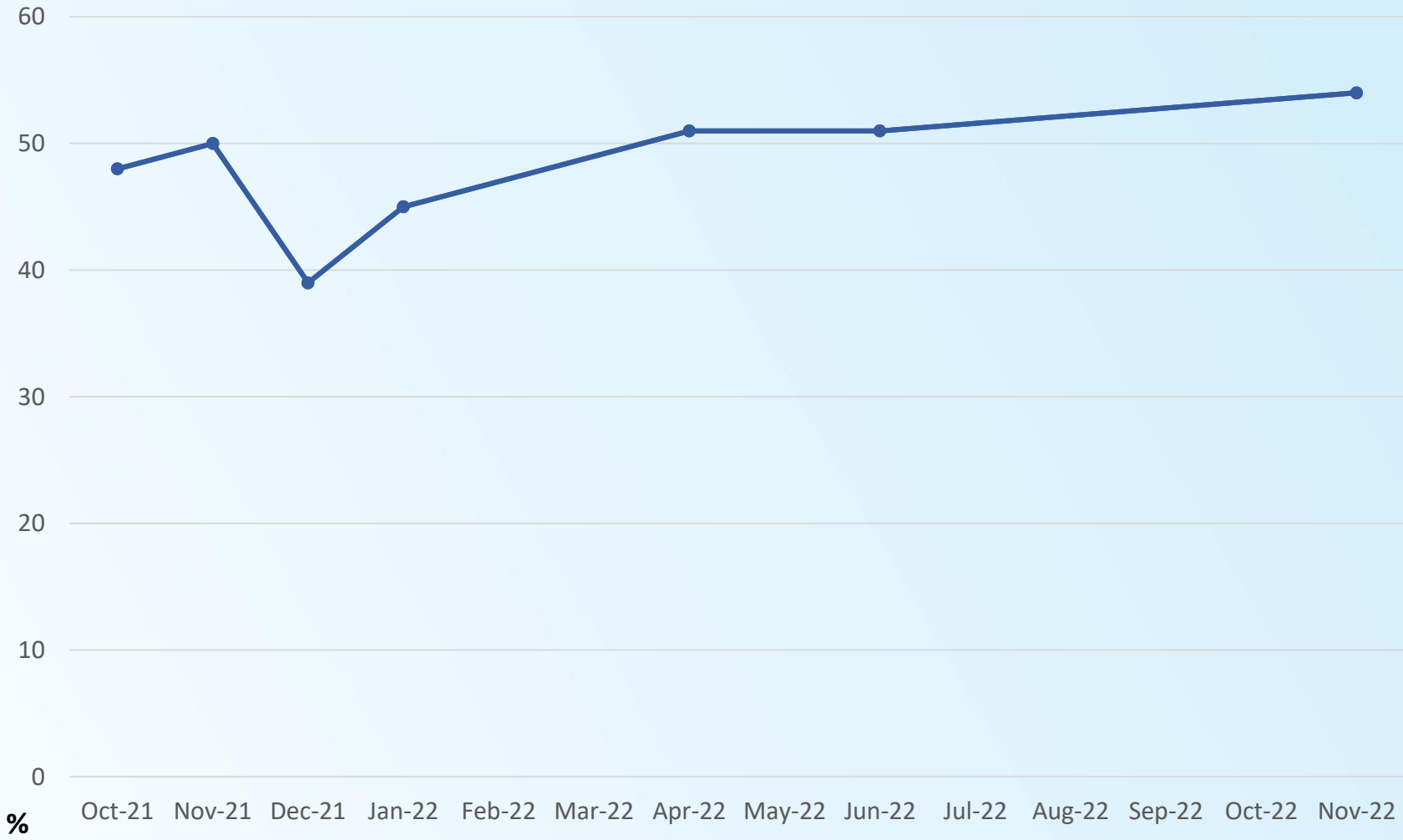
Tossicità da anti-HER-2





Nemeth BT et al. Trastuzumab cardiotoxicity: from clinical trials to experimental studies. Br J Pharmacol. 2017

FRAZIONE D'EIEZIONE durante il FOLLOW-UP

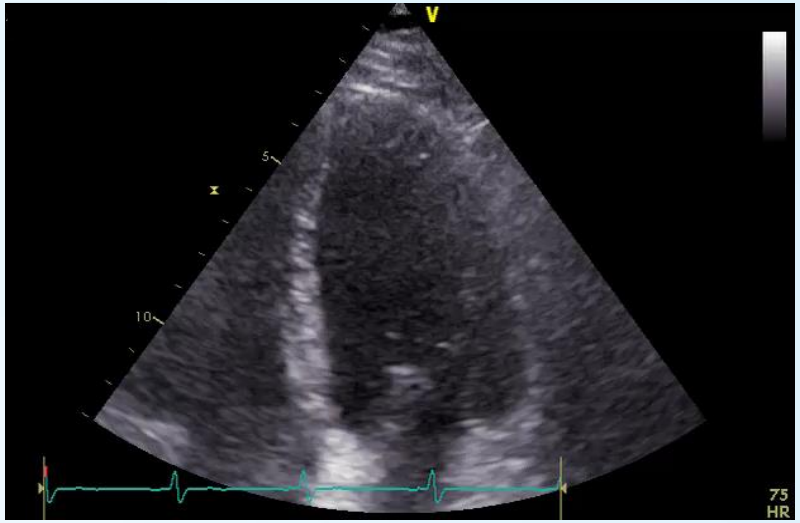


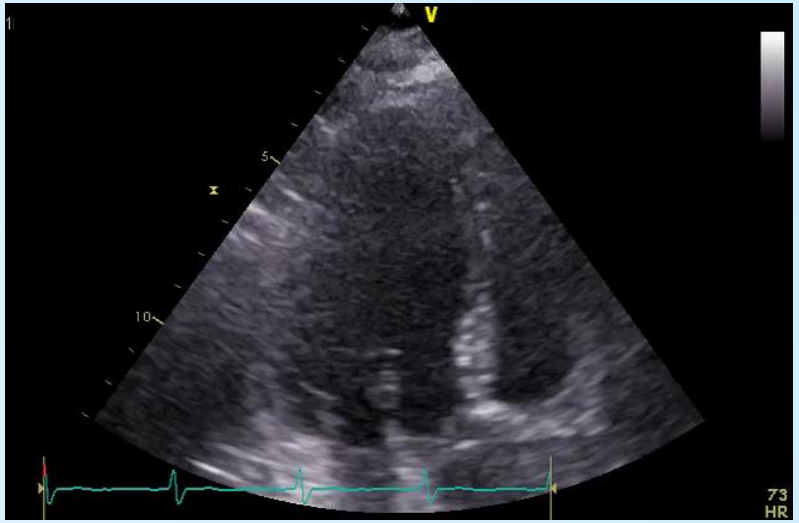
NOVEMBRE 2022

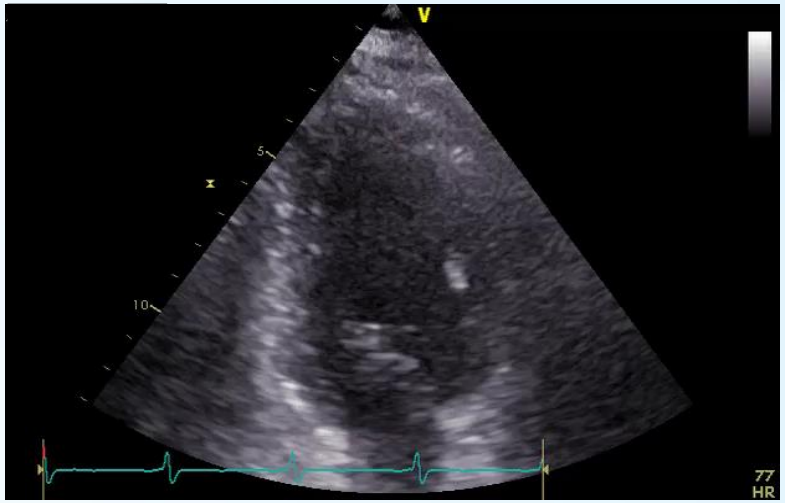
- *da Giugno 2022 in trattamento con Letrozolo*

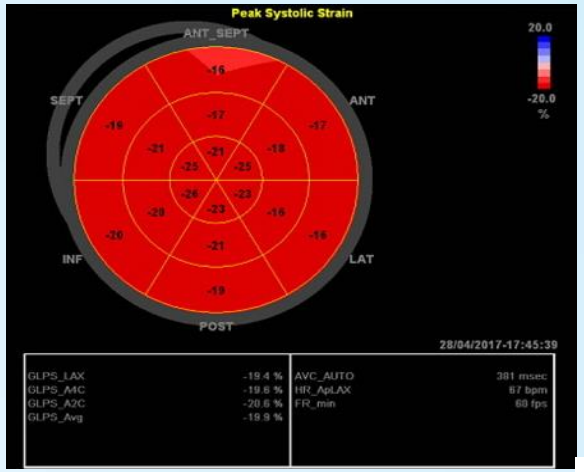
- *Dispnea solo per sforzi moderati*
- *PA 130/80 mmHg*
- *Fc=75 bpm*
- *Hgb=10,8 g/dl*

EF= 55%









CONCLUSIONI

- *Il rischio di cardiotossicità cambia durante (e dopo) il trattamento in base a tipo, dose, frequenza e durata del trattamento oncologico*
- *E' necessario un follow-up personalizzato in base al tipo di patologia oncologica ed al trattamento terapeutico programmato*
- *Nel corso del trattamento è opportuno ristratificare il rischio in relazione al timing terapeutico ed alle condizioni cliniche del paziente*
- *La cardiotossicità deve essere tempestivamente riconosciuta e trattata*
- *E' sempre necessario ed auspicabile un confronto multidisciplinare cardioncologico*

GRAZIE PER L'ATTENZIONE