EORTC-NCI-ASCO Meeting, Brussels 16th October 2009

Polymorphisms in *AKT1* and *EGFR* as possible new biomarkers of clinical outcome and toxicity in non-small-cell lung cancer patients treated with gefitinib

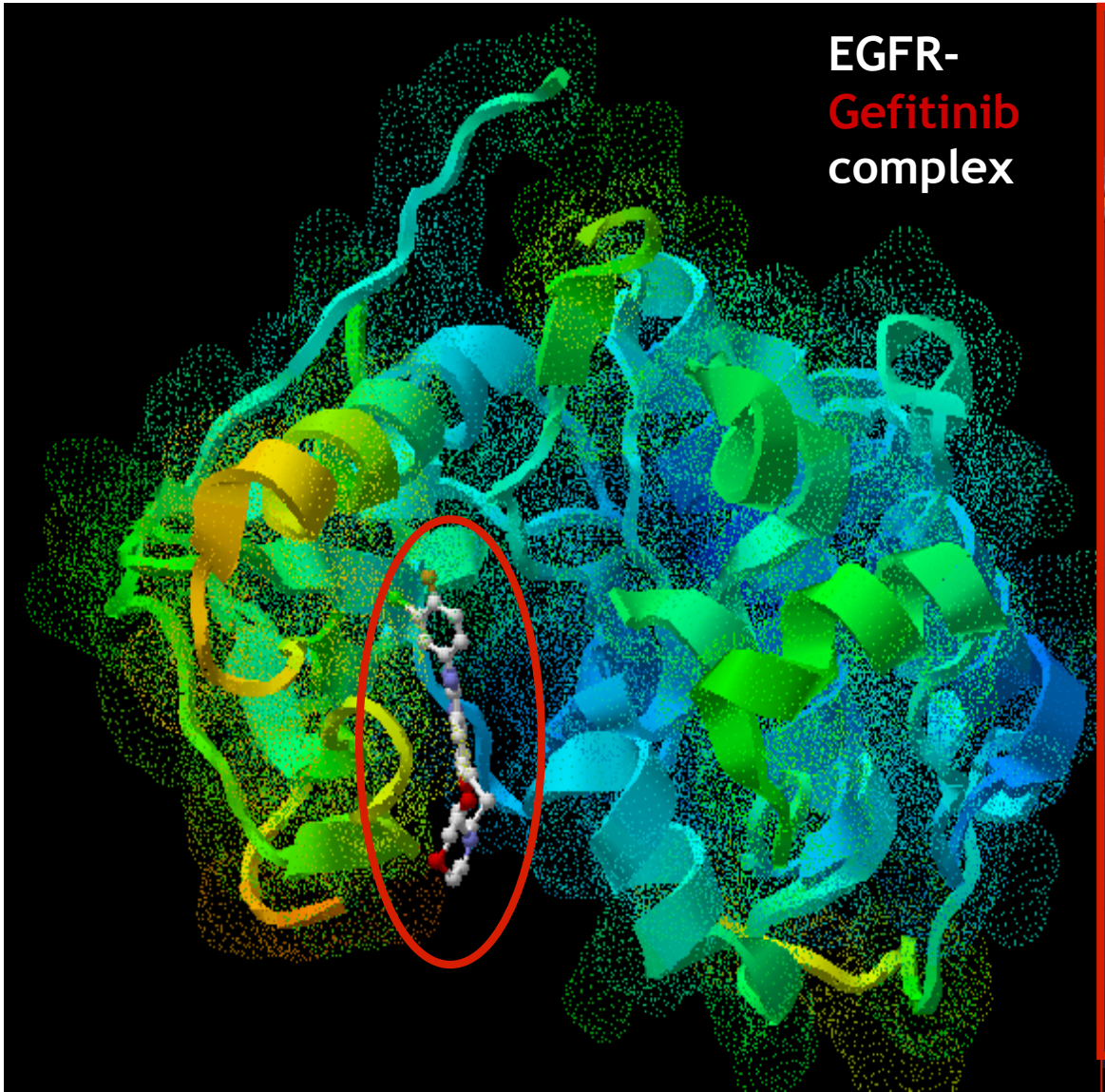
Giovannetti E, Zucali PA, Tibaldi C, Leon GL, Cortesi F, D'Incecco A, Falcone A, Santoro A, Smit EF, Burgers S, Danesi R, Giaccone G, Peters GJ

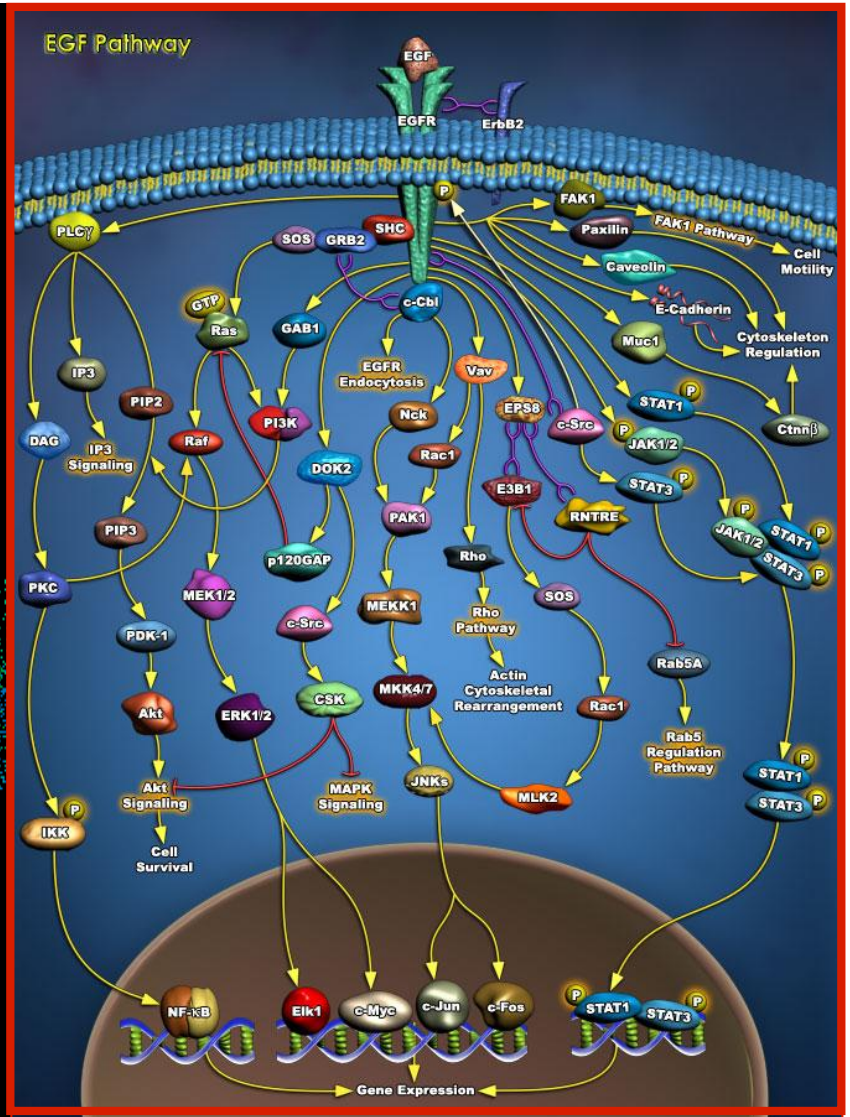
Background: NSCLC

- NSCLC is the leading cause of cancer-related deaths in Western world
- About 75% of NSCLC patients are in advanced stage disease at diagnosis
- Progress with chemotherapy in advanced NSCLC seems to have reached a plateau
- To improve the clinical outcome of NSCLC a targeted therapy approach has been advocated

Targeting EGFR

EGFR overexpression is 1) common in NSCLC and 2) correlates with poorer prognosis

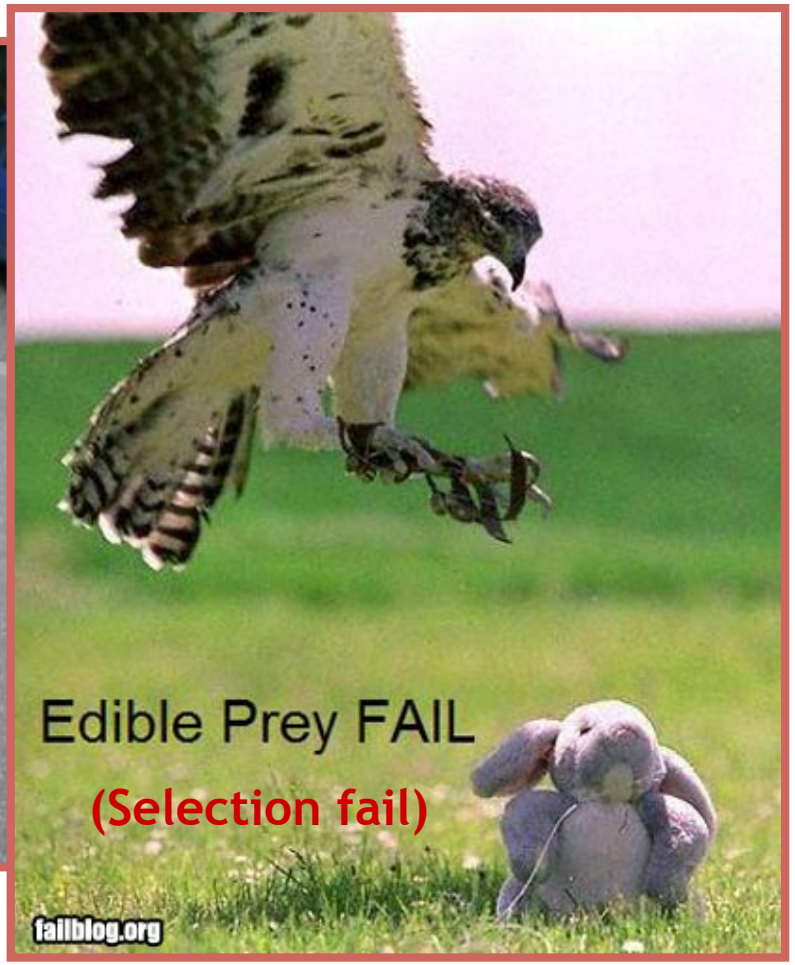




EGFR-TKIs targeted therapy

The EGFR-TKIs have a good clinical activity in 10% of metastatic NSCLC patients

The problem: Have the right target?

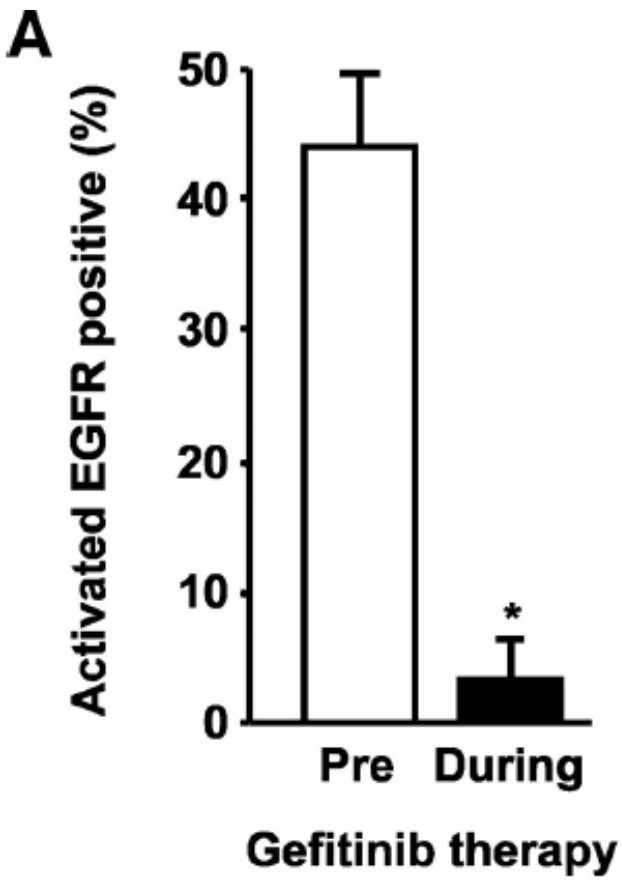


… or make the right selection?

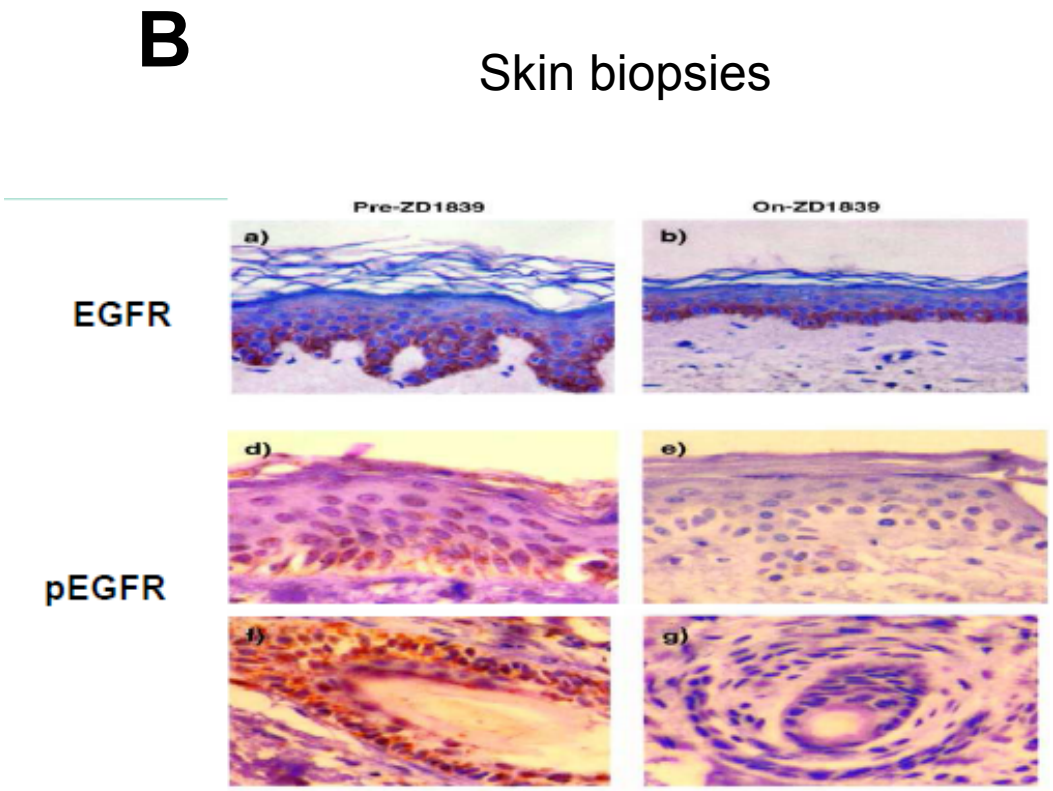
From the Tutorial

By David Mauro

- Early proof of concept: "target engagement"
  - Is your drug doing what you think it doing



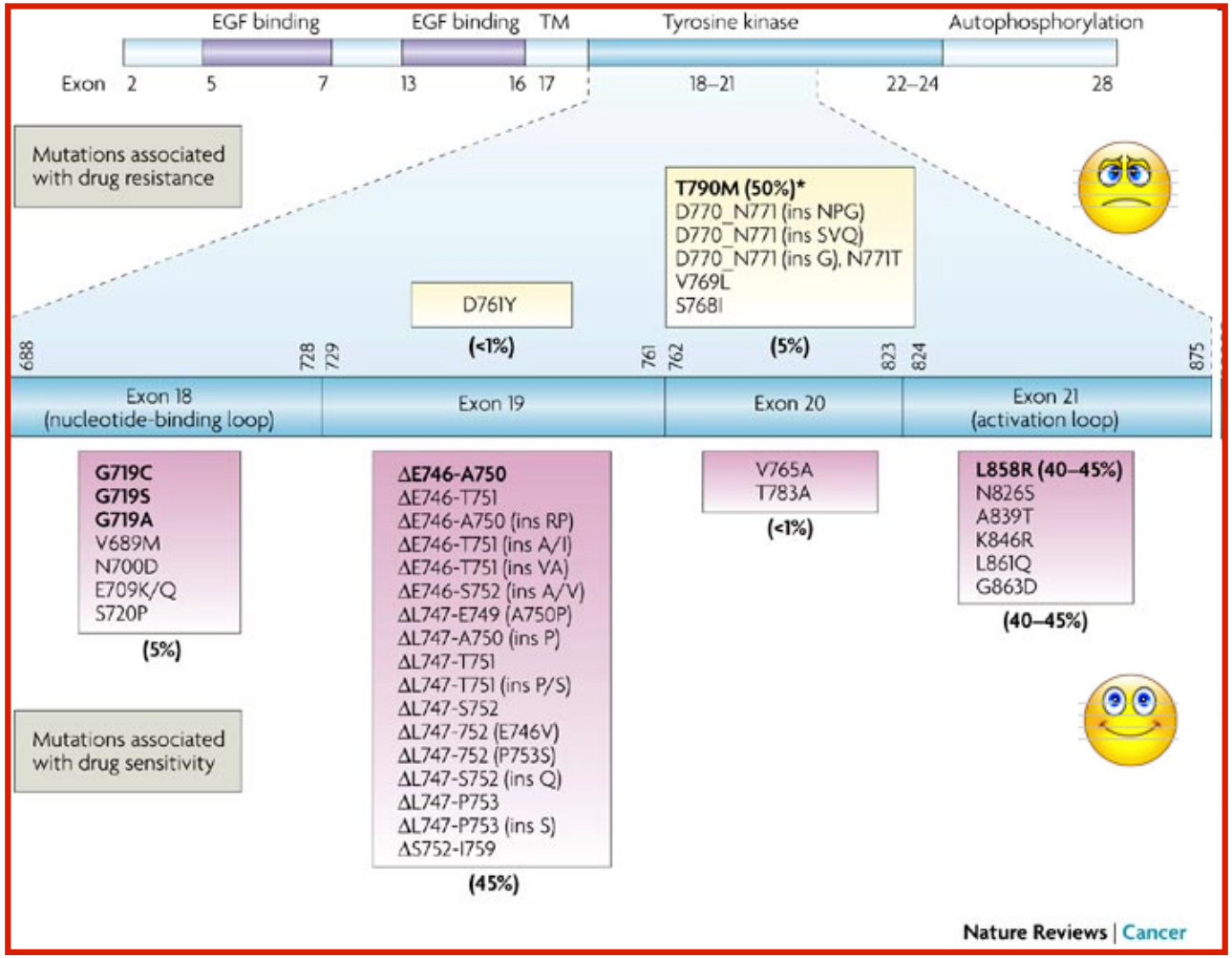
Wolf et al., Clin Cancer Res 2004



Baselga et al., J Clin Oncol 2002

Mutations as biomarkers

Many studies documented a relationship between female gender, adenocarcinoma histology, Asian ethnicity, and never smoking status with higher response rates to EGFR-TKIs



From the Tutorial

By Bruce E. Johnson

Integrating Disease Forecast Biomarkers in Lung Cancer

- **EGFR Mutations are the Leading Forecast Biomarker for EGFR-TKI over Chemotherapy**
- **EGFR Mutations and FISH are Forecast Biomarkers for EGFR-TKI over Placebo**

The search for new biomarkers

But...it is not a "black-or-white" situation

- not 100% (~78%) of the patients with EGFR mutations respond to EGFR-TKIs
- a subset of patients (~13%) with normal EGFR status respond to EGFR-TKIs

1) Identification of additional factors could help in adapting individualized therapy especially for patients with a low frequency of somatic mutations (i.e. Caucasians)

2) In the IPASS trial gefitinib also demonstrated a more favourable tolerability profile than chemotherapy... but there is a large interindividual variability in toxicity

AIM

Recent findings:

1) *Variability in gastrointestinal toxicity in erlotinib-treated patients was associated with* ***polymorphisms in EGFR*** *(Rudin et al, J Clin Oncol 2008)*
2) *Functional* ***polymorphisms*** *affect the expression of the EGFR downstream* ***AKT*** *(Harris et al.; PNAS 2005; Hildebrandt et al, J Clin Oncol 2009)*

to retrospectively evaluate associations between selected functional *EGFR* and *AKT1* variants and clinical outcomes in gefitinib-treated NSCLC patients

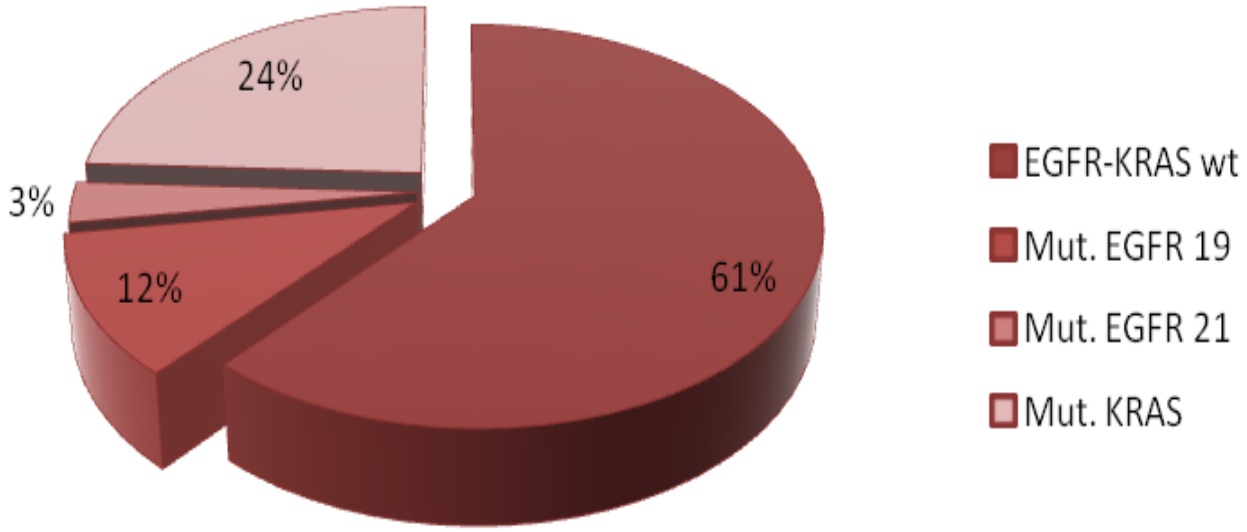
Patients

Gefitinib-treated patients (within Expanded Access Program, EAP)			
Gender		**Performance Status**	
Male	**55**	0-1	**76**
Female	**41**	2-3	**20**
Age		**Histology**	
Median	**64**	Adenocarcinoma (ADC)	**45**
Smokers		Broncoalveolar carcinoma (BAC)	**12**
Non-smokers	**29**	Squamous cellular carcinoma	**16**
Smokers	**66**	Other hystology	**21**

(Zucali et al, Ann Oncol 2008 – Tibaldi et al, Clin Cancer Res 2008)

Outcome according to mutations

Characteristic	Patients n (%)	Response n (%)	*P*	TTP months (95% CI)	*P*	OS months (95% CI)	*P*
EGFR mut							
Wt	53	3 (5.7)	*<0.01*	3.0 (2.6-3.4)	*< 0.01*	6.0 (3.5-8.5)	*0.04*
Mut	9	6 (66.7)		9.0 (3.2-14.8)		18.0(1.6-34.4)	
K-Ras Mut							
Wt	41	7 (17.1)	*0.17*	3.1 (2.7-3.5)	*0.57*	8.3 (3.7-12.8)	*0.39*
Mut	15	0 (0.0)		3.0 (0.0-7.3)		5.2 (2.6-7.7)	



Outcome according to polymorphisms

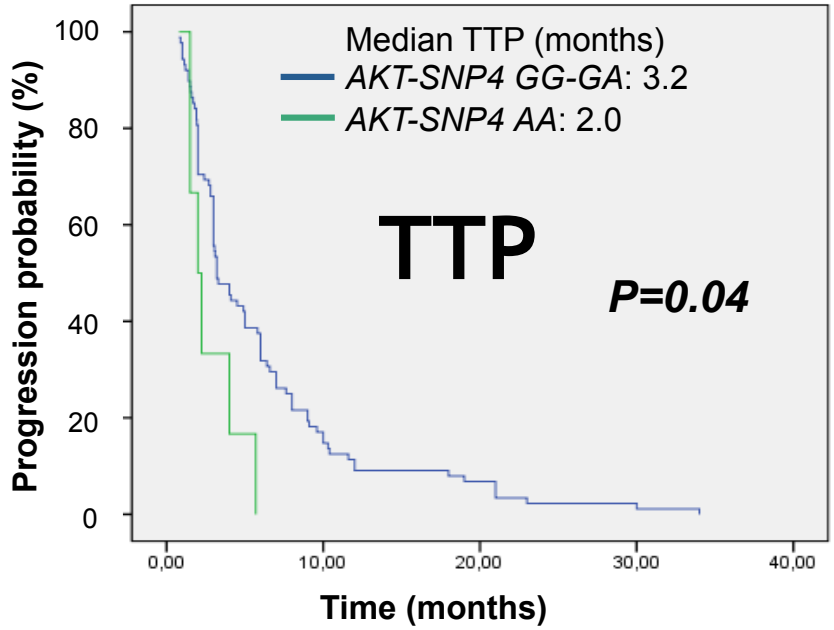
Characteristic	Patients n	Response n (%)	*P*	TTP months (95% CI)	*P*	OS months (95% CI)	*P*
EGFR -191 C/A							
CC	78	14 (17.9)	*0.94*	3.2 (2.5-3.9)	*0.46*	7.9 (7.0-8.7)	*0.37*
CA -AA	16	3 (18.7)		3.2 (3.0-3.4)		6.0 (2.8-9.2)	
EGFR R 497K							
GG -GA	81	13 (16.0)	*0.40*	3.3 (2.4-5.0)	*0.32*	7.4 (6.5-8.4)	*0.55*
AA	11	3 (27.3)		3.1 (1.5-4.7)		8.0 (0.0-17.3)	
AKT SNP3							
CC -CT	89	17 (19.1)	*0.54*	3.2 (2.2-4.1)	*0.92*	7.7 (6.8-8.6)	*0.97*
TT	5	0 (0.0)		3.0 (2.3-3.7)		4.0 (0.2-7.8)	
AKT SNP4							
GG -GA	88	17 (19.8)	*0.23*	3.2 (2.2-4.2)	*0.04*	8.0 (6.7-9.3)	*0.01*
AA	6	0 (0.0)		2.0 (1.1-2.9)		2.2 (0.0-5.7)	

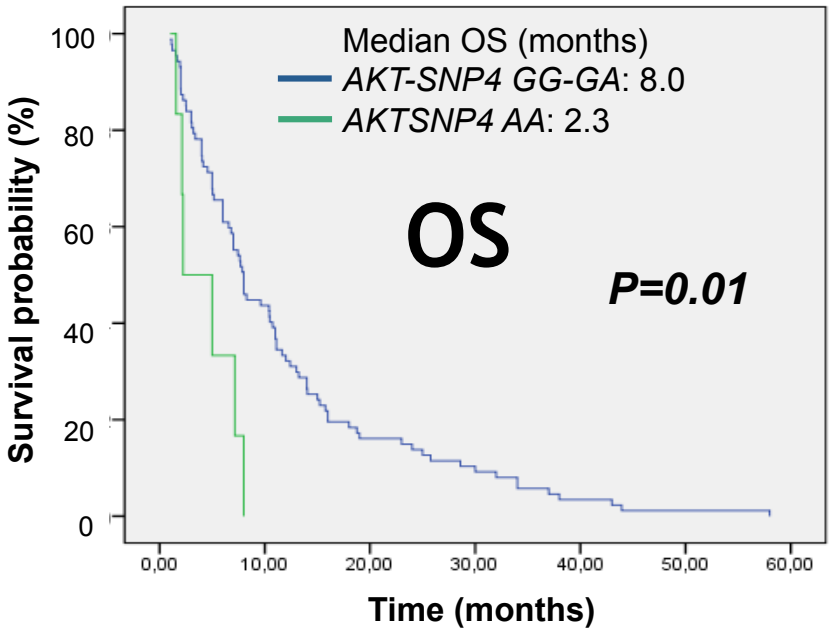
Toxicity according to polymorphisms

Genotype	Skin rash (0 vs 1+)	*P*	Skin rash (0-1 vs 2+)	*P*	Diarrhea (0 vs 1+)	*P*	Diarrhea (0-1 vs 2-3)	*P*
EGFR -191 C/A								
CC	36 vs. 36	*0.27*	54 vs. 18	*0.99*	44 vs. 26	*0.56*	69 vs. 1	*<0.001*
CA-AA	5 vs. 10		11 vs. 4		8 vs. 7		10 vs. 5	
EGFR R497K								
GG-GA	37 vs. 38	*0.83*	56 vs. 18	*0.99*	48 vs. 26	*0.17*	71 vs. 3	*0.02*
AA	4 vs. 7		8 vs. 3		4 vs. 6		7 vs. 3	

Genetic variations might be useful to customize targeted therapy
(not only to predict drug response, but also to avoid severe toxicities)

… focusing on the "brand new" results





Multivariate analysis

Covariates for risk of progression	HR (95% CI)	*Wald P*
Histology: Others vs. BACs	1.4 (0.6-3.2)	*0.47*
EGFR mut: EGFR Wt vs. Mut	2.1 (1.5-3.9)	*0.01*
AKT1-SNP4:AA vs.GG+GA	1.7(1.0-2.6)	*0.06*
Model excluding EGFR mutational status		
Histology: Others vs. BACs	1.3 (0.7-3.4)	*0.09*
AKT1-SNP4:AA vs.GG+GA	3.4 (2.2-5.4)	*0.04*
Covariates for risk of death	HR (95% CI)	*Wald P*
Histology: Others vs. BACs	1.4 (0.6-3.2)	*0.47*
EGFR mut: EGFR Wt vs. Mut	2.1(1.0-4.3)	*0.05*
AKT1-SNP4: AA vs. GG+GA	2.3 (1.2-2.9)	*0.04*
Model excluding EGFR mutational status		
Histology: Others vs. BACs	1.8 (1.0-3.4)	*0.06*
AKT1-SNP4: AA vs.GG+GA	4.8 (1.2-6.3)	*0.02*

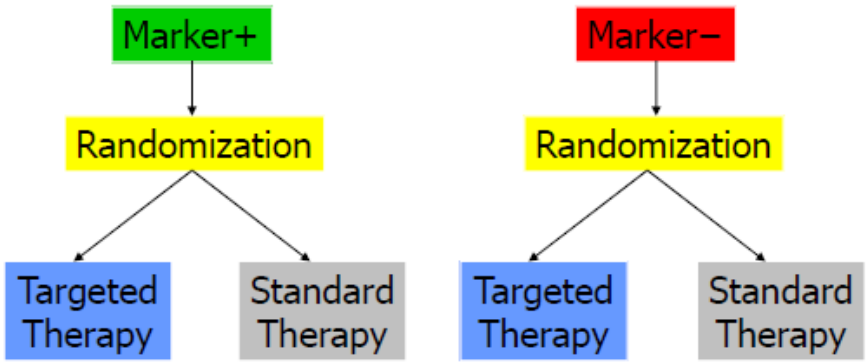
From the Tutorial

By Gary M Clark

Prognostic Factor: Any measurement that is associated with clinical outcome in the absence of therapy, or with the application of a standard therapy that all patients are likely to receive (a predictor of the natural history of the tumor).

Predictive Factor: Any measurement associated with response or lack of response to a particular therapy, where response can be defined using any of the clinical endpoints commonly used in clinical trials (eg, ER for patients with breast cancer).

The most informative design



This is the CTEP trial design for evaluating the predictive utility of EGFR status by FISH (MARVEL Study, N0723)

From the Tutorial

By Nadia Harbeck

Back to the lab

Is Plasminogen Activator Inhibitor-1 the Molecular Switch That Governs Urokinase Receptor-mediated Cell Adhesion and Release?

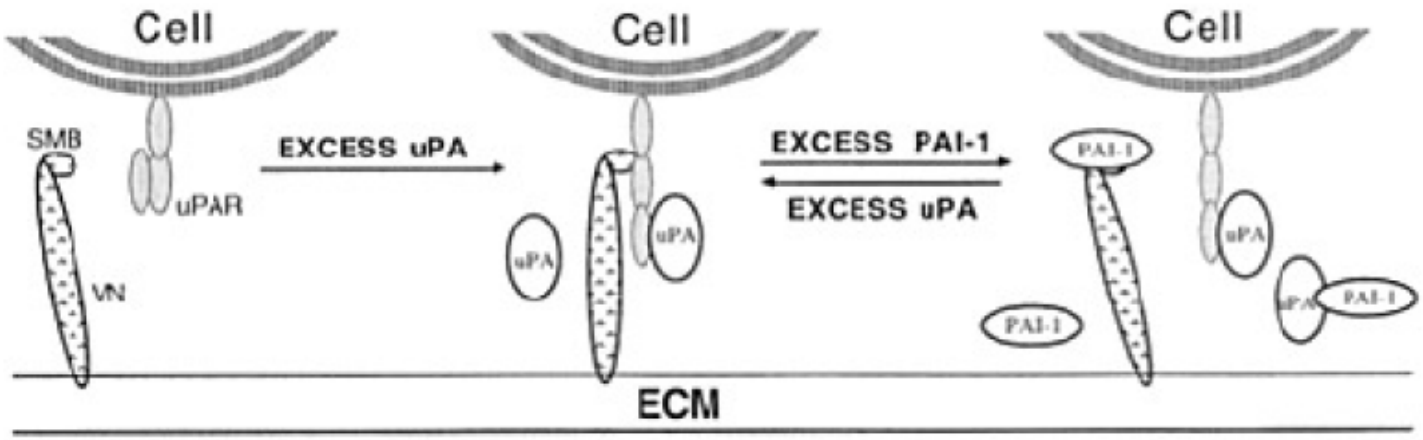
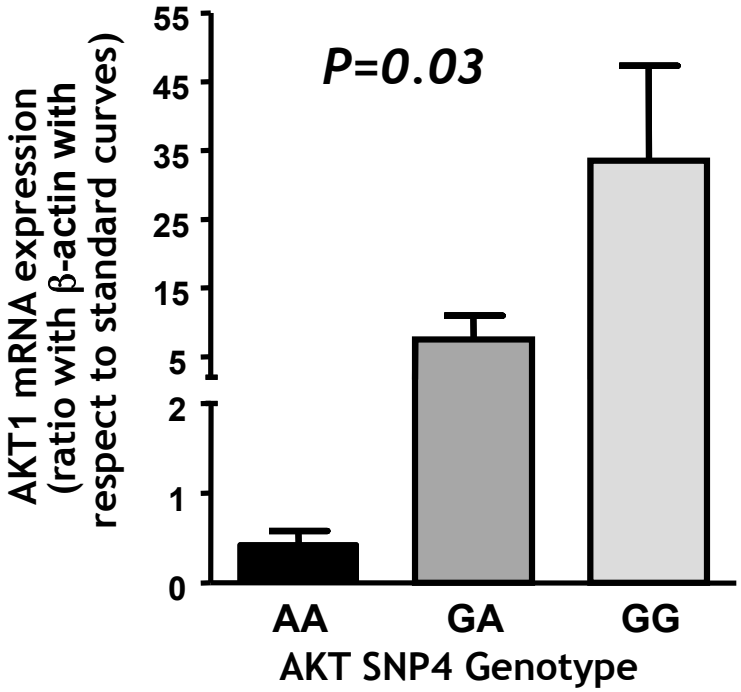
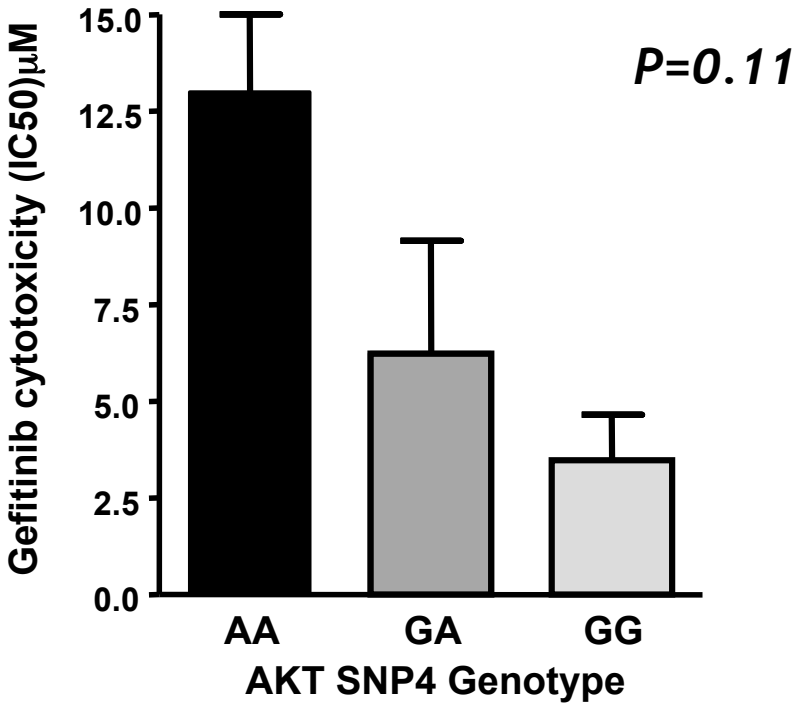
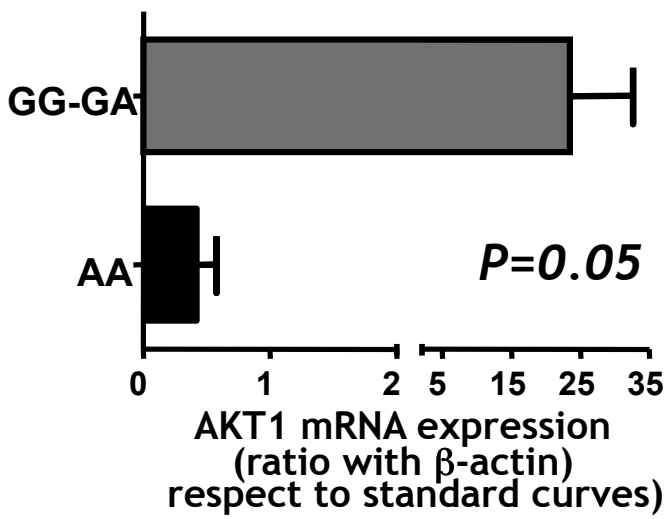


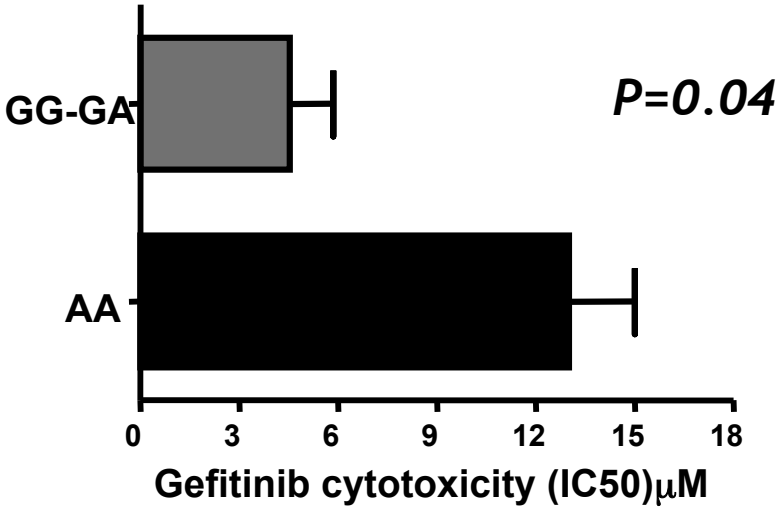
Figure 8. Model for the regulation of uPAR dependent cell adhesion and release by PAI-1 and uPA.

In vitro studies









Conclusions

- This study is the first to suggest the effect of a SNP in *AKT1* on the TTP and OS of NSCLC gefitinib-treated patients

- The pharmacogenetic role of the *AKT1 SNP-4* was evaluated in a chemotherapy-treated/gefitinib-naive population

- To gain further insight into the mechanisms behind our findings we performed *in vitro* studies showing associations with *AKT1* expression and gefitinib IC50s

- Finally, we observed a significant association between *EGFR* polymorphisms and gastrointestinal toxicity in NSCLC EGFR-TKIs treated patients

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From Hypothesis to Product: Diagnostic Development Tutorial
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