DISFUNZIONE VENTRICOLARE SINISTRA E CARDIOTOSSICITÀ

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Carcinoma Mammario Precoce

- il trattamento è prevalentemente chirurgico: 86% delle pazienti è libera da malattia a 5 AA
- INDICATA TERAPIA ADIUVANTE AL FINE DI RIDURRE RISCHIO DI RECIDIVE: ORMONOTERAPIA, CHEMIOTERAPIA +/- TRASTUZUMAB, RT
- SE LE DIMENSIONI DELLA NEOPLASIA NON CONSENTONO DI INTERVENIRE IMMEDIATAMENTE O SE CARATTERISTICHE DI AGGRESSIVITÀ È POSSIBILE FAR PRECEDERE LA CHEMIOTERAPIA ALL'INTERVENTO

Terapia adiuvante: poli-CT

PREOPERATIVE/ADJUVANT THERAPY REGIMENS

HER2-Negative - Preferred regimens:

- Dose-dense AC followed by paclitaxel[1]
  - Doxorubicin 60 mg/m² IV day 1
  - Cyclophosphamide 600 mg/m² IV day 1
    - ◊ Cycled every 14 days for 4 cycles.[O]
    - ◊ Followed by:
  - Paclitaxel 175 mg/m² by 3 h IV infusion day 1
    - ◊ Cycled every 14 days for 4 cycles.[O]
- Dose-dense AC followed by weekly paclitaxel[1]
  - Doxorubicin 60 mg/m² IV day 1
  - Cyclophosphamide 600 mg/m² IV day 1
    - ◊ Cycled every 14 days for 4 cycles.[O]
    - ◊ Followed by:
  - Paclitaxel 80 mg/m² by 1 h IV infusion weekly for 12 weeks.
- TC[2]
  - Docetaxel 75 mg/m² IV day 1
  - Cyclophosphamide 600 mg/m² IV day 1
    - ◊ Cycled every 21 days for 4 cycles.[O]

HER2-Negative - Useful in certain circumstances:

- Dose-dense AC[1]
  - Doxorubicin 60 mg/m² IV day 1
  - Cyclophosphamide 600 mg/m² IV day 1
    - ◊ Cycled every 14 days for 4 cycles.[O]
- AC[3]
  - Doxorubicin 60 mg/m² IV on day 1
  - Cyclophosphamide 600 mg/m² IV day 1
    - ◊ Cycled every 21 days for 4 cycles.
- CMF chemotherapy[4]
  - Cyclophosphamide 100 mg/m² PO days 1–14
  - Methotrexate 40 mg/m² IV days 1 & 8
  - 5-fluorouracil 600 mg/m² IV days 1 & 8
    - ◊ Cycled every 28 days for 6 cycles.
- AC followed by weekly paclitaxel[5]
  - Doxorubicin 60 mg/m² IV day 1
  - Cyclophosphamide 600 mg/m² IV day 1
    - ◊ Cycled every 21 days for 4 cycles.
    - ◊ Followed by
  - Paclitaxel 80 mg/m² by 1 h IV infusion weekly for 12 weeks.

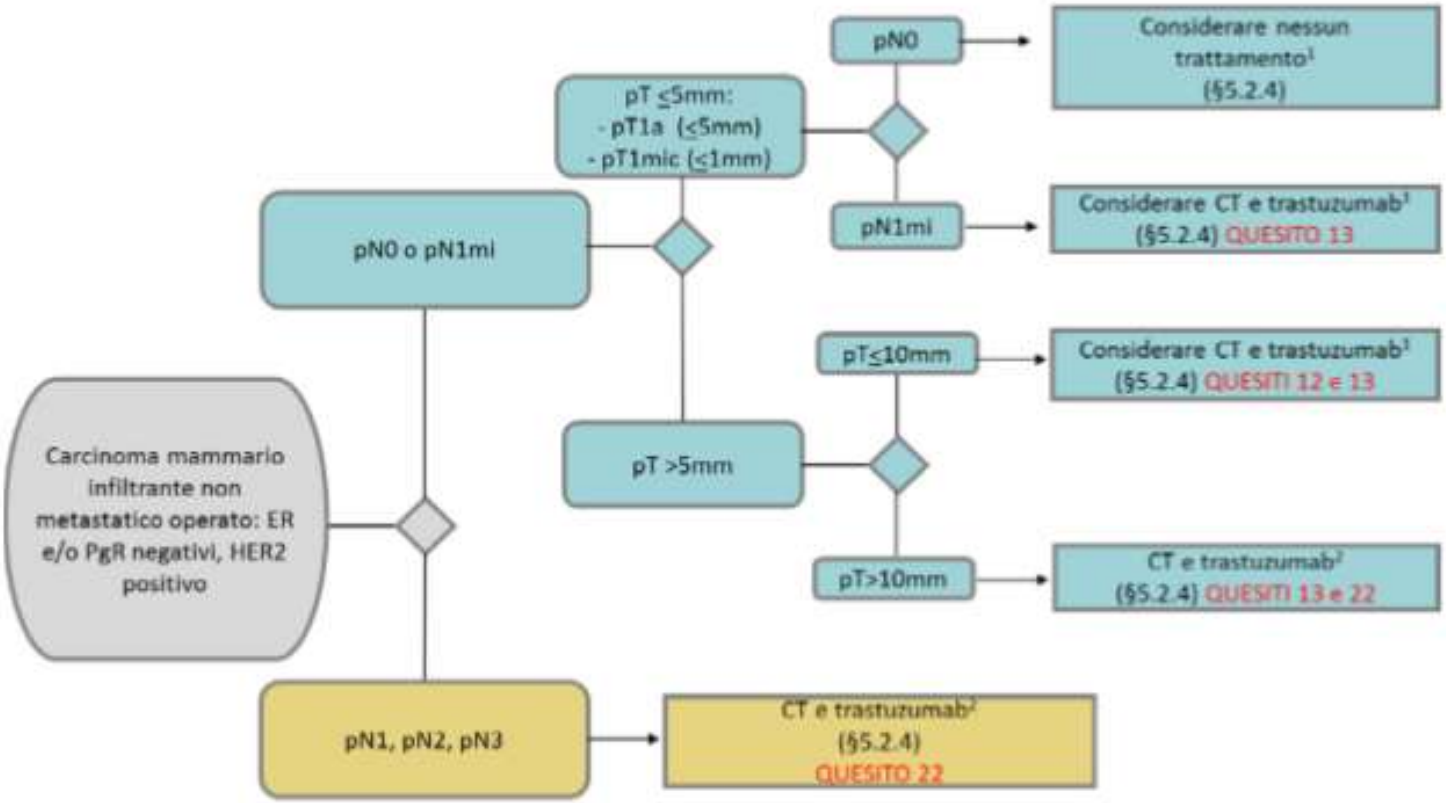
HER2-Negative - Other recommended regimens:

- AC followed by docetaxel chemotherapy[6]
  - Doxorubicin 60 mg/m² IV on day 1
  - Cyclophosphamide 600 mg/m² IV day 1
    - ◊ Cycled every 21 days for 4 cycles.
    - ◊ Followed by:
  - Docetaxel 100 mg/m² IV on day 1
    - ◊ Cycled every 21 days for 4 cycles.
- EC chemotherapy[7]
  - Epirubicin 100 mg/m² IV day 1
  - Cyclophosphamide 830 mg/m² IV day 1
    - ◊ Cycled every 21 days for 8 cycles.
- TAC chemotherapy[8]
  - Docetaxel 75 mg/m² IV day 1
  - Doxorubicin 50 mg/m² IV day 1
  - Cyclophosphamide 500 mg/m² IV day 1
    - ◊ Cycled every 21 days for 6 cycles.[O]

NCCN 2019 Invasive Breast Cancer

Linee guida AIOM malattia HER2

TERAPIA SISTEMICA ADIUVANTE



AIOM 2018

Anti-HER2 nel setting adiuvante

Trial

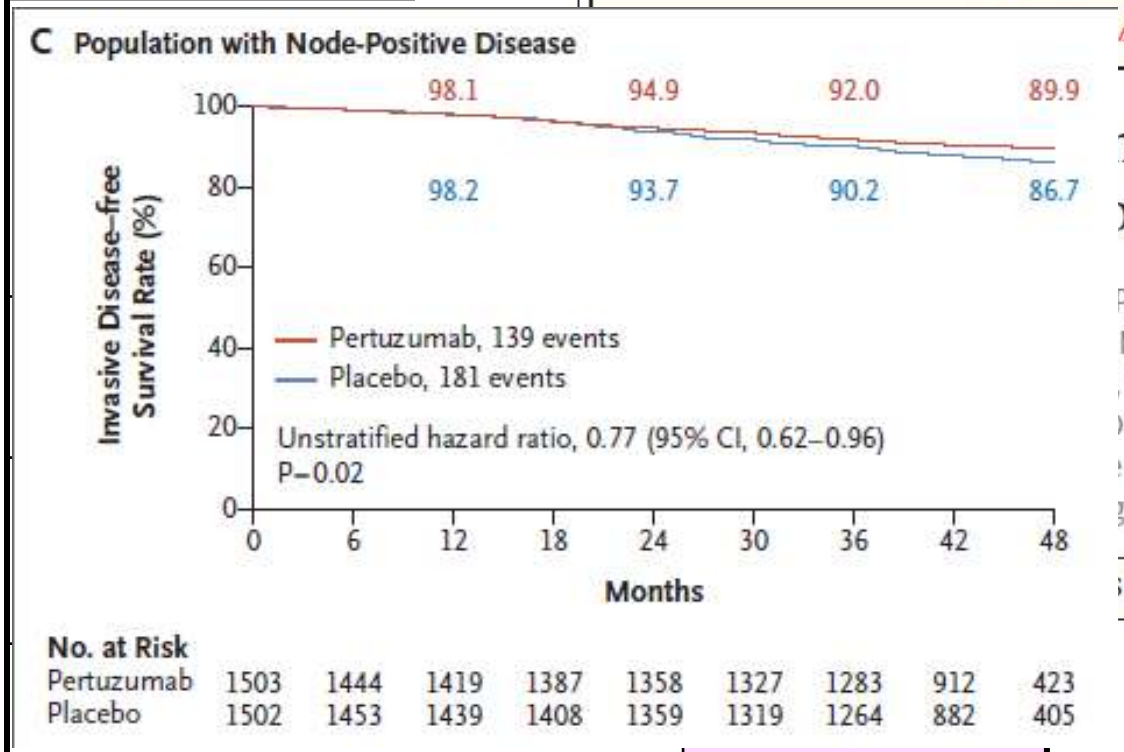
The NEW ENGLAND JOURNAL of MEDICINE

AL ARTICLE

ıab and Trastuzumab
ɔsitive Breast Cancer

Procter, Ph.D., Evandro de Azambuja, M.D.,
M.D., Giuseppe Viale, M.D., Thomas Suter, M.D.,
M.Sc., Emma Clark, M.Sc., Adam Knott, Ph.D.,
., Denise A. Yardley, M.D., Jose Bines, M.D.,
Piccart, M.D., and Jose Baselga, M.D.,
Committee and Investigators*

STRACT



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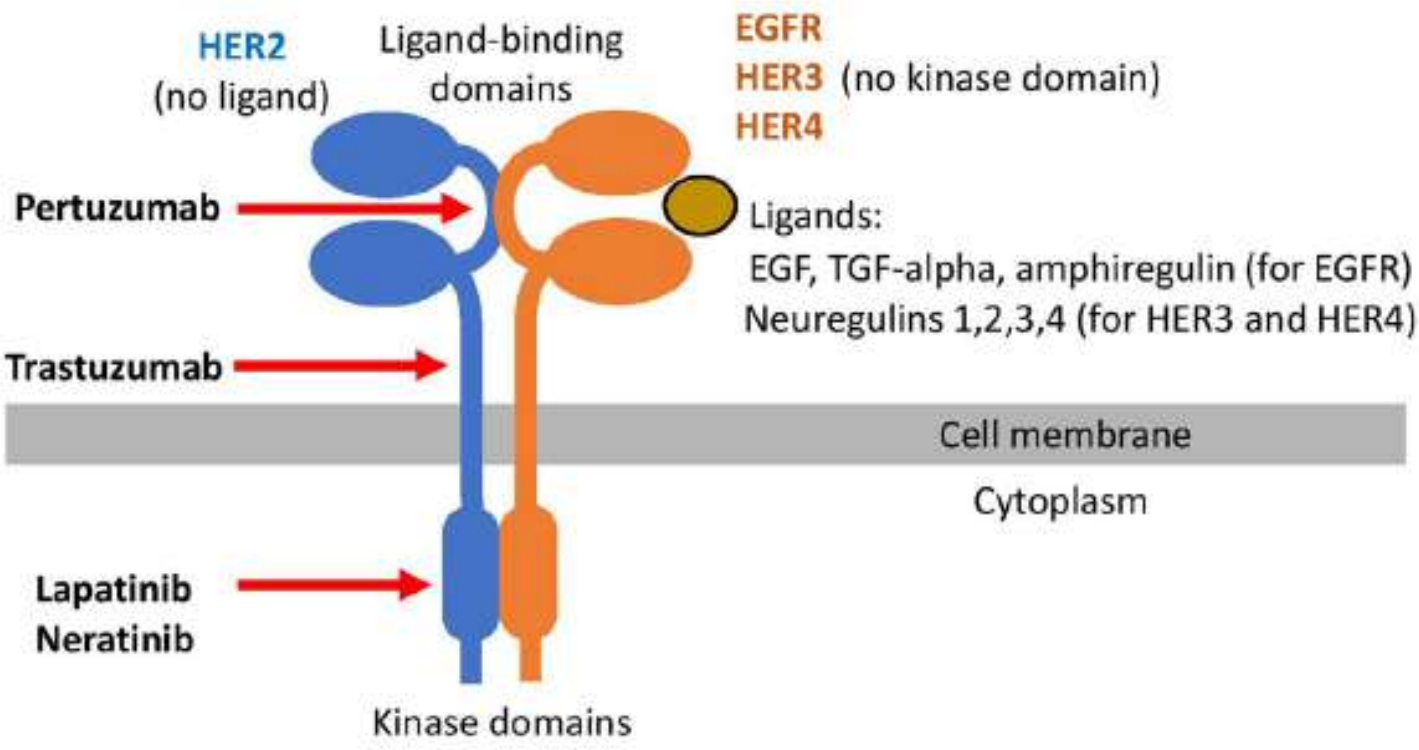
Anti-HER2 nel setting neoadiuvante

Trial	pCR
NOAH	**42.7 %**
braccio con TXT+Trastuzumab +Pertuzumab	
Tryphaena (3 bracci)	**dal 45.3% al 51.9%**

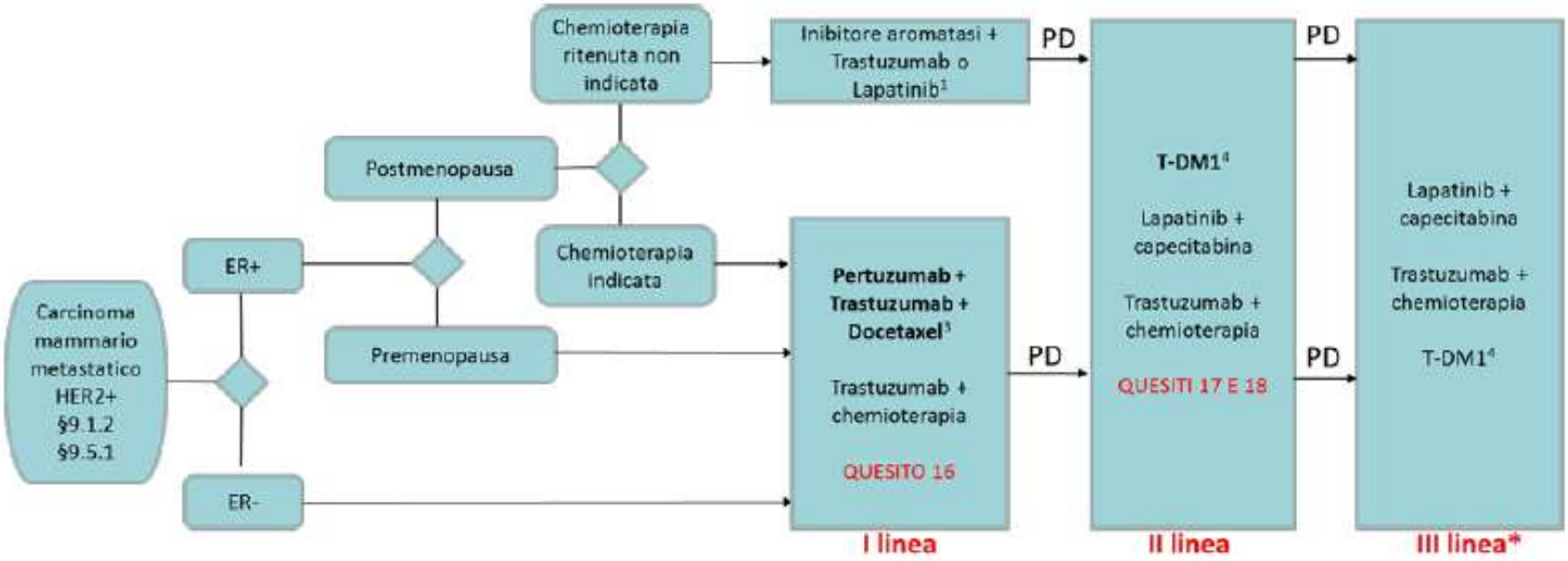
L'uso di pertuzumab, in associazione a trastuzumab e chemioterapia, in fase neoadiuvante è autorizzato ma non rimborsato in Italia per il carcinoma HER2+ localmente avanzato, infiammatorio o allo stadio iniziale ad alto rischio di recidiva (fascia Cnn). Come recita la scheda tecnica aggiornata al 28 giugno 2018: "nel setting neoadiuvante, il carcinoma mammario localmente avanzato e infiammatorio è considerato ad alto rischio indipendentemente dallo stato dei recettori ormonali. Nel carcinoma mammario in fase iniziale, le dimensioni del tumore, il grado, lo stato dei recettori ormonali e le metastasi linfonodali devono essere presi in considerazione nella valutazione del rischio". E' in corso la procedura regolatoria per la rimborsabilità del farmaco.

Linee Guida AIOM 2018

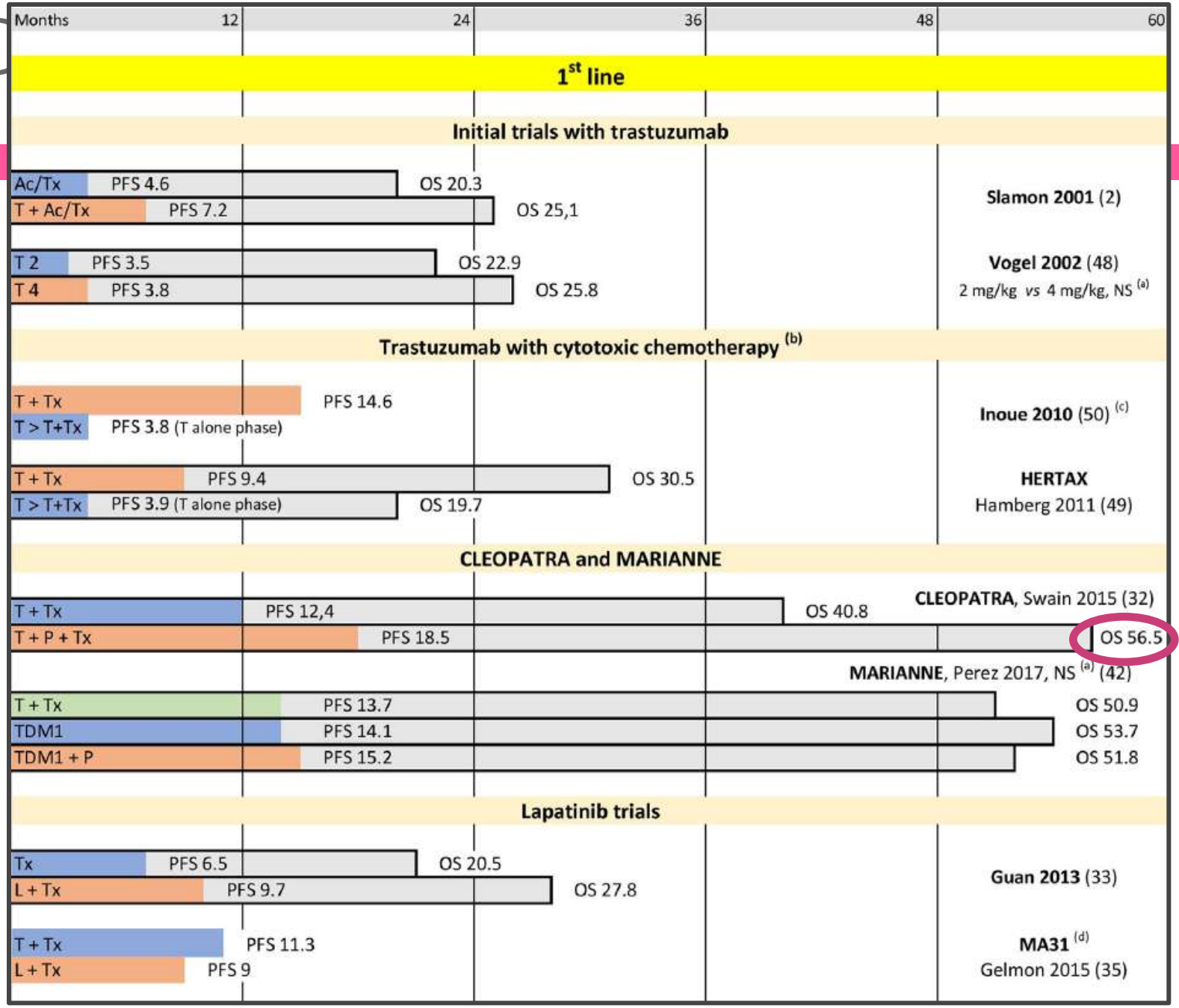
Anti-HER2 setting metastatico



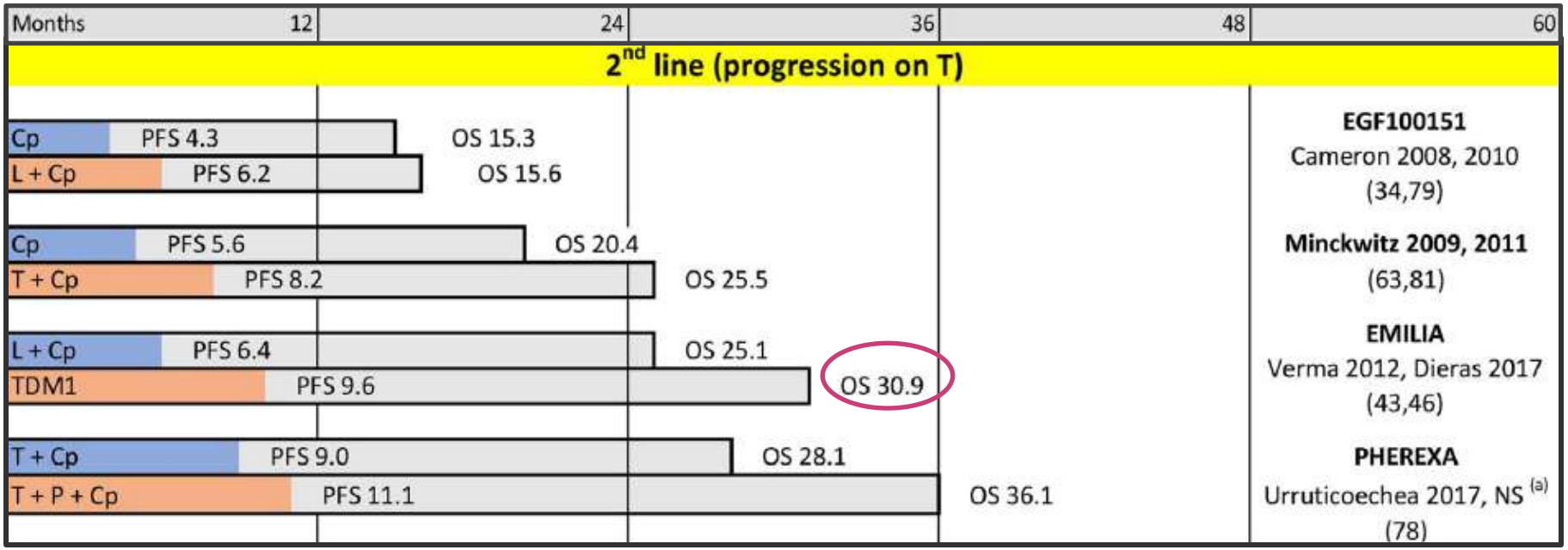
Linee guida AIOM carcinoma mammario metastatico HER2 positivo



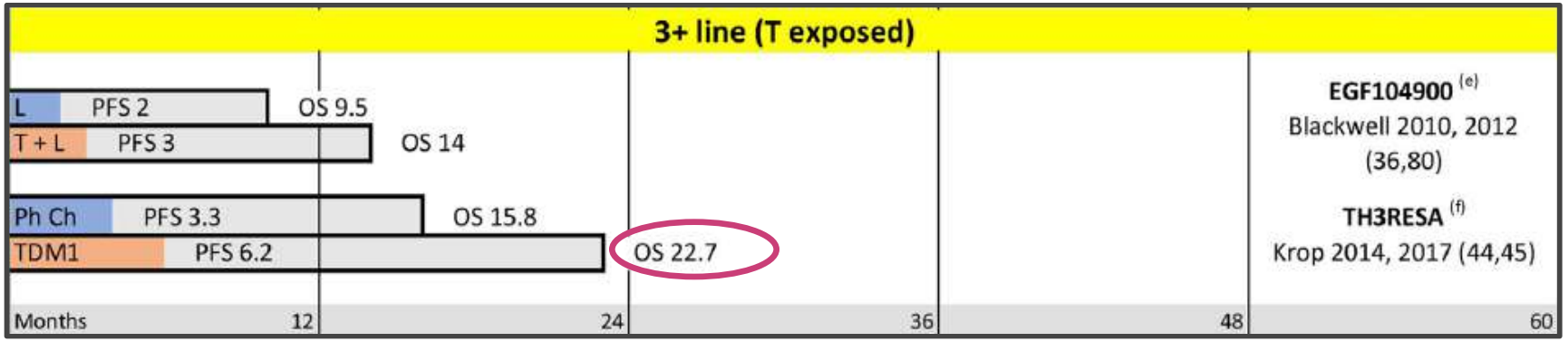
AIOM 2018


Months
12
24
36
48
60
1st line
Initial trials with trastuzumab
Ac/Tx
PFS 4.6
OS 20.3
T + Ac/Tx
PFS 7.2
OS 25,1
Slamon 2001 (2)
T 2
PFS 3.5
OS 22.9
T 4
PFS 3.8
OS 25.8
Vogel 2002 (48)
2 mg/kg vs 4 mg/kg, NS (a)
Trastuzumab with cytotoxic chemotherapy (b)
T + Tx
PFS 14.6
T > T+Tx
PFS 3.8 (T alone phase)
Inoue 2010 (50) (c)
T + Tx
PFS 9.4
OS 30.5
T > T+Tx
PFS 3.9 (T alone phase)
OS 19.7
HERTAX
Hamberg 2011 (49)
CLEOPATRA and MARIANNE
T + Tx
PFS 12,4
OS 40.8
CLEOPATRA, Swain 2015 (32)
T + P + Tx
PFS 18.5
OS 56.5
MARIANNE, Perez 2017, NS (a) (42)
T + Tx
PFS 13.7
OS 50.9
TDM1
PFS 14.1
OS 53.7
TDM1 + P
PFS 15.2
OS 51.8
Lapatinib trials
Tx
PFS 6.5
OS 20.5
L + Tx
PFS 9.7
OS 27.8
Guan 2013 (33)
T + Tx
PFS 11.3
L + Tx
PFS 9
MA31 (d)
Gelmon 2015 (35)

OS in II linea



OS in III linea



FRAMINGHAM RISK SCORE to predict 10 year ABSOLUTE RISK of CHD EVENT

WEST HERTFORDSHIRE CARDIOLOGY

This risk assessment only applies to assessment for PRIMARY PREVENTION of CHD, in people who do not have evidence of established vascular disease.
Patients who ***already*** have evidence of vascular disease usually have a >20% risk of further events of over 10 years, and require vigorous **SECONDARY PREVENTION**.
People with a Family History of premature vascular disease and some Asians are at higher risk than predicted; Southern Europeans may have a lower risk in relation to standard risk factors.

STEP 1: Add scores by sex for Age, Total Cholesterol, HDL-Cholesterol, BP, Diabetes and Smoking. (If HDL unknown, assume 1.1 in Males, 1.4 in Females)

Age	M	F
30-34	-1	-9
35-39	0	-4
40-44	1	0
45-49	2	3
50-54	3	6
55-59	4	7
60-64	5	8
65-69	6	8
70-74	7	8

Total Cholesterol	M	F
< 4.1	-3	-2
4.1 – 5.1	0	0
5.2 – 6.2	1	1
6.3 – 7.1	2	1
>7.2	3	3

HDL Cholesterol	M	F
< 0.9	2	5
0.9 - 1.16	1	2
1.17 - 1.29	0	1
1.30 - 1.55	0	0
≥1.56	-2	-3

Systolic BP	Diastolic BP				
Male	<80	80-84	85-89	90-99	≥100
<120	0	0	1	2	3
120-129	0	0	1	2	3
130-139	1	1	1	2	3
140-159	2	2	2	2	3
≥160	3	3	3	3	3
Female	<80	80-84	85-89	90-99	≥100
<120	-3	0	0	2	3
120-129	0	0	0	2	3
130-139	0	0	0	2	3
140-159	2	2	2	2	3
≥160	3	3	3	3	3

If Systolic and Diastolic BP fall into different categories, use score from higher category

Diabetes	M	F
No	0	0
Yes	2	4

Smoking	M	F
No	0	0
Yes	2	2

Categorisation of 10 year Risk of CHD Event	
Very Low risk	< 10%
Low risk	< 15%
Moderate risk	15-20%
High risk	> 20%

STEP 2: Use total score to determine Predicted 10 year Absolute Risk of CHD Event (Coronary Death, Myocardial Infarction, Angina) by sex

Total Score	≤-2	-1	0	1	2	3	4	5	6	7	8	9	10	11	12	3	14	15	16	≥17
10 year Risk: Male		<2%	3%	3%	4%	5%	7%	8%	10%	13%	16%	20%	25%	31%	37%	45%	≥53%	≥53%	≥53%	≥53%
10 year Risk: Female	<1%	2%	2%	2%	3%	3%	4%	4%	5%	6%	7%	8%	10%	11%	13%	15%	18%	20%	24%	>27%

STEP 3: Compare Predicted 10 year Absolute Risk with "Average" and "Ideal" 10 year Risks, to give Relative Risks

Age	30 - 34	35 - 39	40 - 44	45 - 49	50 - 54	55 - 59	60 - 64	65 - 69	70 - 74
"Average" Male	3%	5%	7%	11%	14%	16%	21%	25%	30%
"Ideal" Male	2%	3%	4%	4%	6%	7%	9%	11%	14%
"Average" Female	< 1%	< 1%	2%	5%	8%	12%	12%	13%	14%
"Ideal" Female	< 1%	1%	2%	3%	5%	7%	8%	8%	8%

"Ideal" risk represents
Total Cholesterol = 4.1 - 5.1
HDL = 1.2 (Male), 1.4 (Female)
BP < 120/80
No Diabetes, Non Smoker

People with an absolute risk of ≥30% should be considered for treatment: with a Statin to achieve a Total Cholesterol <5 and/or LDL cholesterol <3
People with an absolute risk of ≥15% should be considered for treatment with anti-hypertensives to achieve a BP ideally ≤140/90

LINEE GUIDA

clinical practice guidelines

Annals of Oncology 23 (Supplement 7): vii155–vii166, 2012
doi:10.1093/annonc/mds293

Cardiovascular toxicity induced by chemotherapy, targeted agents and radiotherapy: ESMO Clinical Practice Guidelines†

G. Curigliano[1], D. Cardinale[2], T. Suter[3], G. Plataniotis[4], E. de Azambuja[5], M. T. Sandri[6], C. Criscitiello[1], A. Goldhirsch[1], C. Cipolla[2] & F. Roila[7], on behalf of the ESMO Guidelines Working

European Heart Journal (2016) **37**, 2768–2801
doi:10.1093/eurheartj/ehw211

ESC CPG POSITION PAPER

2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines

EXPERT CONSENSUS STATEMENT

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(J Am Soc Echocardiogr 2014;27:911-39.)

LA DISFUNZIONE VENTRICOLARE SINISTRA

<u>Classificazione:</u>

La disfunzione ventricolare sinistra è caratterizzata da almeno uno tra:

- -sintomi di scompenso cardiaco
- -segni di scompenso cardiaco come T3 o tachicardia
- -Riduzione di EF di almeno 5% sotto i 55% con sintomi o segni di scompenso
- -Riduzione del 10% sotto i 55% senza segni o sintomi associati


clinical practice guidelines

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CTCAE heart failure		AHA/ACC heart failure stage	NYHA functional class
Grade 1	Asymptomatic (biomarker or imaging evidence of cardiac dysfunction)	B	I
Grade 2	Symptoms with mild to moderate level of exertion	C	II
Grade 3	Severe symptoms at rest or minimal activity		III-IV
Grade 4	Life threatening	D	IV
Grade 5	Death		

CTCAE Common Terminology Criteria for Adverse Events, AHA American Heart Association, ACC American College of Cardiology, NYHA New York Heart Association

Aiom 2015

ASE CONSENSUS 2014

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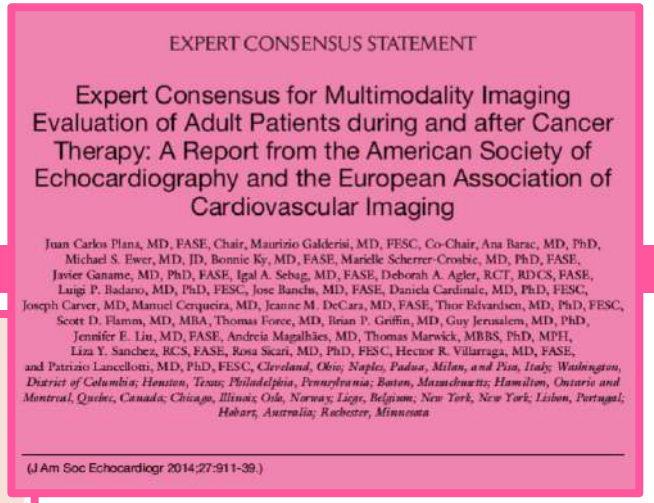
(J Am Soc Echocardiogr 2014;27:911-39.)

1. Definition of Cancer Therapeutics–Related Cardiac Dysfunction (CTRCD). Different definitions of CTRCD have been used historically.[7] It is the consensus of this committee to define CTRCD as a decrease in the LVEF of >10 percentage points, to a value <53% (normal reference value for two-dimensional (2D) echocardiography (2DE) (see Section II). This decrease should be confirmed by repeated cardiac imaging. The repeat study should be performed 2 to 3 weeks after the baseline diagnostic study showing the initial decrease in LVEF. LVEF decrease may be further categorized as symptomatic or asymptomatic, or with regard to reversibility:

- Reversible: to within 5 percentage points of baseline
- Partially reversible: improved by ≥10 percentage points from the nadir but remaining >5 percentage points below baseline
- Irreversible: improved by <10 percentage points from the nadir and remaining >5 percentage points below baseline
- Indeterminate: patient not available for re-evaluation

Protocollo Eco



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(J Am Soc Echocardiogr 2014;27:911-39.)

Standard transthoracic echocardiography
- In accordance with ASE/EAE guidelines and IAC-Echo

2D strain imaging acquisition
- Apical three-, four-, and two-chamber views
  - Acquire ≥3 cardiac cycles
- Images obtained simultaneously maintaining the same 2D frame rate and imaging depth
  - Frame rate between 40 and 90 frames/sec or ≥40% of HR
- Aortic VTI (aortic ejection time)

2D strain imaging analysis
- Quantify segmental and global strain (GLS)
- Display the segmental strain curves from apical views in a quad format
- Display the global strain in a bull's-eye plot

2D strain imaging pitfalls
- Ectopy
- Breathing translation

3D imaging acquisition
- Apical four-chamber full volume to assess LV volumes and LVEF calculation
- Single and multiple beats optimizing spatial and temporal resolution

La valutazione Ecocardiografica:

Guideline statements	Level of evidence	Grade of recommendation
Echocardiography is the standard procedure for basal assessment of cardiac structure, performance and hemodynamics. Multiple gated acquisition (MUGA) scan can reduce interobserver variability with the disadvantages of including the exposure to radioactivity and the limited information than can be obtained on cardiac structure and diastolic function. Magnetic resonance imaging (MRI) is another method used to evaluate myocardial function. Its spatial resolution is higher than that of echocardiography, but its temporal resolution is lower.	I	A
Assessment by ultrasound should obtain 2D or 3D images in the left ventricular parasternal long- and short-axis views and in the apical four- and two-chamber long-axis views. For the analysis of diastolic function, the following parameters should be measured: the ratio of early peak flow velocity to atrial peak flow velocity (E/A ratio; normal value >1), the deceleration time of the early peak flow (DT; normal value <220 ms) and the isovolumic relaxation time (IVRT; normal value <100 ms). Left ventricular end-diastolic diameter (normal value, 47 ± 4 mm) should be measured to test for ventricular dilatation	I	A

ESMO 2012

ECOCARDIOGRAMMA TRANSTORACICO STANDARD

Acquisizione di immagini 2D strain (sec. LG ASE/EAE e IAC-Echo)

Immagini da approccio apicale 3, 4, e 2 camere (acquisire ≥ 3 cicli cardiaci)

Immagini simultanee mantenendo lo stesso 2D frame rate e la stessa profondità (frame rate tra 40 e 90 frames/sec o ≥ 40% della FC)

VTI aortico (tempo di eiezione aortico)

Analisi di immagini 2D strain

Quantificare strain segmentale e globale (GLS)

Acquisire le curve di strain segmentale da approccio apicale

Acquisire il grafico del globale strain

Acquisizione 3D

Full volume da approccio apicale 4 camere per valutare il volume ventricolare sinistro e calcolare FEVS

Ottimizzare la risoluzione spaziale e temporale di battiti singoli e multipli

Report

Data dell'esecuzione dell'ecocardiogramma

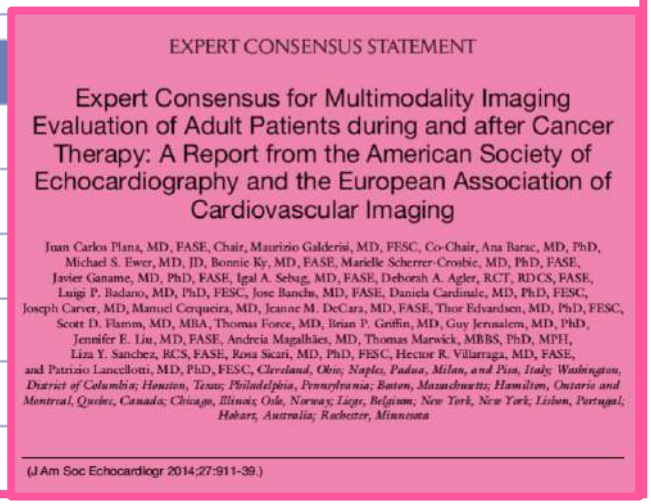
PA e FC

FEVS 3D e/o FEVS con metodo Simpson biplano

GLS (indicare marca ecocardiografo, software e versione utilizzati)

MAPSE e s' mediale e laterale (se non eseguibile GLS)

TAPSE, s' e FAC del ventricolo destro



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Expert Consensus for Multimodality Imaging Evaluation of Adult Patients during and after Cancer Therapy: A Report from the American Society of Echocardiography and the European Association of Cardiovascular Imaging

Juan Carlos Plana, MD, FASE, Chair, Maurizio Galderisi, MD, FESC, Co-Chair, Ana Barac, MD, PhD, Michael S. Ewer, MD, JD, Bonnie Ky, MD, FASE, Marielle Scherrer-Crosbie, MD, PhD, FASE, Javier Ganame, MD, PhD, FASE, Igal A. Sebag, MD, FASE, Deborah A. Agler, RCT, RDCS, FASE, Luigi P. Badano, MD, PhD, FESC, Jose Banchs, MD, FASE, Daniela Cardinale, MD, PhD, FESC, Joseph Carver, MD, Manuel Cerqueira, MD, Jeanne M. DeCara, MD, FASE, Thor Edvardsen, MD, PhD, FESC, Scott D. Flamm, MD, MBA, Thomas Force, MD, Brian P. Griffin, MD, Guy Jerusalem, MD, PhD, Jennifer E. Liu, MD, FASE, Andreia Magalhães, MD, Thomas Marwick, MBBS, PhD, MPH, Liza Y. Sanchez, RCS, FASE, Rosa Sicari, MD, PhD, FESC, Hector R. Villarraga, MD, FASE, and Patrizio Lancellotti, MD, PhD, FESC, *Cleveland, Ohio; Naples, Padua, Milan, and Pisa, Italy; Washington, District of Columbia; Houston, Texas; Philadelphia, Pennsylvania; Boston, Massachusetts; Hamilton, Ontario and Montreal, Québec, Canada; Chicago, Illinois; Oslo, Norway; Liège, Belgium; New York, New York; Lisbon, Portugal; Hobart, Australia; Rochester, Minnesota*

(J Am Soc Echocardiogr 2014;27:911-39.)

Limiti di riferimento per strain GLS

Table 5 Effect of vendor age and gender on global longitudinal strain

Vendor	Age group (y)						*P*
	0–19	20–29	30–39	40–49	50–59	≥60	
V1							
Overall	−22.1 ± 2.4	−21.2 ± 1.9	−21.1 ± 2.1	−21.4 ± 2.0	−21.0 ± 2.2	−20.3 ± 1.9	0.0218
Male	−21.7 ± 3.1	−20.9 ± 1.9	−20.6 ± 1.9	−20.9 ± 1.8	−21.0 ± 1.9	−19.7 ± 1.4	0.1982
Female	−22.4 ± 1.6	−22.3 ± 1.6	−22.8 ± 1.8	−22.6 ± 2.1	−23.3 ± 1.9	−20.9 ± 2.1	0.0348
P (male vs. female)	0.4292	0.0316	<0.0001	0.0178	0.0029	0.1381	
V2							
Overall	−19.9 ± 2.5	−19.0 ± 2.1	−19.5 ± 2.2	−18.2 ± 2.5	−17.6 ± 2.5	−16.7 ± 2.1	<0.0001
Male	−19.4 ± 2.7	−18.8 ± 2.0	−19.1 ± 2.3	−17.9 ± 2.8	−16.9 ± 2.3	−15.8 ± 1.4	0.0019
Female	−20.5 ± 2.2	−20.6 ± 2.3	−20.2 ± 2.0	−19.3 ± 0.9	−20.4 ± 1.5	−17.3 ± 2.3	0.0002
P (male vs. female)	0.1349	0.0248	0.1083	0.4316	0.0294	0.0928	
V3							
Overall	−21.4 ± 1.7	−20.2 ± 2.1	−20.4 ± 2.3	−19.4 ± 2.2	−18.5 ± 2.6	−17.8 ± 2.8	<0.0001
Male	−21.6 ± 2.0	−20.2 ± 2.0	−20.4 ± 2.2	−19.8 ± 2.3	−18.7 ± 2.6	−16.3 ± 3.1	<0.0001
Female	−21.2 ± 1.5	−20.2 ± 2.4	−20.4 ± 2.8	−18.7 ± 1.8	−18.3 ± 2.8	−18.6 ± 2.3	0.0141
P (male vs. female)	0.6076	0.9787	0.9201	0.1415	0.7374	0.0668	

ESC 2016

Eco-sforzo+CPETs

Utility of 3-dimensional echocardiography, global longitudinal strain, and exercise stress echocardiography to detect cardiac dysfunction in breast cancer patients treated with doxorubicin-containing adjuvant therapy

Michel G. Khouri,
Duke Cancer Institute, Duke University Medical Center, Box 3085, Durham, NC 27710, USA

Valutazione di un approccio integrato 3D+GLS+Eco-sforzo per la valutazione della disfunzione subclinica nelle pazienti trattate con doxorubicina.
57 pazienti asintomatiche con tumore mammario e 20 controlli .
Cardiopolmonare con eco.
Risultati: Riduzione 3D EF, VO2 picco e strain GLS nelle pazienti sottoposte a CHT con doxo rispetto ai controlli.

Eco-dobutamina

Int J Cardiol. 2006 Jul 28;111(1):120-6. Epub 2005 Oct 20.

Early reduction in left ventricular contractile reserve detected by dobutamine stress echo predicts high-dose chemotherapy-induced cardiac toxicity.

Civelli M[1], Cardinale D, Martinoni A, Lamantia G, Colombo N, Colombo A, Gandini S, Martinelli G, Fiorentini C, Cipolla CM.

⊕ Author information

Abstract

BACKGROUND: High-dose chemotherapy (HDC) is utilized in high-risk cancer patients. This type of treatment may induce cardiac toxicity which becomes clinically evident weeks or months after HDC. Hence, the possibility of early identification of patients who will develop cardiac impairment is strategic for its clinical implications. The aim of this study was to identify possible early changes of left ventricular contractile reserve (LVCR) in cancer patients undergoing HDC, as well as to evaluate the relevance of such changes as predictors of chemotherapy-induced cardiotoxicity.

METHODS: In forty-nine female patients scheduled for HDC, due to poor-prognosis breast cancer, dobutamine stress echocardiography (DSE) was performed, before each of the three HDC cycles (C1, C2, C3), and 1, 4, and 7 months after the end of chemotherapy. According to rest left ventricular ejection fraction (LVEF) evaluated within 18 months after HDC (f-LVEF), patients were allocated to Group A (LVEF < 50% and >10 absolute units reduction) and to Group B (LVEF > or = 50%).

RESULTS: Rest LVEF didn't show any significant difference between the two groups except at f-LVEF. Peak LVEF and LVCR significantly decreased in Group A only, starting from C3. At C3, a > or = 5 units fall in LVCR was found to be predictive for f-LVEF drop below 50%.

CONCLUSIONS: In patients undergoing HDC, low-dose DSE allows the early identification of patients at a high risk of developing cardiac dysfunction.

RISONANZA MAGNETICA

1-valutazione delle MASSE CARDIACHE: ACCURATEZZA DIAGNOSTICA NEI VARI STUDI 92%→ 100%

The role of cardiac MRI is growing in

Irena Orlov. *Inspiring moments 3*. Digital on canvas, 40" × 60".

2-CARDIOMIOPATIE INFILTRATIVE COME AMILOIDOSI O DEPOSITO DI FERRO, PIU' FREQUENTI NEI PAZIENTI ONCOLOGICI

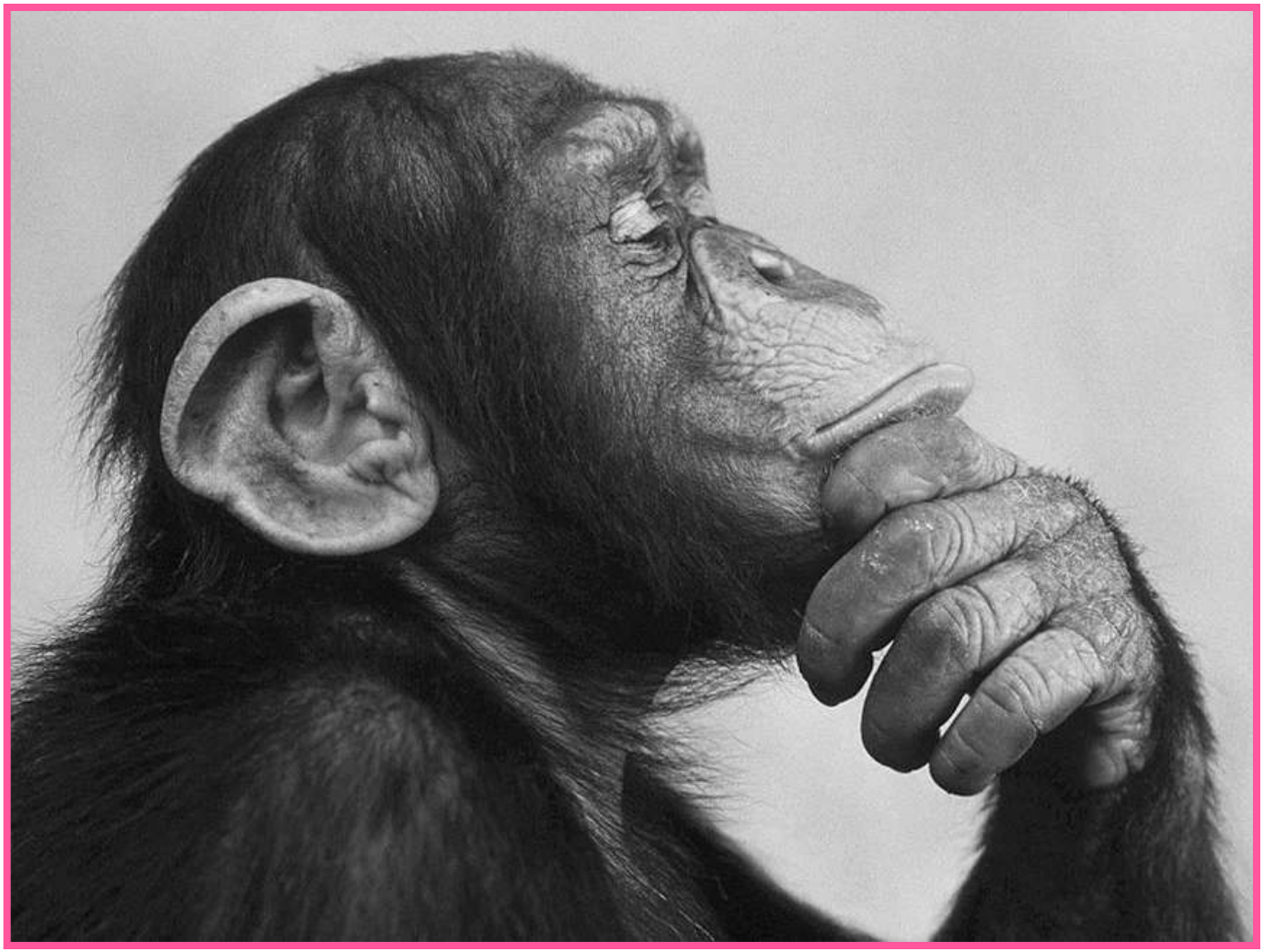
3-VALUTAZIONE FRAZIONE DI EIEZIONE

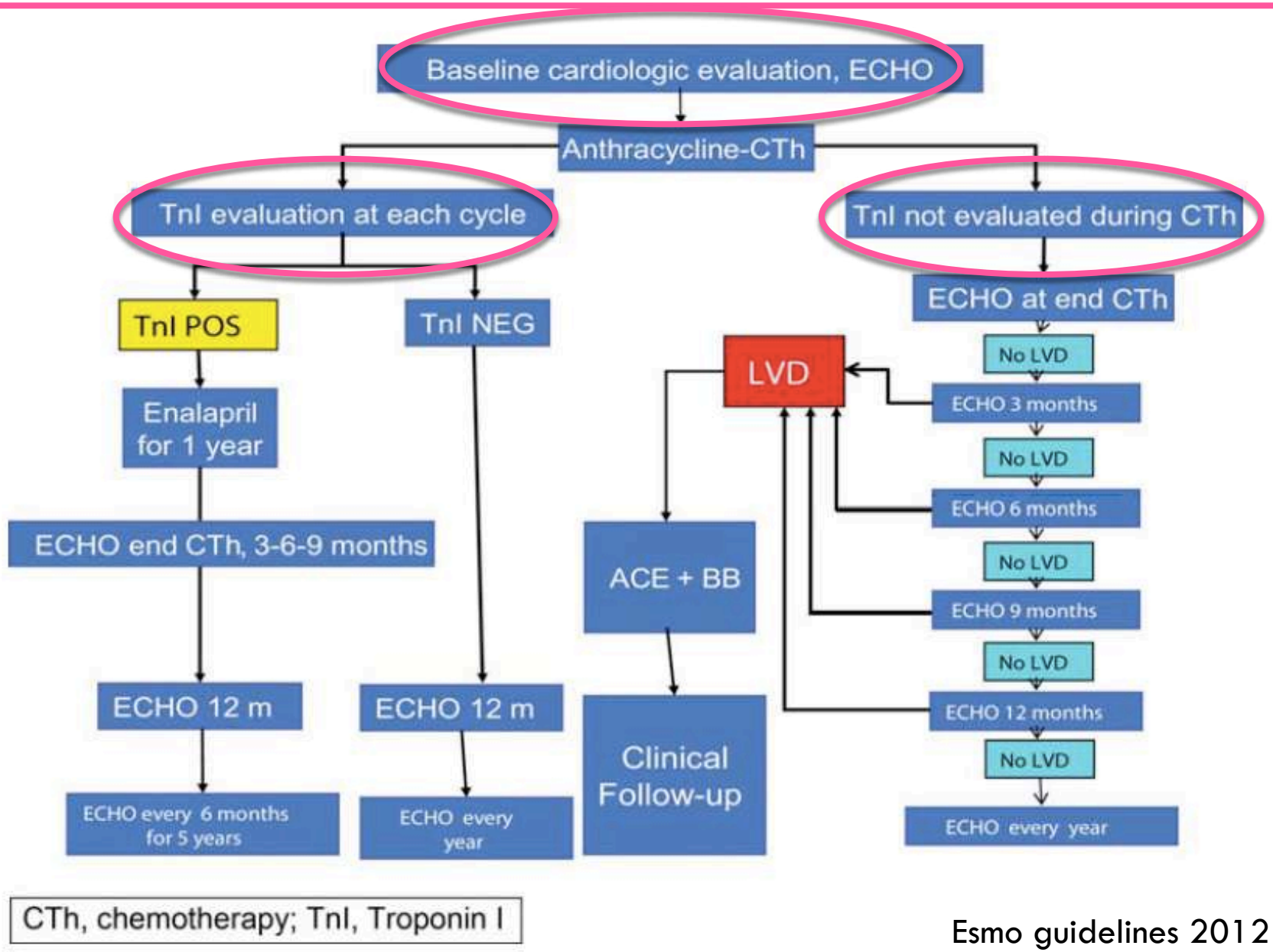
4-T1 MAPPING.

Cardiac Magnetic Resonance Imaging in Oncology

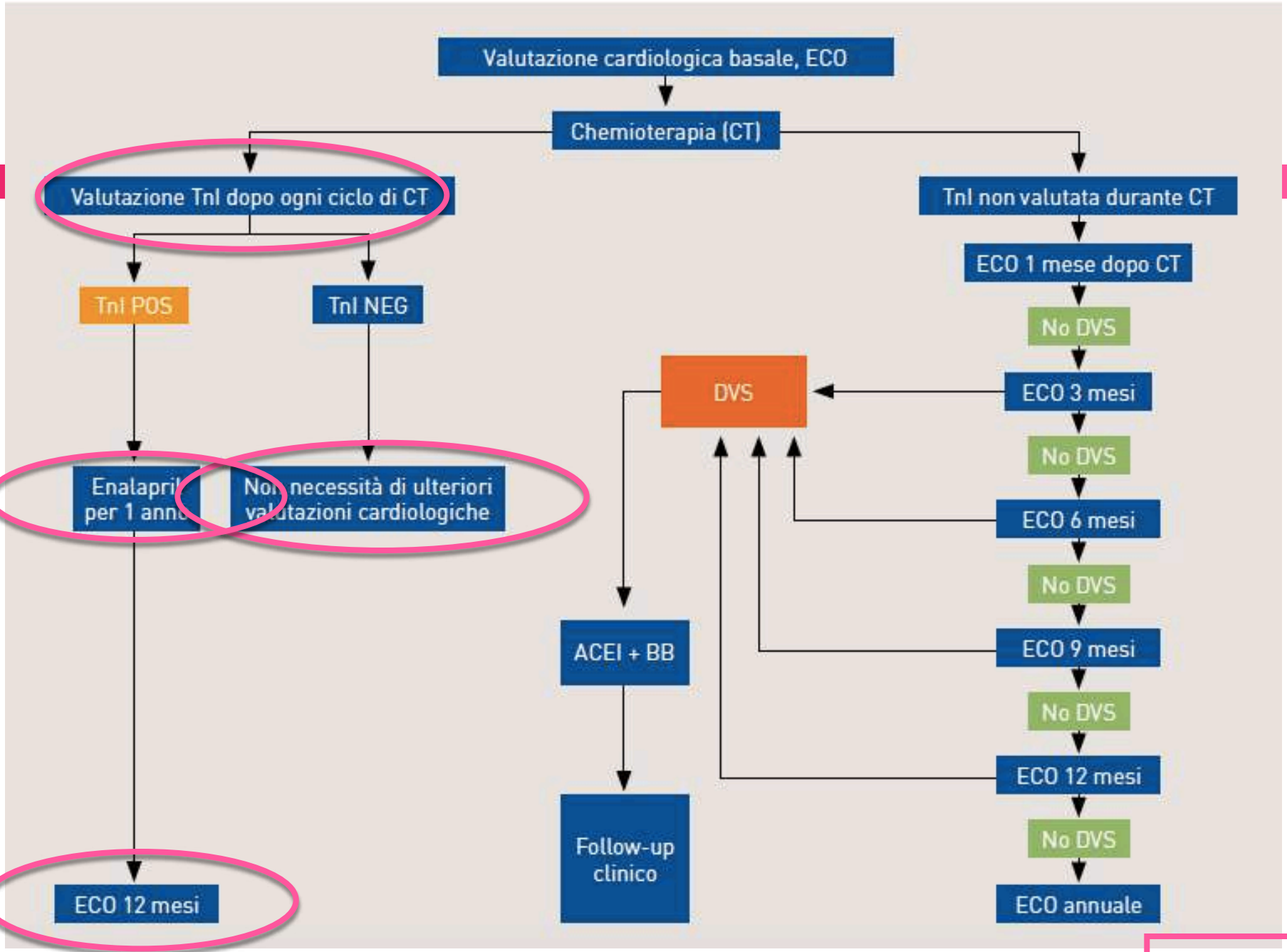
Daniel Jeong, MD, Aarti Patel, MD, Christopher J. François, MD, Kenneth L. Gage, MD, PhD, and Michael G. Fradley, MD

GESTIONE CARDIOTOSSICITA'



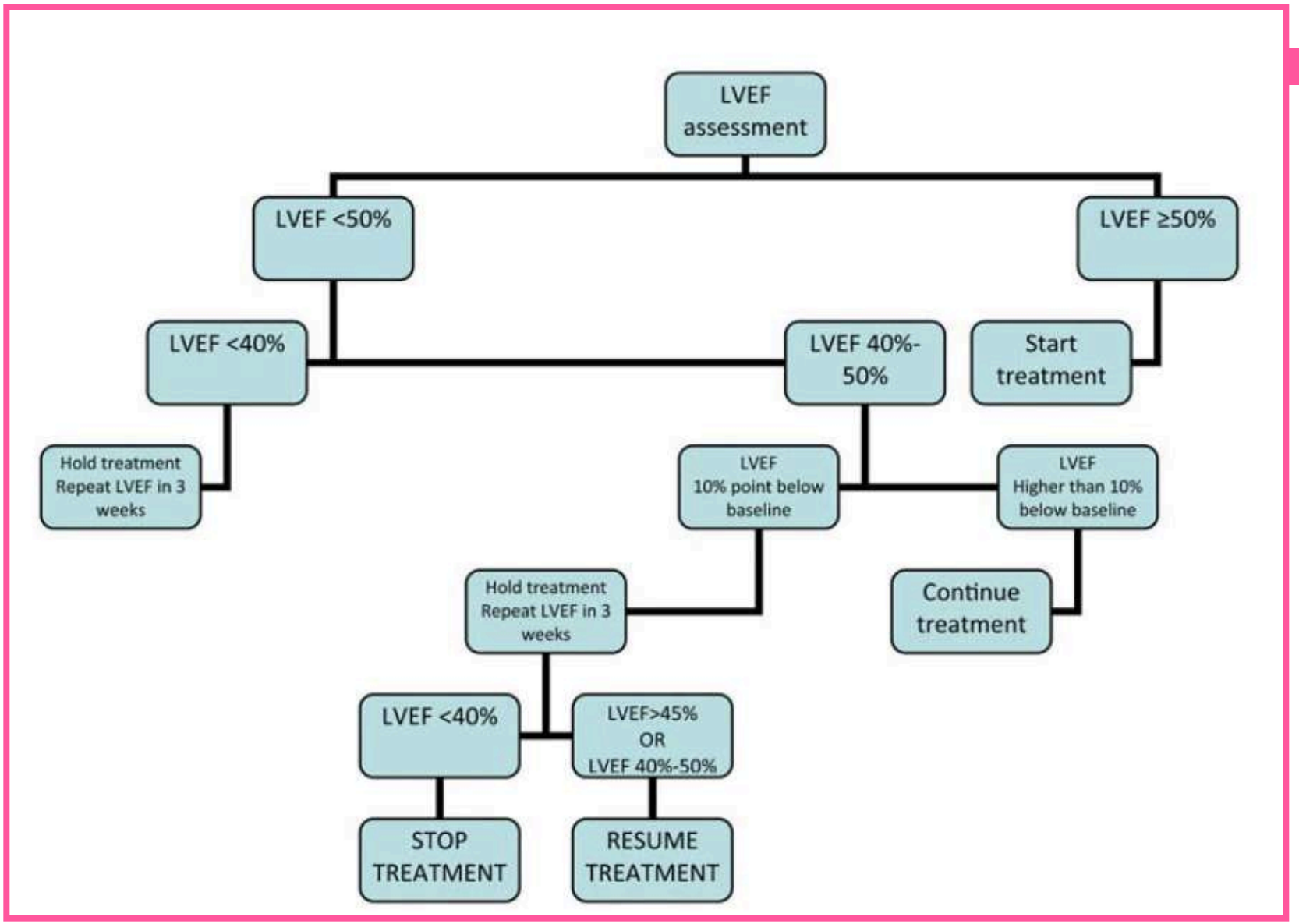


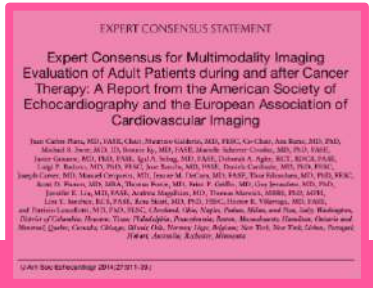
Esmo guidelines 2012


Valutazione cardiologica basale, ECO
Chemioterapia (CT)
Valutazione TnI dopo ogni ciclo di CT
TnI non valutata durante CT
TnI POS
TnI NEG
ECO 1 mese dopo CT
No DVS
DVS
ECO 3 mesi
No DVS
ECO 6 mesi
No DVS
ECO 9 mesi
No DVS
ECO 12 mesi
No DVS
ECO annuale
Enalapril per 1 anno
Non necessità di ulteriori valutazioni cardiologiche
ACEI + BB
Follow-up clinico
ECO 12 mesi

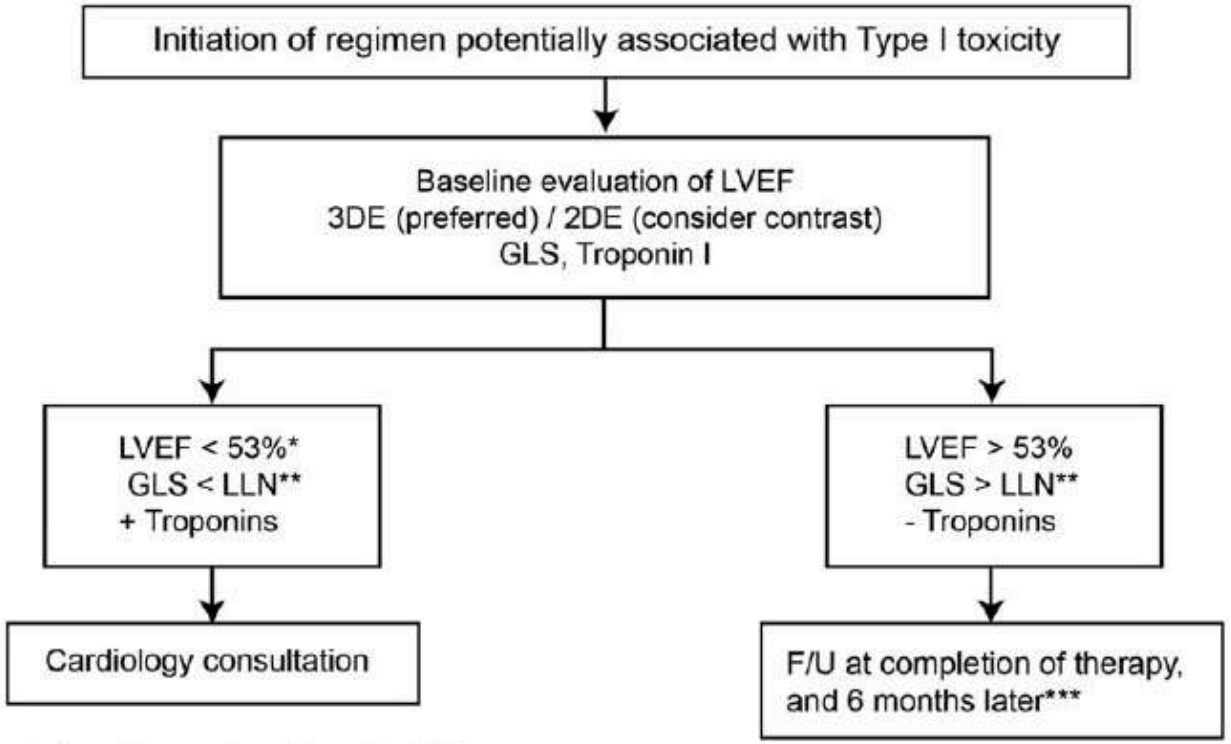
Aiom 2015

Trastuzumab:




EXPERT CONSENSUS STATEMENT

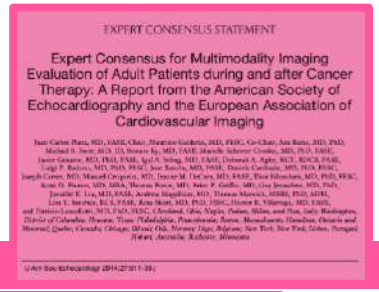
Expert Consensus for Multimodality Imaging Evaluation of Adult Patients during and after Cancer Therapy: A Report from the American Society of Echocardiography and the European Association of Cardiovascular Imaging



* 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/m^2 (or its equivalent), recommend measurement of LVEF, GLS and troponin prior to each additional 50 mg/m^2.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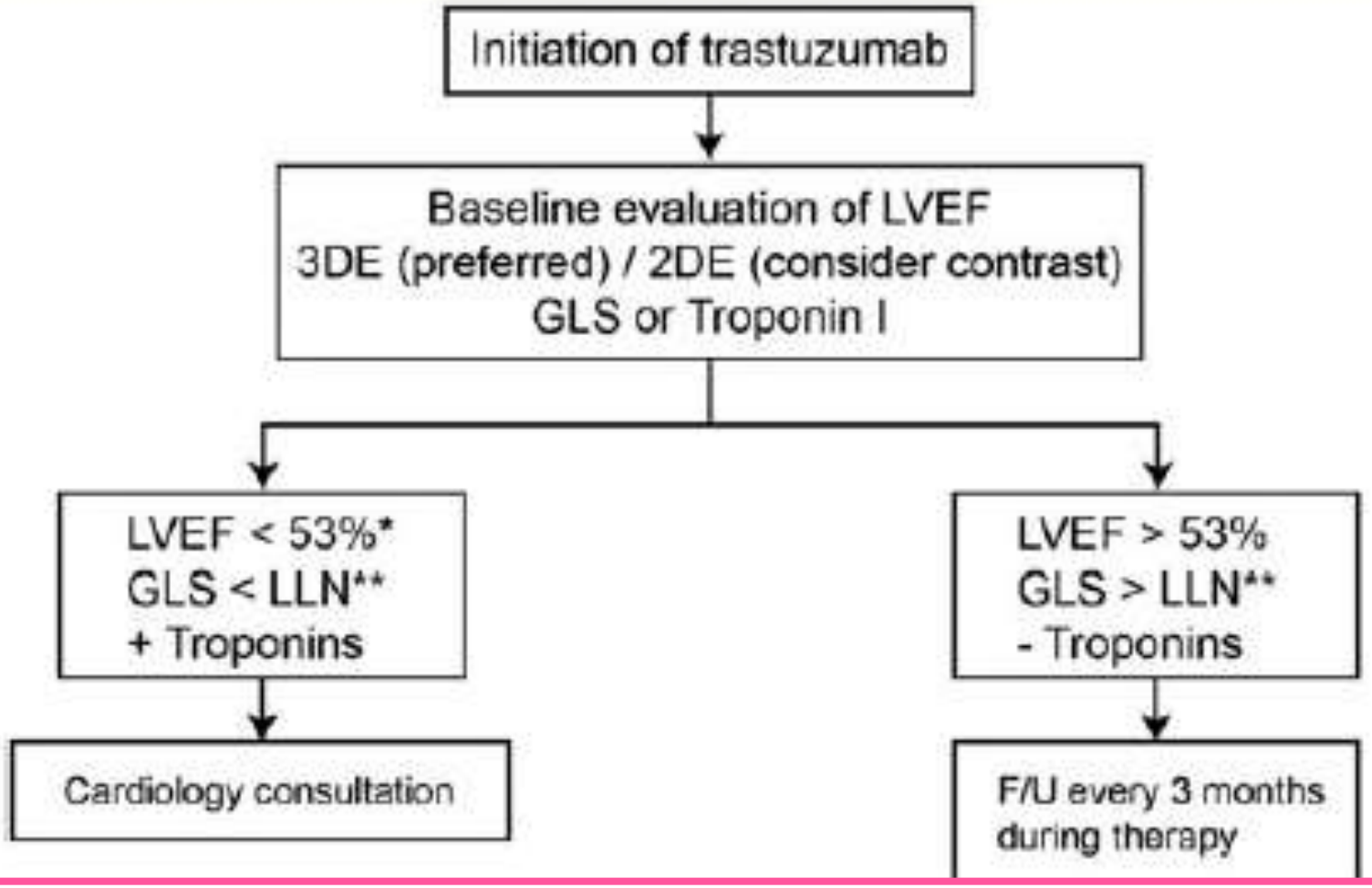
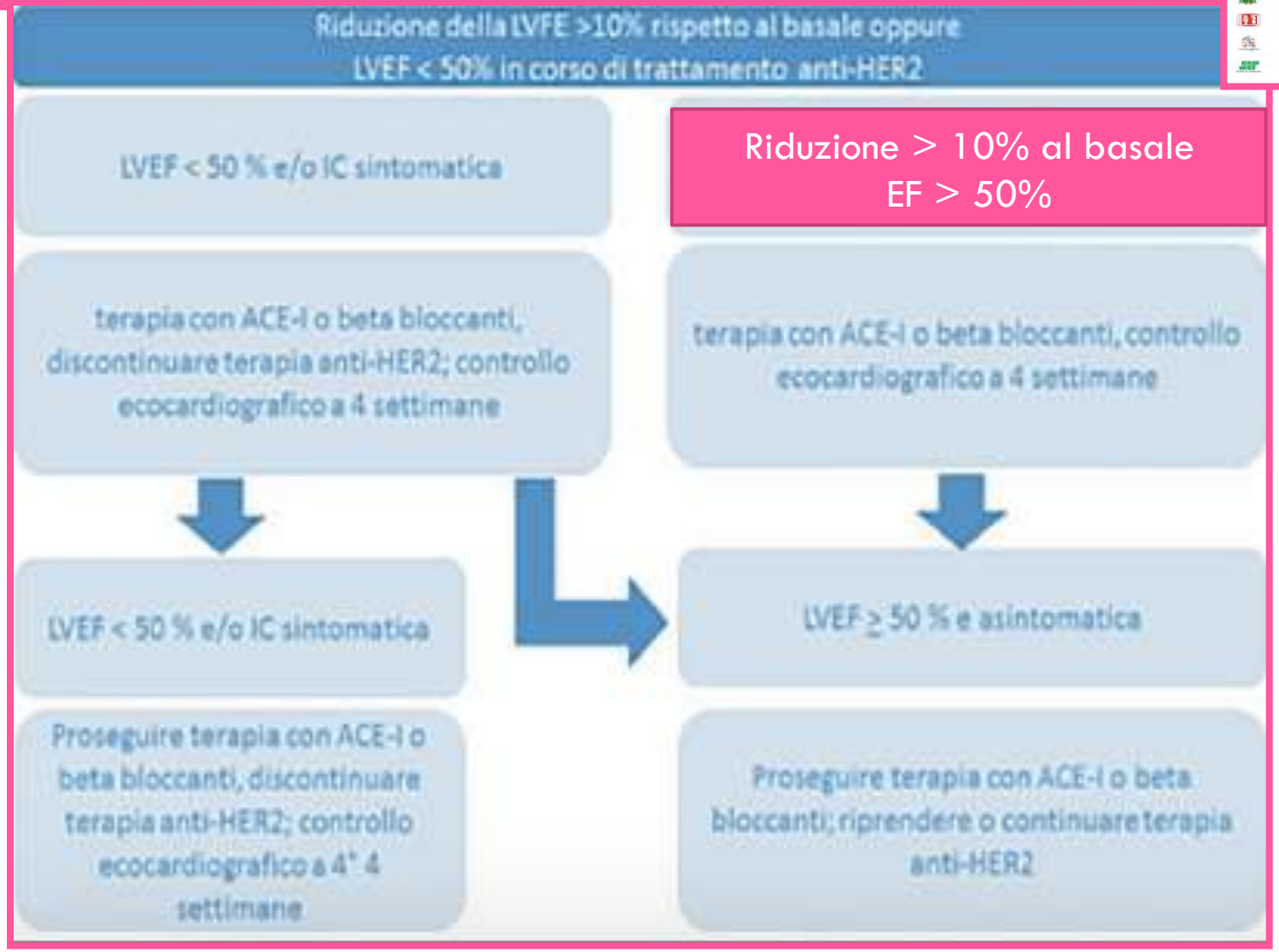


CARDIOTOSSICITA' ANTI HER-2



FARMACI

Setting clinico	Prevenzione primaria	Livello di evidenza	Classe della raccomandazione
Carcinoma mammario (metastatico >388mg/m²)	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

Dexrazoxano

Meccanismo d'azione:

Profarmaco che entra facilmente nel cardiomiocita e viene metabolizzato nella forma attiva→ ferro-chelante, idrolisi ROS ed inibizione Topoisomerasi II.

Studi su animali: hanno dimostrato effetto cardioprotettivo.

Farmacocinetica: distribuzione rapida ai tessuti, 2-4 ore dopo la somministrazione ev; eliminazione renale ed epatica.

Non passa la barriera emato-encefalica

Effetto terapeutico:

Minore incidenza di cardiotossicità è stata osservata nelle donne trattate con dexrazoxano (0-3%, versus 8-27%)→sia in pazienti antracicline-naive sia in pazienti che avevano già subito un trattamento.

La riduzione di scompenso cardiaco (CHF) diventa statisticamente significativa nei trials con dosaggi di doxorubicina>=300 mg/m2 ; epirubicina>=480 mg/m2 (CHF 3 vs 22%)

Marty M., et al., 2004
Speyer JL et al., JCO 1992
Venturini M., et al., JCO 1996
Vici P. et al., Clin Ter 1998

POSSIBILE AUMENTO DI RISCHIO DI SECONDI TUMORI!!

VOLUME 25 · NUMBER 5 · FEBRUARY 10 2007

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Dexrazoxane-Associated Risk for Acute Myeloid Leukemia/Myelodysplastic Syndrome and Other Secondary Malignancies in Pediatric Hodgkin's Disease

Cameron K. Tebbi, Wendy B. London, Debra Friedman, Doojduen Villaluna, Pedro A. De Alarcon, Louis S. Constine, Nancy Price Mendenhall, Richard Sposto, Allen Chauvenet, and Cindy L. Schwartz

Pazienti con LH trattati con polichemioterapia contenente antracicline randomizzati ad assumere dzx/no dxz (farmaco 239/controllo 239)
58 mesi di fu
Tasso di incidenza cumulativa per leucemia/mds 2.55% con dxz versus 0.85% no-dxz (p 0 .160).

Per ogni neoplasia secondaria 3.43% versus 0.85% no dxz (p 0.06).

NON CONFERMATO

VOLUME 26 · NUMBER 7 · MARCH 1 2008

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Absence of Secondary Malignant Neoplasms in Children With High-Risk Acute Lymphoblastic Leukemia Treated With Dexrazoxane

Elly V. Barry, Lynda M. Vrooman, Suzanne E. Dahlberg, Donna S. Neuberg, Barbara L. Asselin,

EUROPEAN JOURNAL OF CANCER 47 (2011) 1373–1379

ELSEVIER

available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejconline.com

The low incidence of secondary acute myelogenous leukaemia in children and adolescents treated with dexrazoxane for acute lymphoblastic leukaemia: A report from the Dana-Farber Cancer Institute ALL Consortium

Nota Informativa Importante su Cardioxane (dexrazoxano) (18/07/2011)

Sicurezza

18/07/201

Informazioni di sicurezza sul medicinale Cardioxane (dexrazoxano)

- Dexrazoxano è ora controindicato per l'uso nei bambini e negli adolescenti.
  - Questa restrizione dell'uso è stata determinata da evidenze di effetti dannosi gravi nei bambini a seguito dell'uso di dexrazoxano, inclusi un aumento del rischio di secondi tumori maligni primari (principalmente leucemia mieloide acuta e sindrome mielodisplastica), grave mielosoppressione, infezione grave e di mancanza di evidenza di efficacia clinica.
- L'uso del dexrazoxano (Cardioxane) è ora ristretto ai pazienti adulti con cancro mammario avanzato e/o metastatico.

Non è raccomandato l'uso del dexrazoxano in combinazione con terapia adiuvante per il cancro mammario o con chemioterapia a scopo curativo.

- La dose cumulativa minima di antracicline che deve essere stata somministrata prima dell'uso di dexrazoxano è di 300 mg/m2 di doxorubicina, o 540 mg/m2 di epirubicina.
- Il rapporto di dosi raccomandato per dexrazoxano:doxorubicina e dexrazoxano:epirubicina è di 10:1.

FARMACI ANTI-SCOMPENSO: DOBBIAMO SEGUIRE LE LINEE GUIDA?

Recommendations	COR	LOE	References
In patients with a history of MI and reduced EF, ACE inhibitors or ARBs should be used to prevent HF	I	A	314, 342–345
In patients with MI and reduced EF, evidence-based beta blockers should be used to prevent HF	I	B	346–348
In patients with MI, statins should be used to prevent HF	I	A	104, 349–354
Blood pressure should be controlled to prevent symptomatic HF	I	A	27, 94, 311–313
ACE inhibitors should be used in all patients with a reduced EF to prevent HF	I	A	65, 344
Beta blockers should be used in all patients with a reduced EF to prevent HF	I	C	N/A
An ICD is reasonable in patients with asymptomatic ischemic cardiomyopathy who are at least 40 d post-MI, have an LVEF ≤30%, and on GDMT	IIa	B	355
Nondihydropyridine calcium channel blockers may be harmful in patients with low LVEF	III: Harm	C	N/A

ACE indicates angiotensin-converting enzyme; ARB, angiotensin-receptor blocker; COR, Class of Recommendation; EF, ejection fraction; GDMT, guideline-directed medical therapy; HF, heart failure; ICD, implantable cardioverter-defibrillator; LOE, Level of Evidence; LVEF, left ventricular ejection fraction; MI, myocardial infarction; and N/A, not available.

Circulation. 2013;128:e240-e327


Grazie per
l'attenzione!

Novità dal 14-05 ad oggi?

DOI: 10.1111/echo.14467

DOPPLER HEMODYNAMICS

Echocardiography WILEY

Early detection of cardiotoxicity by 3D speckle tracking imaging of area strain in breast cancer patients receiving chemotherapy

Jianqiong Chen MD[1] | Ling Wang MD[2] | Fang-Fang Wu MD[2] | Guoping Sun PhD[1]

6 cicli di EC; 83 pazienti, setting adiuvante; 2015→2017
Divise in 4 gruppi : inizio; precoce (120 mg/m2), metà (240 mg/m2), termine (360 mg/m2);
Troponina ENTRO le 24 ore dalla somministrazione della terapia.
Le uniche differenze statisticamente significative sono di Global area strain GAS (Cut-off 31.5%) e global longitudinal strain GLS (-16.5%).

Un case report di riduzione acuta di EF da 5-FU

BMJ Case Rep. 2019 Sep 12;12(9). pii: e230499. doi: 10.1136/bcr-2019-230499.

Acute reversible left ventricular systolic dysfunction associated with 5-fluorouracil therapy: a rare and increasingly recognised cardiotoxicity of a commonly used drug.

Mishra T[1], Shokr M[2], Ahmed A[3], Afonso L[2].

Author information

1 Department of Internal Medicine, Wayne State University, Detroit, Michigan, USA.
2 Division of Cardiology, Wayne State University, Detroit, Michigan, USA.
3 Division of Pulmonary and Critical Care Medicine, Mayo Clinic, Rochester, Minnesota, USA.

Abstract

5-Fluorouracil (5-FU) is the third most common chemotherapeutic agent for treating solid cancers and the second most common to cause cardiotoxicity. We present a rare case of acute reversible severe left ventricular systolic dysfunction associated with 5-FU. A 54-year-old woman with a history of stage IV gastric cancer presented with features of transient ischaemic attack after receiving the first dose of FLOT (5-FU, leucovorin, oxaliplatin and docetaxel). During the diagnostic workup, it was found that her ejection fraction was severely reduced to 15% with features of global hypokinesis, which later improved back to 65% within 13 days. These cases challenge our current understanding of the underlying mechanisms of this cardiotoxicity. Additionally, even though the patient did not experience any cardiac symptoms, it is important to monitor these patients closely as they are at high risk for fatal complications like arrhythmia and thrombus formation.

Riduzione acuta di EF a 15%→ poi normalizzata entro 13 gg

REVIEW ARTICLE

J Thorac Imaging Volume 00, Number 00, 2019

Imaging in Cardio-oncology

An Overview of an Emerging Medical Discipline

,*

THE CARDIOTOXICITY MECHANISM APPROACH

The cardiotoxicity mechanism approach looks into the etiology of the cardiac and cardiovascular side effects. This approach was suggested by Maleszewski et al[7] in their recent (2018) important review on "Neoplasia and the heart." Mechanisms are also discussed in depth in the review by Moslehi[8] in 2016 and in the state of the art review by Chang

(A) *Direct* mechanisms that include hematomyeloid metastasis, direct metastases, primary cardiac tumors, and intraluminal tumor growth.

(B) *Indirect* mechanisms that include thoracic irradiation, carcinoid tumor, chemotherapy agents, and plasma cell dyscrasia (amyloidosis).

THE TIMING OF CARDIOVASCULAR COMPLICATIONS IN THE CANCER PATIENT APPROACH

The timing of cardiovascular complications in the cancer patient approach addressing 3 main groups of patients:

(1) Patients with *known heart disease* who are diagnosed with cancer.

(2) Patients *without known heart disease who are diagnosed and treated for cancer* and only afterward develop cardiovascular complications related either to treatment or to the cancer itself.

(3) Cancer survivors: patients *following the treatment* of cancer who have developed or who are at risk of developing cardiovascular disease with time due to the side effects of previous cancer therapy in addition to cardiovascular risk of the regular aging in the modern world.

J Thorac Imaging Volume 00, Number 00, 2019

Prognostic Value of Cardiac Biomarkers Assessment in Combination with Myocardial 2D Strain Echocardiography for Early Detection of Anthracycline-Related Cardiac Toxicity.

Mahjoob MP[1], Sheikholeslami SA[2], Dadras M[3], Mansouri H[4], Haghi M[5], Naderian M[6], Sadeghi L[7], Tabary M[8], Khaheshi I[1].

CONCLUSION: This study has shown that hs-cTnI with good sensitivity can predict cardiac toxicity in Anthracycline-based chemotherapy receiver. Use of strain with speckle echocardiography method has prognostic value; however, both longitudinal and segmental strain should be

52 pazienti;

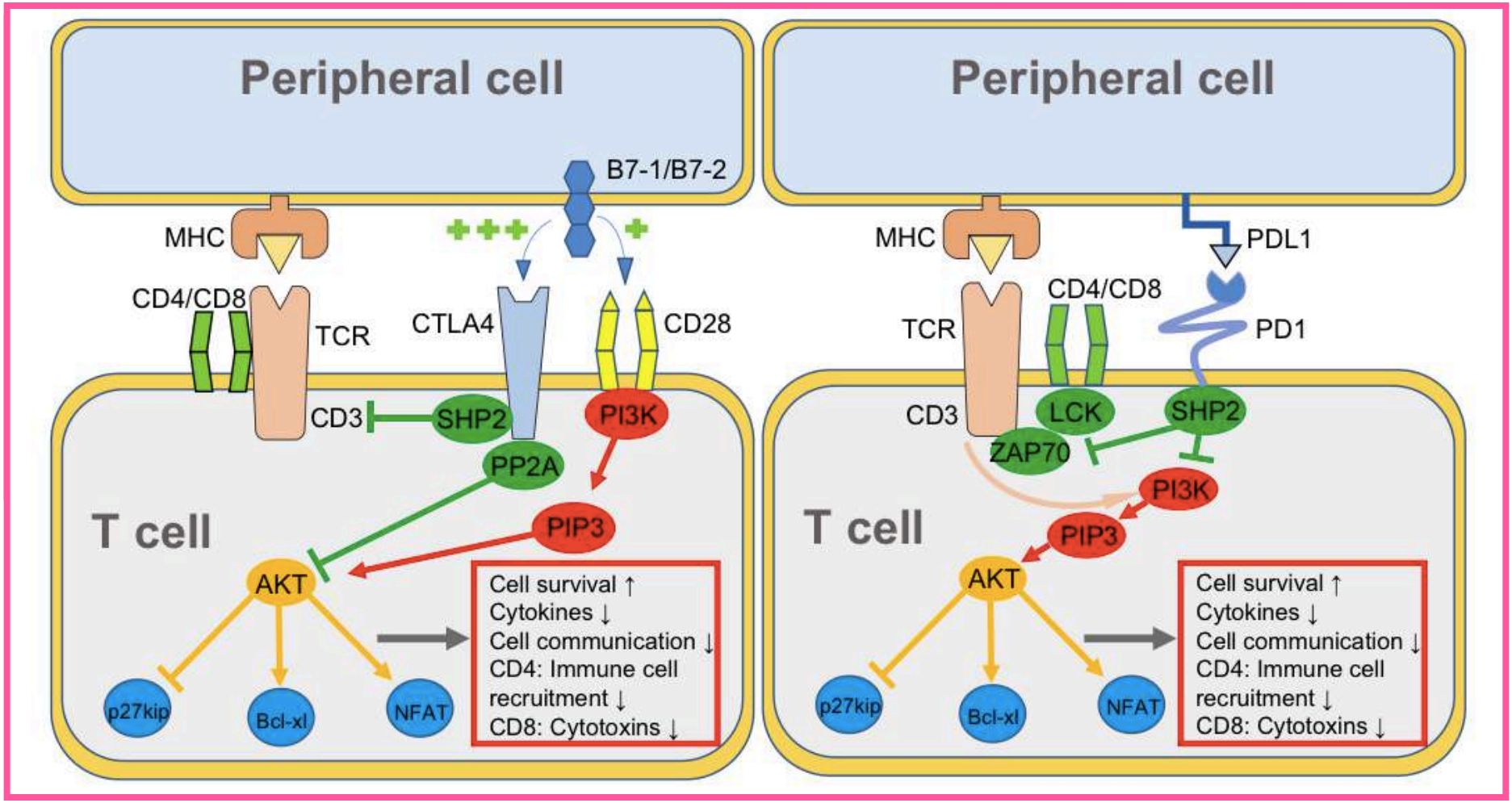
5 cardiotossicità

Buona correlazione troponina T HS/ strain 2D

In particolare: parete laterale ed infero-settale

Cardiovasc Hematol Disord Drug Targets. 2019 Sep 12.

Cardiotossicità da Immunoterapia



L. Michel et al. / IJC Heart & Vasculature 25 (2019)

Eventi avversi

- 1) immuno-relati mediante (Ir-AE):

A esacerbazione di patologie già esistenti.

B trigger auto-immunitari in pazienti geneticamente predisposti.

C induzione di una malattia auto-immunitaria ex-novo.

Di solito si verificano entro le prime 12 settimane, mentre sono molto rari dopo un anno.

L. Michel et al. / IJC Heart & Vasculature 25 (2019)

Gradi di severità delle ir-AE

- basso grado (1-2)
- Alto grado (3-4)
- Letali (5)

L'incidenza e il tipo di organo interessato varia a seconda del tipo di immunoterapico (CTLA4 vs PD1) e della monoterapia/terapia di combinazione.

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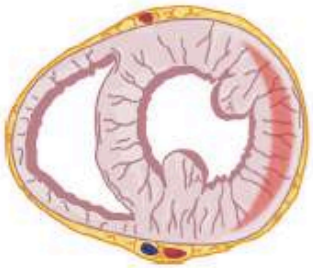
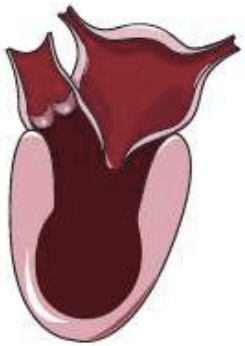
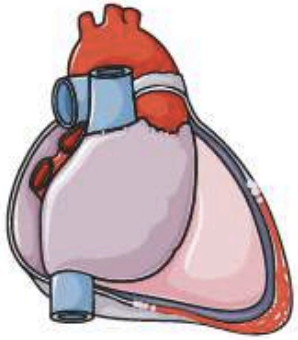
L. Michel et al. / IJC Heart & Vasculature 25 (2019)







	Myocarditis	Takotsubo syndrome	ACS	Pericardial disease
Diagnosis	• ECG • Echocardiography including strain analysis • Troponin, NT-proBNP • Chest X-ray • CMR	• Echocardiography • Troponin, NT-proBNP • CMR • Exclusion of ACS according to ESC and AHA guidelines	• ECG • Troponin • Diagnostic algorithm according to ESC and AHA guidelines	• Echocardiography • CMR • Evaluation of myocarditis • Cardiac fluid pathology • Monitor pericardial effusion
	0.09→1.14%	14%	?	13.6%
Treatment	• Stop ICI therapy permanently • Prednisone adapted to severity (up to 1 g daily) • No response: consider mycophenolate mofetil, infliximab, antithymocyte globulin	• Stop ICI therapy initially • Prednisone 1 g daily • Avoid QT-prolonging drugs	• Treatment according to ESC and AHA guidelines • Stop ICI therapy initially • Consider ICI therapy rechallenge >30 days in stable patient • Consider prednisone in case of coronary vasculitis	• Pericardiocentesis when indicated • Stop ICI therapy initially • 500-1000 mg prednisone daily • Consider colchicin, NSAIDs • Consider ICI therapy rechallenge after recovery

L. Michel et al. / IJC Heart & Vasculature 25 (2019)

Miocardite immuno-relata

-La miocardite ha una prevalenza di 0.09% fino a 1.14% ed ha una elevata letalità: 27→46%

-Di solito si verifica nella prima fase della terapia: 17-34 giorni dall'inizio.

-Meccanismo fisiopatologico sconosciuto, ma verosimilmente dovuto alla produzione di anticorpi (non ritrovati però nel sangue).

-più frequente in ipilimumab + nivolumab che in monoterapia.

L. Michel et al. / IJC Heart & Vasculature 25 (2019)

Miocardite immuno-relata

- L'unico fattore predisponente evidenziato è il diabete.
- Spesso è associata ad altre manifestazioni come la miastenia, epatite, miosite
- Sintomo più comune: dispnea ingravescente, edemi, alterazioni ECG.
- EcoTT con evidenza di EF <50%, troponina T HS elevata.

L. Michel et al. / IJC Heart & Vasculature 25 (2019)

Miocardite immuno-relata

- Valutazione cardiologica di base con EcoTT, Rx torace, e una valutazione aggiuntiva a 4 settimane può essere positiva, specialmente nei pazienti che ricevono combinazione di immunoterapia (raccomandazione ASCO)
- Diagnosi: RM cardiaca-eventuale biopsia endomiocardica.
- Terapia: cortisonici (es 1 g prednisone/die), in caso di mancata risposta eventuale aggiunta di tacrolimus/micofenolato mofetile.
- La terapia standard non ha dimostrato efficacia nella miocardite ICI relata; ACEi+ BB per sintomi di scompenso ma effetto protettivo non provato.

L. Michel et al. / IJC Heart & Vasculature 25 (2019)

Rare immune-related toxicities

Cardiac toxicity

ESMO GUIDELINES 2018

Summary of recommendations	
Circumstances	Cardiac side effects have been reported to occur after treatment with ipilimumab, pembrolizumab and nivolumab and the incidence is higher with the combination of ipilimumab and nivolumab compared with nivolumab alone
Management	• Early consultation with a cardiologist is recommended • High-dose corticosteroids should be instituted rapidly if ICPi-induced cardiac side effects are suspected • Escalation to other immunosuppressive drugs, such as infliximab, MMF and ATG, is recommended if symptoms do not respond promptly to steroids

- In caso di miocardite le linee guida ASCO: sospensione permanente nei gradi elevati, mentre ci sono pareri discordanti riguardo al rechallenge nei gradi lievi (solo movimento troponina asintomatico/ pauci-sintomatico).

Tossicità ICPi

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ASCO SPECIAL ARTICLE

Management of Immune-Related Adverse Events in Patients

9.0 Cardiovascular Toxicities
9.1 Myocarditis, pericarditis, arrhythmias, impaired ventricular function with heart failure and vasculitis
Definition: Signs and symptoms may include chest pain, arrhythmia, palpitations, peripheral edema, progressive or acute dyspnea, pleural effusion, fatigue
Diagnostic work-up
At baseline
ECG
Consider troponin, especially in patient treated with combination immune therapies
Upon signs/symptoms (consider cardiology consult)
ECG
Troponin
BNP
Echocardiogram
CXR
Additional testing to be guided by cardiology and may include
Stress test
Cardiac catherization
Cardiac MRI

Grading
G1: Abnormal cardiac biomarker testing, including abnormal ECG
G2: Abnormal screening tests with mild symptoms
G3: Moderately abnormal testing or symptoms with mild activity
G4: Moderate to severe decompensation, IV medication or intervention required, life-threatening conditions

Management
All grades warrant work-up and intervention given potential for cardiac compromise
Consider the following:
Hold ICPi and permanently discontinue after G1
High-dose corticosteroids (1-2 mg/kg of prednisone) initiated rapidly (oral or IV depending on symptoms)
Admit patient, cardiology consultation
Management of cardiac symptoms according to ACC/AHA guidelines and with guidance from cardiology
Immediate transfer to a coronary care unit for patients with elevated troponin or conduction abnormalities
In patients without an immediate response to high-dose corticosteroids, consider early institution of cardiac transplant rejection doses of corticosteroids (methylprednisolone 1 g every day) and the addition of either mycophenolate, infliximab, or antithymocyte globulin

Anti BRAF e anti MEK

Cardiovascular Effects of the MEK Inhibitor, Trametinib: A Case Report, Literature Review, and Consideration of Mechanism

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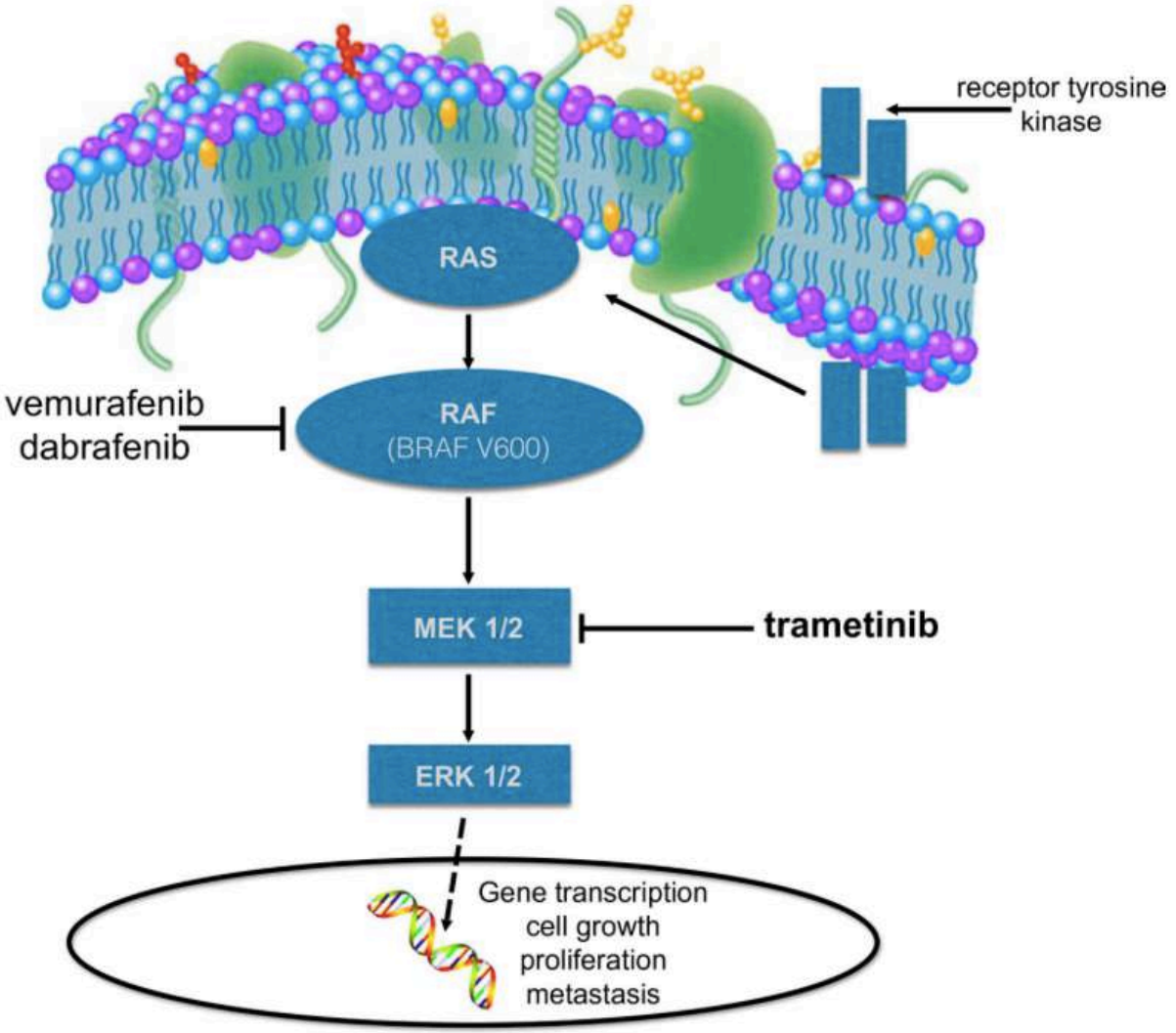
Anti BRAF e anti MEK



Cardiovasc Toxicol. 2017 October ; 17(4): 487–493

Anti BRAF e anti MEK

Summary oftrametinib-associated cardiovascular toxicity in clinical trials

References	Regimen	Cardiac events	Incidence (%)	Subjects treated
[3]	Trametinib and gemcitabine	Decreased EF	3	31
[16]	Trametinib	Decreased EF	7	97
[19]	Trametinib	Decreased EF	3	97
[17]	Trametinib and gemcitabine	Cardiac-related events	3	160
[9]	Trametinib	Decreased EF	7	214
[12]	Trametinib and dabrafenib	Decreased EF	8	350
[13]	Trametinib and dabrafenib	Decreased EF	4	209
[9]	Trametinib	HTN	15	214
[12]	Trametinib and dabrafenib	HTN	26	350
[13]	Trametinib and dabrafenib	HTN	22	209
[23]	Trametinib and afuresertib	HTN	15	20

Cardiovasc Toxicol. 2017 October ; 17(4): 487–493

Meccanismo di cardiotossicità

MEK1-ERK2 Signaling Pathway Protects Myocardium From Ischemic Injury In Vivo

Daniel J. Lips, BS; Orlando F. Bueno, MD, PhD; Benjamin J. Wilkins, BS; Nicole H. Purcell, PhD; Robert A. Kaiser, PhD; John N. Lorenz, PhD; Laure Voisin, PhD; Marc K. Saba-El-Leil, PhD; Sylvain Meloche, PhD; Jacques Pouysségur, PhD; Gilles Pagès, PhD; Leon J. De Windt, PhD; Pieter A. Doevendans, MD; Jeffery D. Molkentin, PhD

Teoria del "doppio colpo": ipertensione+ danno ossidativo

Gestione della cardiotossicità

discontinuation of therapy. The degree of left ventricular dysfunction can range from asymptomatic changes, best diagnosed by echocardiographic strain analysis, to severe cardiac failure. Although BRAFi+MEKi were not included in the European Society for Medical Oncology guidelines on cardiotoxicity, the guideline outlines the diagnostic procedures including cardiac MRI and multigated acquisition scans.[68]

Grade ≥3 decrease in ejection fraction (ie, <40% or decrease of >20% from baseline) was reported in 4%, 2% and 1% in D+T, V+C, and E+B, respectively (table 2). Myocardial dysfunction is modified by genetic factors and impaired myocardial function before initiating cancer treatment, arterial hypertension, >65 years of age, body mass index >30 kg/m^2 and radiotherapy increase the risk. The onset of left ventricular dysfunction after application of MEKi or BRAFi+MEKi therapy ranges from 2 weeks to 5 months and 1–13 months, respectively, and resolved in the majority of cases.[61]

Review

EK inhibitor
vent evaluation

Fluck,[3] Jessica C Hassel,[4]
auschinger,[7] Arndt Vogel,[8]

ng L, et al. ESMO Open 2019

iotossicità

Test	Therapy start	Monthly control	Quarterly control
Blood count			
Differential blood count	x	x	
Clinical chemistry			
Electrolytes (Na, K, Ca, Mg)	x	x	
Creatinine	x	x	
CPK	x	x	
Troponin	x	(x)†	
NT-proBNP	x	(x)†	x
Liver transaminases (AST, ALT, γ-GT)	x	x	
Bilirubin	x	x	
Examinations (non-laboratory tests)			
Skin inspection	x	x‡	x
Visual acuity control §	x	(x)¶	
Ocular OCT		(x)¶	
Blood pressure	x	x	
ECG	x	x‡	
Echocardiography	x		(x)†

†In case of clinically abnormal signs (eg, heart, chest) or increasing CPK.

†In case of clinically abnormal signs (eg, heart, chest) or increasing CPK.

Heinzerling L, et al. ESMO Open 2019