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-adeno	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-adeno	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 tremanet 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 if 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

サブグループ解析の頑健性に関する資料

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 2.5th percentile	HR 97.5th 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.

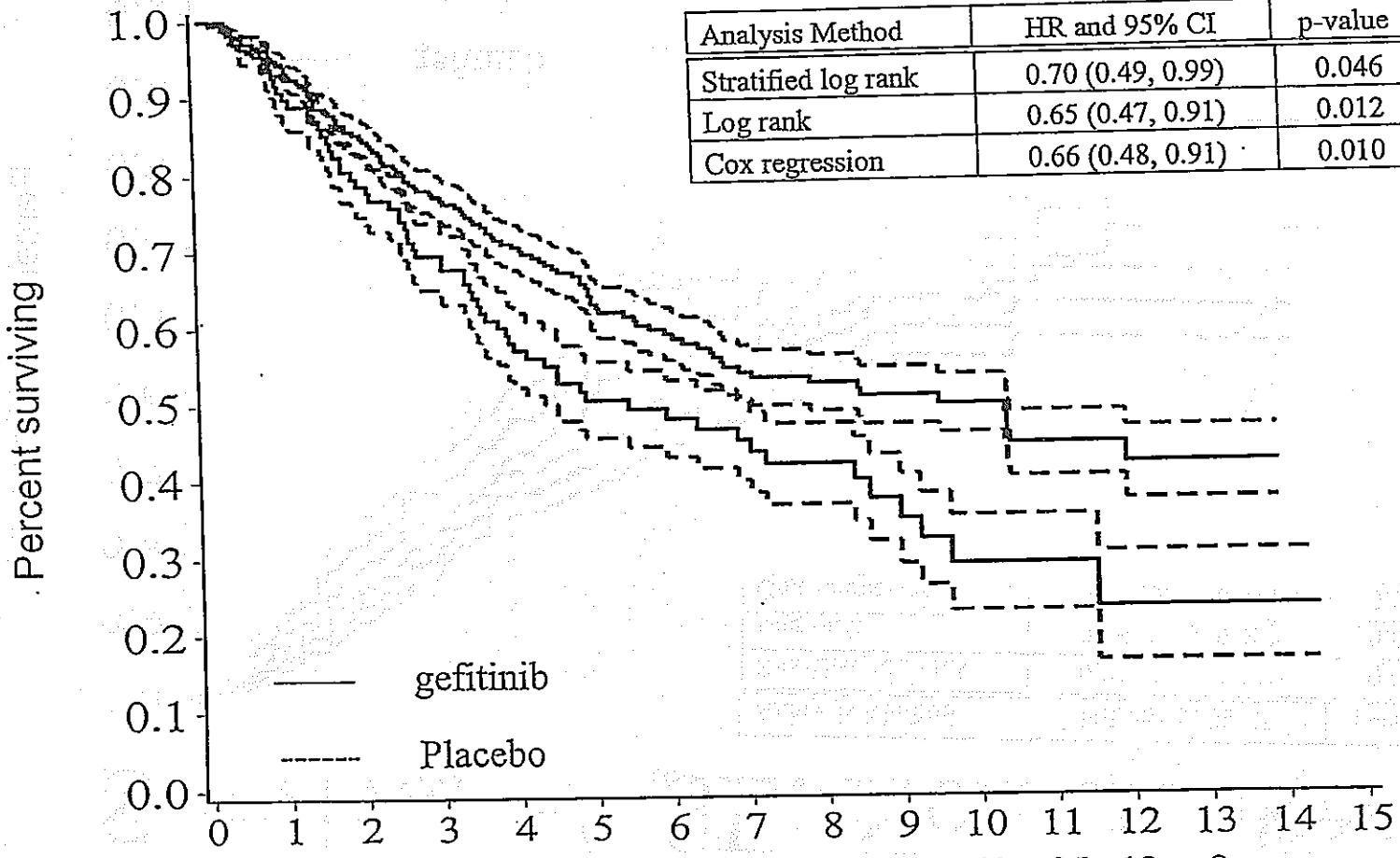
[c] Only 998 resamples returned a hazard ratio estimate; in two samples there were no deaths in the Iressa arm due to the small sample size and a hazard ratio could not be calculated.

[d] Full resampling with replacement.

The resampling results how 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

Analysis Method	HR and 95% CI	p-value
Stratified log rank	0.70 (0.49, 0.99)	0.046
Log rank	0.65 (0.47, 0.91)	0.012
Cox regression	0.66 (0.48, 0.91)	0.010



SE by Greenwoods formula