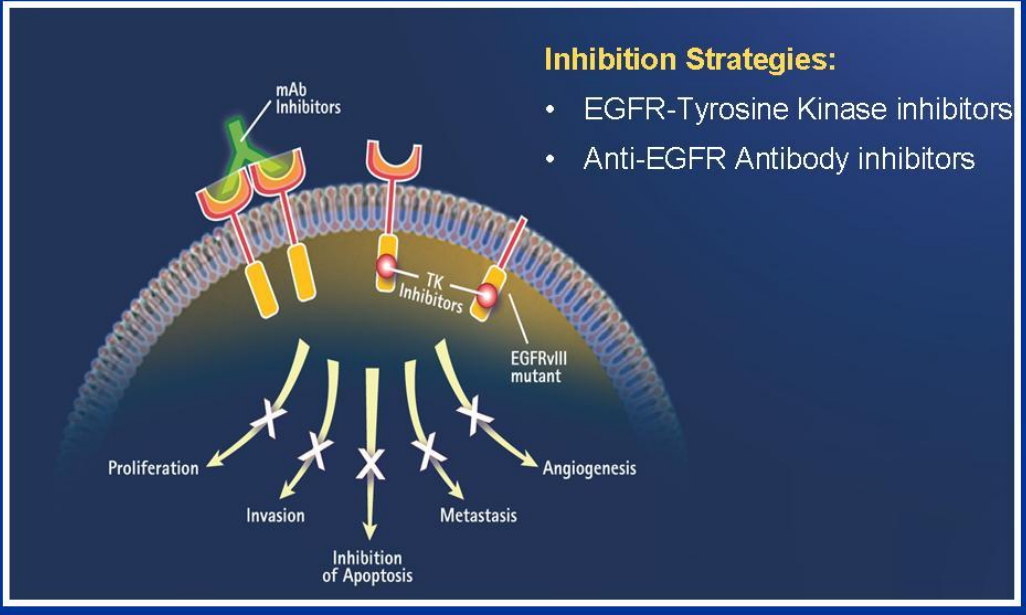
EGFR TKIs

A primer

The EGFR Axis



Activating Mutations in the Epidermal Growth Factor Receptor Underlying Responsiveness of Non-Small-Cell Lung Cancer to Gefitinib

Thomas J. Lynch, M.D., Daphne W. Bell, Ph.D., Raffaella Sordella, Ph.D., Sarada Gurubhagavatula, M.D., Ross A. Okimoto, B.S., Brian W. Brannigan, B.A., Patricia L. Harris, M.S., Sara M. Haserlat, B.A., Jeffrey G. Supko, Ph.D., Frank G. Haluska, M.D., Ph.D., David N. Louis, M.D., David C. Christiani, M.D., Jeff Settleman, Ph.D. and Daniel A. Haber, M.D., Ph.D.

N Engl J Med
Volume 350;21:2129-2139
May 20, 2004

The NEW ENGLAND JOURNAL of MEDICINE

Characteristics of Nine Patients with Non-Small-Cell Lung Cancer and a Response to Gefitinib

Table 1. Characteristics of Nine Patients with Non–Small-Cell Lung Cancer and a Response to Gefitinib.

Patient No.	Sex	Age at Beginning of Gefitinib Therapy	Pathological Type*	No. of Prior Regimens	Smoking-Status†	Duration of Therapy	Overall Survival‡	*EGFR* Mutation§	Response¶
		yr				*mo*			
1	F	70	BAC	3	Never	15.6	18.8	Yes	Major; improved lung lesions
2	M	66	BAC	0	Never	>14.0	>14.0	Yes	Major; improved bilateral lung lesions
3	M	64	Adeno	2	Never	9.6	12.9	Yes	Partial; improved lung lesions and soft-tissue mass
4	F	81	Adeno	1	Former	>13.3	>21.4	Yes	Minor; improved pleural disease
5	F	45	Adeno	2	Never	>14.7	>14.7	Yes	Partial; improved liver lesions
6	M	32	BAC	3	Never	>7.8	>7.8	Yes	Major; improved lung lesions
7	F	62	Adeno	1	Former	>4.3	>4.3	Yes	Partial; improved liver and lung lesions
8	F	58	Adeno	1	Former	11.7	17.9	Yes	Partial; improved liver lesions
9	F	42	BAC	2	Never	>33.5	>33.5	No	Partial; improved lung nodules

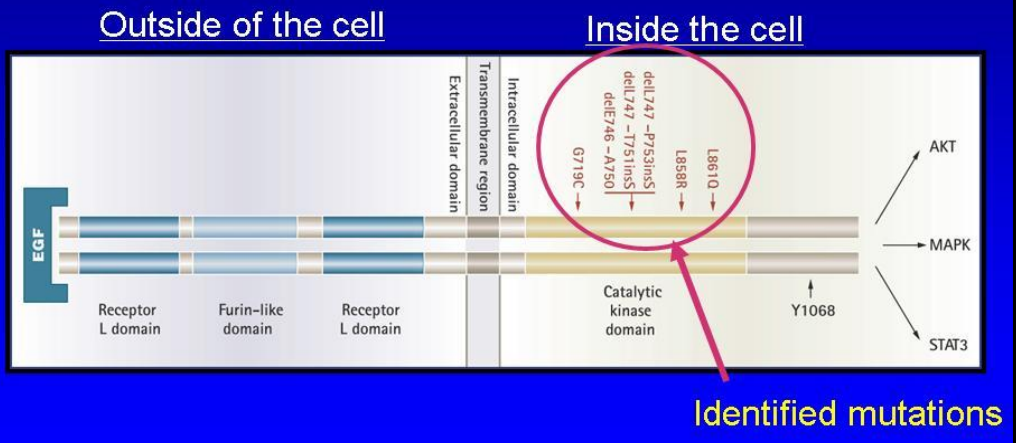
* Adenocarcinoma (Adeno) with any element of bronchoalveolar carcinoma (BAC) is listed as BAC.
† Smoking status was defined as former if the patient had not smoked any cigarettes within 12 months before entry and never if the patient had smoked less than 100 cigarettes in his or her lifetime.
‡ Overall survival was measured from the beginning of gefitinib treatment to death.
§ *EGFR* denotes the epidermal growth factor receptor gene.
¶ A partial response was evaluated with the use of response evaluation criteria in solid tumors; major and minor responses were evaluated by two physicians in patients in whom the response could not be measured with the use of these criteria.

Lynch, T. et al. N Engl J Med 2004;350:2129-2139

The NEW ENGLAND JOURNAL of MEDICINE

Mutations in the *EGFR* Gene in EGFR Inhibitor-Responsive Tumors

- **Mutations are in *EGFR* gene cluster, within the intracellular tyrosine kinase domain**



Adapted from Lynch TJ et al. *New Engl J Med* 4;350:1-11, 2004.

Paez JG et al EGFR Mutations in Lung Cancer: Correlation with Clinical Response to Gefitinib Therapy Science 2004; 304: 1497-1500

16/119 mutations in primary tumours (58, Japan and 61, US)

Adenocarcinomas 21% vs 2% others

Women 20% vs Men 9%

Japanese 26% vs US 2%

Japanese women with adenocarcinoma 57%

5/5 mutations in gefitinib responders vs 1/61 unselected US

Screening for Epidermal Growth Factor Receptor Mutations in Lung Cancer
Rosell R et al NEJM 2009; 361:958-967

	N=350/2105	Frequency
Female	814	30%
Male	1287	8.2%
<56.7	638	13.9%
56.7-69.1	638	15.5%
>69.1	632	22.1%
Former	958	9.5%
Current	424	5.8%
Never	612	37.7%
Adeno	1634	17.3%
BAC	147	23.1%
LCC	287	11.5%

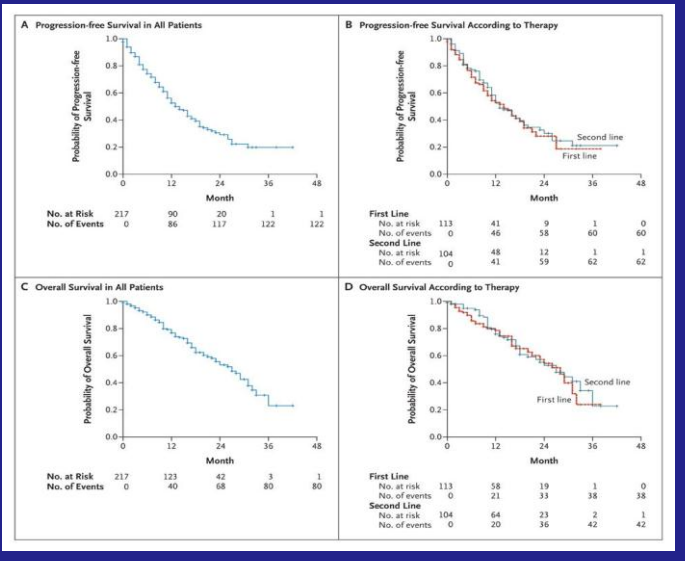
Screening for Epidermal Growth Factor Receptor Mutations in Lung Cancer
Rosell R et al NEJM 2009; 361:958-967

197 evaluable for response

Del 19	62.2%	L858R	37.8%

CR	12.2%
PR	58.4%
SD	19.3%
PD	10.2%

Kaplan-Meier Curves of Progression-free and Overall Survival



Rosell R et al. N Engl J Med 2009;361:958-967

The IPASS Study: 1st line therapy for NSCLC

IPASS: Study Design

Patients

- Adenocarcinoma histology
- Never smokers or light ex-smokers*
- Performance status 0–2
- Provision of tumour sample for biomarker analysis strongly encouraged

IRESSA (250 mg/day)

1:1 randomisation

Doublet chemotherapy (carboplatin (AUC 5 or 6)/paclitaxel (200mg/m²) every 3 weeks

1217 patients from East Asian countries

Endpoints

Primary
- Progression-free survival (non-inferiority)

Secondary
- Objective response rate
- Quality of life
- Disease-related symptoms
- Overall survival
- Safety and tolerability

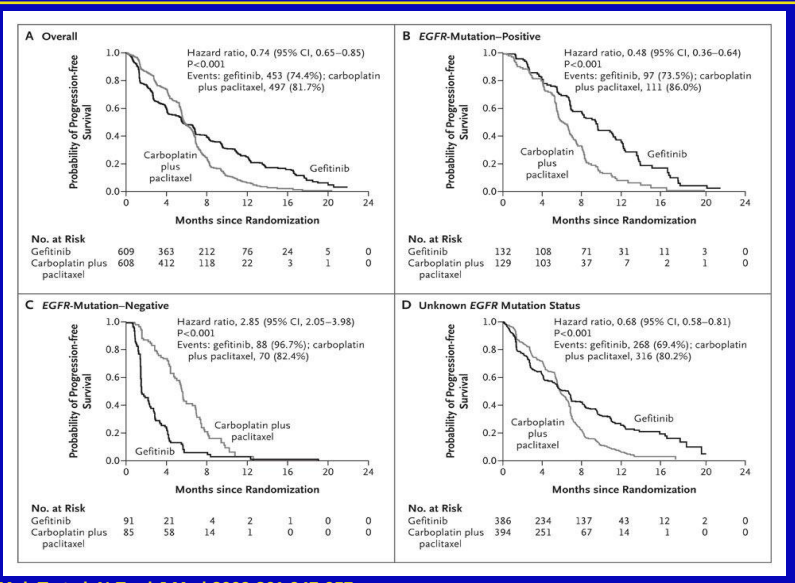
Exploratory
- Biomarkers
  - EGFR mutation
  - EGFR gene copy number
  - EGFR protein expression

*Never smokers:<100 cigarettes in lifetime; light ex-smokers: stopped ≥15 years ago and smoked ≤10 pack yrs

Carboplatin/paclitaxel was offered to IRESSA patients upon progression

Mok T, Wu TL, Thongprasert S et al. *N Engl J Med* 2009; **361:947-995**

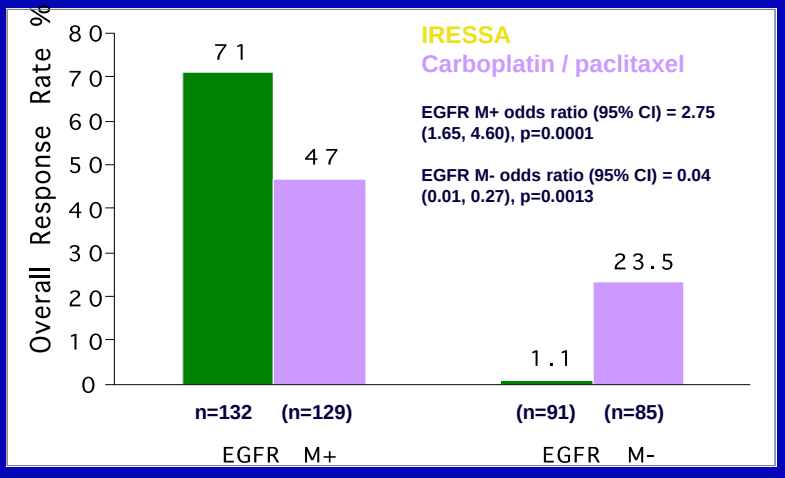
Kaplan-Meier Curves for Progression-free Survival



Mok T et al. N Engl J Med 2009;361:947-957

IPASS: Superior ORR to doublet chemotherapy in the EGFR M+ population

IPASS: Overall Response Rate (EGFR M+)



Mok T, Wu TL, Thongprasert S et al. *N Engl J Med* 2009; **361:947-995**

EURTAC study design

- Chemonaïve
- Stage IIIB/IV NSCLC
- *EGFR* exon 19 deletion or exon 21 L858R mutation
- ECOG PS 0–2

(n=174)

R

Erlotinib 150mg/day → PD

Stratification
- Mutation type
- ECOG PS (0 vs 1 vs 2)

Platinum-based doublet chemotherapy q3wks x 4 cycles* → PD

Primary endpoint
- Progression-free survival (PFS)
  - interim analysis planned at 88 events

Secondary endpoints
- Objective response rate
- Overall survival (OS)
- Location of progression
- Safety
- *EGFR* mutation analysis in serum
- Quality of life

ECOG = Eastern Cooperative Oncology Group; PS = performance status; PD = progressive disease
*Cisplatin 75mg/m^2 d1 / docetaxel 75mg/m^2 d1; cisplatin 75mg/m^2 d1 / gemcitabine 1250mg/m^2 d1,8; carboplatin AUC6 d1 / docetaxel 75mg/m^2 d1; carboplatin AUC5 d1 / gemcitabine 1000mg/m^2 d1,8

PRESENTED AT: ASCO Annual '11 Meeting

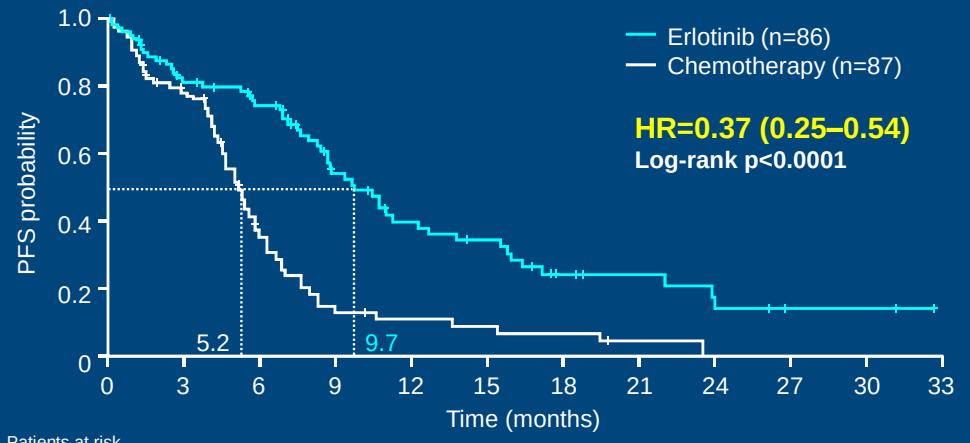
Baseline characteristics

	Interim analysis (Aug 2, 2010)		Updated analysis (Jan 26, 2011)	
	Erlotinib (n=77)	Chemotherapy (n=76)	Erlotinib (n=86)	Chemotherapy (n=87)
Median age, yrs (range)	64 (24–82)	64 (29–82)	65 (24–82)	65 (29–82)
Gender, %				
Male	32	21	33	22
Female	68	79	67	78
ECOG PS, %				
0	30	34	31	34
1	57	54	55	52
2	13	12	14	14
Smoking status, %				
Current smoker	4	13	8	14
Former smoker	26	13	26	14
Never smoker	70	74	66	72
EGFR mutation type, %				
Exon 19 deletion	64	63	66	67
L858R mutation	36	37	34	33

N.B. All patients were Caucasian and the majority (~90%) had stage IV disease and adenocarcinoma

PRESENTED AT: ASCO Annual '11 Meeting

PFS in ITT population (updated analysis 26 Jan 2011)



Patients at risk

Erlotinib	86	63	54	32	21	17	9	7	4	2	2	0
Chemo	87	49	20	8	5	4	3	1	0	0	0	0

Data cut-off: 26 Jan 2011

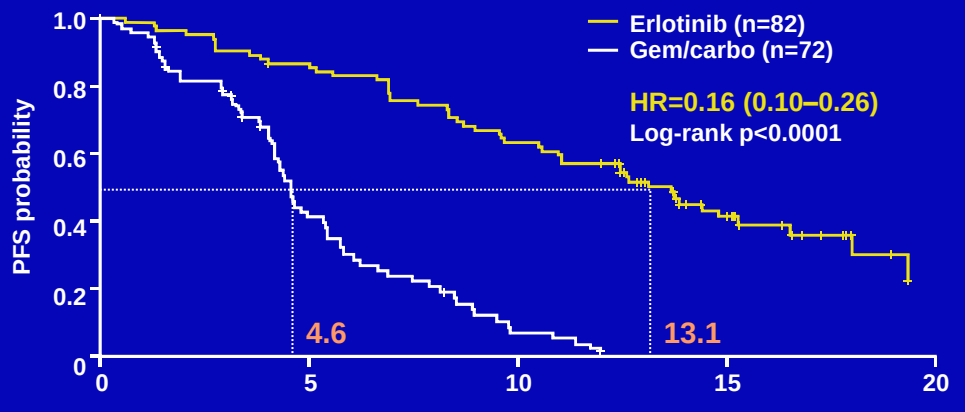
PRESENTED AT: ASCO Annual '11 Meeting

Best overall response in ITT population

	Interim analysis (Aug 2, 2010)		Updated analysis (Jan 26, 2011)	
	Erlotinib (n=77) n (%)	Chemotherapy (n=76) n (%)	Erlotinib (n=86) n (%)	Chemotherapy (n=87) n (%)
Complete response	2 (3)	0 (0)	2 (2)	0 (0)
Partial response	40 (52)	8 (11)	48 (56)	13 (15)
Objective response rate	***42 (55)***	***8 (11)***	***50 (58)***	***13 (15)***
Stable disease	18 (23)	42 (55)	18 (21)	44 (51)
Disease control rate	***60 (78)***	***50 (66)***	***68 (79)***	***57 (66)***
Progressive disease	6 (8)	10 (13)	6 (7)	11 (13)
No response assessment	11 (14)	16 (21)	12 (14)	19 (22)

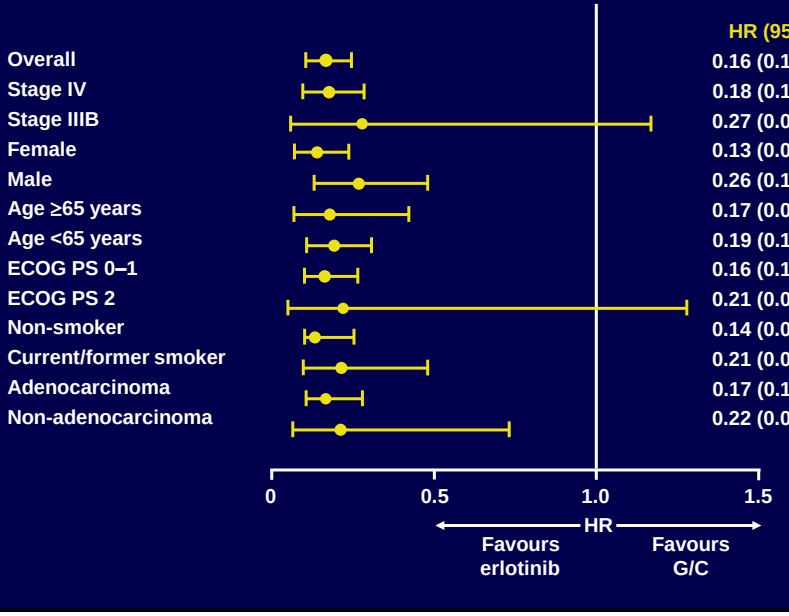
PRESENTED AT: ASCO Annual '11 Meeting

OPTIMAL PFS: updated analysis (ITT)



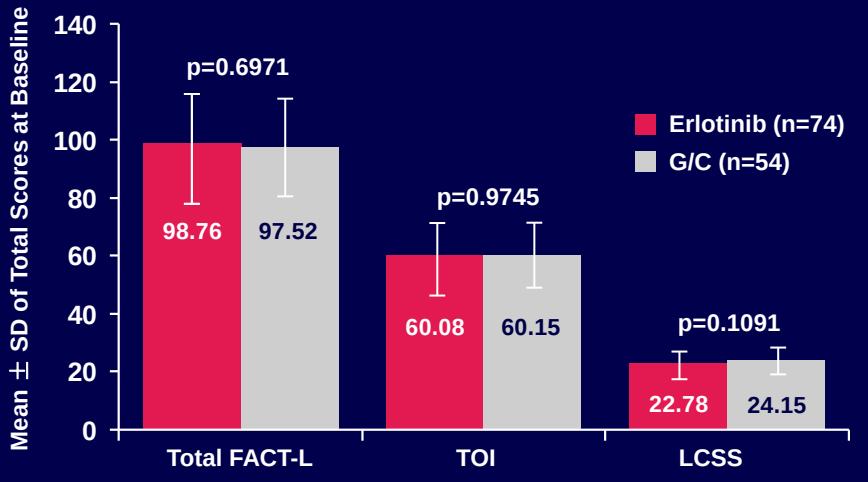
Patients at risk					
Erlotinib	82	70	51	20	2
Gem/carbo	72	26	4	0	0

PFS subgroup analyses

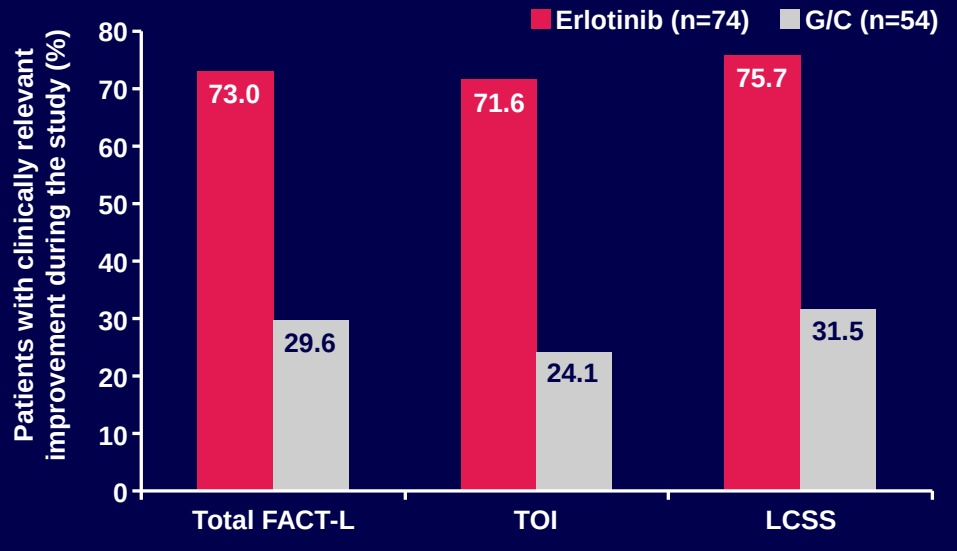


	HR (95% CI)	n
Overall	0.16 (0.10–0.26)	154
Stage IV	0.18 (0.11–0.28)	138
Stage IIIB	0.27 (0.06–1.16)	16
Female	0.13 (0.07–0.24)	91
Male	0.26 (0.14–0.50)	63
Age ≥65 years	0.17 (0.07–0.43)	38
Age <65 years	0.19 (0.11–0.31)	116
ECOG PS 0–1	0.16 (0.10–0.26)	144
ECOG PS 2	0.21 (0.04–1.28)	10
Non-smoker	0.14 (0.08–0.25)	109
Current/former smoker	0.21 (0.09–0.49)	45
Adenocarcinoma	0.17 (0.11–0.28)	134
Non-adenocarcinoma	0.22 (0.06–0.73)	20

Total scores for QoL and symptoms at baseline in the assessable population



Clinically relevant improvements in QoL

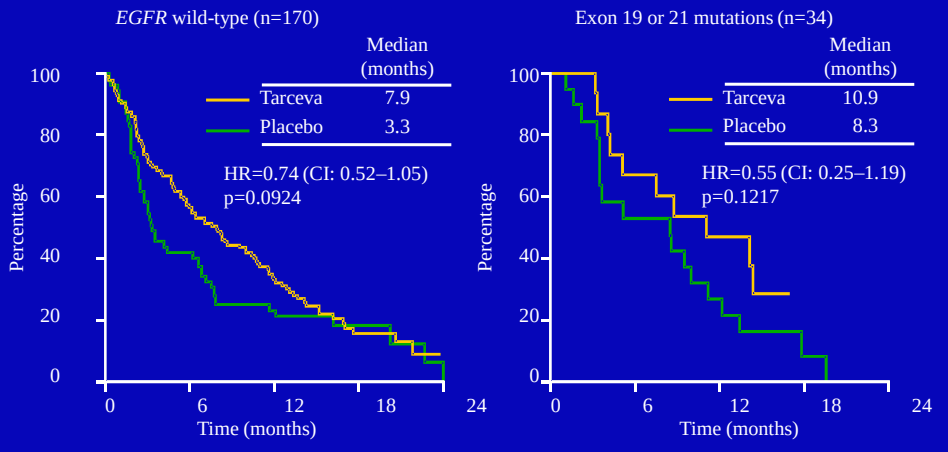


Includes all patients with a baseline and ≥1 post-baseline QoL assessment

Does that mean it is of no value in EGFR wild type patients?

Anti-proliferative vs apoptogenic

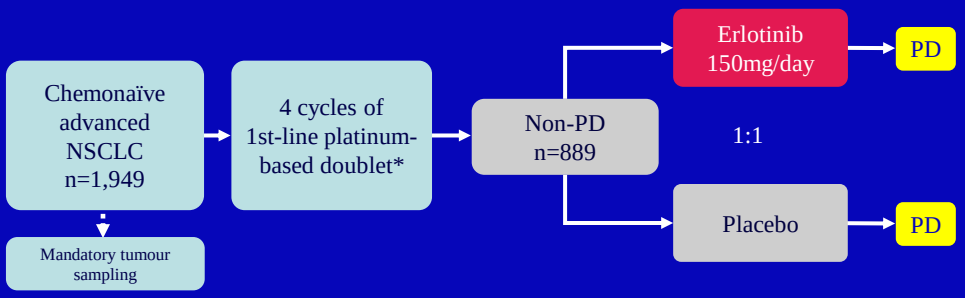
BR.21(retrospective analysis): EGFR WT patients benefit similarly to unselected population



Interaction p=0.47 (not significant)

Adapted from Zhu C-Q et al J Clin Oncol 2008; 26:4268-4275

SATURN study design



Stratification factors:

- **EGFR IHC (positive vs negative vs indeterminate)**
- **Stage (IIIB vs IV)**
- **ECOG PS (0 vs 1)**
- **CT regimen (cis/gem vs carbo/doc vs others)**
- **Smoking history (current vs former vs never)**
- **Region**

Co-primary endpoints:

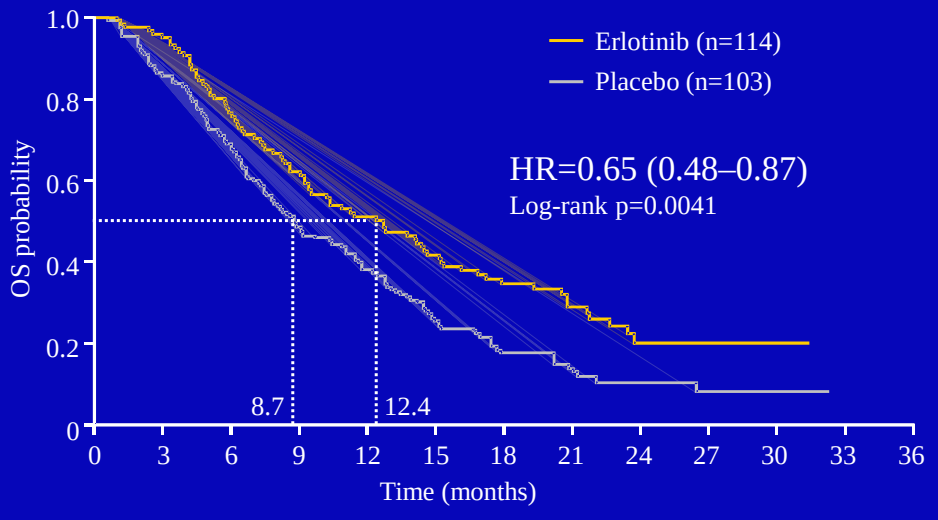
- PFS in all patients
- PFS in patients with EGFR IHC+ tumours

Secondary endpoints:

- Overall survival (OS) in all patients and those with EGFR IHC+ tumours; OS and PFS in EGFR IHC– tumours; biomarker analyses; safety; time to symptom progression; quality of life (QoL)

*Cisplatin/paclitaxel; cisplatin/gemcitabine; cisplatin/docetaxel; cisplatin/vinorelbine; carboplatin/gemcitabine; carboplatin/docetaxel; carboplatin/paclitaxel
EGFR = epidermal growth factor receptor; IHC = immunohistochemistry

OS in *EGFR* wild-type group with SD on first-line chemotherapy

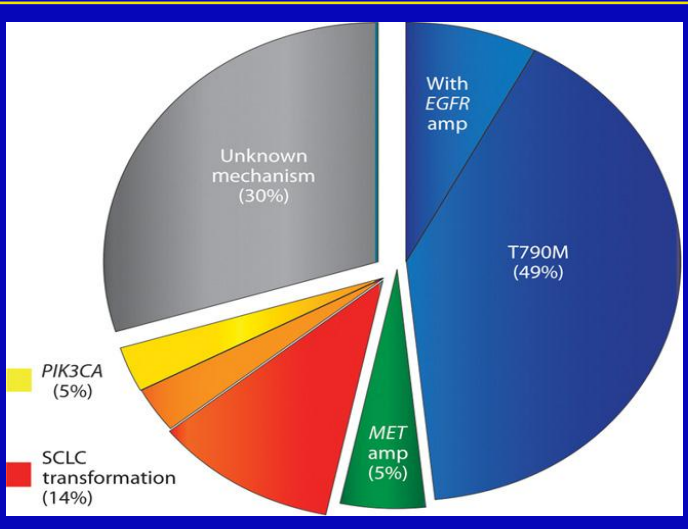


Measured from time of randomisation into the maintenance phase

What do you do at resistance?

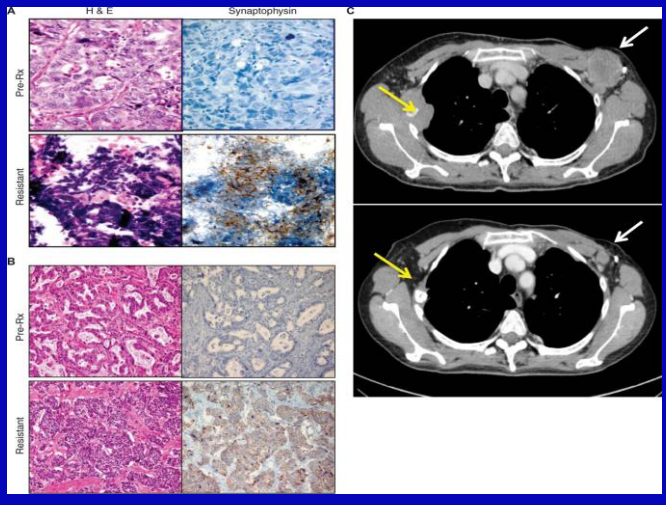
Consider a biopsy

The frequency of observed drug resistance mechanisms.



Sequist L V et al. Sci Transl Med 2011;3:75ra26-75ra26

Drug resistance and transformation of NSCLC to SCLC. The SCLC histological phenotype was observed in five (14%) NSCLC patients who had acquired resistance.



Sequist L V et al. Sci Transl Med 2011;3:75ra26-75ra26

Longitudinal evaluation of patients treated repeatedly with erlotinib.

A

Histology	Adeno	Adeno			Adeno
Genotype	L858R TP53	L858R TP53 T790M			L858R TP53
EGFR TKI status	Sensitive	Resistant			Sensitive
Tumor burden					
Treatment	Chemo	Erlotinib	Chemo	Chemo	Erlotinib*
Timeline	2007	2008	2009		2010

B

Histology	Adeno		SCLC	Adeno	SCLC
Genotype	L858R		L858R PIK3CA	L858R	L858R PIK3CA
EGFR TKI status	Sensitive		Resistant	Sensitive	Resistant
Tumor burden					
Treatment	Erlotinib		C+RT	Erlotinib	C+ RT
Timeline	2008	2009		2010	

Sequist L V et al. Sci Transl Med 2011;3:75ra2675ra26