Terapie antitumorali: tossicità cardiovascolari acute

Dott.ssa Alessandra Emiliani
UOC Oncologia
"SAN GIOVANNI CALIBITA" FATEBENEFRATELLI

Modulo dichiarazione conflitto di interessi

Tutti i rapporti finanziari intercorsi negli ultimi due anni devono essere dichiarati.

☒ Non ho rapporti (finanziari o di altro tipo) con le Aziende del farmaco

☐ Ho / ho avuto rapporti (finanziari o di altro tipo) con le Aziende del farmaco

Relationship	**Company/Organization**

Acute Cardiotoxicity

OUTLINE

1. Cardiotoxicity definition
2. Anthracyclines
3. Anti-HER2 agents
4. CDK4/6 Inhibitors
5. Fluoropirimidine
6. anti VEGF
7. ICIs

Definition of Cardiotoxicity

Table 1 Variation in definitions of cardiotoxicity across standards organisations

Standards organisation	Definition of cardiotoxicity	Comments
ASE/EACVI	LVEF fall by >10% to absolute EF <53%	Change in LV function may be global or regional (septum) Symptomatic or asymptomatic for HF
ESC	LVEF fall by >10% from baseline to EF <50%	Symptomatic or asymptomatic for HF
NCI	CTCAE HF grade 1–5	Grade 1 (asymptomatic) Grade 2 (mild to moderate symptoms) Grade 3 (symptomatic on minimal exertion or at rest) Grade 4 (life-threatening) Grade 5 (death)
CCS	LVEF fall by >10% from baseline or LVEF <53%	Guidelines also recommend (1) 3D echocardiography or same imaging modality during cancer therapy, (2) myocardial strain imaging and (3) cardiac biomarkers (N-terminal pro brain natriuretic peptide, troponin) for early detection
ESMO	Symptomatic decline in LVEF of at least 5% to <55% or asymptomatic decline in LVEF of at least 10% to <55%	Symptoms for congestive HF with signs including but not limited to S3 gallop, tachycardia or both Decline in LVEF either global or more severe in the septum

ASE, American Society of Echocardiography; CCS, Canadian Cardiovascular Society; CTCAE, Common Terminology Criteria for Adverse Events; EACVI, European Association of Cardiovascular Imaging; EF, ejection fraction; ESC, European Society of Cardiology; ESMO,

The most common used definition in clinical practice and clinical trials is:

a LVEF value <50% and a decrease >10% from its baseline value

Adapted from CCS guidelines by Virani *et al* CJC 2016 (32) 831–841 and ESMO statement Curigliano *et al* Annals Oncol 2012 23 (suppl 7);

Definition of Cardiotoxicity

	Type I cardiotoxicity (anthracycline)	Type II cardiotoxicity (trastuzumab)
Clinical course, response to medication	May stabilize, but subclinical damage seems to persist; recurrence in months or years may be related to sequential cardiac stress	High likelihood of complete or near-to-complete recovery upon withdrawal and/or medication
Dose dependence	Cumulative, "lifetime" dose-related	Dose-independent
Mechanism	Free radical formation (?), alcohol metabolite formation (?)	Elimination of HER2-related survival factors
Ultrastructure	Vacuoles, myofibrillar disarray and dropout, apoptosis, and necrosis	With limited exceptions, no apparent ultrastructural abnormalities
Noninvasive cardiac testing	Decreased LVEF, global decrease in wall motion	As in type I
Effect of rechallenge	High probability of recurrent dysfunction that progresses toward treatment-resistant CHF	Increasing evidence for the safety of rechallenge
Effect of late sequential stress	High likelihood of sequential stress-related cardiac dysfunction	Low likelihood of sequential stress-related cardiac dysfunction

CHF: Congestive heart failure; LVEF: Left ventricular ejection fraction.

Temporal classification

Characteristic	Acute cardiotoxicity	Early onset, chronic progressive cardiotoxicity	Late onset, chronic progressive cardiotoxicity
Onset	Within the first week of anthracycline treatment	<1 year after the completion of anthracycline treatment	>1 year after the completion of anthracycline treatment
Risk factor dependence	Unknown	Yes	Yes
Clinical features in adults	Transient depression of myocardial contractility; myocardial necrosis (cTnT elevation); arrhythmia	Dilated cardiomyopathy; arrhythmia	Dilated cardiomyopathy; arrhythmia
Clinical features in children	Transient depression of myocardial contractility; myocardial necrosis (cTnT elevation); arrhythmia	Restrictive cardiomyopathy and/or dilated cardiomyopathy; arrhythmia	Restrictive cardiomyopathy and/or dilated cardiomyopathy; arrhythmia
Course	Usually reversible on discontinuation of anthracycline	Can be progressive	Can be progressive

Cardiotoxicity in Oncology

MECHANISM OF CARDIOTOXICITY
Impaired protein synthesis, formation of reactive oxygen species, inhibition of DNA repair
Inhibition or ErbB2 pathway Inhibits VEGF
Coronary vasospasm
Impaired microtubule function, impaired cell division
Interference with cell cycle degradation proteins
ROS production
Impaired cell signal transduction, cell cycle regulation, metabolism and transcription
Microvascular injury, macrovascular injury, valve endothelial injury and dysfunction

Cardiotoxicity in Oncology

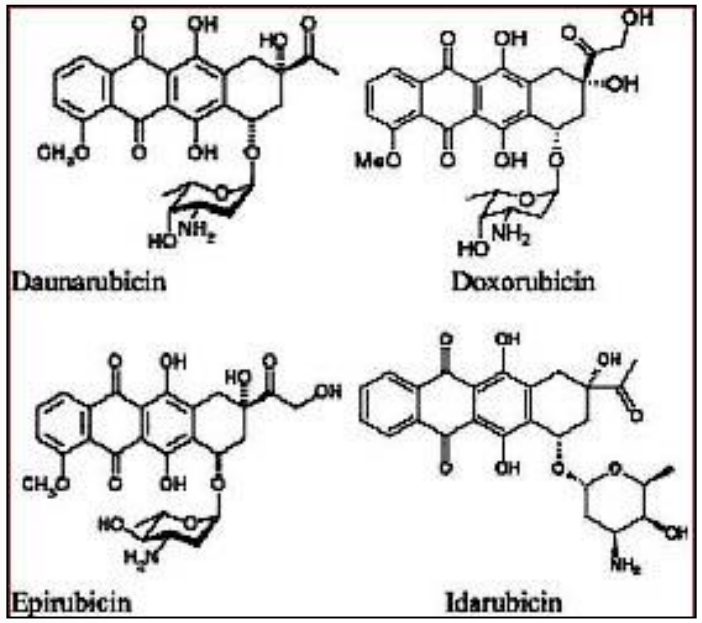
Focus on heart failure and myocardial dysfunction

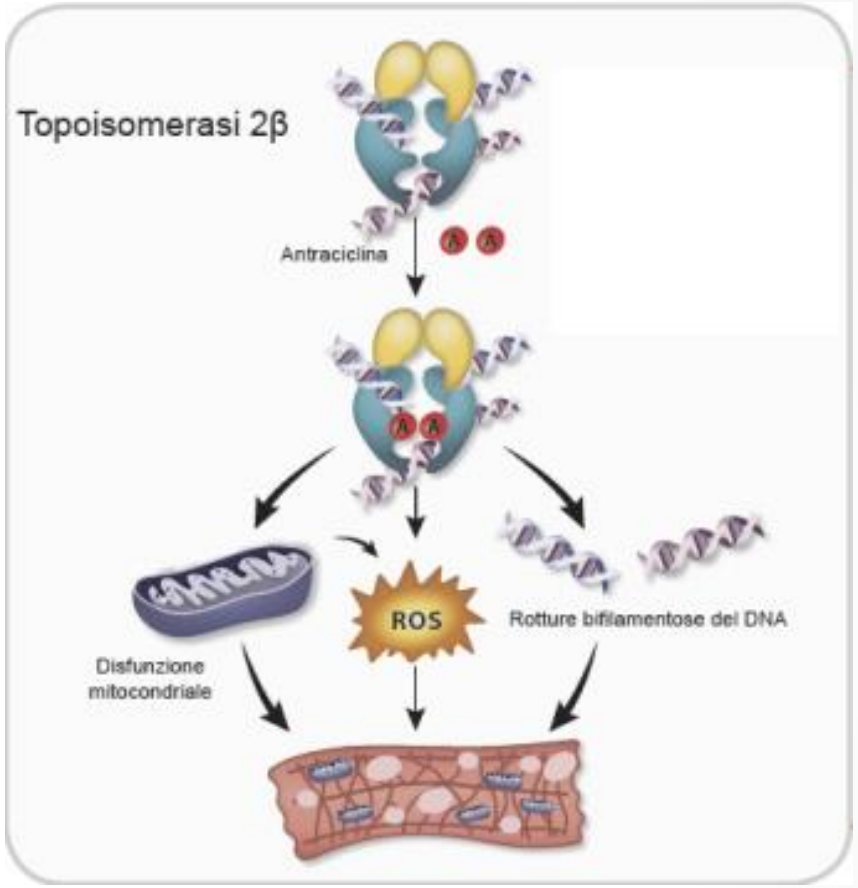
Agent	Incidence (%)	Agent	Incidence (%)
Doxorubicin	2-48	Pertuzumab	<1.5
Epirubicin	1-3.3	Lapatinib	<1
Liposomal A	2	Sunitinib	2.7-19
Cyclophosphamide	7-28	Sorafenib	4-8
Ifosfamide	17	Pazopanib	7-11
Docetaxel	2-13	Imatinib	<3
Paclitaxel	<1	Everolimus	<1
Bevacizumab	1.6-4	Temsirolimus	<1
Trastuzumab	1.7-20		

ESMO

Adapted from ESC Guidelines; European Heart Journal 2016

Cardiotoxicity of Anthracyclines





NUOVA TEORIA - Cardiotossicità mediata dall'inibizione di una topoisomerasi 2ß espressa costitutivamente nei cardiomiociti: Nel cuore, la stabilizzazione di un complesso ternario topoisomerasi 2ß-DNA-antraciclina determina rotture bifilamentose del DNA, con conseguenti alterazioni globali della trascrizione genica e, in ultima analisi, un'alterata biogenesi e funzione mitocondriale, con inadeguata produzione di ATP nel miocardio. Il ruolo dei ROS è tardivo e non esclusivo rispetto ad altri meccanismi[5]

Cardiotoxicity of Anthracyclines

ACUTE (during or a few hours after the infusion, within 2 weeks)

- Rare (**in less than 1%** of patients)
- It presents with **arhythmias** (sinus tachycardia, less frequently tachyarrhythmias including premature ventricular contractions, ventricular tachycardia and bradycardia) and / or electrocardiogram (ECG) abnormalities such as non-specific alterations of ST-T waves.
- **Transient reduction of myocardial contractility**.
- Usually these effects do not predict the subsequent development of cardiotoxicity delayed, **rarely are of clinical importance** and generally not are a valid reason to stop treatment with Anthracyclines (slow down the rate of infusion).

EARLY (within one year of starting treatment)

- The **most common form** (98%, study by Cardinale et al.)
- It occurs more frequently with a **reduction in the LVEF**, mostly asymptomatic
- It is **often irreversible**, even if, in patients treated early, LVEF recovery can be achieved

LATE (over a year after treatment, often 5-10 years)

- It is manifested as progressive congestive heart failure and often refractory to treatment, with high mortality.

Cardiotoxicity of Anthracyclines

RISK FACTORS

- 65 yrs older
- Hypertension (Hypertensive cardiomyopathy)
- Other risk factors (high BMI, smoke, diabetes, dyslipidemia)
- Previous chest radiotherapy
- Cumulative dose

Maximum cumulative dose

Drug	Relative cardiotoxicity	Maximum dose (mg/m²)
Doxorubicin	1	400
Epirubicin	0.7	900
Daunorubicin	0.75	800
Idarubicin	0.53	150

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2019
Invasive Breast Cancer

uidelines Index
le of Contents
Discussion

PREOPERATIVE/ADJUVANT THERAPY

HER

Preferred regimens:
- Dose-dense AC (doxorubicin/cyclophosph
- Dose-dense AC (doxorubicin/cyclo
- TC (docetaxel and cyclopho
- If triple-negative brea
based chemoth

Useful

Pre

- AC
(do
trast
- AC fo
(doxo
trastuz
- Paclitax
- TCH (do boplatin/trastuzumab[j])

ed by paclitaxel plus

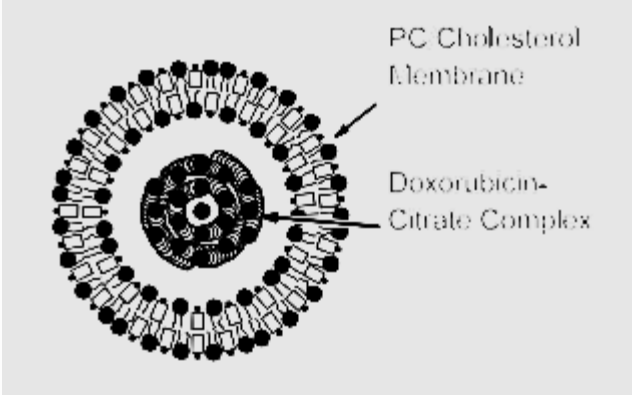
- TCH (docetaxel/carboplatin/trastuzumab[j]) + pertuzumab
- If no residual disease after preoperative therapy or no preoperative therapy: Complete up to one year of HER2-targeted therapy with trastuzumab[j] (category 1) ± pertuzumab.[n]
- If residual disease after preoperative therapy: Ado-trastuzumab emtansine (category 1) alone[o] If ado-trastuzumab emtansine discontinued for toxicity, then trastuzumab[j] (category 1) ± pertuzumab to complete one year of therapy.[n]

Useful in certain circumstances:
- Docetaxel + cyclophosphamide + trastuzumab[j]

Other recommended regimens:
- AC followed by docetaxel + trastuzumab[j,l]
(doxorubicin/cyclophosphamide followed by docetaxel plus trastuzumab)
- AC followed by docetaxel + trastuzumab[j] + pertuzumab[l]
(doxorubicin/cyclophosphamide followed by docetaxel plus trastuzumab plus pertuzumab)

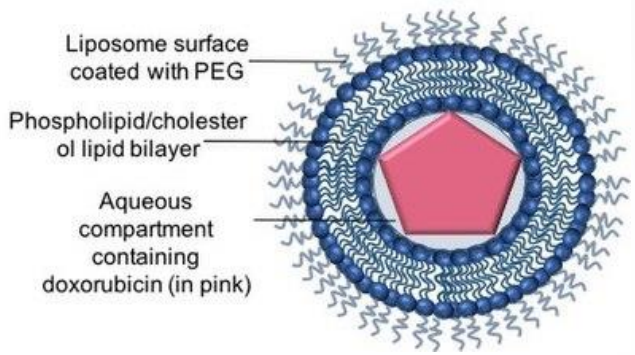
Cardiotoxicity of New Anthracyclines

MYOCET ®
(NON pegylated liposomal anthracyclines)



- A meta-analysis showed a lower rate statistically significant for both clinical (RR = 0.20; p = 0.02) and subclinical heart failure (RR = 0.38, p <0.0001) in patients treated with Myocet compared to those treated with conventional doxorubicin.
- The reduced risk of cardiotoxicity was also demonstrated in a retrospective analysis, in patients who had received previous adjuvant treatment with doxorubicin (log rank P = 0.001, Hazard Ratio = 5.42).

CAELYX ®
(pegylated liposomal anthracyclines)



- Transient ECG alterations (such as T alterations, S-T elevation and benign arrhythmias) are not considered for interruption of Caelyx therapy.
- QRS complex reduction is considered the sign more indicative of cardiac toxicity.

Cardiotoxicity of New Anthracyclines

AGENZIA ITALIANA DEL FARMACO

4.1 Indicazioni terapeutiche

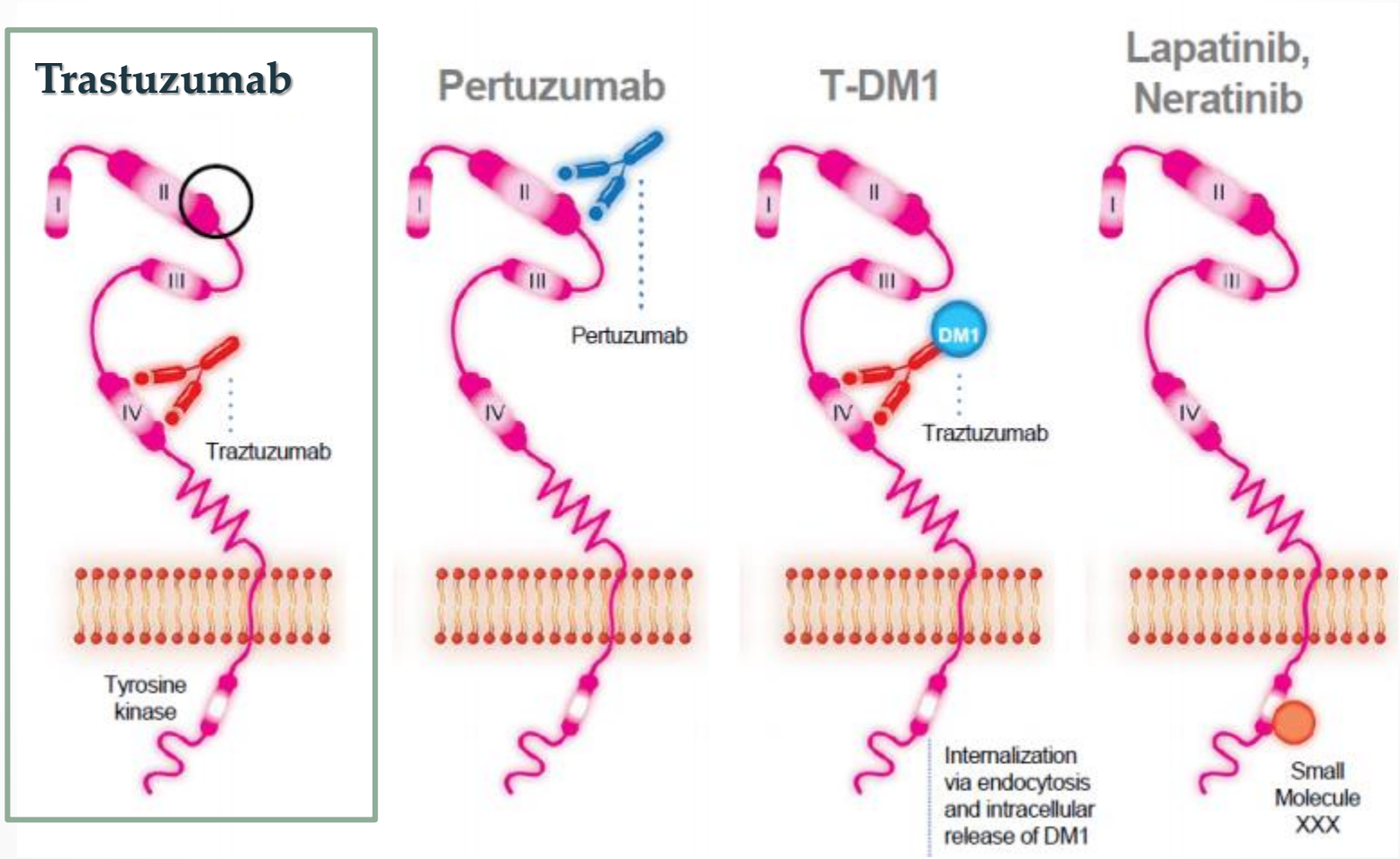
Myocet, in associazione con la ciclofosfamide, è indicato per il trattamento di prima linea del cancro metastatizzato della mammella nelle donne adulte.

4.1 Indicazioni terapeutiche

Caelyx è indicato:

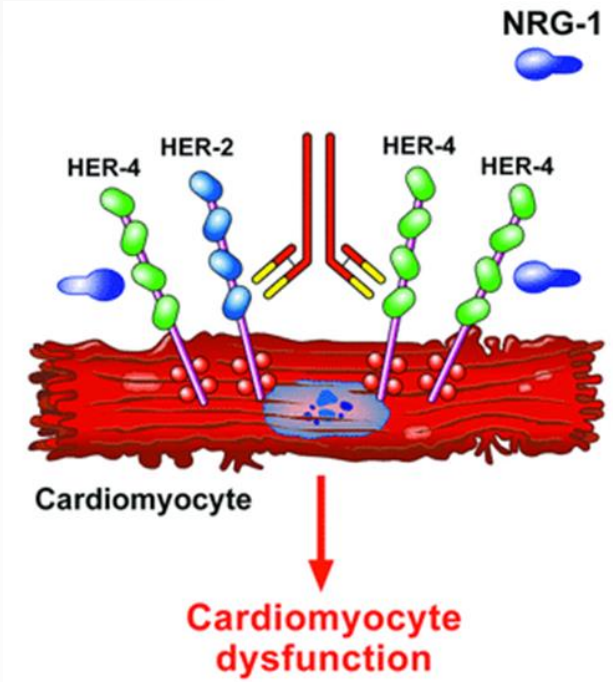
- In monoterapia in pazienti con tumore mammario metastatico, laddove sia presente un rischio cardiaco aumentato.
- Per il trattamento del tumore ovarico in stadio avanzato in donne che abbiano fallito un trattamento chemioterapico di prima linea a base di platino.
- In associazione a bortezomib per il trattamento del mieloma multiplo in progressione in pazienti che hanno ricevuto in precedenza almeno un trattamento e che sono stati già sottoposti, o non possono essere sottoposti, a trapianto di midollo osseo.
- Per il trattamento del sarcoma di Kaposi correlato all'AIDS (KS-AIDS), in pazienti con un basso numero di CD4 (linfociti CD4 < 200/mm^3) e malattia a livello mucocutaneo o viscerale diffusa.
  Caelyx può essere utilizzato come chemioterapia sistemica di prima linea o di seconda linea in pazienti affetti da KS-AIDS con malattia già in stadio avanzato o in pazienti intolleranti ad un precedente trattamento chemioterapico sistemico di associazione con almeno due delle seguenti sostanze: un alcaloide della vinca, bleomicina e doxorubicina standard (o un'altra antraciclina).

Cardiotoxicity of anti-HER2 agents



Cardiotoxicity of anti-HER2 agents

MECHANISMS



- Inhibition of the NR-1 / ErbB signaling pathway
- Alteration of the balance of the apoptotic pathway of BCL
- Angiotensin II overexpression

	Type I	Type II
Agent	Epirubicin	Trastuzumab
Cellular effects	Myocardium death	Dysfunction
Biopsy findings	Typical anthracycline changes	No typical changes
Dose response	Cumulative	Not cumulative
Reversibility	No	Generally reversible

Cardiotoxicity of Trastuzumab

CLINICAL DATA in METASTATIC, ADJUVANT and NEOADJUVANT SETTING

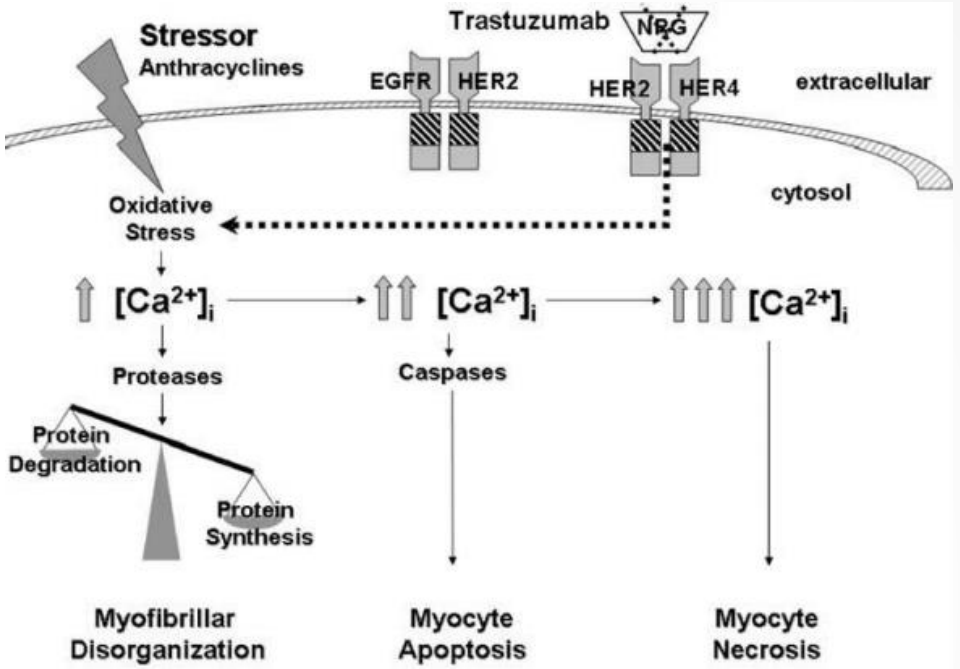
Table 2 Trastuzumab-associated cardiotoxicity in clinical trials

Author (year)	Setting	Study design	Treatment arms	Number of patients	Any LVEF drop Number (%)	Any CHF Number (%)
Slamon *et al* (2001)[4]	MBC first line	Phase 3	AC+trastuzumab	143	Not reported	39 (27.2)
			AC	135		11 (8.1)
			Paclitaxel+trastuzumab	91		12 (13.2)
			Paclitaxel	95		1 (1.1)
Marty *et al* (2005)[22]	MBC first line	Phase 2	Docetaxel+trastuzumab	86	16 (18)	2
			Docetaxel	76	7 (8)	0
Gasparini *et al* (2007)[23]	MBC first line	Phase 2	Paclitaxel+trastuzumab	28	Not reported	0
			Paclitaxel	40	Not reported	0
Von Minckwitz *et al* (2011, 2009)[24 38]	MBC beyond first line	Phase 3	Capecitabine	78	0	0
			Capecitabine+trastuzumab	78	1 (1.28)	1 (1.28)
Kaufman *et al* (2009)[25] (Tandem)	MBC first line	Phase 3	Anastrozole+trastuzumab	103	1 (0.97)	1 (0.97)
			Anastrozole	104	0	0
Buzdar *et al* (2007)[26]	Neoadjuvant	Phase 2	FEC+paclitaxel+trastuzumab (concomitant)	45	Not reported	1
			FEC+paclitaxel	19	1	0
Gianni *et al* (2010)[27]	Neoadjuvant	Phase 3	A+paclitaxel+CMF+trastuzumab	117	30 (27)	2 (1.7)
			A+paclitaxel+CMF	217	33 (15)	0
Untch *et al* (2010)[28] (Gepar quattro)	Neoadjuvant	Phase 3	Chemotherapy+trastuzumab	445	4 (0.89)	1 (0.22)
			Chemotherapy	1050	0	2 (0.19)
Buzdar *et al* (2013)[29]	Neoadjuvant	Phase 3	FEC+paclitaxel+trastuzumab (concomitant)	142	35 (24.6)	1 (0.7)
			FEC+paclitaxel+trastuzumab (sequential)	138	21 (15.2)	0
de Azambuja *et al* (2014)[30] (HERA)	Adjuvant	Phase 3	Chemotherapy+trastuzumab 1 year	1682	120 (7.2)	19 (0.8)
			Chemotherapy+trastuzumab 2 years	1673	69 (4.1)	14 (0.8)
			Chemotherapy	1744	15 (0.9)	0
Romond *et al* (2012)[31] (NSABP-B31)	Adjuvant	Phase 3	AC+paclitaxel	743	Not reported	9 (1.2)
			AC+paclitaxel+trastuzumab	947	114 (12)	36 (3.8)
Advani *et al* (2016)[32] (N9831)	Adjuvant	Phase 3	AC+paclitaxel	664	64 (9.6)	6 (0.9)
			AC+paclitaxel+trastuzumab	710	119 (16.7)	19 (2.6)
			AC+paclitaxel/trastuzumab	570	136 (23.8)	20 (3.5)
Slamon *et al* (2011, 2015)[33 39]	Adjuvant	Phase 3	AC+docetaxel	1073	114 (11.2)	8 (0.8)
			AC+docetaxel+trastuzumab	1074	206 (19.1)	21 (2.0)
			Docetaxel+carboplatin+trastuzumab	1075	97 (9.4)	4 (0.4)
Spielman *et al* (2009)[34]	Adjuvant	Phase 3	FEC/ED	268	7 (2.6)	1 (0.37)
			EC/ED+trastuzumab	260	29 (11.1)	4 (1.5)
Joensu *et al* (2006)[35]	Adjuvant	Phase 3	Docetaxel/vinorelbine+FEC	116	0	2 (1.72)
			Docetaxel/vinorelbine+trastuzumab+FEC	115	0	1 (0.86)
Pivot *et al* (2015)[36]	Adjuvant	Phase 3	Chemotherapy+trastuzumab 6 months	1690	45 (2.7)	9 (0.53)
			Chemotherapy+trastuzumab 1 year	1690	70 (4.1)	11 (0.65)
Tolaney *et al* (2015)[37]	Adjuvant	Phase 2	Paclitaxel+trastuzumab	406	13 (3.2)	2 (0.5)

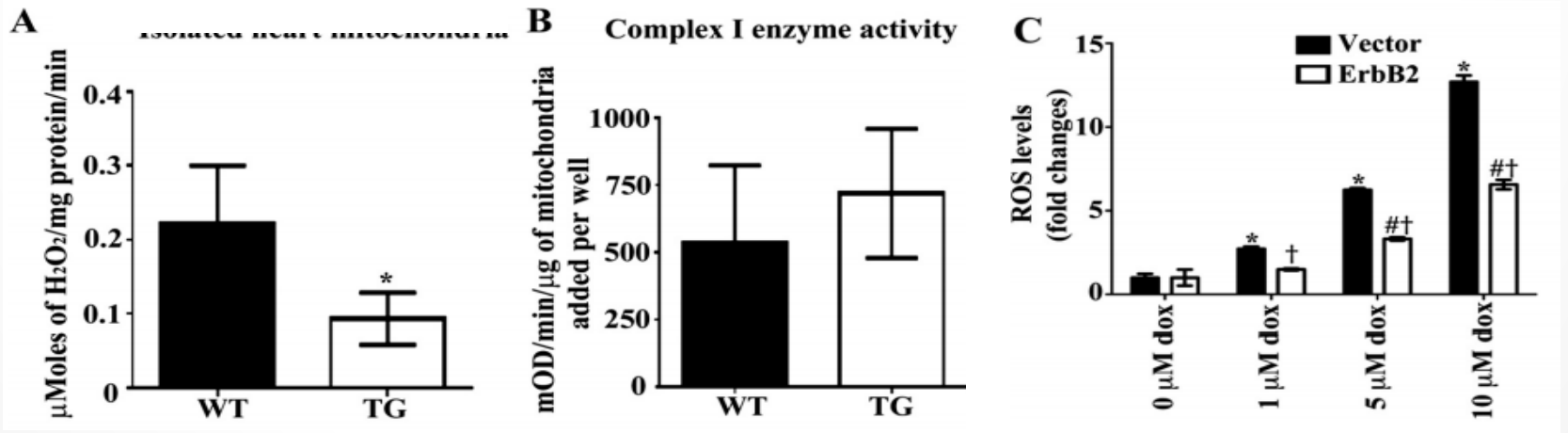
A, doxorubicin; AC, doxorubicin, cyclophosphamide; CHF, cardiac heart failure; CMF, cyclophosphamide, methotrexate, 5-fluorouracil; EC, epirubicin, cyclophosphamide; ED, epirubicin, docetaxel; FEC, 5-fluorouracil, epirubicin, cyclophosphamide; HERA, herceptin adjuvant; LVEF, left ventricular ejection fraction; MBC, metastatic breast cancer.

Cardiotoxicity of Trastuzumab

Fig. 1 Anthracyclines induce myocardial oxidative stress by increasing cytosolic calcium concentration that can lead to cardiac dysfunction and at higher concentration to cell death either by apoptosis or necrosis. Stimulation of the HER2/neu receptor can attenuate oxidative stress and is cardioprotective. Conversely, inhibition of HER2/neu can worsen anthracycline-induced cardiac damage through unopposed oxidative stress



de Azambuja E, *et al.*, Cardiac toxicity with anti-HER-2 therapies-what have we learned so far? Target Oncol 2009;4(2):77–88.



Belmonte F et al. Am J Physiol Heart Circ Physiol 2015;309:H1271–80.

Cardiotoxicity of Trastuzumab

ADVICES IN ANTHRACYCLINES USE

Concomitant use of Anthracyclines and Trastuzumab is not recommended (sequential regimen preferred)

Trastuzumab could remain in circulation up to 7 months after interruption. Patients who receive anthracycline after Trastuzumab may be at greater risk for cardiac dysfunction

(**AC/EC -> Taxane+Trast preferred vs Taxane+Trast -> AC/EC**)

If possible, anthracyclines treatment must be avoid for up to 7 months after stopping Trastuzumab; if Anthracyclines are used after trastuzumab treatment, patient's cardiac function must be closely monitored.

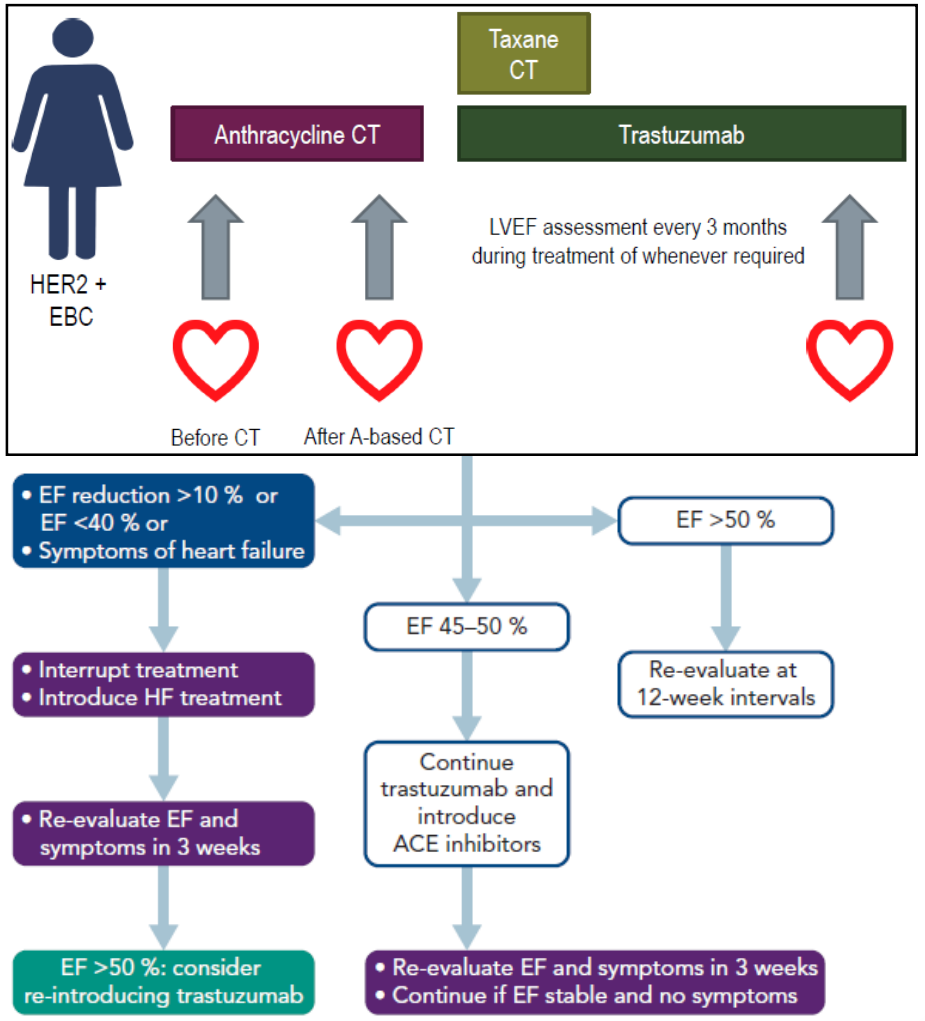
Cardiotoxicity of other anti HER2-agents

RISK FACTORS

- **Previous administration of Anthracycline with a high cumulative dose**
- **Concomitant use of anthracycline or short washout period between anthracycline and Trastuzumab**
- **Ejection fraction reduced to basal evaluation**
- > 65yr older
- Elevated BMI
- Diabetes mellitus
- Renal failure
- Hypertension
- Black race
- History of cardiovascular diseases

Cardiotoxicity of Anthracyclines & Trastuzumab

CLINICAL MANAGEMENT



ACE = angiotensin-converting-enzyme; EF = ejection fraction.

Cardiotoxicity of other anti HER2-agents

CLINICAL DATA

Table 3 Cardiotoxicity in the main phase 3 clinical trials with the use of anti-HER2 targeted agents other than trastuzumab

Author	Setting	Treatment arms	Number of patients	LVEF drop (≥10 points and <50%) N (%)	CHF N (%)
Pertuzumab					
Swain *et al*[49]	MBC, first-line	Docetaxel+trastuzumab +placebo	396	27 (6.6)	13 (3.3)
		Docetaxel+trastuzumab +pertuzumab	408	27 (6.6)	6 (1.5)
T-DM1					
Verma *et al*[67]	MBC, first-line and beyond first-line	T-DM1	495	8 (1.7)	1 (0.2)
		Lapatinib+capecitabine	496	7 (1.6)	0 (0.0)
Krop *et al*[68]	MBC, beyond first-line	T-DM1	404	6 (1.0)	0 (0.0)
		Treatment of physician's choice	198	2 (1.0)	0 (0.0)
Lapatinib					
Geyer *et al*[69]	MBC, beyond first-line	Lapatinib+capecitabine	163	4 (2.5)	0 (0.0)
Cameron *et al*[70]		Capecitabine	161	4 (2.5)	0 (0.0)
de Azambuja *et al*[71]	Neoadjuvant setting	Lapatinib+paclitaxel	154	2 (1.3)	1 (0.6)
		Trastuzumab+paclitaxel	149	2 (1.3)	0 (0.0)
		Lapatinib+trastuzumab +paclitaxel	152	7 (4.6)	2 (1.3)
Piccart-Gebhart *et al*[72]	Adjuvant setting	CT+trastuzumab	2097	97 (4.6)	53 (2.5)
		CT+lapatinib	2100	63 (3.0)	37 (1.8)
		CT+trastuzumab → lapatinib	2091	57 (2.7)	37 (1.8)
		CT+trastuzumab +lapatinib	2093	103 (4.9)	68 (3.2)
Neratinib and afatinib					
Harbeck *et al*[73]	MBC, first-line and beyond first-line	Afatinib+vinorelbine	332	1 (0.3)	0 (0.0)
		Trastuzumab+vinorelbine	168	3 (1.8)	2 (1.2)
Awada *et al*[74]	MBC, first-line	Neratinib+paclitaxel	242	Not reported 3 (1.3%)*	Not reported
		Trastuzumab+paclitaxel	237	Not reported 7 (3.0)*	Not reported
Chan *et al*[75]	Adjuvant setting	Neratinib	1420	4 (0.3)	1 (0.1)
		Placebo	1420	2 (0.1)	0 (0.0)

*Defined as CHF, decreased LVEF, LVSD and peripheral oedema.
CHF, cardiac heart failure; CT, chemotherapy; LVEF, left ventricular ejection fraction; LVSD, left ventricular systolic dysfunction; MBC, metastatic breast cancer; T-DM1, trastuzumab-emtansine.

Cardiotoxicity of CDK4/6 Inhibitors

Palbociclib, Ribociclib and Abemaciclib
are used in combination with hormone therapy in hormone receptor-positive, HER2-negative metastatic breast cancers.

Table 1. Summary of Clinical Trial Data for CDK4/6 Inhibitors for HR+/HER2– Advanced Breast Cancer

Study	Phase	Arms	Description	Median PFS	ORR	Median OS

Table 2. Monitoring Parameters for CDK4/6 Inhibitors

Drug	Dose and Schedule	Pregnancy Test[a]	CBC and Differential	Liver Tests (AST, ALT, and Total Bilirubin)	Serum Electrolytes (K, Ca, Mg, Phos)	ECG
Palbociclib	125 mg daily, 3 wk on, 1 wk off	Baseline	Baseline, every 2 wk for 2 mo, monthly for next 4 mo, then every 3 mo[d]	NA	NA	NA
Ribociclib	600 mg daily, 3 wk on, 1 wk off	600 mg daily, 3 wk on, 1 wk off	Baseline, every 2 wk for 2 mo, monthly for 4 mo	Baseline, every 2 wk for 2 mo, monthly for 4 mo	Baseline, monthly for 6 mo	Baseline, day 14 of cycle 1, day 1 of cycle 2
Abemaciclib	150 mg twice daily[b] OR 200 mg twice daily[c]	Baseline	Baseline, every 2 wk for 2 mo, monthly for 2 mo	Baseline, every 2 wk for 2 mo, monthly for 2 mo	NA	NA

AI = aromatase inhibitor; CDK4/6 = cyclin-dependent kinase 4 and 6; HER2 = human epidermal growth factor receptor 2; HR = hormone receptor; OFS = ovarian function suppression; ORR = objective response rate; OS = overall survival; PFS = progression-free survival.

Cardiotoxicity of CDK4/6 Inhibitors

Table 5. Incidences of QTc prolongation in main ribociclib trials.

	QTc prolongation
MONALEESA-2[5]	G2: ribociclib 3.6% *versus* placebo 0.6%[$] G3: ribociclib 0.6% *versus* placebo 0%[$]
MONALEESA-3[52]	⩾ 2 : ribociclib: 5.6% *versus* placebo: 2.5%[*]
MONALEESA-7[49]	G2 : ribociclib 6% *versus* placebo 1%[*] G3: ribociclib 1% *versus* placebo < 1%[*]
CompLEEment-1[65]	G2: ribociclib: not recorded G3: ribociclib: 0.5%

Different Cardiotoxicity of Palbociclib and Ribociclib in Breast Cancer: Gene Expression and Pharmacological Data Analyses, Biological Basis, and Therapeutic Implications

Matteo Santoni[1] · Giulia Occhipinti[2] · Emanuela Romagnoli[1] · Francesca Miccini[1] · Loredana Scoccia[3] · Matteo Giulietti[2] · Giovanni Principato[2] · Tiziana Saladino[1] · Francesco Piva[2] · Nicola Battelli[1]

- Ribociclib, but not Palbociclib, could act by down-regulating the expression of KCNH2 (encoding for potassium channel hERG) and up-regulating SCN5A and SNTA1 (encoding for sodium channels Nav1.5 and syntrophin-α1, respectively), three genes associated with long QT syndrome.
- Consistent with the cardiotoxicity induced by Ribociclib, its IC50 (hERG)/free concentration (Cmax free) ratio is closer to the safety threshold than that of Palbociclib.

Cardiotoxicity of CDK4/6 Inhibitors

QT prolongation: risk factors

Correctable

Electrolyte imbalance
- Nausea / vomiting
- Diarrhea
- Use of loop diuretics
- Hypokalemia (≤3.5 mEq/L)
- Hypomagnesaemia (≤1.6 mg/dL)
- Hypocalcemia (≤8.5 mg/dL)

Hypothyroidism

Concurrent use of QT-prolonging drugs
- Antiarrhythmic
- Antibiotics or antifungals
- Psychotropic or antipsychotic
- Antidepressant
- Antiemetic
- antihistamine

Non-correctable
- Family history of sudden death
- Personal history of syncope
- Baseline QTc interval prolongation
- Female gender
- Advanced age
- Heart disease
- Myocardial infarction
- Impaired renal function
- Impaired hepatic function

QT prolongation: diagnostic

12-lead ECG at baseline and during treatment (only in selected cases)

QTc interval >450 ms in men and >460 ms in women

QTc prolongation >500 ms and a ΔQT (i.e. change form baseline) of >60 ms are of particular concern

QT prolongation management

Consider stop or alternative treatments if:
- QTc prolongation >500 ms and a ΔQT of >60 ms are particular concern

Correct electrolyte disturbances, thyroid function, etc.

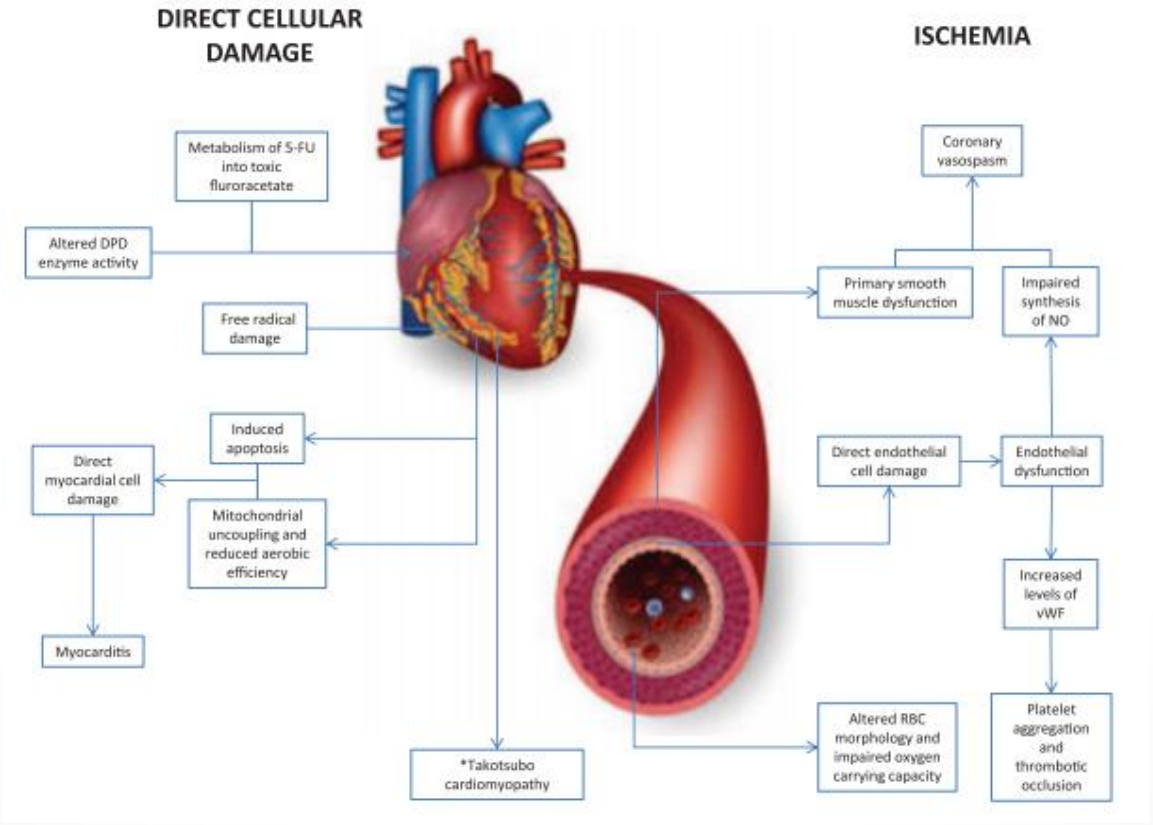
Avoid combining drugs that may increase the risk of QT prolongation

Cardiotoxicity of Fluoropirimidine

5-FLUOROURACILE and CAPECITABINE

MECHANISMS

Therapies	Possible mechanisms	Incidence
Fluoropyrimidines (5-FU, capecitabine)	Endothelial injury and vasospasm	Myocardial ischemia: 18% Silent myocardial ischemia: 50%



Cardiotoxicity of Fluoropirimidine

RISK FACTORS

Table 1. Summary of studies evaluating the incidence of cardiotoxicity in patients treated with 5-FU.

Reference	Sample size	Study design	Drug	Risk estimate
Pottage *et al.*[43]	140	Prospective study	5-FU	2.9% developed cardiotoxicity: 2.1% developed chest pain and ECG changes and 0.8% developed MI
Labianca *et al.*[4]	1083	Retrospective review	5-FU	1.6% of all patients developed angina or MI *versus* 4.5% in patients with previous cardiac disease
Jensen *et al.*[46]	106	Prospective study	Continuous infusions of 5-FU	8.5% developed angina with ECG changes
Blum *et al.*[33]	162	Phase II prospective Study	Capecitabine	0% had any cardiotoxicity
Balloni *et al.*[32]	25	Prospective study	Fluoro-folate	0% developed significant changes in diastolic function on echocardiography
Blum *et al.*[31]	74	Phase II prospective Study	Capecitabine	0% had any cardiotoxicity
Van Cutsem *et al.*[30]	602	Phase III randomized controlled trial	Capecitabine *versus* 5-FU	0.3% had an MI, 0.3% had heart failure and 0.2% had an arrhythmia
Hoff *et al.*[29]	605	Phase III randomized controlled trial	Capecitabine *versus* 5-FU	0.5% developed angina, 0.2% had myocarditis and 0.2% had an MI
Polk *et al.*[16]	452	Retrospective review	Capecitabine	5.3% developed angina or palpitations, 2.4% developed ECG changes, 0.4% had an MI
Kwakman *et al.*[49]	1973	Retrospective review of three phase III randomized controlled trials	Capecitabine	5.9% developed cardiotoxicity: 0.8% developed chest pain, 2.9% developed ischemia or infarction, 2.0% had an arrhythmia and 0.4% had heart failure
Ceyhan *et al.*[25]	37	Prospective study	Continuous infusions of 5-FU	5.4% developed angina and ECG changes
Ng *et al.*[24]	153	Two prospective studies	Capecitabine	6.5% developed cardiotoxicity: 2.6% experienced angina, 2.0% had an MI, 0.7% had heart failure, 0.7% had ventricular tachycardia and 0.7% experienced sudden death

Cardiotoxicity of Fluoropirimidine

Early onset (12-24-36 h after infusion initiation)
High risk of recurrence at drug re-administering
(careful patients risk-benefit analysis)

STRATEGIES TO REDUCE THE RISK OF CARDIOTOXICITY:

Reduction of fluoropyrimidine dose

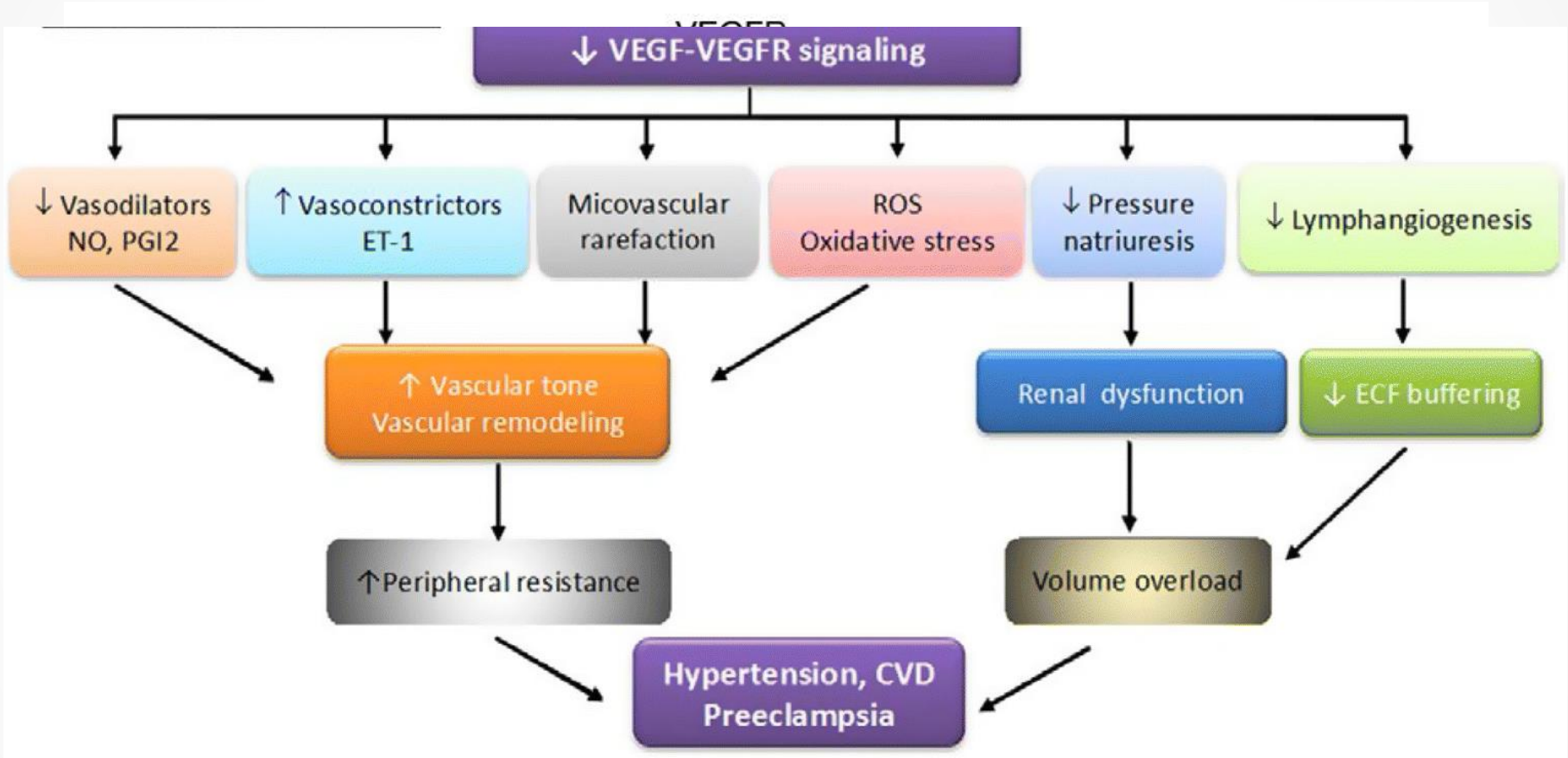
Bolo infusion vs continuous infusion regimen

Prescribe or enhance cardiological therapy

(nitrates, calcium antagonists, ranolazine)

In patients at high risk of ischemic heart disease, it is recommended: correction of risk factors, pre-treatment cardiac evaluation (Holter ECG, ergonomic stress test, coronarography). In the event of significant coronary disease, it is recommended to proceed with PCI stenting, double anti-aggregation and statin before starting the chemotherapy treatment.

Cardiotoxicity of anti VEGF



Angiogenesis inhibition
Prostaglandine and NO production

Modified by Small et al_Canadian J of Cardiology 2014

Hypertension of anti VEGF

Cancer	Reference	CT regimens	Patients	Hypertension	
				All Grades	Grade 3/4
mCRC	Hurwitz et al	IFL IFL + BV 5 mg/kg	397 393	8,3 **22,4**	2,3 **8,3**
	Hurwitz et al	Placebo + IFL 5FU + leucovorin + BV 5 mg/kg	98 10	14,3 **33,9**	3,1 **18,3**
	Van Cutsem et al	FOLFIRI FOLFIRI + aflibercept	614 612	10,7 **41,4**	1,5 **19,3**
	Grothey et al	BSC Regorafenib 160 mg daily	255 505	6 **28**	**1** **7**
mRCC	Escudier et al	Placebo + INFα BV 10 mg/kg + INFα	322 327	9 **26**	<1 **3**
NSCLC	Sandler et al	CBBD + Paclitaxel CBBD + Paclitaxel + BV 15 mg/kg	444 444	NA NA	0,7 **7**
mGC	Fuchs et al	Placebo Ramucirumab	117 238	8 **16**	3 **8**
	Wilke et al	Paclitaxel Paclitaxel + Ramucirumab	335 330	4 **24**	2 **14**

Hypertension of anti VEGF

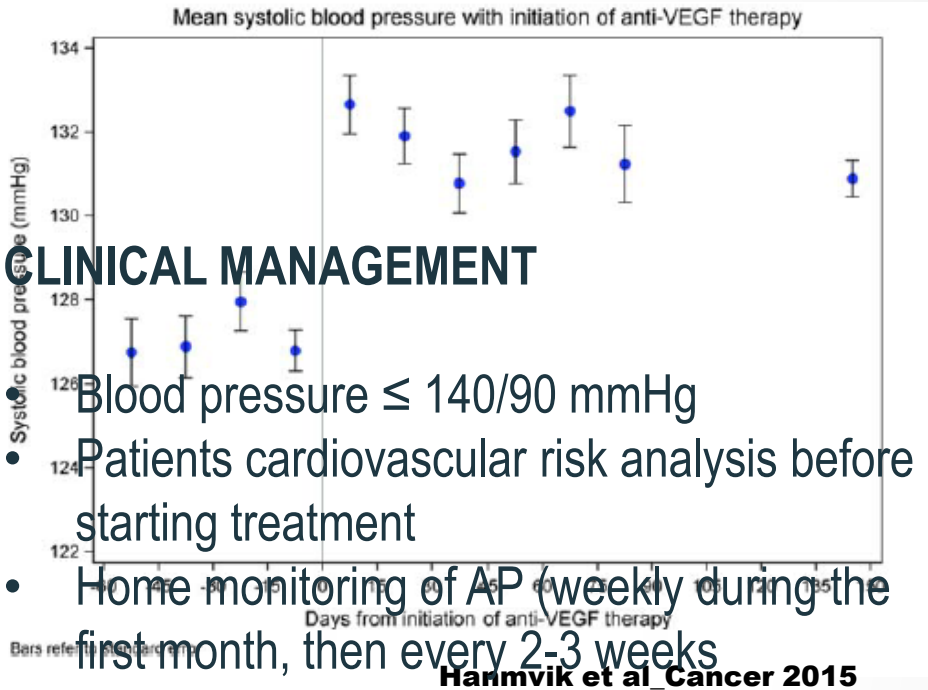
Cancer	Reference	CT regimens	Patients	Hypertension	
				All Grades	Grade 3/4
mBC	Miller et al	Paclitaxel Paclitaxel + BV	346 365	NA NA	0 **14,8**
mRCC	Motzer et al	INFα Sunitinib, 50 mg/d (4w on, 2 w off)	360 375	1 **24**	1 **8**
	Escudier et al	Placebo Sorafenib, 400 mg twice daily	452 451	2 **17**	<1 **4**
	Motzer et al	Sunitinib, 50 mg/d (4w on, 2 w off) Pazopanib 800 mg daily	553 557	**41** **46**	**15** **15**
	Hutson et al	Sorafenib, 400 mg twice daily Axitinib, 5 mg twice daily	96 192	**29** **49**	**1** **13**
GIST	Demetri et al	Placebo Sunitinib, 50 mg/d (4w on, 2 w off)	105 207	4 **11**	0 **3**
	Demetri et al	BSC Regorafenib 160 mg daily	66 133	16,7 **48,5**	3 **23,5**
HCC	Llovet et al	Placebo Sorafenib, 400 mg twice daily	297 302	2 **5**	1 **2**

Hypertension of anti VEGF

- Frequently observed (nearly 40%)
- Early onset
- Dose-related
- Reversible when treatment is stopped

RISK FACTORS

- Prior hypertension or other cardiovascular diseases
- > 60-65 years
- Nephropathy
- BMI, diabetes mellitus, dyslipidemia, smoking



Hammvik et al_Cancer 2015

CLINICAL MANAGEMENT

- Blood pressure ≤ 140/90 mmHg
- Patients cardiovascular risk analysis before starting treatment
- Home monitoring of AP (weekly during the first month, then every 2-3 weeks
- Educating / informing the patient, family members and attending physician
- Immediate management of the pressure increase to limit complications (ACE inhibitors and angiotensin II receptor blockers -ARBs)

Cardiotoxicity of anti VEGF

FOCUS ON BEVACIZUMAB

HYPERTENSION

- 42,1% vs 14% in control-arms
- Hypertension G3 – 4: 0,4%-17,9%
- Hypertension G4 : 1,0% vs 0,2% in control-arms

ARTERIAL THROMBOEMBOLISM

- **3,8% vs 2,1%** in control-arms (11% vs 5,8% in AVF2192g trial)

VENOUS THROMBOEMBOLISM

- **2,8% - 17,3%** vs 3,2%-15,6% in control-arms,
- **7,8% Grade G3-5** vs 4,9% in control-arms

CHRONIC HEART FAILURE (CHF) / CARDIOMIOPATHY

- Few safety data in high risk population (CHF NYHA II-IV patients excluded from RCT)
- **3,5% vs 0,9% in control-arms in AVF2119g trial**
- Predominantly patients with previous RT-chest irradiation and/or Anthracyclines exposure

Cardiotoxicity of Immuno Checkpoint Inhibitors (ICIs)

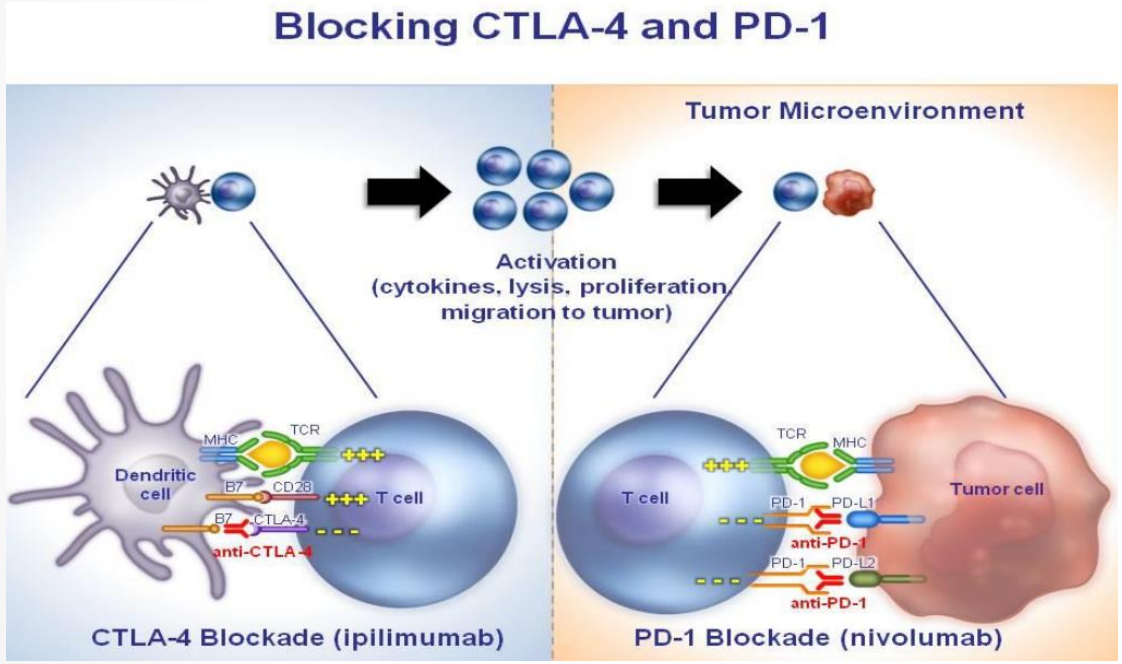
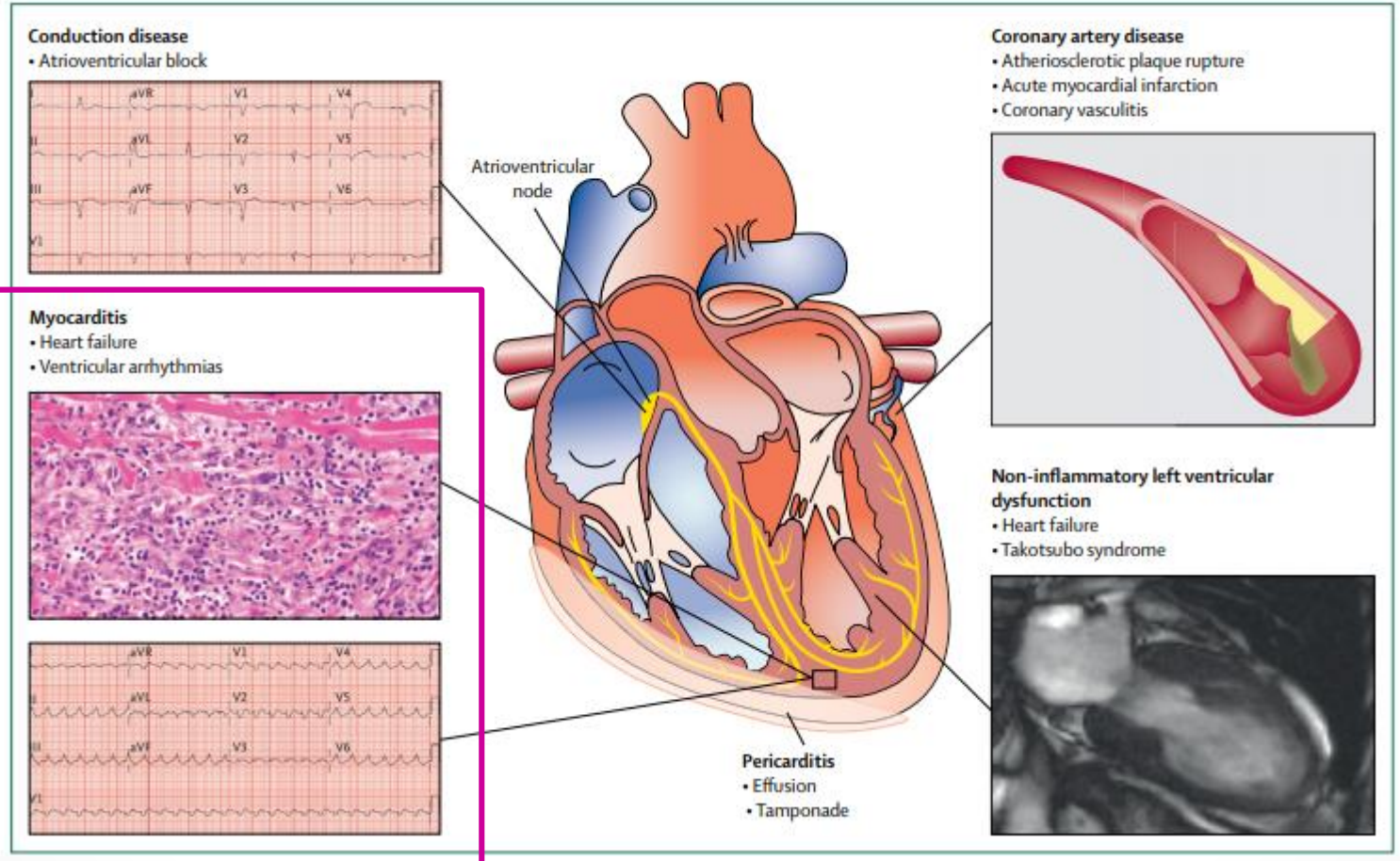


Table 1. Immune Checkpoint–Blocking Antibodies Approved by the Food and Drug Administration.*

Drug	Target	Indication
Ipilimumab	CTLA-4	Melanoma
Nivolumab	PD-1	Melanoma, non–small-cell lung cancer, renal-cell carcinoma, hepatocellular carcinoma, classic Hodgkin's lymphoma, squamous-cell carcinoma of the head and neck, urothelial carcinoma, colorectal cancer with high microsatellite instability or mismatch-repair deficiency
Pembrolizumab	PD-1	Melanoma, non–small-cell lung cancer, classic Hodgkin's lymphoma, squamous-cell carcinoma of the head and neck, urothelial carcinoma, gastric cancer, solid tumors with high microsatellite instability or mismatch-repair deficiency
Atezolizumab	PD-L1	Non–small-cell lung cancer, urothelial carcinoma
Avelumab	PD-L1	Merkel-cell carcinoma, urothelial carcinoma
Durvalumab	PD-L1	Urothelial carcinoma

* CTLA-4 denotes cytotoxic T-lymphocyte antigen 4, PD-1 programmed cell death 1, and PD-L1 programmed cell death ligand 1.

Cardiotoxicity of Immuno Checkpoint Inhibitors (ICIs)



Cardiotoxicity of ICIs

	Molecular target	Indication according to FDA label	Cardiotoxic effects included in FDA label
Ipilimumab	CTLA-4	Metastatic melanoma, metastatic renal cell carcinoma (along with nivolumab)	Pericarditis (incidence <1%, including fatal cases), myocarditis (incidence 0·2%, including fatal cases)
Nivolumab	PD-1	Metastatic melanoma, stage IIIB and IIIC melanoma (adjuvant), metastatic non-small-cell lung cancer, metastatic renal cell carcinoma (alone or in combination with ipilimumab), relapsed Hodgkin's lymphoma, recurrent or metastatic head and neck squamous cell carcinoma	Myocarditis (incidence <1%), ventricular arrhythmia
Pembrolizumab	PD-1	Metastatic melanoma, metastatic non-small-cell lung cancer, recurrent or metastatic head and neck squamous cell carcinoma	Cardiac failure (incidence 0·4%)
Atezolizumab	PD-L1	Metastatic urothelial carcinoma, metastatic non-small-cell lung cancer	Myocardial infarction (including fatal cases)
Avelumab	PD-L1	Metastatic Merkel cell carcinoma	Myocarditis (including fatal cases)
Durvalumab	PD-L1	Unresectable stage III non-small-cell lung cancer	Myocarditis (incidence <1%)

FDA=US Food and Drug Administration.

Table 1: **Licensed immune checkpoint inhibitors and their reported cardiotoxic effects at the time of FDA approval**

Panel 1: **Potential risk factors for immune checkpoint inhibitor-related cardiotoxic effects**

Treatment-related factors
- Dual immunotherapy (eg, ipilimumab and nivolumab)
- Combined immunotherapy and other cardiotoxic cancer therapy (eg, VEGF tyrosine kinase inhibitors)

Concurrent immune-related toxic effects
- Immune checkpoint inhibitor-related skeletal myositis

Previous cardiovascular disease with myocardial injury
- Myocardial infarction
- Heart failure
- Myocarditis
- Previous anthracycline chemotherapy
- Previous cancer therapy-induced left ventricular dysfunction

Previous autoimmune disease
- Systemic lupus erythematosus
- Rheumatoid arthritis
- Sarcoidosis
- Dressler's syndrome

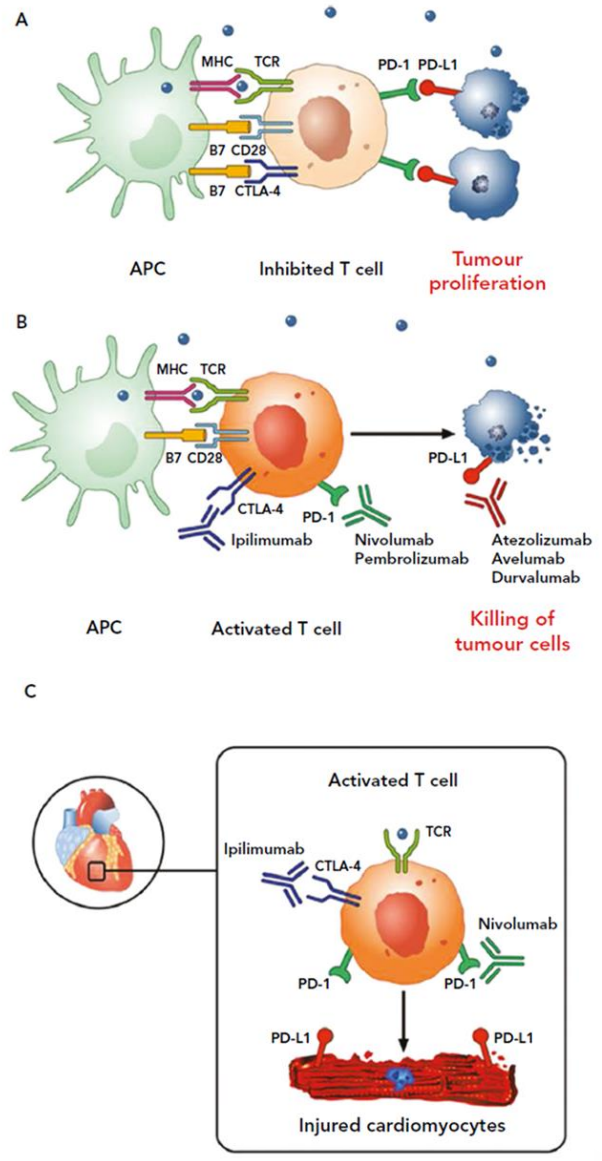
Tumour-related factors
- Cardiac antigens expressed in tumour
- Cardiac T-cell clones

Genetic factors
- Unknown

Lyon AR et al. Lancet Oncol 2018; 19: e447–58

Cardiotoxicity of ICIs

Figure 3: Mechanism of Action of Checkpoint Inhibitors



CLINICAL MANAGEMENT of IMMUNO-RELATED ADVERSE EVENTS (ir-AEs)

Grade 1	Grade 2	Grade 3-4
Observation	1- Hold Immunotherapy 2- Evaluate Hospitalization 3- Prednisolone per os 0.5-1 mg/Kg die for 7 days	1- Permanently discontinue immunotherapy 2- Hospitalization 3- Metilprednisolone 1-2 mg/Kg die iv (at least for 3 days before decalage)
Worsening: Treat as grade 2 or grade 3-4	**Improvement:** Slow steroids decalage in a month and resume immunotherapy **Lack of improvement/worsening:** Treat as grade 3-4	**Improvement:** Slow steroids decalage in a month **Lack of improvement/worsening:** Immunosoppressors (->improvement for> 1 year)

Terapie antitumorali: tossicità cardiovascolari acute
CONCLUSIONI

Strategies for prevention of cardiotoxicity

Identifying patients with high cardiac risk

Modifying life style to decrease cardiac risk

Using less cardiotoxic regimens if possible

The use of dexrazoxane in metastatic patients requiring anthracycline chemotherapy (doses > 300 or >540 mg/m^2 for doxorubicin and epirubicin, respectively)

Prophylactic ACE-I (or ARB) and beta-blockers in selected cases treated with anthracyclines or trastuzumab (small trials)

Enalapril and carvedilol *vs.* normal care before high-dose anthracyclines

- Prevention in 6 months LVEF decrease with both drugs
- Their use in low risk patients remains controversial

Candesartan (ARB) attenuates decrease in LVEF compared to beta blocker or placebo in patients with early breast cancer treated with A-based chemotherapy

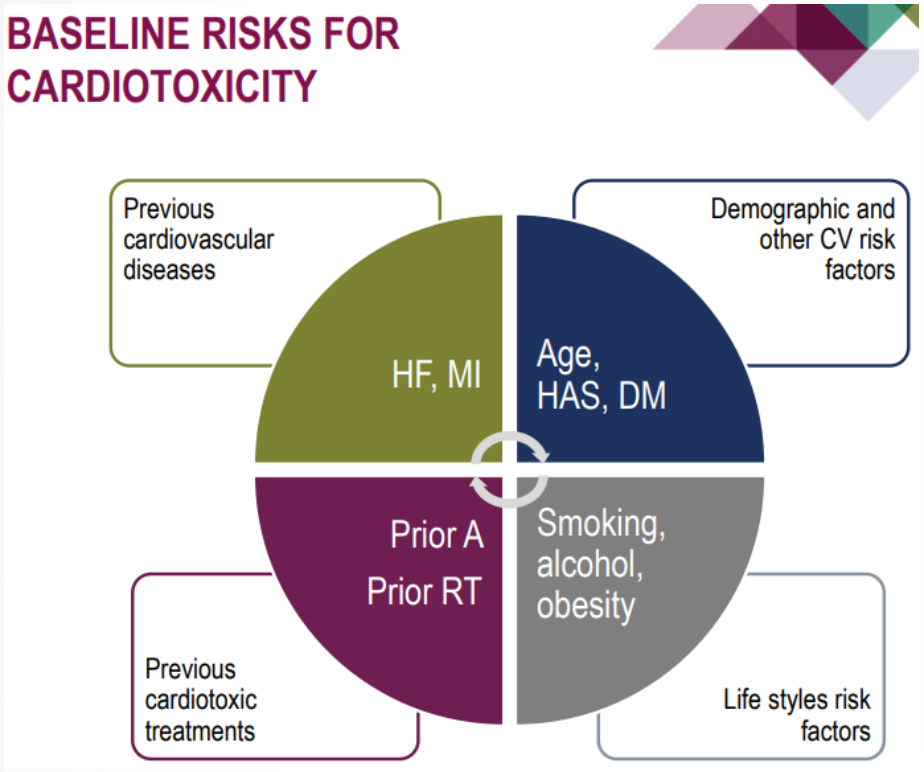
ACEi or beta blockers have no effect on cardiac remodelling in patients treated with trastuzumab

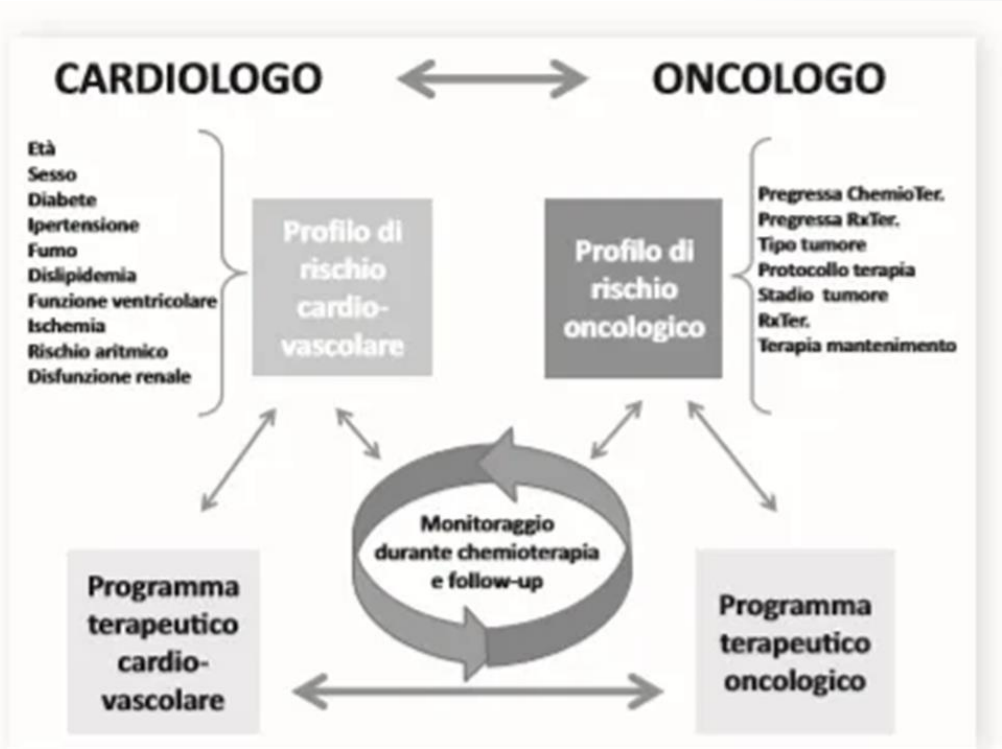
Setting clinico	Prevenzione primaria	Livello di evidenza	Classe della raccomandazione
Carcinoma mammario (metastatico >388mg/m^2)	Dexrazoxano	A	I
Sarcoma	Dexrazoxano Infusione continua	A	IIa
Leucemia linfoblastica acuta pediatrica ad alto rischio	Dexrazoxano	A	IIa
Tutti i pazienti che ricevono antracicline	Beta-bloccanti, ACE inibitori, antagonisti del recettore dell'angiotensina	C	IIb
	Prevenzione secondaria		
Funzione ventricolare sinistra/ strain anormale ± biomarcatori cardiaci elevati	Beta-bloccanti, ACE inibitori, antagonisti del recettore dell'angiotensina	B	IIa

TABELLA 3. Livello di evidenza e classe di raccomandazione dei diversi trattamenti cardioprotettivi (modificata da Vejpongsa P. and Yeh ET. J Am Coll Cardiol, 2014)

Terapie antitumorali: tossicità cardiovascolari acute

CONCLUSIONI





Grazie per l'attenzione