Tossicità da terapia antineoplastica

Quali sono i trattamenti più a rischio cardiovascolare e quando l'oncologo li usa. I farmaci più utilizzati che il cardiologo dovrebbe conoscere.

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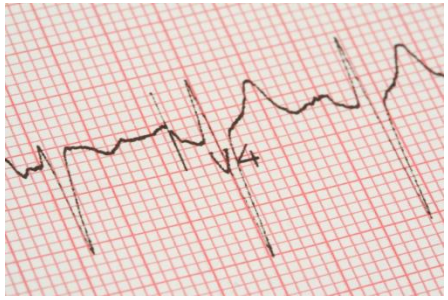
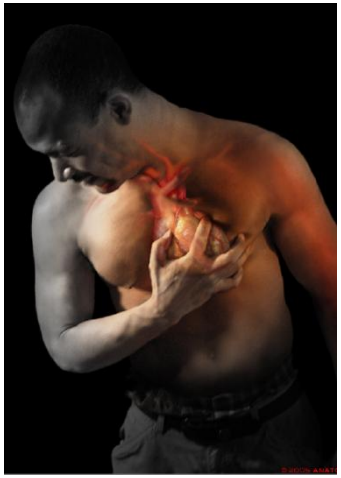
Cardiovascular Side Effects of Cancer Therapy

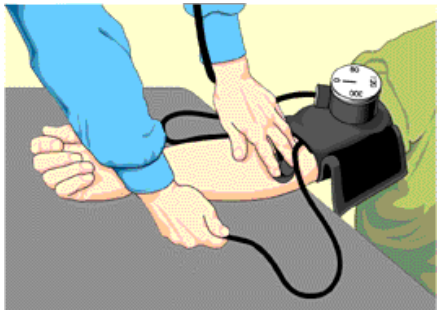


Arrhythmia



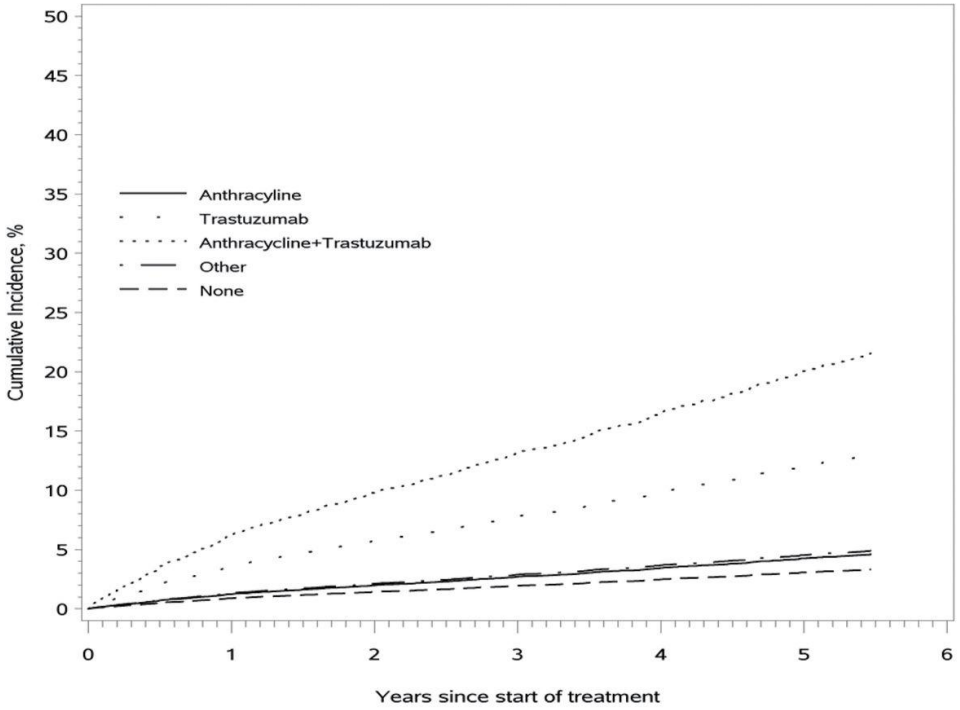
AP / MI

Cardiac Dysfunction
Heart Failure



Hypertension

Risk of heart failure in breast cancer patients after anthracycline and trastuzumab treatment



No. of patients at risk	Year 1	Year 2	Year 3	Year 4	Year 5
Anthracycline only	3443	3125	2699	2146	1659
Trastuzumab only	90	78	49	24	13
Anthracycline+ Trastuzumab	347	339	263	179	94
Other chemotherapy	2159	1905	1548	1192	958
None	5235	4798	4076	3288	2590
Cumulative incidence (95% CI), %					
Anthracycline only	1.2 (1.0 to 1.5)	2.0 (1.6 to 2.4)	2.7 (2.2 to 3.2)	3.5 (2.8 to 4.1)	4.3 (3.5 to 5.0)
Trastuzumab only	3.6 (1.5 to 5.6)	5.8 (2.5 to 8.9)	7.8 (3.4 to 12.0)	9.9 (4.3 to 15.1)	12.1 (5.3 to 18.3)
Anthracycline+ Trastuzumab	6.2 (4.1 to 8.2)	9.8 (6.7 to 12.8)	13.2 (9.1 to 17.1)	16.5 (11.5 to 21.3)	20.1 (14.0 to 25.6)
Other chemotherapy	1.3 (1.0 to 1.6)	2.1 (1.7 to 2.5)	2.9 (2.4 to 3.4)	3.7 (3.0 to 4.3)	4.5 (3.7 to 5.3)
None	0.9 (0.7 to 1.0)	1.4 (1.2 to 1.7)	1.9 (1.6 to 2.3)	2.5 (2.1 to 2.9)	3.1 (2.6 to 3.5)

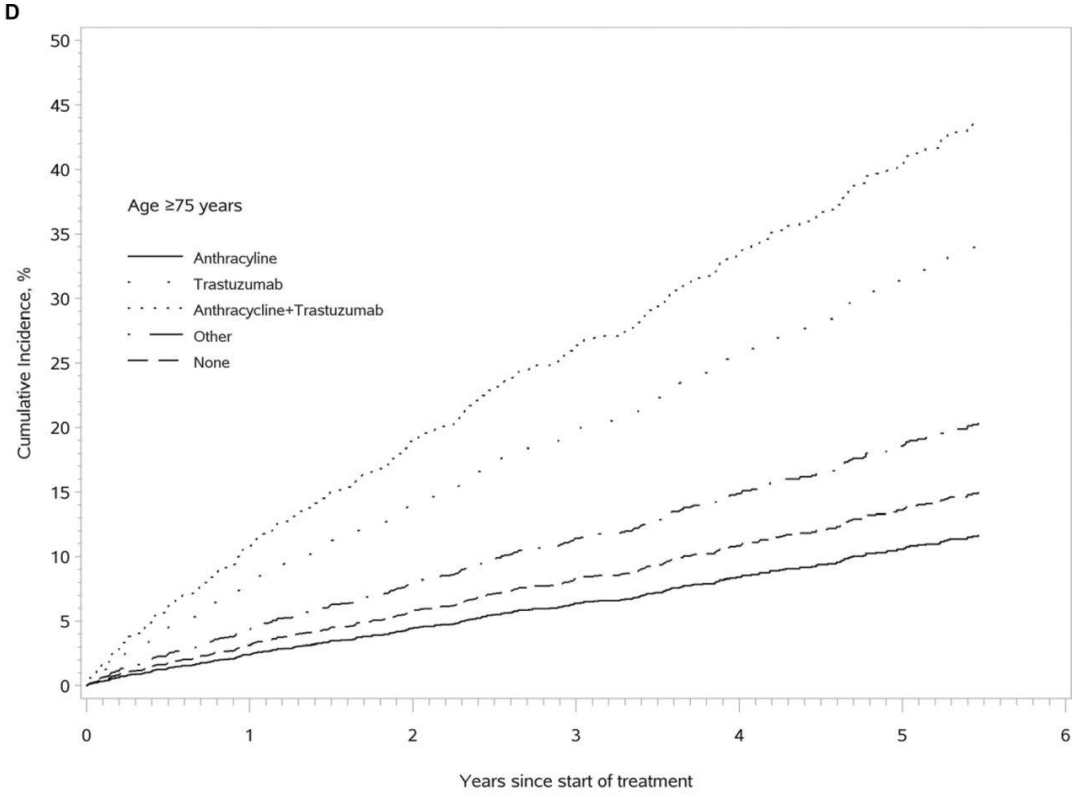
Bowles E J A et al Natl Cancer Inst. 2012 September 5; 104(17): 1293–1305.

Risk of heart failure in breast cancer patients after anthracycline and trastuzumab treatment

Among 12 500 women (mean age = 60 years, range = 22–99 years), 29.6% received anthracycline alone, 0.9% received trastuzumab alone, 3.5% received anthracycline plus trastuzumab, 19.5% received other chemotherapy, and 46.5% received no chemotherapy. Anthracycline and trastuzumab were primarily used in younger, healthier women and associated with increased HF/CM risk compared with no chemotherapy.

Bowles E J A et al Natl Cancer Inst. 2012 September 5; 104(17): 1293–1305.

Risk of heart failure in breast cancer patients after anthracycline and trastuzumab treatment



No. of patients at risk	Year 1	Year 2	Year 3	Year 4	Year 5
Anthracycline only	76	66	52	43	31
Trastuzumab only	13	8	4	3	1
Anthracycline+ Trastuzumab	3	3	2	2	2
Other chemotherapy	412	348	270	184	140
None	1408	1244	1017	778	581
Cumulative incidence (95% CI), %					
Anthracycline only	2.4 (0.8 to 4.0)	4.4 (1.5 to 7.3)	6.4 (2.3 to 10.3)	8.4 (3.0 to 13.5)	10.6 (3.9 to 16.9)
Trastuzumab only	7.9 (0.0 to 16.3)	14.2 (0.0 to 28.1)	19.9 (0.0 to 38.0)	25.7 (0.0 to 47.2)	31.5 (0.0 to 55.7)
Anthracycline+ Trastuzumab	10.8 (0.0 to 24.1)	19.0 (0.0 to 40.0)	26.4 (0.0 to .2)	33.6 (0.0 to 62.7)	40.7 (0.0 to 71.6)
Other chemotherapy	4.4 (3.2 to 5.6)	8.0 (6.0 to 10.0)	11.4 (8.8 to 14.0)	14.9 (11.6 to 18.2)	18.7 (14.5 to 22.6)
None	3.2 (2.4 to 3.9)	5.8 (4.6 to 6.9)	8.3 (6.8 to 9.8)	10.9 (9.0 to 12.8)	13.7 (11.4 to 16.0)

Bowles E J A et al Natl Cancer Inst. 2012 September 5; 104(17): 1293–1305.

Risk of heart failure in breast cancer patients after anthracycline and trastuzumab treatment

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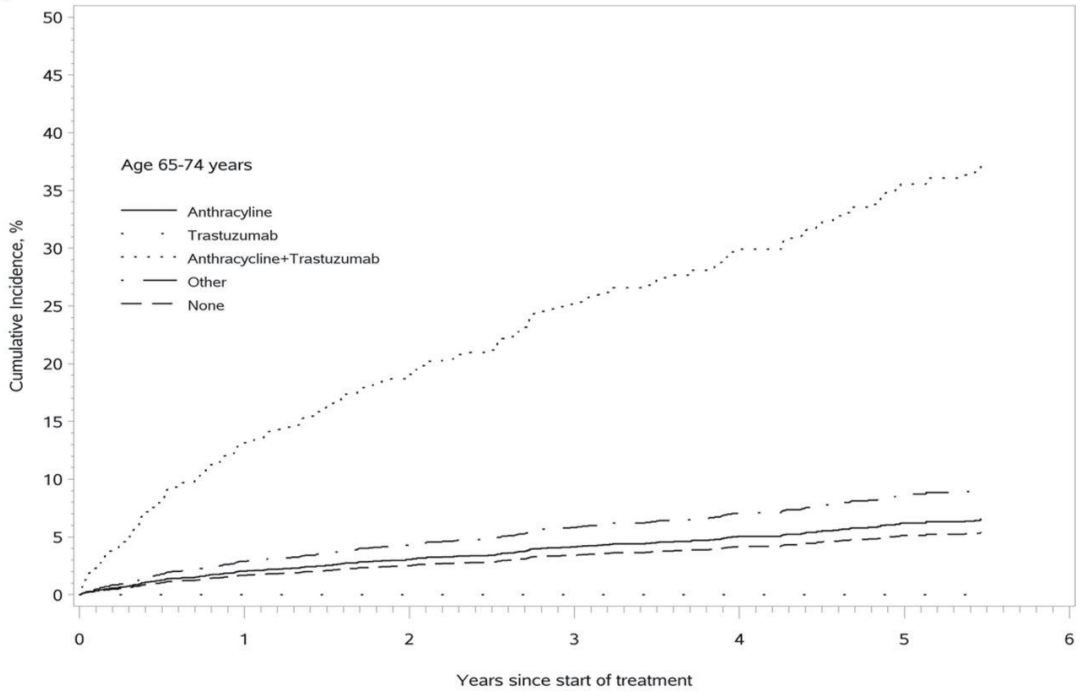


No. of patients at risk	Year 1	Year 2	Year 3	Year 4	Year 5
Anthracycline only	395	360	312	252	200
Trastuzumab only	17	16	9	3	1
Anthracycline+ Trastuzumab	29	27	22	15	6
Other chemotherapy	549	501	409	322	262
None	1492	1408	1218	1025	825
Cumulative incidence (95% CI), %					
Anthracycline only	2.1 (1.2 to 2.9)	3.0 (1.8 to 4.2)	4.1 (2.6 to 5.7)	5.0 (3.2 to 6.9)	6.2 (3.9 to 8.5)
Trastuzumab only	0.0	0.0	0.0	0.0	0.0
Anthracycline+ Trastuzumab	13.4 (3.8 to 21.9)	19.1 (5.9 to 30.4)	25.1 (8.3 to 38.9)	29.9 (10.2 to 45.3)	35.6 (12.5 to 52.5)
Other chemotherapy	2.9 (2.0 to 3.9)	4.3 (3.0 to 5.5)	5.8 (4.2 to 7.4)	7.1 (5.1 to 9.0)	8.7 (6.3 to 11.0)
None	1.7 (1.2 to 2.2)	2.5 (1.8 to 3.2)	3.4 (2.5 to 4.3)	4.2 (3.1 to 5.2)	5.1 (3.9 to 6.4)

Bowles E J A et al Natl Cancer Inst. 2012 September 5; 104(17): 1293–1305.

Anticancer Treatment associated with Left Ventricular Dysfunction

DRUG	TOXIC DOSE RANGE	TUMOR TYPE	%
Chemotherapeutics			
Doxorubicin **Epirubicin** **Idarubicin**	> 450 mg/m^2 > 720 mg/m^2	Breast cancer Leukemia	3-12% 0.9-3.3%
Paclitaxel **Docetaxel**	Conventional dose	Breast cancer Lung cancer Prostate cancer	5-15% 2.3-8%
Cyclophosphamide **Ifosfamide**	>100–120 mg/kg	Breast cancer Sarcomas	3-5%

Modified T. Yeh et al. JACC 2009; 53: 2231-2247

Anticancer Treatment associated with Left Ventricular Dysfunction

DRUG	TOXIC DOSE RANGE	TUMOR TYPE	%
Monoclonal Antibodies and Tyrosine Kinase Inhibitors			
Bevacizumab	Standard Dose	Breast cancer	1.7-3%
		Colorectal cancer	
		Renal cancer	
		NSCLC	
Trastuzumab		Breast cancer	2-25%
Bortezomib	Standard Dose	Multiple Myeloma	2-5%
Dasatinib	Standard dose	CML	2-4%
Imatinib mesylate		CML and GIST	0.5-1.7%
Lapatinib		Breast cancer	1.5-2.2%
Sunitinib		Renal Cancer and GIST	2.7-8.0%

Modified T. Yeh et al. JACC 2009; 53: 2231-2247

Anticancer Treatment associated with Ischemia

DRUG	TOXIC DOSE RANGE	TUMOR TYPE	%
Chemotherapeutics			
Capecitabine **Fluouracil**	Conventional dose	Breast Gastrointestinal	3-9% 1-68%
Paclitaxel **Docetaxel**	Conventional dose	Breast Lung Prostate	<1-5% 1.7%
Trabedectin	Conventional dose	Sarcomas	1%

Mod. T. Yeh et al. JACC 2009; 53: 2231-2247

Anticancer Treatment associated with Ischemia

DRUG	TOXIC DOSE RANGE	TUMOR TYPE	%
Monoclonal Antibodies and Tyrosine Kinase Inhibitors			
Bevacizumab	Standard Dose	Breast cancer Colorectal cancer Renal cancer NSCLC	0.6-1.5%
Erlotinib/Gefitinib		NSCLC	2-5%
Bortezomib	Standard Dose	Multiple Myeloma	2-3%
Sorafenib	Standard dose	Renal Cancer	2.7-3%
Sunitinib		CML and GIST Renal cancer	0.5-1.7%

Mod. T. Yeh et al. JACC 2009; 53: 2231-2247

Anticancer Treatment associated with Hypertension

DRUG	TOXIC DOSE RANGE	TUMOR TYPE	%
Anticancer Agents			
Bevacizumab	Standard Dose	Breast cancer Colorectal cancer Renal cancer NSCLC	4-35%
Sorafenib	Standard dose	Renal Cancer	17-43%
Sunitinib		CML and GIST	5-47%
		Renal cancer	
Pazopanib		Renal cancer	
Axitinib			45%

Mod. T. Yeh et al. JACC 2009; 53: 2231-2247

Anticancer Treatment associated with Venous Thromboembolism

DRUG	TOXIC DOSE RANGE	TUMOR TYPE	%
Anticancer Agents			
Cisplatin	Conventional dose	Lung Germ cell tumors	8.5%
Vinorelbine	Conventional dose	Breast Lung Prostate	<1-5% 3%
Lenalinomide **Thalidomide** **Bevacizumab** **Vorinostat**	Conventional dose	Myeloma TCL	1-75% 1-58% 5-15% 4.7-8%

Mod. T. Yeh et al. JACC 2009; 53: 2231-2247

Anticancer Treatment associated with bradycardia and QTc prolongation

DRUG	TOXIC DOSE RANGE	TUMOR TYPE	%
Anticancer Agents			
Thalidomide	Conventional dose	Myeloma	0.1-50%
Paclitaxel		Lung, breast	0.1-31%
Arsenic trioxide	Conventional dose	APL	26-93%
Dasatinib	Conventional dose	CML	1-3%
Lapatinib		Breast	1-16%
Sunitinib		Renal, GIST	4.7-8%
Nilotinib		CML	1-10%

Mod. T. Yeh et al. JACC 2009; 53: 2231-2247

QTc prolongation and drug development

Drug-induced QTc interval prolongation: A proposal towards an efficient and safe anticancer drug development

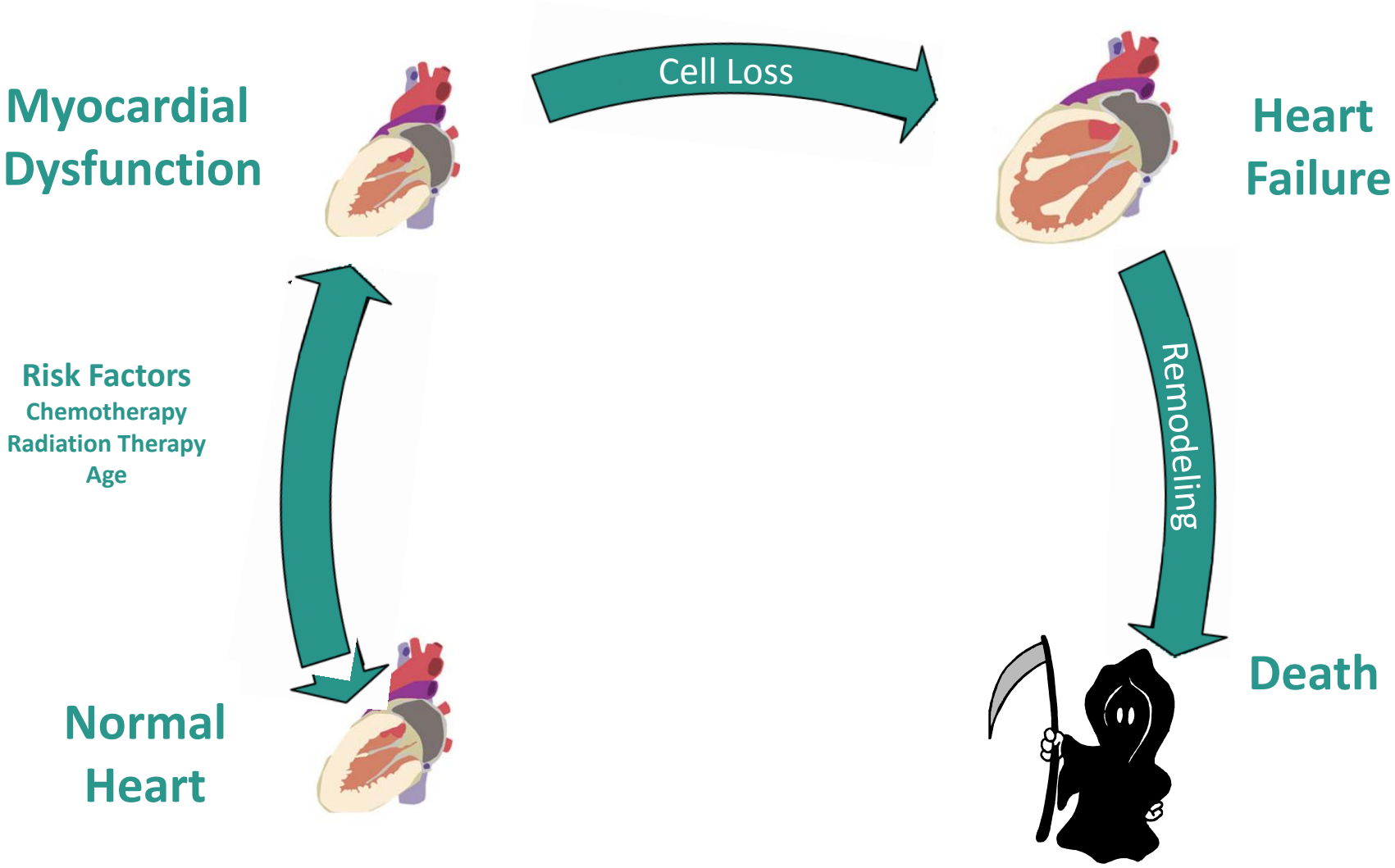
Giuseppe Curigliano[a,*], *Gianluca Spitaleri*[a], *Howard J. Fingert*[b], *Filippo de Braud*[a], *Cristiana Sessa*[c], *Elwyn Loh*[d], *Carlo Cipolla*[e], *Tommaso De Pas*[a], *Aron Goldhirsch*[a], *Rashmi Shah*[f]

Editorial Comment

QTc prolongation and/or oncology drug development: Who's in danger?

Maja de Jonge[*], *Jaap Verweij*

The cardiovascular disease continuum



Anthracycline Cardiotoxicity Dimension of the Problem

- Anthracycline cardiotoxicity is exponentially dose-dependent, with an average incidence of 5.1% at 400 mg/m^2 that becomes higher above 500 mg/m^2, with substantial individual variation.
- Dose-limitation strategies have reduced the incidence of anthracycline-related cardiac events. Actually the incidence of heart failure is approximately 1.6%, increasing to approximately 2.1% in patients who receive doxorubicin followed by paclitaxel.

Gianni L, Minotti G, Sawyer D.. JCO; 2008: 3777-3784

Anthracycline Cardiotoxicity
What we need from cardiologist?

- **Long-Term Studies in Animal Models**
- Long-term studies of anthracycline cardiotoxicity in animals must take precedence over short-term in vitro treatments of isolated cells

- **To identify Predictive Markers of Cardiac Damage**

Gianni L, …Minotti G, Sawyer D.. JCO; 2008: 3777-3784

Anthracycline Cardiotoxicity
What we need from cardiologist?

- To Understand Drug Interactions in New Combination Therapies

- To Assess Risk-Benefit Factors in Groups With Compounding Risk Factors for Cardiomyopathy

Gianni L,… Minotti G, Sawyer D.. JCO; 2008: 3777-3784

Anthracycline Cardiotoxicity
What we need from cardiologist?

- To Educate Clinicians: Anthracycline-Induced Cardiotoxicity Can Initially Respond to Cardiac Medications

Gianni L,… Minotti G, Sawyer D.. JCO; 2008: 3777-3784

Anthracycline Cardiotoxicity
What we need from cardiologist?

- To Define Risks and Benefits for Subgroups of Patients
- To Understand the Progression of Anthracycline Cardiomyopathy: Systolic Versus Diastolic Heart Dysfunction
- To help us in expanding rationally the Use of Dexrazoxane and Liposomal Anthracyclines

Gianni L, …Minotti G, Sawyer D.. JCO; 2008: 3777-3784

Target therapy: Cardiotoxicity

Efficacy and cardiotoxicity of trastuzumab for patients with advanced breast cancer

Table 1 Efficacy and cardiotoxicity from selected trials of trastuzumab for patients with advanced breast cancer.

Reference	Trial regimen	Setting	Sample size	Response rates	Cardiotoxicity
Baselga *et al.* (1996)[9]	Trastuzumab[a] weekly	Metastatic breast cancer; IHC HER2 overexpression	46	12%	1 cardiac death (previous anthracycline)
Cobleigh *et al.* (1999)[10]	Trastuzumab[b] weekly	Relapsed disease after 1–2 lines of chemotherapy; 2+ or 3+ IHC	222	15%	4.7% heart failure, cardiomyopathy, or LVEF drop >10%; 1 cardiac death
Vogel *et al.* (2002)[11]	Trastuzumab[b/c]	Progressive, metastatic disease, chemonaive for advanced disease; 2+ or 3+ IHC	114	26% total group 24% (2 mg/kg group) 28% (4 mg/kg group)	2.7% heart failure, cardiomyopathy, or LVEF drop >10%. Trastuzumab withdrawal in 1 patient due to persisting reduced LVEF, 1 patient due to progressive atrial and right ventricular enlargement, and 1 patient due to reduced LVEF secondary to malignant pericardial effusion
Slamon *et al.* (2001)[12]	AC/EC or P ± H[b] (weekly, concurrent with chemotherapy)	First-line metastatic disease; 2+ or 3+ IHC	234	50% chemotherapy + H 32% H alone	(A)symptomatic cardiac dysfunction in: 27% anthracycline + H 8% anthracycline alone 13% P + H 1% P alone 2 cardiac deaths (both with anthracycline-based regimens)

[a]Trastuzumab 250 mg loading, followed by 100 mg weekly for 10 doses. [b]Trastuzumab 4 mg/kg loading, 2 mg/kg maintenance weekly. [c]8 mg/kg loading, 4 mg/kg maintenance weekly. Abbreviations: AC/EC, doxorubicin 60 mg/m^2 or epirubicin 75 mg/m^2 and cyclophosphamide (6 chemotherapy cycles intended, 3-weekly); H, trastuzumab (Herceptin®); IHC, immunohistochemistry; LVEF, left ventricular ejection fraction; P, paclitaxel 175 mg/m^2 (6 chemotherapy cycles intended, 3-weekly).

Popat S and Smith IE (2008) Nat Clin Pract Oncol

Summary of cardiac toxicity with trastuzumab from adjuvant studies

Table 3 Summary of cardiac toxicity with trastuzumab from adjuvant studies.

Study and reference	Treatment arm	Arm sample size	Median follow-up (months)	Baseline LVEF (%)	Grade III/IV NYHA heart failure (%)	Cardiac deaths (*n*)
NCCTG N9831 Romond *et al*. (2005)[5] Baselga *et al*. (2006)[18] Perez *et al*. (2005)[20]	AC→P	819	18	≥50[a]	0	0
	AC→P→H	981			2.2	1
	AC→PH	814			3.3	1
NSABP B-31 Romond *et al*. (2005)[5] Tan-Chiu *et al*. (2005)[6]	AC→P	1,024	28.8	≥50[a]	0.8	1
	AC→PH	1,019			4.1	0
HERA Piccart-Gebhart *et al*. (2005)[15] Smith *et al*. (2007)[16]	Protocol specified chemotherapy alone	1,698	23.5	≥55[b]	0	1
	Protocol specified chemotherapy→H	1,703			0.6	0
FinHer Joensuu *et al*. (2006)[40]	T or V→FEC	116	35	NR	3[d]	0
	HT or HV→FEC	116	37		0[d]	0
BCIRG006 Slamon *et al*. (2006)[19]	AC→T	1,073	36	≥50[c]	0.3	0
	AC→TH	1,074			1.8	0
	TCH	1,075			0.3	0
E2198 Sledge *et al*. (2006)[41]	PH→AC	115	NR	≥50[c]	2.6[d]	0
	PH→AC→H	112	NR		3.6[d]	0

[a]Post-chemotherapy; [b]post-chemotherapy and pre-trastuzumab; [c]pre-chemotherapy; [d]congestive heart failure grade not defined. Abbreviations: AC, doxorubicin and cyclophosphamide; FEC, fluorouracil, epirubicin, and cyclophosphamide; H, trastuzumab (Herceptin®); HERA, HERceptin Adjuvant; LVEF, left ventricular ejection fraction; NCCTG, North Central Cancer Treatment Group; NR, not reported; NSABP, National Surgical Adjuvant Breast and Bowel Project; NYHA, New York Heart Association; P, paclitaxel; T, docetaxel; TCH, docetaxel, carboplatin, and trastuzumab; V, vinorelbine.

Popat S and Smith IE (2008) Nat Clin Pract Oncol

Risk factors for cardiotoxicity

Table 5 Risk factors for cardiotoxicity.

Patient characteristics	RR of Slamon pivotal[a] trial[12]	RR MD Anderson series[b,14]	RR NSABP B-31[6]
Age	1.56 (1.12–2.17)[c]	1.00 (0.98–1.03)	2.7 (1.2–6.2)[c,d]
Pre-existing hypertension	1.01 (0.44–2.31)	0.76 (0.37–1.56)	2.0 (0.95–4.3)
Prior RT	0.64 (0.34–1.23)	0.92 (0.53–1.62)	0.80 (0.38–1.7)[e]
Baseline LVEF	1.46 (0.56–3.79)	0.94 (0.91–0.98)[c]	0.15 (0.06–0.39)[c,f]
Diabetes	NE	2.38 (0.94–6.03)	0 (–)[g]
Coronary artery disease	NE	2.39 (0.94–6.05)	NE
Hyperlipidemia	NE	NE	0.44 (0.06–3.2)

[a]Data on patients receiving AC and trastuzumab. [b]Hazard ratio adjusted for trastuzumab use. [c]Significant results (relative risk with 95% CI). [d]For age 50–59 years compared with less than 50 years reference group. [e]Data on left-sided tumors treated by radiation. [f]Data presented on baseline LVEF >65%, similar significant result for baseline LVEF 55–64%. [g](–), no cardiac events observed in one comparator. Abbreviations: LVEF, left ventricular ejection fraction; NE, not evaluated; NSABP, National Surgical Adjuvant Breast and Bowel Project; RR, relative risk; RT, radiotherapy.

Popat S and Smith IE (2008) Nat Clin Pract Oncol

Trastuzumab Cardiotoxicity – Reversible !

HERA

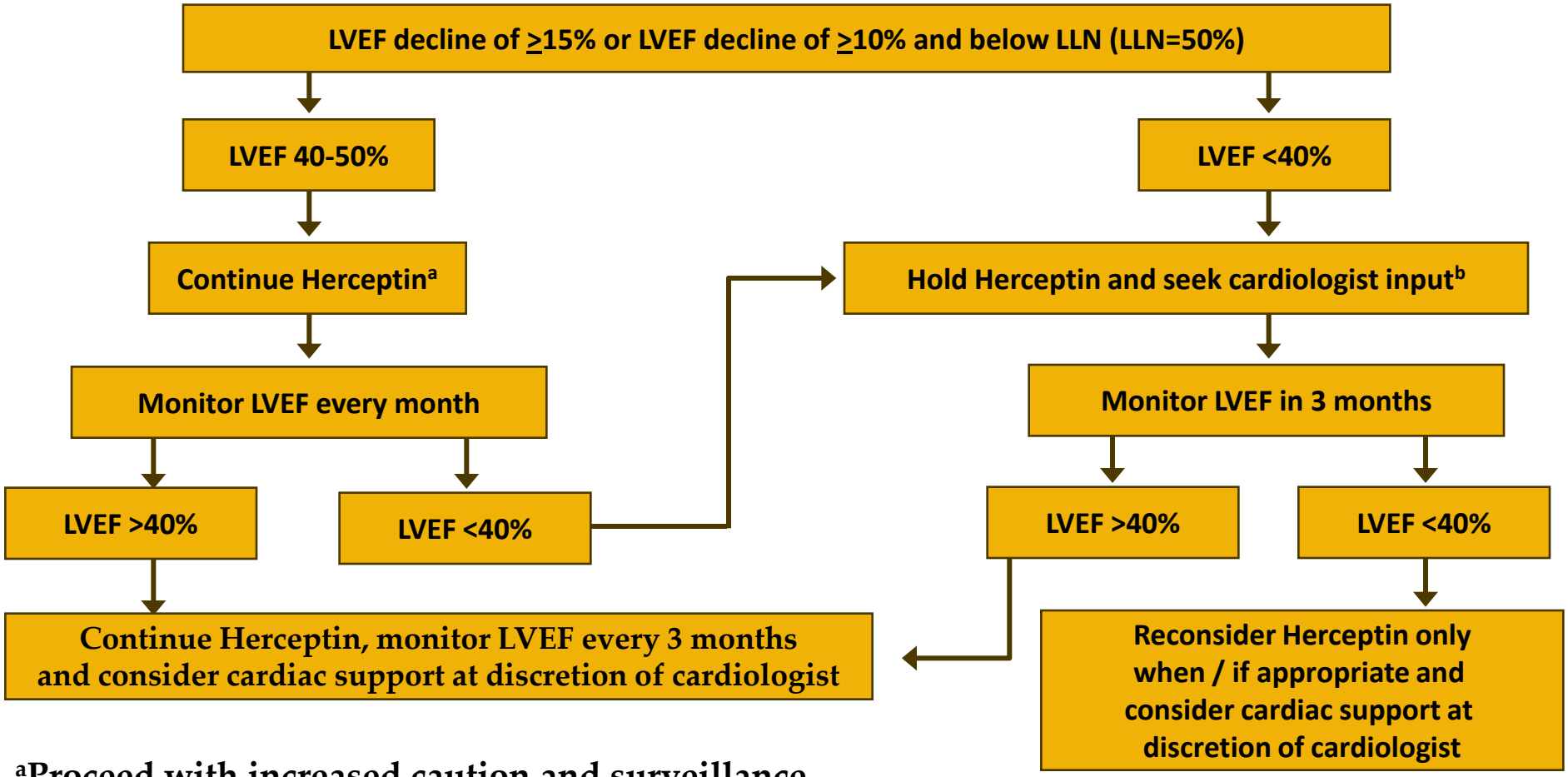
	Recovery (%)	Median Time (days)
Cardiac death	-	-
Severe CHF	80	124
Symptomatic CHF	67	151
Confirmed LVEF drop	69	192

NSABP B31

	Recovery (%)	Median Time (days)
Cardiac death	-	-
Severe CHF	-	-
Symptomatic CHF	85	-
Confirmed LVEF drop	-	-

Suter TM et al. JCO; 2007

Reporting and managing the safety of Trastuzumab



[a]Proceed with increased caution and surveillance
[b]Proceed with great caution

Ewer, St Gallen 2007

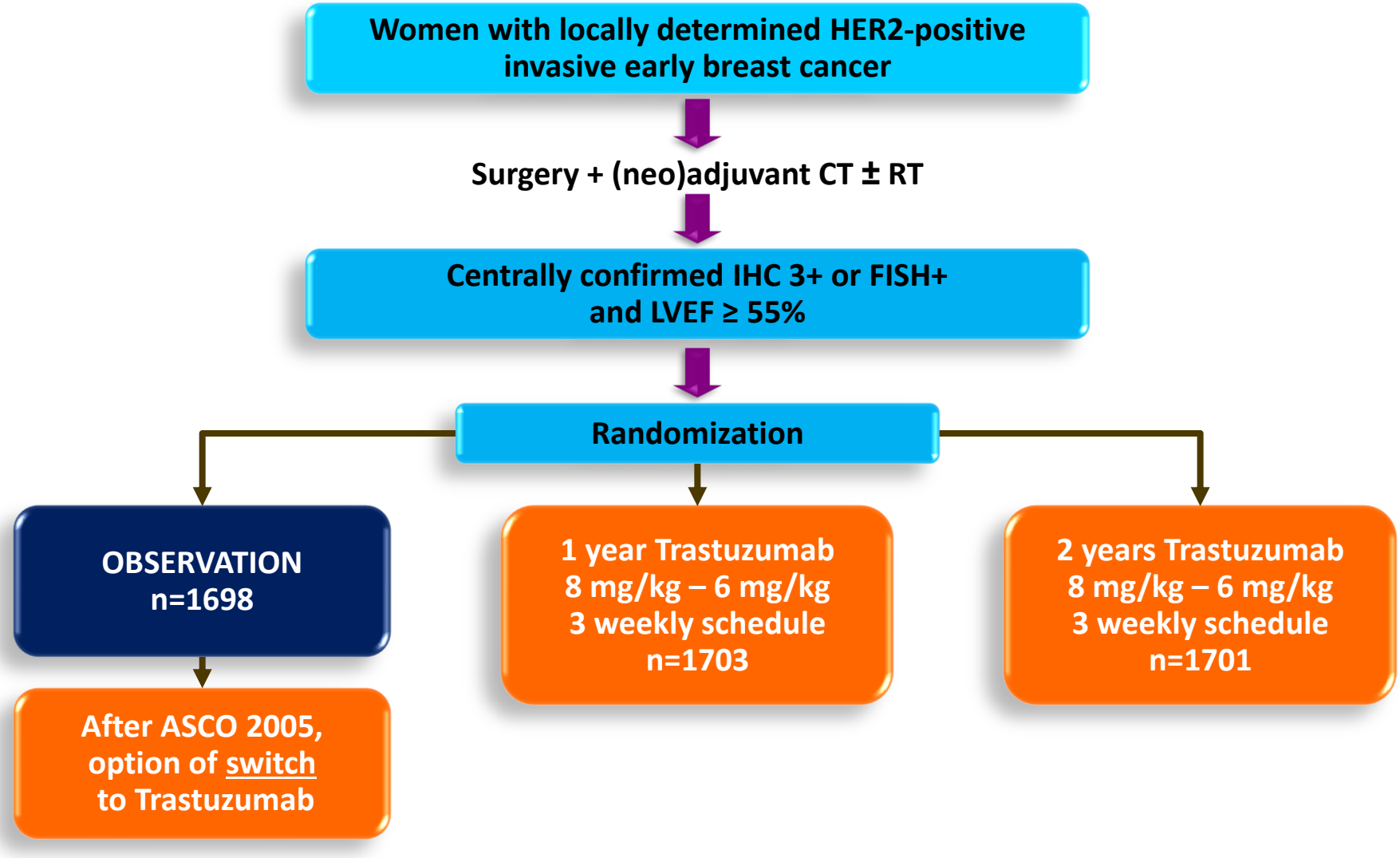
Assessing toxicity

CARDIAC GENERAL						Page 2 of 3
		Grade				
Adverse Event	Short Name	1	2	3	4	5
Hypotension	Hypotension	Changes, intervention not indicated	Brief (<24 hrs) fluid replacement or other therapy; no physiologic consequences	Sustained (≥24 hrs) therapy, resolves without persisting physiologic consequences	Shock (e.g., acidemia; impairment of vital organ function)	Death
ALSO CONSIDER: Syncope (fainting).						
Left ventricular diastolic dysfunction	Left ventricular diastolic dysfunction	Asymptomatic diagnostic finding; intervention not indicated	Asymptomatic, intervention indicated	Symptomatic CHF responsive to intervention	Refractory CHF, poorly controlled; intervention such as ventricular assist device or heart transplant indicated	Death
Left ventricular systolic dysfunction	Left ventricular systolic dysfunction	Asymptomatic, resting ejection fraction (EF) <60 – 50%; shortening fraction (SF) <30 – 24%	Asymptomatic, resting EF <50 – 40%; SF <24 – 15%	Symptomatic CHF responsive to intervention; EF <40 – 20% SF <15%	Refractory CHF or poorly controlled; EF <20%; intervention such as ventricular assist device, ventricular reduction surgery, or heart transplant indicated	Death
NAVIGATION NOTE: Myocardial infarction is graded as Cardiac Ischemia/Infarction in the CARDIAC GENERAL CATEGORY.						

Common Terminology Criteria for Adverse Events v 3.0 (CTCAE)

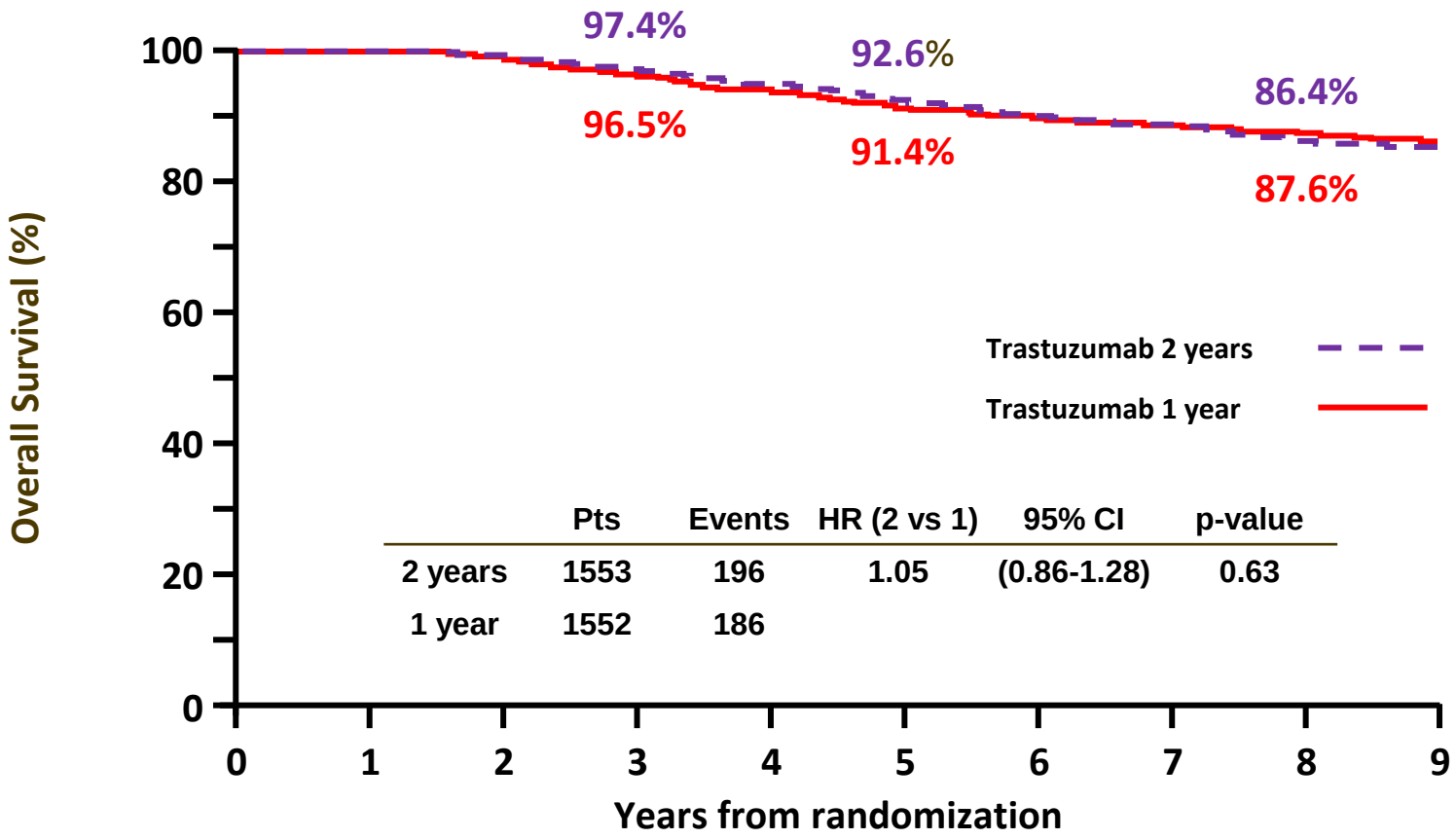
HERA TRIAL DESIGN

Accrual 2001 – 2005 (n=5102)



CT, chemotherapy; RT, radiotherapy

OS FOR 2 YEARS VS. 1 YEAR TRASTUZUMAB AT 8 YRS MFU



No. at risk										
Trastuzumab 2 years	1553	1553	1525	1485	1438	1382	1317	1193	708	208
Trastuzumab 1 year	1552	1552	1513	1461	1413	1364	1329	1218	732	225

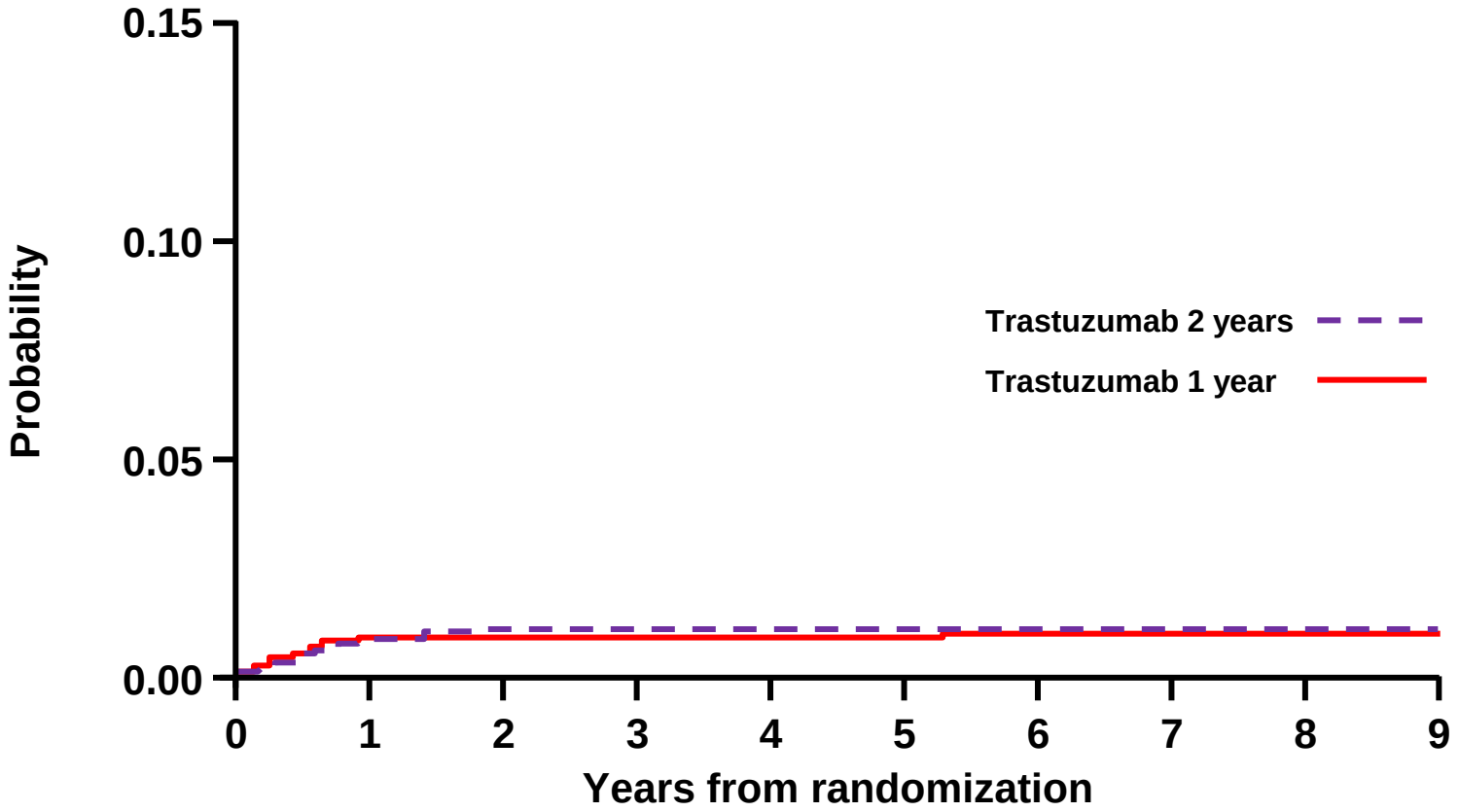
ADVERSE EVENTS (SAFETY ANALYSIS POPULATION)

	Observation Only N=1744	Trastuzumab 1 Year N=1682	Trastuzumab 2 Years N=1673
≥ 1 grade 3 or 4 AE	8.2%	16.3%	20.4%
Fatal adverse event	0.4%	1.1%	1.2%
Primary Cardiac[1]	0.1%	0.8%	1.0%
Secondary Cardiac[2]	0.9%	4.1%	7.2%

[1] NYHA class III or IV, confirmed by a cardiologist, and LVEF < 50% and ≥ 10% below baseline, OR cardiac death.

[2] LVEF < 50% and ≥ 10% below baseline confirmed by repeat assessment, excluding patients with a primary cardiac endpoint.

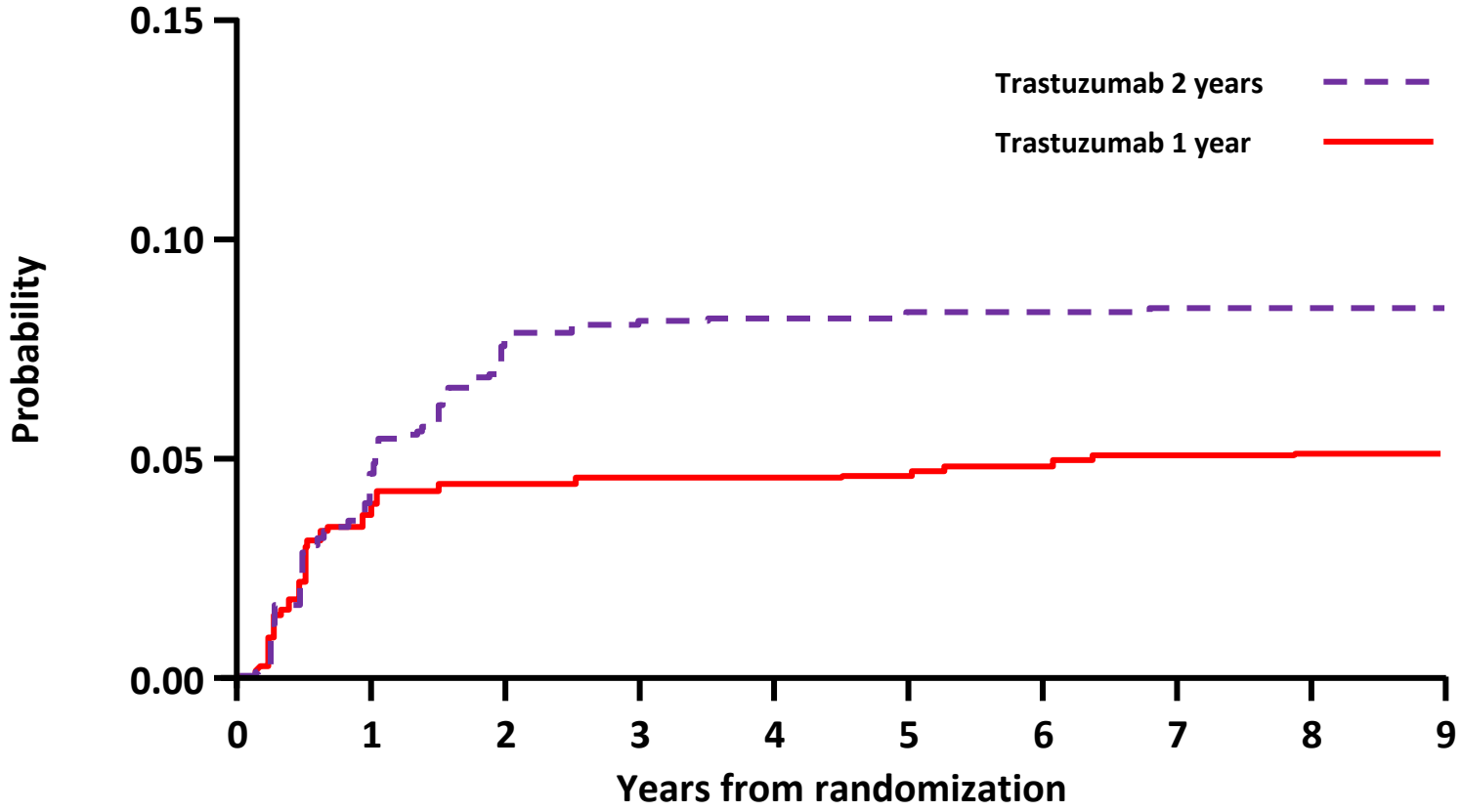
Cumulative incidence of PRIMARY CARDIAC ENDPOINTS*



No. at risk										
Trastuzumab 2 years	1673	1533	1423	1345	1276	1207	1137	1038	637	186
Trastuzumab 1 year	1682	1536	1399	1306	1254	1203	1169	1063	659	203

* Competing risk analysis with disease-free survival events considered as competing risks

CUMULATIVE INCIDENCE OF PRIMARY OR SECONDARY CARDIAC ENDPOINTS*



No. at risk										
Trastuzumab 2 years	1673	1466	1323	1248	1182	1116	1047	952	589	171
Trastuzumab 1 year	1682	1488	1350	1257	1206	1158	1125	1017	629	190

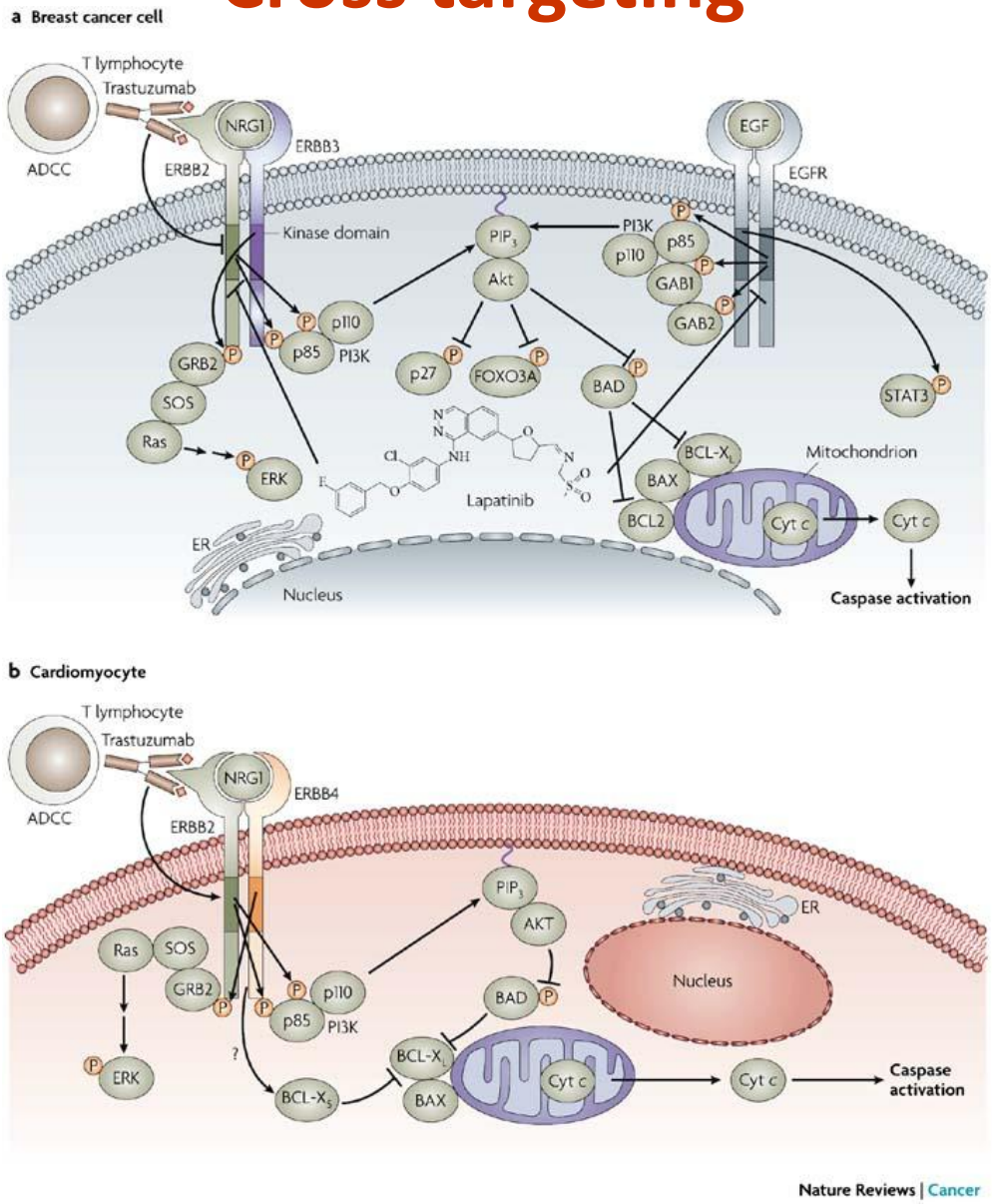
* Competing risk analysis with disease-free survival events considered as competing risks

SUMMARY: ANALYSIS OF 2 YEARS VS. 1 YEAR TRASTUZUMAB

- No evidence of long-term benefit of 2 years compared to 1 year trastuzumab when administered as sequential treatment following chemotherapy.
- Secondary cardiac endpoints and other adverse events are increased in the 2 years trastuzumab arm.
- Short term DFS gain for the 2 years arm in the hormone receptor negative cohort raises hypotheses, and illustrates need to evaluate results by receptor status.

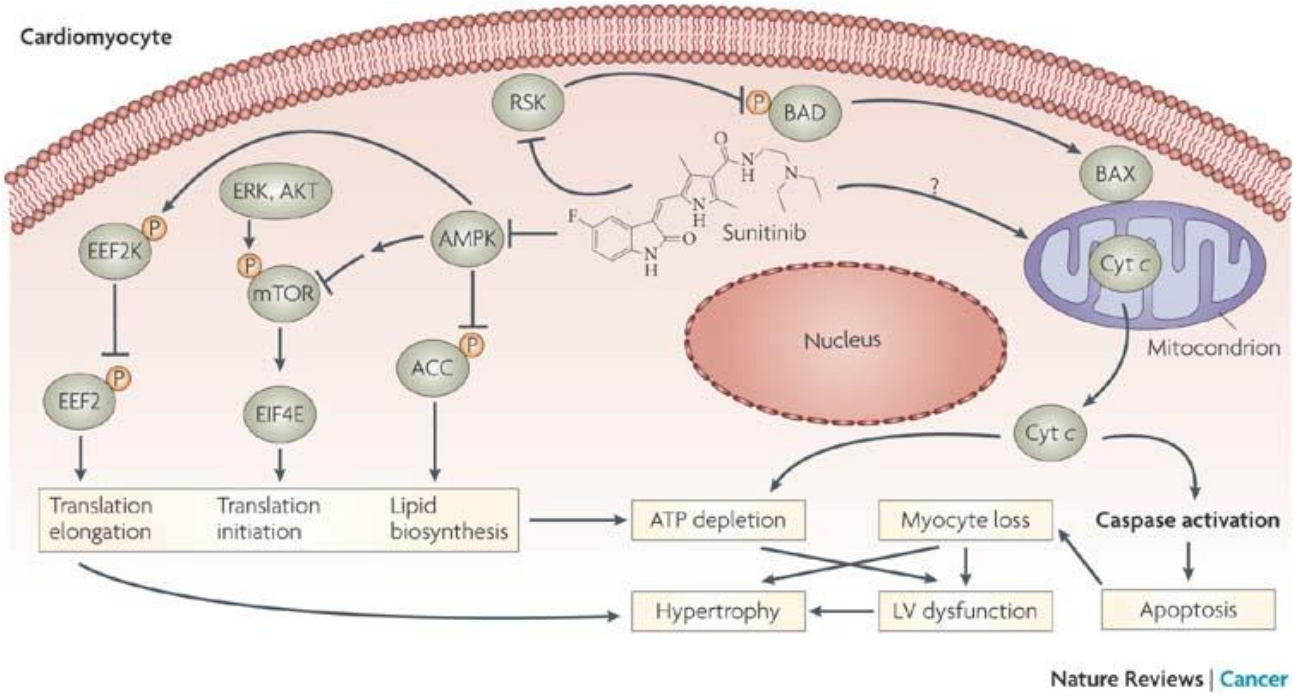
Cancer-Drug Associated Cardiotoxicity
The Future

Cross targeting



Force T *et al. Nature Reviews Cancer*, 2007

Cross targeting



Force T *et al. Nature Reviews Cancer*, 2007

Collaboration

Conclusions

- Is It Time for Oncologists to Get to Know Their Cardiologists?

- It is time for oncologists to engage cardiologists in the development of new drugs for cancer treatment!