

Interrogating mTOR Inhibition in Patients with HRPC

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Disclosures

- Scientific Research: Abbott, AMGEN, BMS, Dendreon, GSK, Novacea, Novartis, Pfizer, Veridex
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- Employment: None
- Other: None



Challenges for Phase I/II Drug Development in HRPC

- Few established biomarkers for response besides PSA
- Limited access to tissue
- Limited sensitivity of traditional response measures of cancer (ie RECIST)
- Heterogeneous disease
- Limited understanding of HRPC biology

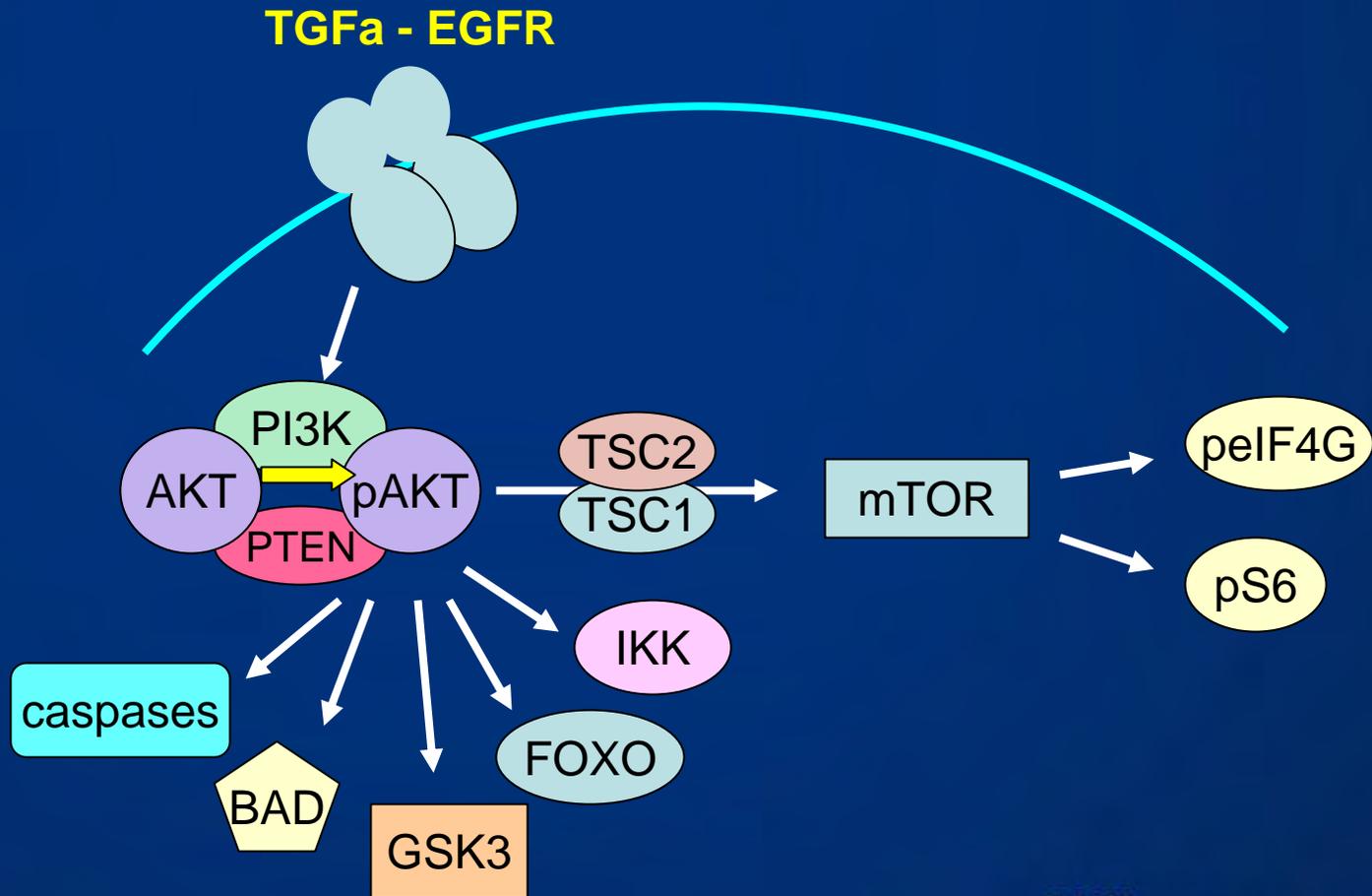


PTEN Tumor Suppressor Gene in Prostate cancer

- Results in constitutive activation of AKT
- Correlates with aggressive phenotype in early stage disease
- Biallelic Loss of PTEN on Chr 10q23 occurs in 50% of HRPC tumors
- Possible mechanism of androgen-independent AR activation



AKT inhibits TSC1/2 deactivation of mTOR



An Akt transgenic mouse

IGF-I

IGF1R

PI3K

myr

Akt

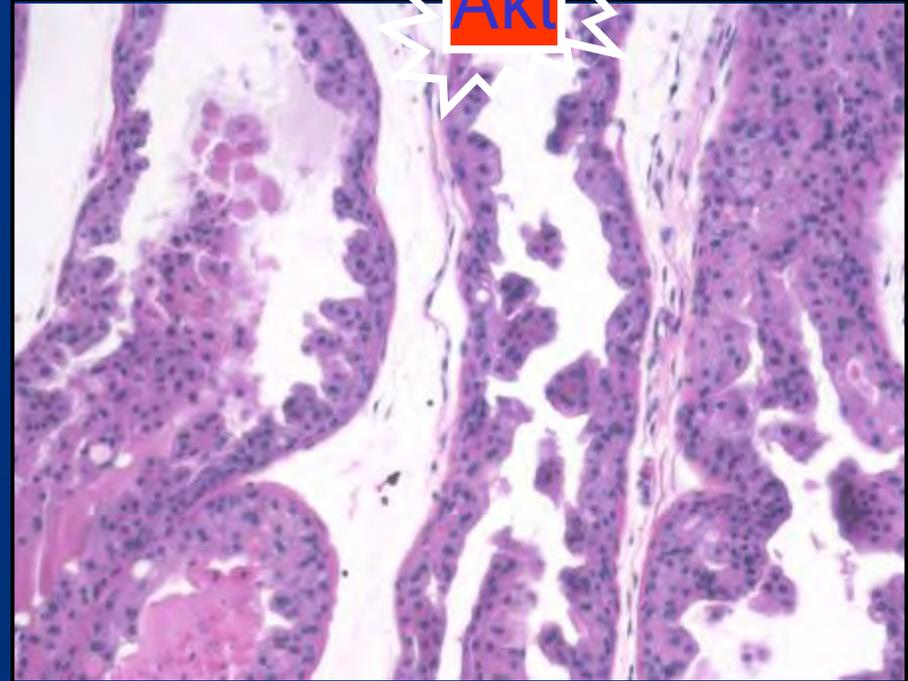
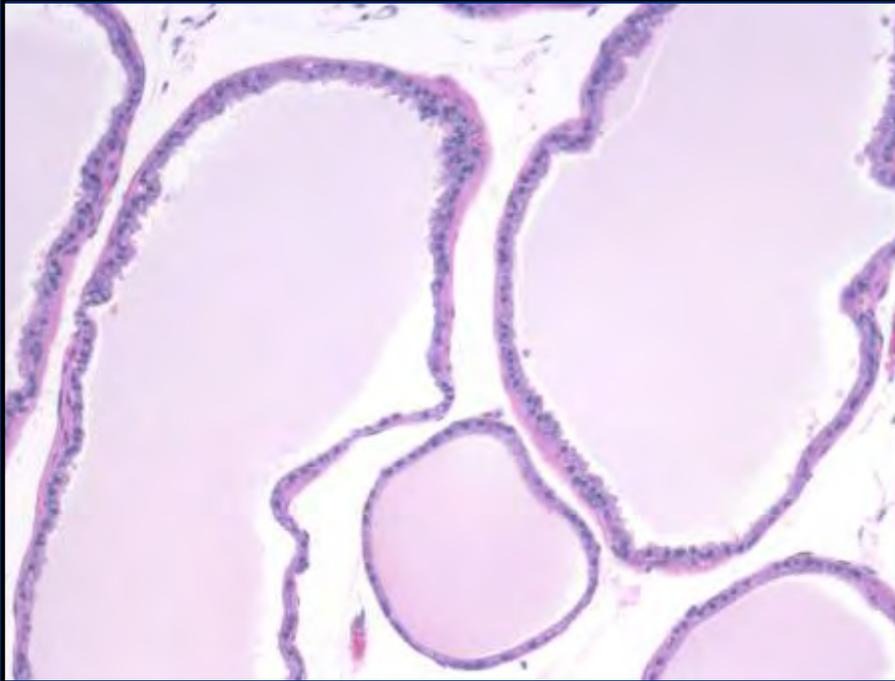
Probasin promoter

Myr HA

HuAkt-1

Akt-dependent PIN phenotype

Wild-type



Myr

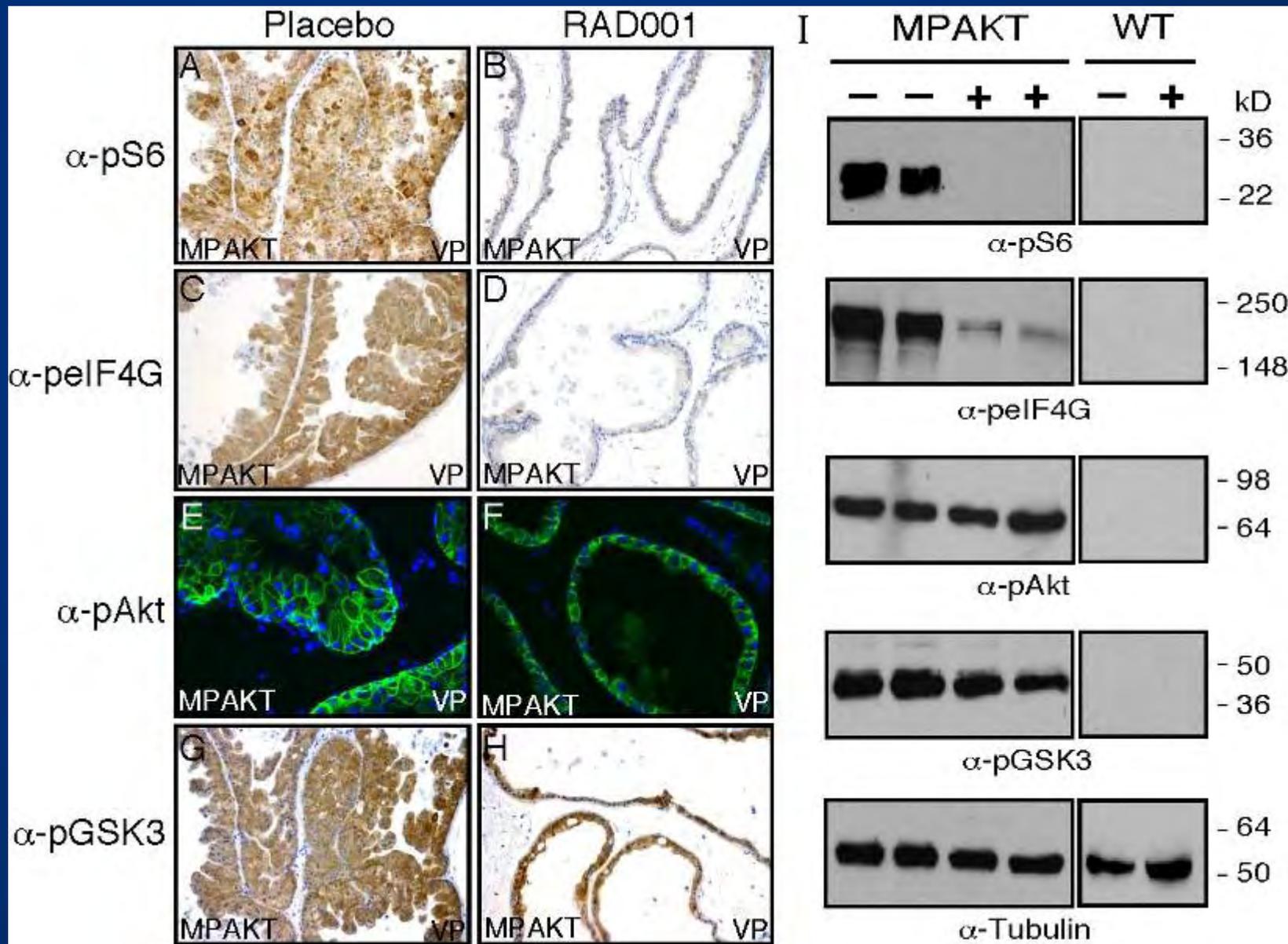
Akt



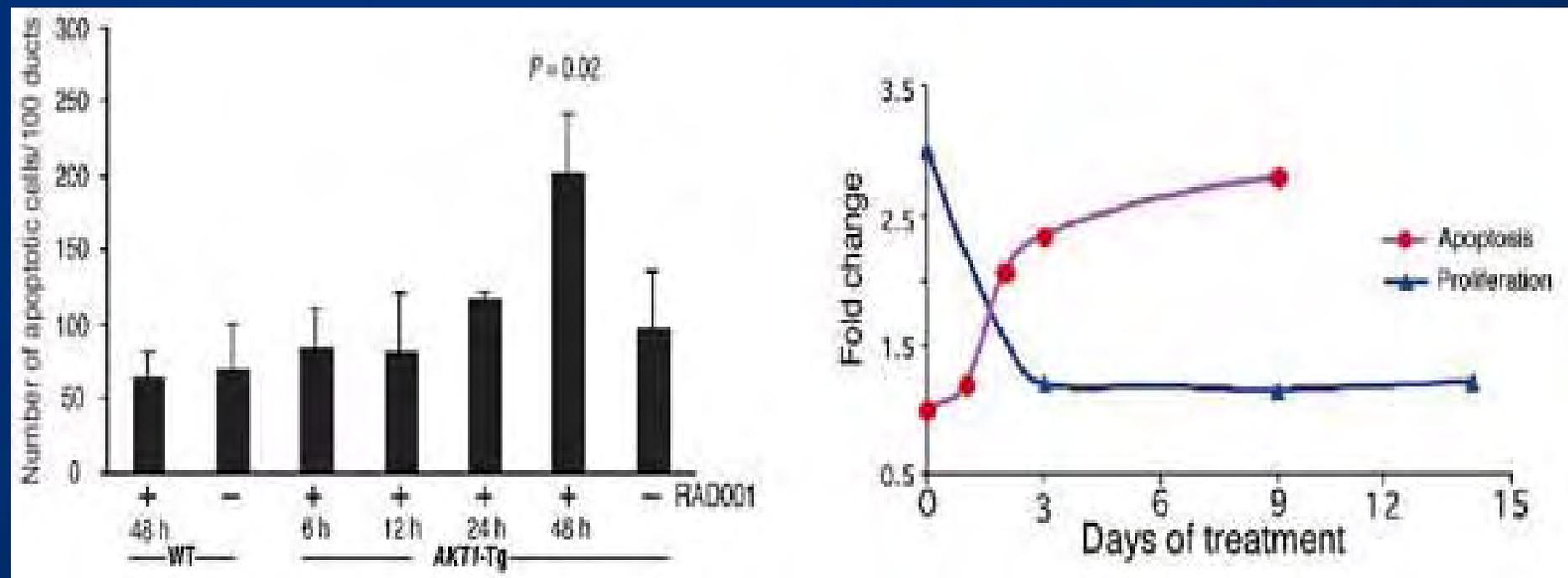
RAD001 (Everolimus)

- **RAD001 derivative of rapamycin from Novartis Pharmaceuticals**
- **Inhibitor of mTOR**
- **Orally bioavailable**
- **Immunosuppressant in combination with CSA**
- **Used to test the extent to which inhibition of mTOR will reverse the biologic effects of Akt activation.**





RAD001 Effects on Apoptosis and Proliferation

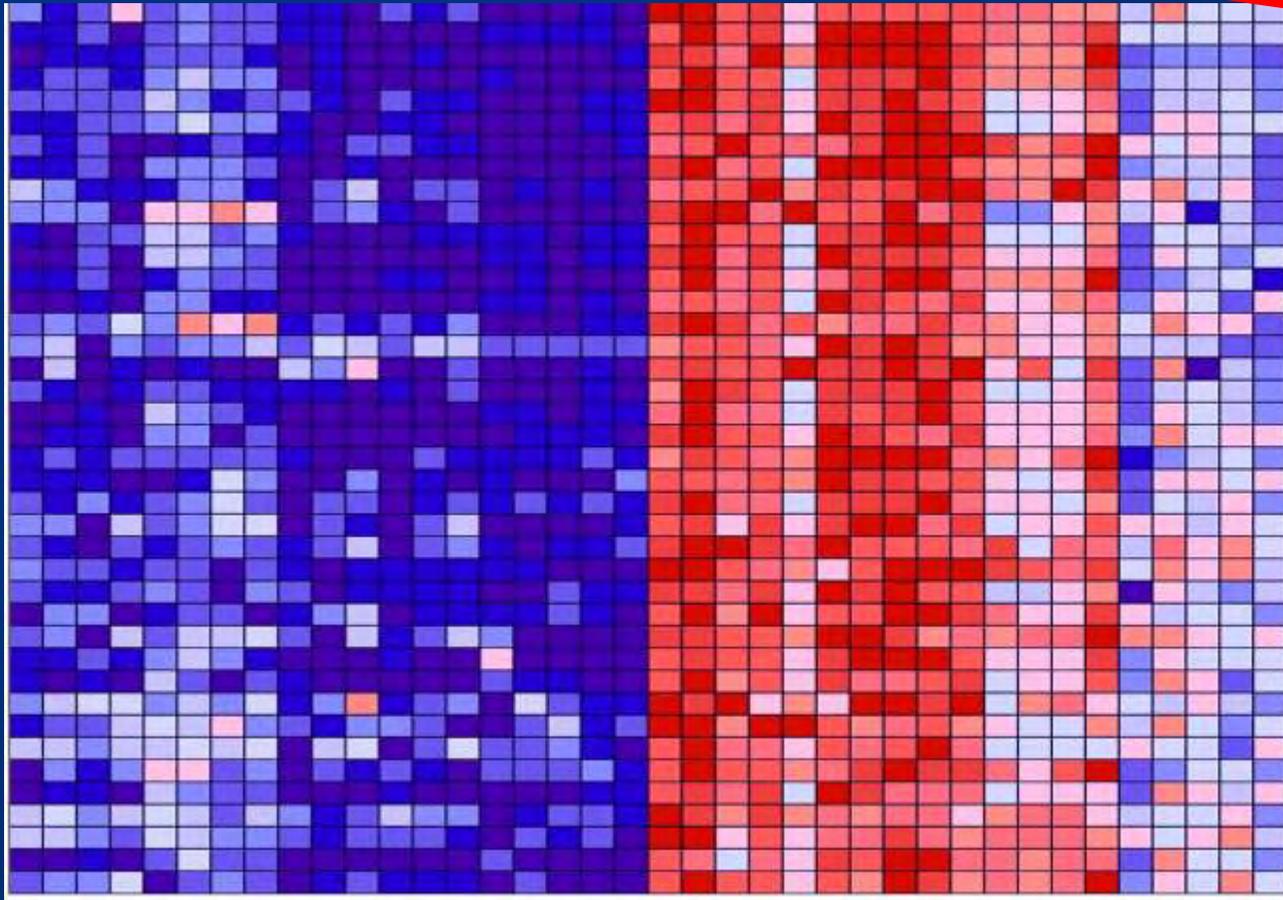


Expression Profiling In Tg-Akt Mouse Prostate

0h 12h 48h

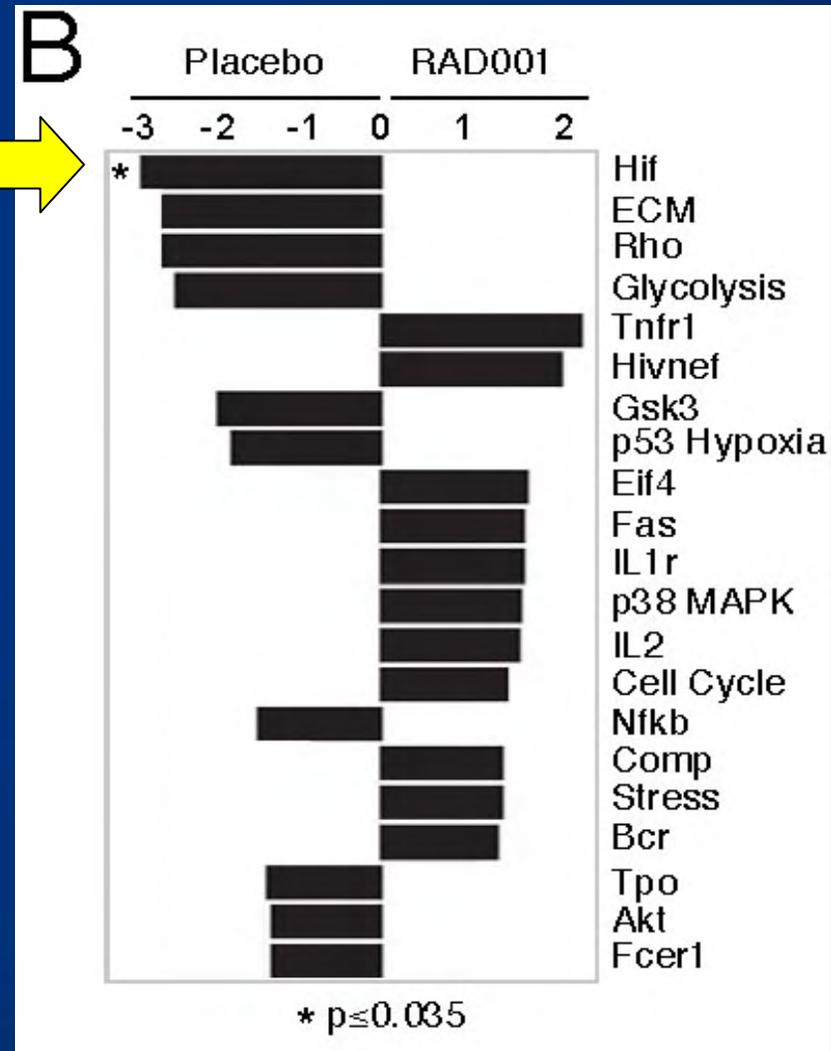
Controls

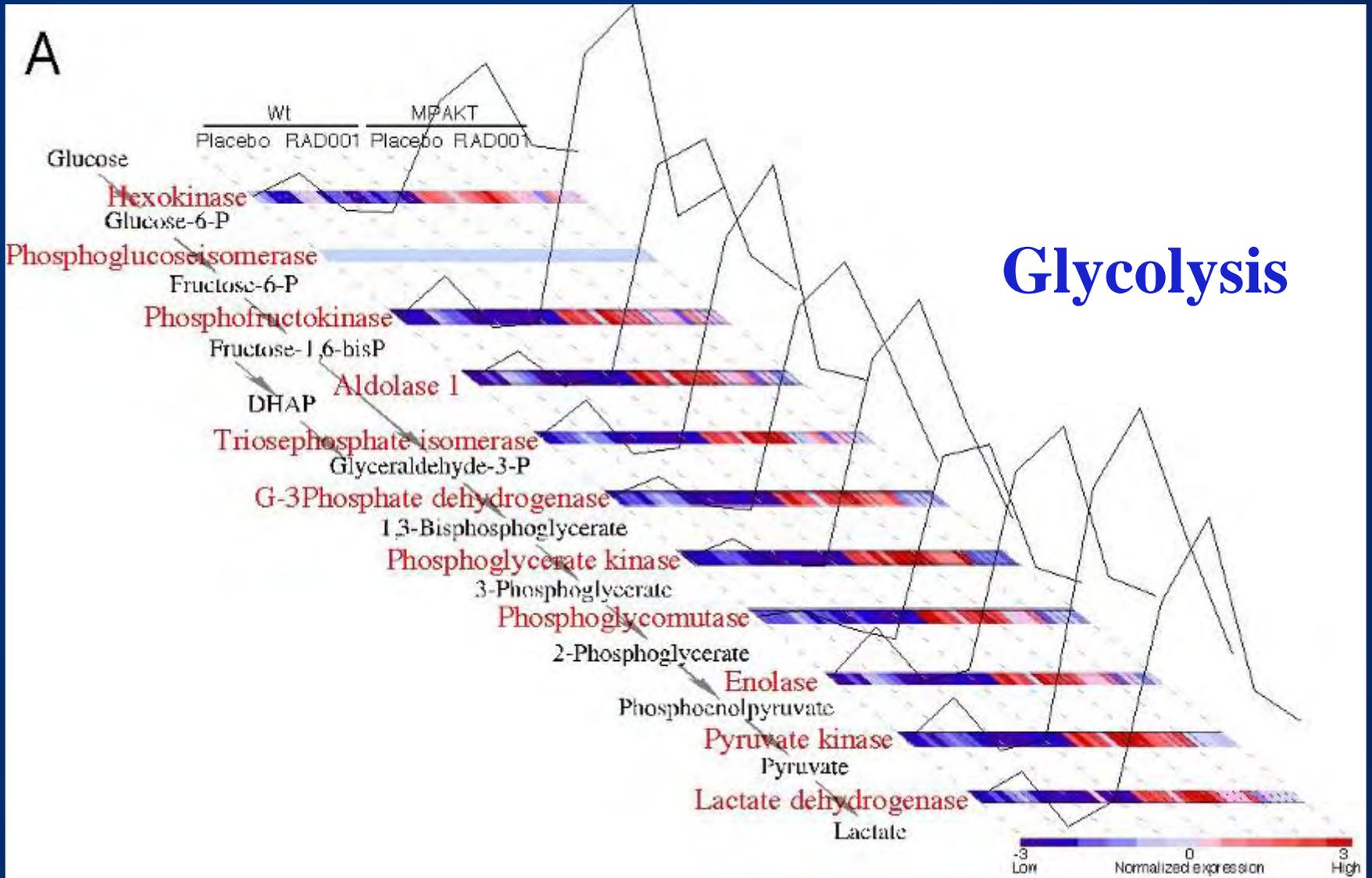
+RAD001



Gene Set Enrichment Analysis

Tested 192 Biocarta pathway sets for enrichment



A

Rationale for mTOR Inhibition in Prostate Cancer

- Frequent biallelic loss of PTEN in HRPC
- Loss of PTEN leads to activation of AKT
- mTOR activated downstream of AKT
- AKT activity associated with cell survival, proliferation
- In preclinical models RAD001 reverses the effects of AKT-activated prostate cancer



Phase II Study of RAD001 in HRPC patients

- **Single arm, open label daily oral RAD**
- **Tumor biopsies before and during Tx**
Hormone-refractory patients, prior
chemotherapy allowed
- **Treatment until disease progression or**
toxicity
- **Stats: 2 stage design – 1st stage 39 pts (3 or**
more responses proceed to 61 pts. 15 % RR
with 80% power.



Objectives

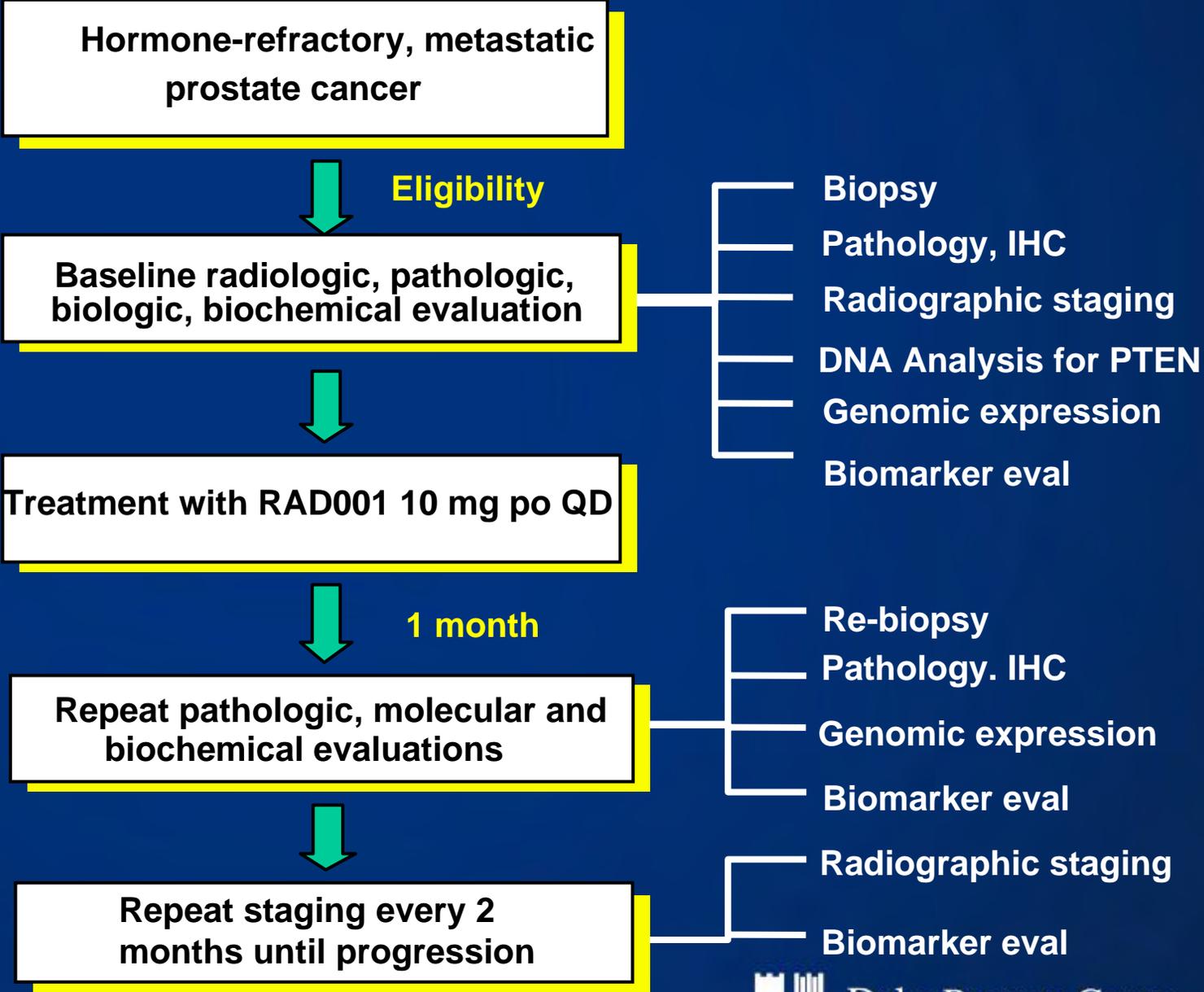
- **Determine extent of mTOR inhibition in prostate tumors**
- **Evaluate pathologic effects of mTOR inhibition (+/- PTEN)**
- **Identify retrospectively HRPC tumors more likely to respond to mTOR inhibition**
 - **By Expression profiles**
 - **By PTEN status**
 - **By Biomarker profiles**



Endpoints

- ***Biochemical:*** PSA, biomarker changes
- ***Radiographic:*** Objective response and TTP
- ***Pathologic:*** 50% increase in apoptosis, 50% decrease in proliferation
- ***Genomic:*** Expression profiles associated with AKT activation and mTOR inhibition
- ***Genetic:*** Evaluation of PTEN status





Patient Demographics (19 Patients)

Characteristics	Median (range)
Age	70 years (52-91)
Race	95% white; 5% AA
Gleason score	7 (6-9)
Time from Dx to study entry	8 years (2-14)
Time on ADT	6 years (1-4)
Prior Primary Treatment:	
-RP	25%
-XRT	20%
-RP + XRT	30%
-None (Hormonal Tx)	20%
Prior Metastatic Treatment:	
-2 nd Hormonal therapy	75% (20% > 2 courses)
-Chemotherapy	80% (15% > 2 courses)
-Radiation therapy	45% (15% ≥ 2 courses)



Baseline Characteristics

Characteristic	Median (range)
PSA level	156 ng/ml (4.5 - 2927.6)
Pain scale	0 (0-6)
Alk Phos (nl 70-110)	139 mg/ml (54 - 2137)
LDH (nl 300-600)	657 u/ml (396 - 1681)
Hgb (14.2-16.4)	12.2 g/dl (8.8 – 14.8)
PSA doubling time	1.42 months (0.66-8.85)
KPS	90 (80-100)
Skeletal mets present	95%
Soft tissue mets present	45%



Clinical Results

PSA Response

	Initial PSA	Final PSA	% Change
MEDIAN	115.4	282.6	72%
RANGE	4.5-2927.6	5.7-6591.8	15%-276%

TTP

	Time on Drug (days)	TTP (days)
Median	62	70
Range	27-139	36-195

LDH Changes

	Initial LDH	Final LDH	% Change	Post-TX % Change from Final LDH (7 patients)
MEDIAN	630	1130	+60%	-30%
RANGE	194-3363	192-4937	-4% to +288%	-10%-85%



Severe Adverse Events

Event	Grade	Incidence
Fatigue	3	11%
Pulmonary infiltrates	2	5%
Rash	3	5%
Hypophosphotemia	4	5%

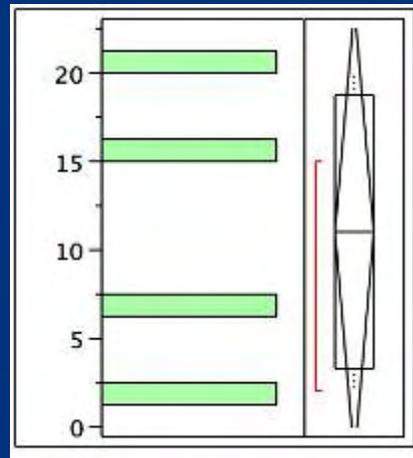
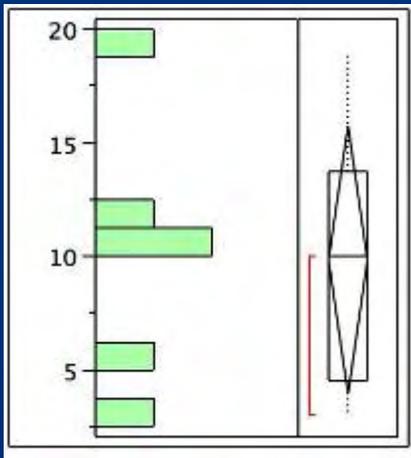


Pathologic Assessments

MIB-1 Labelling per HPF

Pre

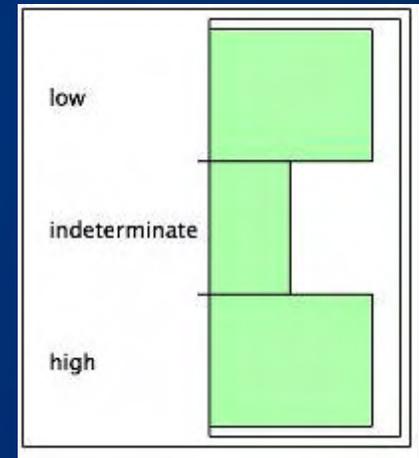
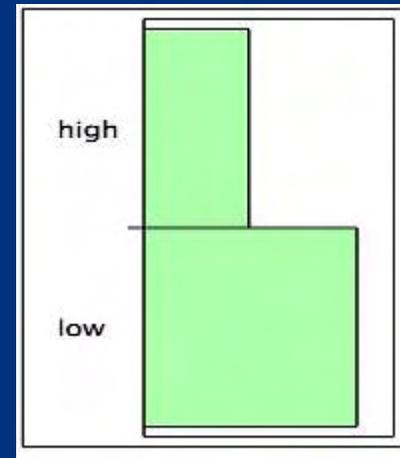
Post



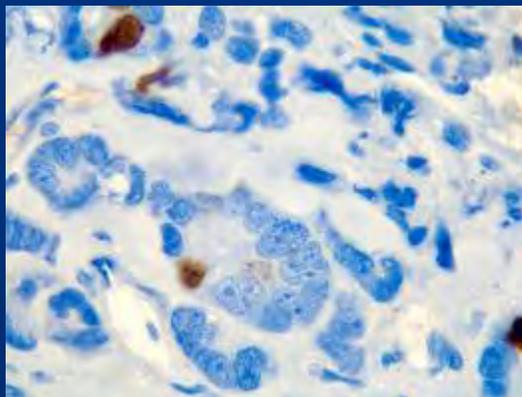
Apoptosis per HPF

Pre

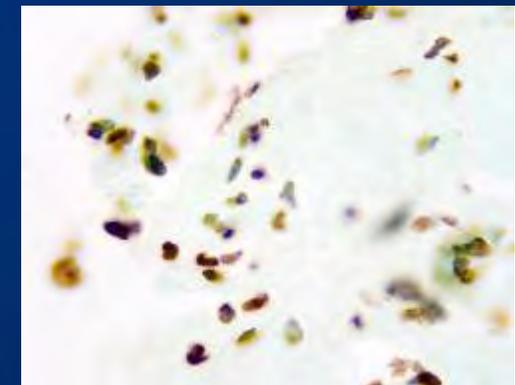
Post



Post-Tx
MIB-1 Label



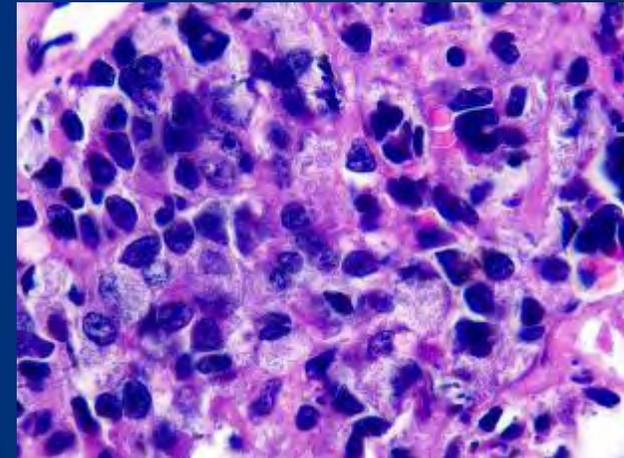
Post-Tx
TUNEL



Morphologic Assessments

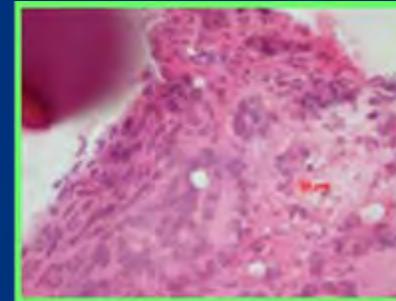
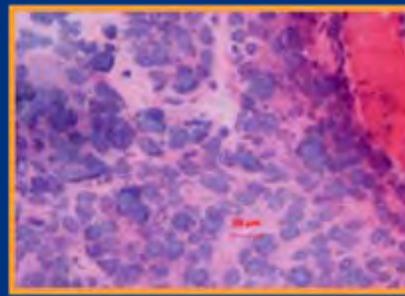
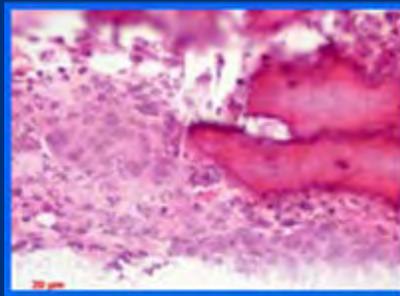
	Architectural Grade	Nuclear Grade
	2 vs 3	2 vs 3
Pre-Tx	6 /1	6/1
Post-Tx	7/0	6/1

Post-Tx H&E Staining

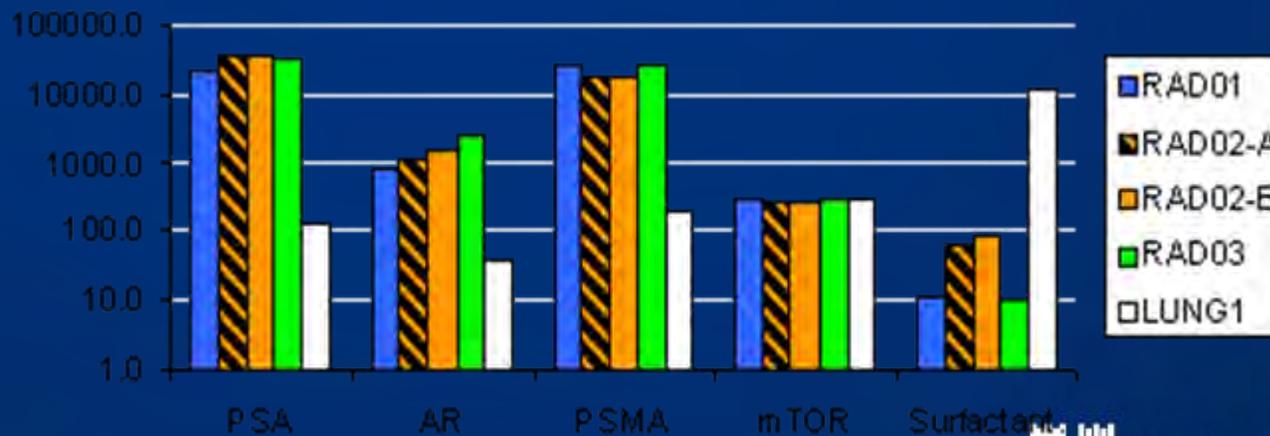


Genomic Studies in Metastatic Prostate Cancer

Histology



Tissue-Specific Gene Expression

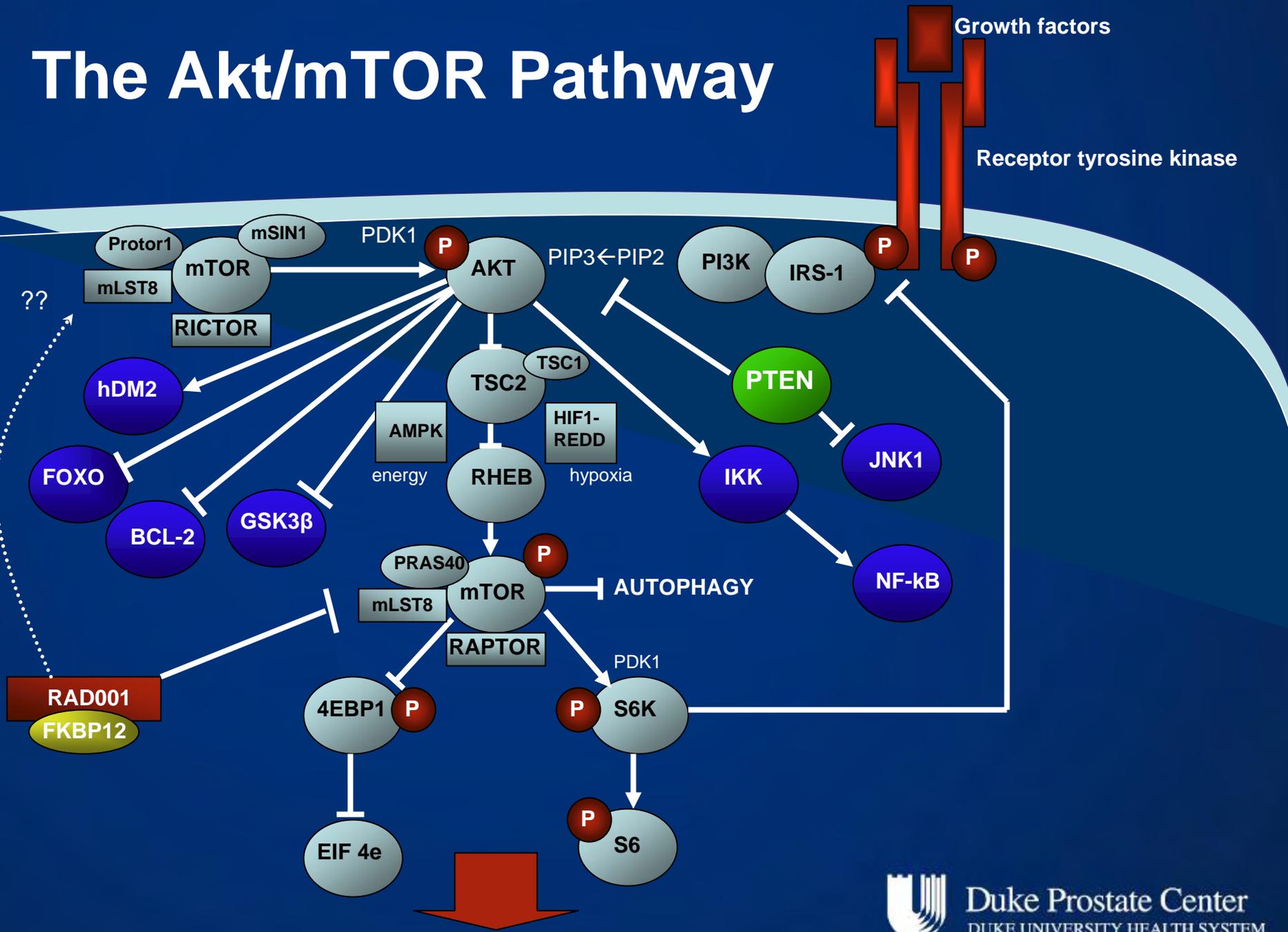


Summary (so far)

- RAD001 is well tolerated at full dose
- PSA and radiographic stable disease is seen in some patients (no evidence of objective or PSA response to date)
- Image-guided BMBxs are well tolerated and feasible in patients with HRPC allowing for pathologic and genomic studies
- Pathologic assessments suggest evidence of apoptosis in some tumor samples
- Genomic assessments suggest profiles specific for prostate cancer
- LDH increases with treatment suggest glycolysis may be activated (rather than inhibited) in some patients.



The Akt/mTOR Pathway



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