# Cardiovascular Toxicity of Cancer Therapy

Todd S. Perlstein, MD MMSc. Tri-City Cardiology. August 17, 2024.

# Cancer Therapy-Related Cardiac Dysfunction (CRTCD)

Journal of the American Heart Association

SPECIAL REPORT

# Cardiovascular Toxicity Related to Cancer Treatment: A Pragmatic Approach to the American and European Cardio-Oncology Guidelines

Joachim Alexandre, MD, PhD*; Jennifer Cautela, MD*; Stéphane Ederhy, MD; Ghandi Laurent Damaj, MD, PhD; Joe-Elie Salem, MD, PhD; Fabrice Barlesi, MD, PhD; Laure Farnault, MD, PhD; Aude Charbonnier, MD; Mariana Mirabel, MD, PhD; Stéphane Champiat, MD, PhD; Alain Cohen-Solal, MD, PhD; Ariel Cohen, MD, PhD; Charles Dolladille, MD; Franck Thuny, MD, PhD

American Cancer Society

cancer.org | 1.800.227.2345

# How Chemotherapy Drugs Work

Cancer cells tend to **form new cells more quickly than normal cells** and this makes them a **better target** for chemotherapy drugs. However, **chemo drugs can't tell the difference between healthy cells and cancer cells**. This means normal cells are damaged along with the cancer cells, and this causes side effects. Each time chemo is given, it means trying to find a balance between killing the cancer cells (in order to cure or control the disease) and sparing the normal cells (to lessen side effects).

# Chemotherapy Classes, Mechanisms, Toxicities

| Class | Representatives | Mechanism of Action | Toxicity |
|---|---|---|---|
| Alkylating Agents | Carboplatin | Bomb the DNA!!! | Leukemia |
| Antimetabolites | 5-Flourouracil, Gemcitabine | Impersonate the building blocks of DNA!!! | Epithelial annihilation endothelial inflammati |
| Anthracyclines | Doxorubicin (Adriamycin) | Sabotage the replication of DNA!!! | Cardiomyopathy |
| Mitotic Inhibitors | Vincristine | Prevent cell division!!! | Neuropathy |

In normal cells, **hundreds of genes intricately control the process of cell division.** Normal growth requires a balance between the activity of those genes that promote cell proliferation and those that suppress it. It also relies on the activities of genes that signal when damaged cells should undergo apoptosis.

**Cells become cancerous after mutations accumulate** in the various genes that control cell proliferation. According to research findings from the Cancer Genome Project, most cancer cells possess 60 or more mutations. The challenge for medical researchers is to identify **which of these mutations are responsible** for particular kinds of cancer.

Adverse events affecting the cardiovascular system are one of the greatest challenges in the overall management of patients with cancer, as they can compromise the success of the optimal treatment against the tumor.

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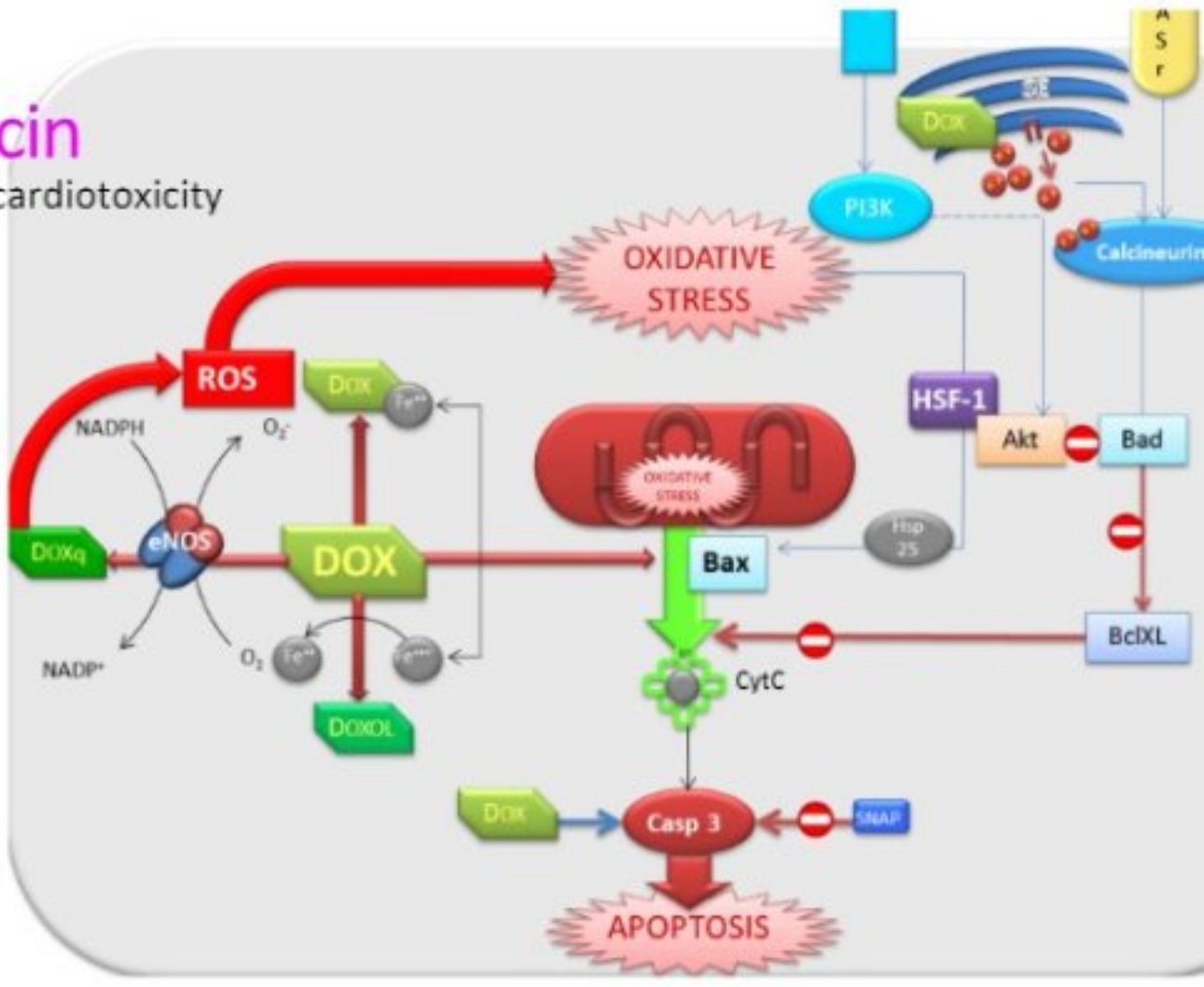
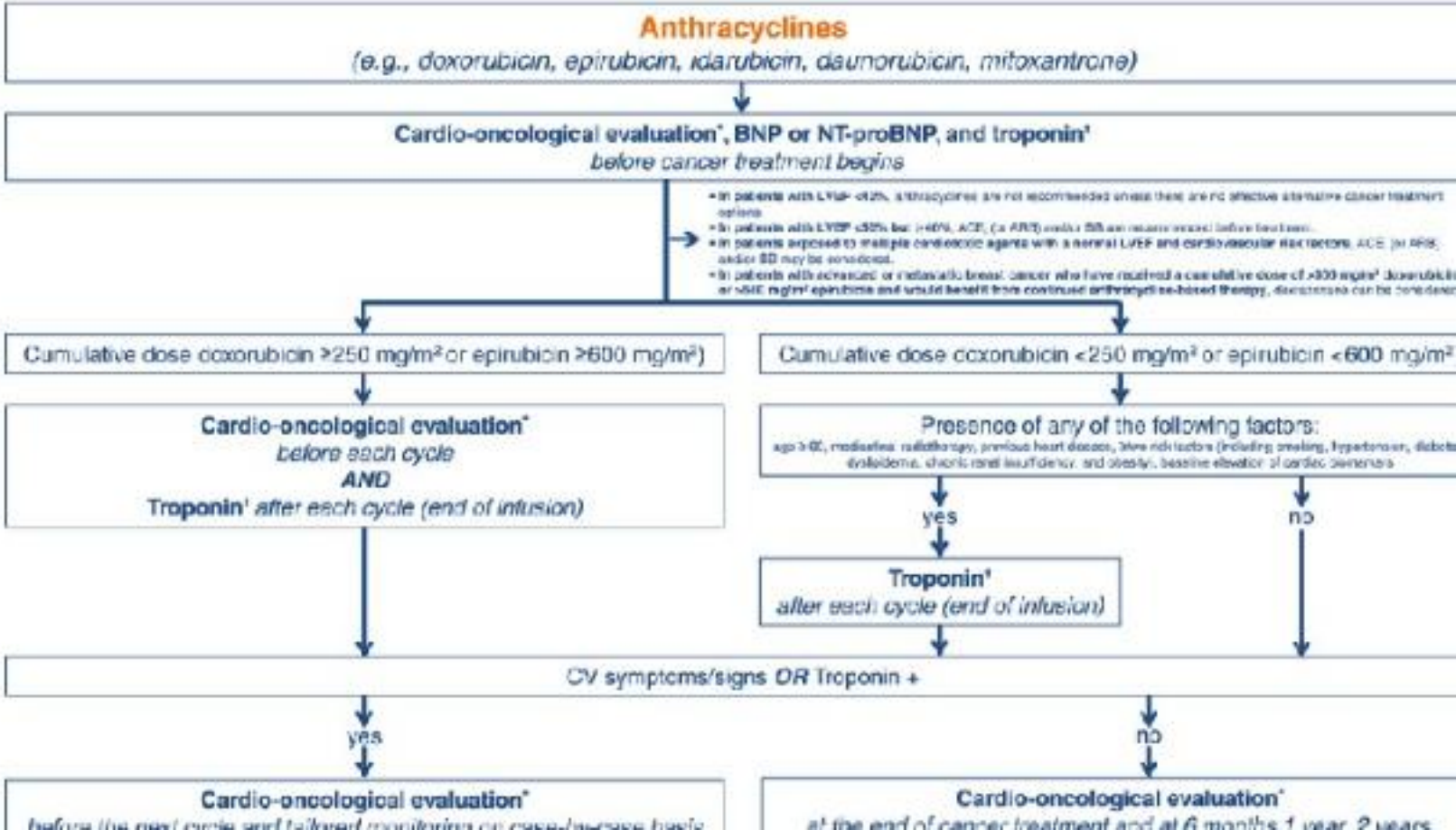
Volume 9, Number 18

# Adriamycin

Classic chemotherapy cardiotoxicity

- Alkylating agent
- Widely used multiple cancer types
- Dose >=250 mg/m2 high risk of cardiomyopathy
- Damage is irreversible




Anthracyclines
(e.g., doxorubicin, epirubicin, idarubicin, daunorubicin, mitoxantrone)
Cardio-oncological evaluation*, BNP or NT-proBNP, and troponin†
before cancer treatment begins
Cumulative dose doxorubicin >250 mg/m² or epirubicin >600 mg/m²)
Cumulative dose doxorubicin <250 mg/m² or epirubicin <600 mg/m²
Cardio-oncological evaluation*
before each cycle
AND
Troponin† after each cycle (end of infusion)
Presence of any of the following factors:
yes
no
Troponin†
after each cycle (end of infusion)
CV symptoms/signs OR Troponin +
yes
no
Cardio-oncological evaluation*

# Adriamycin Cardiotoxicity Management

- Do not give if moderate LV dysfunction (LVEF <40%)
- Recommend ACEi/ARB and BB if mild LV dysfunction (LVEF 40-49%) or multiple risk factors for CVD (or known CAD)
- If high-risk dose (>= 250 mg/m2); Intensive cardiac surveillance (e.g. serial ECHO, EKG and troponin)
- If low-risk dose (< 250 mg/m2); Moderate cardiac surveillance (e.g. serial troponin)

# Initial evaluation of patients receiving cardiotoxic therapy

- Clinical consultation (including BP measurement)
- ECG
- Blood glucose,* lipid profile,* glomerular filtration rate calculation
- Cardiovascular global risk assessment using guidelines
- TTE including measurements of LVEF measurements (ideally 3-dimensional but at least 2-dimensional Simpson biplane method) and GLS. In the absence of GLS quantification of LV longitudinal function, use mitral annular displacement by M-mode echocardiography and/or peak systolic velocity of the mitral annulus by pulsed-wave DT
- LV contrast agents could be potentially useful in 2-dimensional echochardiography
- CMR is recommended if the quality of TTE is suboptimal
- Use the same imaging modality for monitoring
- Actively manage modifiable cardiovascular risk factors and diseases
- Encourage exercise on a regular basis and healthy dietary habits

Journal of the American Heart Ass
Volume 9, Number 18

# Initial evaluation of patients receiving cardiotoxic therapy

- Baseline cardiovascular risk is strongest predictor of CRTCD (cancer therapy-related cardiac dysfunction)

- **Carefully assess LV systolic function in a precise and repeatable manner; ECHO LVEF is NOT good enough (e.g. strain imaging, pulsed-wave tissue Doppler, cardiac MRI)**

- Optimal management of cardiovascular risk reduces risk of CRTCD

# Newer Cancer Therapies Are Targeted

- Cell surface receptors
- Cell signaling mechanisms
- Cell protein degradation pathways
- Target consequence of mutation unique to cancer cells
- OR, specifically target malignant pathogenesis in a manner less blunt then attacking DNA

- **Immunotherapy**: Activate immune system to attack cancer cells

The New England
Journal of Medicine



VOLUME 344 MARCH 15, 2001 NUMBER 11

# USE OF CHEMOTHERAPY PLUS A MONOCLONAL ANTIBODY AGAINST HER2 FOR METASTATIC BREAST CANCER THAT OVEREXPRESSES HER2

DENNIS J. SLAMON, M.D., PH.D., BRIAN LEYLAND-JONES, M.D., STEVEN SHAK, M.D., HANK FUCHS, M.D., VIRGINIA PATON, PHARM.D., ALEX BAJAMONDE, PH.D., THOMAS FLEMING, PH.D., WOLFGANG EIERMANN, M.D., JANET WOLTER, M.D., MARK PEGRAM, M.D., JOSE BASELGA, M.D., AND LARRY NORTON, M.D.*

## ABSTRACT

***Background*** The *HER2* gene, which encodes the growth factor receptor HER2, is amplified and HER2 is overexpressed in 25 to 30 percent of breast cancers, increasing the aggressiveness of the tumor.

***Methods*** We evaluated the efficacy and safety of

DESPITE advances in the diagnosis and treatment of breast cancer, more than 44,000 women in the United States will die this year of metastatic disease.[1,2] Although objective responses to some chemotherapy regimens are common, few patients with metastatic

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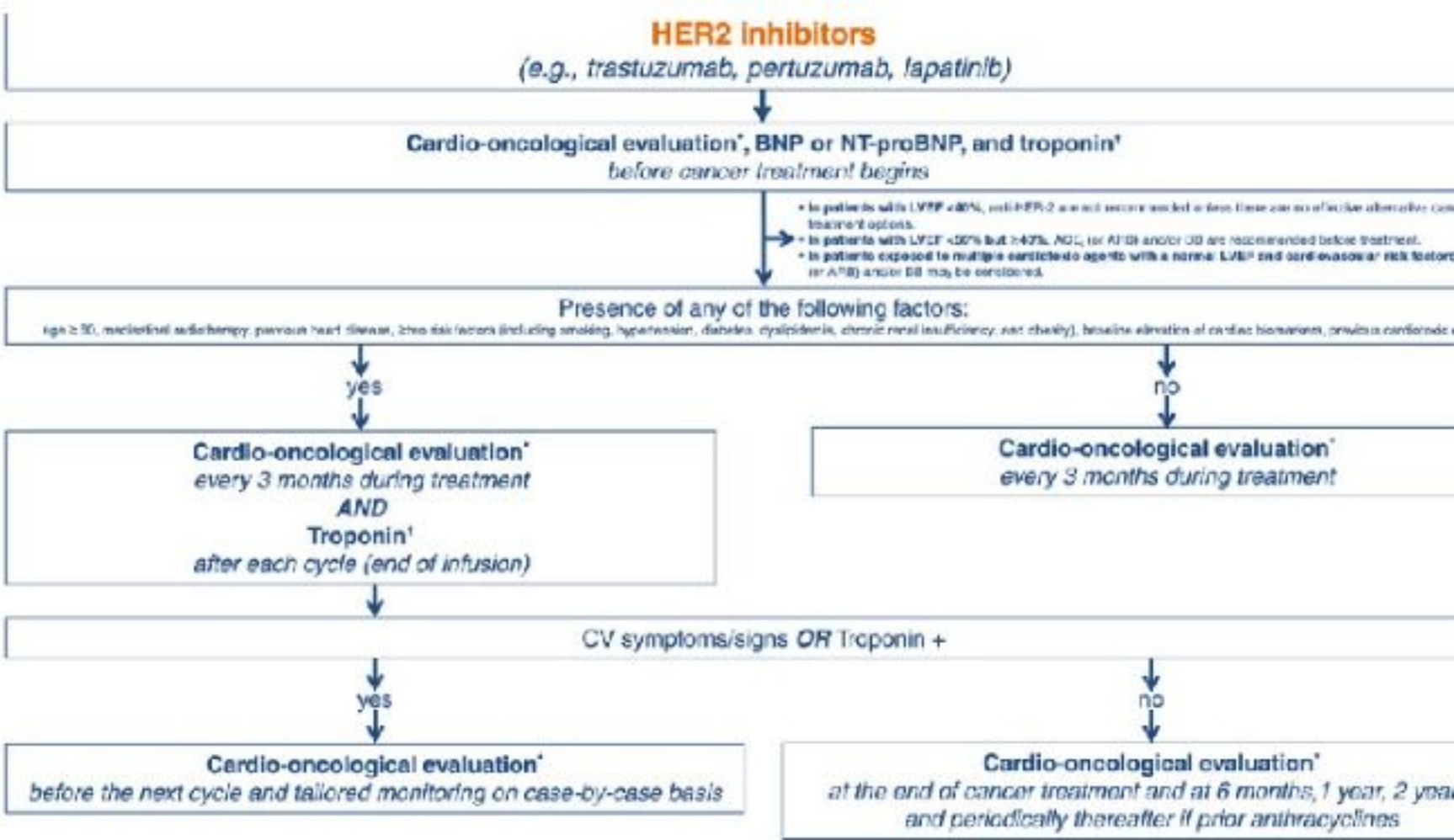
# Herceptin (Trastuzamab) HER2i In Metastatic Breast Cancer

- Improved disease response rate by 18%
- Improved 1-year survival by 11%
- **27% rate of cardiac dysfunction** in anthracycline/trastuzamab treated patients (higher than anthracycline alone)
- **16% rate of NYHA Class III/IV heart failure**
- Only 1 death due to cardiac dysfunction
- Only 3% had HF refractory to medical therapy


HER2 inhibitors
(e.g., trastuzumab, pertuzumab, lapatinib)
Cardio-oncological evaluation*, BNP or NT-proBNP, and troponin†
before cancer treatment begins
Presence of any of the following factors:
yes
no
Cardio-oncological evaluation*
every 3 months during treatment
AND
Troponin†
after each cycle (end of infusion)
Cardio-oncological evaluation*
every 3 months during treatment
CV symptoms/signs OR Troponin +
yes
no
Cardio-oncological evaluation*
before the next cycle and tailored monitoring on case-by-case basis
Cardio-oncological evaluation*
at the end of cancer treatment and at 6 months, 1 year, 2 year
and periodically thereafter if prior anthracyclines

# HER2i Cardiotoxicity Management

## Key Points

- Do not give if moderate LV dysfunction (LVEF <40%)
- Recommend ACEi/ARB and BB if mild LV dysfunction (LVEF 40-49%) or risk factors for CVD
- If high-risk (radiotherapy, multiple risk factors); Intensive cardiac surveillance (e.g. serial ECHO, EKG and troponin) q 3 months
- If low-risk; Moderate cardiac surveillance (e.g. serial clinical exam)

The New England
Journal of Medicine



VOLUME 344 APRIL 5, 2001 NUMBER 14

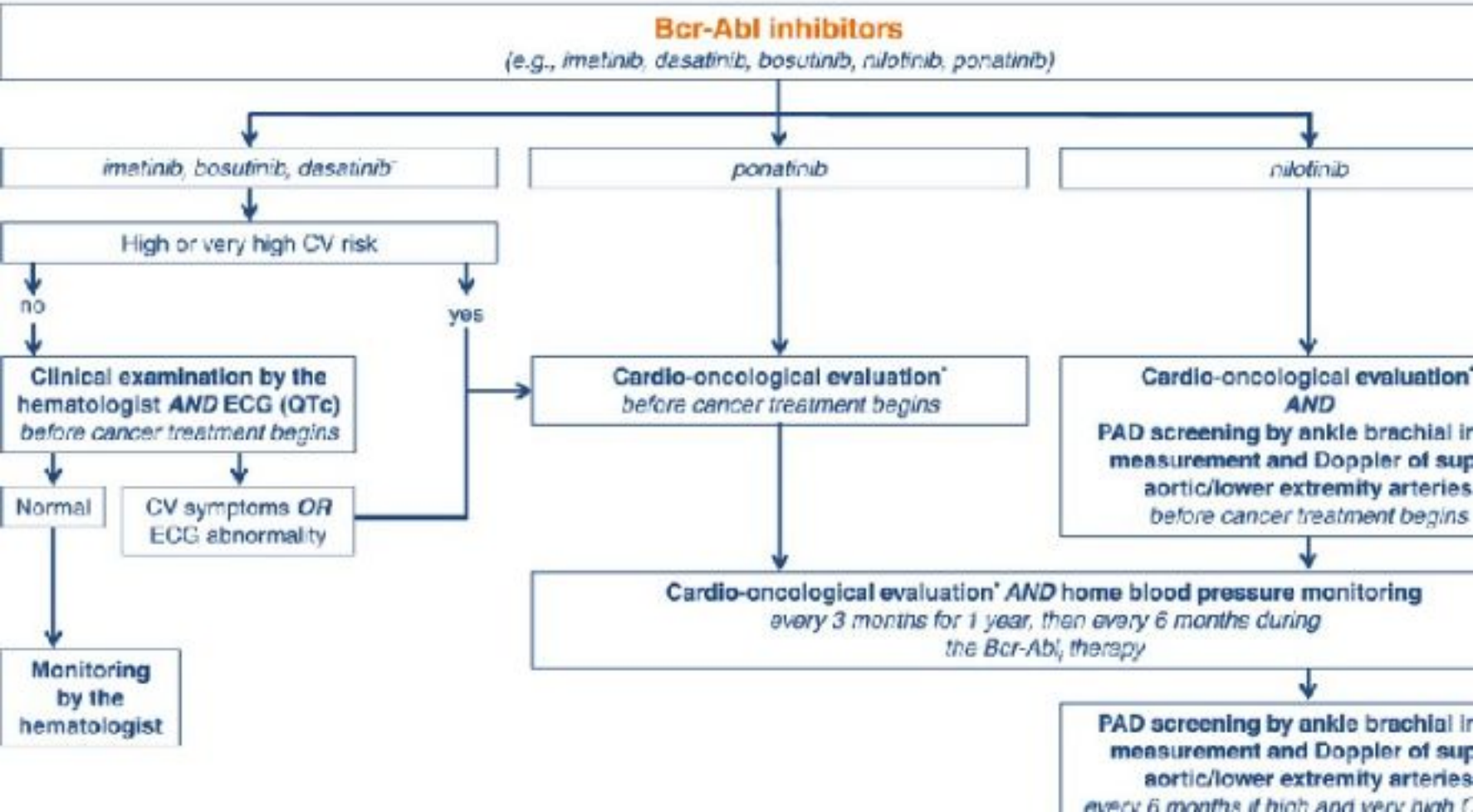
# EFFICACY AND SAFETY OF A SPECIFIC INHIBITOR OF THE BCR-ABL TYROSI KINASE IN CHRONIC MYELOID LEUKEMIA

BRIAN J. DRUKER, M.D., MOSHE TALPAZ, M.D., DEBRA J. RESTA, R.N., BIN PENG, PH.D., ELISABETH BUCHDUNGER, P
JOHN M. FORD, M.D., NICHOLAS B. LYDON, PH.D., HAGOP KANTARJIAN, M.D., RENAUD CAPDEVILLE, M.D.,
SAYURI OHNO-JONES, B.S., AND CHARLES L. SAWYERS, M.D.

# Imatinib (Gleevec) BCR-ABL TKi in CML

- Enrolled if treatment with Interferon-alpha had failed
- Complete hematological response in 53/54 patients treated with >= 300 mg

- A subsequent 5-year study of 553 patients showed a 87% sustained response rate
- 60% rate of peripheral or periorbital edema,
- <1% incidence of CHF, cardiomyopathy, **predicted by baseline CV risk**


Bcr-Abl inhibitors
(e.g., imatinib, dasatinib, bosutinib, nilotinib, ponatinib)
imatinib, bosutinib, dasatinib
ponatinib
nilotinib
High or very high CV risk
no
yes
Clinical examination by the hematologist AND ECG (QTc)
before cancer treatment begins
Normal
CV symptoms OR ECG abnormality
Monitoring by the hematologist
Cardio-oncological evaluation*
before cancer treatment begins
Cardio-oncological evaluation*
AND
PAD screening by ankle brachial in
measurement and Doppler of sup
aortic/lower extremity arteries
before cancer treatment begins
Cardio-oncological evaluation* AND home blood pressure monitoring
every 3 months for 1 year, then every 6 months during
the Bcr-Abl therapy
PAD screening by ankle brachial in
measurement and Doppler of sup
aortic/lower extremity arteries
every 6 months if high and very high

# BCR-ABL TKi Cardiotoxicity Management

- Imatinib (Gleevec); Low risk of cardiotoxicity, serial cardiac surveillance if high risk for CVD

  *Malignant cells can develop mutations that confer resistance to Imatinib

- Ponatinib (Iclusig); Arterial thrombotic events up to 25%, Venous thrombotic events up to 12%, heart failure events up to 13%, severe hypertension up to 14%, pleural or pericardial effusion 4-10%, serious arrhythmia 4%,
- Peripheral artery disease—ABI q 6 months!!!
- Nilotinib (Tasigna); Prolongs QT interval, requires serial EKG. Other CV risks similar to Ponatinib.

ORIGINAL ARTICLE

# Ibrutinib as Initial Therapy for Patients with Chronic Lymphocytic Leukemia

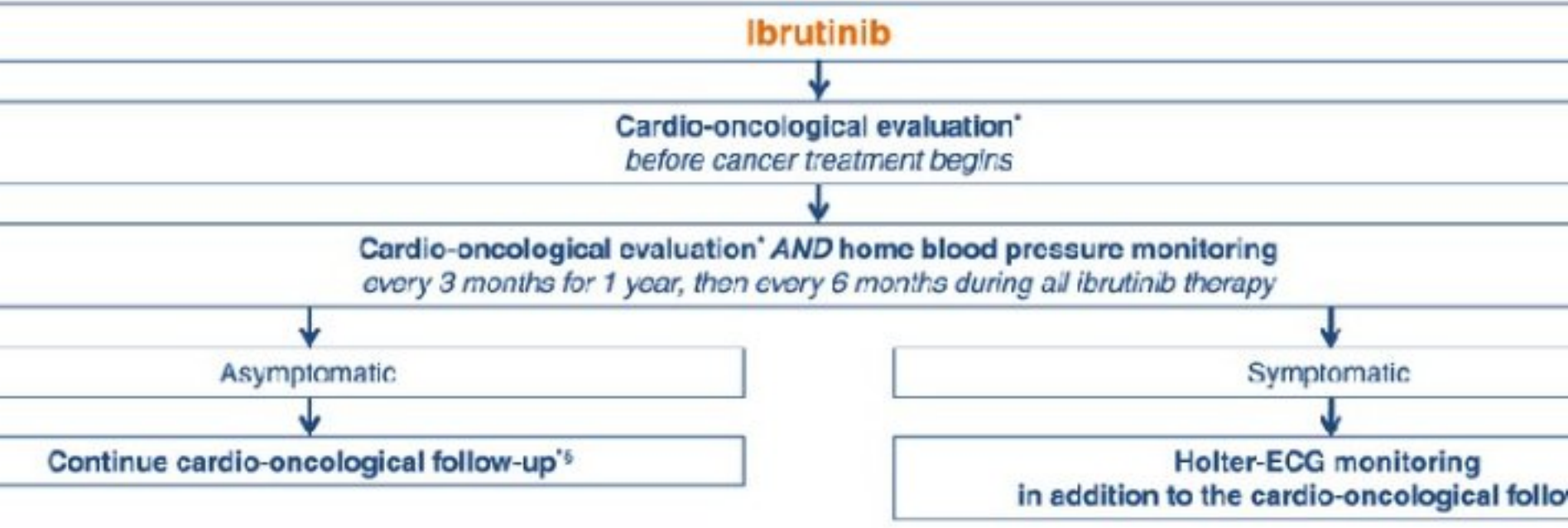
J.A. Burger, A. Tedeschi, P.M. Barr, T. Robak, C. Owen, P. Ghia, O. Bairey, P. Hillmen, N.L. Bartlett, J. Li, D. Simpson, S. Grosicki, S. Devereux, H. McCarthy, S. Coutre, H. Quach, G. Gaidano, Z. Maslyak, D.A. Stevens, A. Janssens, F. Offner, J. Mayer, M. O'Dwyer, A. Hellmann, A. Schuh, T. Siddiqi, A. Polliack, C.S. Tam, D. Suri, M. Cheng, F. Clow, L. Styles, D.F. James, and T.J. Kipps, for the RESONATE-2 Investigators*

N Engl J Med 2015;373:2425

# Ibrutinib (Imbruvica) in CLL

- Inhibits Bruton's tyrosine kinase
- 2-year survival 98% versus 85%
- Response rate 86% versus 35%


- Hemorrhage (28%), Hypertension (20%), Atrial fibrillation (12%)
- About 1% excess risk of severe arrhythmia, heart failure, stroke


Ibrutinib
Cardio-oncological evaluation*
before cancer treatment begins
Cardio-oncological evaluation* AND home blood pressure monitoring
every 3 months for 1 year, then every 6 months during all ibrutinib therapy
Asymptomatic
Symptomatic
Continue cardio-oncological follow-up*§
Holter-ECG monitoring
in addition to the cardio-oncological follo

# Targeting Unique Cancer Pathways Not Mutation Based

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 3, 2004 VOL. 350 NO. 23

# Bevacizumab plus Irinotecan, Fluorouracil, and Leucovorin for Metastatic Colorectal Cancer

Herbert Hurwitz, M.D., Louis Fehrenbacher, M.D., William Novotny, M.D., Thomas Cartwright, M.D., John Hainsworth, M.D., William Heim, M.D., Jordan Berlin, M.D., Ari Baron, M.D., Susan Griffing, B.S., Eric Holmgren, Ph.D., Napoleone Ferrara, M.D., Gwen Fyfe, M.D., Beth Rogers, B.S., Robert Ross, M.D., and Fairooz Kabbinavar, M.D.

## ABSTRACT

**BACKGROUND**

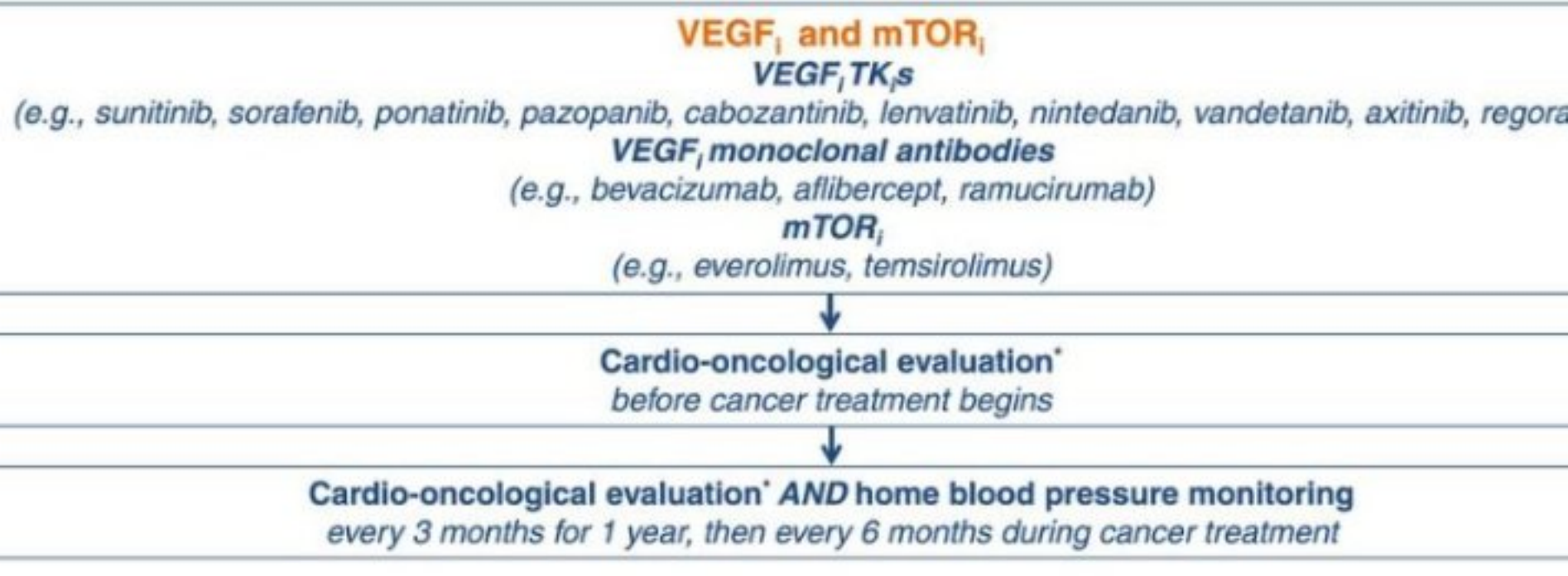
Bevacizumab, a monoclonal antibody against vascular endothelial growth factor, has

From Duke University, Durham, N.C.

# Bevacizumab (Avastin) VEGFi In Metastatic Colorectal Cancer

- Median survival 20.3 months compared to 15.6 months
- Cancer response rates 44.8% compared to 34.8%

- Grade III hypertension 11.3% versus 2.0% (easily treated)
- 3% increased risk of thrombotic events (P=NS)
- VEGFi associated with 2-4% (Bevacizum**ab**) or 3-8% (TKIs (e.g. Sunitinib)) rate of CHF
- **Prior CAD confers 17-fold increased risk of CHF**


VEGF$_i$ and mTOR$_i$
VEGF$_i$ TK$_i$s
(e.g., sunitinib, sorafenib, ponatinib, pazopanib, cabozantinib, lenvatinib, nintedanib, vandetanib, axitinib, regora
VEGF$_i$ monoclonal antibodies
(e.g., bevacizumab, aflibercept, ramucirumab)
mTOR$_i$
(e.g., everolimus, temsirolimus)
Cardio-oncological evaluation*
before cancer treatment begins
Cardio-oncological evaluation* AND home blood pressure monitoring
every 3 months for 1 year, then every 6 months during cancer treatment

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

# Bortezomib or High-Dose Dexamethasone for Relapsed Multiple Myeloma

Paul G. Richardson, M.D., Pieter Sonneveld, M.D., Michael W. Schuster, M.D., David Irwin, M.D., Edward A. Stadtmauer, M.D., Thierry Facon, M.D., Jean-Luc Harousseau, M.D., Dina Ben-Yehuda, M.D., Sagar Lonial, M.D., Hartmut Goldschmidt, M.D., Donna Reece, M.D., Jesus F. San-Miguel, M.D., Joan Bladé, M.D., Mario Boccadoro, M.D., Jamie Cavenagh, M.D., William S. Dalton, M.D., Anthony L. Boral, M.D., Ph.D., Dixie L. Esseltine, M.D., Jane B. Porter, M.S., David Schenkein, M.D., and Kenneth C. Anderson, M.D., for the Assessment of Proteasome Inhibition for Extending Remissions (APEX) Investigators*

# Bortezomib Proteasome Inhibition in Relapsed Multiple Myeloma

- 38% versus 18% response rates
- 1-year survival 80% versus 66%

- Infrequent cardiovascular events

- Additional trials of proteasome inhibitors in multiple myeloma, 1-2% excess cardiovascular event rates including HF, MI, HTN

**Proteasome inhibitors**

*(e.g., bortezomib, carfilzomib, ixazomib)*

↓

**Cardio-oncological evaluation* *AND* BNP or NT-proBNP‡**

*before cancer treatment begins*

↓

**Cardio-oncological evaluation* *AND* home blood pressure monitoring, BNP or NT-proBNP**

*every 3 months for 1 year, then every 6 months during all proteasome inhibitors therapy*

# Immunotherapy: Immune Checkpoint Inhibitors

- Immune checkpoints are cell surface receptors that can inhibit immune response
- Immune checkpoint inhibtors boost antitumor immune response via activating T lymphocytes
- Blockade of PD-1/PD-L1 and CTLA-4 molecules
- “Unleash the immune system”

- Has revolutionized treatment of several cancers including melanoma and renal cancer

# Immunotherapy: Immune Checkpoint Inhibitors

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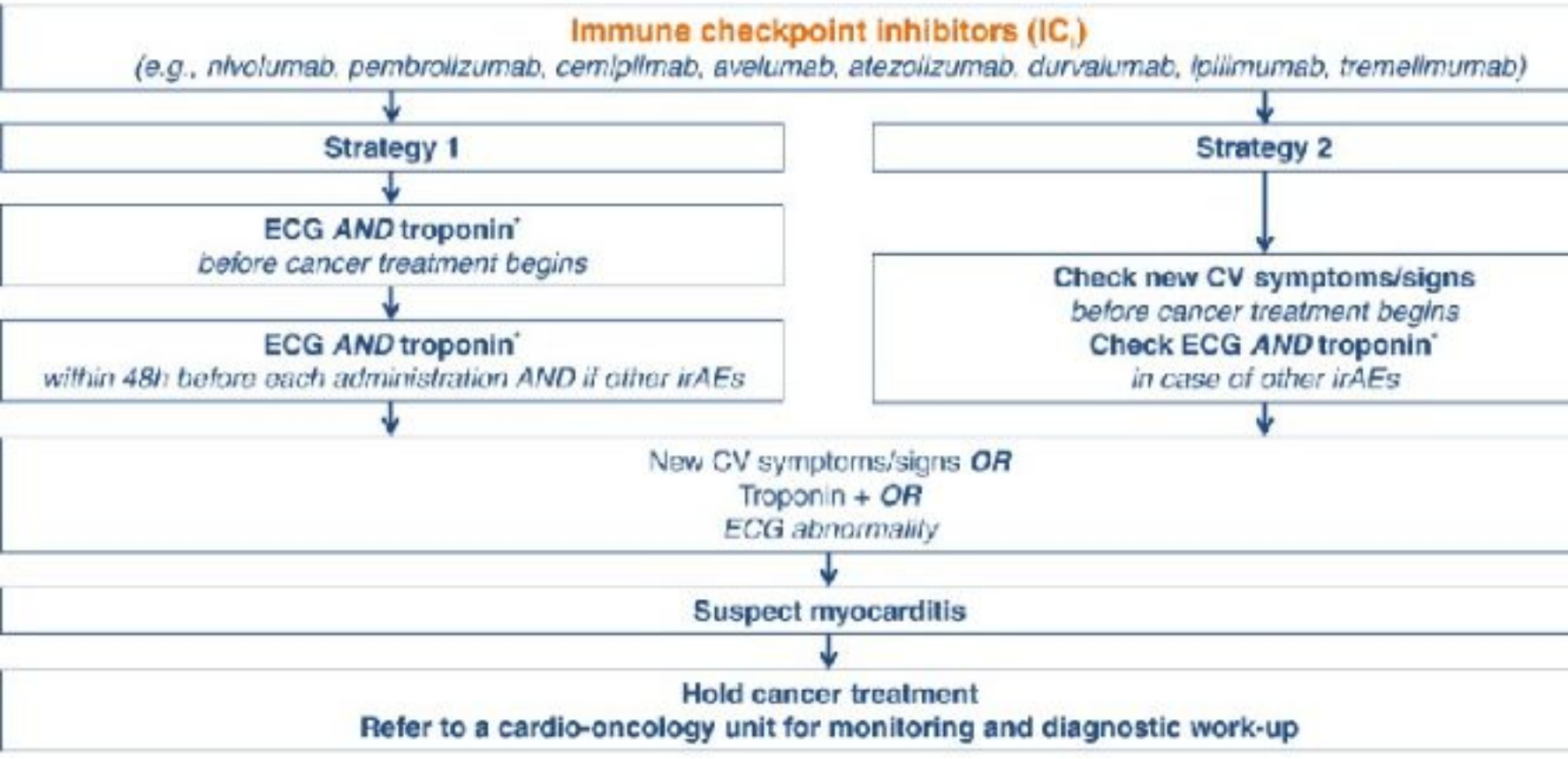
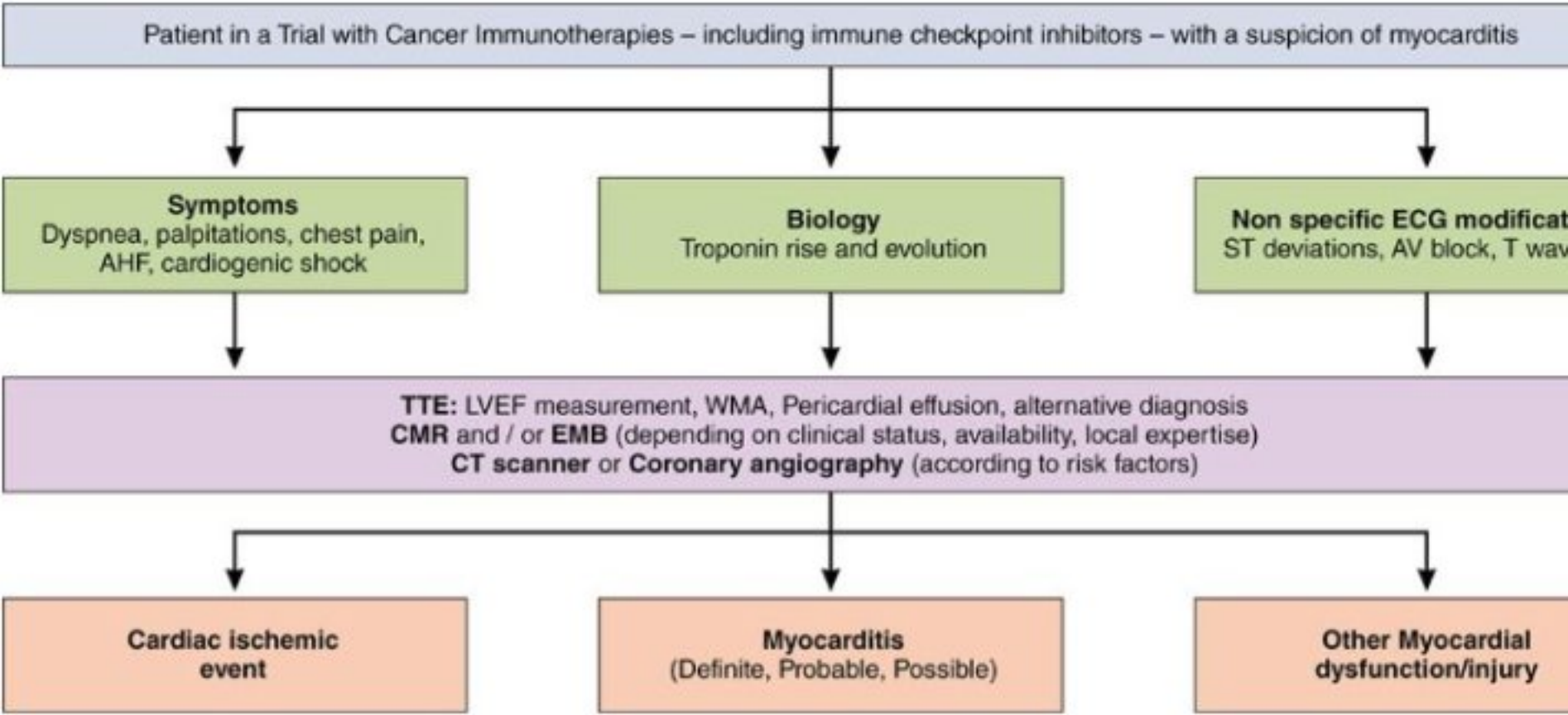
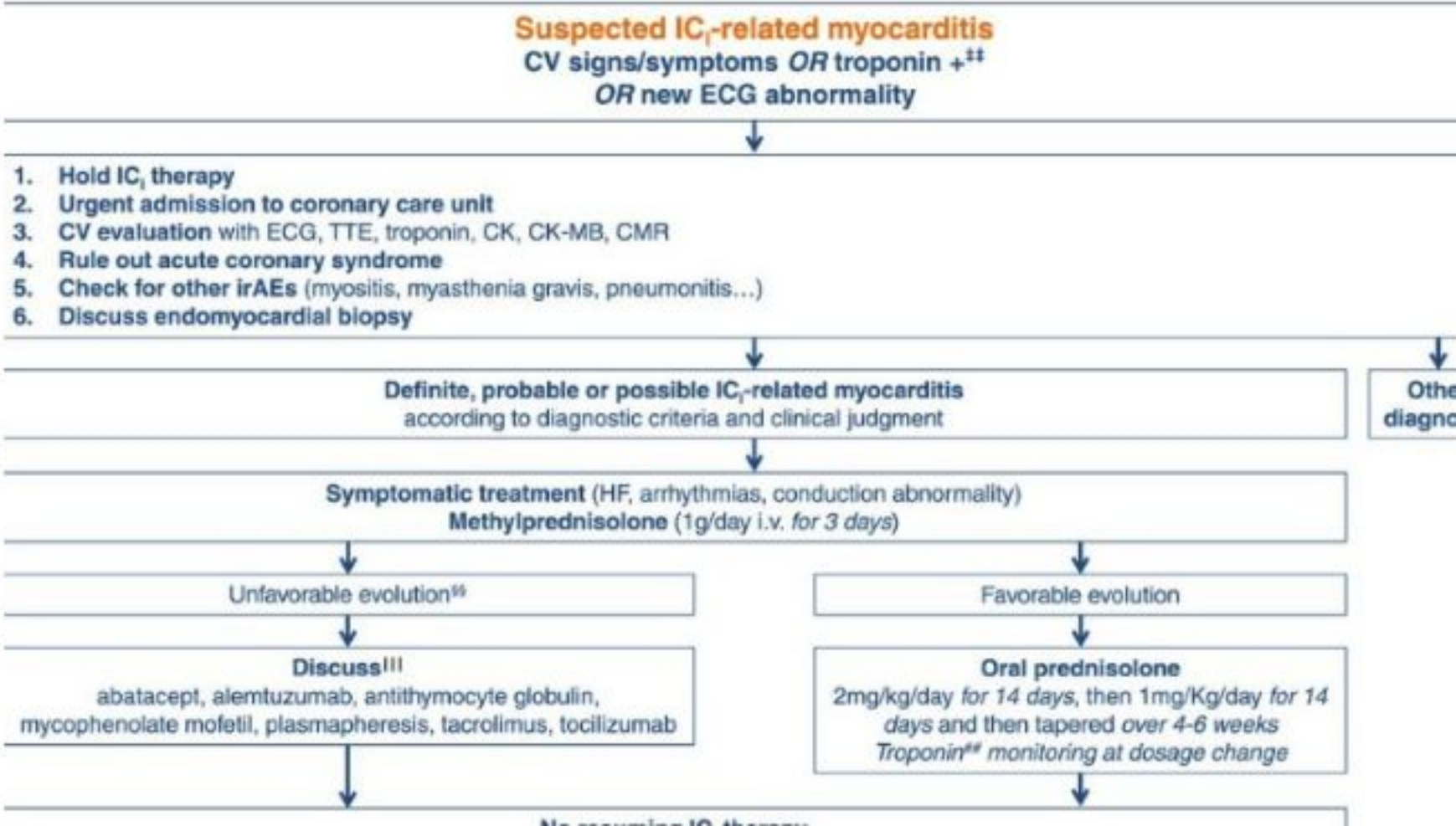
- Immune checkpoint inhibtors boost antitumor immune response via activating T lymphocytes
- Blockade of PD-1/PD-L1 and CTLA-4 molecules
- "Unleash the immune system"

- Acute, fulminant myocarditis up to 1% incidence
- Severe pneumonitis


Immune checkpoint inhibitors (ICI)
(e.g., nivolumab, pembrolizumab, cemiplimab, avelumab, atezolizumab, durvalumab, ipilimumab, tremelimumab)
Strategy 1
Strategy 2
ECG AND troponin*
before cancer treatment begins
ECG AND troponin*
within 48h before each administration AND if other irAEs
Check new CV symptoms/signs
before cancer treatment begins
Check ECG AND troponin*
in case of other irAEs
New CV symptoms/signs OR
Troponin + OR
ECG abnormality
Suspect myocarditis
Hold cancer treatment
Refer to a cardio-oncology unit for monitoring and diagnostic work-up

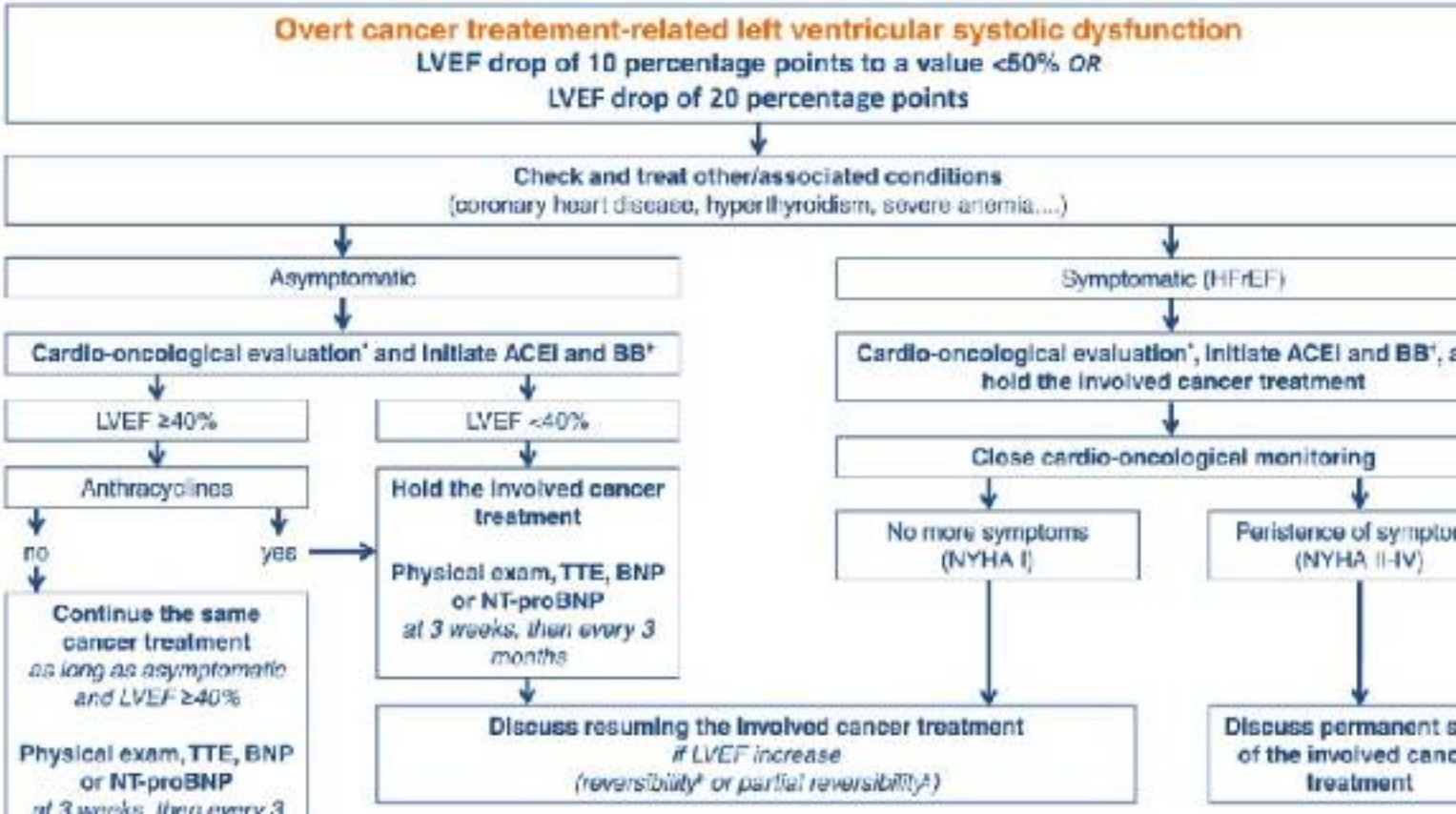
If a patient receiving immunotherapy (immune-checkpoint inhibitor) presents with symptoms and signs of acute MI or acute heart failure, suspect myocarditis, discontinue ICI, begin high-dose steroids immediately, while performing standard cardiac evaluation (e.g. cardiac catheterization).


Patient in a Trial with Cancer Immunotherapies – including immune checkpoint inhibitors – with a suspicion of myocarditis
Symptoms
Dyspnea, palpitations, chest pain, AHF, cardiogenic shock
Biology
Troponin rise and evolution
Non specific ECG modificat
ST deviations, AV block, T wav
TTE: LVEF measurement, WMA, Pericardial effusion, alternative diagnosis
CMR and / or EMB (depending on clinical status, availability, local expertise)
CT scanner or Coronary angiography (according to risk factors)
Cardiac ischemic event
Myocarditis
(Definite, Probable, Possible)
Other Myocardial dysfunction/injury

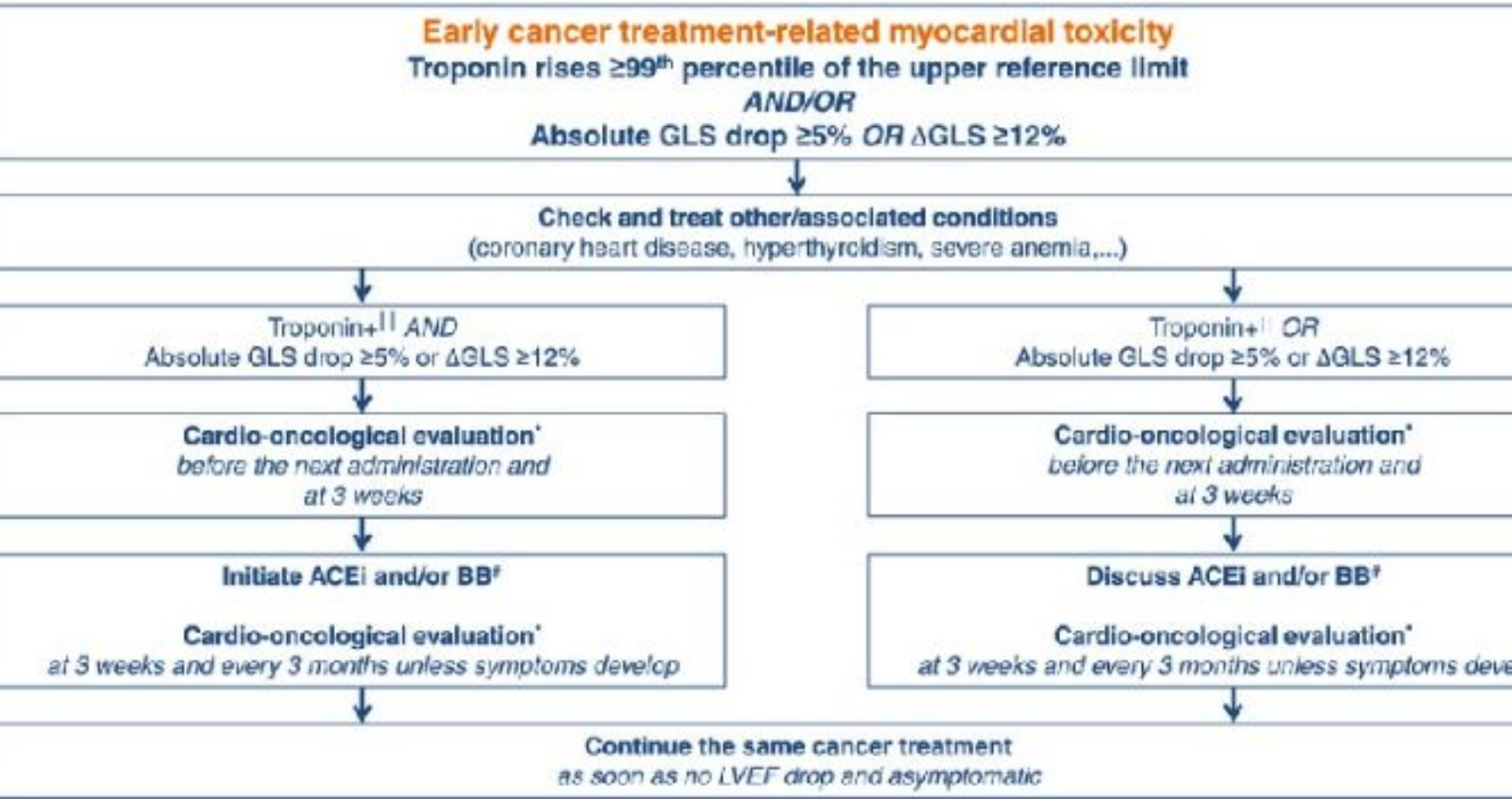

Suspected IC$_i$-related myocarditis
CV signs/symptoms *OR* troponin +‡‡
*OR* new ECG abnormality
1. Hold IC$_i$ therapy
2. Urgent admission to coronary care unit
3. CV evaluation with ECG, TTE, troponin, CK, CK-MB, CMR
4. Rule out acute coronary syndrome
5. Check for other irAEs (myositis, myasthenia gravis, pneumonitis…)
6. Discuss endomyocardial biopsy
Definite, probable or possible IC$_i$-related myocarditis
according to diagnostic criteria and clinical judgment
Othe
diagnc
Symptomatic treatment (HF, arrhythmias, conduction abnormality)
Methylprednisolone (1g/day i.v. *for 3 days*)
Unfavorable evolution§§
Favorable evolution
Discuss¶¶
abatacept, alemtuzumab, antithymocyte globulin,
mycophenolate mofetil, plasmapheresis, tacrolimus, tocilizumab
Oral prednisolone
2mg/kg/day *for 14 days*, then 1mg/Kg/day *for 14 days* and then tapered *over 4-6 weeks*
*Troponin‡‡ monitoring at dosage change*

# Patients at higher risk of cardiotoxicity

- High-dose anthracycline (eg, doxorubicin ≥250 mg/m2)
- High-dose radiotherapy (≥30 Gy) where the heart is in the treatment field
- Lower-dose anthracycline (eg, doxorubicin <250 mg/m2) or HERi or VEGFi or proteasomei or Bcr-Abli and presence of any of the following factors:
  - Age ≥60 y
  - Lower-dose radiotherapy (<30 Gy) where the heart is in the treatment field
  - ≥2 Risk factors, including smoking, hypertension, diabetes mellitus, dyslipidemia, chronic renal insufficiency, and obesity•
- Previous heart disease
- Elevated cardiac biomarkers* before initiation of anticancer therapy


Overt cancer treatement-related left ventricular systolic dysfunction
LVEF drop of 10 percentage points to a value <50% OR
LVEF drop of 20 percentage points
Check and treat other/associated conditions
(coronary heart disease, hyperthyroidism, severe anemia....)
Asymptomatic
Symptomatic (HFrEF)
Cardio-oncological evaluation* and initiate ACEI and BB*
Cardio-oncological evaluation*, initiate ACEI and BB*, a
hold the involved cancer treatment
LVEF ≥40%
LVEF <40%
Close cardio-oncological monitoring
Anthracyclines
no
yes
Hold the involved cancer treatment
Physical exam, TTE, BNP or NT-proBNP
at 3 weeks, then every 3 months
No more symptoms (NYHA I)
Persistence of symptom
(NYHA II-IV)
Continue the same cancer treatment
as long as asymptomatic and LVEF ≥40%
Physical exam, TTE, BNP or NT-proBNP
Discuss resuming the involved cancer treatment
if LVEF increase
(reversibility* or partial reversibility*)
Discuss permanent s
of the involved canc
treatment

B


Early cancer treatment-related myocardial toxicity
Troponin rises ≥99th percentile of the upper reference limit
AND/OR
Absolute GLS drop ≥5% OR ΔGLS ≥12%
Check and treat other/associated conditions
(coronary heart disease, hyperthyroidism, severe anemia,...)
Troponin+ AND
Absolute GLS drop ≥5% or ΔGLS ≥12%
Troponin+ OR
Absolute GLS drop ≥5% or ΔGLS ≥12%
Cardio-oncological evaluation*
before the next administration and
at 3 weeks
Cardio-oncological evaluation*
before the next administration and
at 3 weeks
Initiate ACEi and/or BB#
Cardio-oncological evaluation*
at 3 weeks and every 3 months unless symptoms develop
Discuss ACEi and/or BB#
Cardio-oncological evaluation*
at 3 weeks and every 3 months unless symptoms deve
Continue the same cancer treatment
as soon as no LVEF drop and asymptomatic

# Summary

- Targeted cancer therapies have remarkable benefits, but present unique cardiovascular risks
- Individual patient risk by concurrent therapies and risk factor burden
- Precise and repeatable evaluation of LV systolic function (strain)
- Serial assessments, intensity by treatment risk and patient risk
- Optimal treatment of CV risk factors
- Use of cardiomyopathy medications in those at significant risk

# Summary

- Herceptin (Her2i): cardiomyopathy and heart failure
- Avastin (VEGFi): hypertension, thrombosis, heart failure
- Gleevec (BCR-ABL TKi): low CV risk, 2nd line agents (Tasigna) HIGH risk, various CV outcomes including PAD, pleural/pericardial effusions
- Bortezomib (Proteasome Inh): low rates of MI, HF, HTN
- Ibrutinib (Bruton TKI): hemorrhage, atrial fibrillation, hypertension
- Immunotherapy (checkpoint inhibitor): infrequent but severe myocarditis, pneumonitis

The End