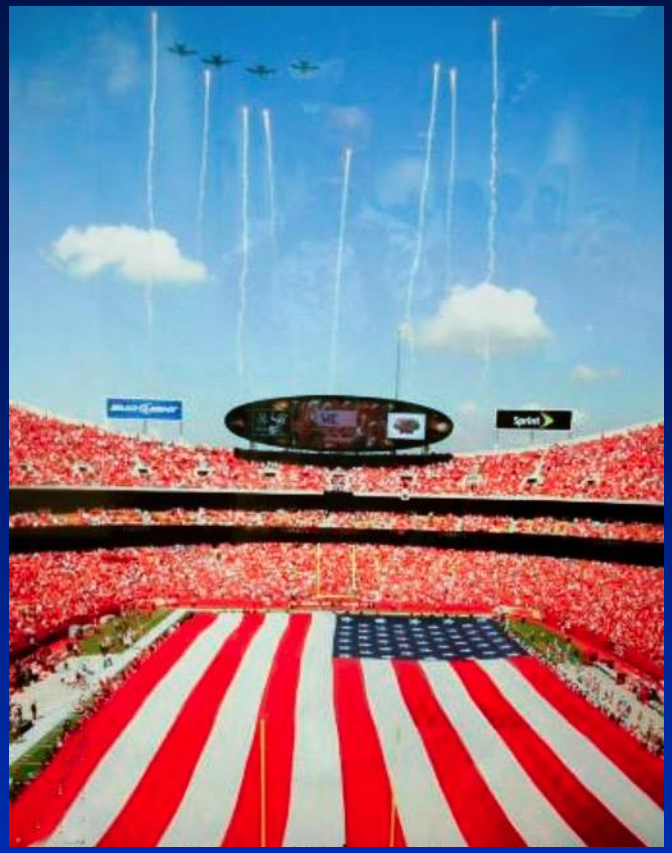
Kansas City Region
American Heart Association
Cardiac Symposium
November 7, 2019



A Cardiooncology Flyby

Charles B. Porter, MD

Medical Director Cardiooncology

University of Kansas Health System

cbporter@kumc.edu

No Conflict of Interest Disclosures

Will Discuss off label uses

THE UNIVERSITY OF KANSAS HOSPITAL

Goals for this presentation

KUH Cambridge Tower

- Maintain your attention
  - Send <2 texts
  - Check email <2x
  - No checking newsfeeds or Facebook
  - Twitter & Instagram 1x each about Conference
- Recall **3 facts** from this talk on Monday such as
  - New cancer therapies
  - New approaches to preventing/managing cardiac toxicities
  - CV risks in cancer survivors
  - Cardiac therapies in cancer patients
- Email your **3 facts** on Monday to cbporter@kumc.edu

CV Med Cardiooncology Team

Cardiooncology team:

cardiooncology@kumc.edu

Dawn Piper RN

Zubair Shah MD

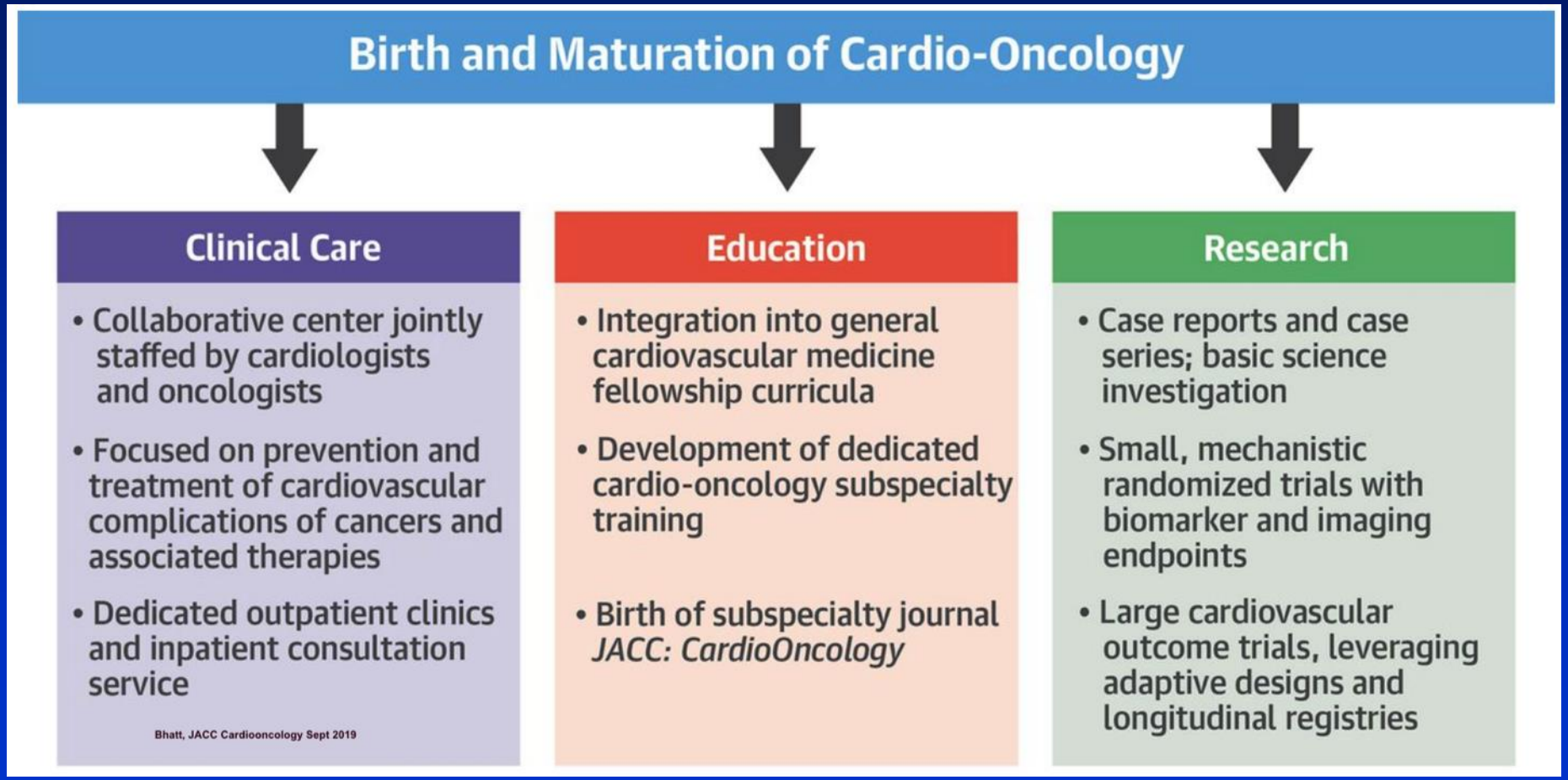
Jill Tibke APRN

Charles Porter MD, Medical Director

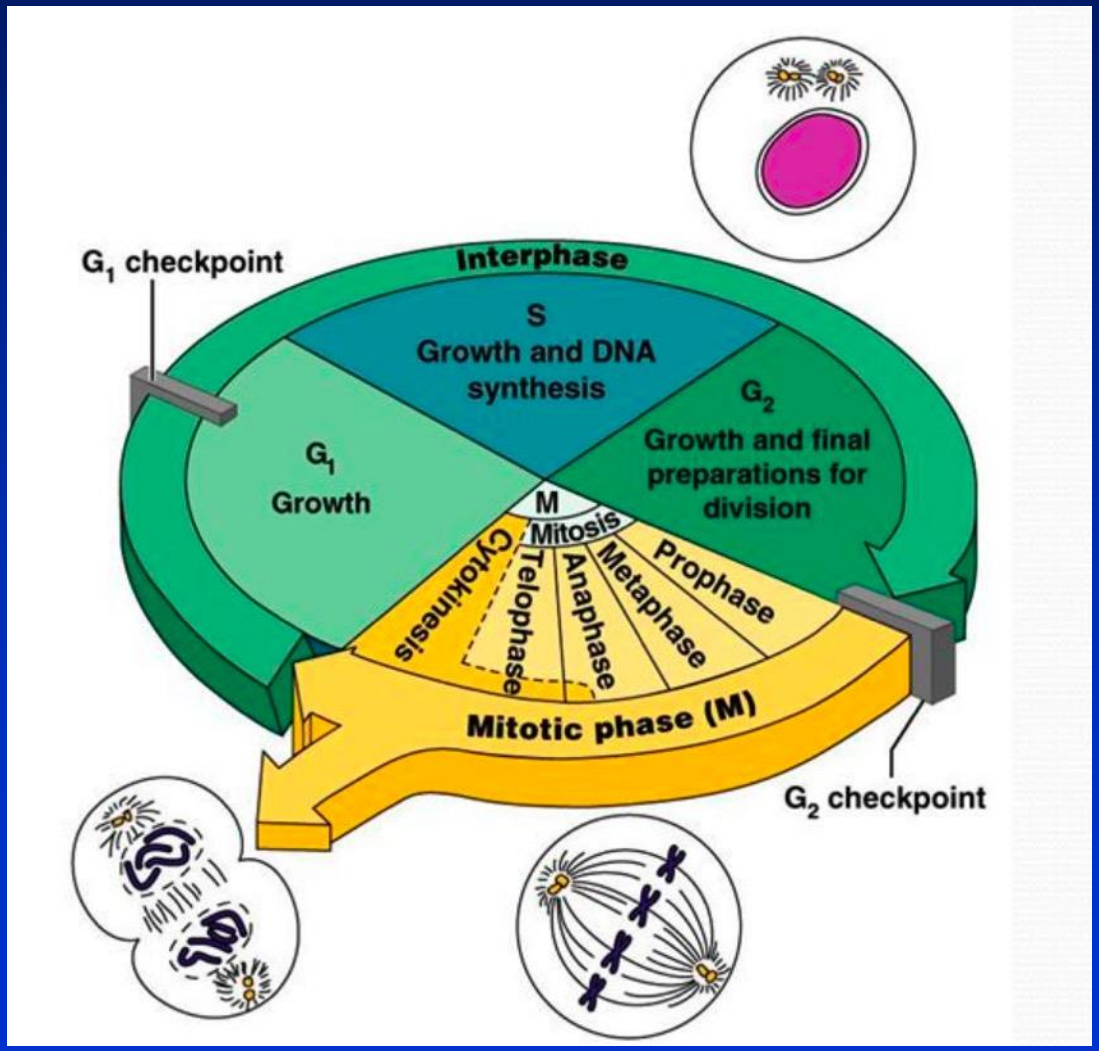
Coverage today

- Define cardiooncology
- Discuss
  - New cancer therapies that improve cancer survival but create new cardiac toxicities
  - Minimizing cardiac toxicities while optimizing cancer treatment outcomes: New and established therapies
  - Impact of cancer and cancer treatment on
  - Cardiovascular risk factors
  - CV prognosis
  - Assessing and managing CV risks and disease in cancer patients and survivors

Three Facets of Cardiooncology
Clinical Care, Education & Research



Clinical care starts with understanding Traditional Cancer Chemotherapy & Targeted therapies



Traditional Chemo:
Cancer cell growth interrupted at specific points in cell cycle along with healthy cells using same pathways create broad array of side effects related to inhibition of cell growth and recovery

Targeted therapies:
neutralize specific cell mutations that promote uncontrolled cell growth, invasion and metastasis

- Same mutation may promote carcinogenesis for different cancers

2005: Two Cardiotoxic chemo classes Anthracyclines (adriamycin/doxorubicin) and Anti-HER2 agents (Trastuzumab/Herceptin)

	Type I (myocardial damage)	Type II (myocardial dysfunction)
Characteristic agent	Doxorubicin	Trastuzumab
Clinical course, response to CRCD therapy	May stabilize, but underlying damage appears to be permanent and irreversible; recurrence in months or years may be related to sequential cardiac stress	High likelihood of recovery (to or near baseline cardiac status) in 2-4 months (reversible)
Dose effects	Cumulative, dose related	Not dose related
Mechanism	Free radical formation, oxidative stress/damage TopIIB Inhib	Blocked ErbB2 signaling
Ultrastructure	Vacuoles; myofibrillar disarray and dropout; necrosis (changes resolve over time)	No apparent ultra structural abnormalities
Noninvasive cardiac testing	Decreased ejection fraction by ultrasound or nuclear determination: global decrease in wall motion	Decreased ejection fraction by ultrasound or nuclear determination: global decrease in wall motion
Effect of rechallenge	High probability of recurrent dysfunction that is progressive, may result in intractable heart failure and death	Increasing evidence for the relative safety of rechallenge; additional data needed
Effect of late sequential stress	High likelihood of sequential stress related cardiac dysfunction	Low likelihood of sequential stress-related cardiac dysfunction

Abbreviation: CRCD, chemotherapy-related cardiac dysfunction.

Ewer & Lippmann, JCO May 2005

2019: Multiple classes of anti-cancer agents with cardiac and vascular toxicities

Table 1. Cancer Therapies, Cellular Targets, and Associated Cardiovascular Toxic Effects.* Moslehi NEJM Oct 13, 2016; 375:15

Class	Drug	Cellular Target	Common Cardiovascular Toxic Effects
Traditional cancer therapies			
Radiation	NA	NA	Myocardial ischemia, pericarditis, myocarditis, valvular heart disease, arrhythmia
Anthracyclines	Doxorubicin, daunorubicin, idarubicin, epirubicin, mitoxantrone	Type II topoisomerase, DNA and RNA synthesis	Cardiomyopathy, arrhythmia, acute myocarditis or pericarditis
Platinum	Cisplatin, carboplatin, oxaliplatin	Cross-link DNA	Hypertension, myocardial ischemia
Antimetabolites	Fluorouracil	Thymidylate synthase	Myocardial ischemia
	Capecitabine	Thymidylate synthase	Myocardial ischemia, arrhythmias
Alkylating agents	Cyclophosphamide	Cross-link DNA	Congestive heart failure, myocarditis, pericarditis
Antimicrotubule agents	Paclitaxel	Microtubule	Arrhythmias (including bradycardia, heart block, premature ventricular contractions, and ventricular tachycardia), thrombosis
	Vinca alkaloids	Microtubule	Myocardial ischemia, coronary spasm
Targeted cancer therapies			
HER2 inhibitors			
HER2 monoclonal antibody	Trastuzumab	HER2	Decline in LVEF, congestive heart failure
Newer HER2 inhibitors	Pertuzumab, trastuzumab emtansine, lapatinib	HER2	Decline in LVEF, congestive heart failure
VEGF signaling pathway inhibitors		VEGF signaling pathway	Hypertension, venous or arterial thromboembolic events, proteinuria, cardiomyopathy
VEGFA monoclonal antibody	Bevacizumab		
VEGF trap	Aflibercept		
VEGFR2 monoclonal antibody	Ramucirumab		
Tyrosine kinase inhibitor with anti-VEGF activity	Sunitinib, sorafenib, pazopanib, axitinib, vandetanib, regorafenib, cabozantinib, lenvatinib	VEGF receptors (mainly VEGFR2) and other kinases; PDGFR	
Multitargeted tyrosine kinase inhibitors	Dasatinib	ABL, ABL mutants (except T315I), and other kinases; SRC, KIT, PDGFR, EGFR, BRAF, DDR1, DDR2, ephrin receptors	Pulmonary hypertension, vascular events, prolongation of QT interval corrected for heart rate
	Nilotinib	ABL, ABL mutants (except T315I), and other kinases; ABL2 (also called ARG), KIT, DDR1, NQO2	Coronary, cerebral, and peripheral vascular events, hyperglycemia, prolongation of QT interval corrected for heart rate
	Ponatinib	ABL, ABL mutants (including T315I), and other kinases; FGFR, VEGFR, PDGFR, ephrin receptors, SRC, KIT, RET, TEK (also called TIE2), FLT3	Coronary, cerebral, and peripheral vascular events
Other multitargeted tyrosine kinase inhibitors			
Anaplastic lymphoma kinase inhibitors	Crizotinib, ceritinib	Anaplastic lymphoma kinase	Bradycardia, prolongation of QT interval corrected for heart rate
PI3K–AKT–mTOR inhibitors†	Everolimus, temsirolimus	PI3K–AKT–mTOR signaling pathway	Cardiometabolic toxic effects, including hypercholesterolemia, hypertriglyceridemia, hyperglycemia
Bruton's tyrosine kinase inhibitors	Ibrutinib	Bruton's tyrosine kinase	Atrial fibrillation, other arrhythmias
MEK inhibitors	Trametinib	MEK1, MEK2	Cardiomyopathy
Immunomodulatory drugs	Thalidomide, lenalidomide, pomalidomide	Lymphoid transcription factors IKZF1 and IZKF3	Venous or arterial thromboembolic events
Proteasome inhibitors	Bortezomib, carfilzomib	Ubiquitin–proteasome system	Cardiomyopathy, hypertension, venous or arterial thromboembolic events, arrhythmia
Immune checkpoint inhibitors	Pembrolizumab, nivolumab	Programmed cell death 1	Myocarditis
	Ipilimumab	CTLA4	Myocarditis

* CTLA4 denotes cytotoxic T-lymphocyte–associated protein 4, DDR discoidin domain receptor tyrosine kinase, FGFR fibroblast growth factor receptor, FLT3 fms-related tyrosine kinase 3, HER2 human epidermal growth factor receptor 2, IKZF IKAROS family zinc finger, LVEF left ventricular ejection fraction, MEK mitogen-activated protein kinase, mTOR mammalian (or mechanistic) target of rapamycin, NA not applicable, NQO2 NAD(P)H quinone dehydrogenase 2, PDGFR platelet-derived growth factor receptor, PI3K phosphatidylinositol 3-kinase, and VEGF vascular endothelial growth factor.
† Only two drugs targeting the PI3K–AKT–mTOR signaling pathway, everolimus and temsirolimus, which are mTOR complex 1 inhibitors, have been approved by the Food and Drug Administration. Many other inhibitors targeting this signaling pathway are currently in clinical trials.

TABLE 1 | Anticancer Therapies Associated With Vascular Side Effects.

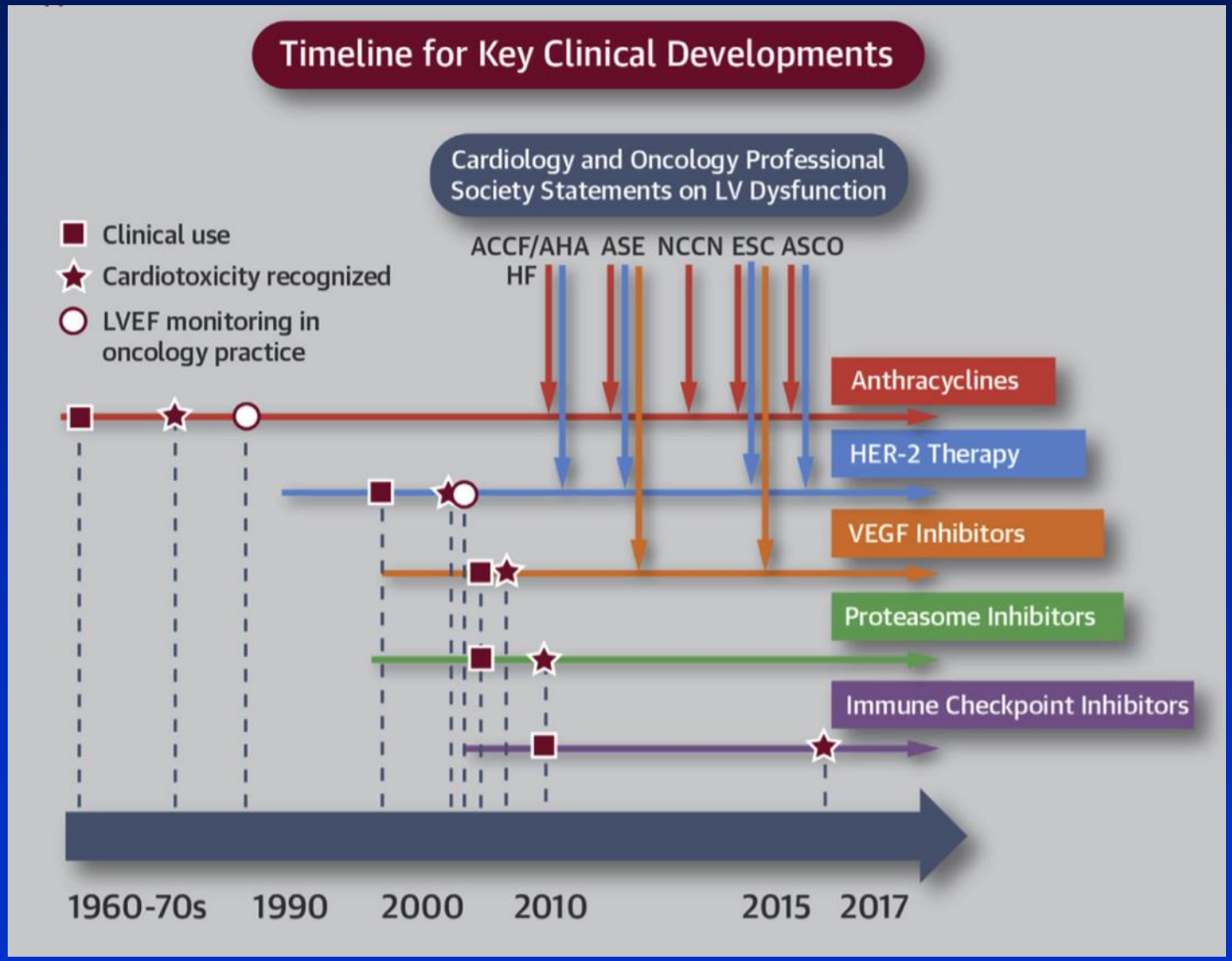
Chemotherapy Agents	Adverse Cardiovascular Effects	Possible Mechanism
Antimetabolites		
5-Fluorouracil	Angina, vasospasm, MI, SC	Vasospasm
Capecitabine	Angina, vasospasm, MI, SC	Vasospasm
Gemcitabine	Angina, vasospasm, MI	Vasospasm
Antimicrotubule agents		
Paclitaxel	Angina, vasospasm, MI	Vasospasm
Vinblastine (16, 79)	Angina, MI	Endothelial injury
Monoclonal antibody-based tyrosine kinase inhibitor		
Bevacizumab	Angina, MI, SC	Endothelial injury
Small molecule tyrosine kinase inhibitors		
Sorafenib	Angina, vasospasm, MI	Vasospasm
Sunitinib	Angina, MI, SC	Unknown
BCR-ABL targeted tyrosine-kinase inhibitors		
Nilotinib	Angina, MI, progression of CAD, PAD	Unknown
Ponatinib	Angina, MI, progression of CAD	Unknown
Hormone therapy		
Aromatase inhibitors (anastrozole, letrozole, exemestane)	Angina, MI	Unknown
Gonadotropin-releasing hormone agonists (goserelin)	Angina, MI	Unknown
Radiotherapy	Angina, MI, progression of CAD, PAD	Endothelial injury

MI indicates myocardial infarction; SC, stress-induced cardiomyopathy; CAD, coronary artery disease; PAD, peripheral artery disease.

Interventional Cardiooncology. Ilescu et ak Frontiers in CV Medicine May 2018

50 year timeline of Cardiotoxicity

2 drug families with echo surveillance recommendations: Anthracycliness & Anti HER2s



JACC HF
Feb, 2018

Development of Anthracyclines

- Derived from Italian soil streptomyces near Adriatic Sea
  - Area was near home of ancient Dauna tribe
  - Reddish (ruby) color
  - Hence names adriamycin, daunarubicin
- Daunorubicin (Daunomycin) First anthracycline developed
  - ALL, AML
- Adriamycin (Doxorubicin)
  - Breast, sarcomas, lung, ovarian, lymphoma, Wilms, GI
- Epirubicin
  - Breast, Gastric, Carcinoid, Ovarian, Esophageal, Soft Sarcoma
- Idarubicin (4-demethoxyDaunorubicin) : AML
- Valrubicin: Bladder

Daunomycin* introduced 1967 with concerns about cardiotoxicity

DAUNOMYCIN, AN ANTITUMOR ANTIBIOTIC, IN THE TREATMENT OF NEOPLASTIC DISEASE

Clinical Evaluation with Special Reference to Childhood Leukemia

CHARLOTTE TAN, MD, HIDEKO TASAKA, MD, KOU-PING YU, MD, M. LOIS MURPHY, MD, AND DAVID A. KARNOFSKY, MD

Cancer 1967;20:333

Daunomycin is a new antibiotic in the anthracycline group obtained from Streptomyces peucetius. It consists of a pigmented aglycone (daunomycinone) in glycoside linkage with an amino sugar (daunosamine). Differences in the biological effects of daunomycin, which reacts with DNA, and actinomycin D which complexes with DNA in a different manner to inhibit RNA production, are discussed. The toxic effects of daunomycin are a severe local reaction if the drug extravasates, bone marrow depression resulting in leucopenia, anemia, thrombocytopenia and bleeding, fever, oral ulcers and alopecia. In patients receiving maintenance doses of daunomycin the development of tachypnea, tachycardia pulmonary insufficiency, heart failure and hypotension possibly is associated with daunomycin but the evidence is unclear. Sixty per cent of children with leukemia obtained brief complete or partial hematological remissions from a single course of daunomycin. The remission could be prolonged by maintenance therapy. Daunomycin is temporarily effective in some cases of neuroblastoma, reticulum cell sarcoma and rhabdomyosarcoma.

1967: 60% tumor response was major breakthrough in ALL

Cardiotoxicity: "The Evidence is Unclear"

*Daunomycin=Daunorubicin

1973: 1st focused report on anthracycline cardiotoxicity

Pathology accurate, Safe dose overestimated

- 399 treated patients, 11 acute HF, 8 deaths all within 3 weeks of onset of HF
- Dose Dependent: 0.27% HF <550mg/M^{2}BSA, 30%>550
- EKG: Loss of voltage, CXR: Pulmonary edema, *No Echoes*, Microscopy: Cardiomyocyte vacuolization
- Safe dose <500mg/m^{2}BSA

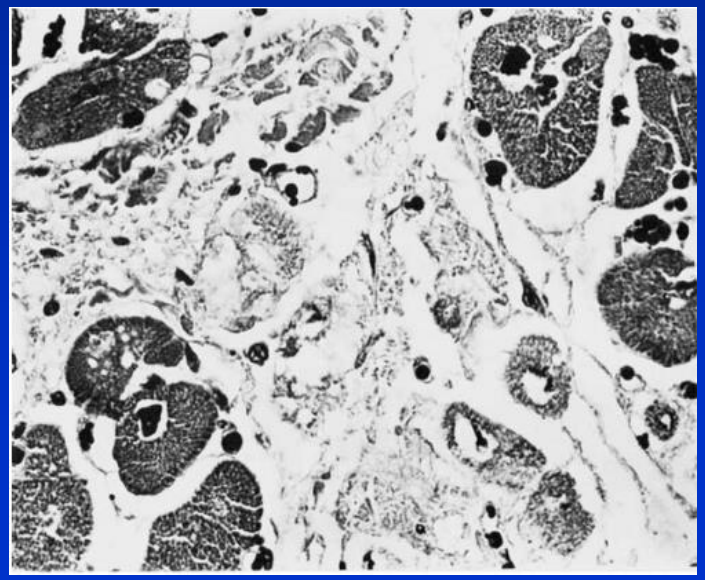
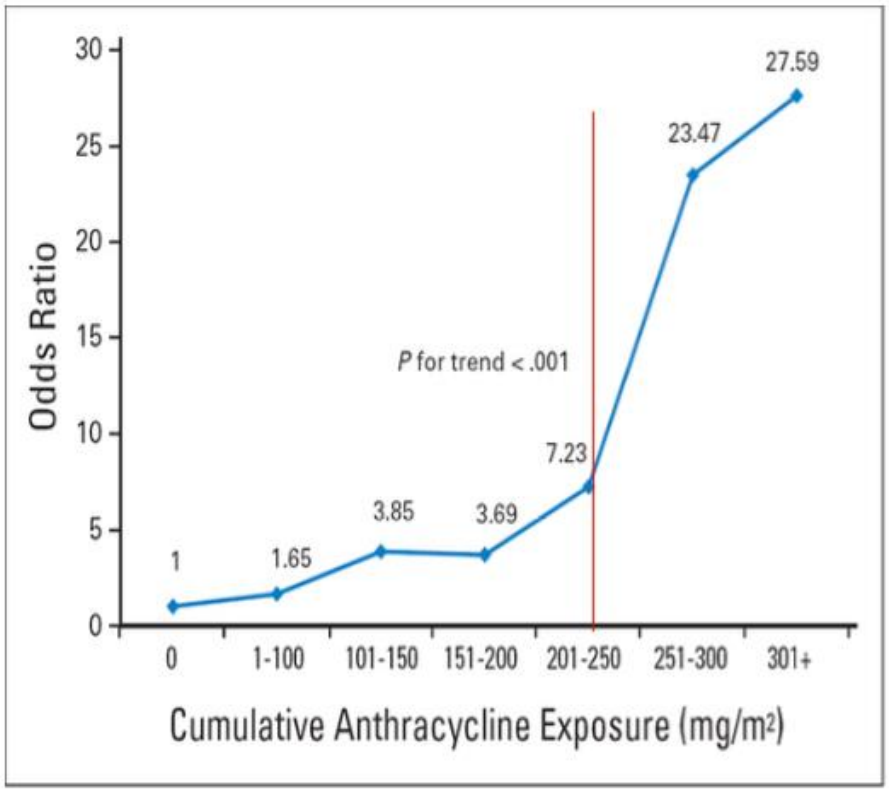


TABLE 2. Relationship between the Total Dose of Adriamycin Administered and the Incidence of Subsequent Congestive Heart Failure

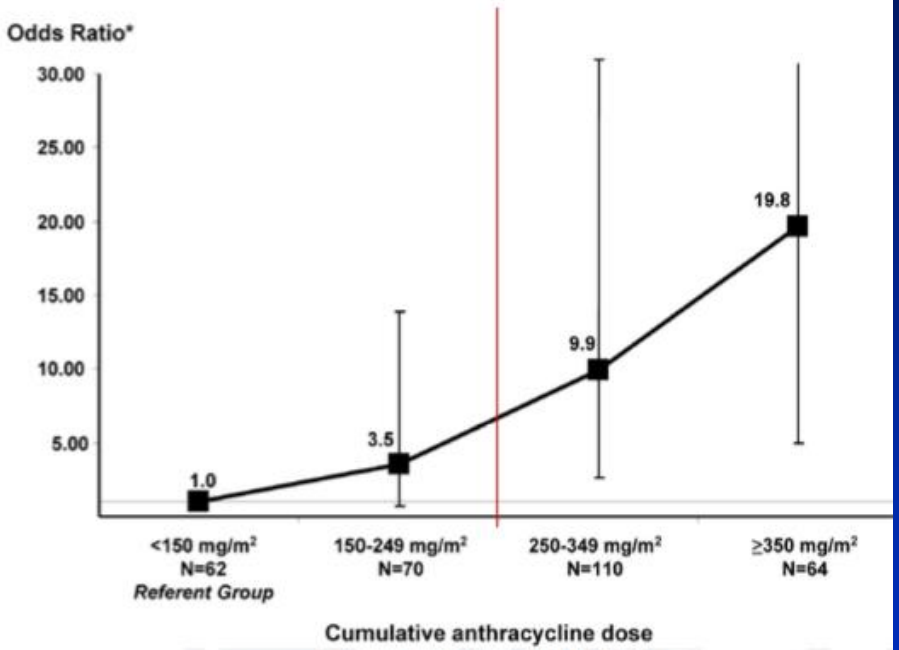
Total cumulative dose of adriamycin (mg/m²)	No. patients	Congestive heart failure developed
Less than 450	327	0
451–500	16	0
501–550	23	1
551–600	11	2
More than 601	22	8
TOTAL	399	11

Lefrak et al Cancer 1973;32:302

2019: Dose Dependent HF risk 150, 250, 350 mg/M^2 BSA thresholds



Blanco JG, et al. *J Clin Oncol*. 2012; 30(13):1415-21



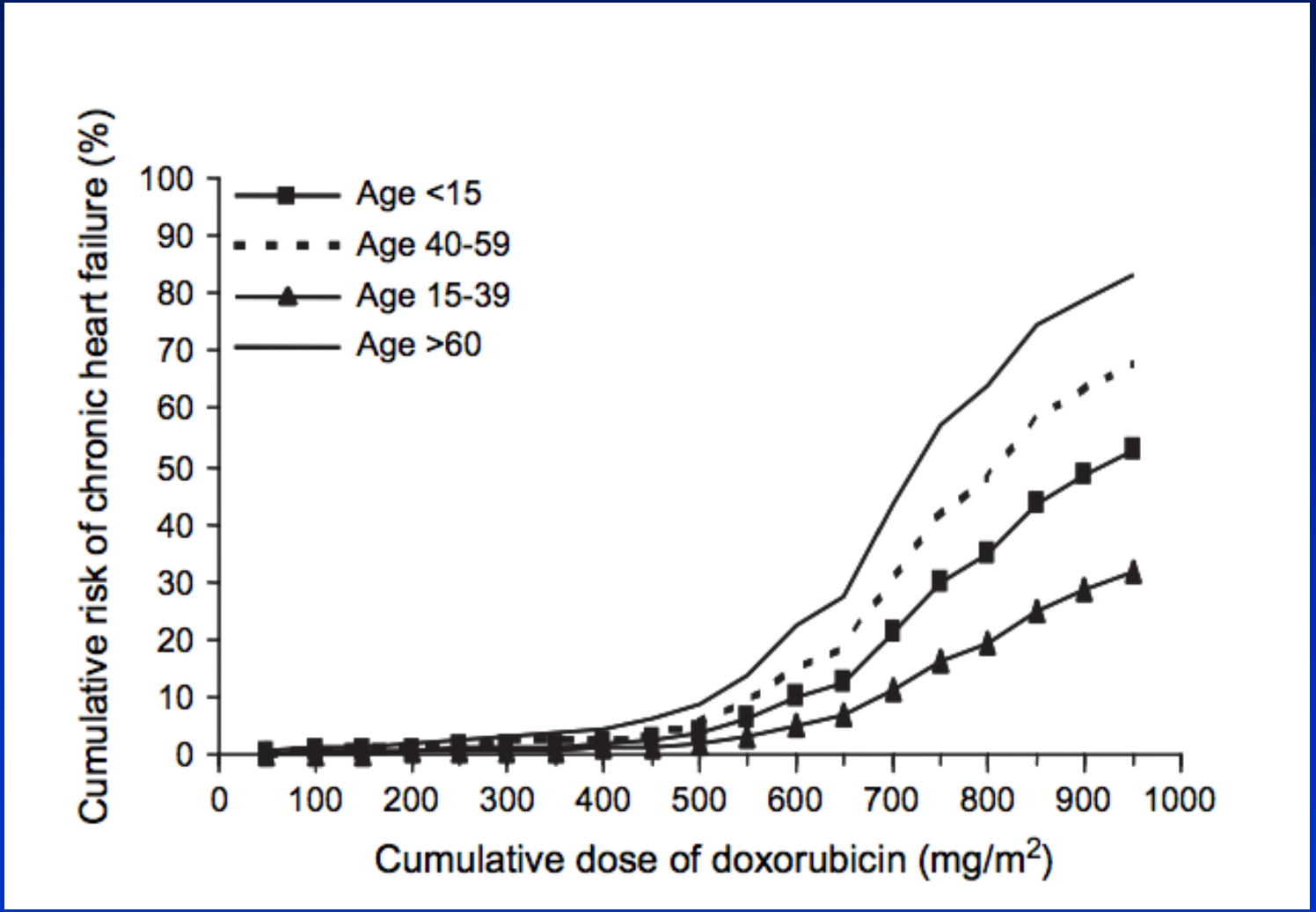
Armenian S, et al. *Blood*. 2011; 118(23)

AMERICAN COLLEGE of CARDIOLOGY

There is no safe therapeutic dose of Adriamycin
Liposomal or pegylated liposomal doxorubicin somewhat less toxic
Varying infusion rate or dose frequency used to mitigate toxicity

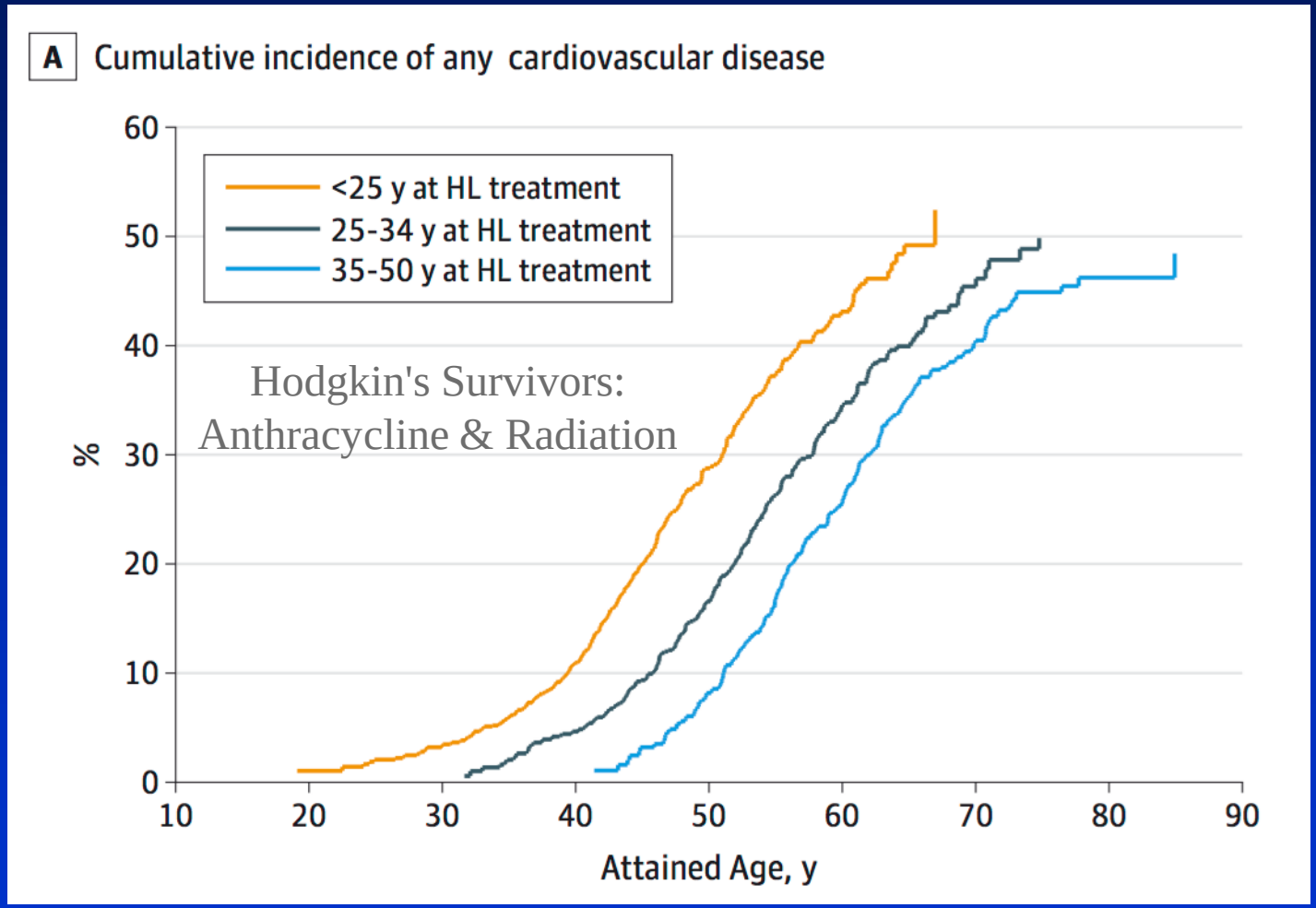
Figures: Saro Armenian

1979: Advancing age at treatment increases HF risk



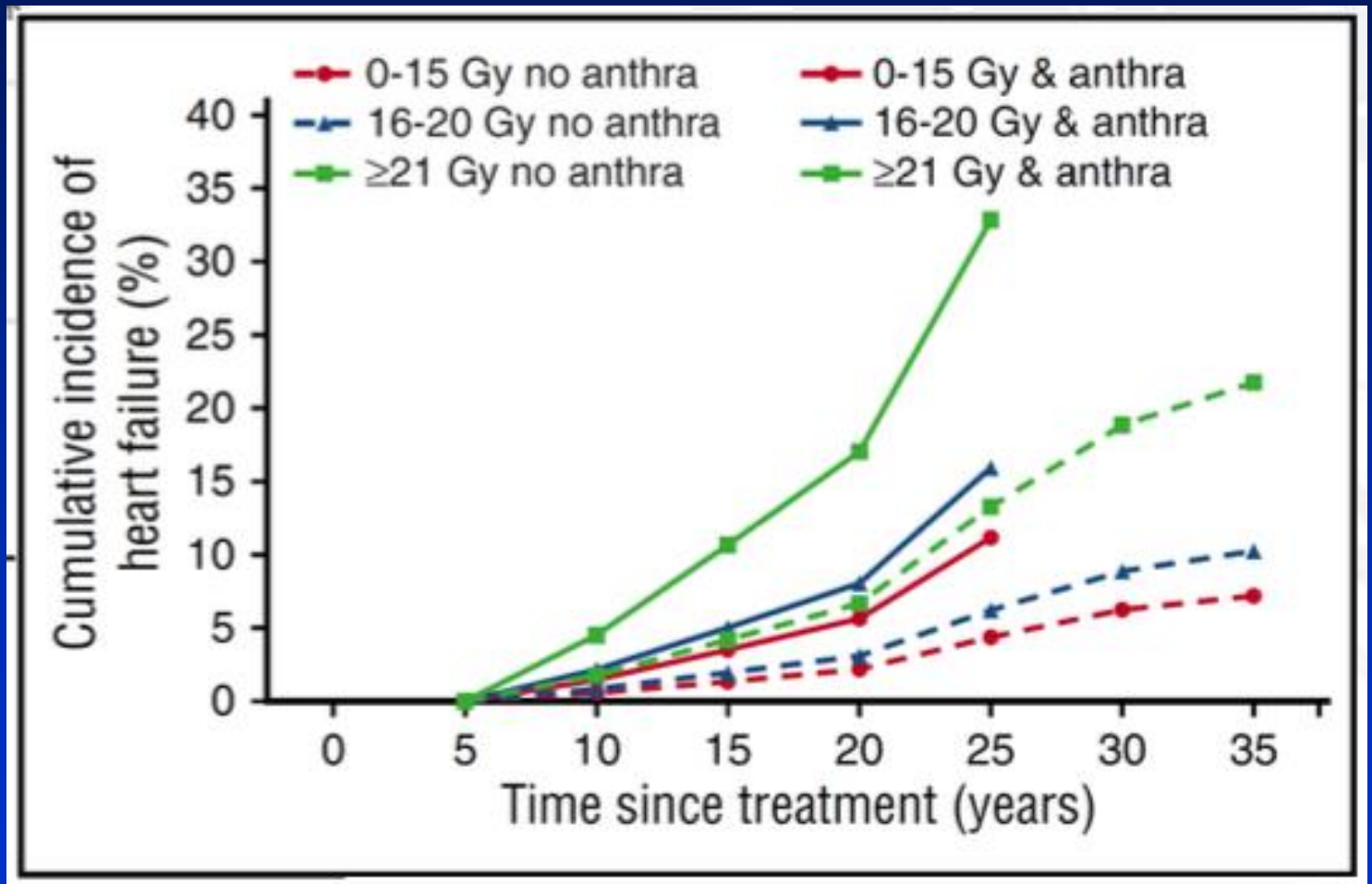
VonHoff et al Annals Int Med 1979; 91: 710

2015: Younger age at treatment: *Longer latency*, similar CVD risk curves



JAMA Int Med 2015; 175:1007

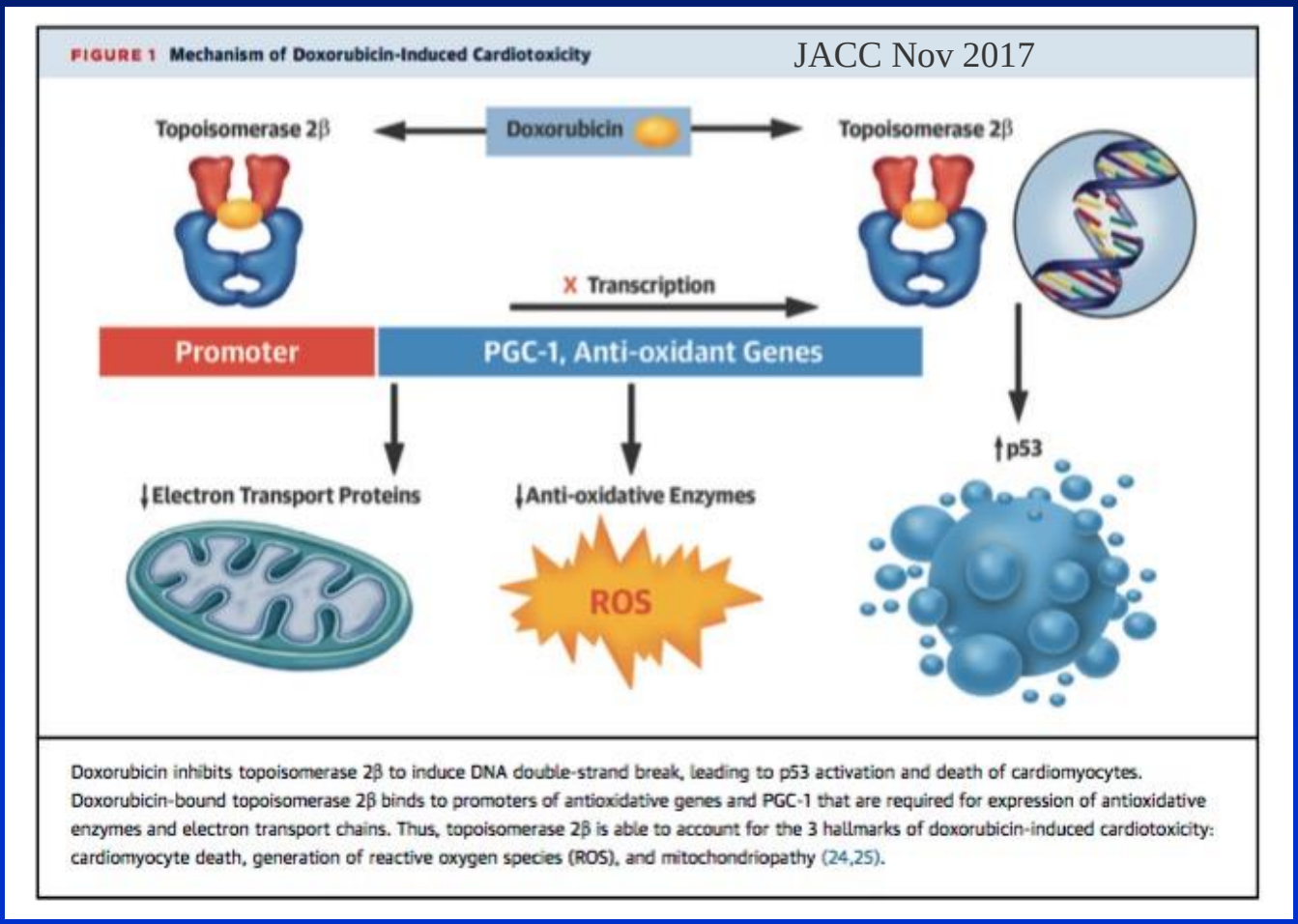
Radiation dose amplifies anthracycline risk



Van Nimwegen FA et al. *Blood*. 2017 Apr 20;129(16):2257-2265

Dexrazoxane: Specific inhibition of anthracycline effect on Topoisomerase 2β

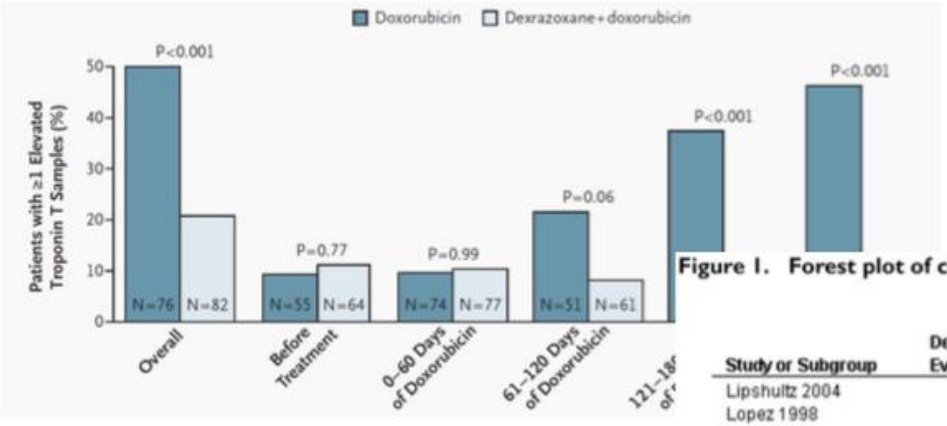
- Anthracyclines inhibit Topoisomerase 2α in cancer cells & inhibit Topoisomerase 2β in cardiomyocytes causing DNA breaks, ROS generation and mitochondria inhibition
- Dexrazoxane inhibits Top2β to protect myocardial cells with no effect on Top2α in cancer cells



Dexrazoxane prevents anthracycline cardiotoxicity in childhood ALL

Cardioprotectants: *Dexrazoxane*

The Effect of Dexrazoxane on Myocardial Injury in Doxorubicin-Treated Children with Acute Lymphoblastic Leukemia N Engl J Med 2004;351:145-53.



Citation: van Dalen EC, Caron HN, Dickinson HO, Kremer LCM. thracyclines. *Cochrane Database of Systematic Reviews* 2011, Issue 6. Art.

Figure 1. Forest plot of comparison: 1 Dexrazoxane versus no dexrazoxane / placebo, outcome: 1.1 C heart failure.

Study or Subgroup	Dexrazoxane Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Lipshultz 2004	0	105	0	101		Not estimable
Lopez 1998	4	63	13	66	18.4%	0.32 [0.11, 0.94]
Marty 2006	1	85	8	79	12.0%	0.12 [0.01, 0.91]
Schwartz 2009	0	107	2	109	3.6%	0.20 [0.01, 4.19]
Speyer 1992	2	76	20	74	29.4%	0.10 [0.02, 0.40]
Swain 1997a(088001)	0	168	15	181	21.7%	0.03 [0.00, 0.58]
Swain 1997a(088006)	2	81	7	104	8.9%	0.37 [0.08, 1.72]
Venturini 1996	2	84	4	78	6.0%	0.46 [0.09, 2.46]
Total (95% CI)		**769**		**792**	**100.0%**	**0.18 [0.10, 0.32]**
Total events	11		69			

Heterogeneity: Chi² = 5.49, df = 6 (P = 0.48); I² = 0%
Test for overall effect: Z = 5.67 (P < 0.00001)

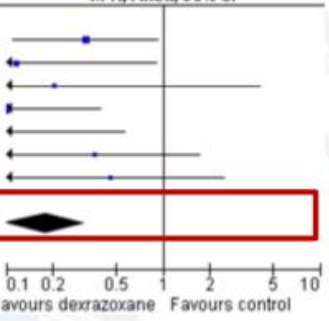
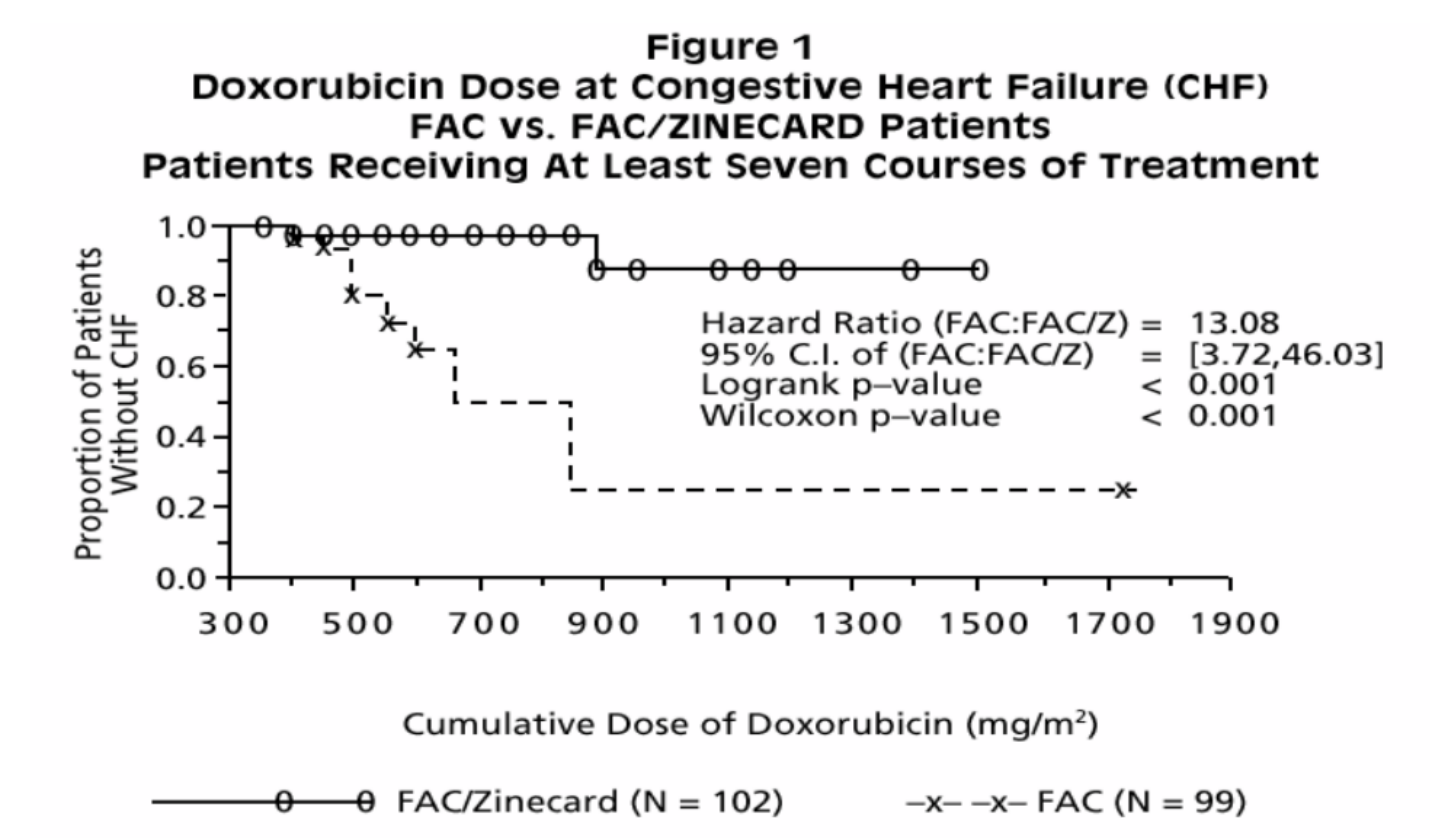


Figure: SArmenian ACC Cardio-Oncology symposium Feb 2018

Dexrazoxane FDA approved for metastatic breast cancer with advancing dose af adriamycin >300 mg/m^2

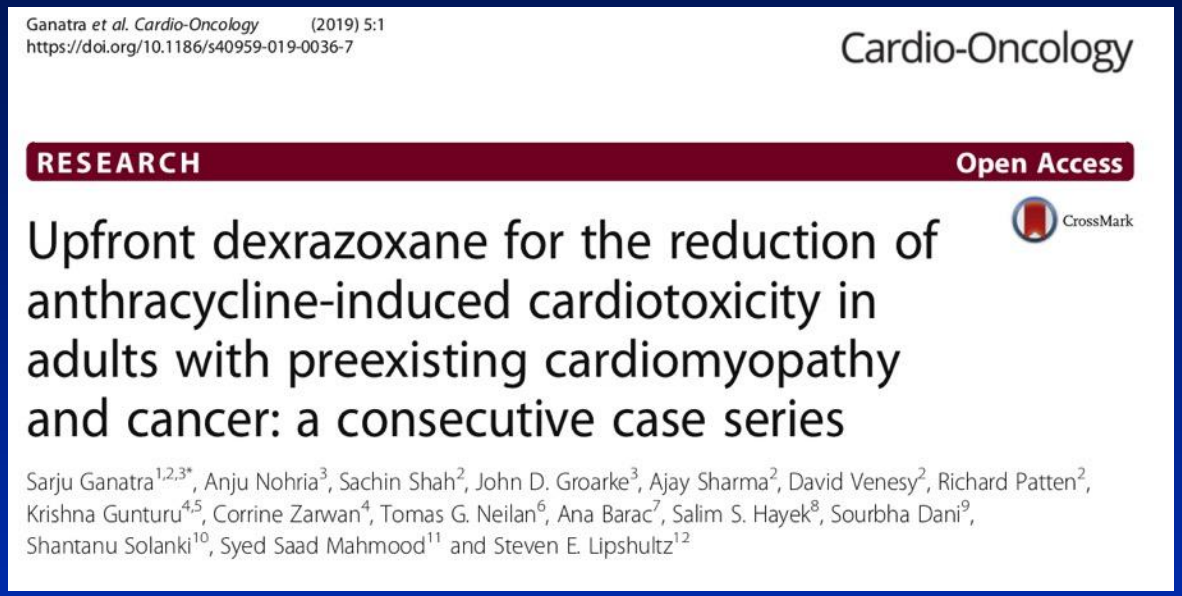


ZINECARD is indicated for reducing the incidence and severity of cardiomyopathy associated with doxorubicin administration in women with metastatic breast cancer who have received a cumulative doxorubicin dose of 300 mg/m2 and who will continue to receive doxorubicin therapy to maintain tumor control. It is not recommended for use with the initiation of doxorubicin therapy

Anthracycline therapy with preexisting LV dysfunction

- Absence of anthracyclines reduces response and survival likelihoods in Lymphomas, acute Leukemias
- No randomized trials or guidelines for anthracycline therapy with preexisting LV systolic dysfunction

Case series in 2019: Upfront Dexrazoxane + doxorubicin: "Dex-Dox" with baseline LV dysfunction



Ganatra *et al. Cardio-Oncology* (2019) 5:1
https://doi.org/10.1186/s40959-019-0036-7

Cardio-Oncology

RESEARCH Open Access

Upfront dexrazoxane for the reduction of anthracycline-induced cardiotoxicity in adults with preexisting cardiomyopathy and cancer: a consecutive case series

Sarju Ganatra[1,2,3*], Anju Nohria[3], Sachin Shah[2], John D. Groarke[3], Ajay Sharma[2], David Venesy[2], Richard Patten[2], Krishna Gunturu[4,5], Corrine Zarwan[4], Tomas G. Neilan[6], Ana Barac[7], Salim S. Hayek[8], Sourbha Dani[9], Shantanu Solanki[10], Syed Saad Mahmood[11] and Steven E. Lipshultz[12]

All patients stable on max tolerated GDMT Stage B or C heart failure

Prior to Dexrazoxane protocol:
3 patients, 76 years,
EF 42.5%

Dexrazoxane protocol before each dose anthracycline:
5 patients , 70.6 years
EF 39%, 1 w/ ICD baseline

Case series in 2019: Upfront Dexrazoxane + doxorubicin: "Dex-Dox" with baseline LV dysfunction

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<u>Outcomes without Dexrazoxane:</u>

EF 18% p treatment (Baseline 42%)

All 3 admitted with ADHF, 2 died

<u>Outcomes with Dexrazoxane:</u>

All completed planned chemo 280-300mg/m^2

No decompensated HF or marker abnormality

EF 34% post treatment (Baseline 39%)

All alive 12-30 months: 4 complete 1 partial remission

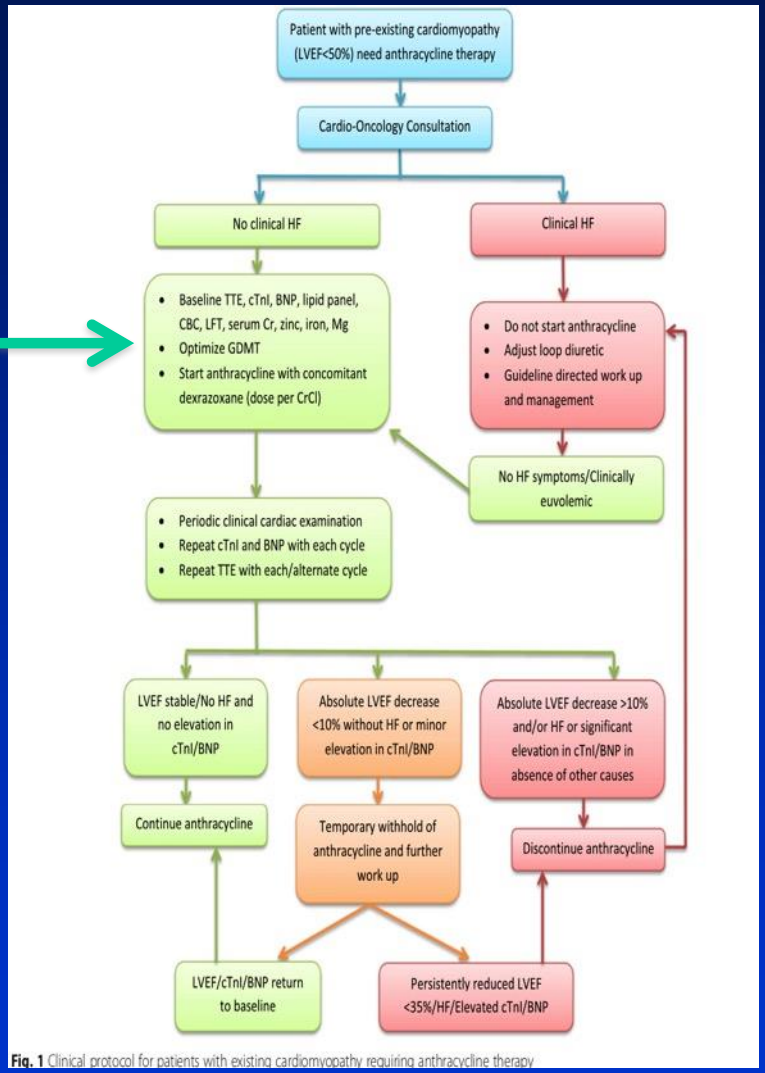
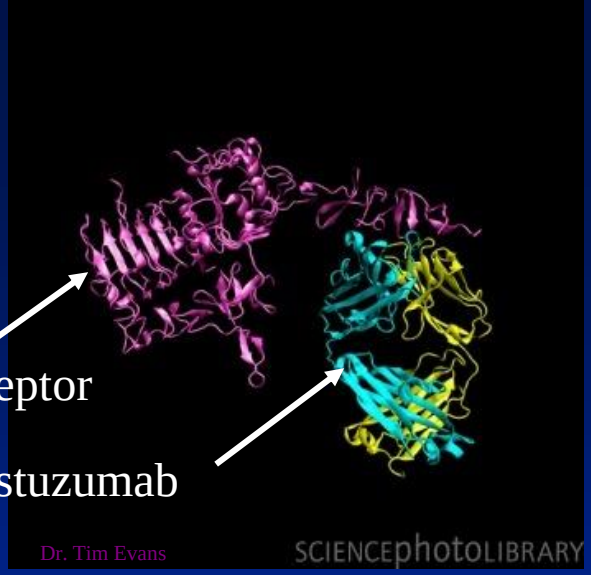


Fig. 1 Clinical protocol for patients with existing cardiomyopathy requiring anthracycline therapy

Summary: Preventing & treating Adriamycin Cardiotoxicity

- First Objective: Treat Curable Cancer with full front line chemotherapy
- No clinically relevant cardioprotection from ACEI/ARB or Beta Blocker with normal EF
- Baseline EF reduction commonly deters use of adria
  - HFrEF meds if EF reduced
  - Dexrazoxane up-front promising but off label
- Abnormalities in diastolic function or strain should not stop cancer treatment
  - No proof that interventions have merit but cardio-protection possibly beneficial

Trastuzumab-First in class antibody targeting HER-2 receptor in breast cancer cells



- **Rapidly developed science**
  - **1987: c-erbB-2c gene described that codes for Human Epidermal growth factor Receptor protein 2 (HER2) with intracellular tyrosine kinase activity**
  - **25% breast cancer patients HER2/neu+**
  - **Earliest trials: Significant reduction in mortality with metastatic breast cancer in HER2+ patients**
  - **1998: trastuzumab (Herceptin) FDA approved as HER2/*neu* receptor blocker in metastatic breast cancer**

Herceptin now approved for HER2 positive breast cancer or metastatic gastric cancer

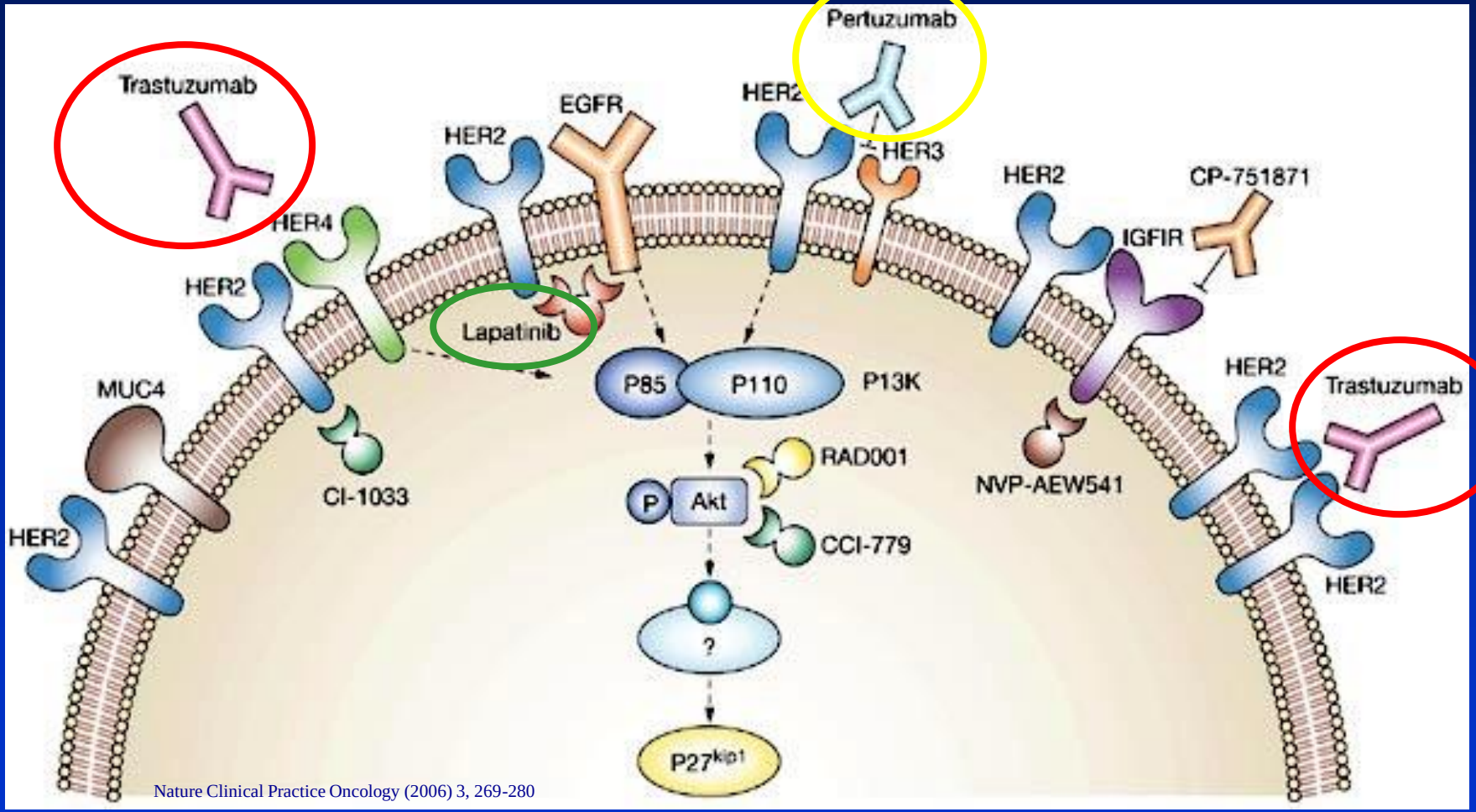
- September, 1998: HER2 overexpressing Metastatic Breast Cancer (MBC)

- October, 2006 HER2 overexpressing node positive or node negative (ER/PR negative or with one high risk feature) non-MBC

- October, 2010: Initial therapy for HER2 overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma

Multiple drugs target HER subtypes

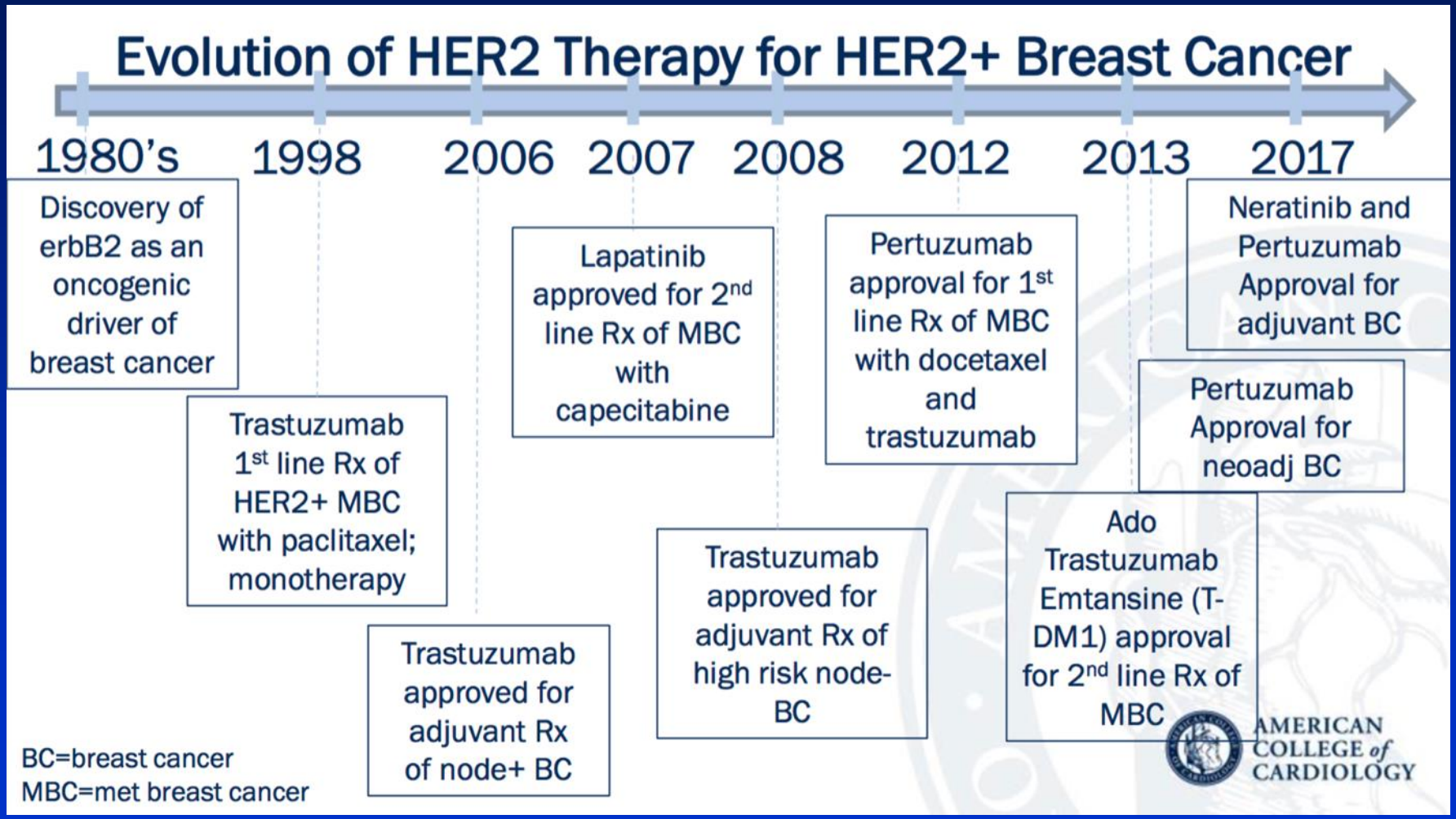
Trastuzmab is prototype, Lapatinib 2nd entry, Pertuzumab, Kadcyla later to market



Nature Clinical Practice Oncology (2006) 3, 269-280

Anti tumor efficacies and cardiotoxicities may vary among anti HER2 agents

20 year evolution of HER2 based therapies



Trastuzumab cardiac toxicity

Early Trials: Trastuzumab

- 5% develop findings LV dysfunction
- 1% develop symptomatic heart failure
- Enhanced by concurrent anthracyclines
  - Concurrent anthracycline & trastuzumab contraindicated
- Not dose dependent
- Frequently reversible
- No clinical issues with HFpEF or diastolic dysfunction

Time course of CV events with trastuzumab

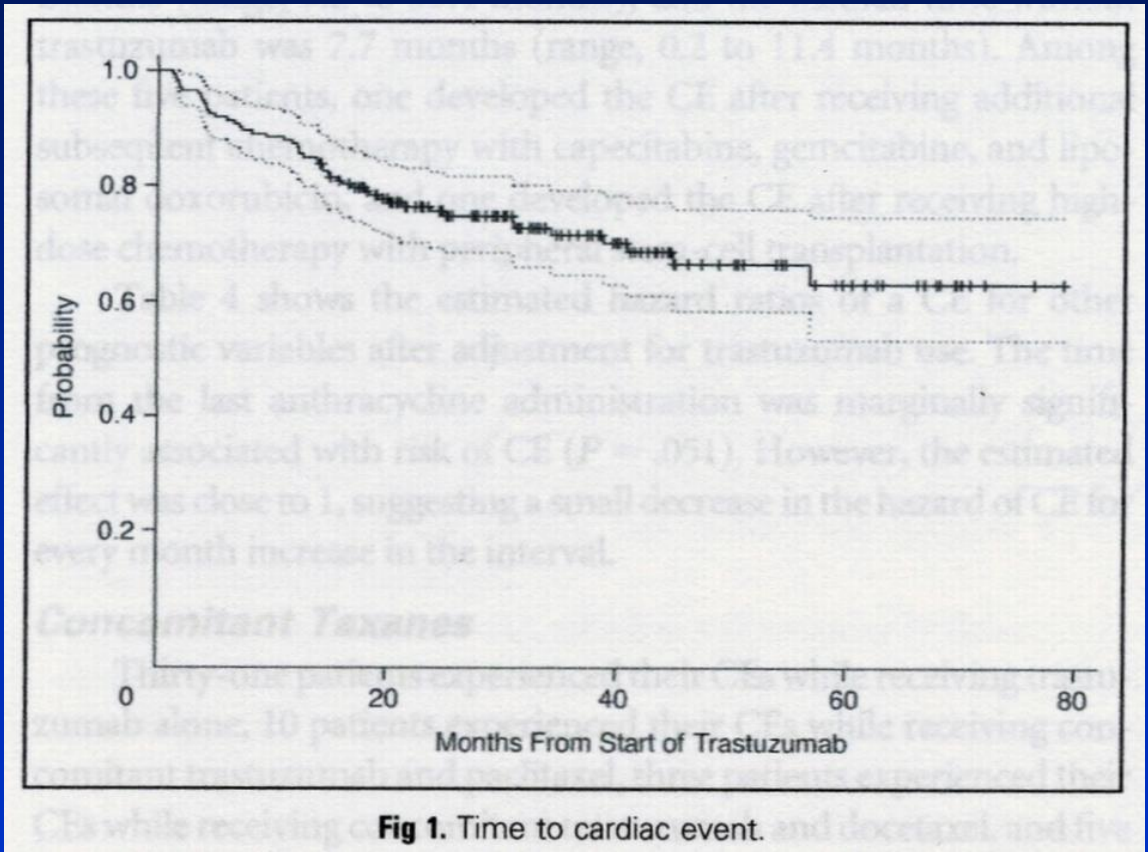


Fig 1. Time to cardiac event.

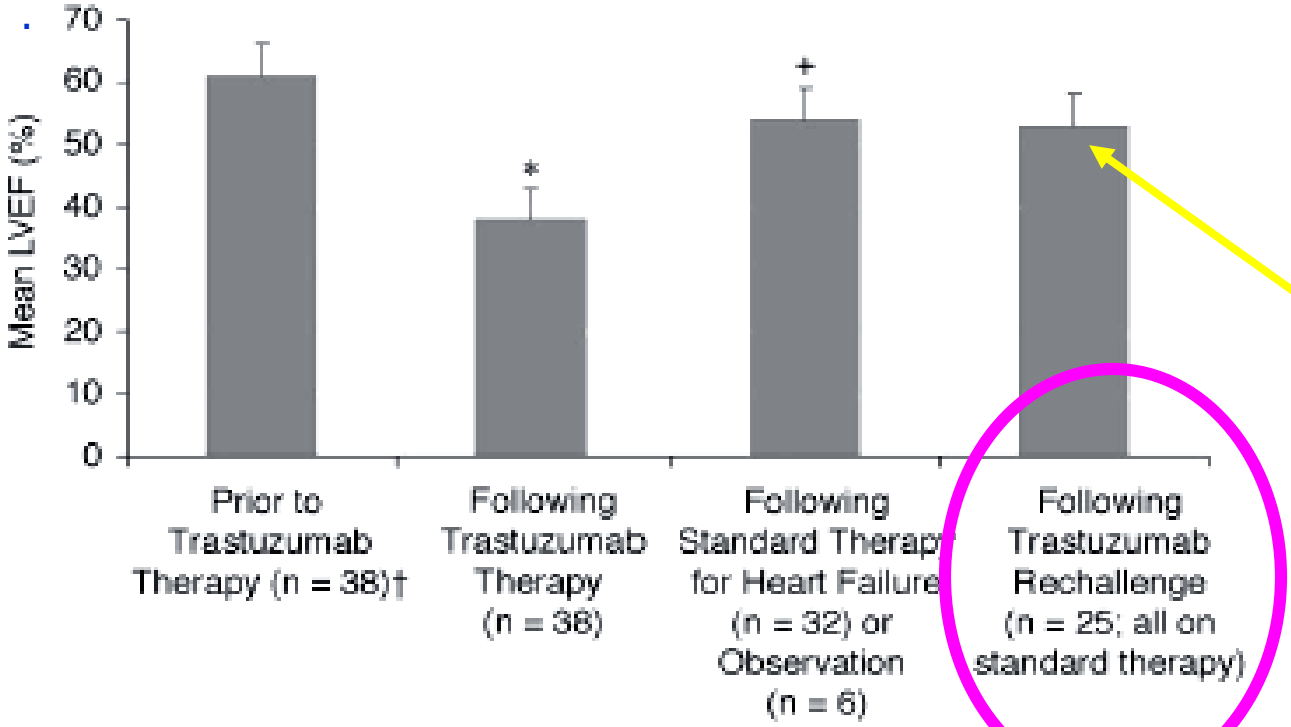
- No early peak
- Plateau seen at approximately 40 months
- Predictors of CV Event
  - Baseline EF
  - Concurrent Taxane therapy

MD Anderson experience Guarneri, J Clin Oncol 2006;24:4107

Significant reversibility reported with trastuzumab related cardiac toxicity

resumption of trastuzumab tolerated

MD Anderson experience 38 patients post anthracycline
Referred for trastuzumab related cardiotoxicity



25/38 retreated after HF Rx

22/25 without recurrent LV dysfunction
- **$\overline{EF}$ rise sustained**

3/25 recurrent LV dysfx

13/38
No further trastuzumab
- **7-HF Rx**
- **6-No HF Rx**
- **13/13 No further events**

Ewer, et al J Clinical Oncol 2005,23;p 7820-6

Reversibility of trastuzumab cardiotoxicity not universal

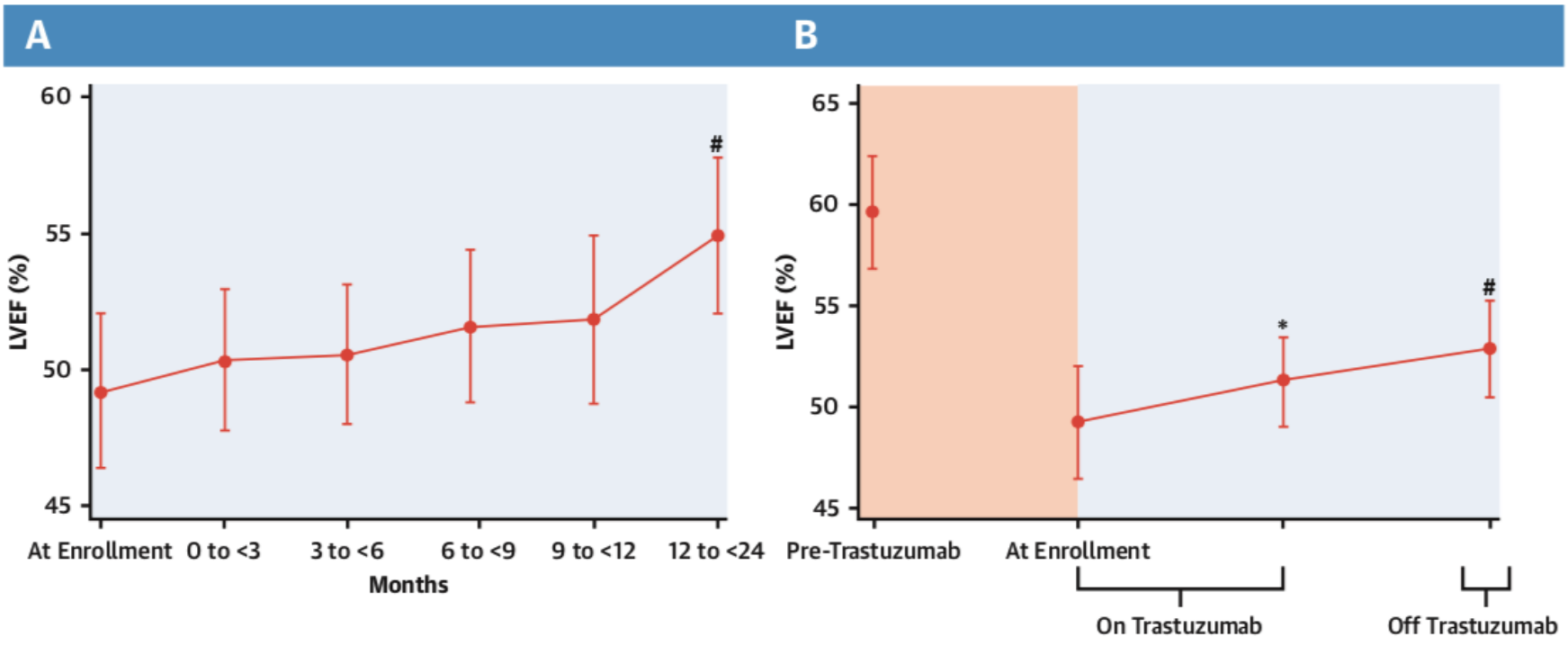
- Major adjuvant trastuzumab trials
  - NSABP B-31
    - 4.1% severe CHF, 2/3 Rx chronically for HF, 71% w/ persisting reduction EF
    - 14% trastzumab DC'd d/t decline LVEF
  - BCIRG 006
    - 17.3% w/ > 10% decline EF vs baseline
    - 26% w/ persisting decline EF at 6 weeks off trastuzumab
  - NCCTG: 29% w/ EF drop persisted at 6 months
  - FinHER-No CHF or EF drop>10% after 9 weeks trastuzumab

KU Cardio-oncology approach from 2007

- Balance risk of heart failure with risk of death from breast cancer is Cardiology/Oncology collaboration
- Advanced heart failure reported in early series with little active cardiology input
- KUH approach 2007 EF<50%: pause Herceptin , add beta blocker and ACEI inhibitor, resume at 6 weeks if echo stable or improved
  - Advance carvedilol first, then ACEI if BP tolerates
  - Monitor BNPs, clinical status but EF primary endpoint
  - ~2014, =/- herceptin pause while adding HFrEF Rx

SCHOLAR Trial supports KU Herceptin continuation approach

Initiation of ACEI &/or BB If EF drop >15% or to below 50%
Open label, single arm trial



Leong, D.P. et al. J Am Coll Cardiol CardioOnc. 2019;1(1):1-10.

(A) Left ventricular ejection fraction (LVEF) progressively increased despite ongoing trastuzumab in individuals with mild trastuzumab cardiotoxicity when trastuzumab was accompanied by the administration of an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker and/or a beta-blocker. #$p < 0.001$ as compared with the enrollment left ventricular ejection fraction indicating significant improvement in left ventricular ejection fraction as compared with the left ventricular

18/20 completed therapy, no treatment>1year for metastatic disease

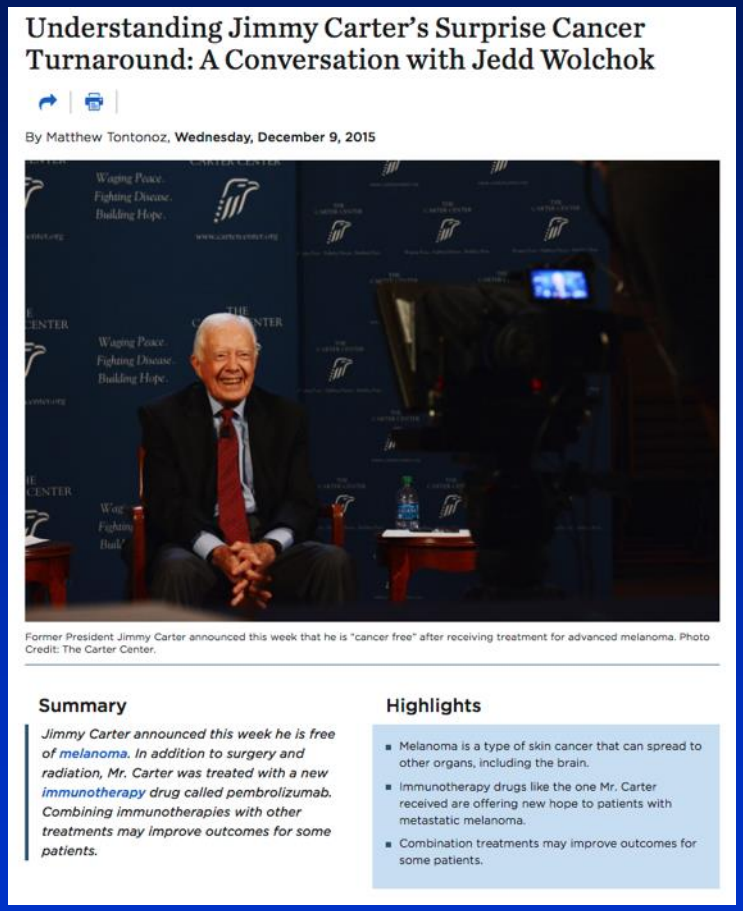
Surveillance & management trastuzumab toxicity

- Package insert: Quarterly echoes recommended
  - Limited yield for MBC patients on chronic Trastuzumab
    - Less frequent if stable normal EF no prior toxicities:
- Aggressive risk factor management to minimize CVD
- ACEI/Beta blocker for decline in EF >10% esp if below LLN
  - Variability in EF problematic
  - Markers, LV strain decline may be helpful in identifying high risk
    - Markers, Strain, diastolic dysfunction don't warrant DC Herceptin
  - Patients favor effective cancer therapy over total heart protection
- Interruption of therapy with EF >40% not mandatory
  - Prolonged Herceptin for metastatic breast cancer feasible

Immune Checkpoint Inhibitors:
High profile targeted Cancer therapy
High impact cardiotoxicity

Immune Checkpoint Inhibitors in the spotlight

December, 2015: Pembrolizumab pardons a president with metastatic melanoma



Understanding Jimmy Carter's Surprise Cancer Turnaround: A Conversation with Jedd Wolchok

By Matthew Tontonoz, **Wednesday, December 9, 2015**

Former President Jimmy Carter announced this week that he is "cancer free" after receiving treatment for advanced melanoma. Photo Credit: The Carter Center.

Summary

Jimmy Carter announced this week he is free of melanoma. In addition to surgery and radiation, Mr. Carter was treated with a new immunotherapy drug called pembrolizumab. Combining immunotherapies with other treatments may improve outcomes for some patients.

Highlights

- Melanoma is a type of skin cancer that can spread to other organs, including the brain.
- Immunotherapy drugs like the one Mr. Carter received are offering new hope to patients with metastatic melanoma.
- Combination treatments may improve outcomes for some patients.

May 2019: President Carter fractures hip while Turkey hunting, Home after surgery

DTC advertising: Longer life spans with nivolumab for relapsed non-small Cell lung cancer

2018 Nobel Prize in Medicine awarded to 2 developers of immunotherapy as cancer treatment

Immune Checkpoint Inhibitors (ICI)
2011: 1st FDA approved ICI-Ipilimumab for Melanoma
2019: Multiple drugs & indications

U.S. FDA Approved Immune-Checkpoint Inhibitors

Squamous Cell Head & Neck Cancer
1L nivolumab after platinum chemotherapy
1L pembrolizumab after platinum chemotherapy

Malignant Melanoma
Adj./1L ipilimumab
1L nivolumab ± ipilimumab
Adj. nivolumab
1L pembrolizumab

Merkel Cell Carcinoma
2L avelumab

Hepatocellular Carcinoma
2L nivolumab after sorafenib

Adv. Renal Cell Carcinoma
2L nivolumab after anti-angiogenic therapy

Locally Adv. or Met. Urothelial Cancer
1L nivolumab after platinum chemotherapy
1L pembrolizumab after platinum chemotherapy or in platinum-ineligible patients
1/L atezolizumab after platinum chemotherapy
1L avelumab after platinum chemotherapy
1L durvalumab after platinum chemotherapy

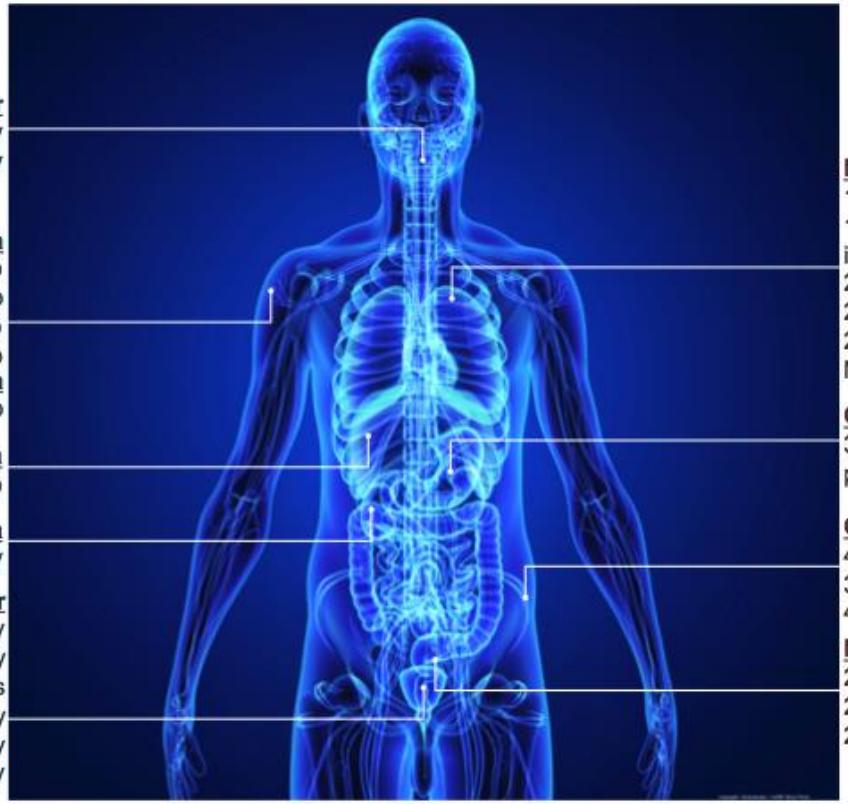


Figure: medi-paper.com

Non-Small Cell Lung Cancer
1L pembrolizumab TPS≥50%
1L pembrolizumab +pemetrexed/carboplatin in non-squamous NSCLC
2L pembrolizumab TPS≥1%
2L nivolumab
2L atezolizumab NSCLC
Maintenance durvalumab after chemoradiation

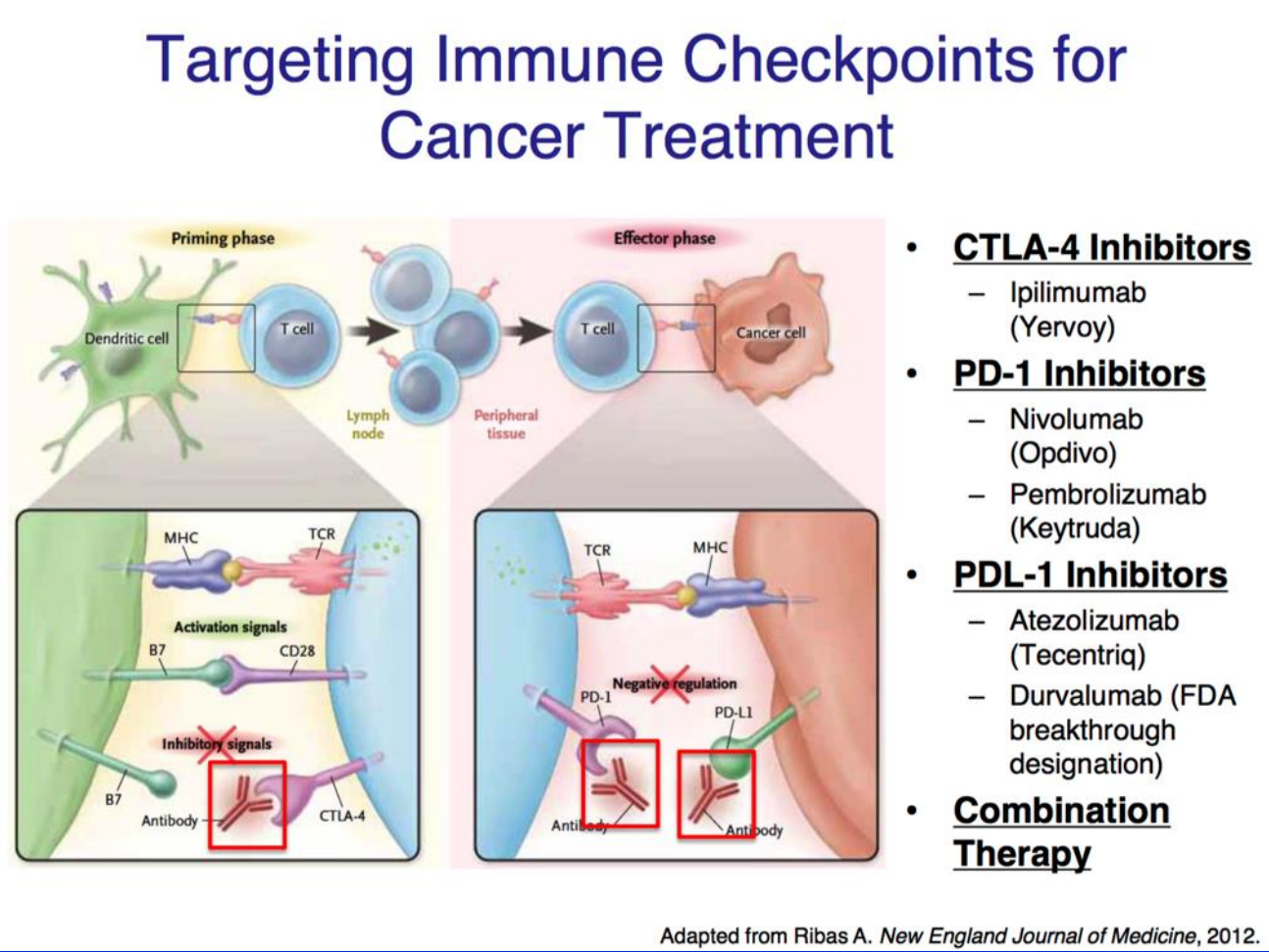
Gastric & GEJ Carcinoma
3L pembrolizumab after fluoropyrimidine- and platinum-CTx +/- HER2 therapy & CPS≥1

Classical Hodkin Lymphoma
4L pembrolizumab
3L nivolumab after auto-HSCT and BV
4L nivolumab and after auto-HSCT

MSI-H or dMMR Cancers
2L nivolumab in CRC after FOLFOXIRI
2L pembrolizumab in CRC after FOLFOXIRI
2L pembrolizumab in any MSI-H/dMMR cancer

March 8, 2019 FDA approves atezolizumab for triple Neg Stage II or IV Breast Ca

Immune Checkpoint Inhibition (ICI): Multifaceted facilitation of natural immune response to tumors

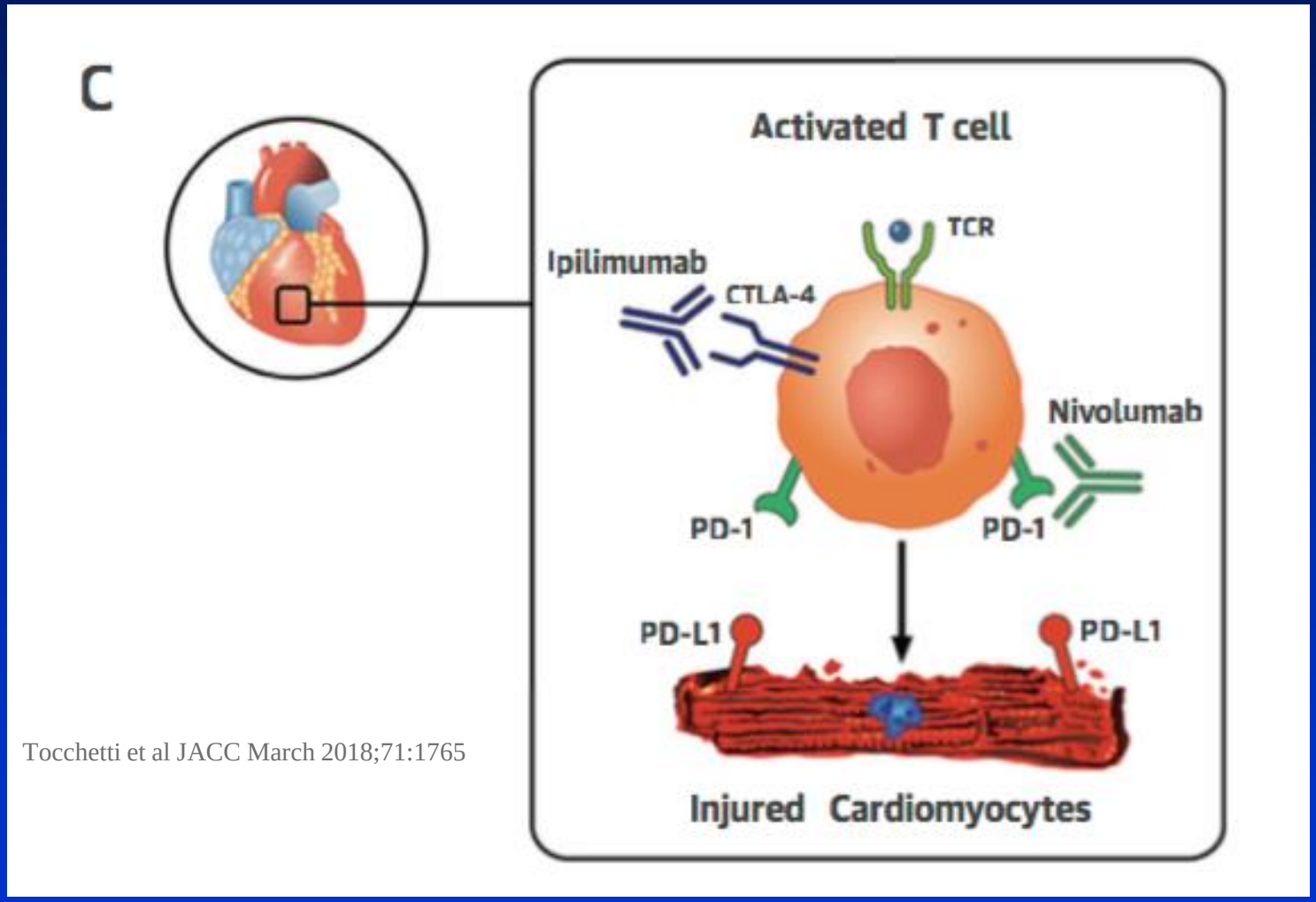


Dual Checkpoint Inhibition

- More effective
- More Toxicity
- Common combination
  - CTLA -4
  - PD-1

Figure Moslehi, ACC CardioOncology 2018

Autoimmune reaction against many tissues
Myocarditis mechanism?: Activated T Cells attack Cardiomyocytes with PD-L1, shared tumor antigens



Tocchetti et al JACC March 2018;71:1765

Fatal Myocarditis
Dual Checkpoint inhibition therapy
Ipilimumab & Nivolumab

Initial report of two fatal cases NEJM Nov 2016

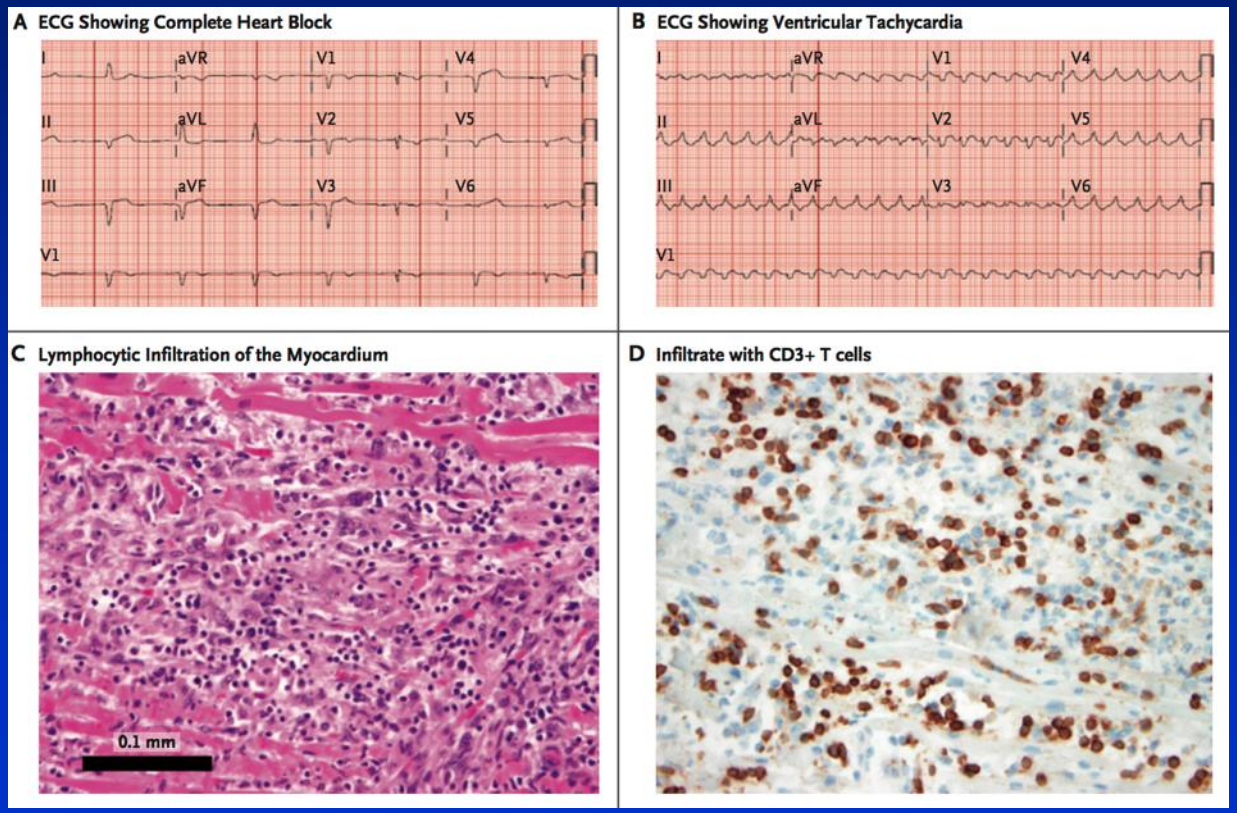
BRIEF REPORT

Fulminant Myocarditis with Combination Immune Checkpoint Blockade

Douglas B. Johnson, M.D., Justin M. Balko, Pharm.D., Ph.D., Margaret L. Compton, M.D., Spyridon Chalkias, M.D., Joshua Gorham, B.A., Yaomin Xu, Ph.D., Mellissa Hicks, Ph.D., Igor Puzanov, M.D., Matthew R. Alexander, M.D., Ph.D., Tyler L. Bloomer, M.D., Jason R. Becker, M.D., David A. Slosky, M.D., Elizabeth J. Phillips, M.D., Mark A. Pilkinton, M.D., Ph.D., Laura Craig-Owens, M.D., Nina Kola, M.D., Gregory Plautz, M.D., Daniel S. Reshef, M.D., M.P.H., Ph.D., Jonathan S. Deutsch, M.D., Raquel P. Deering, Ph.D., Benjamin A. Olenchock, M.D., Ph.D., Andrew H. Lichtman, M.D., Dan M. Roden, M.D., Christine E. Seidman, M.D., Igor J. Koralnik, M.D., Jonathan G. Seidman, Ph.D., Robert D. Hoffman, M.D., Ph.D., Janis M. Taube, M.D., Luis A. Diaz, Jr., M.D., Robert A. Anders, M.D., Jeffrey A. Sosman, M.D., and Javid J. Moslehi, M.D.

SUMMARY

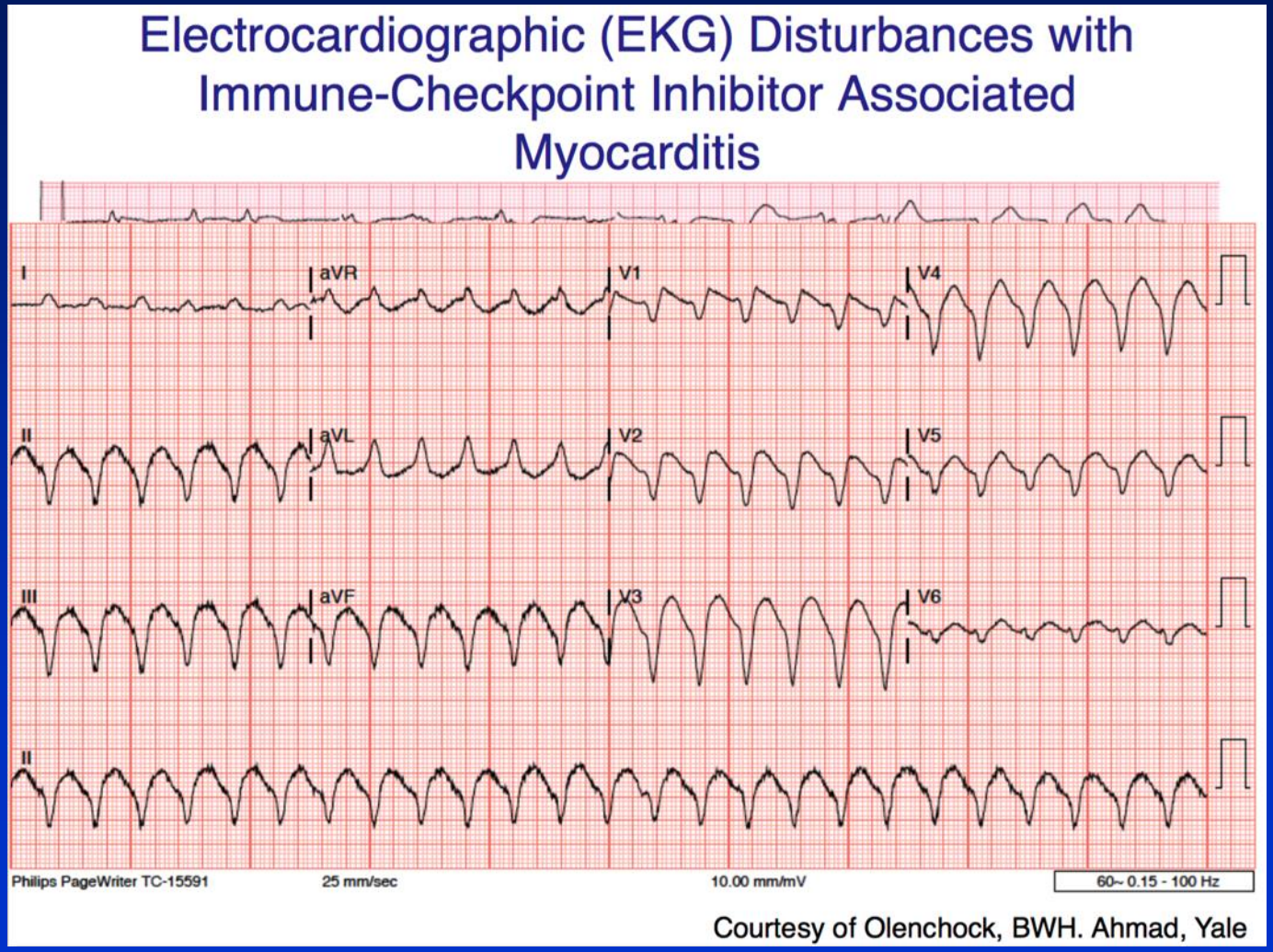
Immune checkpoint inhibitors have improved clinical outcomes associated with numerous cancers, but high-grade, immune-related adverse events can occur, particularly with combination immunotherapy. We report the cases of two patients with melanoma in whom fatal myocarditis developed after treatment with ipilimumab and nivolumab. In both patients, there was development of myositis with rhabdomyolysis, early progressive and refractory cardiac electrical instability, and myocarditis with a robust presence of T-cell and macrophage infiltrates. Selective clonal T-cell populations infiltrating the myocardium were identical to those present in tumors and skeletal muscle. Pharmacovigilance studies show that myocarditis occurred in 0.27% of patients treated with a combination of ipilimumab and nivolumab, which suggests that our patients were having a rare, potentially fatal, T-cell–driven drug reaction. (Funded by Vanderbilt-Ingram Cancer Center Ambassadors and others.)



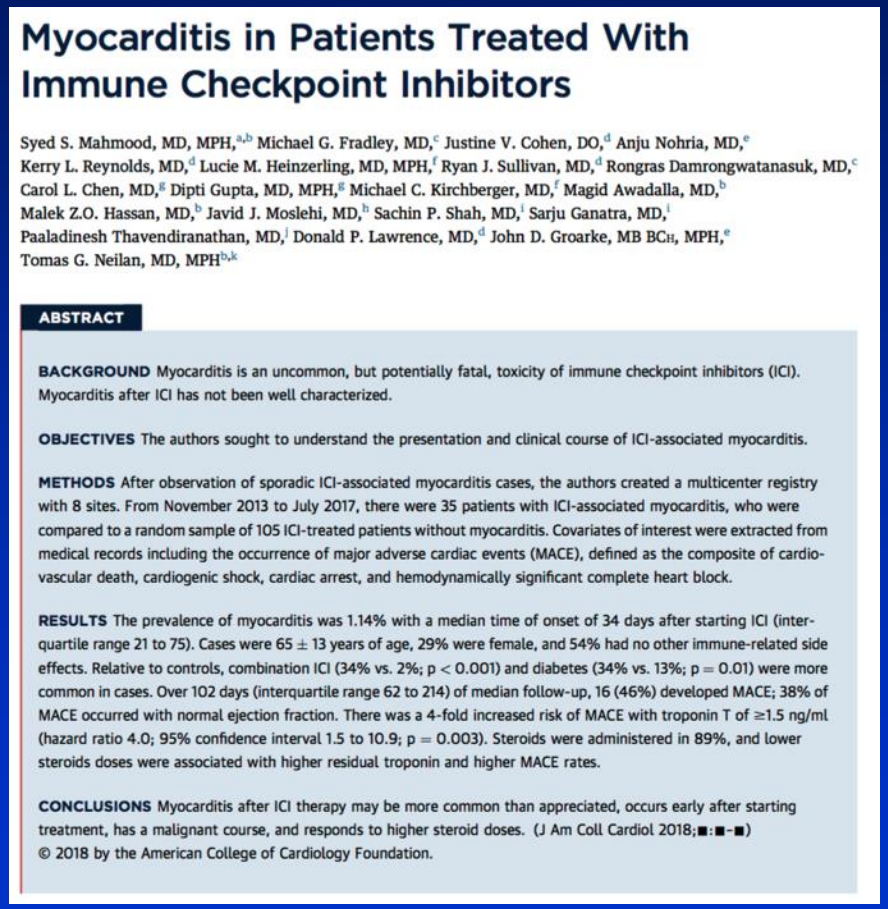
Normal LVSF, Refractory arrhythmias, death

Sine Wave Ventricular Tachycardia

not torsades des pointes



8 Center registry findings: ICI myocarditis



Myocarditis in Patients Treated With Immune Checkpoint Inhibitors

Syed S. Mahmood, MD, MPH,[a,b] Michael G. Fradley, MD,[c] Justine V. Cohen, DO,[d] Anju Nohria, MD,[e] Kerry L. Reynolds, MD,[d] Lucie M. Heinzerling, MD, MPH,[f] Ryan J. Sullivan, MD,[d] Rongras Damrongwatanasuk, MD,[c] Carol L. Chen, MD,[g] Dipti Gupta, MD, MPH,[g] Michael C. Kirchberger, MD,[f] Magid Awadalla, MD,[b] Malek Z.O. Hassan, MD,[b] Javid J. Moslehi, MD,[h] Sachin P. Shah, MD,[i] Sarju Ganatra, MD,[i] Paaladinesh Thavendiranathan, MD,[j] Donald P. Lawrence, MD,[d] John D. Groarke, MB BCh, MPH,[e] Tomas G. Neilan, MD, MPH[b,k]

ABSTRACT

BACKGROUND Myocarditis is an uncommon, but potentially fatal, toxicity of immune checkpoint inhibitors (ICI). Myocarditis after ICI has not been well characterized.

OBJECTIVES The authors sought to understand the presentation and clinical course of ICI-associated myocarditis.

METHODS After observation of sporadic ICI-associated myocarditis cases, the authors created a multicenter registry with 8 sites. From November 2013 to July 2017, there were 35 patients with ICI-associated myocarditis, who were compared to a random sample of 105 ICI-treated patients without myocarditis. Covariates of interest were extracted from medical records including the occurrence of major adverse cardiac events (MACE), defined as the composite of cardiovascular death, cardiogenic shock, cardiac arrest, and hemodynamically significant complete heart block.

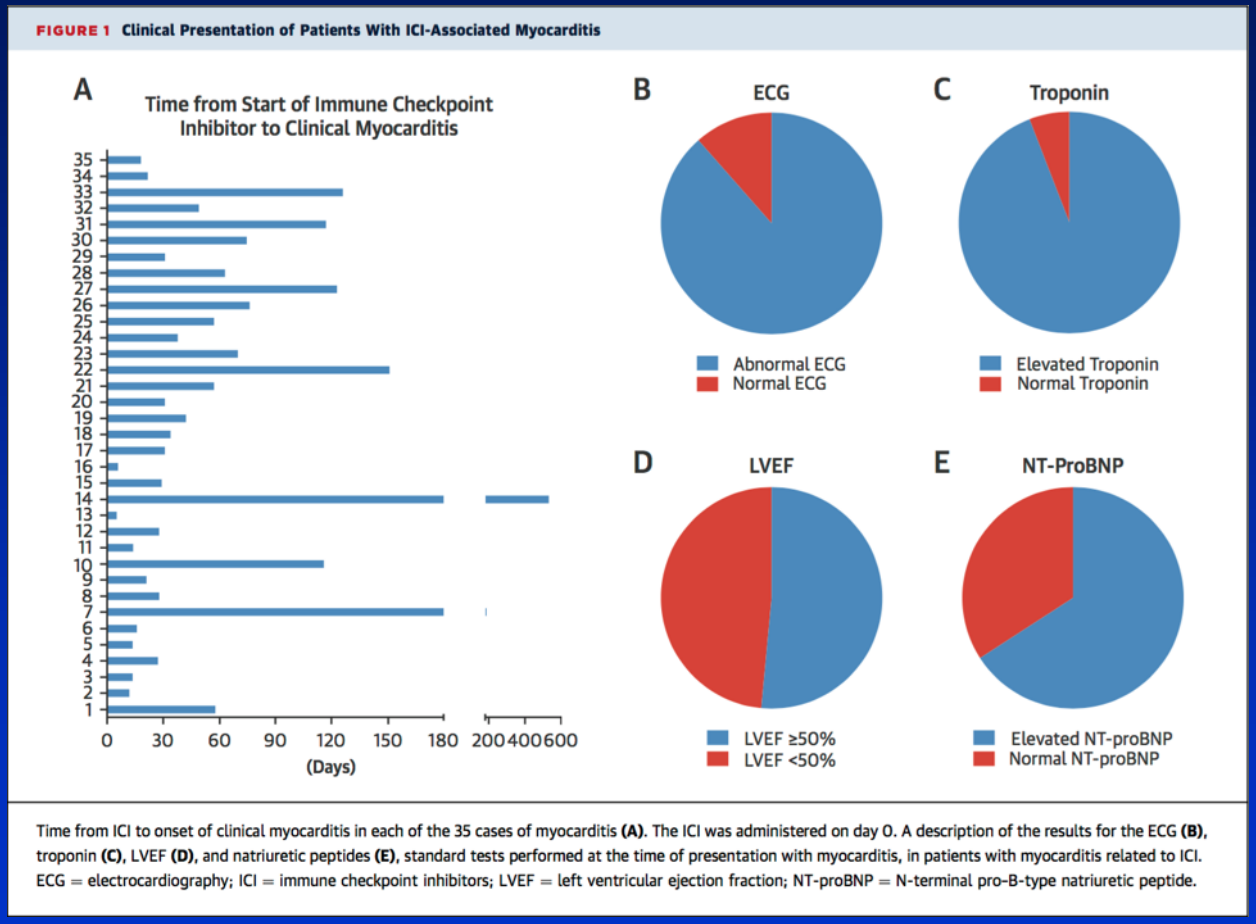
RESULTS The prevalence of myocarditis was 1.14% with a median time of onset of 34 days after starting ICI (interquartile range 21 to 75). Cases were 65 ± 13 years of age, 29% were female, and 54% had no other immune-related side effects. Relative to controls, combination ICI (34% vs. 2%; $p < 0.001$) and diabetes (34% vs. 13%; $p = 0.01$) were more common in cases. Over 102 days (interquartile range 62 to 214) of median follow-up, 16 (46%) developed MACE; 38% of MACE occurred with normal ejection fraction. There was a 4-fold increased risk of MACE with troponin T of ≥1.5 ng/ml (hazard ratio 4.0; 95% confidence interval 1.5 to 10.9; $p = 0.003$). Steroids were administered in 89%, and lower steroids doses were associated with higher residual troponin and higher MACE rates.

CONCLUSIONS Myocarditis after ICI therapy may be more common than appreciated, occurs early after starting treatment, has a malignant course, and responds to higher steroid doses. (J Am Coll Cardiol 2018;■:■-■)

- 35 patients
  - 1.14% incidence at MGH
- 29% Female
- 54% Myocarditis sole SE
- Risk Factors
  - 34% Dual ICI therapy
  - 66% Single agent ICI
  - DM in 34% RR 3.36
- 46% w/ MACE (Major Adverse CV events)
  - CV death, cardiac arrest, cardiogenic shock, and hemodynamically significant complete heart block

Mahmood et al JACC Pub Online March 2018

Troponin elevation, abnormal EKG, abnormal BNP more common than EF<50%

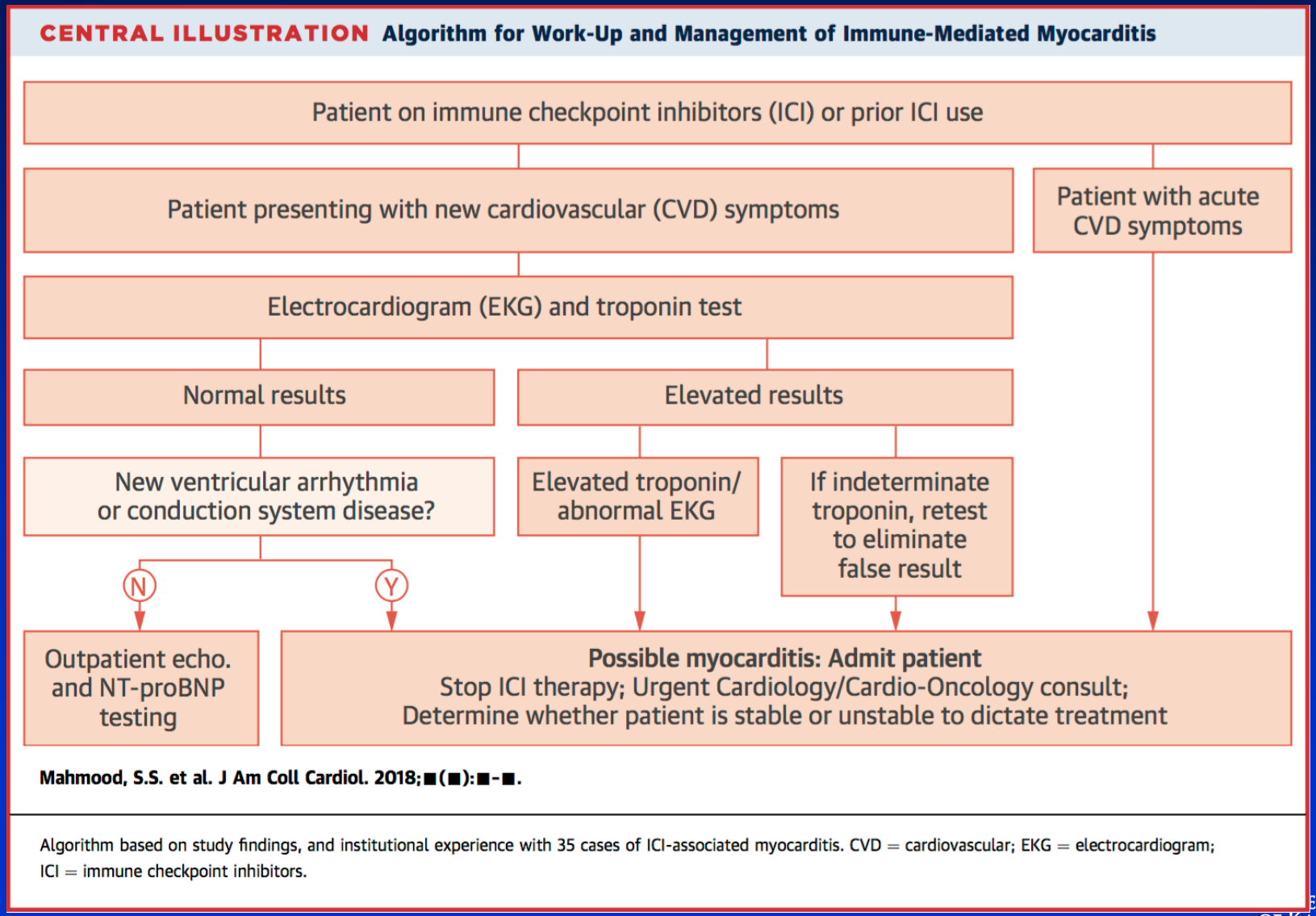


Time from ICI to onset of clinical myocarditis in each of the 35 cases of myocarditis **(A)**. The ICI was administered on day 0. A description of the results for the ECG **(B)**, troponin **(C)**, LVEF **(D)**, and natriuretic peptides **(E)**, standard tests performed at the time of presentation with myocarditis, in patients with myocarditis related to ICI. ECG = electrocardiography; ICI = immune checkpoint inhibitors; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal pro-B-type natriuretic peptide.

- Mean Onset 34 Days after start of therapy
- +Troponin >90%
- ~50% with EF <50%
- 38% w/ MACE had EF>50%
- ~90% treated with steroids
  - Higher troponins and higher MACE rates with lower steroid doses

Mahmood et al JACC Pub Online March 2018

Cardiac Symptoms in patient on Immune Checkpoint Inhibitor therapy? Consider Myocarditis



ICI: LVSD with Shock or VT without LVSD: Empiric management

Immune-Checkpoint Inhibitor Cardiovascular Toxicity in 2018

- Screening
  - ECG, troponin in high-risk individuals (combination therapy)
- Diagnosis
  - Combination of biomarkers, imaging and biopsy
  - Much consider biopsy
- Treatment
  - High dose steroids
  - Antithymoglobulin (ATG)
  - Other therapies directed at T cells? Tacrolimus, MMF

Figure Moslehi, ACC CardioOncology 2018

Questions/Comments?