Pharmacogenomic markers in EGFR-targeted therapy of lung cancer

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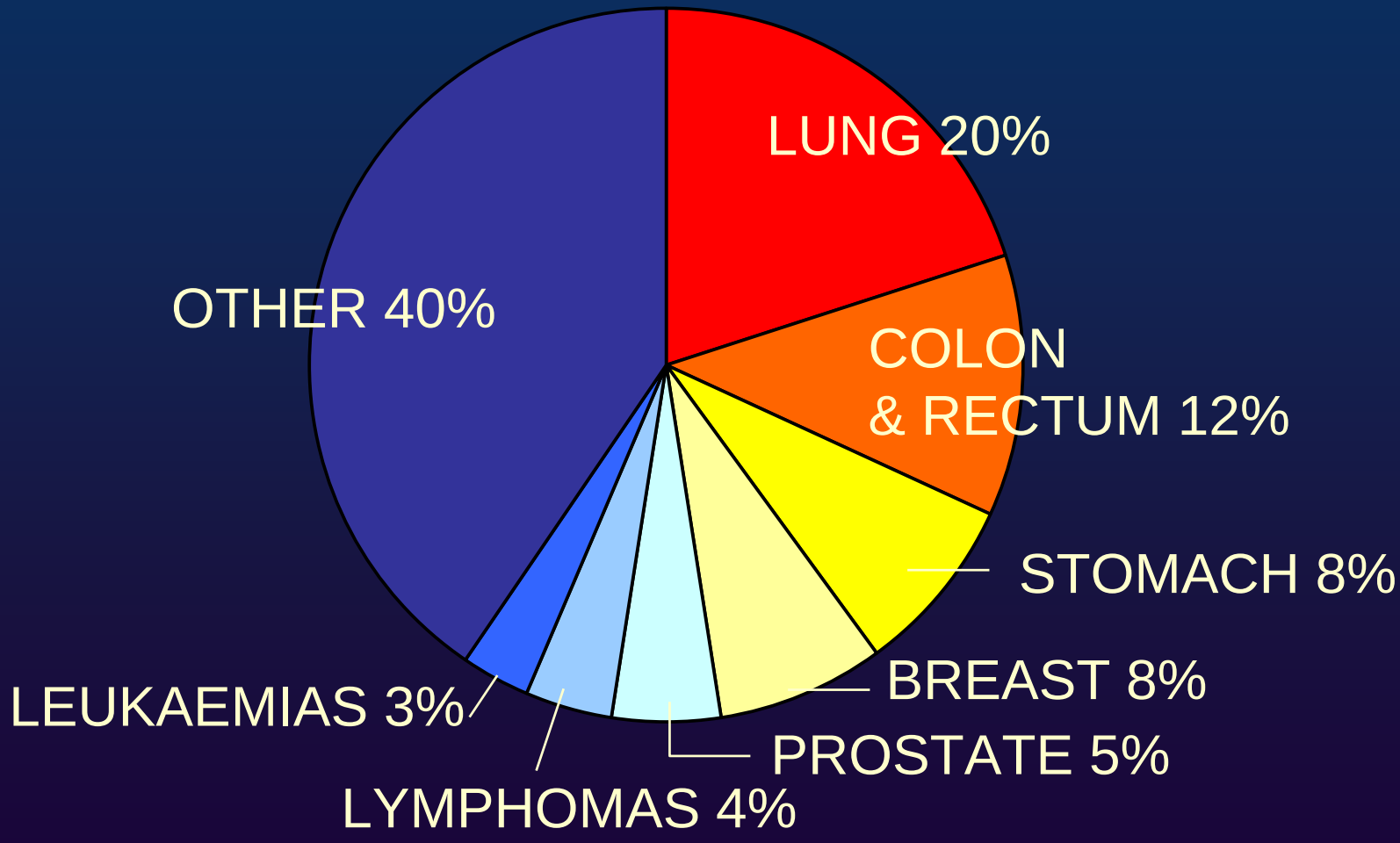
Cancer mortality in the European Union; 2004



Boyle et al., Ann Oncol 2005

Rationale for targeted therapy of lung cancer

- Standard chemotherapy provides modest survival benefit at the expense of significant toxicity and costs
- Survival rates from lung cancer almost unchanged for decades
- Significant improvement from targeted therapies in other solid tumors (breast cancer, renal cancer, GIST) and haematologic malignancies

Classes of EGFR inhibitors under clinical development

- Orally available EGFR tyrosine kinase inhibitors (TKIs: gefitinib, erlotinib, lapatinib, canertinib, HKI 272)
- Anti-EGFR monoclonal antibodies (cetuximab, panitumumab, matuzumab, pertuzumab)

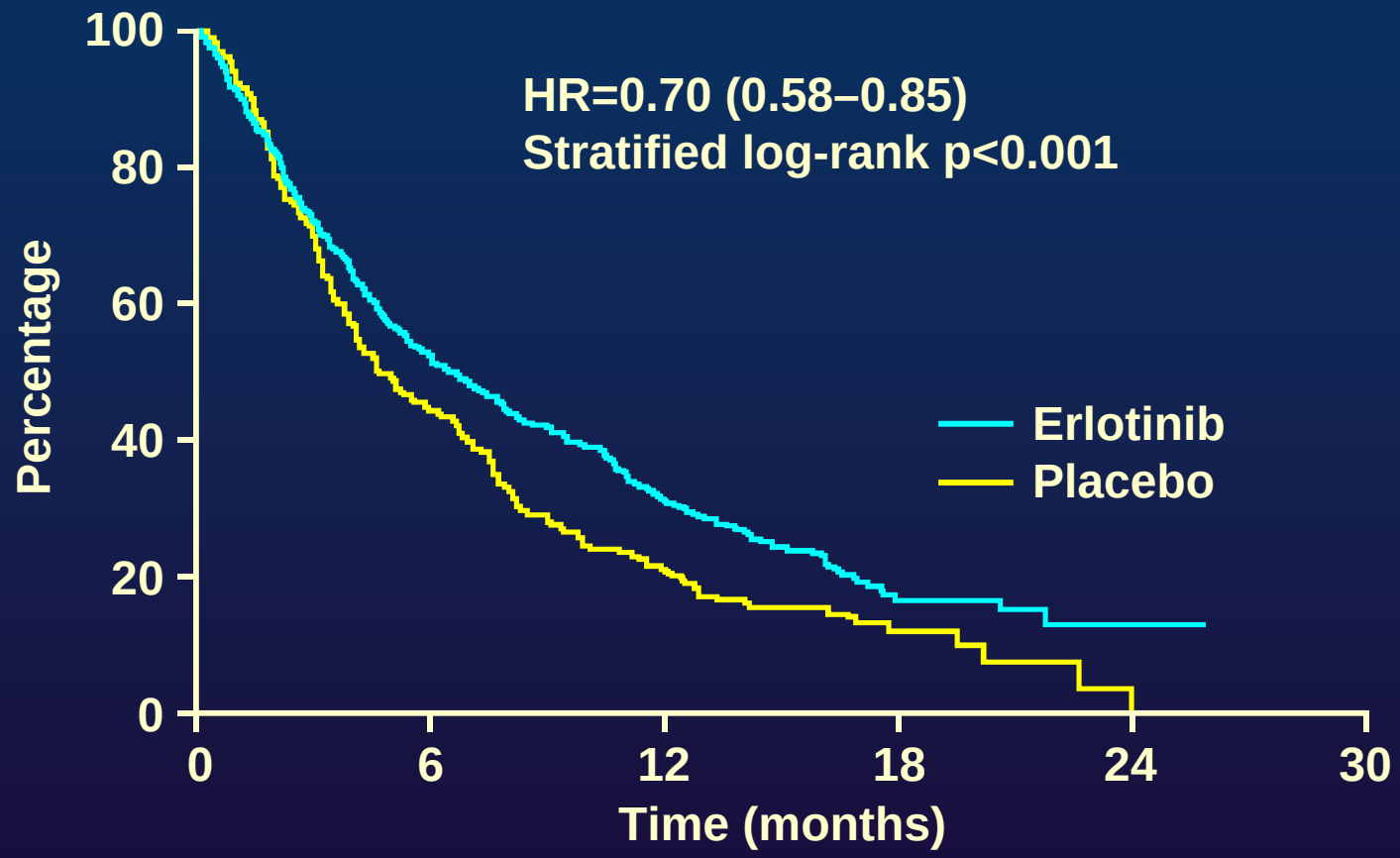
Gefitinib and erlotinib: findings from early clinical studies

- Phase I studies: relatively good tolerance; dose limiting toxicities: skin rash and diarrhea
- Phase II monotherapy studies in non-small cell lung cancer (NSCLC): ~10-20% response rates and ~40% disease control rates in pretreated patients

Gefitinib and erlotinib: findings from phase III studies

- No advantage of EGFR TKIs combined with chemotherapy in unselected NSCLC patients in the first-line treatment (four phase III studies; >4.000 patients)
- Significant survival benefit (HR=0.70) with erlotinib monotherapy vs placebo in unselected patients relapsed after one or two lines of chemotherapy (BR.21)
- Insignificant survival benefit (HR=0.89) with gefitinib monotherapy in a similar setting (ISEL)

BR.21: survival



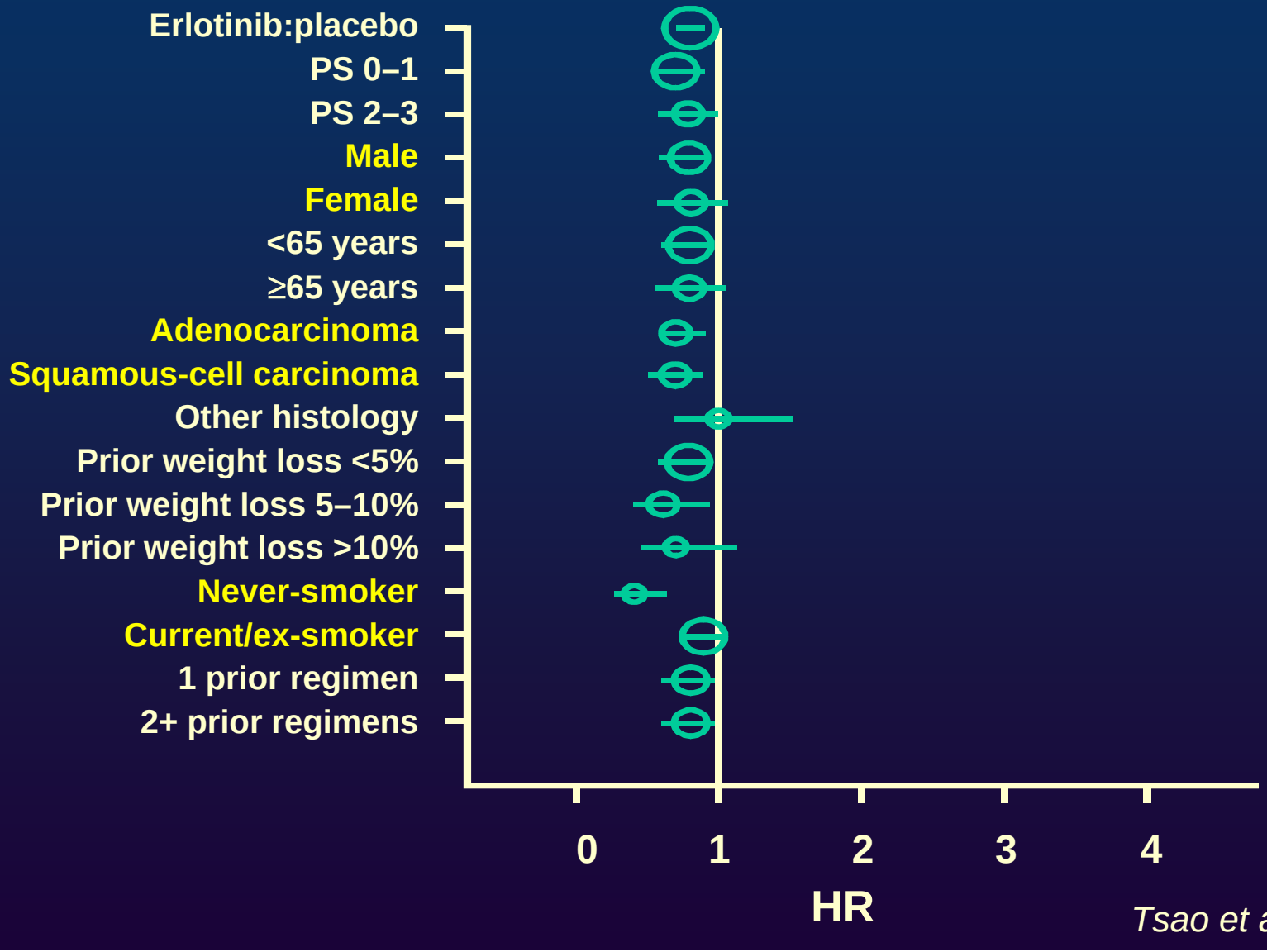
At risk						
Erlotinib	488	255	145	23	4	0
Placebo	243	107	50	9	0	0

Shepherd et al., NEJM, 2005

Clinical markers of increased responsiveness to EGFR TKIs

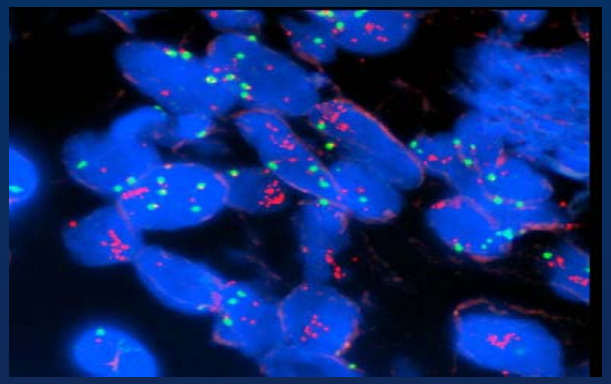
- Never-smokers (RRs ~ 20-30%)
- Asian ethnicity (RRs ~ 30%)
- Female gender (RRs ~ 15-20%)
- Adenocarcinoma (RRs ~ 10-20%)

BR.21: Forest plot of survival by subsets

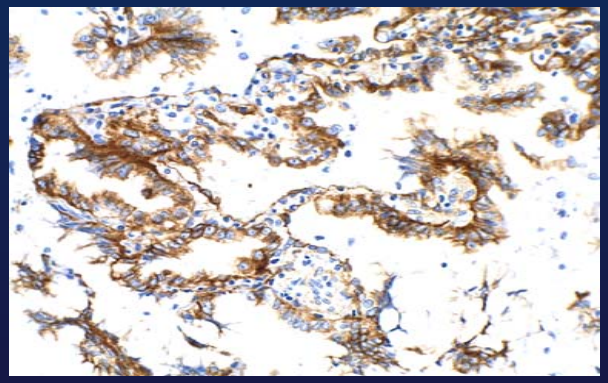


Tsao et al., NEJM, 2005

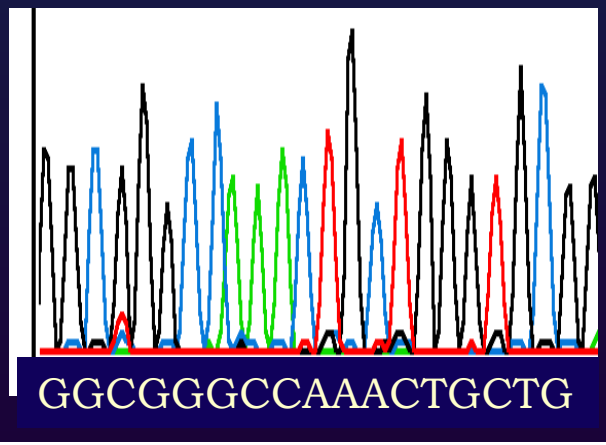
Biologic selection to EGFR TKIs



EGFR **gene copy number by FISH**



EGFR protein expression by IHC

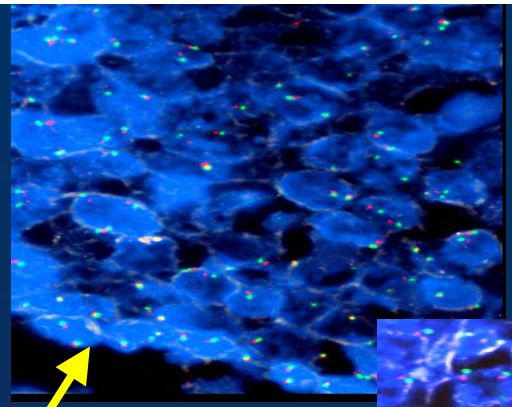


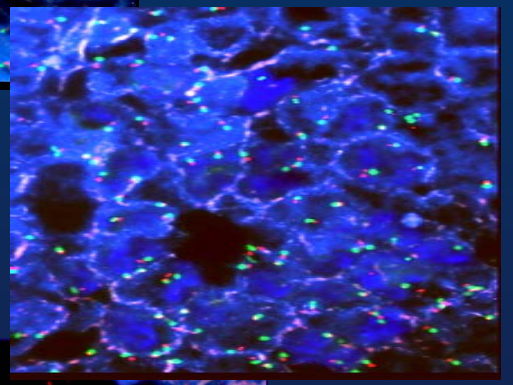
EGFR **gene mutations**

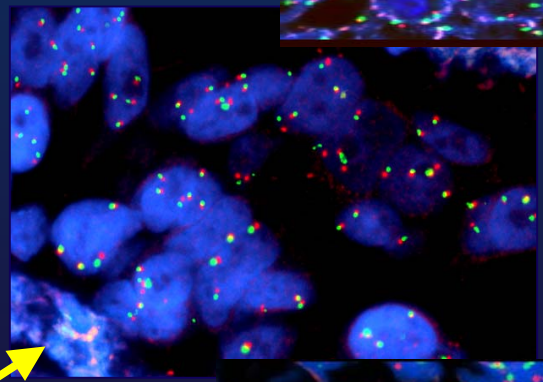
EGFR FISH

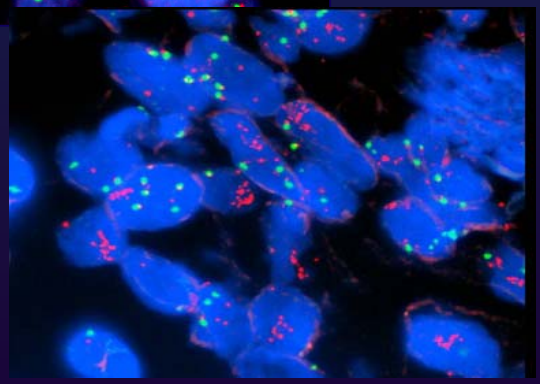
ISEL STUDY

PATTERN	EGFR (%)
Disomy	15.7%
Low Trisomy	24.1%
High Trisomy	2.2%
Low Polysomy	27.3%
High Polysomy	17.0%
Gene Amplification	13.8%









Hirsch et al., J Clin Oncol 2006

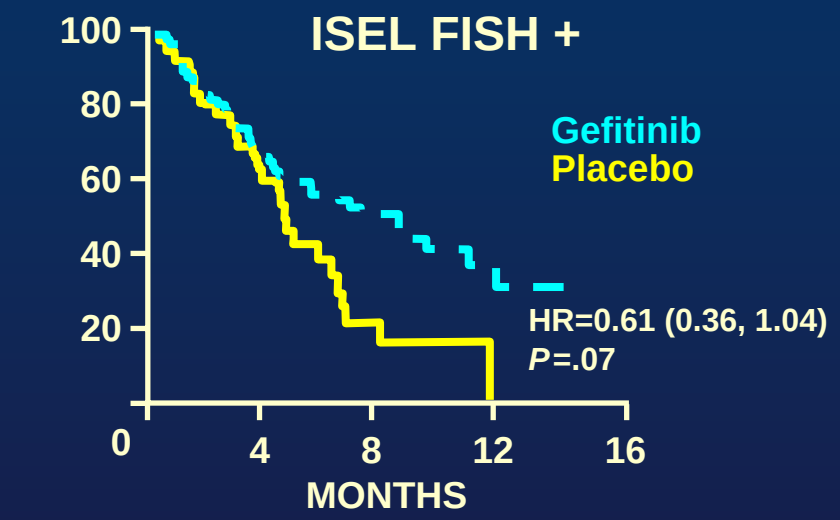
EGFR TKIs studies: impact of gene copy number by FISH

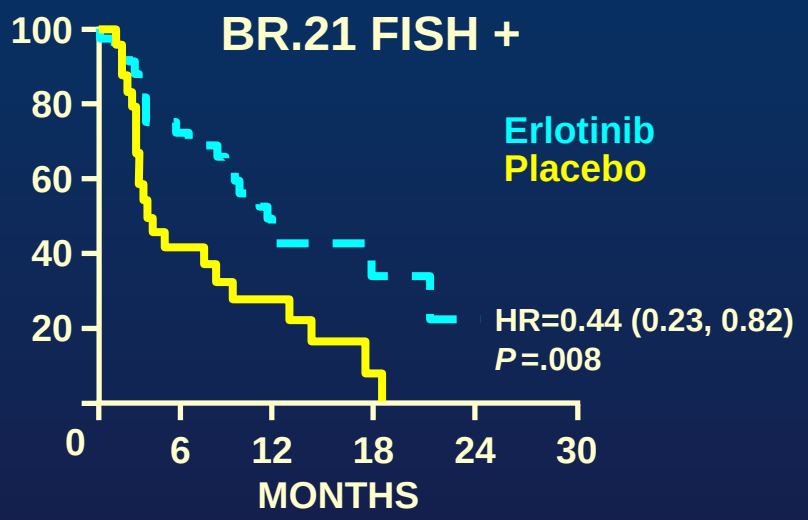
Author	N	Drug	% FISH Positive	RR FISH+ vs. FISH-	HR (95% CI)
Cappuzzo et al.	102	Gefitinib 250 mg/d	32%	36% vs. 3%	0.44* (0.23-0.82)
Hirsch et al. *SWOG 0126*	82	Gefitinib 500 mg/d	32%	26% vs. 11%	0.50* (0.25-0.97)
Tsao et al. *BR.21*	125	Erlotinib 150 mg/d	45%	20% vs. 2%	0.44** (0.23-0.82)
Hirsch et al. *ISEL*	370	Gefitinib 250 mg/d	31%	16% vs. 3%	0.61** (0.36-1.03)

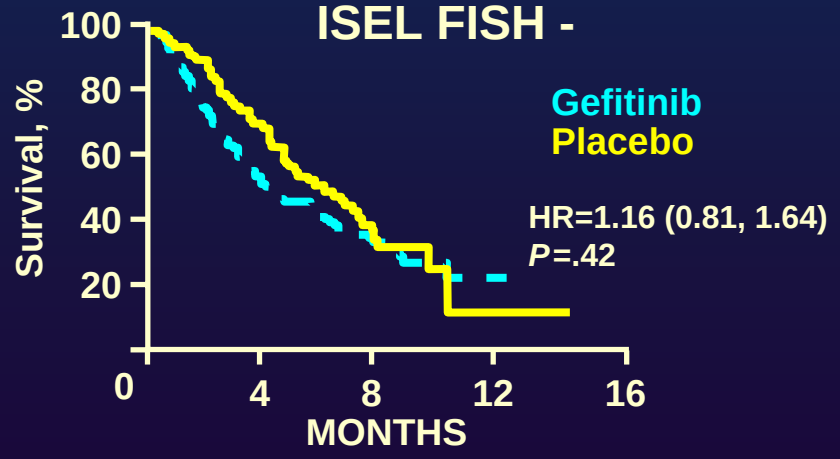
**HR for FISH+ vs. FISH- subsets; all patients treated with gefitinib*

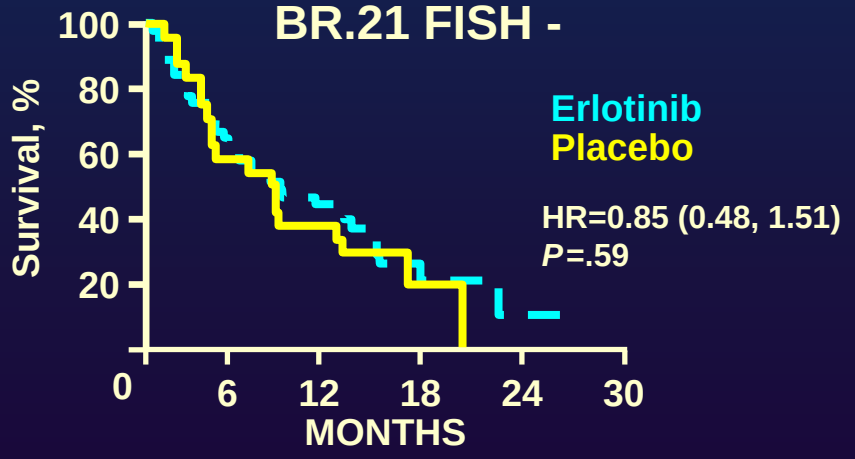
***HR for EGFR TKI vs. placebo in FISH+ patients*

Survival according to EGFR gene copy number – BR.21 and ISEL







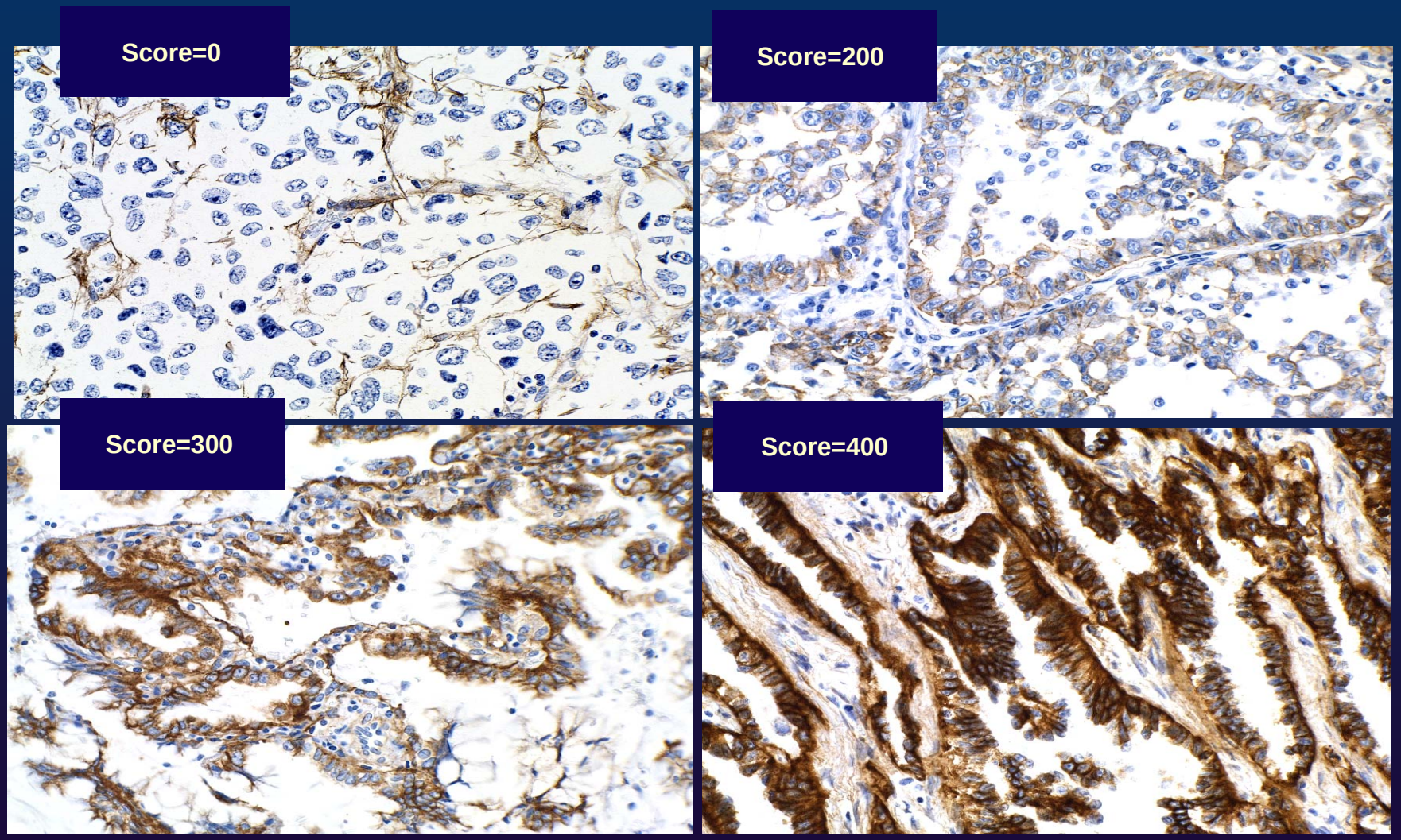


ISEL FISH interaction test *P*=.04

• BR.21 FISH interaction test *P*=.10

Tsao et al, NEJM 2005; Hirsch et al., J Clin Oncol 2006

IHC and EGFR status: scoring system

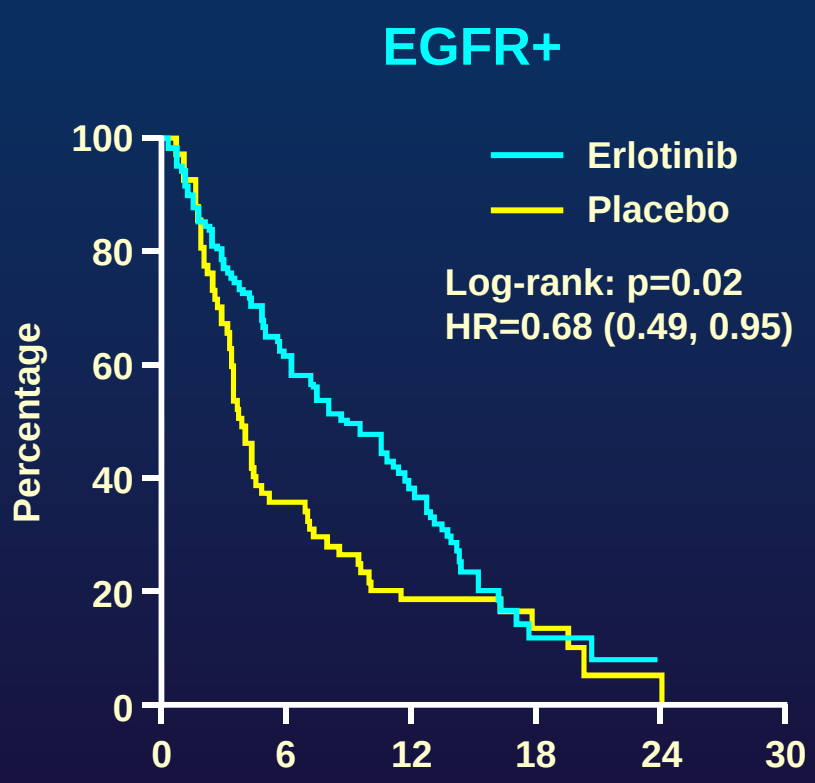


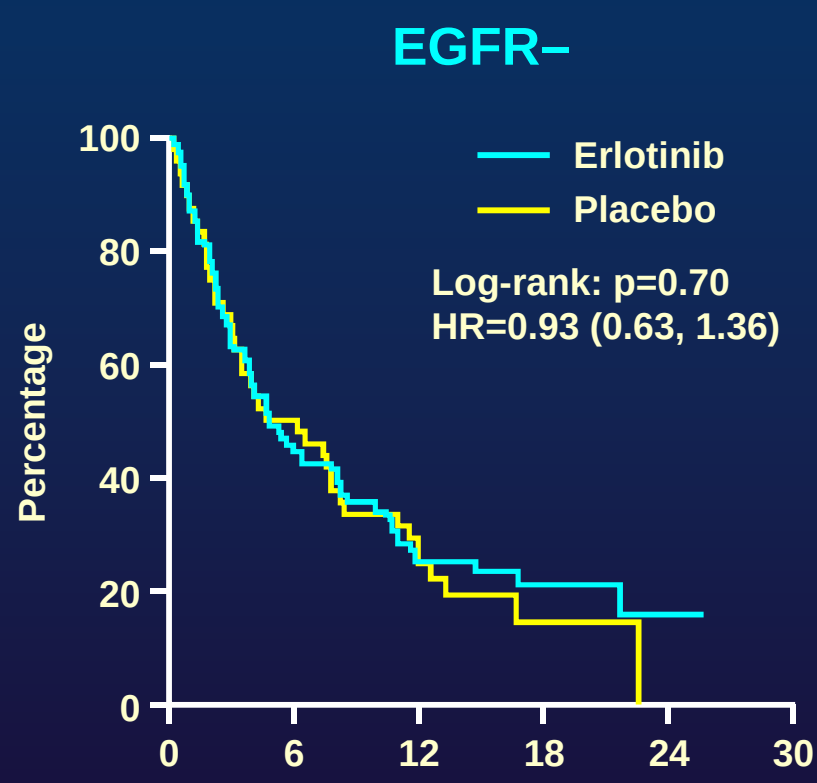
EGFR POSITIVE: 62/100 pts=62%

Response according to EGFR protein expression (IHC)

EGFR Status	ISEL	IDEAL	BR.21	TOTAL
	ORR (%)	ORR (%)	ORR (%)	ORR (%)
EGFR +	N=158 13 (8.2%)	N=84 13 (13.4%)	N=106 12 (11.3%)	N=348 38 (10.9%)
EGFR -	N=69 1 (1.5%)	N=17 1 (5.6%)	N=80 3 (3.8%)	N= 166 5 (3.0%)

BR.21: Survival according to EGFR protein expression

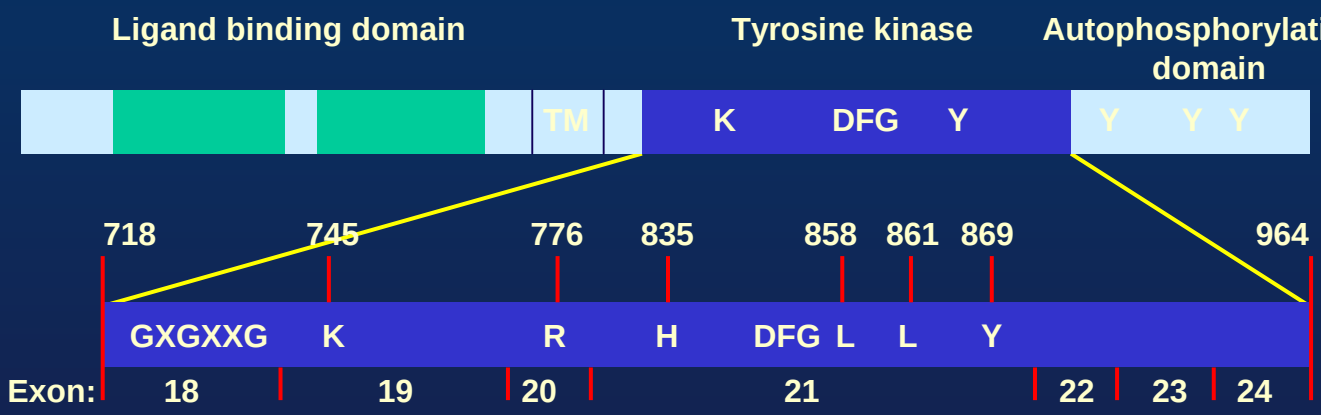




Interaction *P* = 0.25

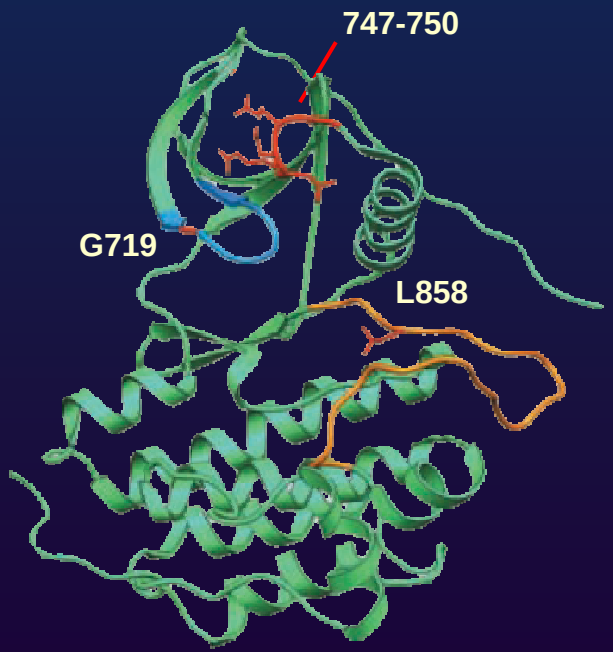
Tsao et al., NEJM 2005

EGFR gene mutations



Mutacje punktowe

Delecje



Pao et al., PNAS 2004

Retrospective studies: impact of *EGFR* mutations

Author	N	Drug	% Mut+	RR Mut+ vs. Mut-	HR (95% CI)
Mitsudomi et al.	59	Gefitinib 250 mg/d	56%	83% vs. 10%	0.34* (0.12-0.99)
Takano et al.	66	Gefitinib 250 mg/d	59%	82% vs. 11%	0.27* (0.13-0.53)
Han et al.	90	Gefitinib 250 mg/d	18.9%	64.7% vs. 13.7%	0.16* (0.05-0.52)
Cappuzzo et al.	89	Gefitinib 250 mg/d	17%	54% vs. 5%	NS
Cortes-Funes et al.	83	Gefitinib 250 mg/d	12%	60% vs. 8.8%	0.32* (0.12-0.91)

*Mut+ vs. mut- subsets
NS - non significant

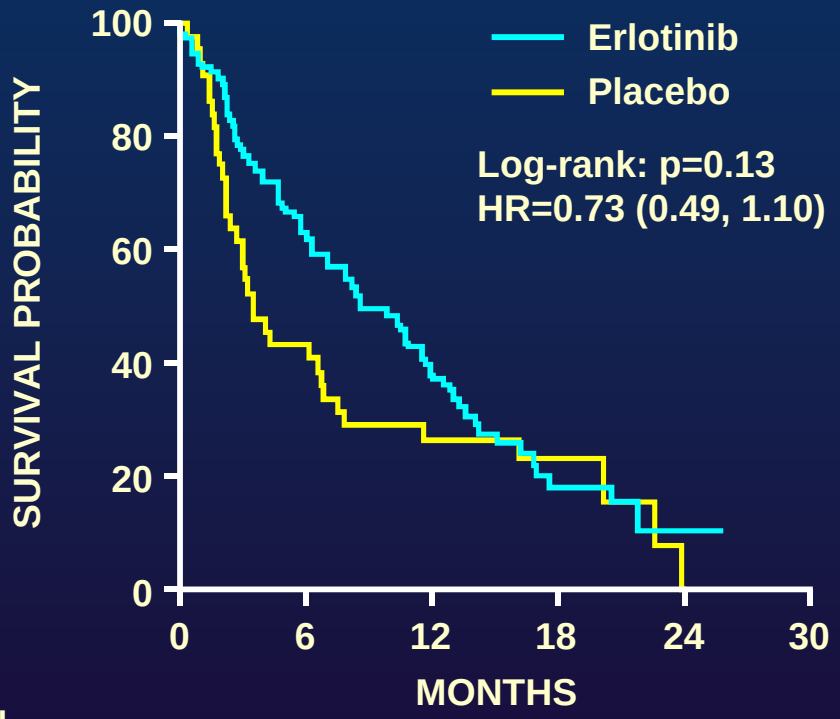
Prospective studies: impact of *EGFR* mutations

Author	N	Drug	% Mut+	RR Mut+ vs. Mut-	HR (95% CI)
Tsao et al. BR.21	197	Erlotinib 150 mg/d	22.6%	16% vs. 7%	0.77 (0.40-1.50)
Hirsch et al. ISEL	215	Gefitinib 250 mg/d	12%	37.5% vs. 2.6%	NR
Bell et al. IDEAL INTACT	79 312	Gefitinib 250 and 500 mg/d	18% 10%	46% vs. 10% 72% vs. 55%	NR 1.77 (0.25-0.97)
Eberhardt et al. TRIBUTE	228	Erlotinib 150 mg/d	12.7%	53% vs. 18%	NR (NS)

NR – not reported; NS – non significant

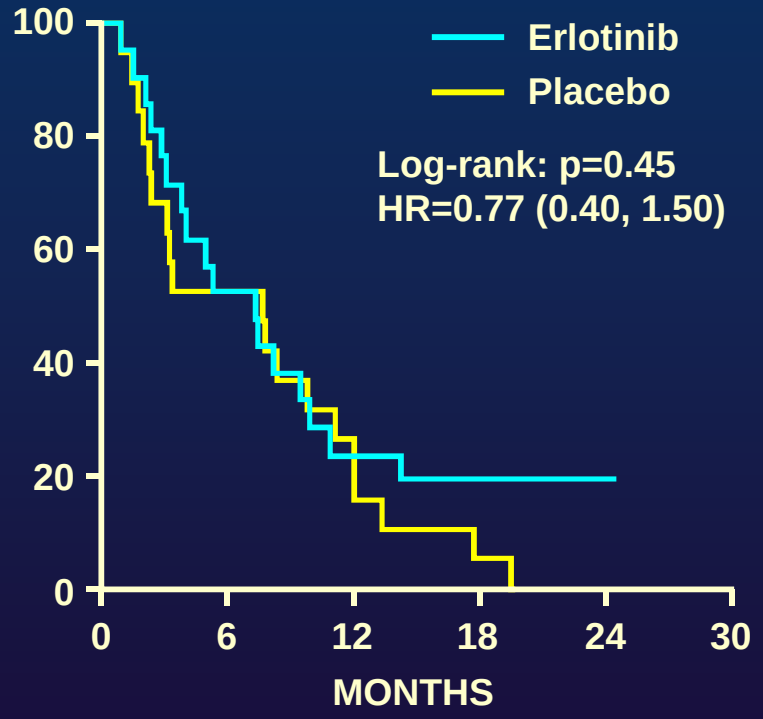
BR.21: Survival according to *EGFR* mutations

Wild-type *EGFR*



N						
Erlotinib	93	59	34	9	1	0
Placebo	44	18	11	6	0	0

Mutant *EGFR*

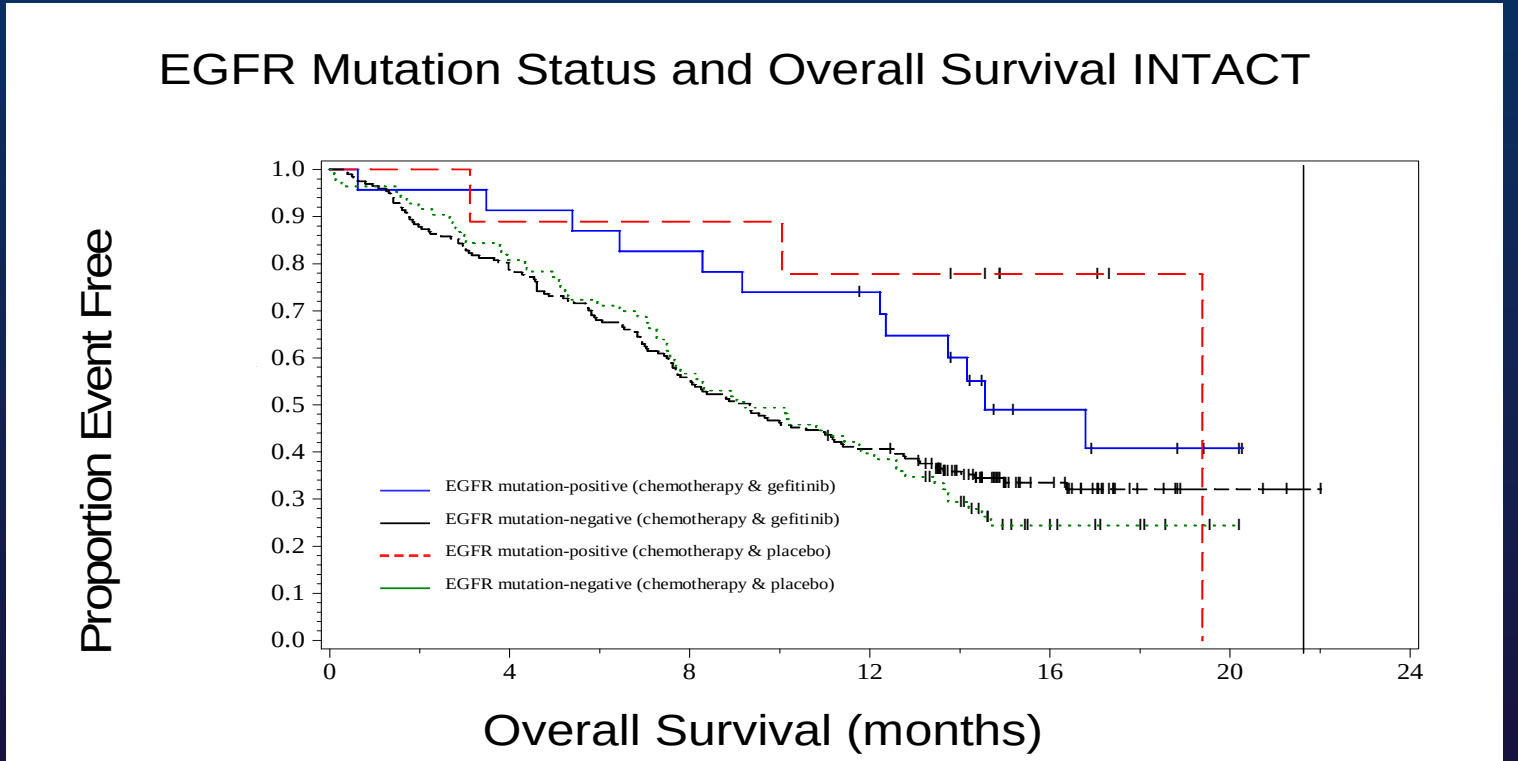


N						
Erlotinib	21	11	5	1	1	0
Placebo	19	10	5	1	0	0

Interaction test, *P*= 0.97

Tsao et al., NEJM 2005

Prognostic value of *EGFR* mutations in advanced NSCLC



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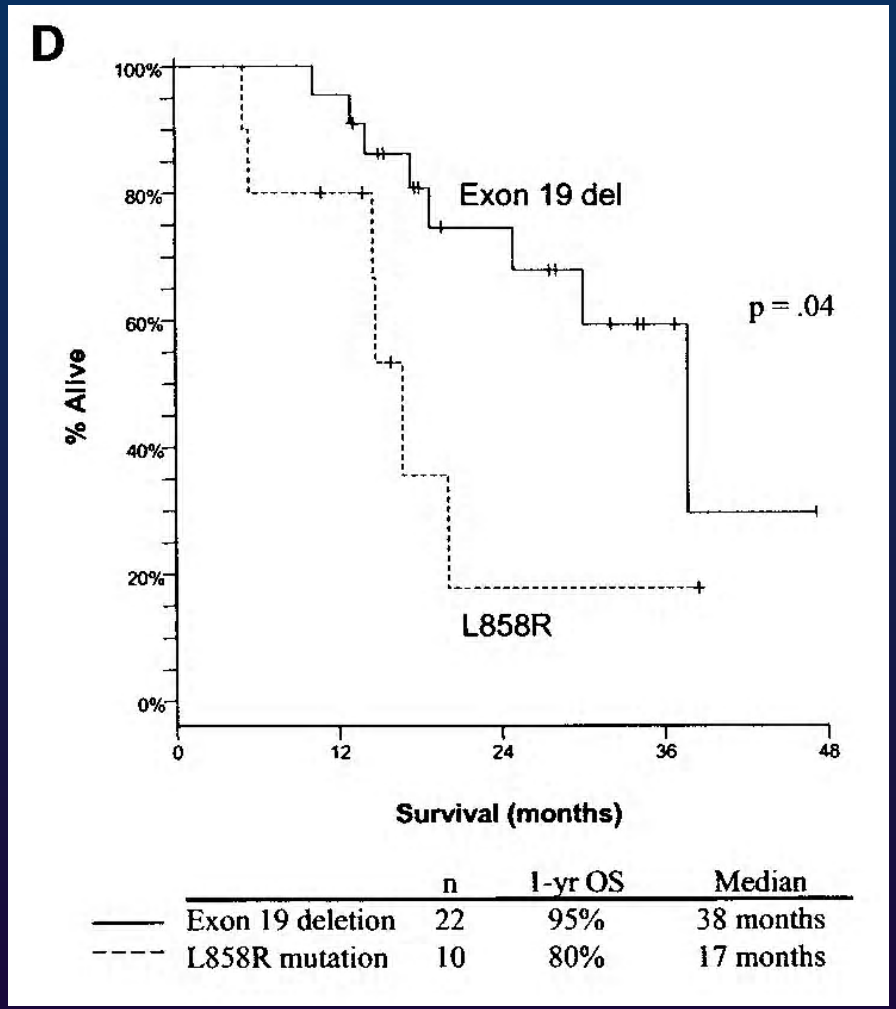
Bell et al., Clin Cancer Res, 2006

Survival vs. *EGFR* mutation type



	n	1-yr OS	Median
Exon 19 deletion	22	95%	38 months
L858R mutation	10	80%	17 months

Jackman et al., Clin Cancer Res, 2006

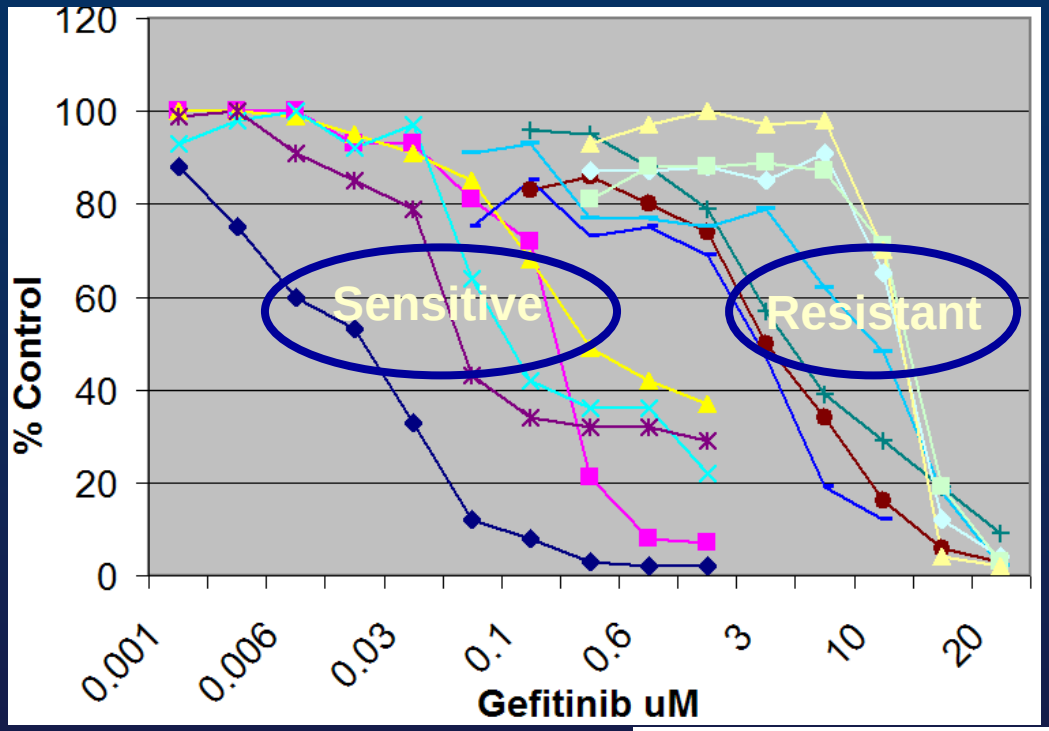
Current status of biomarkers for selection of NSCLC patients to EGFR TKIs

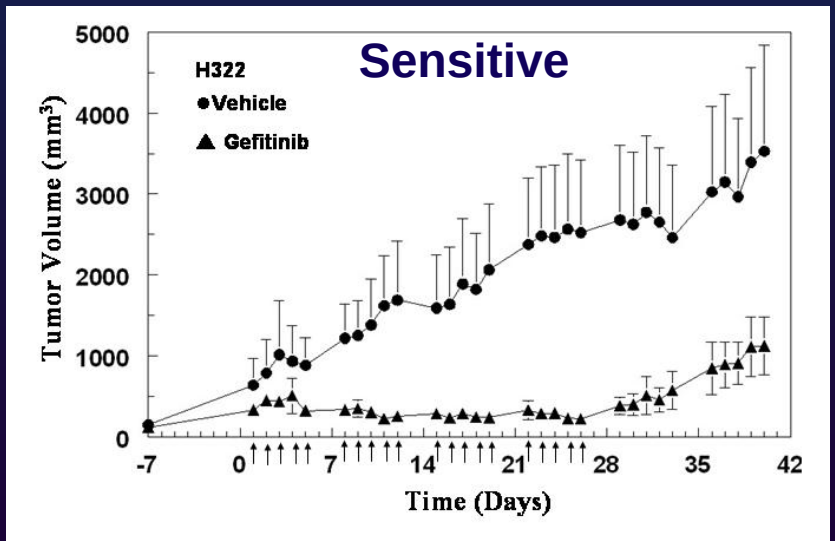
- Several biomarkers identified (gene copy number, EGFR protein expression, EGFR mutations, serum proteomics)
- None routinely used for patient selection
- Clinical trials in selected patient populations or stratified for these markers ongoing

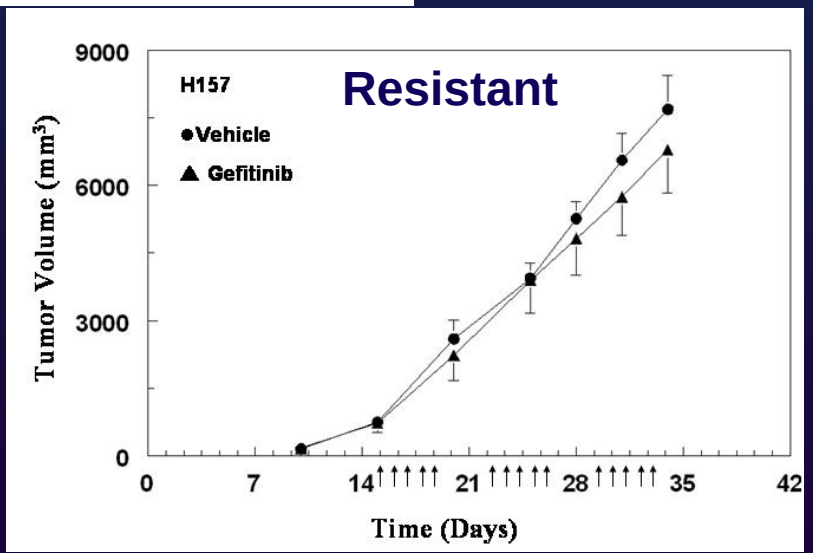
What went wrong with biomarkers in clinical development of EGFR TKIs in NSCLC?

- Poor translational components of clinical studies (none prospectively enriched or stratified for biomarkers)
- Neglecting differences in biology according to demographic and clinical characteristics (i.e. smoking history, ethnicity)
- Poor standarization and validation of technologies for biomarker assesment

EGFR TKI preclinical studies in Colorado







Clinical trial design issues

Prognostic marker

- Associates with main effect regardless of treatment
- May be used for risk-stratified treatment
- Not suitable for targeted-therapy trial designs

Predictive marker

- Interaction with treatment
- Appropriate for targeted-therapy trial designs

Crowley J., Taormina IASLC Meeting, 2006

Targeted therapy clinical trial designs

- All-comers design: Randomize everyone, measure marker / stratify by marker

Register → Measure marker → Randomize → A, B

- Targeted design: Randomize positive patients only

Register → Measure marker → Randomize M+ → A, B

- Strategy design: Randomize to strategy based on marker

Register → Measure marker → Randomize → **Tx based on marker** → A or B; **Tx not based on marker** → A or B

Crowley J., Taormina IASLC Meeting, 2006

Future directions

- Incorporation of biomarker studies
  early in preclinical and clinical development
- Understanding of biomarker significance
  for disease biology (prognostic vs. predictive)
- Better standarization and validation
  of technologies for biomarker assesment