

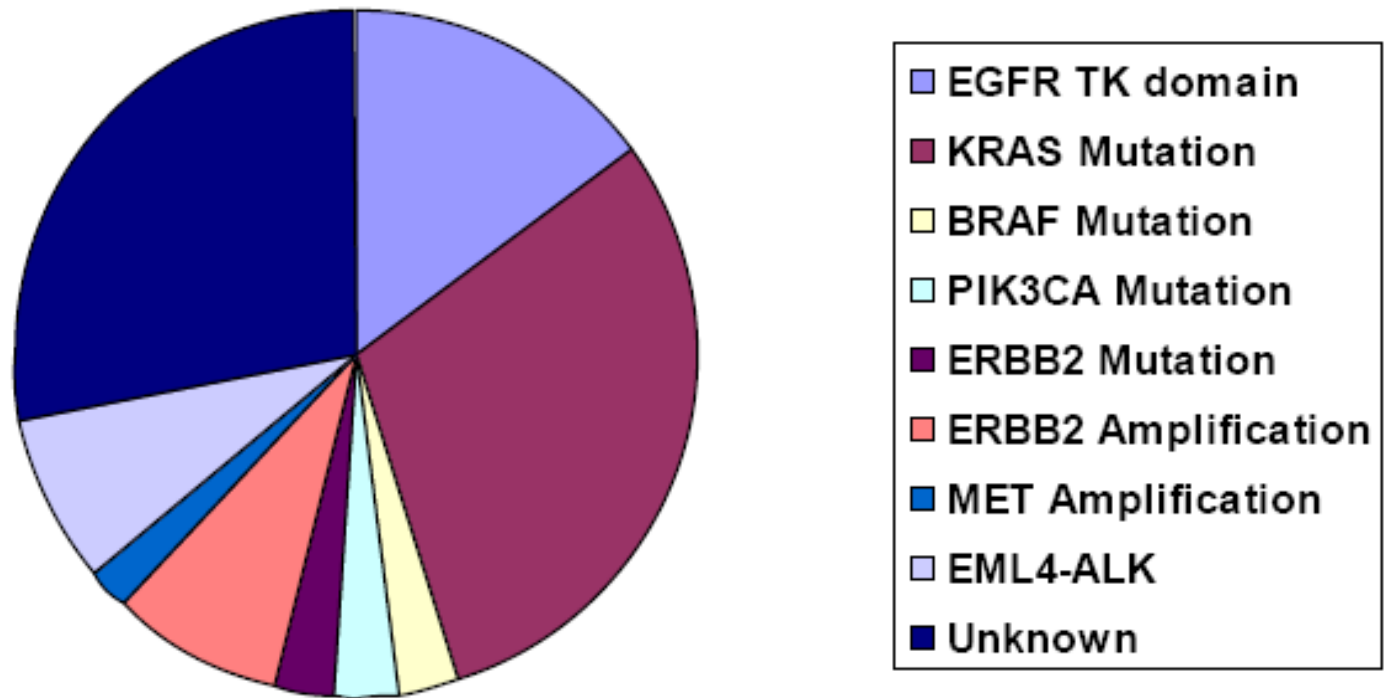
2nd International Thoracic Oncology Congress Dresden
September 16-18, 2010
The Westin Bellevue Hotel & Congress Center, Dresden

NOVEL AGENTS

m-TOR inhibitors

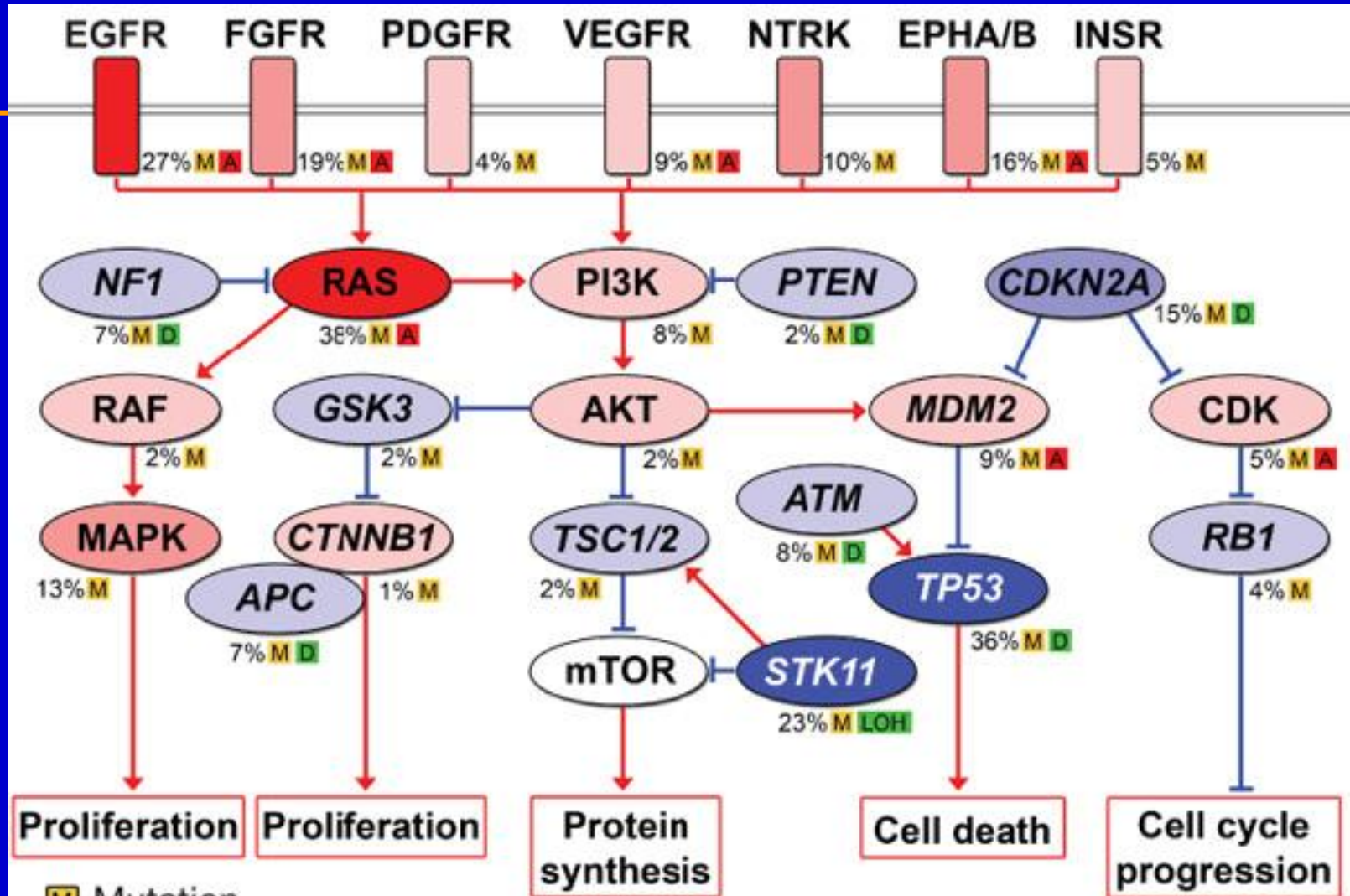
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Lung Adenocarcinoma 2009 - a genetically diverse collection of cancers



Significantly mutated pathways in lung adenocarcinomas

L Ding et al. Nature 455, 1069-1075 (2008)



- M** Mutation
- D** Deletion
- A** Amplification
- LOH** Loss of heterozygosity

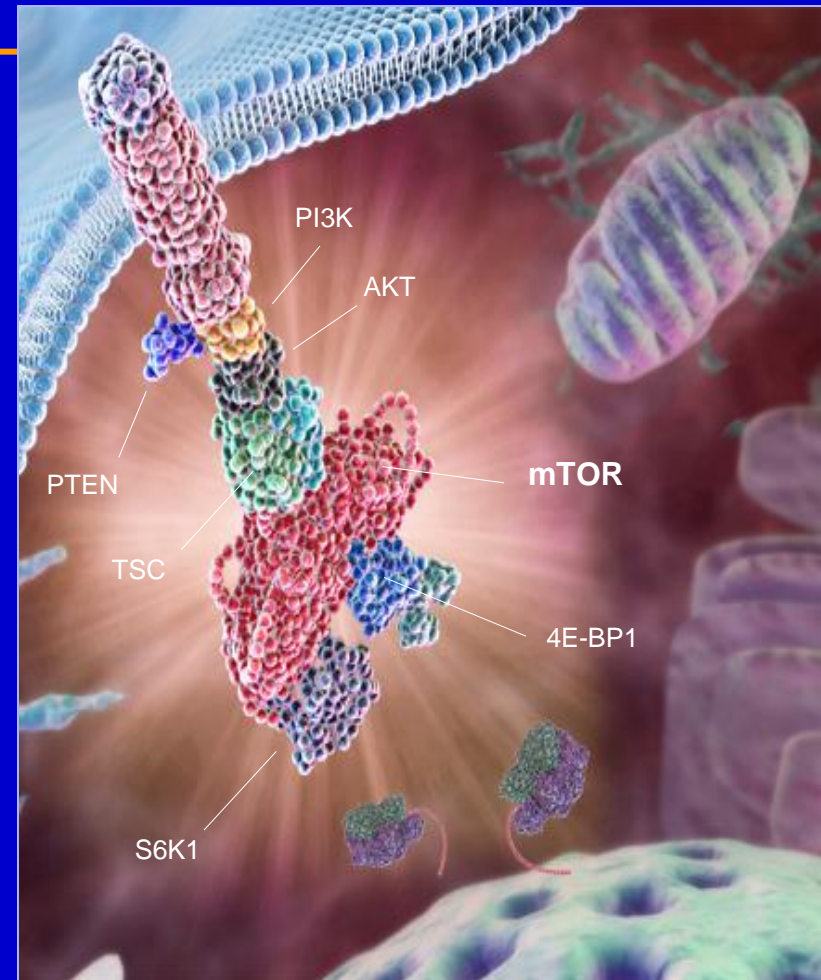
188 adenoca x 623 genes

nature

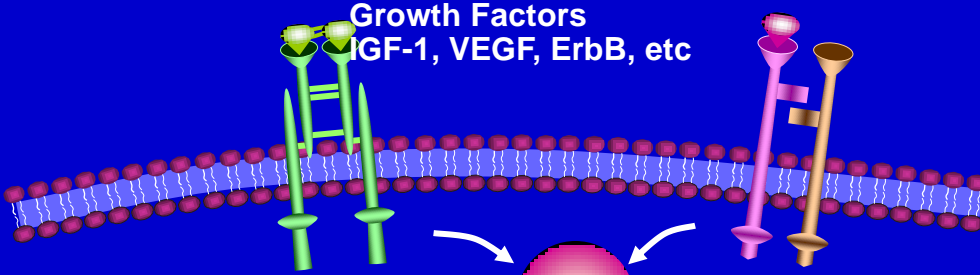
Why mTOR?

- PI3K-Akt-mTOR pathway is activated in multiple human cancers

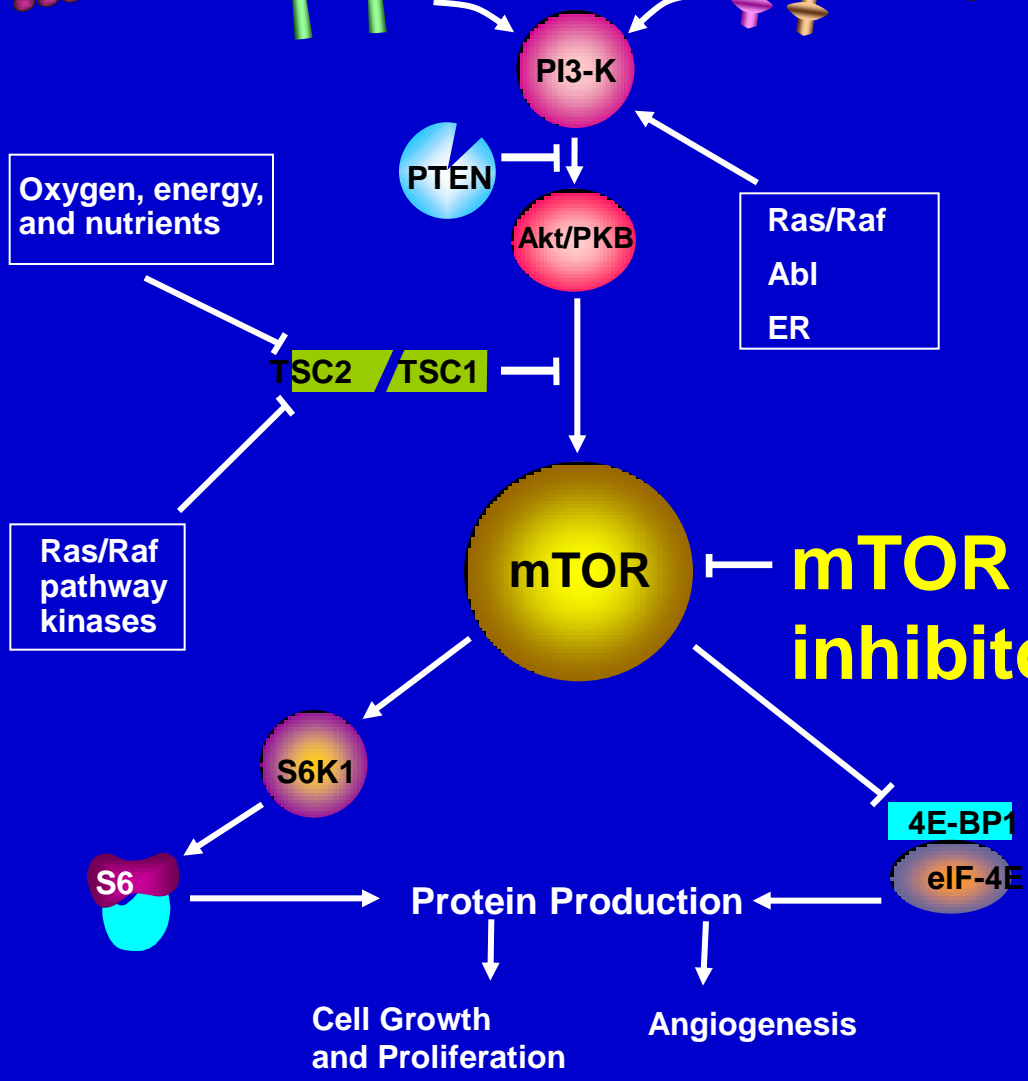
Tumors	Percent Pathway Activation
NSCL	50 - 60
Breast	30 - 50
Prostate	50 - 60
Sarcomas	20 - 40
Endometrial	50 - 70



Growth Factors
IGF-1, VEGF, ErbB, etc



Growth Factors and the mTOR Pathway



- Mammalian target of rapamycin (mTOR) is a central regulator of cell growth and proliferation in response to environmental and nutritional conditions.
- mTOR signaling is deregulated in many types of cancer
- mTOR inhibitors act functionally as a downstream multikinase inhibitor (DMI)

mTOR inhibitors have achieved some clinical success

- Dysregulation of the PI3K/Akt pathway linked to oncogenesis in many tumour types¹⁻³
- Key mTOR inhibitors in development⁴ are:
 - Rapamycin (sirolimus)
 - Rapamycin derivatives
 - Temsirolimus (CCI-779)
 - Everolimus (RAD001)
 - Deforolimus (AP23573)
- mTOR validated as a target by results of two Phase III randomised study of first-line temsirolimus⁵ and of second-line Everolimus⁶ in pts with advanced RCC

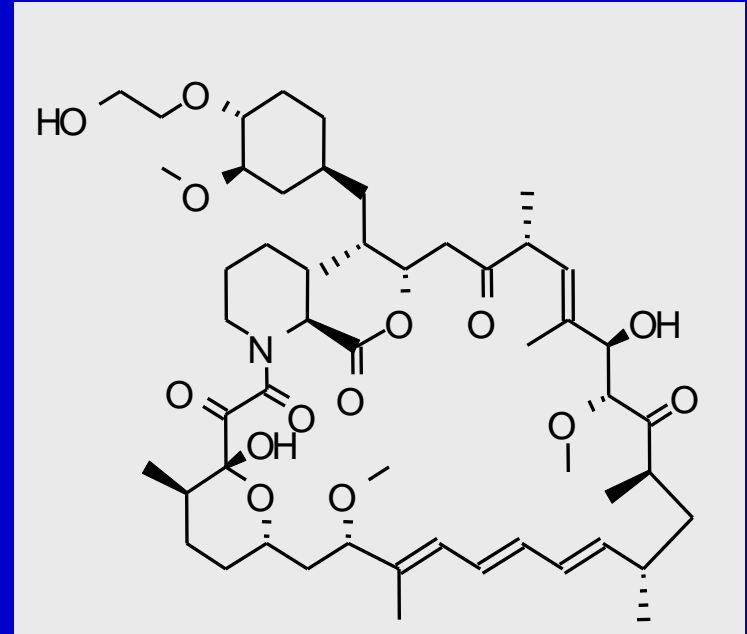
RAD001 - Oncology

An Oral mTOR pathway inhibitor

- Oral tablets (2.5, 5 & 10 mg)
- Broad antiproliferative and antitumor properties
- Anti-angiogenic properties
- Inhibits cell growth



G1/S phase progression
“Stress” sensitisation



Rapamycin derivative

- Enhances the cytotoxicity of DNA damaging agents
- Phase IB/II & III clinical trials in Oncology

mTOR inhibitors in Lung Cancer - Rationale

- Disease biology:
 - Postulated association of PI3K/AKT/mTOR cell-signaling pathway targeted by mTOR inhibitors in: oncogenesis, disease progression, response/resistance to treatment
- Preclinical efficacy:
 - mTOR inhibitors active in preclinical models of lung cancer
 - Increased efficacy of combinations of chemo, EGFRIs and mTOR inhibitors (in vitro and in vivo) as compared to single agents
- Clinical efficacy:
 - Early reports of clinical responses to monotherapy with mTOR inhibitors in advanced NSCLC

Efficacy of everolimus (RAD001) in patients with advanced NSCLC previously treated with chemotherapy alone or with chemotherapy and EGFR inhibitors

J.-C. Soria, F. A. Shepherd, J.-Y. Douillard, J. Wolf, G. Giaccone, L. Crino, F. Cappuzzo, S. Sharma, S. H. Gross⁹, S. Dimitrijevic, L. Di Scala, H. Gardner, L. Nogova & V. Papadimitrakopoulou*

Annals of Oncology Advance Access published June 23, 2009

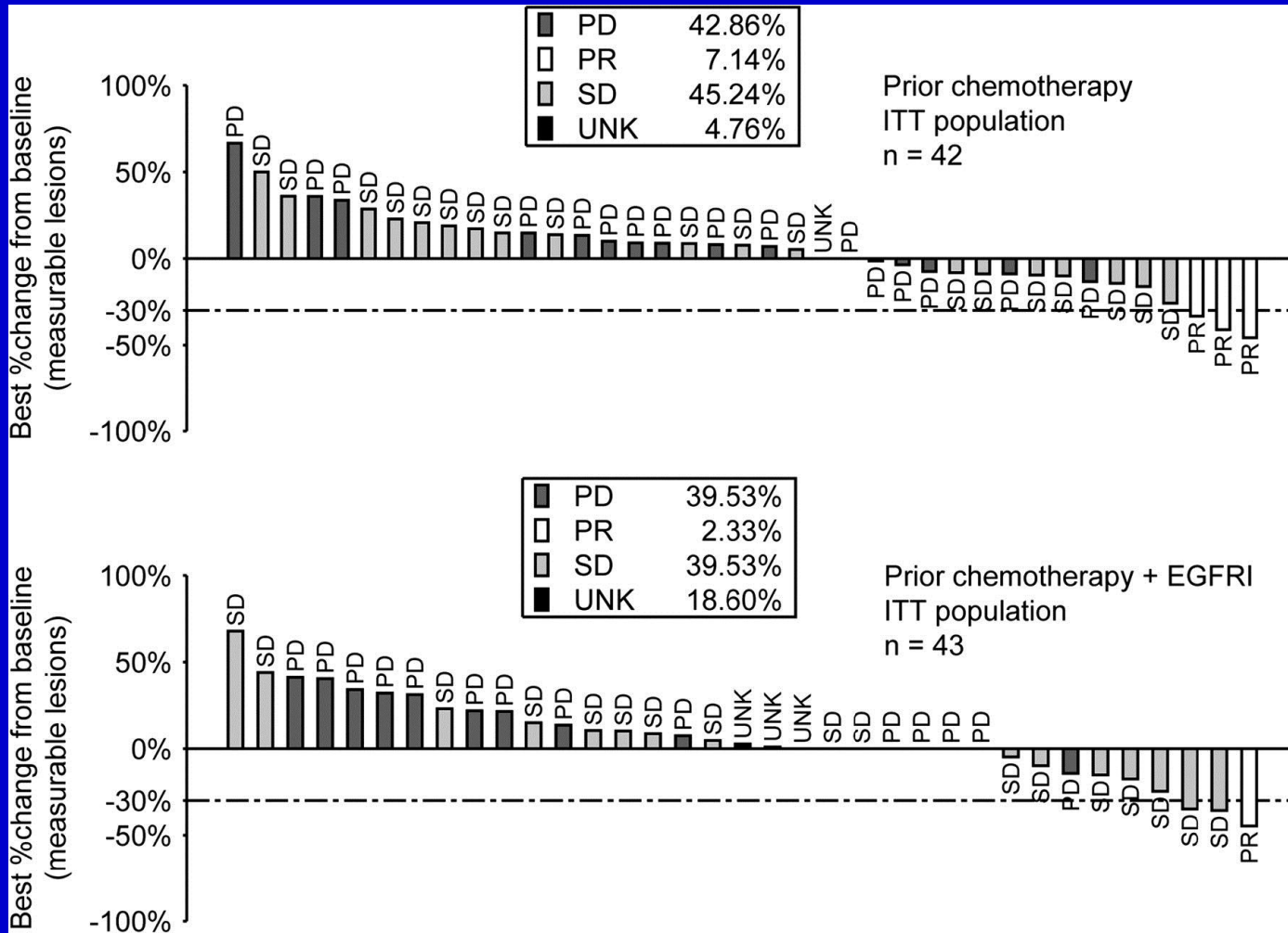
Baseline characteristics of patients (1)

	Prior chemotherapy (n=42), n (%)	Prior chemotherapy + EGFR TKI (n=43), n (%)	Total (N=85), n (%)
Median age, years (range)	59.5 (39-74)	61.0 (21-72)	60.0 (21-74)
Gender (male : female)	26 : 16 (61.9 : 38.1)	21 : 22 (48.8 : 51.2)	47 : 38 (55.3 : 44.7)
Race			
Caucasian	35 (83.3)	33 (76.7)	68 (80.0)
Asian	4 (9.5)	8 (18.6)	12 (14.1)
Black	1 (2.4)	2 (4.7)	3 (3.5)
Pacific Islander	1 (2.4)	0 (0)	1 (1.2)
Others	1 (2.4)	0 (0)	1 (1.2)
Smoking history			
Ever smoked	36 (85.7)	24 (55.8)	60 (70.6)
Never smoked	6 (14.3)	19 (44.2)	25 (29.4)
Tumor histology			
Adenocarcinoma	24 (57.1)	27 (62.8)	51 (60.0)
Squamous cell carcinoma	9 (21.4)	6 (14)	15 (17.6)
Others	9 (21.4)	10 (23.3)	19 (22.4)

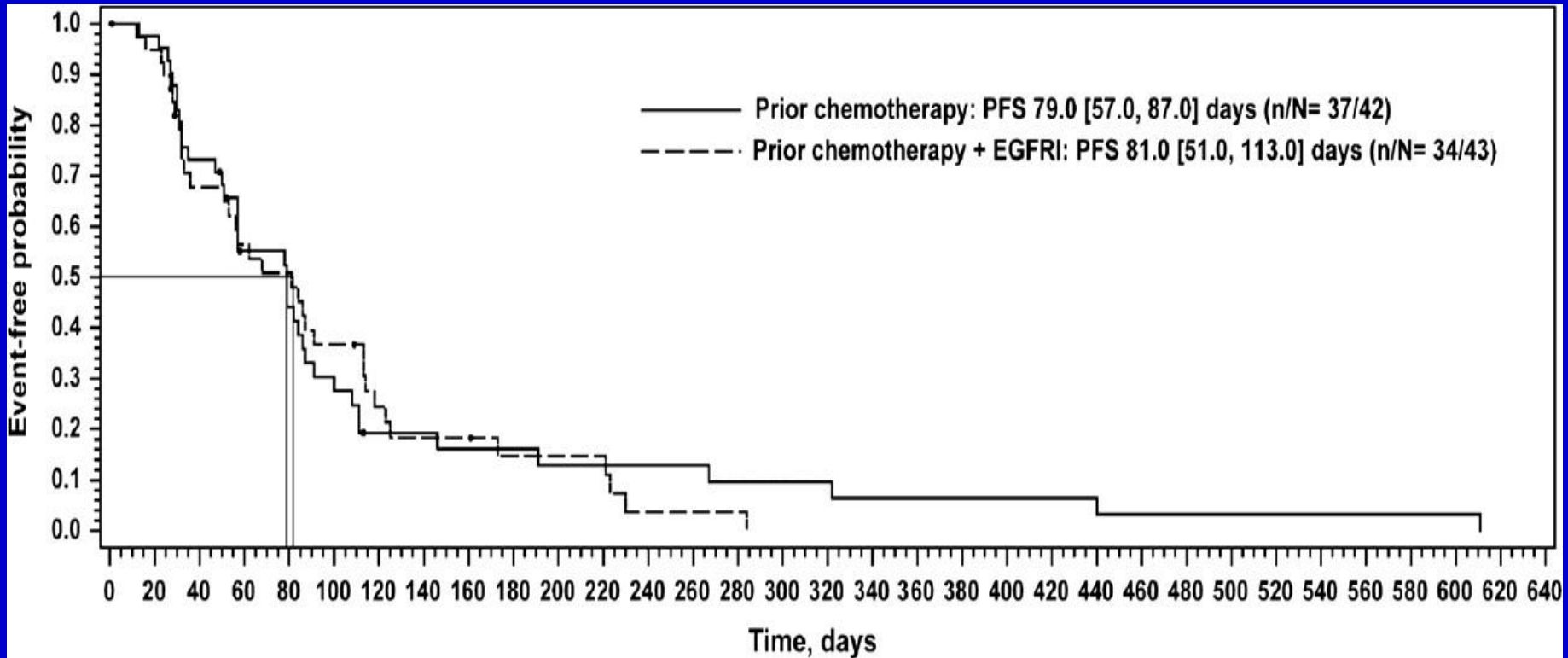
Baseline characteristics of patients (2)

	Prior chemotherapy (n=42), n (%)	Prior chemotherapy + EGFR TKI (n=43), n (%)	Total (N=85), n (%)
Current stage of cancer			
Stage IIIb	4 (9.5)	4 (9.3)	8 (9.4)
Stage IV	38 (90.5)	39 (90.7)	77 (90.6)
Performance status			
0	15 (35.7)	9 (20.9)	24 (28.2)
1	20 (47.6)	27 (62.8)	47 (55.3)
2	7 (16.7)	6 (14.0)	13 (15.3)
Missing	0 (0)	1 (2.3)	1 (1.2)
Time since initial diagnosis (months)			
≤ 12	21 (50.0)	10 (23.3)	31 (36.5)
> 12 to ≤ 24	9 (21.4)	15 (34.9)	24 (28.2)
> 24	12 (28.6)	18 (41.9)	30 (35.3)
Number of any prior antineoplastic therapy regimens			
1	22 (52.4)	0 (0)	22 (25.9)
2	20 (47.6)	16 (37.6)	36 (42.4)
≥ 3	0 (0)	27 (62.8)	27 (31.8)

Best percentage change from baseline



Progression-free survival

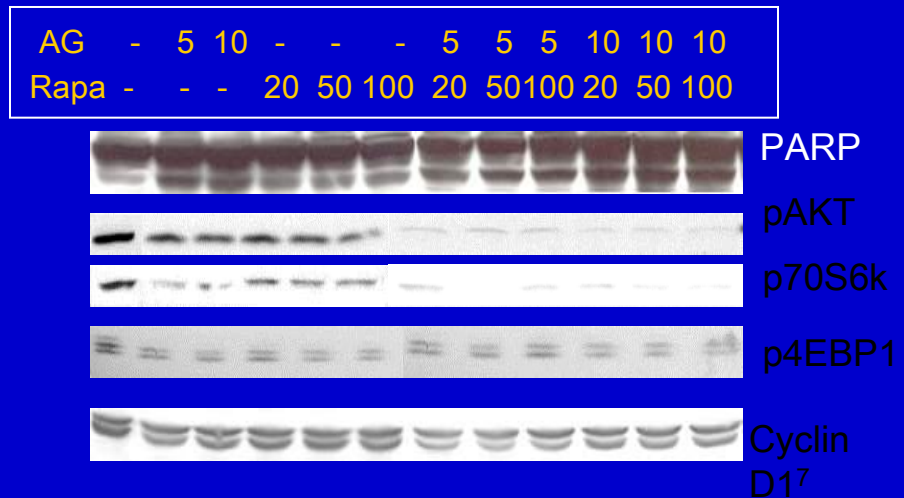
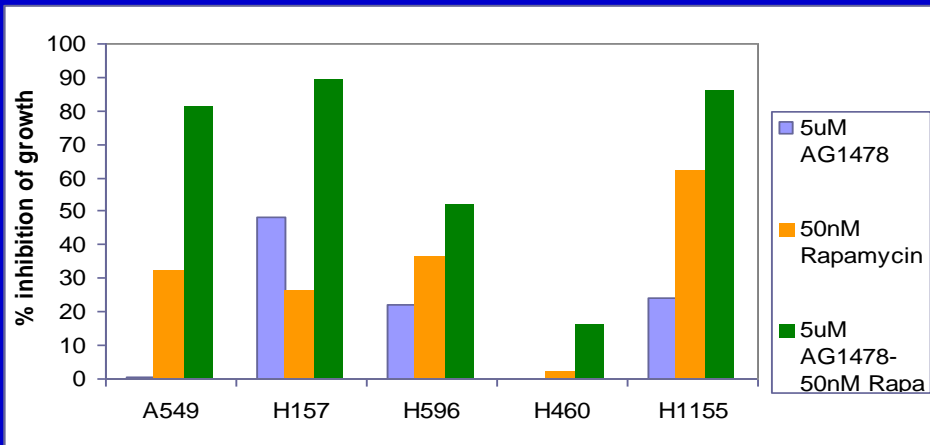


Adverse events

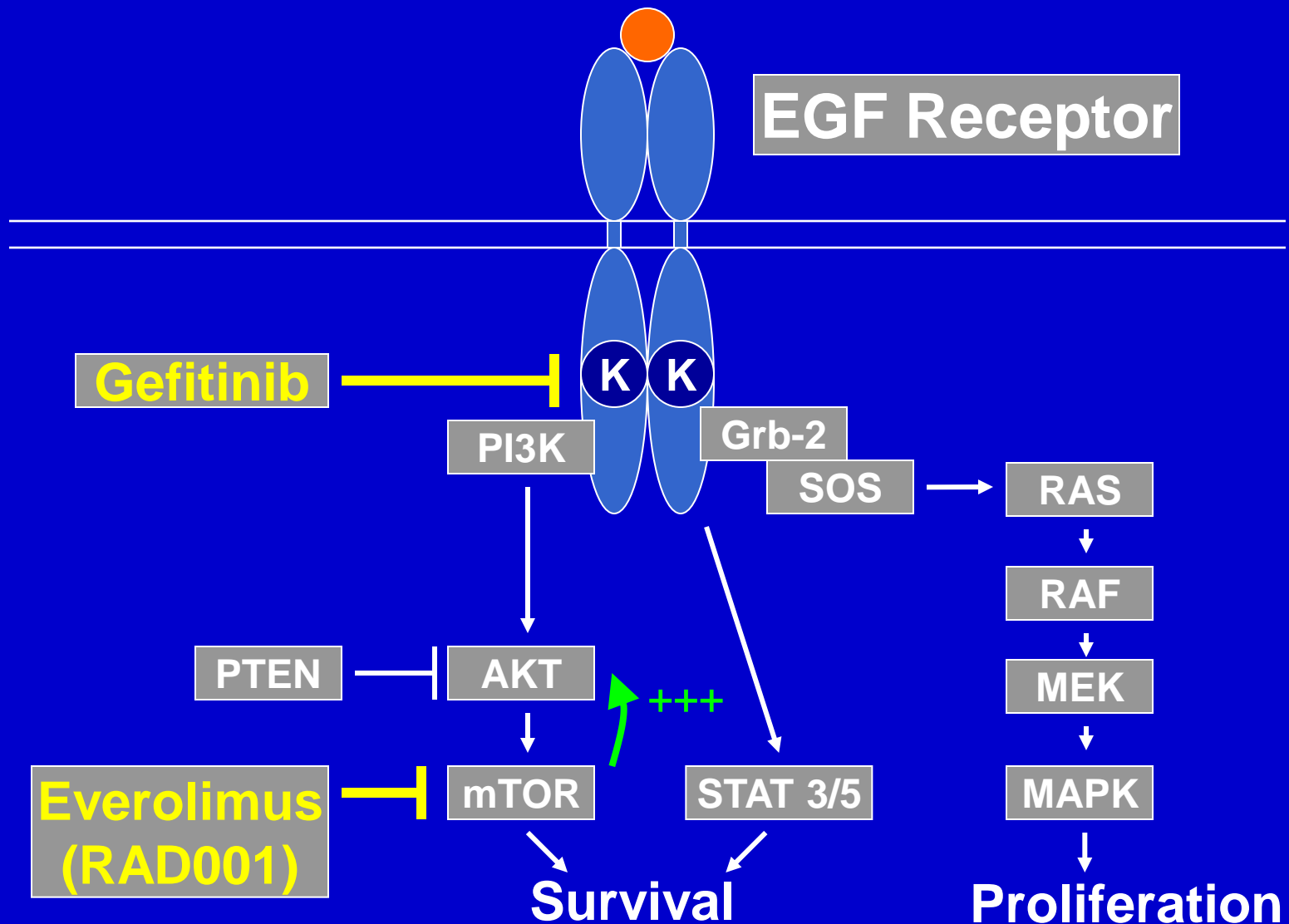
	All CTCAE grades			CTCAE grades 3/4		
	Prior chemotherapy (n=42), n (%)	Prior chemotherapy + EGFRi (n=43), n (%)	All patients (N=85), n (%)	Prior chemotherapy (n=42), n (%)	Prior chemotherapy + EGFRi (n=43), n (%)	All patients (N=85), n (%)
Total no. Of patients with AEs	41 (97.6)	41 (95.3)	82 (96.5)	21 (50.0)	24 (55.8)	45 (52.9)
Stomatitis	22 (52.4)	17 (39.5)	39 (45.9)	2 (4.8)	3 (7.0)	5 (5.9)
Dyspnea	17 (40.5)	17 (39.5)	34 (40.0)	3 (7.1)	5 (11.6)	8 (9.4)
Rash	17 (40.5)	9 (20.9)	26 (30.6)	0	0	0
Anemia/hemoglobin decreased	16 (38.1)	8 (18.6)	24 (28.2)	3 (7.1)	3 (7.0)	6 (7.1)
Fatigue	13 (31.0)	12 (27.9)	25 (29.4)	5 (11.9)	5 (11.6)	10 (11.8)
Anorexia	11 (26.2)	12 (27.9)	23 (27.1)	0	1 (2.3)	1 (1.2)
Cough	13 (31.0)	8 (18.6)	21 (24.7)	1 (2.4)	0	1 (1.2)
Nausea	10 (23.8)	9 (20.9)	19 (22.4)	0	0	0
Diarreha	12 (28.6)	6 (14.0)	18 (21.2)	2 (4.8)	0	2 (2.4)
Epistaxis	11 (26.2)	7 (16.3)	18 (21.2)	0	0	0
Thrombocytopenia	5 (11.9)	9 (20.9)	14 (16.5)	1 (2.4)	3 (7.0)	4 (4.7)
Vomiting	8 (19.0)	7 (16.3)	15 (17.6)	0	1 (2.3)	1 (1.2)

RAD001/EGFR Inhibitor Combinations – Targeting EGFR^T resistance

- RAD001 / EGFR inhibitor combinations promising preclinically.
- Combination of EGFR inhibitor+rapamycin additive in NSCLC cell lines⁷.
- Combinations of RAD001 / gefitinib in breast / prostate tumor lines are additive / synergistic (also observed in a line relatively resistant to gefitinib). (Di Cosimo et al, AACR / ASCO 2004)
- *In vitro* gefitinib-resistant lines are sensitive to RAD001 alone. (Carlos Arteaga, AACR-NCI-EORTC presentation 2003)



A Phase II Study on Dual Inhibition of The EGFR Pathway



RAD001 + Iressa in pretreated advanced NSCLC

Ph 1: N = 10

Iressa 250 mg/d + RAD 5mg/d (n=7) & 10mg/d (n=3)

- ≥ 1 Previous chemo

AE:

- RAD 5mg/d

G2: stomatitis (1), fatigue(2), rash(2), Thrombopen. (1), Lymphopen.(1)

G3: Lymphopen.(1)

- RAD 10 mg/d

G2: diarrhea (2), Trigl (1), Thrompen. (1), Lymphpen.(1)

G3: stomatitis(1); \uparrow creat. \downarrow K+, G4: acidosis, G5: hypotension (1)

Efficacy:

- 2 PR (5mg)
 - Male, smokers
 - 1SCC 1 ADC
 - No mutations in *ErbB1* (Ex 19 & 21)

Results

Prior Chemotherapy	Yes	No
Entered & Response Assessed	17	15
Confirmed Partial Responses (%) (95% Confidence Intervals)	3 (18%) (4 to 43%)	2 (13%) (2 to 41%)
Response Duration (months)	3, 4, 8	12+, 21+
Median Survival (months)	12	Not Reached
One Year Survival	36%	68%

Overall PR Rate - 16% (95% CI: 5 to 33%)

- Major Findings

- Combination of Gefitinib and Everolimus attained tumor response rate of 16%
- All responders are male, smoker and adenocarcinoma

- Implications

- Is this an answer to EGFR TKI resistance (primary or secondary)
- Do the tumor responders have cMET amplification?

Association between response to everolimus and occurrence of genetic alterations in the PI3K or KRAS pathway

	PR + SD	PD	P
All tumor types			
WT KRAS (31/43)	15 (1 PR + 14 SD)	16	0.0171
Mutant KRAS (12/43)	1 (SD)	11	
PTEN loss or mutant PIK3CA (12/43)	SD8 (1 PR + 7 SD)	4	0.0128
PTEN loss or mutant PIK3CA with concomitant KRAS/BRAF alterations (7/43)	0	7	
Colorectal cancer			
WT KRAS (13/23)	8 (1 PR + 7 SD)	5	0.0288
Mutant KRAS (10/23)	1 (SD)	9	

The number of patients achieving some clinical benefit (PR + SD) and non-responders (SD) is indicated according to KRAS mutational status in all tumor types in the subgroup of colorectal cancer. KRAS mutation inversely correlate with response to everolimus treatment (P=0.0171 and P=0.0288, 2-tailed Fisher's exact test). The number of patients achieving some clinical benefit (PR + SD) and non-responders (PD) is indicated according to PTEN status and PIK3CA mutations on the basis of their occurrence with BRAF/KRAS mutations in all tumor samples (p=0.0128, 2-tailed Fisher's exact test).