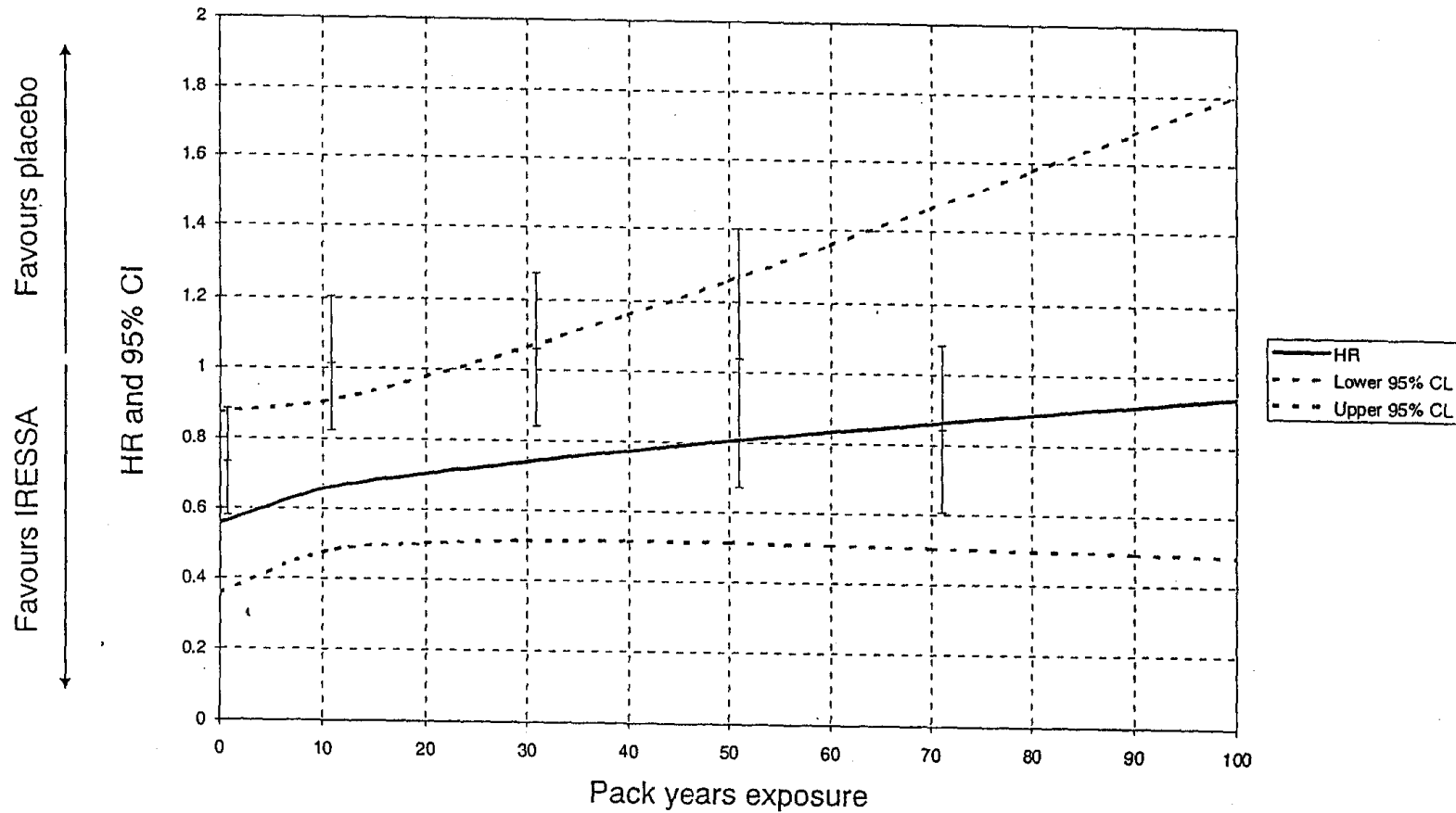


Plot of hazard ratio as a function of smoke exposure



Hazard ratio and 95% CI from the model

Smoke Exposure (pack years)	HR	Lower 95% CL	Upper 95% CL
0	0.556	0.354	0.873
10	0.655	0.474	0.905
20	0.701	0.504	0.976
30	0.739	0.514	1.063
40	0.772	0.516	1.157
50	0.803	0.513	1.256
60	0.832	0.509	1.360
70	0.859	0.503	1.466
80	0.885	0.497	1.576
90	0.911	0.491	1.688
100	0.935	0.485	1.804

As can be seen, allowing for the skewed distribution of smoke exposure, the relationship between smoke exposure and the hazard ratio is modelled a little better. The difference in log likelihood between the Cox model with treatment as the only covariate and with curvilinear smoking exposure and smoking exposure by treatment interaction was 7.564 on 2 degrees of freedom, $p=0.02$. With smoke exposure as curvilinear factor, zero smoke exposure now yields a hazard ratio and 95% CI of 0.56 (0.35, 0.87) as compared to 100 pack years exposure which yields a hazard ratio and 95% CI of 0.94 (0.49, 1.80). These results are therefore generally more consistent with the simple subset analyses of Oriental never smokers [Cox regression HR and 95% CI, 0.37 (0.21, 0.64)] and Oriental smokers [Cox regression HR and 95% CI, 0.85 (0.58, 1.25)].

Justification that Cox regression analysis is more appropriate for use than log-rank test in the subgroups, non smokers, Oriental patients and non smoking Oriental patients:

For those subsets showing statistical significance by Cox regression analysis in slide 13, namely non smokers, Oriental patients and non smoking Oriental patients, it can be seen in Table 1 statistical significance is maintained for all three of these subsets in the simple log rank test, thereby supporting the findings from the Cox regression analysis.

As requested, with respect to non smokers, Oriental patients and non smoking Oriental patients, the parameter estimates for factors in the Cox model are given below in order from highest to lowest significance. In line with ICH E9 [1], since all factors were prespecified for adjustment in the protocol, all have been retained in the Cox analysis irrespective of significance.

Survival: Cox model

Non-smokers

		HR	Chi-square	P-value
PS	0,1 : 2,3	0.45	26.65	<0.0001
Reason for prior chemo failure	Refractory: Intolerant	1.56	2.05	0.1520
Number of prior lines	1:2	1.11	0.43	0.5118
Sex	Female: male	0.95	0.12	0.7340
Histology	Adenocarcinoma: non-adeno	0.99	0.01	0.9335

Survival: Cox model

Oriental

		HR	Chi-square	P-value
PS	0,1 : 2,3	0.40	31.98	<0.0001
Smoking history	Never: ever	0.56	7.77	0.0053
Reason for prior chemo failure	Refractory: Intolerant	3.58	6.13	0.0133
Number of prior lines	1:2	0.88	0.64	0.4239
Sex	Female: male	0.87	0.45	0.5029
Histology	Adenocarcinoma: non-adenocarcinoma	0.92	0.23	0.6313

Survival: Cox model

Oriental Non-smokers

		HR	Chi-square	P-value
PS	0,1 : 2,3	0.49	6.14	0.0132
Reason for prior chemo failure	Refractory: Intolerant	1.46	0.13	0.7180
Number of prior lines	1:2	0.96	0.02	0.8901
Sex	Female: male	1.32	0.62	0.4294
Histology	Adenocarcinoma: non-adenocarcinoma	0.77	0.56	0.4530

Further, the Cox model fit, adding covariates sequentially from most significant to least is as follows:

1839IL/0709 Cox model fitting – adding variables one-by one

Non-smoking (n=375)

Model number	Variable	HR (95% CI) p-value
1	Treatment	0.66 (0.49, 0.90) p=0.0089
	PS	0.44 (0.33, 0.60) p<0.0001
2	Treatment	0.66 (0.48, 0.90) p=0.0081
	PS	0.44 (0.33, 0.60) p<0.0001
	Response to prior chemo	1.58 (0.86, 2.91) p=0.1439
3	Treatment	0.67 (0.49, 0.91) p=0.0114
	PS	0.45 (0.33, 0.61) p<0.0001
	Response to prior chemo	1.57 (0.85, 2.90) p=0.1481
	Number of prior lines	1.10 (0.81, 1.50) p=0.5317
4	Treatment	0.67 (0.49, 0.92) p=0.0118
	PS	0.45 (0.33, 0.61) p<0.0001
	Response to prior chemo	1.57 (0.85, 2.89) p=0.1518
	Number of prior lines	1.11 (0.81, 1.51) p=0.5150
	Gender	0.94 (0.68, 1.31) p=0.7277
5	Treatment	0.67 (0.49, 0.92) p=0.0124
	PS	0.45 (0.33, 0.61) p<0.0001
	Response to prior chemo	1.56 (0.85, 2.89) p=0.1520
	Number of prior lines	1.11 (0.81, 1.51) p=0.5118
	Gender	0.95 (0.68, 1.31) p=0.7340
	Histology	0.99 (0.70, 1.39) p=0.9335

Oriental (n= 342)

Model number	Variable	HR (95% CI) p-value
1	Treatment	0.64 (0.47, 0.88) p=0.0052
	PS	0.44 (0.33, 0.60) p<0.0001
2	Treatment	0.68 (0.50, 0.92) p=0.0138
	PS	0.42 (0.31, 0.57) p<0.0001
	Smoking history	0.53 (0.38, 0.74) p=0.0001
3	Treatment	0.67 (0.49, 0.92) p=0.0128
	PS	0.41 (0.30, 0.56) p<0.0001
	Smoking history	0.51 (0.37, 0.70) p<0.0001
	Response to prior chemo	3.31 (1.22, 8.95) p=0.0184
4	Treatment	0.67 (0.49, 0.91) p=0.0110
	PS	0.41 (0.30, 0.56) p<0.0001
	Smoking history	0.51 (0.37, 0.70) p<0.0001
	Response to prior chemo	3.52 (1.28, 9.63) p=0.0145
	Number of prior lines	0.89 (0.65, 1.21) p=0.4589
5	Treatment	0.66 (0.48, 0.91) p=0.0097
	PS	0.40 (0.29, 0.55) p<0.0001
	Smoking history	0.55 (0.37, 0.82) p=0.0033
	Response to prior chemo	3.54 (1.29, 9.71) p=0.0140
	Number of prior lines	0.88 (0.65, 1.20) p=0.4201
	Gender	0.87 (0.59, 1.29) p=0.4947
6	Treatment	0.66 (0.48, 0.91) p=0.0100
	PS	0.40 (0.29, 0.55) p<0.0001
	Smoking history	0.56 (0.37, 0.84) p=0.0053
	Response to prior chemo	3.58 (1.30, 9.83) p=0.3581
	Number of prior lines	0.88 (0.65, 1.20) p=0.4239
	Gender	0.87 (0.59, 1.30) p=0.5029
	Histology	0.92 (0.67, 1.28) p=0.6313

Oriental, Non-smoking (n=141)

Model number	Variable	HR (95% CI) p-value
1	Treatment	0.37 (0.21, 0.63) p=0.0003
	PS	0.48 (0.28, 0.84) p=0.0098
2	Treatment	0.37 (0.22, 0.64) p=0.0004
	PS	0.49 (0.28, 0.86) p=0.0126
	Response to prior chemo	1.55 (0.21, 11.62) p=0.6679
3	Treatment	0.37 (0.21, 0.65) p=0.0005
	PS	0.49 (0.28, 0.87) p=0.0137
	Response to prior chemo	1.57 (0.21, 11.92) p=0.6657
	Number of prior lines	0.99 (0.56, 1.74) p=0.9589
4	Treatment	0.37 (0.21, 0.65) p=0.0005
	PS	0.50 (0.29, 0.88) p=0.0165
	Response to prior chemo	1.54 (0.20, 11.71) p=0.6780
	Number of prior lines	0.98 (0.56, 1.74) p=0.9531
	Gender	1.31 (0.66, 2.62) p=0.4410
5	Treatment	0.37 (0.21, 0.64) p=0.0004
	PS	0.49 (0.27, 0.86) p=0.0132
	Response to prior chemo	1.46 (0.19, 11.14) p=0.7180
	Number of prior lines	0.96 (0.54, 1.71) p=0.8901
	Gender	1.32 (0.66, 2.64) p=0.4294
	Histology	0.77 (0.39, 1.52) p=0.4530

Also, the adjusted treatment effect (all pre-specified covariates retained in the model) is shown in the following with the standard error estimated by sandwich estimator :

Hazard ratio using the Sandwich Estimator

Population	HR (95% CI) p-value
Never smoked	0.67 (0.49, 0.92) p=0.0125
Oriental	0.66 (0.48, 0.91) P=0.0110
Oriental never smoked	0.37 (0.20, 0.66) P=0.0007

The need for adjustment for important prognostic factors in clinical trials is stated in the literature. Hauck et al [2] report that failure to adjust for prognostic factors in the analysis of randomized trials leads to a loss of efficiency as well as bias in the treatment effect being estimated, recommending that analyses adjust for important prognostic covariates. Further, Akawaza et al [3] report that when a trial population is heterogeneous with several strongly prognostic factors, as is often the case in advanced cancer patients, a simple logrank test can yield misleading results and should not be used. Further, the authors note that the stratified logrank test may suffer some power loss when many prognostic factors need to be considered and the number of patients within stratum is small. To address these problems, the Cox regression methods are advised.

References:

- [1] ICH Topic E9. Statistical Principles for Clinical Trials. CPMP/ICH/363/96, 1996.
- [2] Hauck, WW., Anderson, S., and Marcus, SM. Should We Adjust for Covariates in Nonlinear Regression Analyses of Randomized Trials? *Controlled Clinical Trials*, 1998, 19:249–256
- [3] Akazawa, K., Nakamura, T. and Palesch, Y. Power of logrank test and Cox regression model in clinical trials with heterogeneous samples. *Statistics in Medicine*, 1997, 16: 583–597

Robustness of the subgroup analysis for non smokers, Oriental patients and non smoking Oriental patients:

In order to check the robustness of findings in the subsets of never smokers, Oriental patients and Oriental never smokers, a resampling procedure was adopted as follows:

For each subset, a given number of patients were sampled with replacement from Iressa and placebo treated patients on a 2:1 basis to reflect the trial randomization. The hazard rate amongst the sampled patients was then calculated for Iressa and placebo and the hazard ratio computed. This procedure was repeated 1000 times. The mean and spread of the resulting (log) hazard ratios was then calculated. The results are shown in Table 1.

Table 1. Results of resampling simulations in never smokers, Oriental patients and Oriental never smokers.

Subset	N ^a resampled (Iressa:placebo)	HR ^b	HR 2.5 th percentile	HR 97.5 th percentile
Oriental non Smokers (N=141)	20:10	0.355 ^c	0.081	1.283
	40:20	0.361	0.138	0.839
	60:30	0.361	0.171	0.763
	Full resampling ^d	0.368	0.208	0.647
Orientals (N=342)	20:10	0.671	0.215	2.002
	50:25	0.681	0.339	1.368
	100:50	0.662	0.413	1.051
	150:75	0.661	0.458	1.002
	Full resampling	0.664	0.486	0.896
Non Smokers (N=375)	20:10	0.660	0.213	2.289
	50:25	0.670	0.340	1.260
	100:50	0.674	0.413	1.120
	150:75	0.673	0.438	1.001
	200:100	0.679	0.464	0.981
	Full resampling	0.681	0.496	0.930

^a 1000 resamples per row.

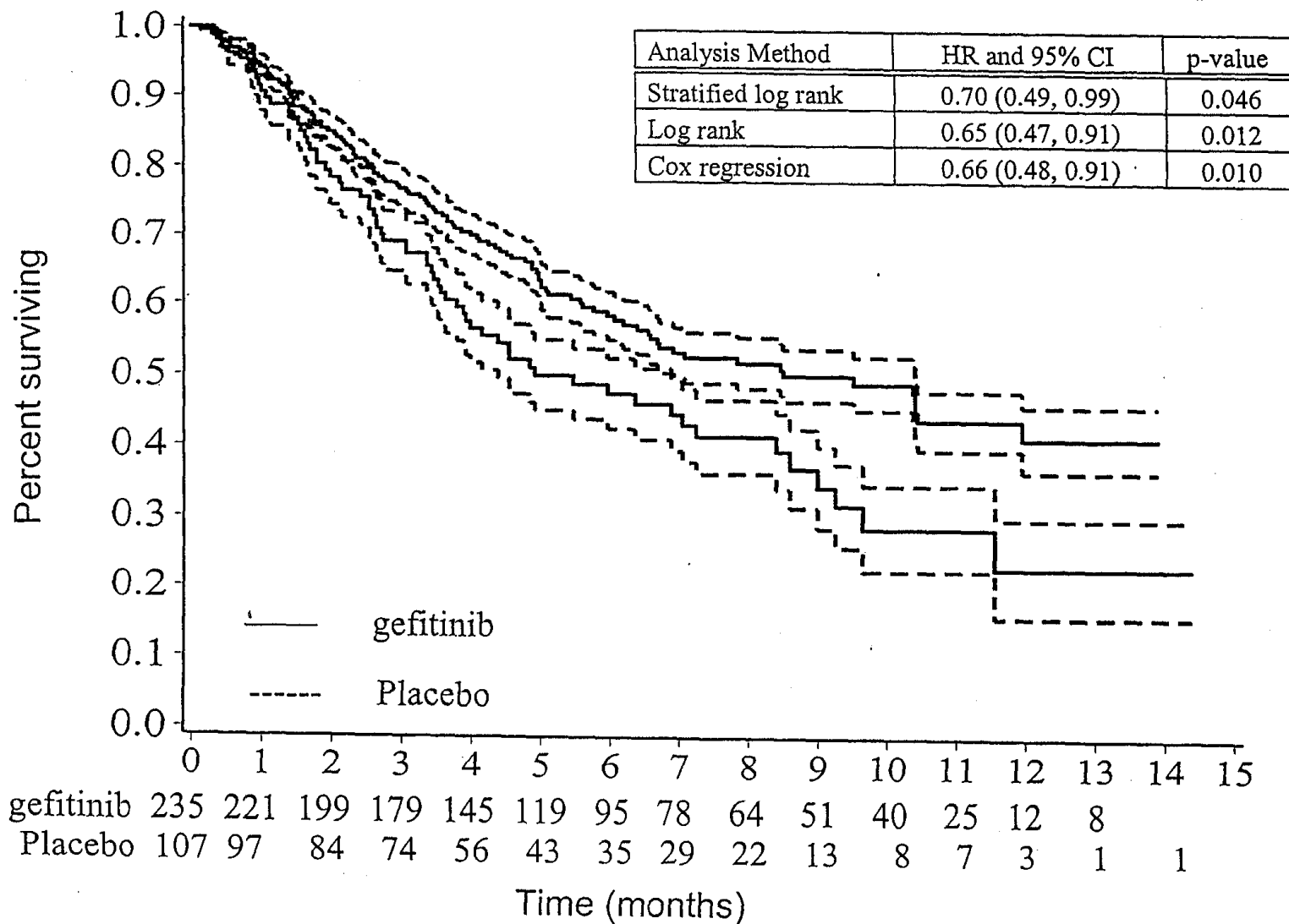
^b Hazard ratio.

^c Only 998 resamples returned a hazard ratio estimate; in two samples there were no deaths in the Iressa arm due to the small sample size and a hazard ratio could not be calculated.

^d Full resampling with replacement.

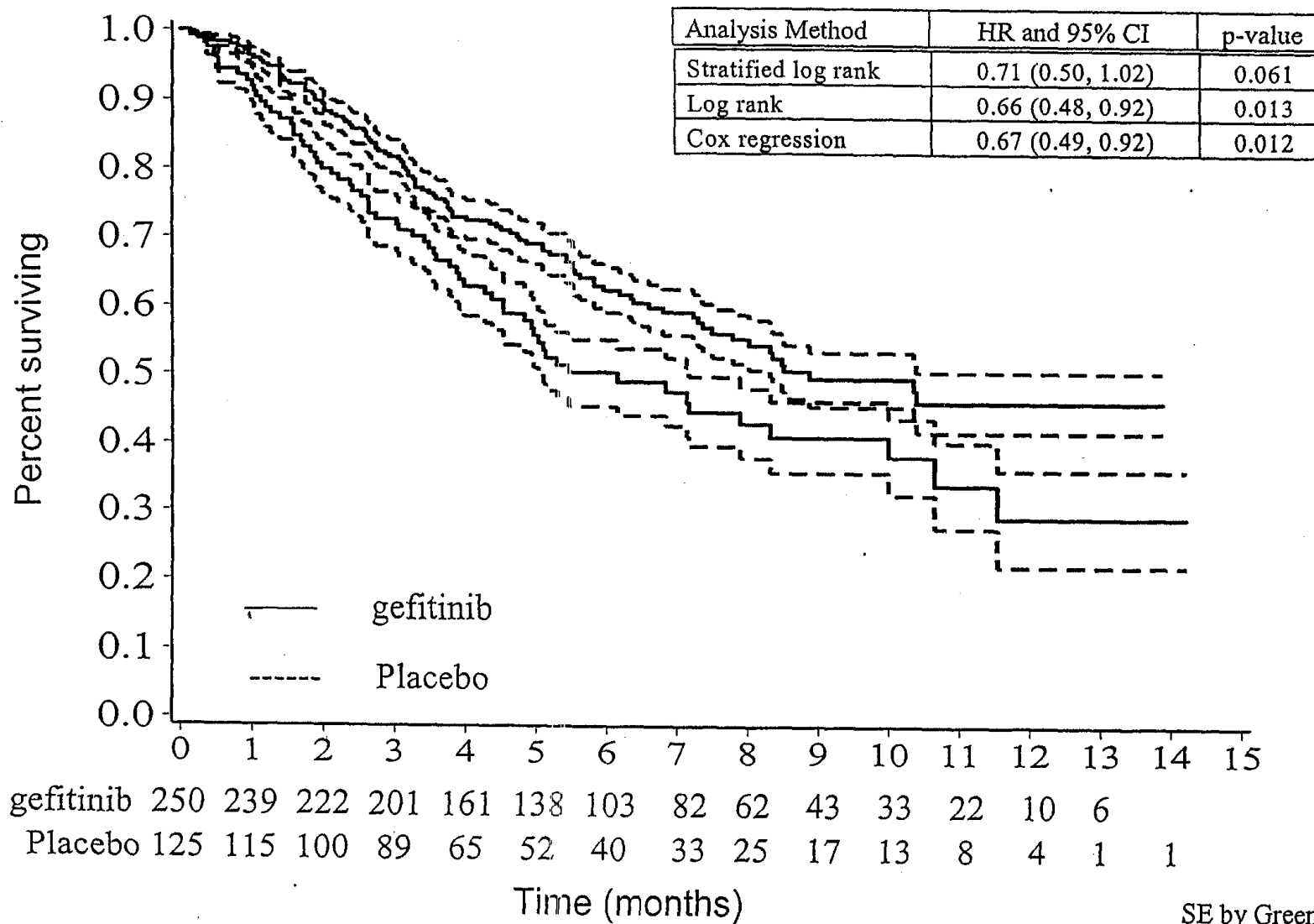
The resampling results show that the findings in non smokers, Oriental and Oriental non smokers are robust. Even with small sample sizes, a treatment effect in favour of Iressa treated patients is evident. Full resampling confirms statistical significance in all three subsets.

Survival +/- SE: Orientals



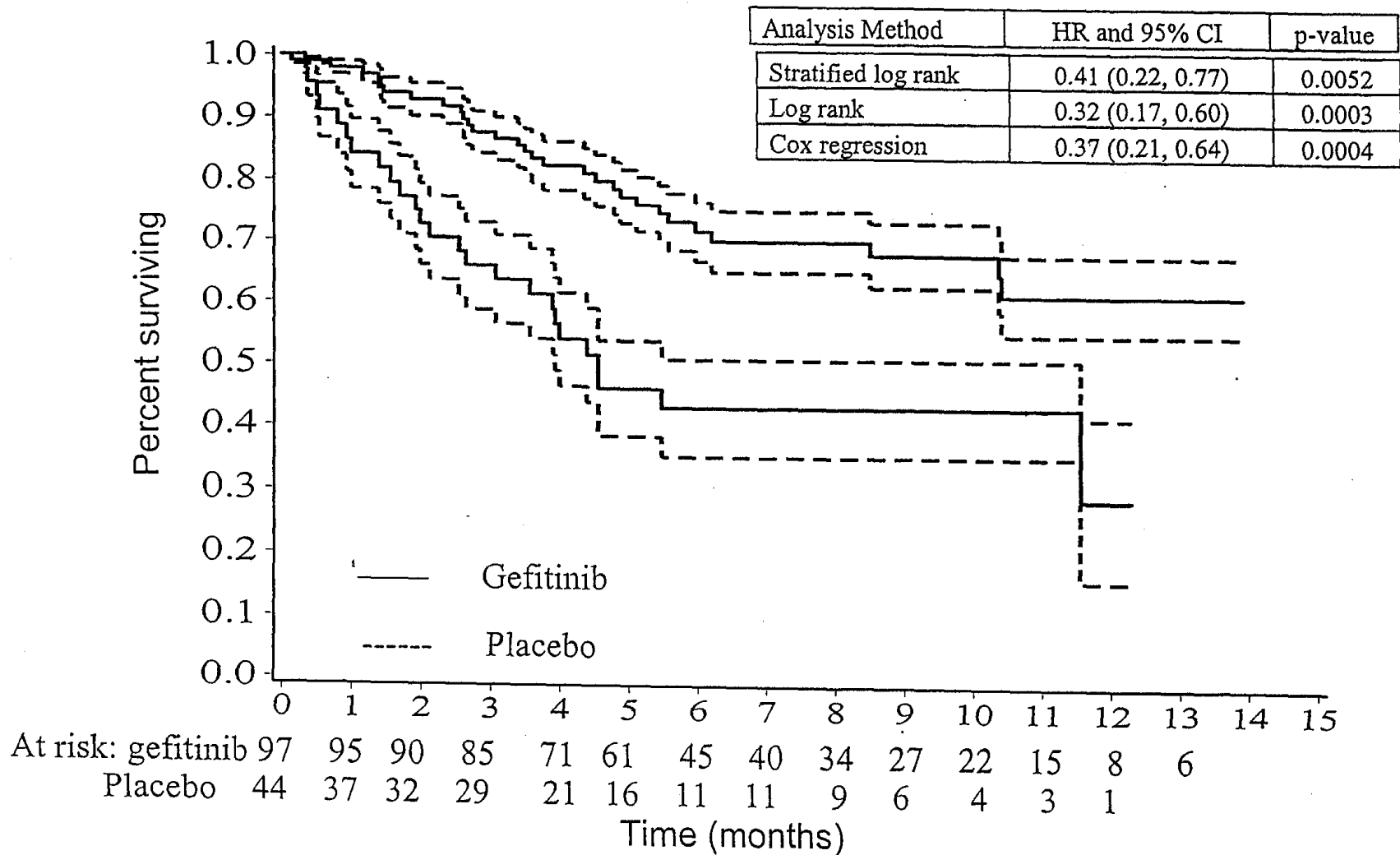
SE by Greenwoods formula

Survival +/- SE: Non-smokers



SE by Greenwoods formula

Survival +/- SE : Oriental non-smokers



東洋人及び非喫煙者の患者背景に関する資料

Within the Non Oriental patient subset, demography was well balanced at baseline

	All patients		Never smoked		Ever smoked		
	Gefitinib	Placebo	Gefitinib	Placebo	Gefitinib	Placebo	
	N=894	N=456	N=153	N=81	N=741	N=375	
Age (median)	62 years	61 years	62 years	63 years	62 years	61 years	
Age < 65 years	61%	62%	56%	54%	62%	64%	
Age ≥ 65 years	39%	38%	44%	46%	38%	36%	
Male	69%	69%	34%	37%	77%	76%	
PS 0-1	64%	68%	66%	64%	63%	69%	
Never smoked	17%	18%	100%	100%	0	0	
2nd line	47%	45%	48%	52%	47%	44%	
Refractory	89%	90%	86%	85%	89%	90%	
Intolerant	11%	10%	13%	12%	11%	9%	
Adenocarcinoma histology	44%	45%	71%	62%	38%	41%	
Time from diagnosis to randomisation	<6 months	26%	23%	35%	21%	24%	24%
	6-12 months	36%	40%	29%	42%	38%	39%
	> 12 months	37%	37%	35%	37%	38%	37%
Best response to prior chemotherapy	CR/PR	17%	19%	11%	24%	18%	18%
	SD	37%	38%	42%	39%	36%	38%
	PD/NE	46%	43%	46%	33%	45%	44%

Within the Oriental patient subset, demography was well balanced at baseline

		All patients		Never smoked		Ever smoked	
		Gefitinib	Placebo	Gefitinib	Placebo	Gefitinib	Placebo
		N=235	N=107	N=97	N=44	N=138	N=63
Age (median)		61 years	61 years	58 years	55 years	64 years	64 years
Age < 65 years		59%	64%	68%	82%	53%	52%
Age >= 65 years		41%	36%	32%	18%	47%	48%
Male		60%	60%	21%	27%	87%	83%
PS 0-1		72%	72%	72%	70%	72%	73%
Never smoked		41%	41%	100%	100%	0	0
2nd line		54%	65%	52%	64%	55%	65%
Refractory		93%	97%	94%	100%	93%	95%
Intolerant		7%	3%	6%	0	7%	5%
Adenocarcinoma histology		64%	64%	77%	84%	55%	49%
Time from diagnosis to randomisation	<6 months	25%	32%	22%	41%	27%	25%
	6-12 months	40%	38%	38%	34%	41%	41%
	> 12 months	35%	30%	40%	25%	32%	33%
Best response to prior chemotherapy	CR/PR	21%	21%	22%	16%	21%	24%
	SD	34%	32%	35%	32%	34%	32%
	PD/NE	44%	48%	43%	52%	45%	44%

癌の組織型、性別、喫煙歴の別による有効性

癌の組織型、性別、喫煙歴の別によるイレッサの有効性の日本及びアジア地域での報告についてを、以下の表にまとめた。

Fukuoka et al (IDEAL1 試験日本人サブセット)

	奏効	非奏効	病勢コントロール	非病勢コントロール
女性	6	10	13	3
男性	8	27	23	12
腺癌	13	25	30	8
非腺癌	1	12	6	7

[奏効率/性別] 感度 (奏効例に占める女性の割合) 6/14 (42.9%)
 特異度 (非奏効例に占める男性の割合) 27/37 (73.0%)
 [奏効率/組織型] 感度 (奏効例に占める腺癌の割合) 13/14 (92.9%)
 特異度 (非奏効例に占める非腺癌の割合) 12/37 (32.4%)
 [病勢コントロール率/性別] 感度 (病勢コントロール例に占める女性の割合) 13/36 (36.1%)
 特異度 (非病勢コントロール例に占める男性の割合) 12/15 (80%)
 [病勢コントロール率/組織型] 感度 (病勢コントロール例に占める腺癌の割合) 30/36 (83.3%)
 特異度 (非病勢コントロール例に占める非腺癌の割合) 7/15 (46.7%)

Takano et al

	奏効	非奏効
女性	17	15
男性	15	51
腺癌	31	50
非腺癌	1	16
非喫煙者	20	12
喫煙者	12	54

[性別] 感度 (奏効例に占める女性の割合) 17/32 (53.1%)
 特異度 (非奏効例に占める男性の割合) 51/66 (77.3%)
 [組織型] 感度 (奏効例に占める腺癌の割合) 31/32 (96.9%)
 特異度 (非奏効例に占める非腺癌の割合) 16/66 (24.2%)
 [喫煙歴] 感度 (奏効例に占める非喫煙者の割合) 20/32 (62.5%)
 特異度 (非奏効例に占める喫煙者の割合) 54/66 (81.8%)

Kaneda et al

	奏効	非奏効
女性	14	23
男性	6	58
腺癌	20	61
非腺癌	0	20
非喫煙者	15	40
喫煙者	5	41

- [性別] 感度 (奏効例に占める女性の割合) 14/20 (70%)
 特異度 (非奏効例に占める男性の割合) 58/81 (71.6%)
- [組織型] 感度 (奏効例に占める腺癌の割合) 20/20 (100%)
 特異度 (非奏効例に占める非腺癌の割合) 20/81 (24.7%)
- [喫煙歴] 感度 (奏効例に占める非喫煙者の割合) 15/20 (75%)
 特異度 (非奏効例に占める喫煙者の割合) 41/81 (50.6%)

Hotta et al

	奏効	非奏効
女性	6	13
男性	9	28
腺癌	13	32
非腺癌	2	9
喫煙量 BI < 600	8	20
喫煙量 BI ≥ 600	7	21

BI: Brinkman Index

- [性別] 感度 (奏効例に占める女性の割合) 6/15 (40%)
 特異度 (非奏効例に占める男性の割合) 28/41 (68.3%)
- [組織型] 感度 (奏効例に占める腺癌の割合) 13/15 (86.7%)
 特異度 (非奏効例に占める非腺癌の割合) 9/41 (22.0%)
- [喫煙歴] 感度 (奏効例に占める喫煙量 BI < 600 の割合) 8/15 (53.3%)
 特異度 (非奏効例に占める喫煙量 BI ≥ 600 の割合) 21/41 (51.2%)

Kim et al

	奏効	非奏効
女性	10	9

男性	7	10
非喫煙者	11	9
喫煙者	6	10

【性別】 感度（奏効例に占める女性の割合） 10/17 (58.8%)
 特異度（非奏効例に占める男性の割合） 10/19 (52.6%)
 【喫煙歴】 感度（奏効例に占める非喫煙者の割合） 11/17 (64.7%)
 特異度（非奏効例に占める喫煙者の割合） 10/19 (52.6%)

Katakami et al

	奏効	非奏効
女性	17	17
男性	10	30

【性別】 感度（奏効例に占める女性の割合） 17/27 (63.0%)
 特異度（非奏効例に占める男性の割合） 30/47 (63.8%)

Niho et al

	奏効	非奏効
女性	9	7
男性	3	21
腺癌	11	19
非腺癌	1	9
非喫煙者	6	2
喫煙者	6	26

【性別】 感度（奏効例に占める女性の割合） 9/12 (75%)
 特異度（非奏効例に占める男性の割合） 21/28 (75%)
 【組織型】 感度（奏効例に占める腺癌の割合） 11/12 (91.7%)
 特異度（非奏効例に占める非腺癌の割合） 9/28 (32.1%)
 【喫煙歴】 感度（奏効例に占める非喫煙者の割合） 6/12 (50%)
 特異度（非奏効例に占める喫煙者の割合） 26/28 (92.9%)

Goto et al

	奏効	非奏効
女性	36	45
男性	24	117
腺癌	56	110

非腺癌	4	52
非喫煙者	42	35
喫煙者	18	127

[性別]	感度 (奏効例に占める女性の割合)	36/60 (60%)
	特異度 (非奏効例に占める男性の割合)	117/162 (72.2%)
[組織型]	感度 (奏効例に占める腺癌の割合)	56/60 (93.3%)
	特異度 (非奏効例に占める非腺癌の割合)	52/162 (32.1%)
[喫煙歴]	感度 (奏効例に占める非喫煙者の割合)	42/60 (70%)
	特異度 (非奏効例に占める喫煙者の割合)	127/162 (78.4%)

引用文献

1. Multi-Institutional Randomized Phase II Trial of Gefitinib for Previously Treated Patients With Advanced Non-Small-Cell Lung Cancer
Fukuoka et al, Journal of Clinical Oncology, 21(12), 2237-2246 (2003)
2. Risk factors for interstitial lung disease and predictive factors for tumor response in patients with advanced non-small cell lung cancer treated with gefitinib
Takano et al, Lung Cancer, 45, 93-104, 2004
3. Retrospective analysis of the predictive factors associated with the response and survival benefit of gefitinib in patients with advanced non-small-cell lung cancer
Kaneda et al, Lung Cancer, 46, 247-254, 2004
4. Effect of gefitinib ('Iressa', ZD1839) on brain metastases in patients with advanced non-small-cell lung cancer
Hotta et al, Lung Cancer, 46, 255-261, 2004
5. Dominant papillary subtype is a significant predictor of the response to Gefitinib in adenocarcinoma of the lung
Kim et al, Clin Cancer Research, 10, 7311-7317, 2004
6. A retrospective analysis of the outcome of patients in advanced recurrent adenocarcinoma of the lung who have received gefitinib after treatment of platinum-based regimen

Katakami et al, ASCO 2003, Abs 2679 + presentation

7. First-line single agent of gefitinib in patients with advanced non-small cell lung cancer (NSCLC): A Phase II study

Niho et al, ASCO 2004, Abs 7059 + presentation

8. Association of multiple pulmonary metastases with response to gefitinib in patients with non-small cell lung cancer

Goto et al, ASCO 2004, Abs 7098 + presentation