Cardiotoxicity of molecular targeting agents

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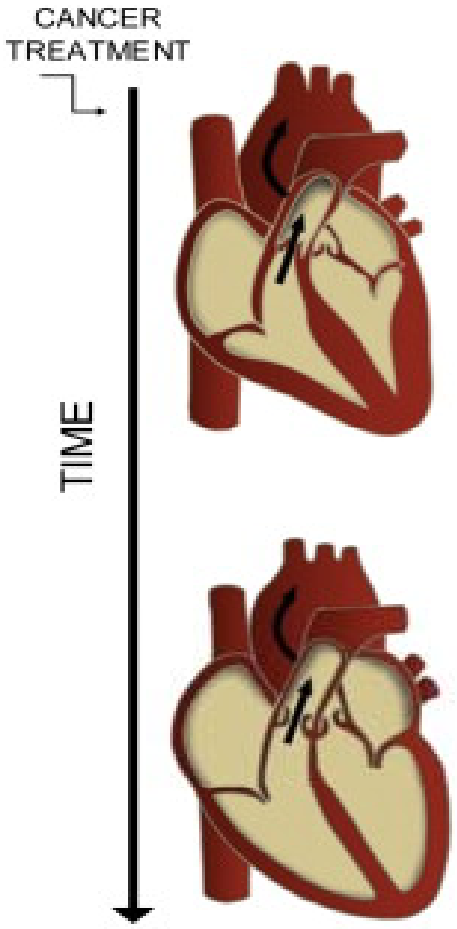
Hadassah Ein Kerem

Cardiac toxicity



	TIME TO DETECTION OF HEART DYSFUNCTION WITH DIFFERENT STRATEGIES
NORMAL HEART	- GENETIC SUSCEPTIBILITY - PRE-EXISTING RISK FACTORS FOR CARDIOVASCULAR DISEASE - FACTORS ASSOCIATED WITH AN INCREASED RISK OF CARDIOTOXICITY
MYOCYTE DYSFUNCTION WITHOUT LEFT VENTRICULAR DYSFUNCTION	- SERUM AND CELLULAR BIOMARKERS - MOLECULAR IMAGING - ECHOCARDIOGRAPHY
LEFT VENTRICULAR DYSFUNCTION	- ECHOCARDIOGRAPHY - ECG

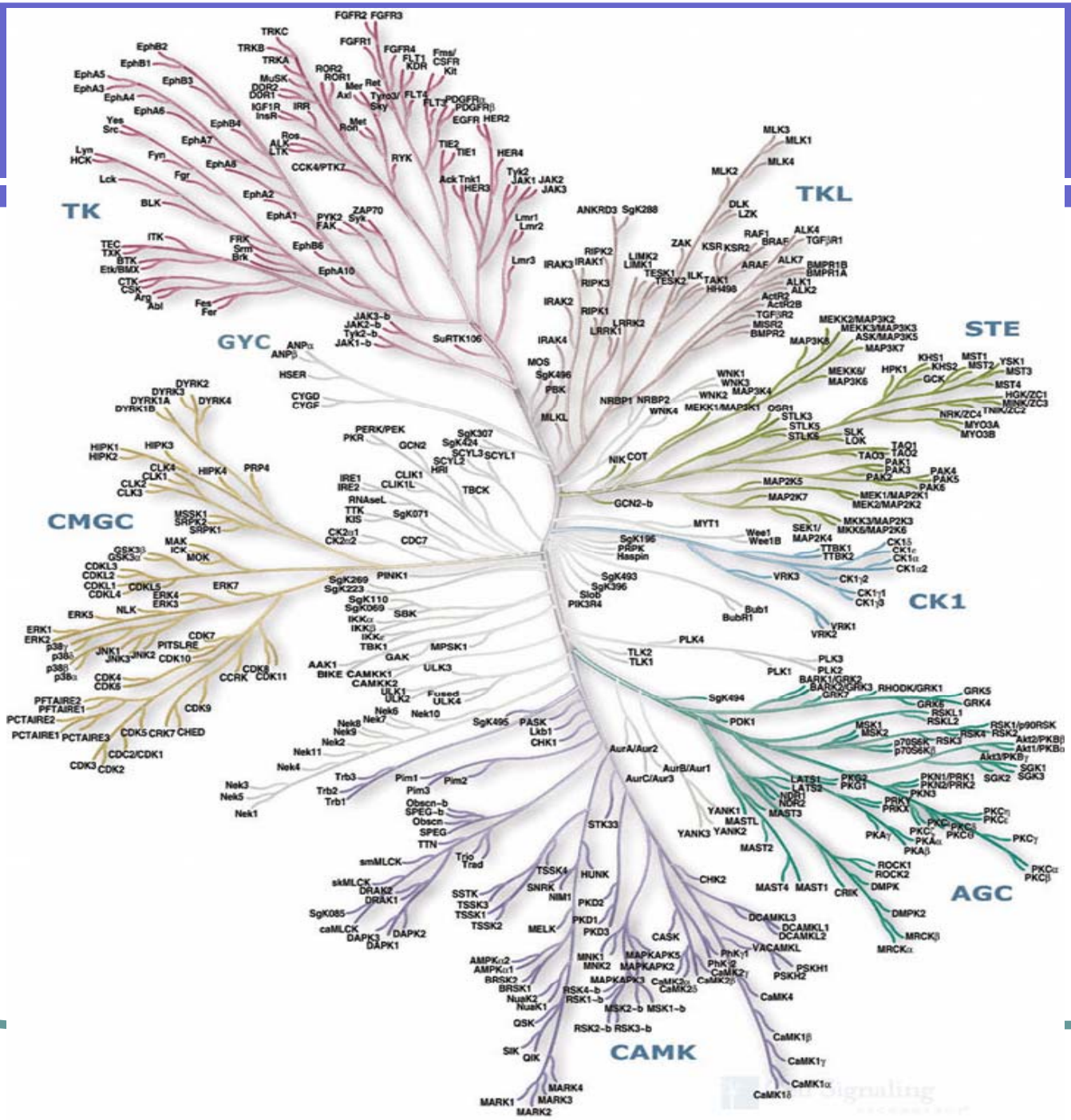
- Markers and imaging to identify early cardiac dysfunction are outside the scope of this lecture
- Interesting to note that most recently proBNP a protein elevated in cardiac dysfunction has been claimed to be an earlymarker for efficiency of sunitinib in RCC

Outline

- Molecular targeting agents
  - More specific, less toxicity
  - Unexpected toxicity
- ErbB2
  - Herceptin, Lapatinib
- KIT
  - Imatinib, dasatinib, nilotinib
- Multitarget vegf inhibition
  - Sorafenib, Sunitinib

Tyrosine kinase inhibitors

- Currently around 80% of cancer developmental funds to these kind of drugs
- 20% of total drug development in medicine!!
- (cir research 6-2010)


TK
TKL
STE
GYC
CMGC
CK1
AGC
CAMK
FGFR2 FGFR3
TRKC
FGFR1
FGFR4
FLT1
KDR
Fms/
CSFR
Kit
TRKB
TRKA
EphB2
EphB1
EphA5
EphA3
EphB3
EphA4
EphA6
EphB4
EphA7
EphA8
EphA2
EphA1
EphB6
EphA10
Yes
Src
Lyn
HCK
Fyn
Fgr
Lck
BLK
ITK
TEC
TXK
BTK
Etk/BMX
CTK
CSK
Arg
Abl
Fes
Fer
FRK
Srm
Brk
MuSK
DDR2
DDR1
IGF1R
InsR
IRR
ROR2
ROR1
Ret
Mer
Axl
Tyro3/
Sky
FLT4
FLT3
PDGFRα
PDGFRβ
EGFR
HER2
HER4
Met
Ron
Ros
ALK
LTK
RYK
CCK4/PTK7
TIE2
TIE1
Ack
Tnk1
HER3
Tyk2
JAK1
JAK2
JAK3
ZAP70
Syk
PYK2
FAK
Lmr1
Lmr2
Lmr3
JAK3-b
JAK2-b
Tyk2-b
JAK1-b
SuRTK106
ANPα
ANPβ
HSER
CYGD
CYGF
MLK3
MLK1
MLK4
MLK2
DLK
LZK
ZAK
KSR
KSR2
RAF1
BRAF
ARAF
ALK4
TGFβR1
ALK7
BMPR1B
BMPR1A
ALK1
ALK2
ActR2
ActR2B
TGFβR2
MISR2
BMPR2
ANKRD3
SgK288
RIPK2
IRAK3
IRAK1
LIMK2
LIMK1
TESK1
TESK2
ILK
TAK1
HH498
RIPK3
IRAK2
RIPK1
LRRK2
LRRK1
IRAK4
MOS
SgK496
PBK
MLKL
NRBP1
NRBP2
WNK4
MEKK1/MAP3K1
OSR1
MEKK2/MAP3K2
MEKK3/MAP3K3
ASK/MAP3K5
MAP3K6
MAP3K7
MEKK6/
MAP3K6
HPK1
KHS1
KHS2
MST1
MST2
YSK1
MST3
GCK
MST4
HGK/ZC1
MINK/ZC3
TNIK/ZC2
NRK/ZC4
MYO3A
MYO3B
WNK1
WNK3
WNK2
MAP3K4
STLK3
STLK5
STLK6
SLK
LOK
TAO3
TAO1
TAO2
PAK1
PAK3
PAK2
PAK4
PAK5
PAK6
NIK
COT
MAP2K5
MAP2K7
GCN2-b
MEK1/MAP2K1
MEK2/MAP2K2
MKK3/MAP2K3
MKK6/MAP2K6
SEK1/
MAP2K4
MYT1
Wee1
Wee1B
SgK196
PRPK
Haspin
TTBK1
TTBK2
CK1δ
CK1ε
CK1α
CK1α2
VRK3
CK1γ2
SgK493
SgK396
Slob
PIK3R4
CK1γ1
CK1γ3
Bub1
BubR1
VRK1
VRK2
PERK/PEK
PKR
GCN2
SgK307
SgK424
SCYL3
SCYL2
SCYL1
HRI
IRE1
IRE2
CLIK1
CLIK1L
TBCK
RNAseL
TTK
KIS
SgK071
CK2α1
CK2α2
CDC7
HIPK1
HIPK2
HIPK3
HIPK4
PRP4
CLK4
CLK1
CLK2
CLK3
DYRK2
DYRK3
DYRK1A
DYRK1B
DYRK4
MSSK1
SRPK2
SRPK1
MAK
ICK
MOK
GSK3β
GSK3α
CDKL3
CDKL2
CDKL1
CDKL5
CDKL4
ERK7
ERK4
ERK3
ERK5
NLK
ERK1
ERK2
p38γ
p38δ
p38β
p38α
JNK1
JNK3
JNK2
PITSLRE
CDK10
CDK7
CDK4
CDK6
CDK8
CCRK
CDK11
CDK9
PFTAIRE2
PFTAIRE1
PCTAIRE2
PCTAIRE1
PCTAIRE3
CDK5
CRK7
CHED
CDC2/CDK1
CDK3
CDK2
SgK269
SgK223
PINK1
SgK110
SgK069
SBK
IKKα
IKKβ
IKKε
TBK1
MPSK1
GAK
ULK3
AAK1
BIKE
CAMKK1
CAMKK2
ULK1
ULK2
Fused
ULK4
Nek6
Nek7
Nek10
Nek8
Nek9
Nek2
Nek11
Nek4
Nek3
Nek5
Nek1
Trb3
Trb2
Trb1
Pim1
Pim2
Pim3
Obscn-b
SPEG-b
Obscn
SPEG
TTN
Trio
Trad
smMLCK
skMLCK
DRAK2
DRAK1
SgK085
caMLCK
DAPK3
DAPK2
DAPK1
SgK495
PASK
Lkb1
CHK1
TLK2
TLK1
PLK4
PLK1
PLK3
PLK2
BARK1/GRK2
BARK2/GRK3
GRK7
SgK494
PDK1
RHODK/GRK1
GRK5
GRK6
GRK4
RSKL1
RSKL2
RSK1/p90RSK
RSK2
RSK4
RSK3
p70S6K
p70S6Kβ
Akt2/PKBβ
Akt1/PKBα
Akt3/PKBγ
SGK1
SGK3
SGK2
MSK1
MSK2
AurA/Aur2
AurB/Aur1
AurC/Aur3
LATS1
LATS2
PKG2
PKG1
NDR1
NDR2
PKN1/PRK1
PKN2/PRK2
PKN3
PRK1
PRK2
YANK1
YANK3
YANK2
MASTL
MAST3
MAST2
PKCδ
PKCε
PKCζ
PKCι
PKCθ
PKCγ
PKA
PKCα
PKCβ
ROCK1
ROCK2
DMPK
DMPK2
CRIK
MAST4
MAST1
MRCKβ
MRCKα
STK33
CHK2
TSSK4
HUNK
SNRK
NIM1
SSTK
TSSK3
TSSK1
TSSK2
PKD2
PKD1
PKD3
MELK
CASK
DCAMKL3
DCAMKL1
DCAMKL2
VACAMKL
PSKH1
PSKH2
MNK1
MNK2
MAPKAPK5
MAPKAPK2
MAPKAPK3
PhK1
PhK2
CaMK2γ
CaMK2δ
CaMK2β
CaMK2γ
CaMK4
AMPKα2
AMPKα1
BRSK2
BRSK1
NuaK2
NuaK1
RSK4-b
RSK1-b
MSK2-b
MSK1-b
RSK2-b
RSK3-b
QSK
SIK
QIK
CaMK1β
CaMK1γ
CaMK1α
CaMK1δ
MARK4
MARK3
MARK2
MARK1

able 2. Kinase Targets in Cancer and Their Roles in the Cardiovascular System

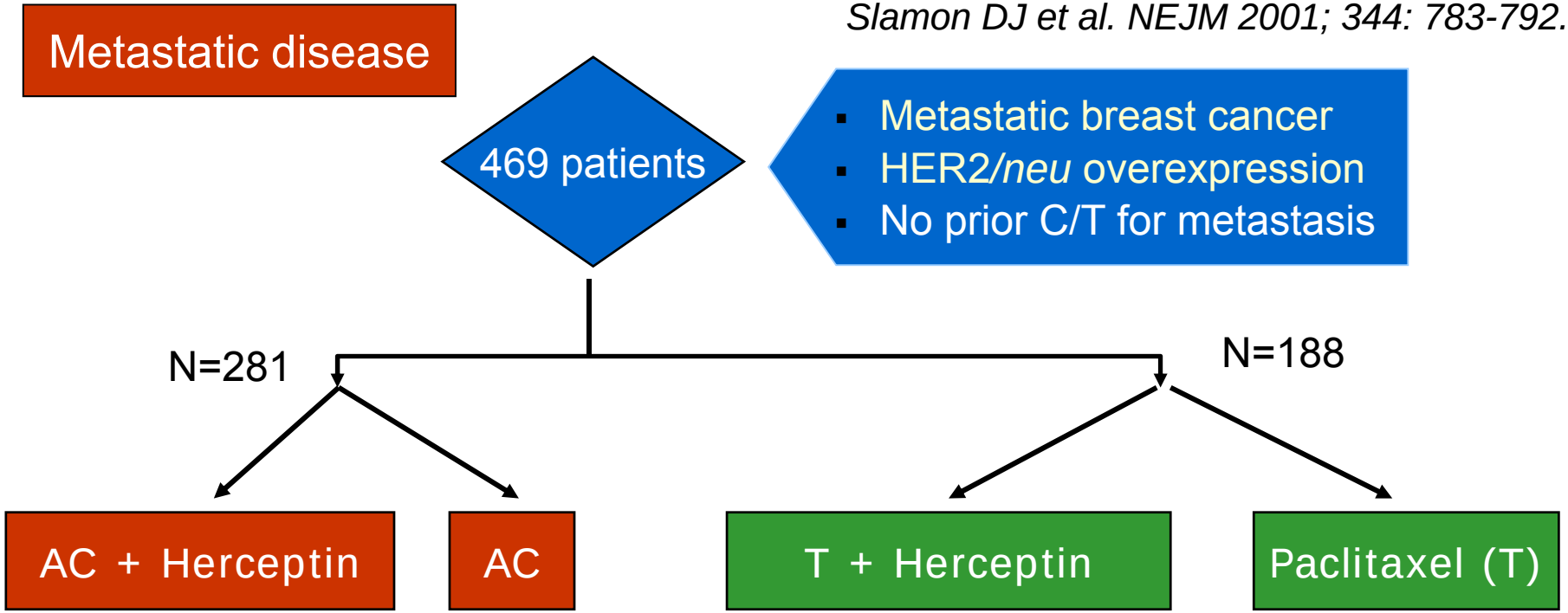
inase	Inhibitors	Role of Kinase in the Heart/Vasculature/Models Used
bl	Imatinib/D/N bosutinib, etc[9]	Inhibition of Abl by imatinib induced ER stress and cell death in cardiomyocytes[19,22]
rowth factor receptors		
EGFR (ERBB1)	Gefitinib, erlotinib, lapatinib, XL647, BIBW-2992[7]	Inhibition of EGFR by erlotinib led to reduced LV function under conditions of chronic catecholamine stimulation[71]
HER2 (ERBB2)	Lapatinib, XL647, BIBW-2992[7]	Conditional deletion of ERBB2 led to DCM[72]
c-Kit	Imatinib/D/N sunitinib, sorafenib vatalanib	c-Kit deficiency blocked: (1) homing of CSC to sites of post-MI injury[67]; 2) CSC differentiation[65]; and (3) cardiomyocyte terminal differentiation.[68] Imatinib reduced stenosis after arterial injury[65]
VEGFRs	Sunitinib, sorafenib pazopanib, vandetanib, cediranib, vatalanib	VEGF trap[31] or inhibition[32] caused cardiac dysfunction after PO
PDGFRs	Imatinib/D/N sunitinib, sorafenib pazopanib, vatalanib	Intramyocardial delivery of PDGF improved post-MI ventricular function[73]; deletion of PDGFRβ led to LV dysfunction after PO[64]
I3K pathway		
PI3K(p110α)	SF-1126, XL765[34]	Mediates physiological heart growth and provides protection from pathological stress[36]
PI3K(p110γ)	SF-1126, XL765	Regulates contractility and pathological hypertrophy[74,75]
Akt	VQD-002, perifosine	Regulates cardiomyocyte growth, proliferation, survival and metabolism[76–78]; promotes CSC proliferation and expansion[79]; inhibits cardiac sarcolemmal Na(+)/H(+) exchanger activity[80]
PDK1	UCN-01	A dual effector for cardiac cell survival and beta-adrenergic response[39]

Ras/Raf/MEK/ERK pathway		
Raf-1/B-Raf	Sorafenib RAF-265	Conditional deletion/DN led to LV dilatation and HF after PO[62,63]; specific gain-of-function mutations cause an HCM phenocopy[61]
MEK1/2	PD-0325901, AZD-6244, ARRY-162	Regulation of cardiac hypertrophy and cell survival[81]
Cell cycle regulation		
CDK	Alvocidib, BI2526[45]	Cardiomyocyte cell cycle control in normal development and in response to injury[44,82]
Aurora kinases	AZD-1152	
PLKs	BI2526	
Others		
mTOR	Temsirolimus, everolimus, sirolimus, deforolimus	Central regulator of cardiac cell growth/hypertrophy[41,42]; integrates energy/metabolic status
JAK2	Lestaurtinib, CP-690550, TG101348	JAK2-STAT3 generally protective, especially in I/R injury, hypertrophy, and postpartum cardiomyopathy[56,57]
p38	GW856553	p38 inhibition attenuated biomarkers of atherosclerosis[49]; reduced inflammatory burden in subjects already on statin therapy and undergoing PCI[50]

Anti Her2 therapies

- Herceptin in breast cancer patients
- A critical point is the relationship with prior anthracycline treatments

Slamon DJ et al. NEJM 2001; 344: 783-792.

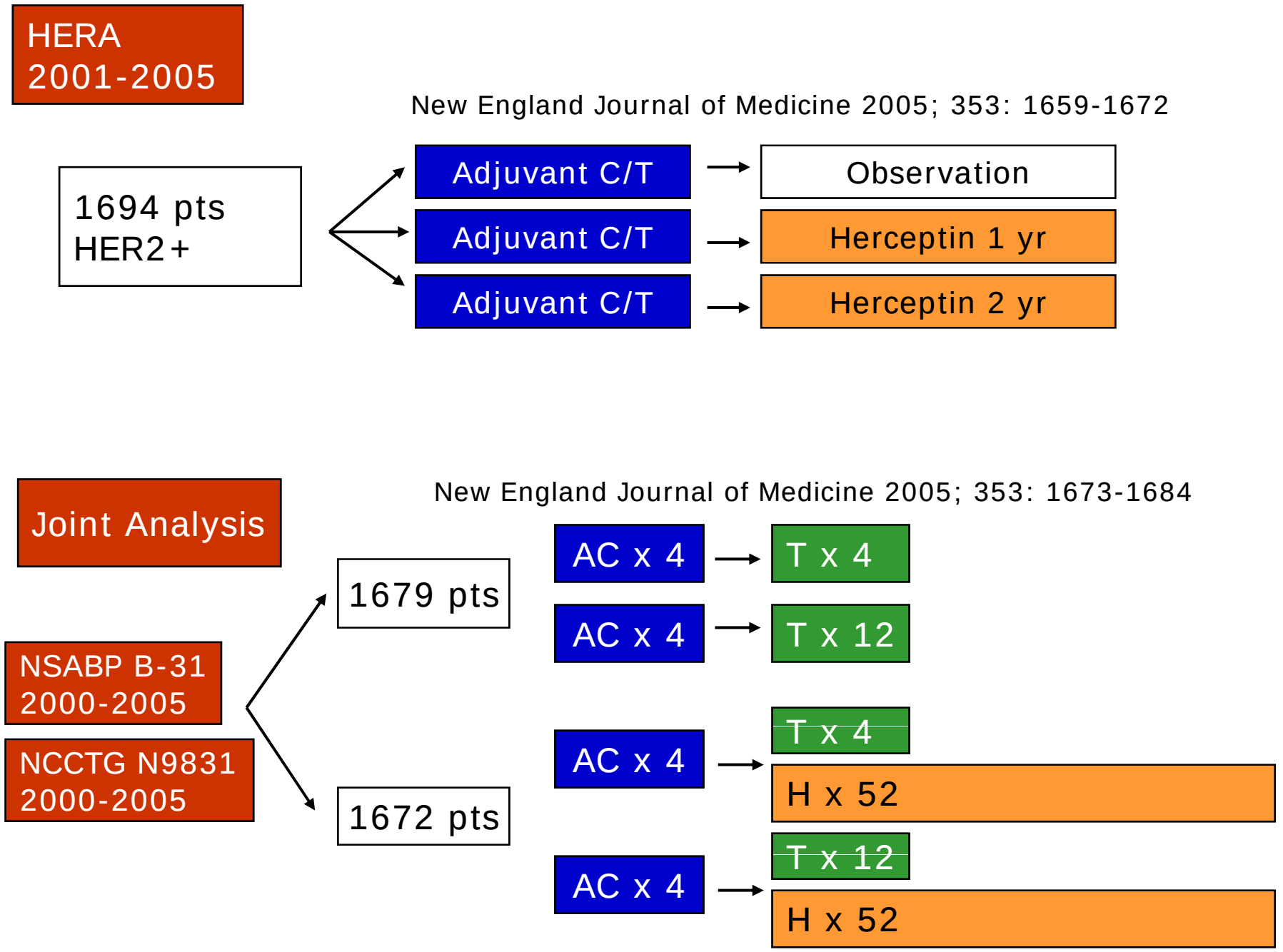


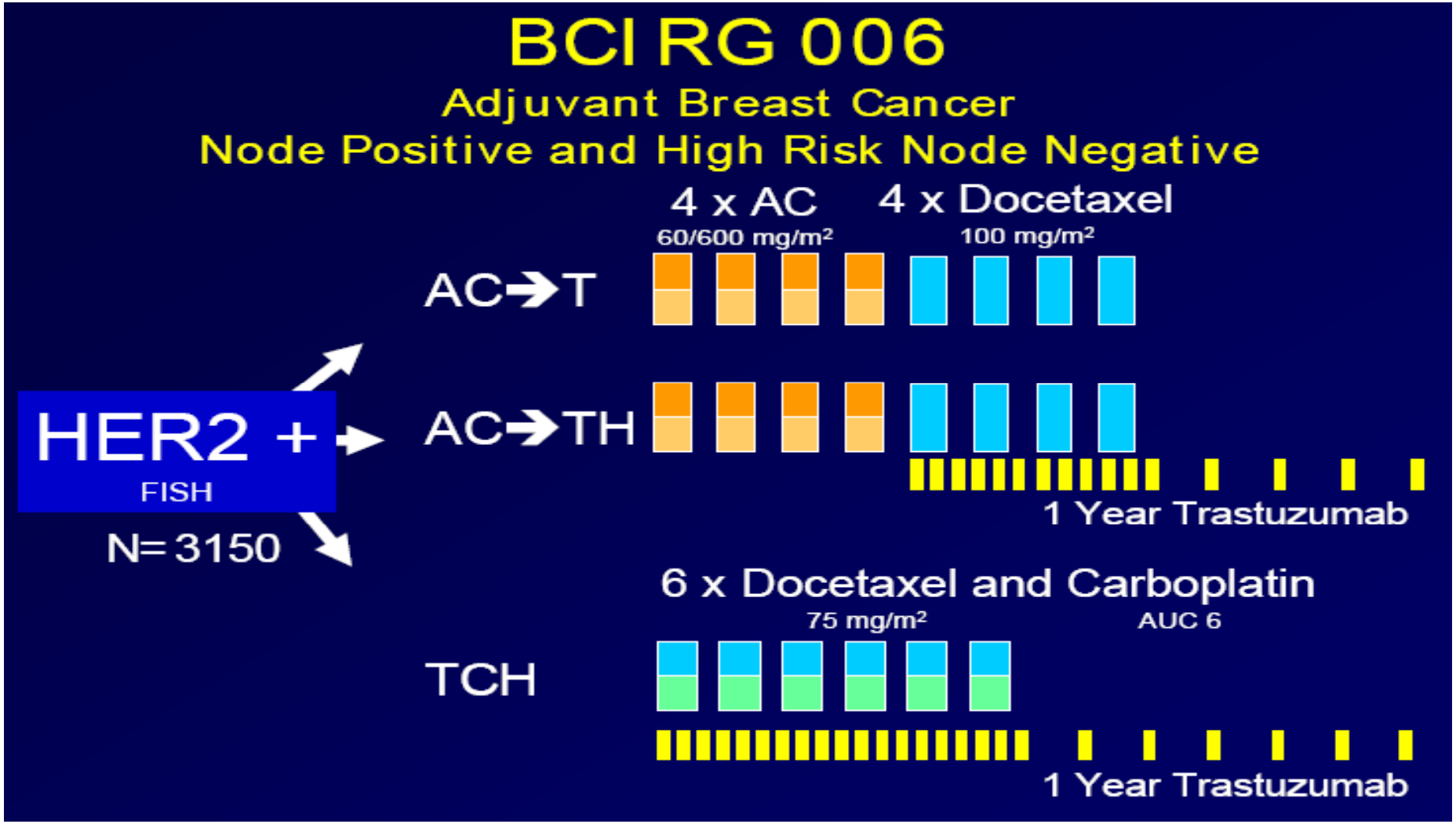
	C/T + H	C/T alone	AC+H	AC	T+H	T
RR	50%	32%	56%	42%	31%	14%
TTP	7.4	4.6	7.8	6.1	6.9	3.0
OS	25.1	20.3	26.8	21.4	22.1	18.4
Cardiac dysfunction	Total 63 patients		27%	8%	13%	1%

Metastatic breast cancer

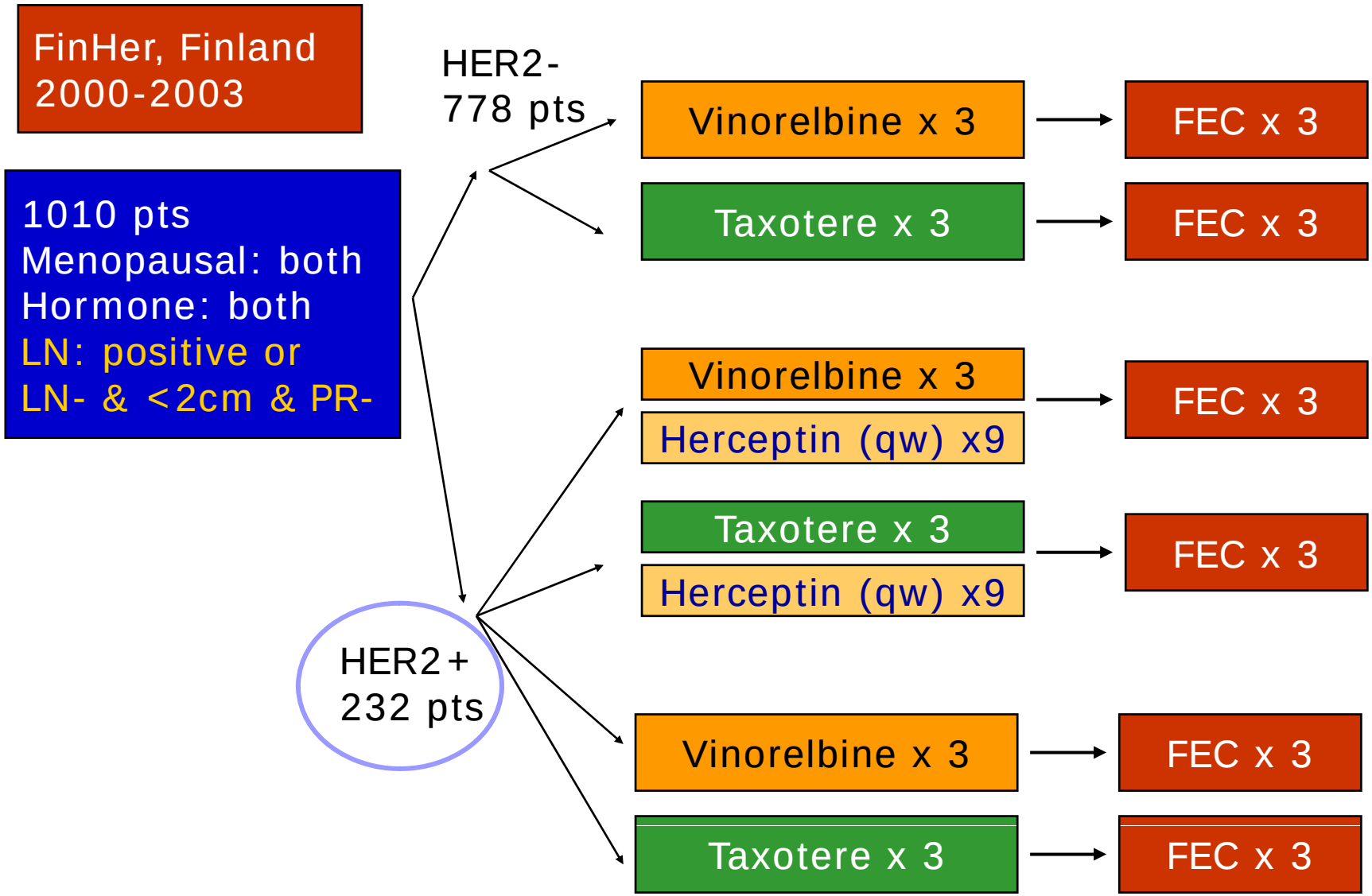
- 1219 pts, Herceptin +/- chemotherapy
- Cardiac dysfunction, meta-analysis
  - Herceptin + AC: 27%
  - Herceptin + Paclitaxel: 13%
  - Herceptin alone: 3-7%
  - AC: 8%
  - Paclitaxel: 1%

Journal of Clinical Oncology 2002; 20: 1215-1221


HERA
2001-2005
New England Journal of Medicine 2005; 353: 1659-1672
1694 pts
HER2+
Adjuvant C/T
Adjuvant C/T
Adjuvant C/T
Observation
Herceptin 1 yr
Herceptin 2 yr
Joint Analysis
New England Journal of Medicine 2005; 353: 1673-1684
NSABP B-31
2000-2005
NCCTG N9831
2000-2005
1679 pts
1672 pts
AC x 4
AC x 4
AC x 4
AC x 4
T x 4
T x 12
T x 4
H x 52
T x 12
H x 52



Breast Cancer Research and Treatment 2005; 94(supp1): S5



New England Journal of Medicine 2006; 354:809-20

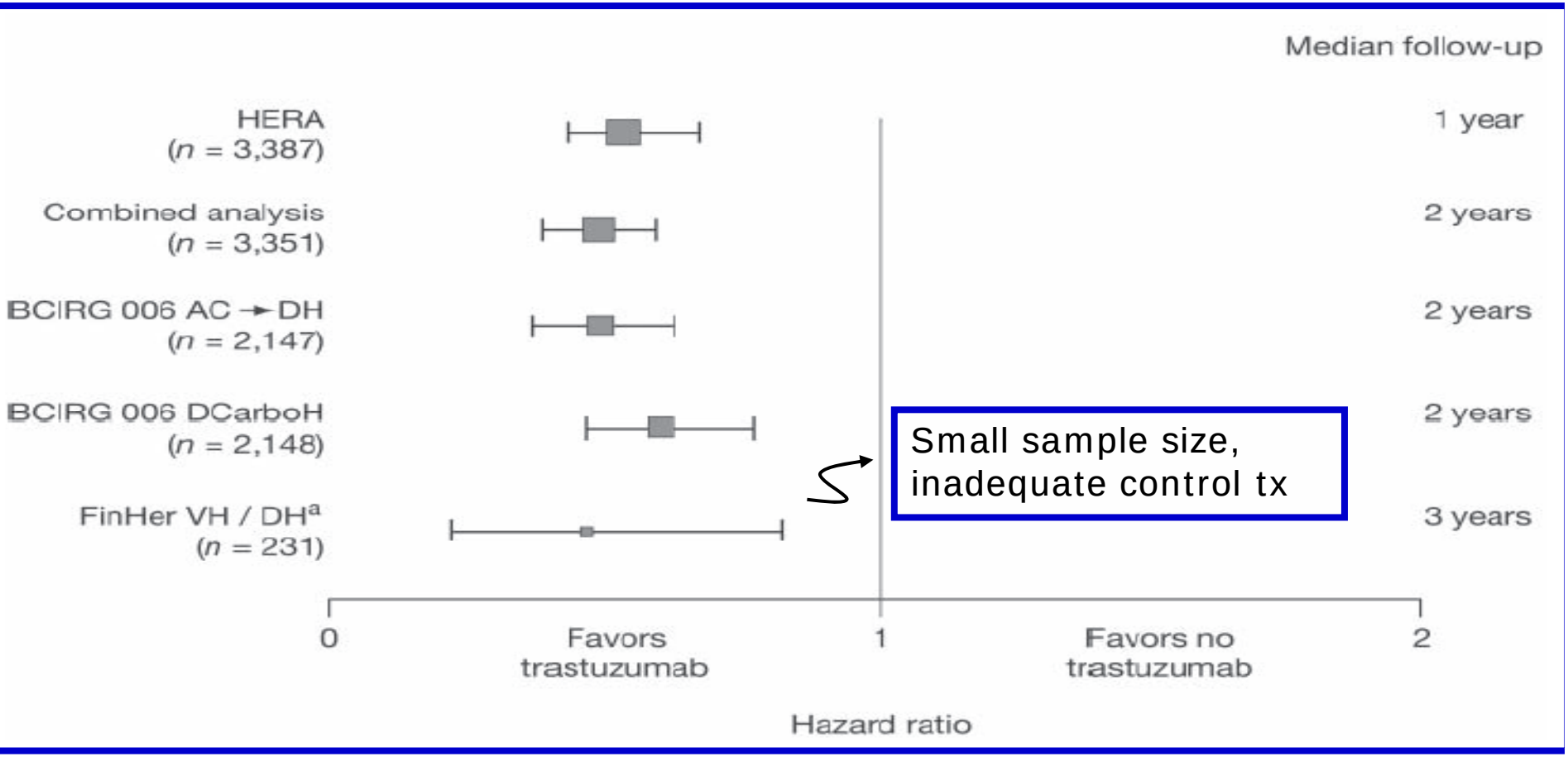

Median follow-up
HERA
(n = 3,387)
1 year
Combined analysis
(n = 3,351)
2 years
BCIRG 006 AC → DH
(n = 2,147)
2 years
BCIRG 006 DCarboH
(n = 2,148)
2 years
FinHer VH / DH[a]
(n = 231)
3 years
Small sample size,
inadequate control tx
0
Favors
trastuzumab
1
Favors no
trastuzumab
2
Hazard ratio

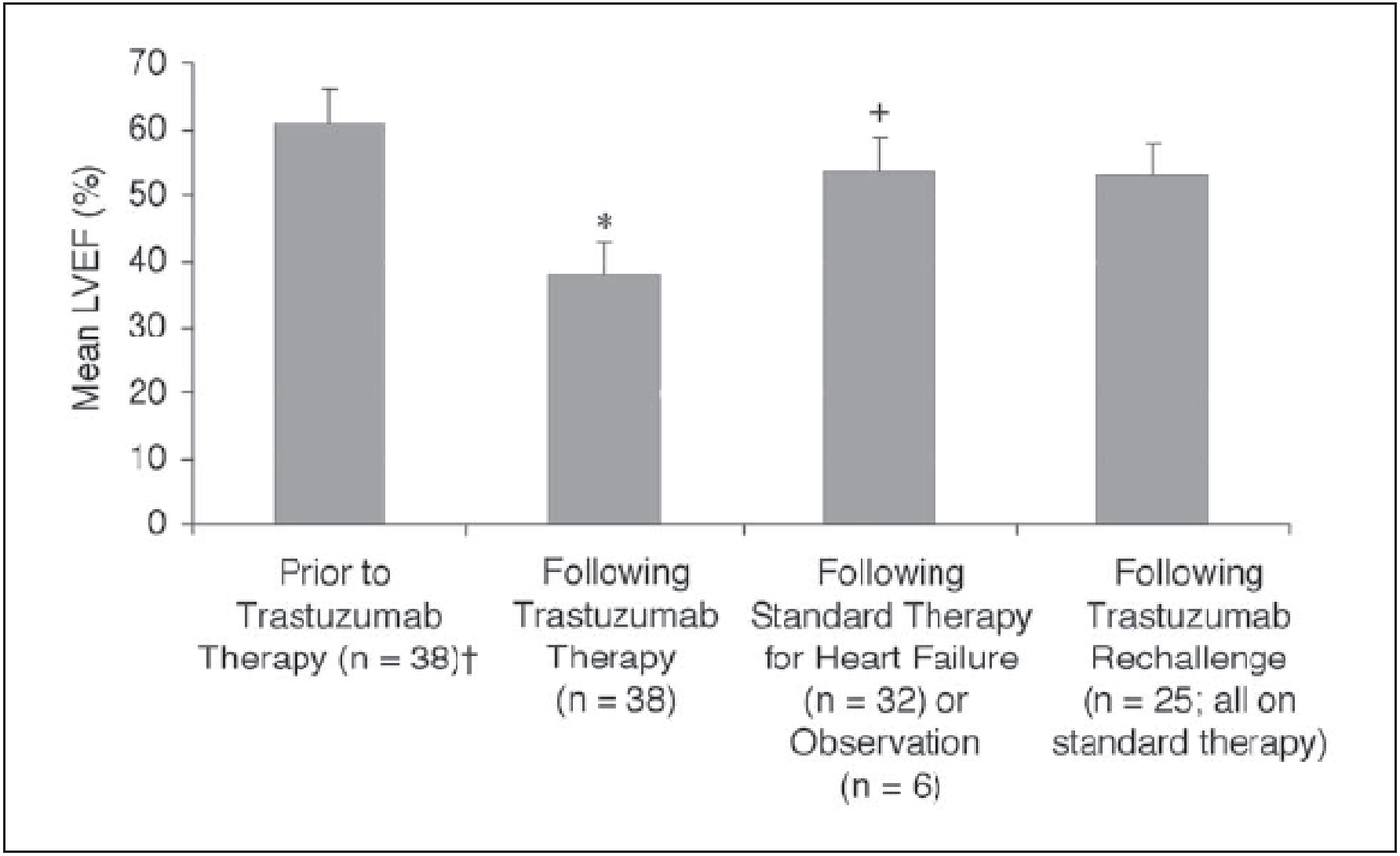
Table 1. Summary of cardiac safety with trastuzumab in early breast cancer [8, 10, 11, 13, 14]

Trial	Arm	Baseline LVEF (%)	CHF (%)	Cardiac death (*n*)
HERA	Nil	≥55	0	1
	H 1 year		0.6	0
NSABP B-31	AC→P	≥50	0.8^{cum}	1
	AC→PH		4.1^{cum}	0
NCCTG N9831	AC→P	≥50	0.3^{cum}	1
	AC→P→H		2.5^{cum}	1
	AC→PH		3.5^{cum}	0
BCIRG 006	AC→D	≥50	0.3	0
	AC→DH		1.6	0
	DCarboH		0.4	0
FinHer	No H		3	0
	H		0	0

Concurrent > sequential > TCH > FinHer

Herceptin cardiotoxicity

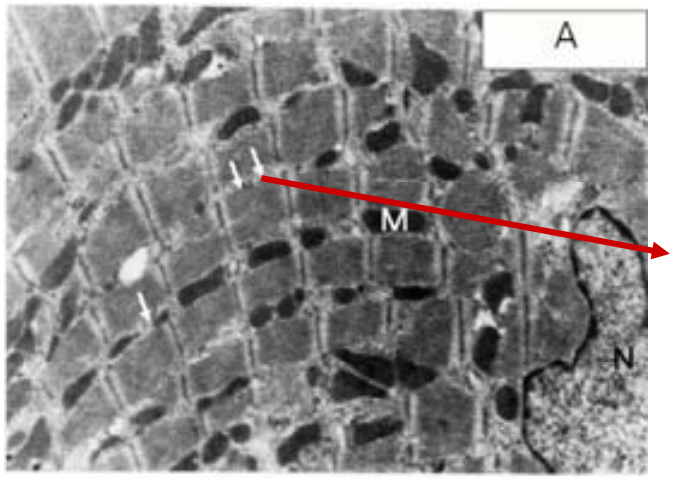
- Distinct from antracycline
  - Reversibility
  - Morphology



Journal Clinical Oncology 2005; 23: 7820-26

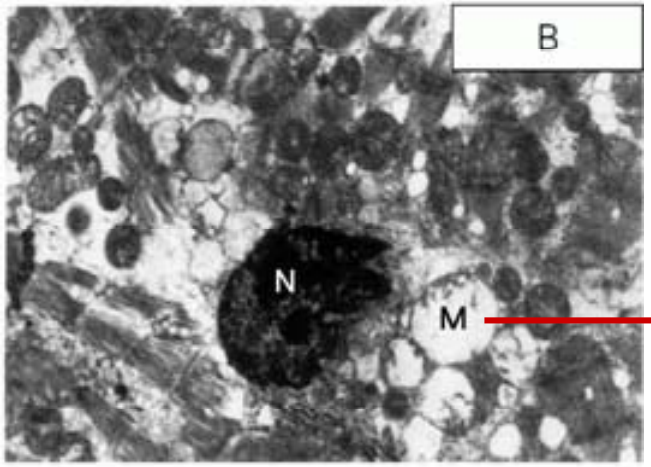
Rat,
cardiomyocyte

Control



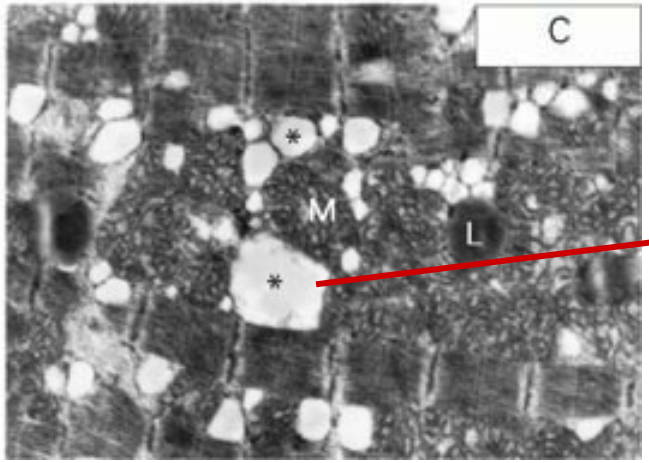
Sarcoplasmic reticulum

Idarubicin treated



Mitochondria, swelling

Idarubicin treated



Sarcoplasmic reticulum,
dilatation

Herceptin treated, human myocyte

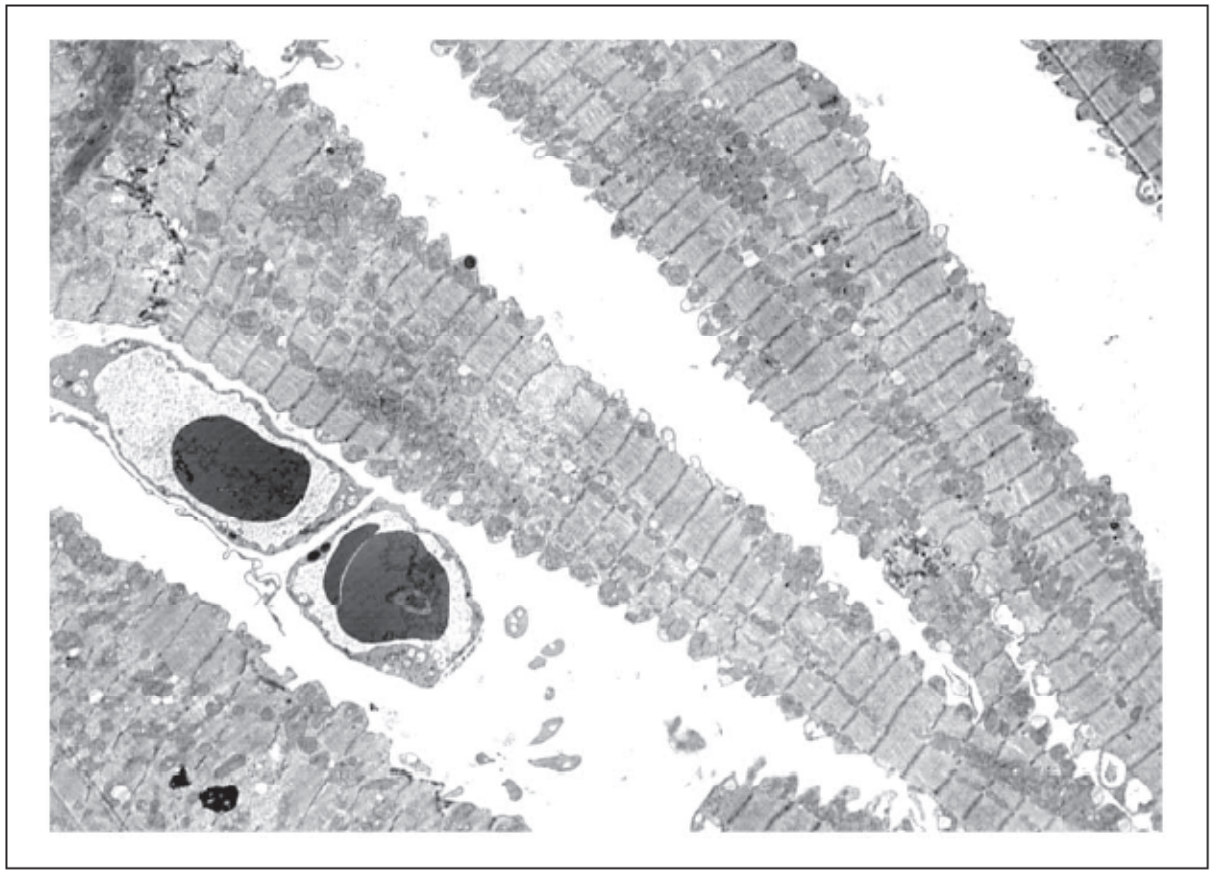


Fig 4. Typical biopsy (×4,000) from a patient with left ventricular dysfunction on trastuzumab alone. Representative biopsy specimen from a patient with trastuzumab-related cardiotoxicity demonstrating no ultrastructural changes.

Role of Her2 in heart

- Animal studies
  - Knock out Her2, observe heart change
  - Define downstream molecules
- In mice
  - Germline deletion of ErbB2, ErbB4, NRG1 is lethal in mid-gestation
    - Nature 1995; 378: 386-90, 90-94, 94-98

Mice study

- Cardiac-specific ErbB2 deletion is viable, but develop DCM and pressure overload

Table 1 Echocardiographic analysis of *in vivo* cardiac size and function in *Erbb2*-CKO mice

	LVEDD (mm)	LVESD (mm)	FS (%)	SEPth (mm)	PWth (mm)	Mean Vcf (circ/s)	Heart rate (beats/min)	BW (g)	Age (d)
Erbb2-WT ($n = 6$)	3.73 ± 0.12	2.33 ± 0.10	37.9 ± 2.65	1.05 ± 0.03	1.09 ± 0.04	6.64 ± 0.70	378 ± 29	30.1 ± 2.86	90 ± 1
Erbb2-CKO ($n = 8$)	4.60 ± 0.20	3.72 ± 0.22	19.4 ± 1.630.	94 ± 0.01	0.95 ± 0.03	3.95 ± 0.03	378 ± 19	28.2 ± 1.20	90 ± 1
P value	0.006	0.0005	< 0.0001	0.005	0.01	0.006	1	0.5	1

FS, percent fractional shortening calculated as ((LVEDD – LVESD) / LVEDD) × 100; SEPth, septal wall thickness; PWth, posterior wall thickness; mean Vcf, mean velocity of circumferential fiber shortening; BW, body weight. All values ± s.e.m.

Nature medicine 2002; 8: 459-465

Rat ventricular myocyte

- Neuregulin-1β(NRG-1β)
  - A ligand of erbB family receptors
- NRG-1β/erbB2/Src/FAK pathway
  - Maintenance and repair of electrical and mechanical coupling
  - Anti-erbB2 Ab blocks these phenomenon

Journal of molecular and cellular cardiology 2006; 41: 228-35

Herceptin cardiotoxicity

- Her2 pathway is critical for heart
- How about the sequence ?
  - AC→TH : 1.6-4.1%
  - AC→T→H: 0.6-2.5%
  - TCH: 0.4%
  - TH→FEC (FinHer): 0

Lapatinib, phase I

- Reversible EGFR and Her2 TKI
- 67 pts, heavily pretreated solid tumors
  - EGFR+, Her2+
  - 500-1600mg/d, phase I study
- Diarrhea (42%), rash (31%) common
- No cardiac dysfunction
- Well-tolerated

Journal of Clinical Oncology 2005; 23: 5305-13

Lapatinib, phase III

- Randomized phase III, 324 MBC
  - Progress under Antra, Taxane, Herceptin
  - Her2+
  - Lapatinib + Capecitabine vs. Capecitabine
    - 1250mg/d, 2000mg/m2/d x 14d/21d, 2500mg/m2/d x 14d/21d
  - Time to progression: 8.4m vs. 4.4m, HR:0.49, p<0.001

New England Journal of Medicine 2006; 355: 2733-43.

Lapatinib, phase III

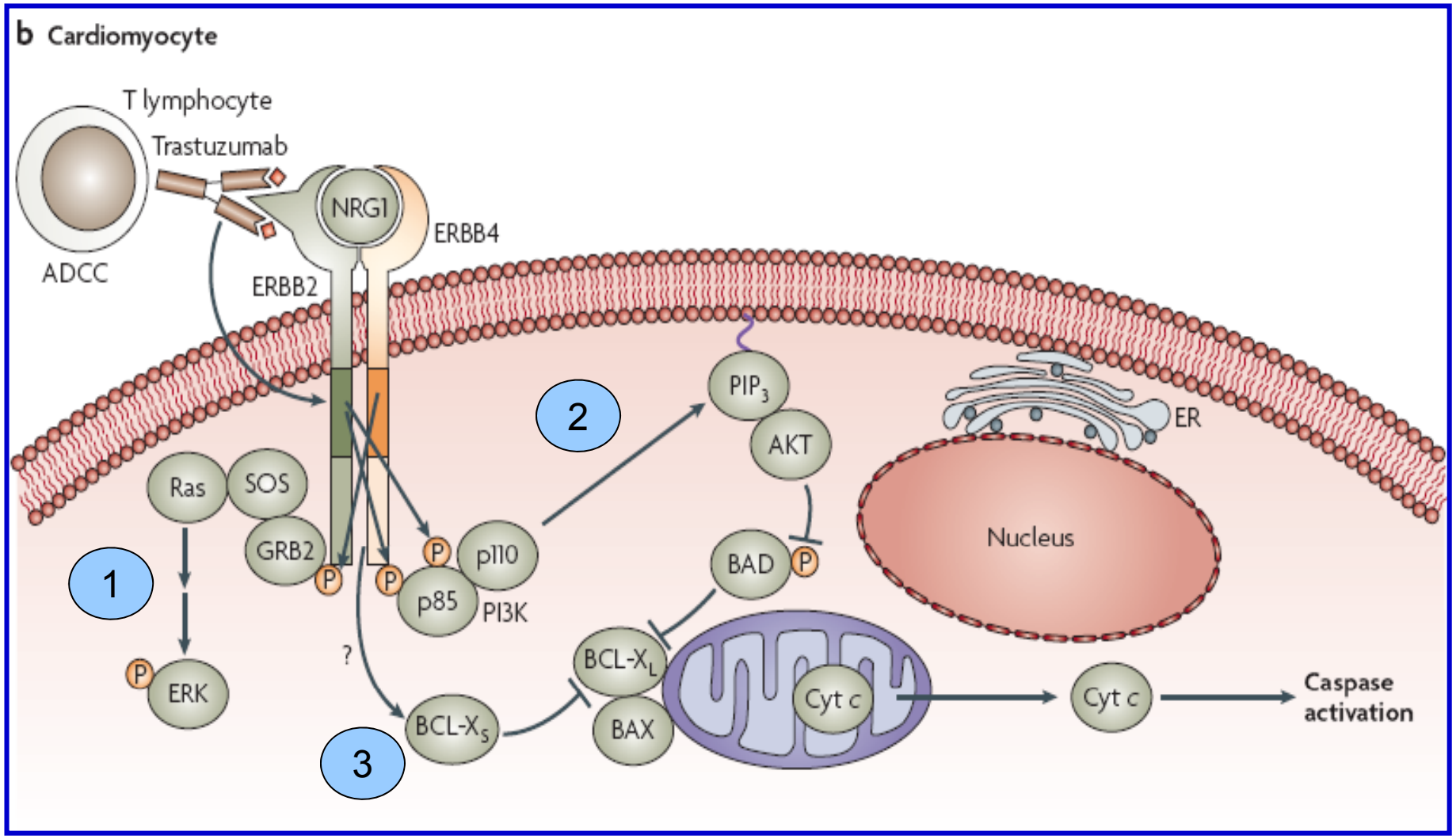
- Cardiac safety
  - Prospective monitor of LVEF
  - 4 pts (2.4%) asymptomatic LVEF decreasing
    - Far more less than Herceptin (?)
    - Other mechanisms than Her2 (?)
    - Cardioprotection through AMPK activation?
- By retrospective study,
  - Herceptin alone : 3-7%

New England Journal of Medicine 2006; 355: 2733-43.

Herceptin + Capecitabine

- 27 pts, MBC, Her2+, phase II
  - Exposed to Anthracycline and Taxane
    - Adjuvant, neoadjuvant, palliative
- Herceptin + Xeloda
- CR/PR/SD: 15/30/33%, RR: 45%
- Hand-foot syndrome most common
- No reported cardiotoxicity

Journal of Clinical Oncology 2007; Aug.1; E-published



Nature Review Cancer 2007; 7: 332-344

ABL kinase inhibitor

- Imatinib, nilotinib
  - Bind to inactive conformation of ABL domain
  - Nilotinib 20 times potent than imatinib
- Dasatinib
  - Bind to both active and inactive of ABL
- They also block
  - ARG (ABL-related gene), PDGFRα/β, KIT

Imatinib

- Randomized phase III (IRIS)
  - Imatinib vs. interferon-α+ low-dose AraC
    - Cross-over allowed
  - 1106 pts, fresh CML
  - Major cytogenic response: 85.2% vs. 22.1%
  - CHF: 1%, no difference between arms

New England Journal of Medicine 2003; 348: 994-1004
Nature Review Cancer 2007; 7: 332-344

Supplementary Table 1. Clinical characteristics of patients with imatinib-associated heart failure

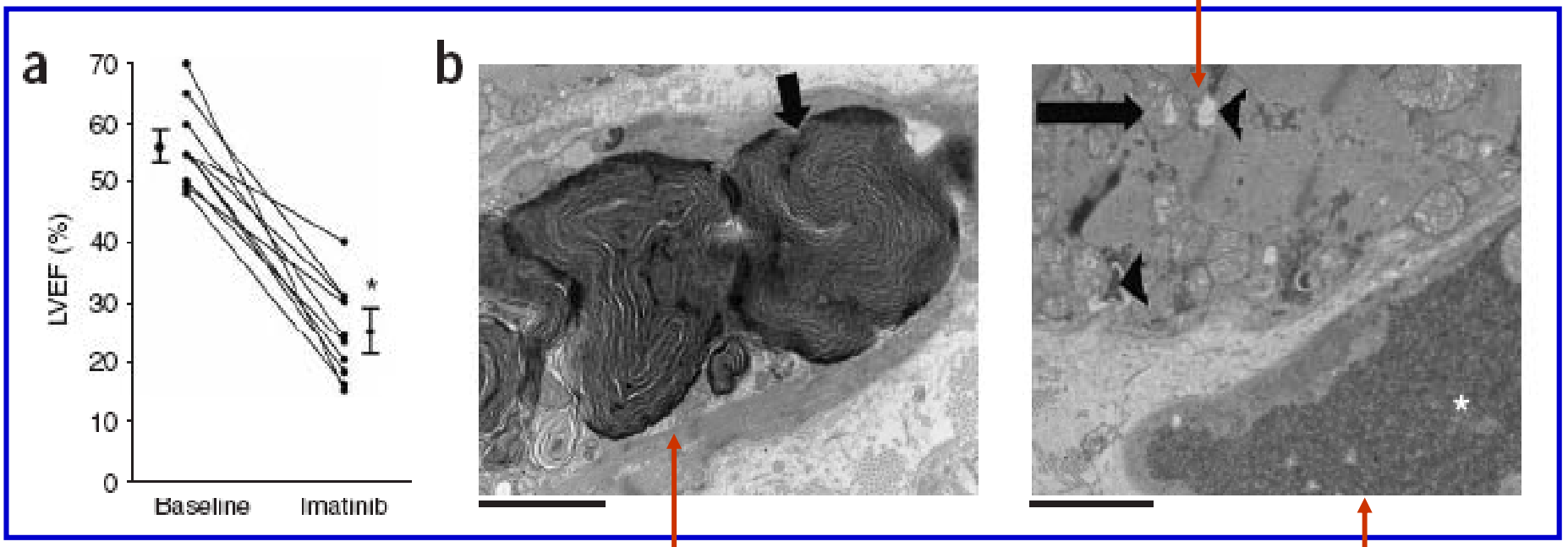
Patient	1	2	3	4	5	6	7	8	9	10	Summary
Age	72	76	61	59	45	69	75	75	62	49	64.3 ± 11.0
Sex	M	M	F	F	M	M	M	M	F	F	N/A
Diagnosis	CML	CML	MF	CML	CML	CML	ALL	CML	CML	CML	N/A
Imatinib dose (mg/day)	600	800	800	400	600	800	400	400	600	800	620 ± 166
Drug to diagnosis (months)	14	14	1	9	1	1	1.5	14	8	8	7.15 ± 5.4
Prior CAD	Y	N	N	N	N	BG	N	BG	N	N	3/10
Stress test	Neg	Neg	Neg	Neg	Neg	Neg	Neg	Ang	Neg	Neg	N/A
Catheterization	PS	NL	NL	ND	NL	PG	ND	PS	NL	NL	N/A
Diabetes	N	Y	N	N	N	N	Y	Y	N	Y	4/10
Hypertension	Y	Y	N	Y	N	Y	Y	Y	N	Y	7/10
NYHA (pre-Rx)	1	1	1	1	1	1	1	1	1	1	1
NYHA (post-Rx)	3	3	4	3	4	4	3	4	3	4	3.5 ± 0.53*
EF (pre-Rx)	55	60	65	50	70	49	55	48	55	55	56 ± 7.0
EF (post-Rx)	40	24	31	23	15	30	31	16	20	18	25 ± 8.0*

Nature medicine 2006; 12: 908-16

M, male; F, female; N/A not applicable; CML, chronic myelogenous leukemia; MF, myelofibrosis; ALL, acute lymphoblastic leukemia; CAD, coronary artery disease; BG, coronary artery bypass graft; Neg, negative for ischemia; Ang, angina; PS, patent stent; NL, normal catheterization; ND, not done; PG, patent graft; NYHA, New York Heart Association functional class; EF, ejection fraction. Data are mean ± SD. *$P < 0.001$ versus pre-imatinib.

Human, heart biopsy

sarcoplasmic reticulum
with membrane whorls



dense membrane whorl

effaced myofilaments and
glycogen accumulation

Nature medicine 2006; 12: 908-16

Retrospective study

- Italian Cooperative Study Group on CML (ICSG on CML)
  - Four consecutive studies
- 833 pts, 296 Late Chronic Phase, 537 ECP
  - Median observation 64m
- 77 death, 68 LCP, 9 ECP
  - 3 cardiac death(0.3%), MI, 59/78/84 year-old
  - No previous LV dysfunction
- Cardiotoxicity, really ?

Nature medicine 2007; 13: 15-16

Retrospective study

- M. D. Anderson Cancer Center,
  - from 1998-7 to 2006-7. 1276 patients enrolled
- The median time from imatinib therapy: 162 days
- 22 (1.8%) systolic heart failure
- 8 (0.6%) were considered possibly related to imatinib
- 11/ 22 patients continued imatinib
  - Dose adjustments and management for the CHF symptoms
  - No further complications.

Blood, prepublished online April 20, 2007

Imatinib and ER stress

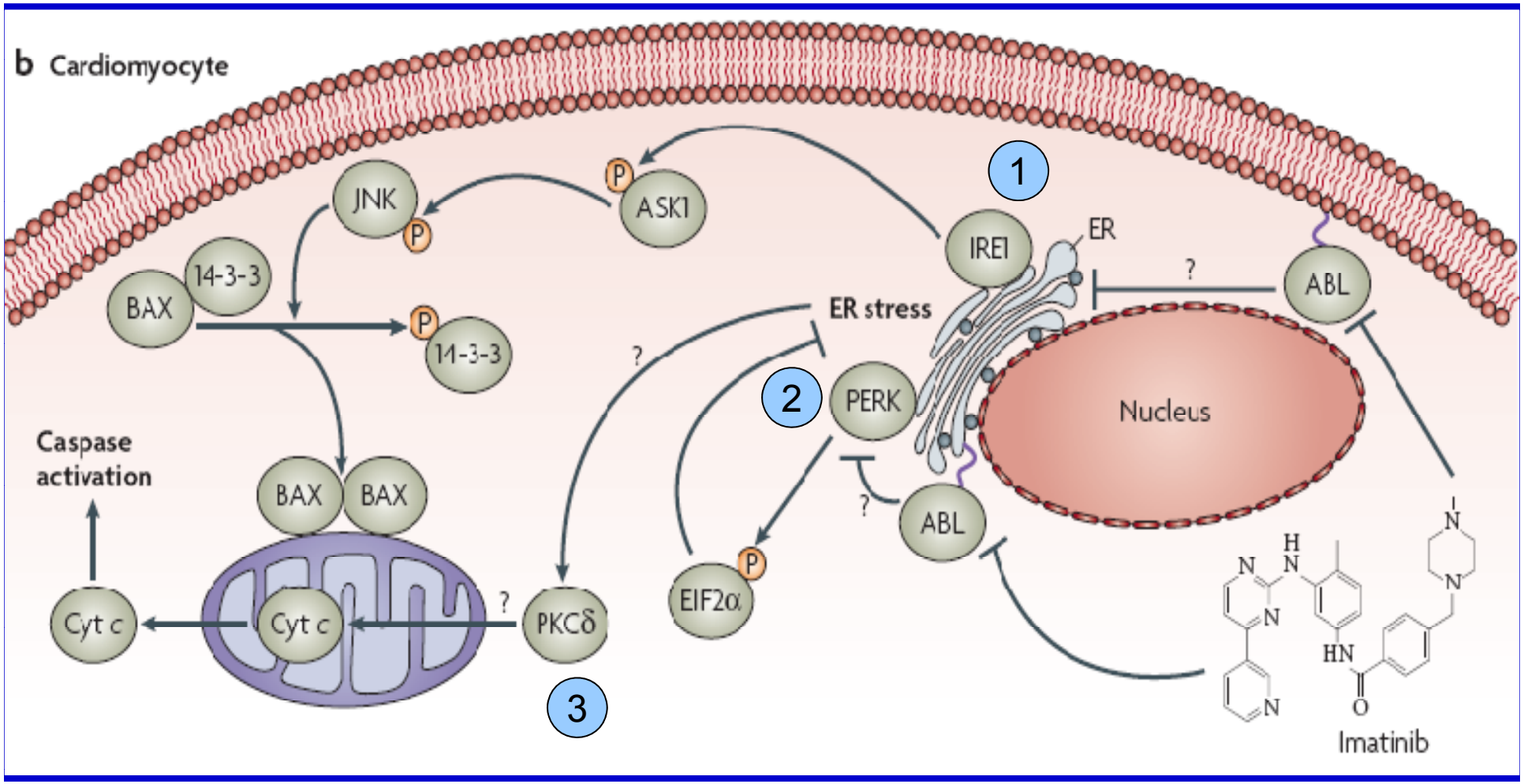
- Rat cardiomyocte study
- ER (endoplasmic reticulum) stress
  - Detail linkage of ABL and ER stress not clear
  - Initiated by unfold protein in ER
  - Activate distinct pathways
    - PPR-like ER kinase (PERK)
    - IRE1
    - Protein kinase Cδ

Nature medicine 2006; 12: 908-916

Imatinib and ER stress

- ER stress
  - Release cytochrome c → apoptosis
  - Mitochondria dysfunction, loss membrane potential
    - Impaired energy generation, decrease ATP
- Expression of imatinib-resistant mutant, ABL T315I,
  - partially rescued cells from imatinib toxicity

Nature medicine 2006; 12: 908-916



Nature Review Cancer 2007; 7: 332-344

Nilotinib

- More potent binding to ABL than Imatinib
  - 20-50 times
- Phase I study, 119 pts
  - Imatinib-resistant CML, or Ph+ ALL
  - 50-1200mg/d
- Efficacy
  - Blast crisis: 13/33 hematological response
  - Accelerated: 33/46 hematological response
  - Chronic phase: 11/12 hematological response

New England Journal of Medicine 2006; 354: 2542-51

Nilotinib

- Adverse effect
  - Myelosuppression
  - Transient indirect hyperbilirubinemia
  - Rash
- Cardiac
  - QTc prolongation, incidence?
  - Only 1 pt had two events,
    - Pericardial effusion and Af

New England Journal of Medicine 2006; 354: 2542-51

Dasatinib

- Inhibit
  - active and inactive ABL
  - SRC
- Phase I, 84 pts
  - CML(chronic/accelerate/blast), Ph+ ALL
- Efficacy and AE
  - CML chronic: 37/40 hematological response
  - Others: 31/44 hematological response
  - No reported cardiotoxicity

New England Journal of Medicine 2006; 354: 2531-41

Dasatinib, pharmaceutical information

Table 4: Adverse Events Reported ≥10% in Clinical Studies

	All Patients (n=911)		Chronic Phase (n=488)	Accelerated Phase (n=186)	Myeloid Blast Phase (n=132)	Lymphoid Blast Phase and Ph+ ALL (n=105)
	All Grades	Grades 3/4	Grades 3/4	Grades 3/4	Grades 3/4	Grades 3/4
Preferred Term	Percent (%) of Patients					
Fluid Retention	50	9	6	6	23	9
Superficial Edema	36	1	0	2	3	2
Pleural Effusion	22	5	3	3	14	8
Other Fluid Retention	14	5	4	4	12	3
Generalized Edema	5	1	<1	0	2	1
Congestive Heart Failure/Cardiac Dysfunction[a]	4	2	3	1	5	1
Pericardial Effusion	4	1	<1	1	3	0
Pulmonary Edema	4	1	1	2	0	1
Ascites	1	1	0	1	2	2
Pulmonary Hypertension	1	0	<1	1	2	0

(continued)

ABL kinase inhibitor

- Really cardiotoxic ?
  - Even existed, very low, <1%
  - More observation, carefully

Multi-target inhibitor

- Sorafenib
  - RAF1, BRAF, VEGFR2,3, PDGFR, KIT, and FLT3
- Sunitinib
  - VEGFR1-3, PDGFRα/β, KIT, FLT3, CSF1R, RET
- Dirty drug
  - Off-target effect

Sunitinib for GIST

- Randomized phase III double blind
  - 312 pts with GIST, progress under Imatinib
- Sunitinib versus Placebo, 2:1
  - 50mg/d, 4-wk-on, 2-wk-off, 6-wk/cycle
- Efficacy and AE
  - TTP: 27.3 vs. 6.4 wks, HR: 0.33, $p<0.001$
  - PR/SD/PD: 7/58/19%, 0/48/37%
  - Fatigue, diarrhea, skin discoloration, nausea
  - No decline in LVEF (prospectively)
  - 4% hypothyroidism

Lancet 2006; 368: 1329-38

http://www.pfizer.com/pfizer/download/uspi_sutent.pdf

Table 2. Laboratory Abnormalities Reported in Study A in at Least 10% of GIST Patients Who Received SUTENT or Placebo*

Laboratory Parameter, n (%)	GIST			
	SUTENT (n=202)		Placebo (n=102)	
	All Grades*	Grade 3/4*[a]	All Grades*	Grade 3/4*[b]
Any		68 (34)		22 (22)
Gastrointestinal				
AST / ALT	78 (39)	3 (2)	23 (23)	1 (1)
Lipase	50 (25)	20 (10)	17 (17)	7 (7)
Alkaline phosphatase	48 (24)	7 (4)	21 (21)	4 (4)
Amylase	35 (17)	10 (5)	12 (12)	3 (3)
Total bilirubin	32 (16)	2 (1)	8 (8)	0 (0)
Indirect bilirubin	20 (10)	0 (0)	4 (4)	0 (0)
Cardiac				
Decreased LVEF	22 (11)	2 (1)	3 (3)	0 (0)
Renal/Metabolic				
Creatinine	25 (12)	1 (1)	7 (7)	0 (0)
Potassium decreased	24 (12)	1 (1)	4 (4)	0 (0)
Sodium increased	20 (10)	0 (0)	4 (4)	1 (1)
Hematology				
Neutrophils	107 (53)	20 (10)	4 (4)	0 (0)
Lymphocytes	76 (38)	0 (0)	16 (16)	0 (0)
Platelets	76 (38)	10 (5)	4 (4)	0 (0)
Hemoglobin	52 (26)	6 (3)	22 (22)	2 (2)

Sunitinib for metastatic RCC

- Phase II, single arm
  - 106 pts with mRCC, 2nd-line
  - Progression under cytokine tx
- Efficacy and AE
  - PR: 34%
  - TTP: 8.3m
  - ↓LVEF: 4.7%(8pts)
    - 5 pts ↓LVEF>20%
    - No symptom/signs of heart failure

JAMA 2006; 295: 2516-24

Sunitinib for metastatic RCC

- Randomized phase III double blind
  - 750 pts with mRCC, 1st-line
- Sunitinib vs. IFN-α
  - Sunitinib 50mg/d, 4-wk-on, 2-wk-off
  - IFN-α: 9MU tiw
  - Cross-over allowed
- Efficacy and AE
  - TTP: 11 vs. 5m, HR: 0.42, p<0.001
  - RR: 31% vs. 6%, p<0.001
  - Gr.3 LVEF ↓ : 2%, 1%; reversible

New England Journal of Medicine 2007; 356: 115-124

Sorafenib in RCC, phase II

- Randomized discontinuation trial
  - 202 RCC pts, prior treatment (+)
  - 73 pts tumor↓>25% → go on sorafenib
  - 65 pts tumor ↓<25% ~↑<25%
    → randomize, sorafenib or placebo
  - 24wk-PFS: 50% vs. 18% (p=0.0077)
  - Median PFS: 24wk vs. 6wk
- No cardiotoxicity

Journal of Clinical Oncology 2006; 24: 2505-12

Sorafenib in RCC, phase III

- 903 pts, resistant to cytokine therapy
  - Sorafenib 400mg bid po, or Placebo
- Efficacy
  - PFS: 5.5 vs. 2.8m, HR: 0.44, p<0.01
  - RR: 10% vs. 2%
- Adverse effect
  - Diarrhea, rash, fatigue, hand-foot syndrome
  - Cardiac event(ACS): 3%(12) vs. 0.4%(2)

New England Journal of Medicine 2007;356:125-34

Sorafenib in melanoma and HCC

- Randomized discontinuation trial, 37 pts
- Efficacy : little or no activity
- No cardiotoxicity
  - British Journal of Cancer 2006; 95: 581-586
- 137 HCC pts, Child A/B, advanced HCC
- Phase II, little efficacy, still active
- No cardiotoxicity
  - Journal of Clinical Oncology 2006; 24: 4293-30

Cardiotoxicity

- Sunitinib: 11% (by pharmaceutical com.)
  - (22+8+22)/(312+106+750) = 4.5%
- Sorafenib: 3% (by pharmaceutical com.)
  - (0+14+0+0)/(202+903+37+137) = 1%

In rat study

- PDGF
  - Artificial MI
  - Release of PDGF had better outcome
- VEGF
  - Artificial cardiac stress,
    - Aortic bending or gene activation
    - Increased angiogenesis
  - VEGF blockade
    - LV dilatation, cardiac dysfunction, ↓angiogenesis

Circulation 2006; 114: 637-44
J Clin Invest 2005; 115: 2108-2118
Hypertension 2006: 47: 887-893

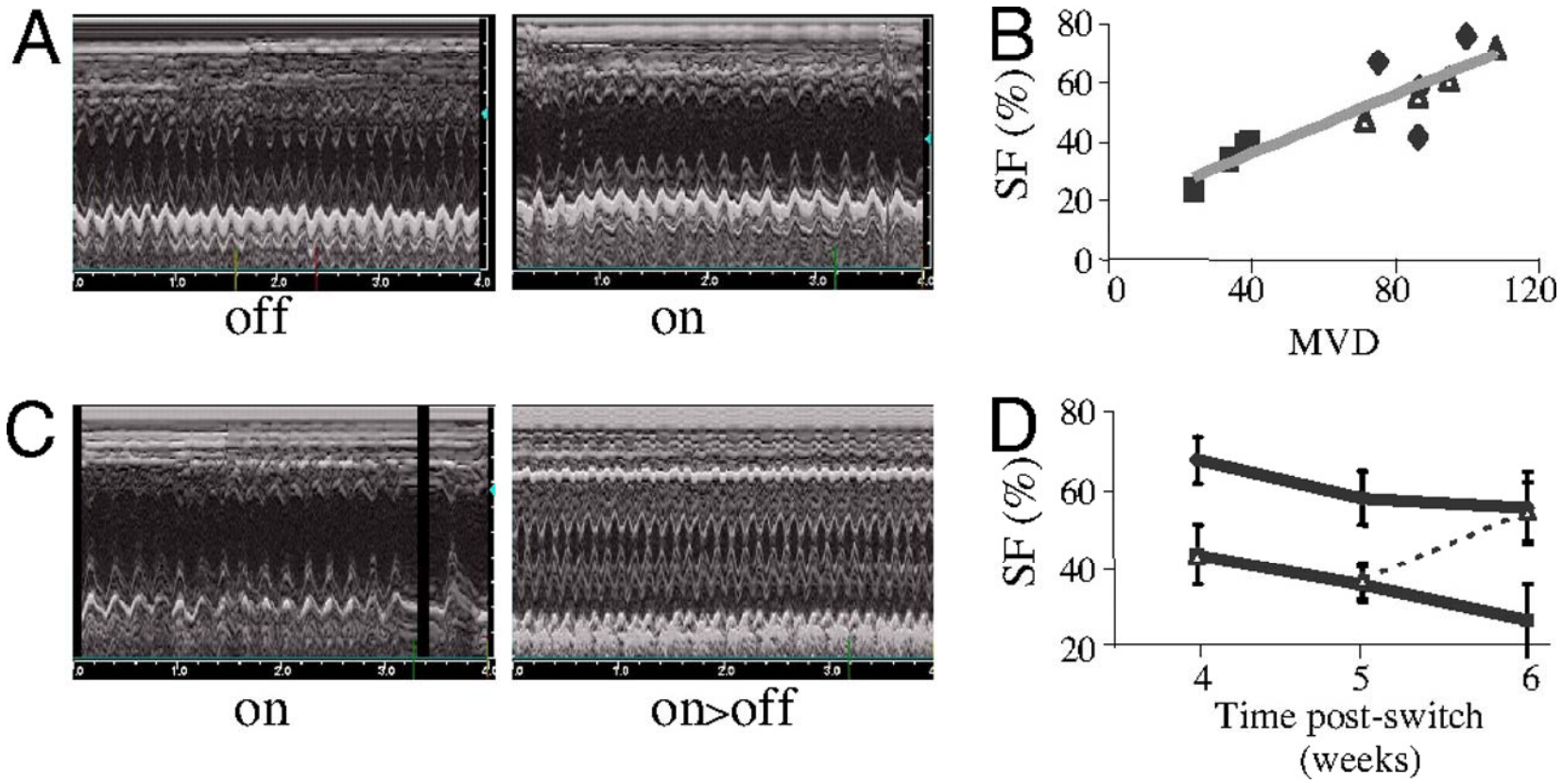
VEGF inhibition

- Has effect on blood vessel densitiy in the heart
- This effect is much more pronounced in younger animals but could also be detected in older animals (MICE)

VEGF INHIBITION

- Its important to note that vegf inhibition results in blood pressure elevation
- Also may result in significant proteinurea
- Both may have significant cardiac effects
- Treatment including ACE inhibitors has some importance in these patients
- Interestingly in a recent meta-analysis, Bevacizumab manifested a not negligible risk of cardiac ischemia and arterial thromboembolic events (3.3%)

Induction of chronic, yet reversible, cardiomyocytes dysfunction.



May D et al. PNAS 2008;105:282-287

RAF1 and cardiac dysfunction

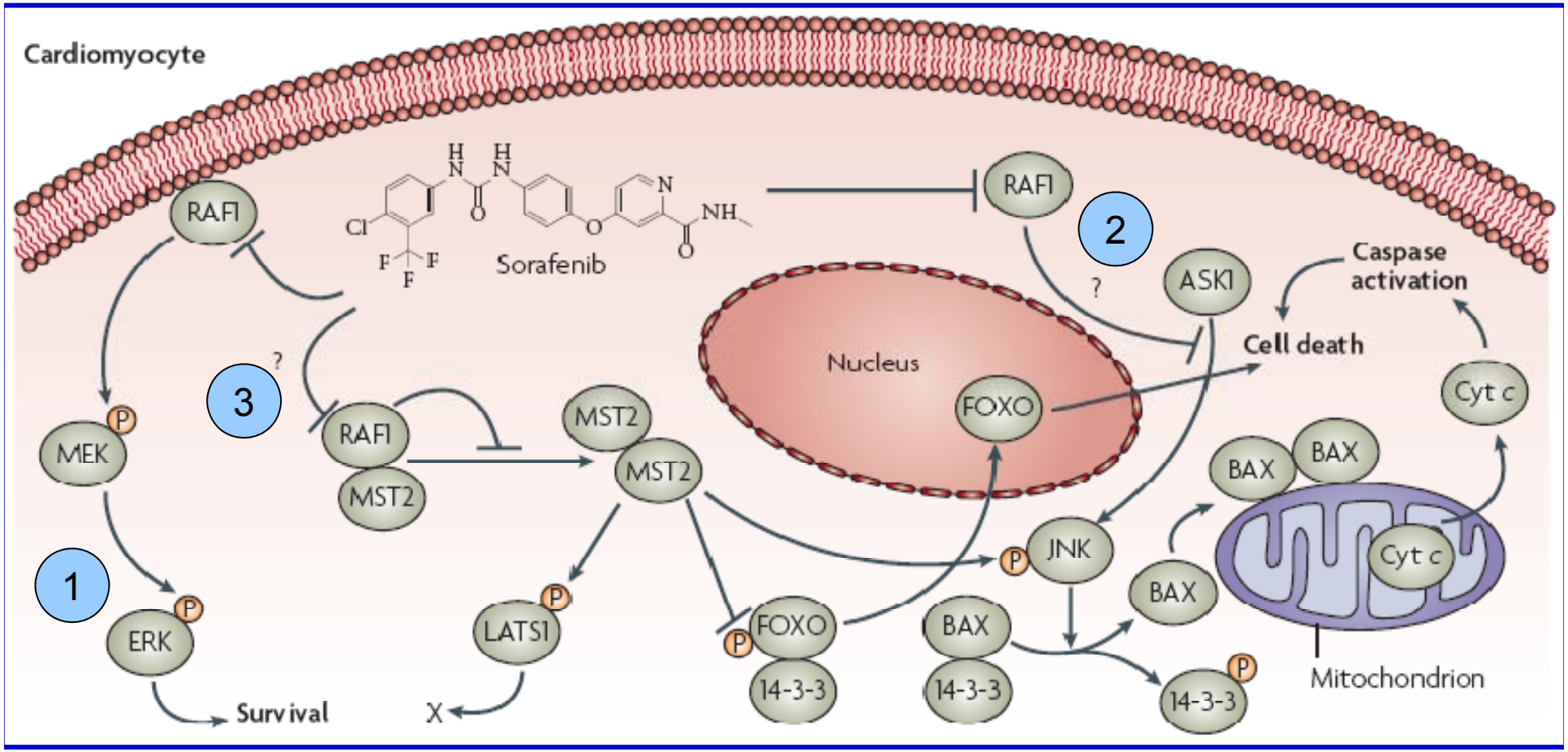
- Cardiac muscle-specific Raf-1-knockout mice
  - LV systolic dysfunction and heart dilatation
  - Increase in apoptotic cardiomyocytes.
  - MEK / ERK : no difference in expression
  - ASK1, JNK, or p38: Increased significantly
- The ablation of ASK1
  - Rescued heart dysfunction and dilatation
- Raf-1 promotes cardiomyocyte survival through a MEK/ERK-independent mechanism

Journal of Clinical Investigation 2004; 114: 937-43

1. RAF1 -> MEK -> ERK

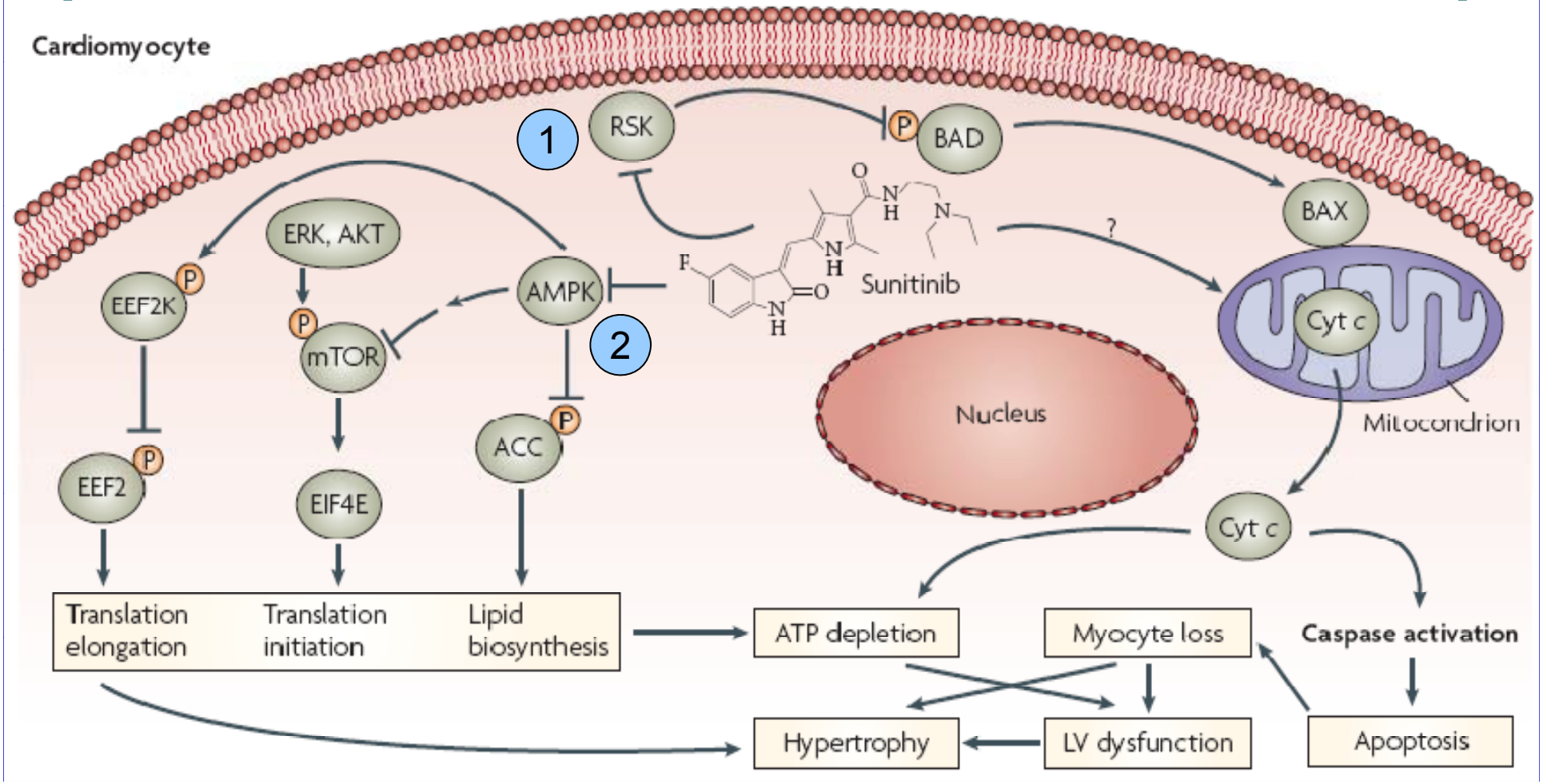
2. RAF1-> ASK1,
3. RAF1-> MST2,

Independent of RAF1 kinase activity, really blocked by Sorafenib ?



Off-target effect

- RSK, AMPK

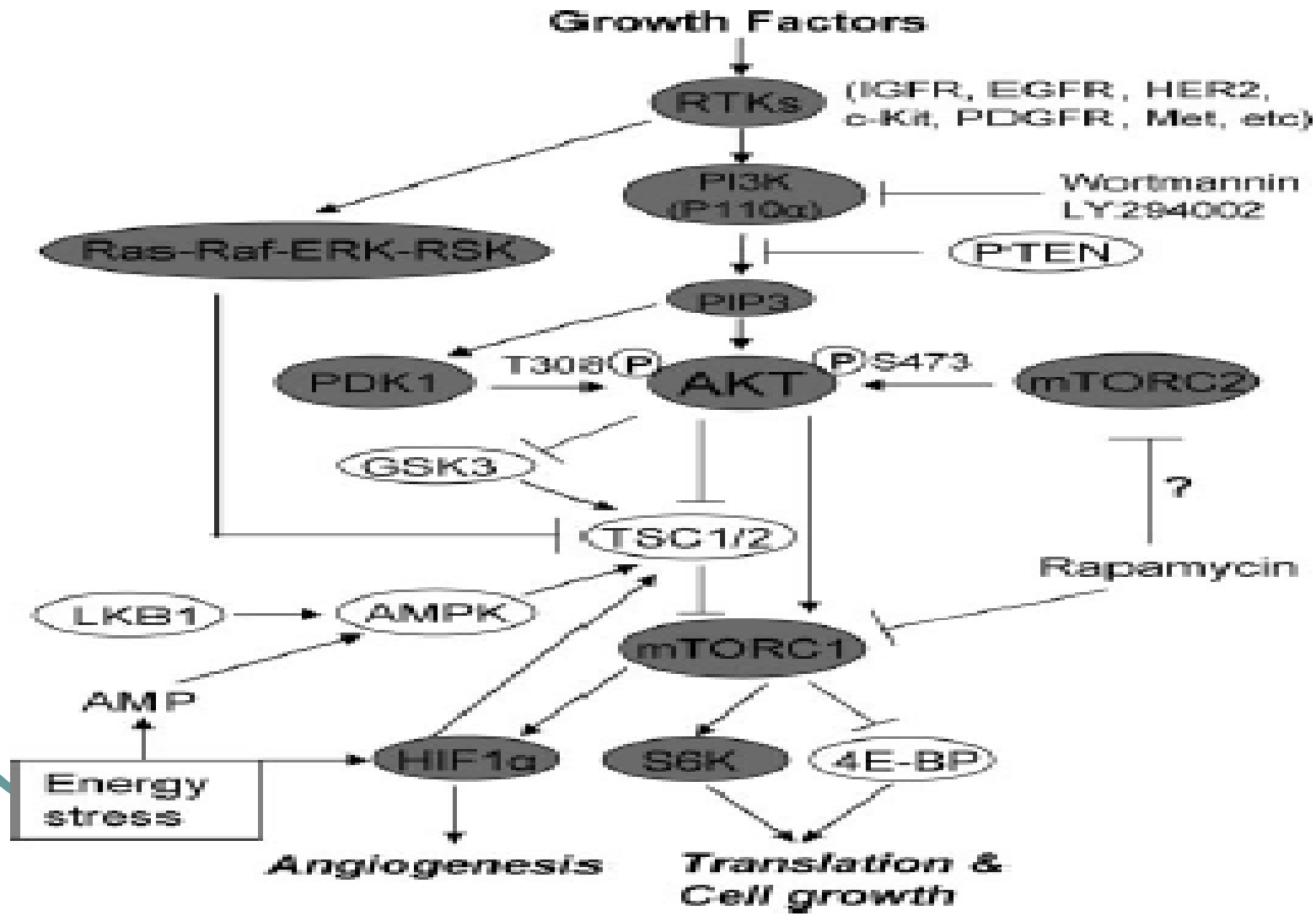


- Sutent a direct inhibitor of AMPK
- Adenoviral delivery of constituvely active AMPK blocked some of the cardiomyocite cell death induced by sunitinib
- Its important to note that AMPK is now considered one of the important possible targets for anticancer therapy (metformin = Glucophage)

Sunitinib

- most of the sunitinib related cardiotoxicity is considered reversible
- It is not always the case
- This is critical if one plans to use high dose IL2 in patients previously treated with vegf inhibitors
- In Israel several patients underwent this treatment safely after a around 4 weeks without sunitinib

Other inhibitors – the PI3K AKT mTOR inhibitors



Summary – 1

- Her2 pathway
  - Herceptin: evident, reversible,
    - Herceptin alone: 3-7%(metastatic)
    - Adjuvant
      - AC→TH : 1.6-4.1%
      - AC→T→H: 0.6-2.5%
      - TCH: 0.4%
      - TH→FEC (FinHer): 0
  - Lapatinib: 2.4%, less than Herceptin (?)

Summary – 2

- ABL pathway
  - Imatinib, Dasatinib, Nilotinib
  - Not sure for cardiotoxicity, very low
  - ER stress-related
    - Actual relation to ABL is not known

Summary – 3

- Multi-target inhibitor
  - Sunitinib: more cardiotoxic according to
  - The sorafenib people….
  - Sorafenib:
  - PDGF, VEGF, RAF1
  - Off-target effect

RAF1 and cardiac dysfunction

- Transgenic mice
  - Cardiac-specific expression of a dominant negative form of Raf-1 (DN-Raf).
- DN-Raf mice
  - Normal cardiac structure and function in the absence of provocative stimulation.
- In response to pressure overload,
  - ERK activation was inhibited
  - Development of cardiomyocyte apoptosis
  - 35% of animals died within 7 days

Circulation 2004; 110: 718-23