Cardiovascular Effects of $ErbB_2$ & VEGF/ R Inhibitors

NZW 2008

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Objectives

- Describe the cardiovascular effects of the ErbB2 (HER-2) and VEGF/R inhibitors
- Identify risk factors associated with the development of cancer treatment related cardiovascular disease (CVD)
- Provide patient specific guidelines for the monitoring and treatment of cancer therapy induced CVD

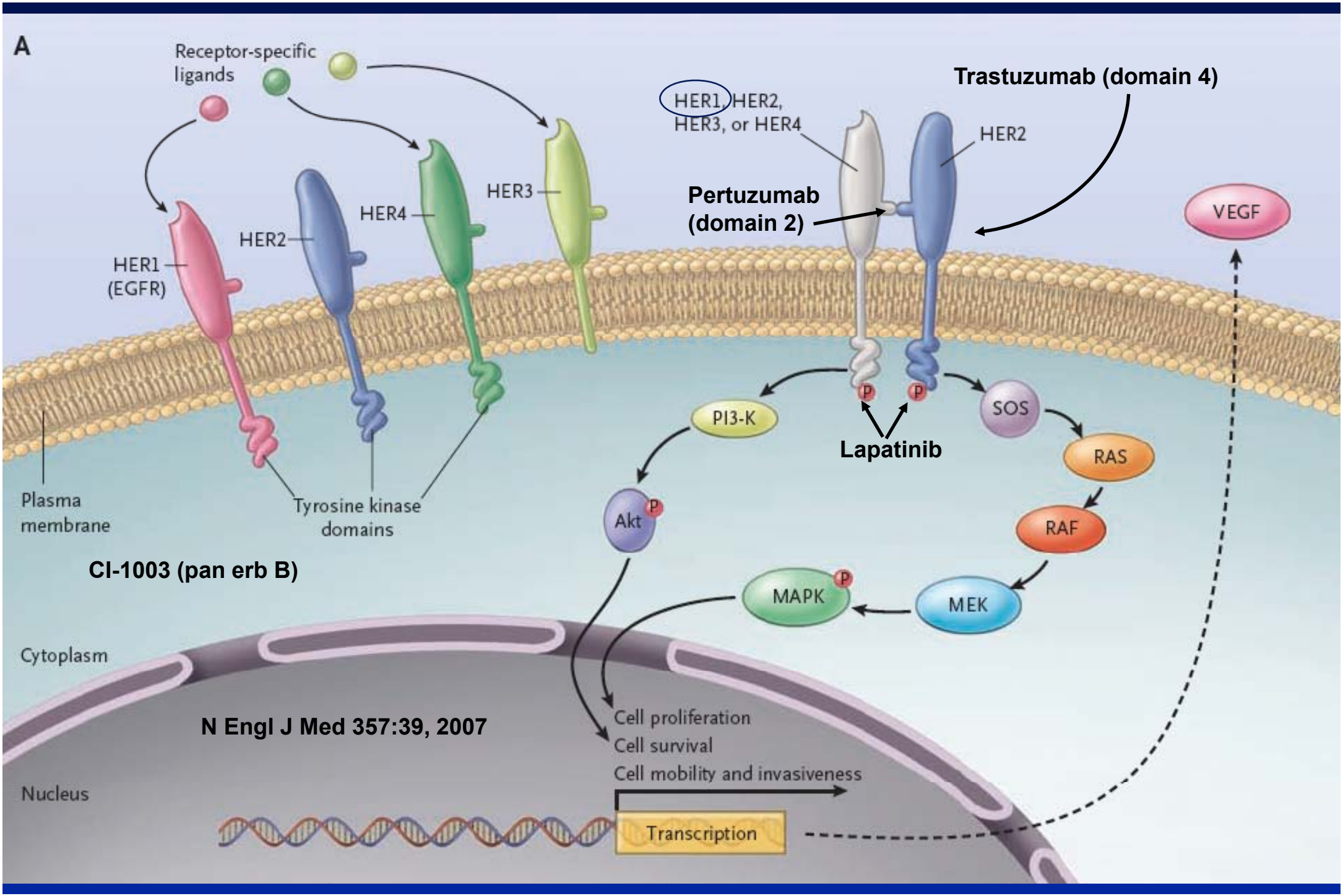
HER Family of Receptors

QuickTime™ and a
TIFF (Uncompressed) decompressor
are needed to see this picture.

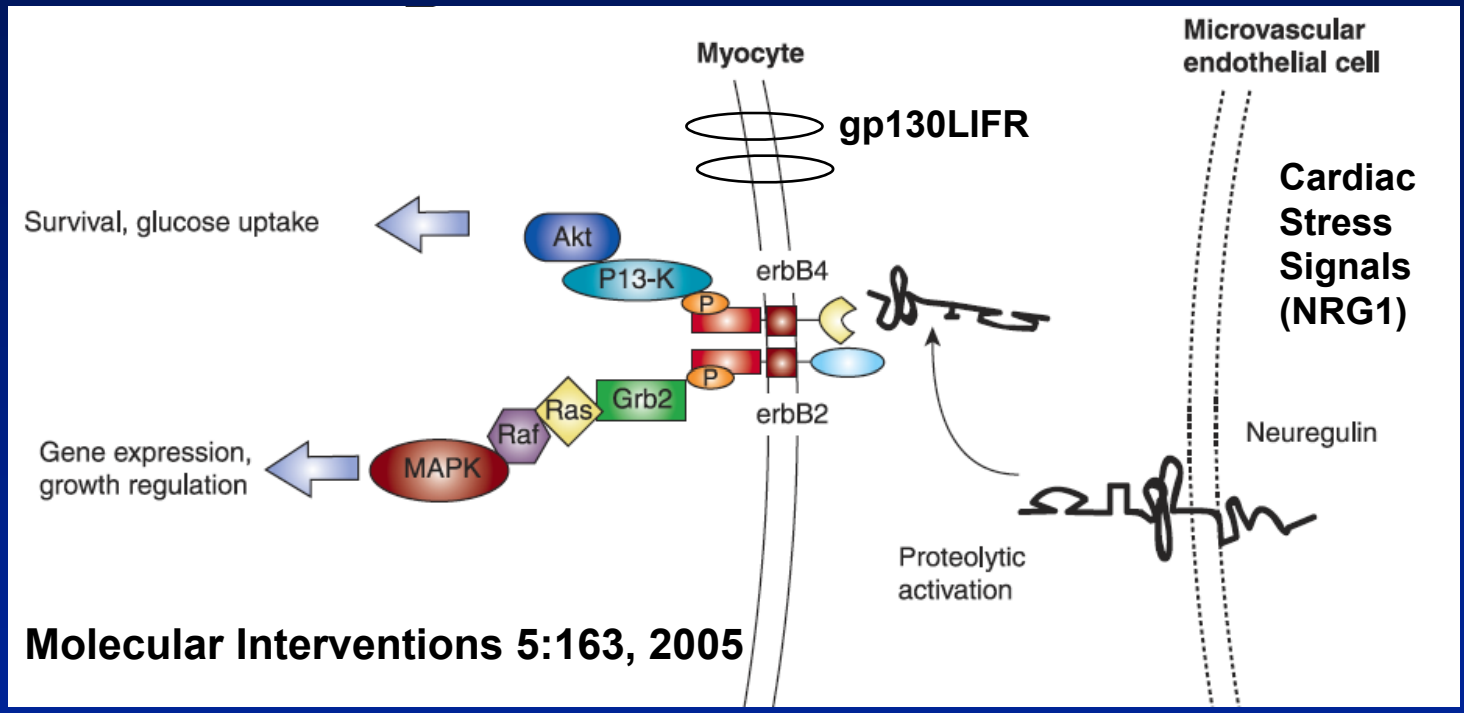
Mol Cell Proteomics 3:379, 2004

HER2 (HER2/neu or erbB$_2$) Receptor (4 domains)

- **Homo/Hetero** - dimerization with HER family
- Dimerization in **absent** of ligand
- Prolongs/Enchanges **activation** of signal transduction pathways: PIK$_3$/AKT; RAS/RAF
- Overexpressed (IHC) / Amplified (FISH) in **25%** breast cancer
- Correlates with **poor** prognosis
- **Trastuzumab** (adjuvant/metastatic) & Lapatinib + Capecitabine (Metastatic) FDA approved. Pertuzumab (Omnitarg) & CI-1033 Investigational


A
Receptor-specific ligands
HER1 (EGFR)
HER2
HER4
HER3
Plasma membrane
Tyrosine kinase domains
HER1, HER2, HER3, or HER4
HER2
Trastuzumab (domain 4)
Pertuzumab (domain 2)
VEGF
PI3-K
SOS
RAS
RAF
MEK
MAPK
Akt
P
Lapatinib
CI-1003 (pan erb B)
Cytoplasm
Nucleus
Cell proliferation
Cell survival
Cell mobility and invasiveness
Transcription
N Engl J Med 357:39, 2007

ErbB 2 and Cardiac Function



- ErbB2 essential for cardiac development (Nature 378:294, 1995)
- ErbB2 essential for maintenance of cardiac structure and function (Nat Med 8:459, 2002 & Proc. Natl Acad Sci 99:8880, 2002)

Characterization of Cardiac Dysfunction

Asymptomatic, decreased left ventricular ejection fraction (LVEF)

- Declines in **LVEF of ≥10%** from baseline

Symptomatic congestive heart failure (CHF)

- New York Hear Association (NYHA) Class III or IV

Class	Definition (Patients with Cardiac Disease)
1	Asymptomatic with ordinary activity
2	Symptomatic* with ordinary activity
3	Symptomatic with < ordinary activity
4	Symptomatic at rest

*(fatigue, palpitations, dyspnea, angina)

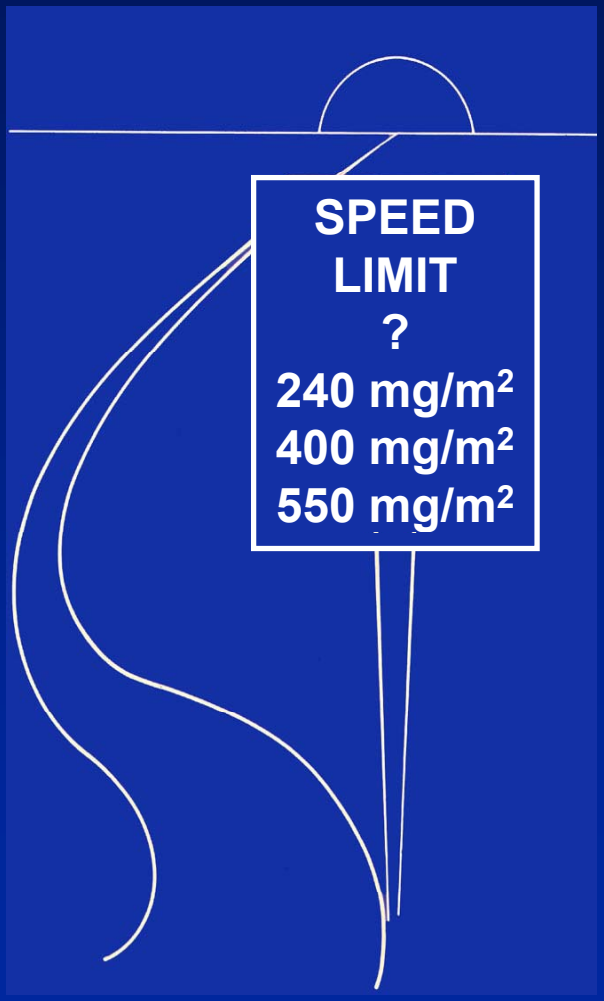
Anthracycline's Associated Cardiotoxicity

- Acute EKG changes - PVCs, ST-Twave changes (usually transient)
- Chronic - CHF (cumulative & dose related)
  - Ultrastructural changes on myocardial biopsy (Type I) JCO 23:2900, 2005

Total dose Doxorubicin (incidence)

240 mg/m^2 (3%); 400 mg/m^2 (5%); 550 mg/m^2 (26%); 700 mg/m^2 (48%) Cancer 97:2869, 2003; JCO 20:1215, 2002

- Other risk factors (age, mediastinal radiation [250 mg/m^2 = 500 mg/m^2]), preexisting cardiac disease, concurrent cytotoxics/biologics, schedule (Contin infusion/weekly < IV bolus Q 3 wks) Leukemia/Lymphoma 47:1599, 2006
- Dexrazoxane cumulative anthracycline dose of >300 mg/m^2 (JCO 17:333, 1999)



Good News

- Doxorubicin induced cardiomyopathy (CMP) previously associated with poor prognosis

	Doxorubicin-induced CMP (n=19)	
	Baseline	Treatment*
NYHA	Class 3/4 76%	↓Class 1 (53%)E2
LVEF	↓26 ± 9%	↑35 ± 17%

*(ACE inhibitors + Beta blockers)
J Heart Lung Transplant 24:2196, 2005

Adjuvant Trastuzumab Cardiotoxicity

NSABP B-31	AC → P	AC → PH
Asymptomatic ↓ LVEF ≥ 10%	17%	34%
%CHF (NYHA 3/4) JCO 23:7811, 2005	0.8%	3.9%

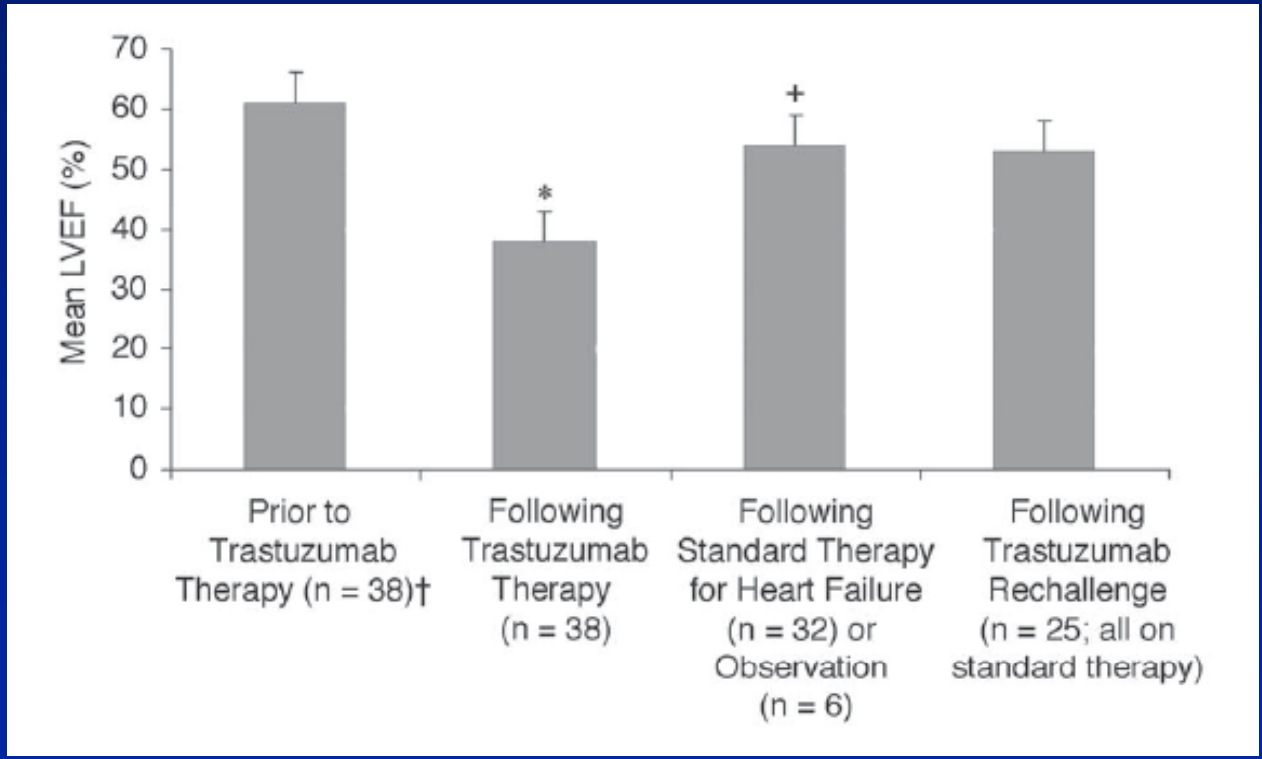
BCIRG (SABC, 2006)	AC → D	AC → DH	DCH
Asymptomatic ↓ LVEF ≥10%	10%	18%	8.6%
% CHF (NYHA 3/4)	0.3%	1.9%	0.3%

BETH Study

Chemotherapy + H +/- Bevacizumab (Benefit of anthracycline confined to HER2 + with Topo2 co-amplification)

Better News - Reversibility of Trastuzumab Cardiotoxicity

- **Type II** myocardial dysfunction - no ultra structural abnormalities. JCO 23:2900, 2005
- Changes in LVEF from baseline to re-treatment with trastuzumab



JCO 23:7820, 2005

Assessment & Medical Management

- **Risk** factors: (Cumulative dose, hypertension, CAD, schedule of administration)
- Cardiac **monitoring**: echocardiography/radionuclide ventriculography (Doppler echo, troponin I & T, B-type natriuretic peptide) no prospective trials (J Nucl Cardiol 13:415, 2006)
- **Beta-blockers** and **angiotension-converting enzyme** (ACE) **inhibitors** (ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure in the adult) Circulation 112:154, 2005

Recommendation (Stage A & B) - At Risk

I. **Stage A** (Asymptomatic, No S&S, or structural disease) patients at risk (hypertension, DM, metabolic syndrome, cardiotoxins)
   - ACE inhibitors (ACEIs) or Angiotension Receptor Blockers (ARB) - intolerant to ACEIs (Level of Evidence:A)

II. **Stage B** (Asymptomatic (NYHA Class I) Left Ventricular Systolic Dysfunction
   - ACEIs in patients with a reduced LVEF (≤40%) & no symptoms of HF (level of Evidence:A)
   - β blockers in all patients who have a reduced LVEF (≤40%) (Level of Evidence:C)
   - ACEIs & β blockers in all patients with a recent or remote HX of MI regardless of HF (Level of Evidence:A)

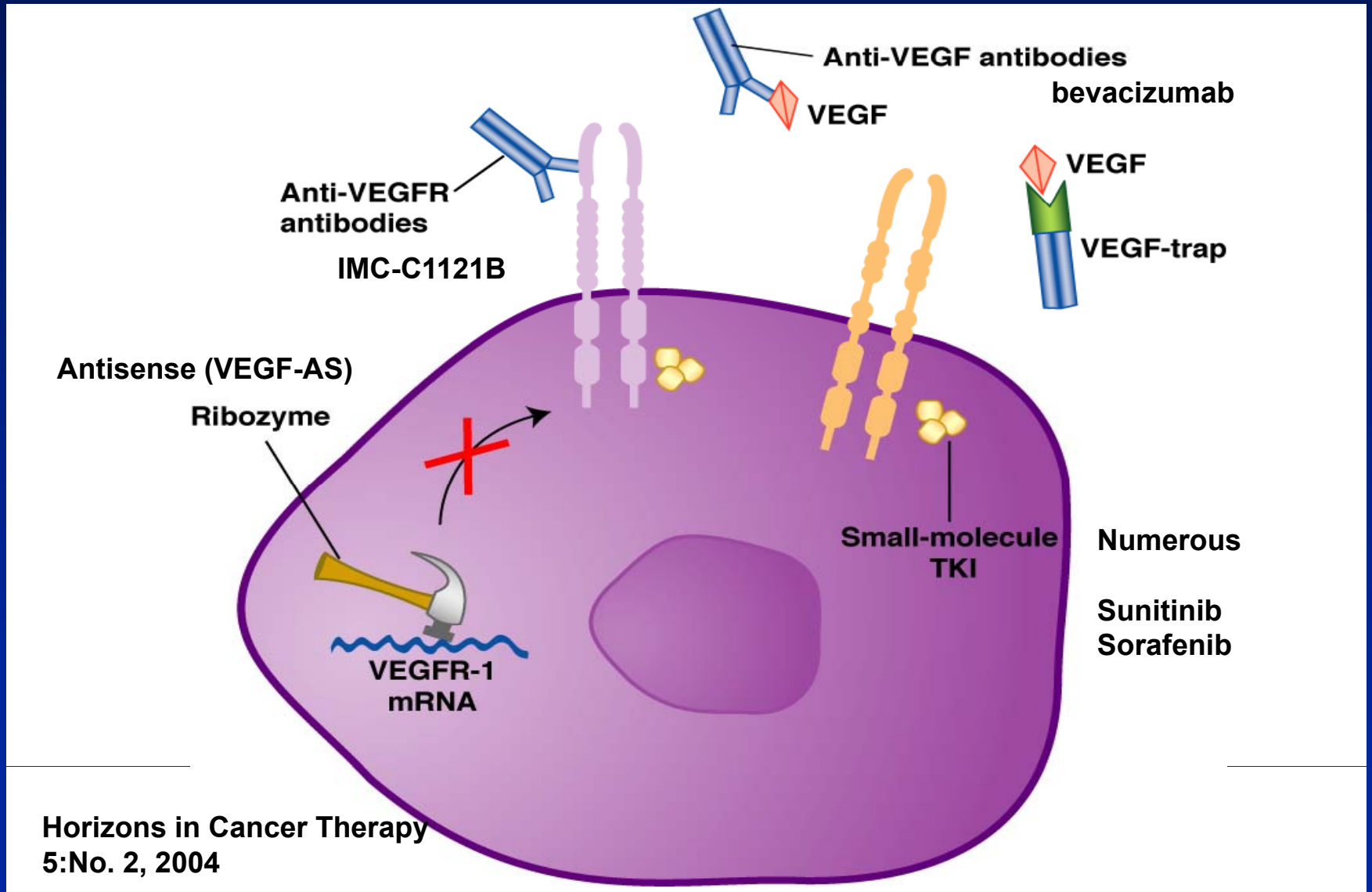
Circulation 113:2851, 2006 J Cardiac Failure 12:10, 2006

Medications for Treatment of Various Stage of Heart Failure

Drug Class	Stage A	Stage B (NYHA Class I)	Stage C (NYHA Class II/III)	Metabolism (CYP)
ACE Inhibitors				
Captopril (Capoten)	H, DN	Post MI	HF	2D6/renal
Enalapril (Vasotec)	H, DN	↓ LVSD	HF	3A4/renal
Lisinopril (Zestril/Primivil)	H, DN	Post MI	HF	None/renal
Angiotension Receptor Blockers				
Valsartan (Diovan)	H, DN	Post MI	HF	None
Candesartan (Atacand)	H	--	HF	None
β-blockers				
Atenolol (Tenormin)	H	Post MI	--	None/renal
Bisoprolol (Zebeta)	H	--	HF	3A4 (major) 2D6 (minor) renal
Carvedilol (Coreg)	H	Post MI	HF	2C9 (major) 2D6 (major)
Metoprolol (Toprol XL) Succinate	H	--	HF	2D6 (major) Inhibits 2D6 (weak)

H-Hypertension; DN-diabetic nephrophathy; HF-Heart failure

Approaches to Modulating VEGF (R)



Horizons in Cancer Therapy
5:No. 2, 2004

What was the incidence of Grade 3*/4 hypertension for bevacizumab in the ECOG 4599 FDA registration trial?

1. 0.7%
2. 2%
3. 8%
4. 17%

*Grade 3 Systolic ≥180 mm Hg/Diastolic ≥105 mmHg

Answer (3)

1. 0.7% (Paclitaxel/Carboplatin)
2. 2%
3. 8% (Paclitaxel/Carboplatin + bevacizumab)
4. 17%

www.FDA.Gov/cder/foi/label/2006/125085s085lbl.pdf

"Hypertension with VEGF inhibitors is an emerging toxicity that Oncology Physicians, Nurses & Pharmacists must be comfortable in managing" (JCO 25:2993, 2007)

Incidence of Antiangiogenic Drug-Related Adverse Events*

Bevacizumab†	Sunitinib	Sorafenib
Hypertension (8%)	28% Hypertension (6%)	17% Hypertension (3%)
Diarrhea (25%)	40% Diarrhea (4%)	43% Diarrhea (2%)
17% Proteinuria (2%)	53% Neutropenia (10%)	18% Neutropenia (5%)
Bleeding (3%)	38% Thrombocytopenia (5%)	12% Thrombocytopenia (1%)
DVTs (9%)	22% Asthenia (5%)	31% Fatigue (5%)
2% GI Perforation	14% Hand-foot skin rxn (4%)	30% Hand-foot- skin rxn (6%)
Hemoptysis (31% squamous; 4% adeno)	14 % Rash (1%)	40% Rash (1%)

*(Grade 3/4 compared to placebo) MicroMedex •ECOG 4599 †incidence dose dependent
JCO 25:2993, 2007

Angiogenesis Inhibitors (AI): Hypertension Monitoring & Management

NCI Grade	Bp Monitoring	Antihypertensive RX
Grade 1 <140 mmHg Systolic <90 mmHg Diastolic	• Standard (JNC7-JAMA 289:2560, 2003)	• None • Consider Diuretic (Chlorthalidone) Hypertension 47:352, 2006
Grade 2 - Mild 140-149 Systolic 90-99 Diastolic	• Increase frequency until stabilized	• Increase (max dose) of existing Meds or • Initiate BB or • Initiate DHP-CCB
Persistent Moderate* 150-179 Systolic 100-105 Diastolic	• Increase frequency until stabilized (eq. q48 hrs) • Supervised by Healthcare professional	• Initiate BB or • Initiate DHP-CCB • ACEI &/or ARB OR • Vasodilator &/or • Increase (max dose of existing Meds)

*Dose modifications: Partial or no control for 24-48 hrs, hold agent(s)
Add additional drugs (max dose) until hypertension controlled
Consider dose reduction of AI (monitor for hypotension)

Angiogenesis Inhibitors (AI): Hypertension Monitoring & Management (Cont.)

NCI Grade	Bp Monitoring	Antihypertensive RX	AI Dose Modification
Grade 3 - Severe ≥180 mmHg Systolic ≥105 mmHg Diastolic	• Every 48 hrs until stabilized • Supervised by healthcare professional	• 2 drug combination (DHP-CCB plus ____) • Dose escalated to max dose • Partial or no BP control, add additional agents	• Hold agent(s) • Bp Mild range, restart AI lower dose level • Partial or no Control reduce AI dose another level or DC AI
Grade 4 Hypertensive Crisis	• Hospitalize for management	• Optimal support in ICU	• DC AI Monitor for hypotension

(BB) Selective Beta Blockers (DHP-CCB) Dihydropyridine Calcium-Channel Blockers
(ACEI) Angiotension Converting Enzyme Inhibitor (ARB) Angiotension II Receptor Blockers
†AZD2171 - 3 patients hypertensive crisis (JCO 25:3045, 2007)

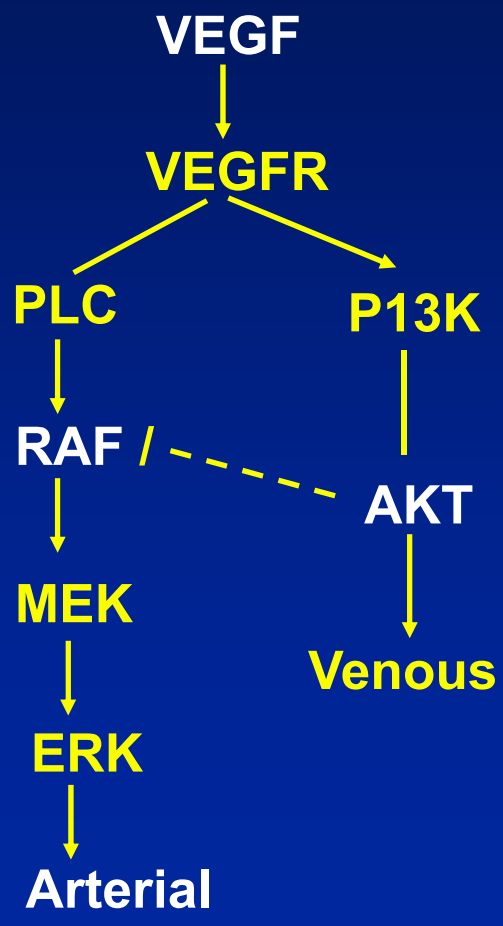
Footnotes

- **Calcium antagonists & α-blockers are less effective in preventing heart failure**
- **ACEIs and β-blockers, as single therapies are not superior to other antihypertensive drug classes in reduction of all cardiovascular outcomes**

ACC/AHA 2005 Guideline: Circulation 112:154, 2005

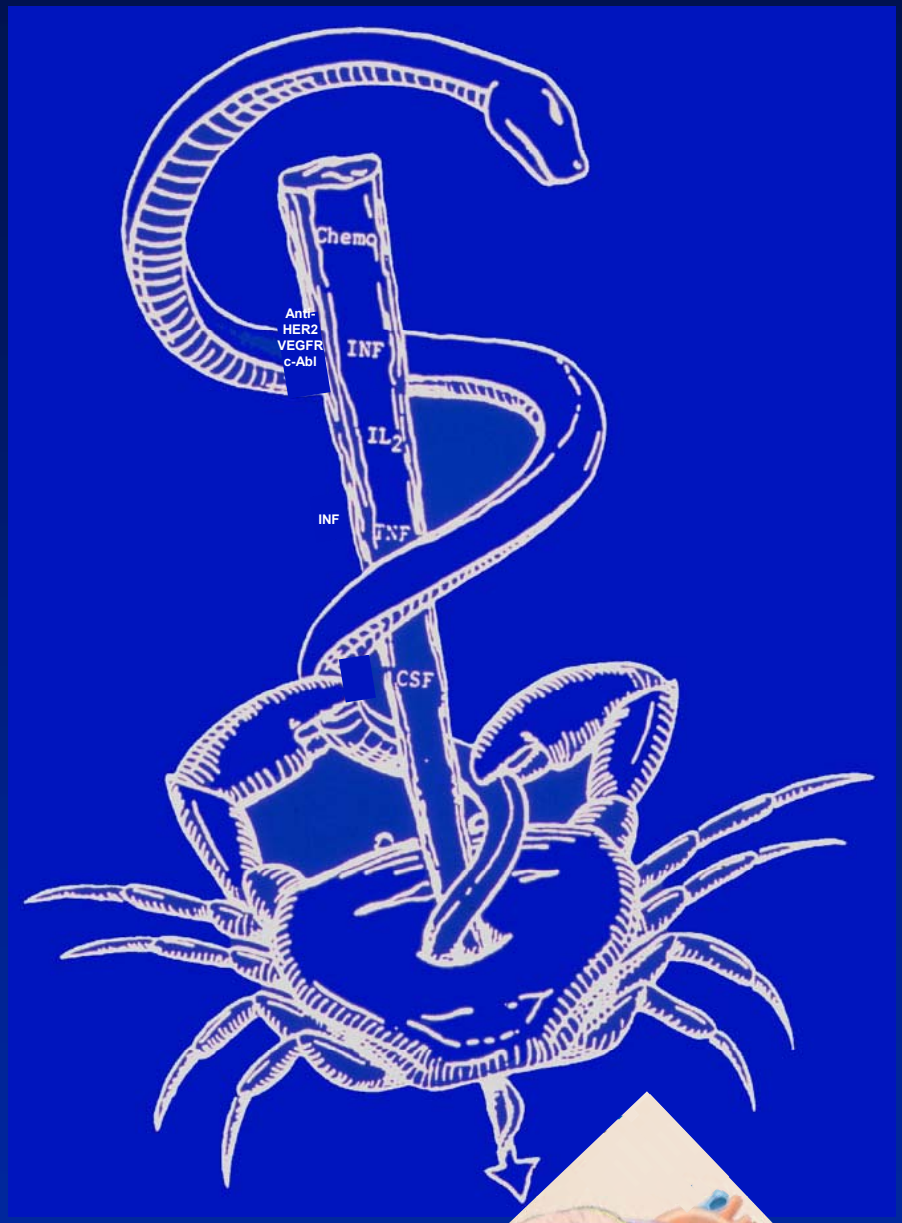
Clinical Pearls

- **Heart Failure** induced by **Non**-Cardiac Drugs (eg. Glitazones, NSAIDs) Drug Safety 29:567, 2006
- Rosiglitazone (Avandia®), insulin sensitizer, decreases **VEGF**-endothelial cell migration (Life Sciences 78:1520, 2006) Black Box
- Artery/Vein **differentiation** governed by opposing P13K and MAPK/ERK signaling
- **Aldosterone** reduces mRNA levels of VEGFR2 & phosphorylation of Akt (Hypertension 48:490, 2006)
  - Spironolactone augments cisplatin **nephrotoxicity** (Food Chem Tox 44:1173, 2006)



Current Biol 16:1366, 2006

THANK YOU



NEJM 354:789, 2006