THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

Early-Phase Clinical Trials in Oncology
Any Concerns for Cardiovascular Toxicity?

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Background

- Assessment of risk factors for cardiovascular toxicity of investigational agents
- Assessment of patient risk factors for cardiovascular events
- Clinical trial design of patient eligibility and safety monitoring
- Management of cardiovascular complications

Tsimberidou AM, Minotti G, Cardinale D. Tex Heart Inst J. 2011;38(3):266-7

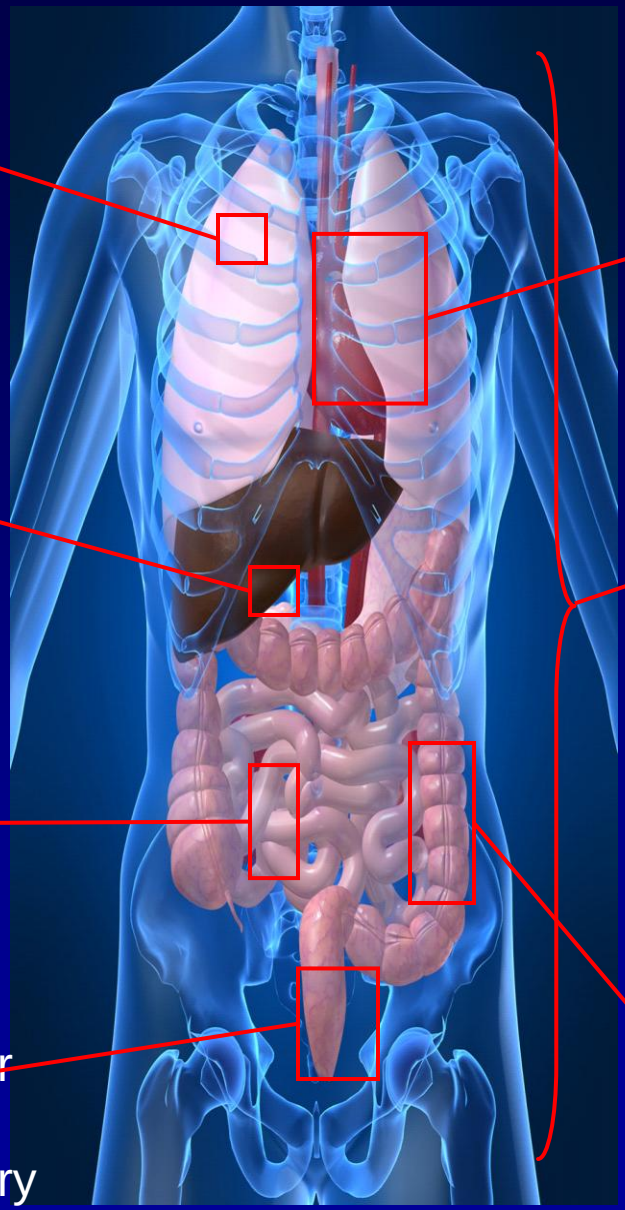
Tumor Tissues
(VEGF upregulated)

Lung cancer
(bevacizumab)
Inhibition of tumor
growth & cavitation

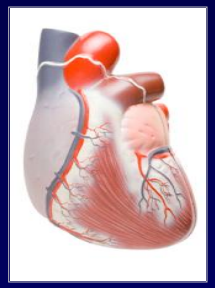
Hepatocellular
carcinoma
(sorafenib)
Tumor necrosis

Renal cell
carcinoma (sunitinib)
Tumor shrinkage,
tumor cell necrosis

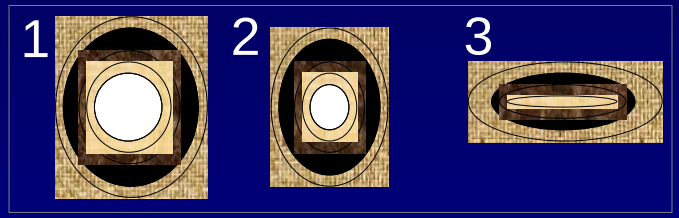
Colorectal cancer
(bevacizumab)
Deceleration of tumor
growth, efficient
chemotherapy delivery



Normal Tissues
(VEGF constitutively expressed)



Hypertensive remodeling
Microvascular rarefaction
Cardiomyopathy
(sunitinib & sorafenib)



Microcirculation: 1. normal arteriole,
2. functional rarefaction (endothelial
dysfunction, vasoconstriction)
3. anatomic rarefaction

Thrombotic microangiopathy
Glomerulopathy /
glomerulonephritis
Proteinuria
Hypertensive nephropathy

Vaklavas, Lenihan, Kurzrock & Tsimberidou, The Oncologist 2010 15:130

Anti-VEGF Therapies. Grade 3-4 Hypertension

Phase	I	II	III	Total
Bevacizumab				
Patients	170	1519	3075	4764
Events	16	157	261	434
Average, %	9.4	10.3	8.5	9.2
Range, %	0 - 33	0 - 48	3 - 18	
Sunitinib				
Patients	55	546	577	1178
Events	4	41	36	81
Average, %	7.3	7.5	6.2	6.9
Range, %	6 - 8	2 - 18	3 - 8	
Sorafenib				
Patients	446	822	748	2016
Events	25	98	22	145
Average, %	6.0	12.0	3.0	7.2
Range, %	0 - 19	0 - 31	2 – 4	

Vaklavas, Lenihan, Kurzrock & Tsimberidou, *The Oncologist* 2010 15:130

Anti-VEGF. Grade 3-4 Left Ventricular Systolic Dysfunction

Phase	I	II	III	Total
Bevacizumab				
Patients	170	1519	3075	4764
Events	NR	4	11	15
Average, %	NR	0.3	0.4	**0.3**
Range, %	NR	0 – 12	0 - 3	
Sunitinib				
Patients	55	546	577	1178
Events	2	7	7	16
Average, %	3.6	1.3	1.2	**1.4**
Range, %	0 - 13	0 – 5	0 - 2	
Sorafenib				
Patients	446	822	748	2016
Events	1	NR	NR	1
Average, %	0.2	NR	NR	**0.05**
Range, %	0 - 3	NR	NR	

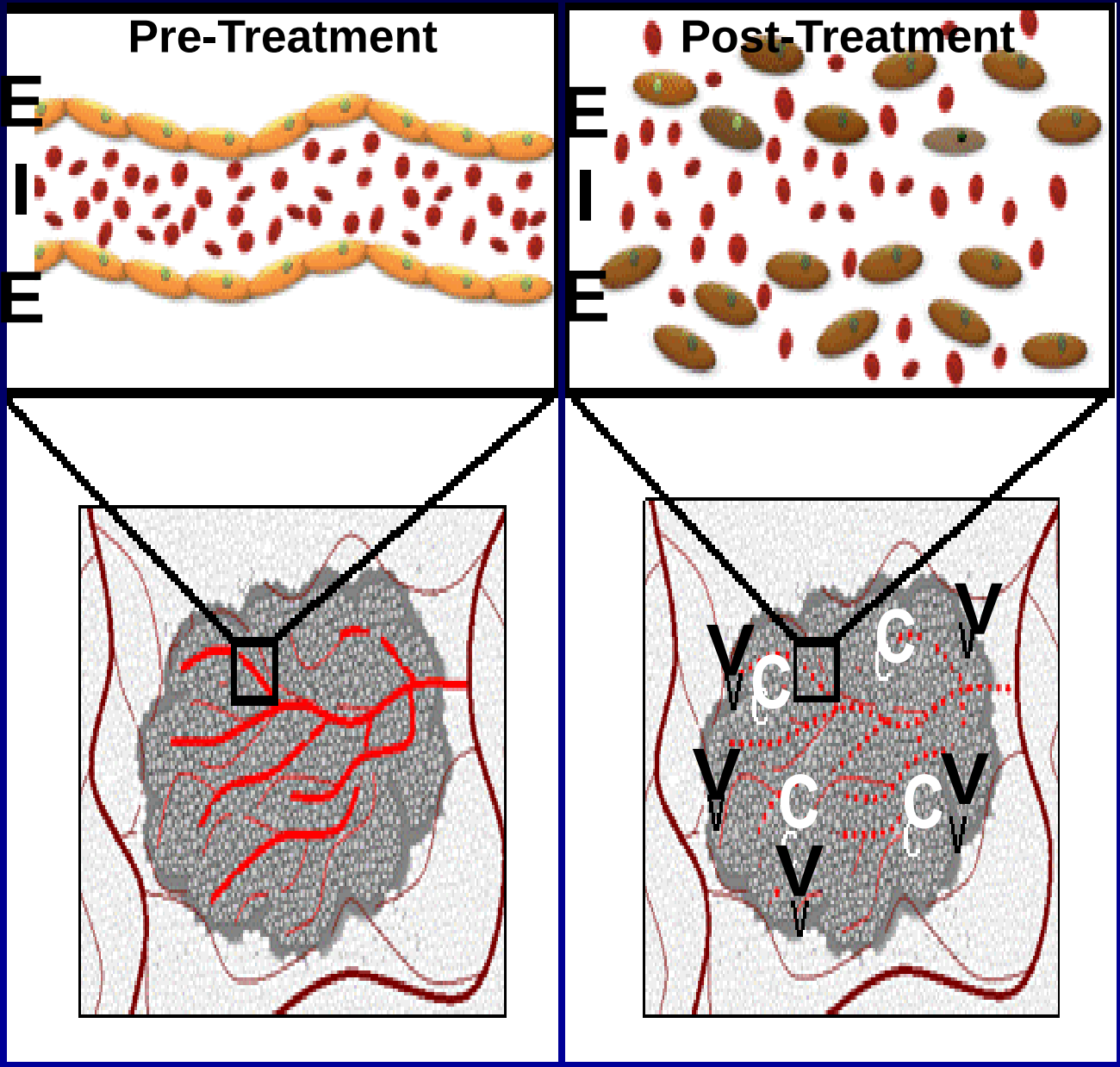
Vaklavas, Lenihan, Kurzrock & Tsimberidou, *The Oncologist* 2010 15:130

Anti-VEGF Therapies. Grade 3-4 Hemorrhagic/Thrombotic Complications

Phase	I	II	III	Total
Bevacizumab				
Patients	170	1519	3075	4764
Events	12	165	282	459
Average, %	7.0	11.0	9.2	**9.6**
Range, %	0 – 18	0 – 32	3 – 23	
Sunitinib				
Patients	55	546	577	1178
Events	3	11	NR	14
Average, %	5.5	2.0	NR	**1.2**
Range, %	0 – 13	0 – 4	NR	
Sorafenib				
Patients	446	822	748	2016
Events	13	15	48	76
Average, %	3.0	2.0	6.4	**3.8**
Range, %	0 - 14	0 – 8	6 – 7	

Vaklavas, Lenihan, Kurzrock &Tsimberidou, *The Oncologist* 2010 15:130

Vascular-Disrupting Agents. Mechanism of action



- Microtubule depolymerization and/or local increase in inflammatory cytokines
- Breakdown of endothelial monolayer
- Extravasation of intravascular macromolecules
- Cessation of tumor blood flow
- Tumor hypoxia
- Central tumor necrosis
- Robust reactive angiogenesis and tumor regrowth on the periphery

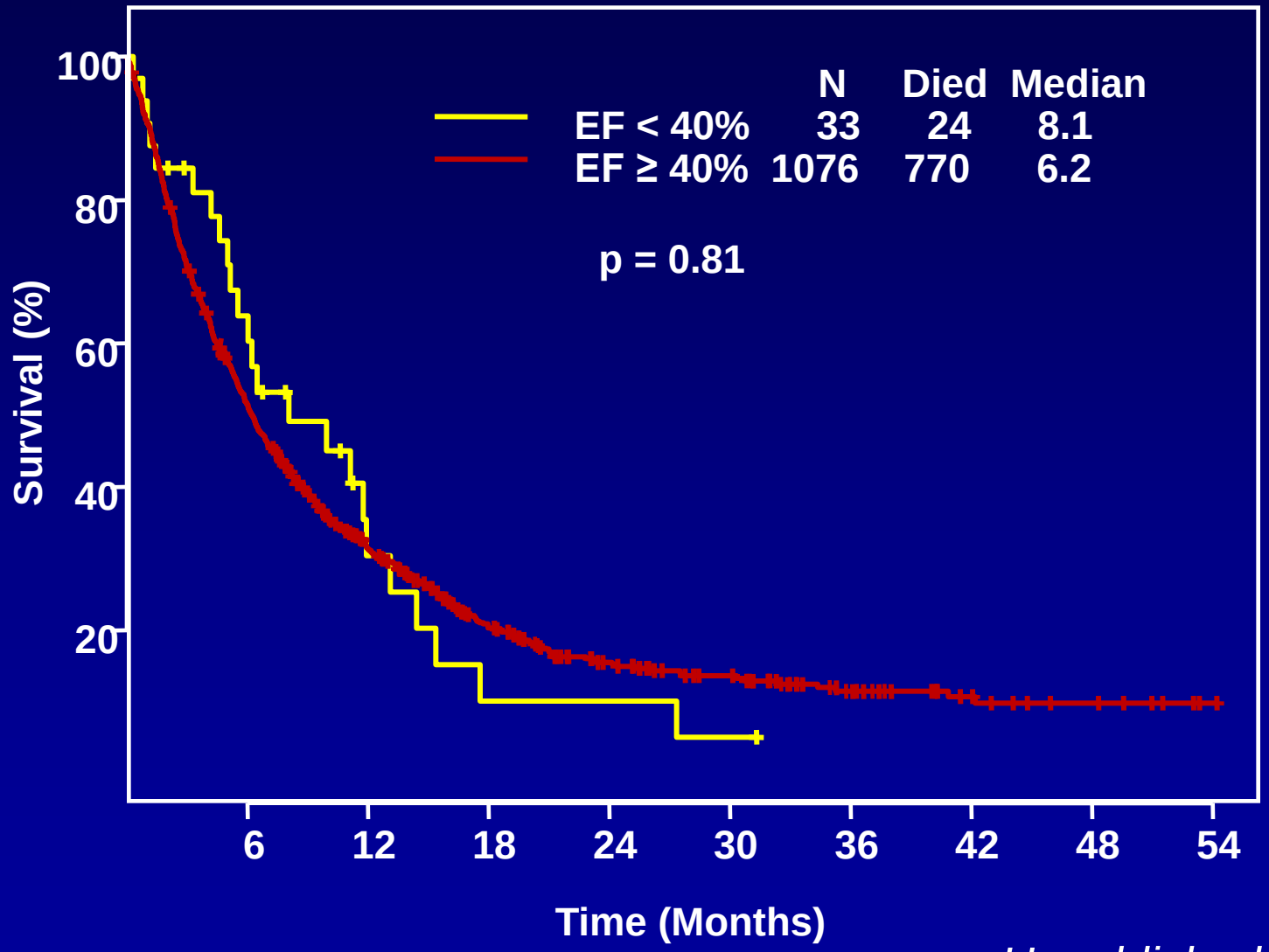
Subbiah, Lenihan, Tsimberidou The Oncologist 2011 : 16: 1120-30

Vascular-Disrupting Agents in Clinical Trials

Drug	Phase	Common cardiotoxicity
Vadimezan (ASA404, DMXAA)	I, II, III	Transient QTc prolongation; Atrial fibrillation; HTN; Myocardial ischemia
Ombrabulin (AVE8062)	I	None
BNC105P	I	G4 NSTEMI (DLT)
OXi4503 (Combretastatin A1 phosphate, CA1P)	I, II	Atrial fibrillation; G3 HTN (DLT)
Combretastatin A4 phosphate (CA4P)	I, II	HTN; QTc prolongation; MI
CKD-516	I	Data not reported.
Crolibulin (EPC2407, Crinobulin)	I	Cardiac ischemia (DLT); Transient low-grade HTN; Transient QTc prolongation
Azixa™(MPC-6827, Verubulin)	I	G3/4 MI (DLT); G4 NSTEMI (DLT); G1/2 bradycardia; G1/2 first-degree AV block; G1/3 HTN.
Plinabulin (NPI-2358)	I, II	Transient HTN
ANG453 (ZD6126)	I	G1/2 myocardial ischemia (5%) (DLT); G3 troponin elevation (5%) (DLT); G1 decrease in LVEF (2%) (DLT); G3 hypotension (DLT)

Subbiah, Lenihan, Tsimberidou The Oncologist 2011 : 16: 1120-30

Survival by EF in Patients Seen in the Phase I Program (n=1109)



Unpublished data

Neuroendocrine
Impact of Chronic Stress on Cancer

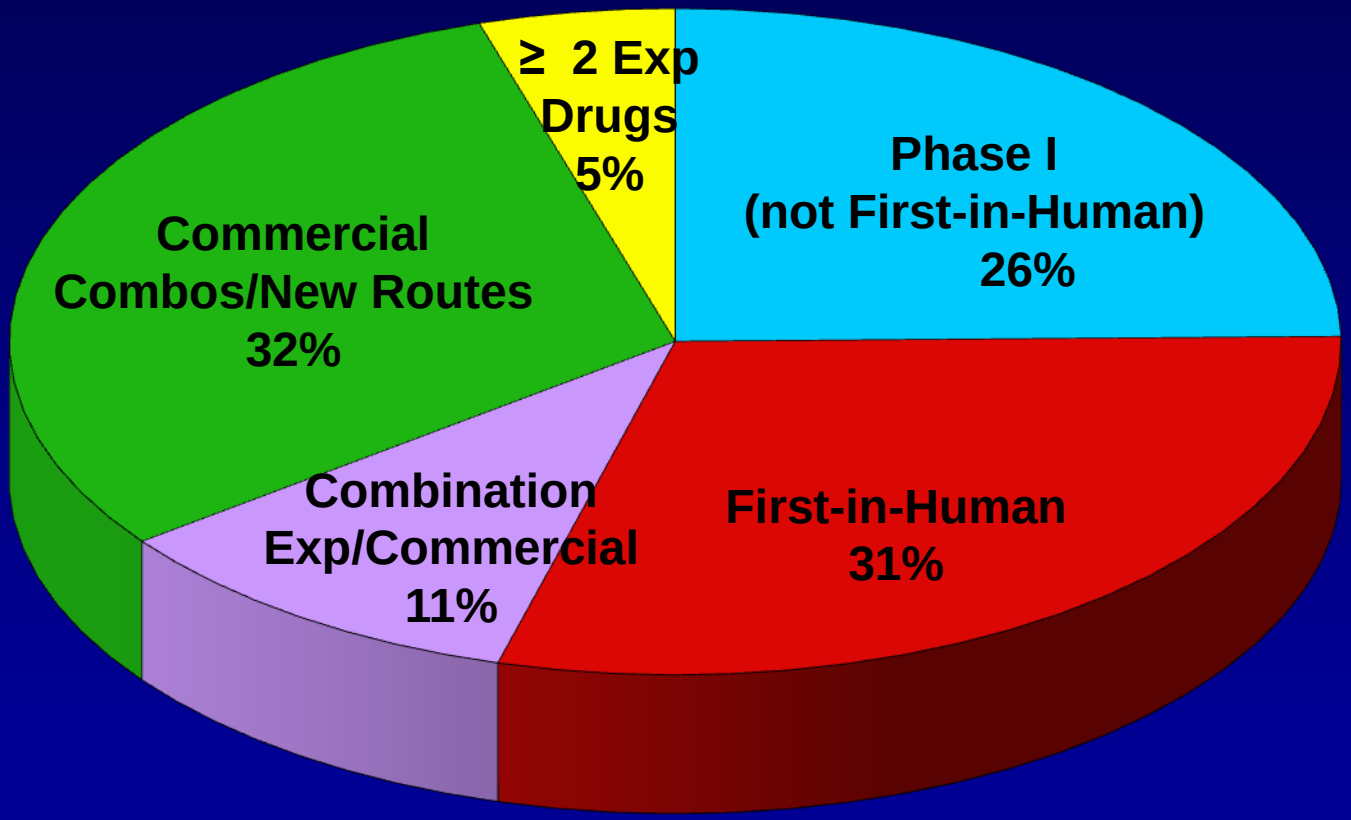
- Neurohumoral stress responses influence tumor progression and metastasis
- *In vivo* data suggest that β2-adrenergic stimulation leads to greater tumor burden and more invasive tumor growth
- β-blockers - rational choice in patients with cancer
- Superiority of inhibitors of the RAAS or the sympathetic nervous system in the management of anti-VEGF therapy–related hypertension

Thaker *et al*, *Cell Cycle* 2007 6:430

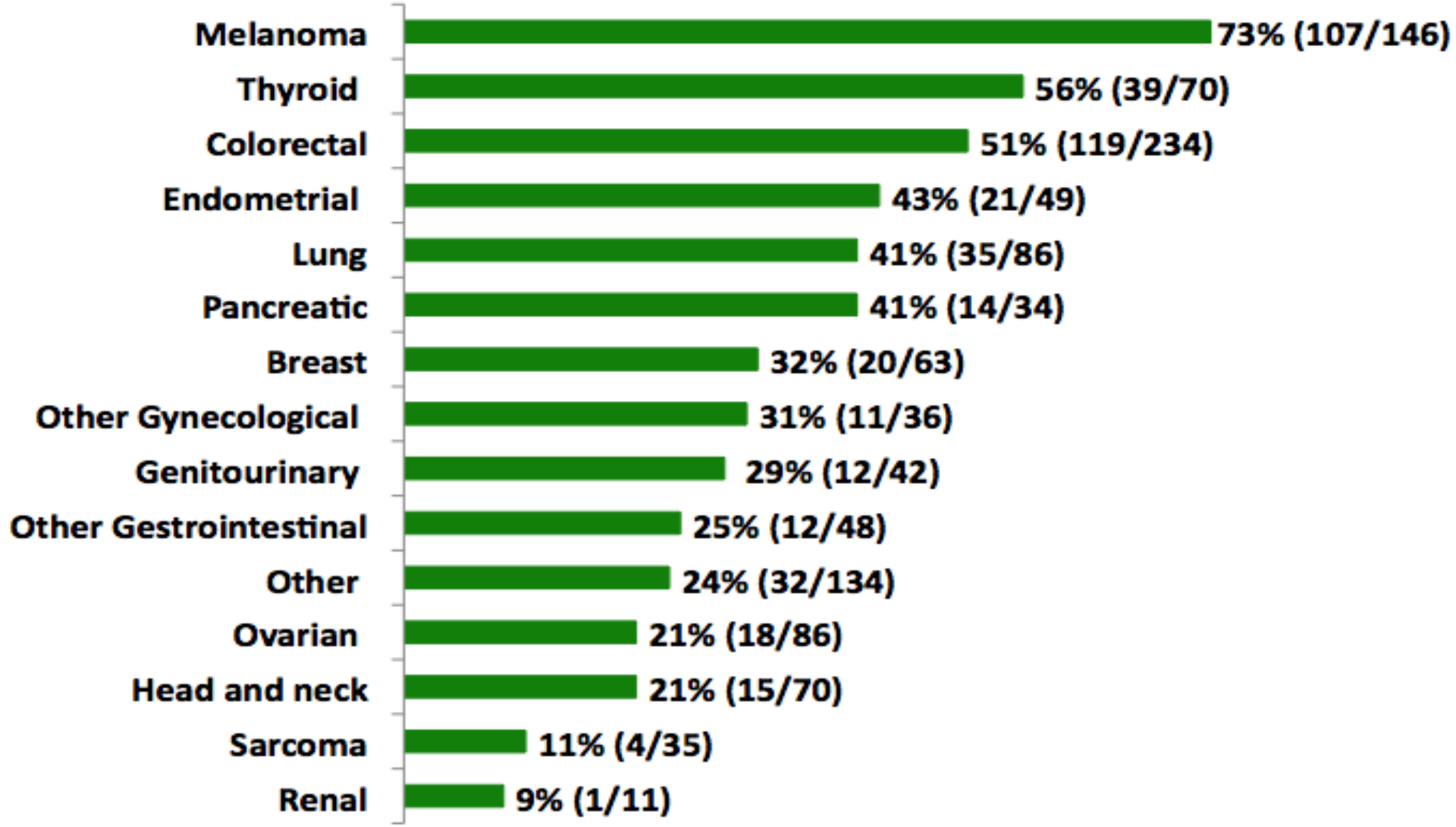
Challenges in Management of Cardiovascular Complications

- Use of preclinical data for tailoring study design
- Refinement of eligibility criteria
- Selection of screening tests
- Close monitoring for cardiotoxicity particularly for first-in-human agents
- Accurate publication of data
- Standardization of screening and monitoring: use clinically meaningful surrogate markers
- Development of models to predict risk

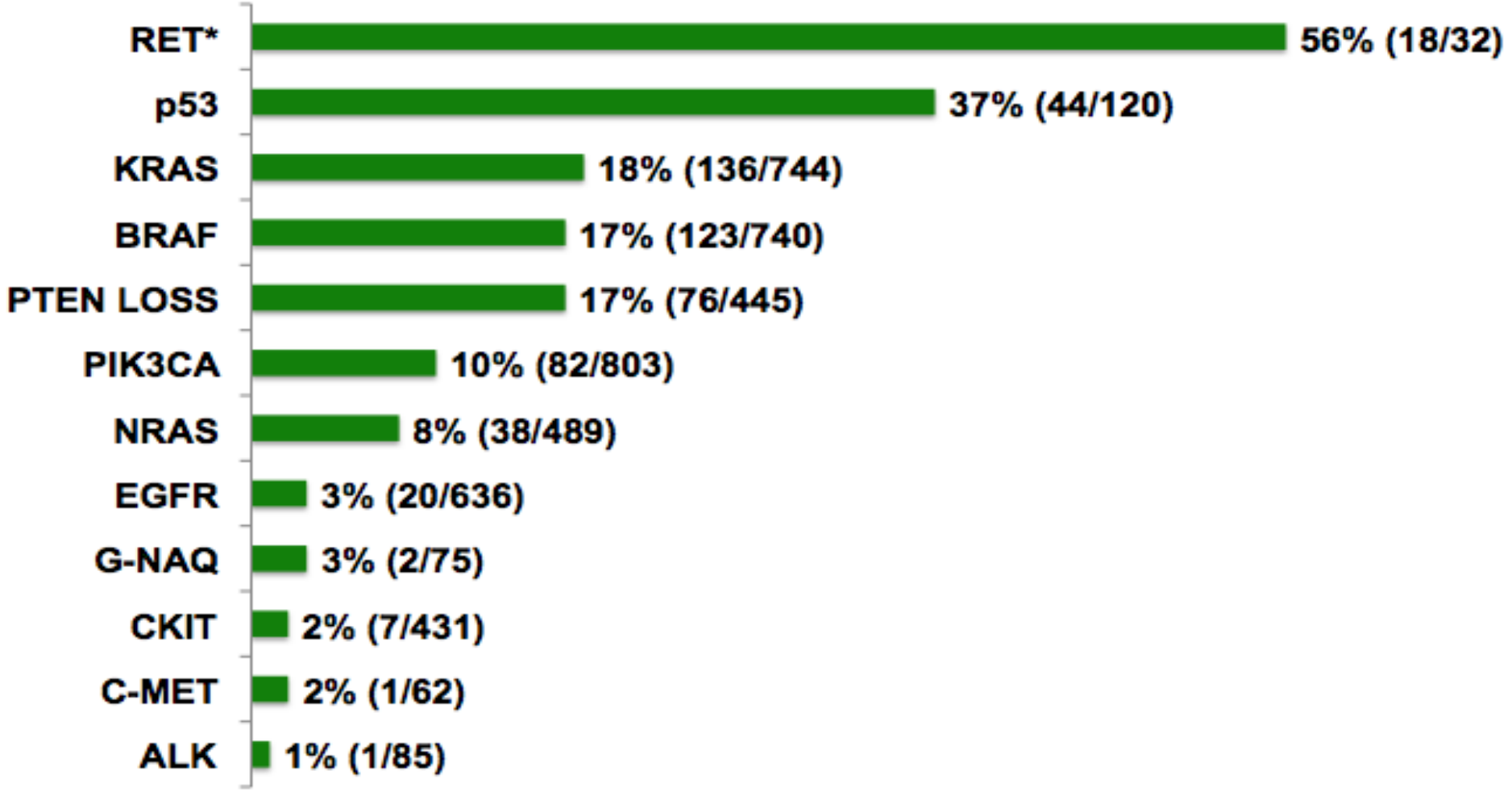
Dept of Investigational Cancer Therapeutics
Types of Studies (N=118)



Molecular Aberrations by Tumor Type (N=1144)



Proportions of Molecular Aberrations (N=1144)

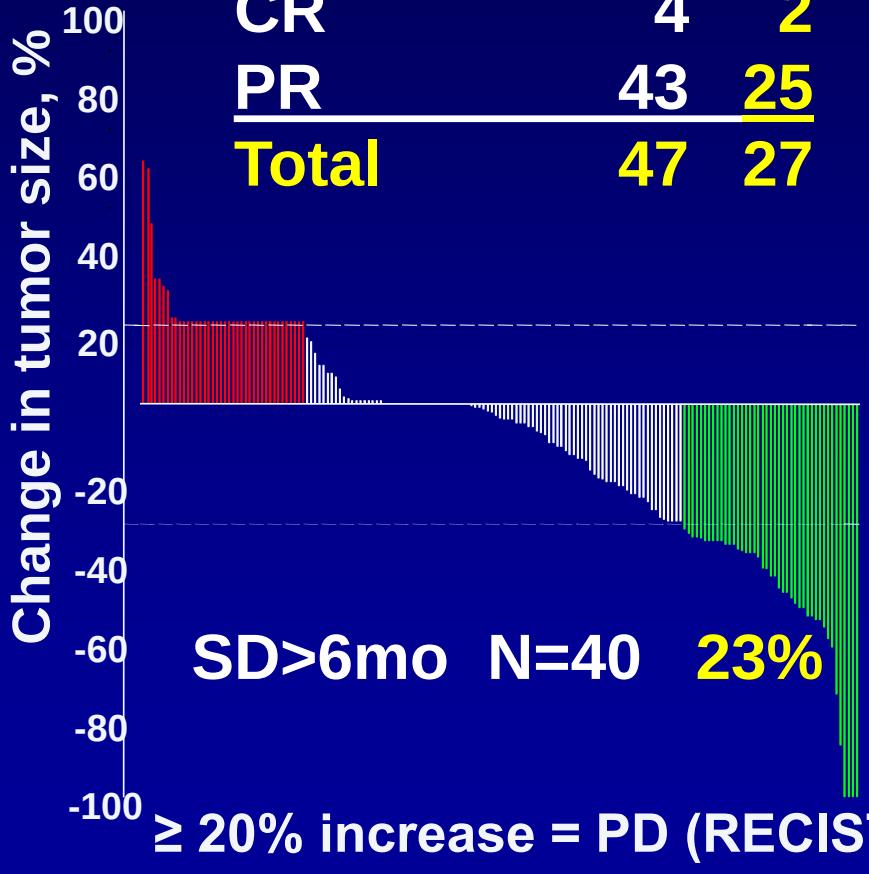


* Mostly patients with medullary thyroid cancer

Best RECIST Response. Patients with 1 Aberration

Matched therapy
N=175

Response	N	%
CR	4	2
PR	43	25
Total	47	27



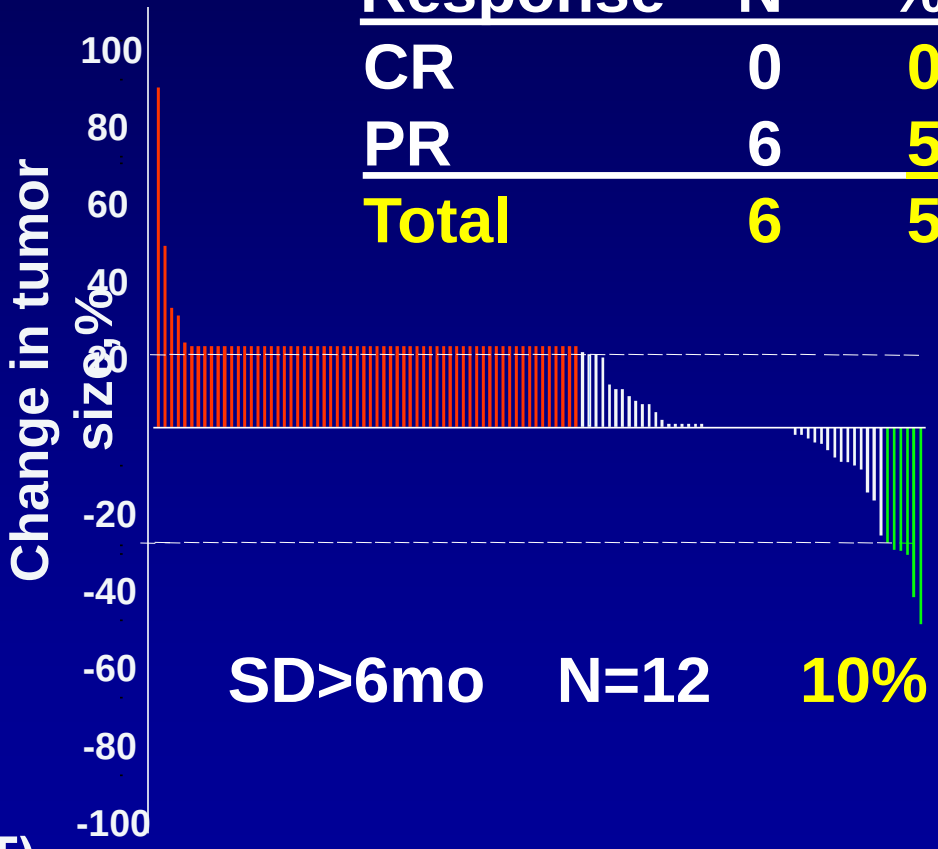
SD>6mo N=40 23%

≥ 20% increase = PD (RECIST)

p <.0001

Therapy without matching
N=116

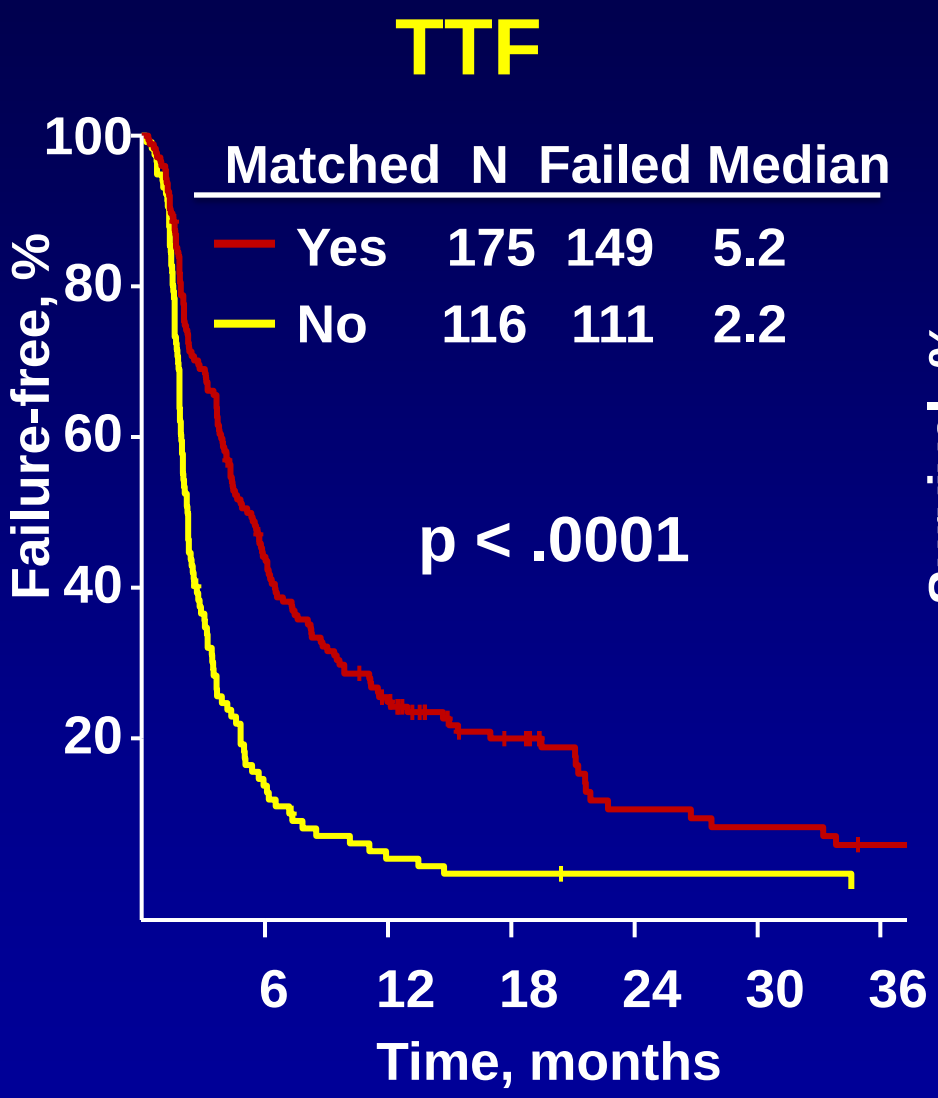
Response	N	%
CR	0	0
PR	6	5
Total	6	5

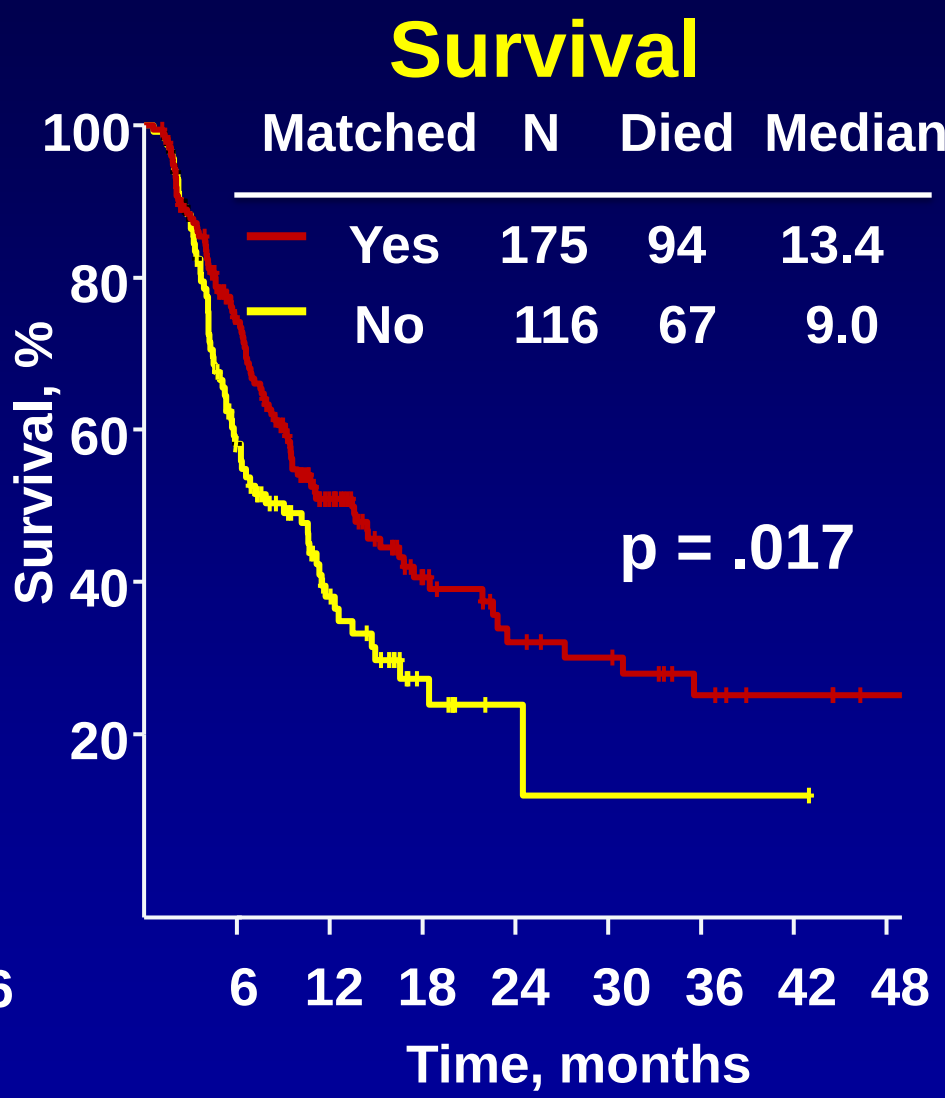


SD>6mo N=12 10%

AM Tsimberidou et al, ASCO 2011, Abstr. 2500

TTF and Survival by Therapy. Patients with 1 Molecular Aberration

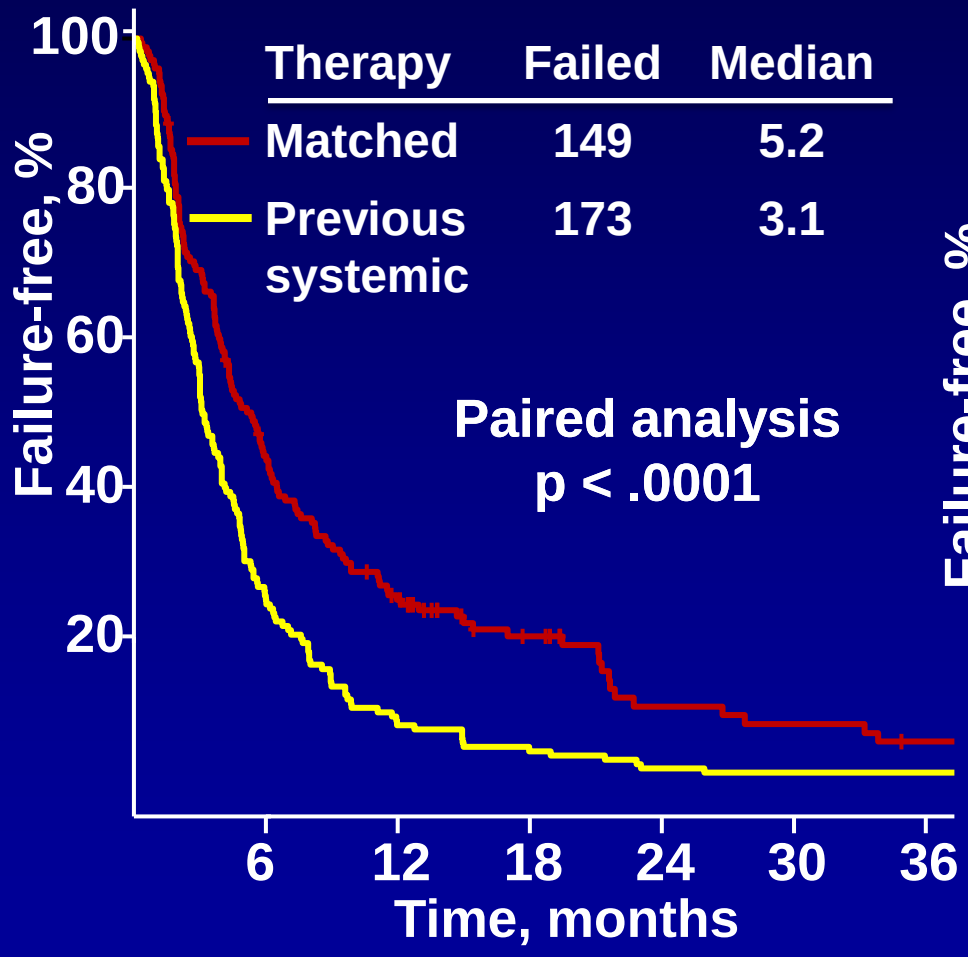




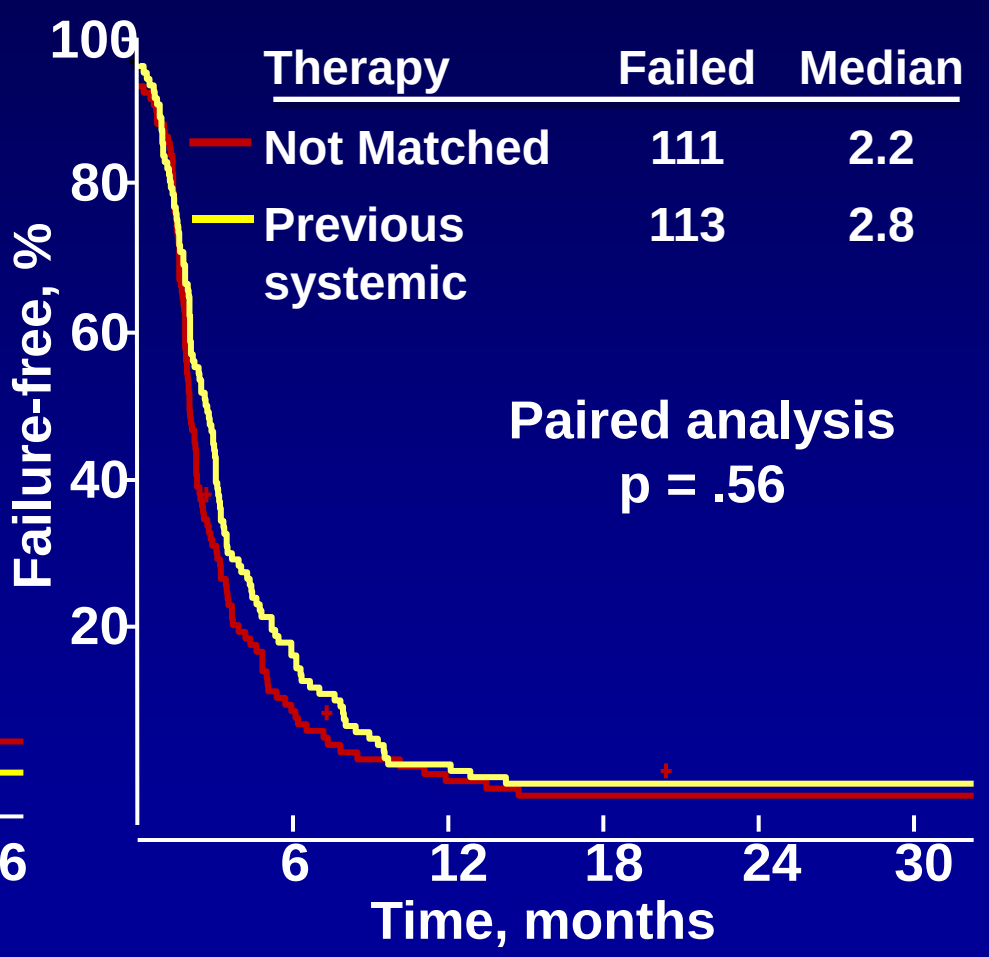
AM Tsimberidou et al, ASCO 2011, Abstr. 2500

TTF. Comparison with Previous Systemic Therapy

Matched therapy
N=175, 1 aberration



Non-matched therapy
N=116, 1 aberration



AM Tsimberidou et al, ASCO 2011, Abstr. 2500

Future Perspectives: Short-Term Goals

- Carefully design prospective clinical trials to assess cardiotoxicity in early phase clinical trials based on the novel drug and patient risk factors
- Refine eligibility criteria
- Raise awareness in academic and community practice about cardiotoxicity
- Develop algorithms to guide prevention and management of cardiotoxicity (FDA, ASCO, NCCN)
- Focus of long-term CV complications: more important with the use of personalized therapy
- Foster collaboration of cardiologists with oncologists

Future Perspectives: Long-Term

- Use results of prospective clinical trials to develop a model predicting risk of cardiotoxicity
- Use patient tumor tissue sequencing molecular profiling to identify high-risk phenotype
- Develop strategies to prevent/reverse cardiotoxicity
- Stratify patients according to cardiovascular risk for participation in early phase clinical trials and exclude high-risk patients
- Develop/use tissue banks: cardiovascular complication in patients with cancer vs. others

Questions

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