

The vertical bars are hazard ratio estimates +/- SE for a simple categorisation of the data in to [1] zero smoke exposure (N=141), [2] 0 to 20 pack years smoke exposure (N=65), [3] 20 to 40 pack years smoke exposure (N=51), [4] 40 to 60 pack years smoke exposure (N=28) and [5] greater than 60 years smoke exposure (N=39).

The difference in log likelihood between the Cox model with treatment as the only covariate and with smoking exposure and smoking exposure by treatment interaction was 4.645 on 2 degrees of freedom,  $p=0.10$ . The difference in log likelihood between the model with treatment as the only covariate and with smoking exposure and smoking exposure by treatment interaction with smoke exposure categorised as in [1]-[5] was 21.423 8 degrees of freedom,  $p=0.01$ .

Given the skewed distribution for smoke exposure, a better continuous model fit may be obtained by considering smoke exposure on a different scale. The results of an analysis looking at smoke exposure as a curvilinear continuous factor (i.e. at the square root of smoke exposure) are provided below:

## Analysis of survival by smoking exposure in Oriental patients

- Model

$$\text{Log (HR)} = \beta_1 + \beta_{12} \times \sqrt{\text{Smoke exposure}}$$

- $\beta_1 = -0.58784$

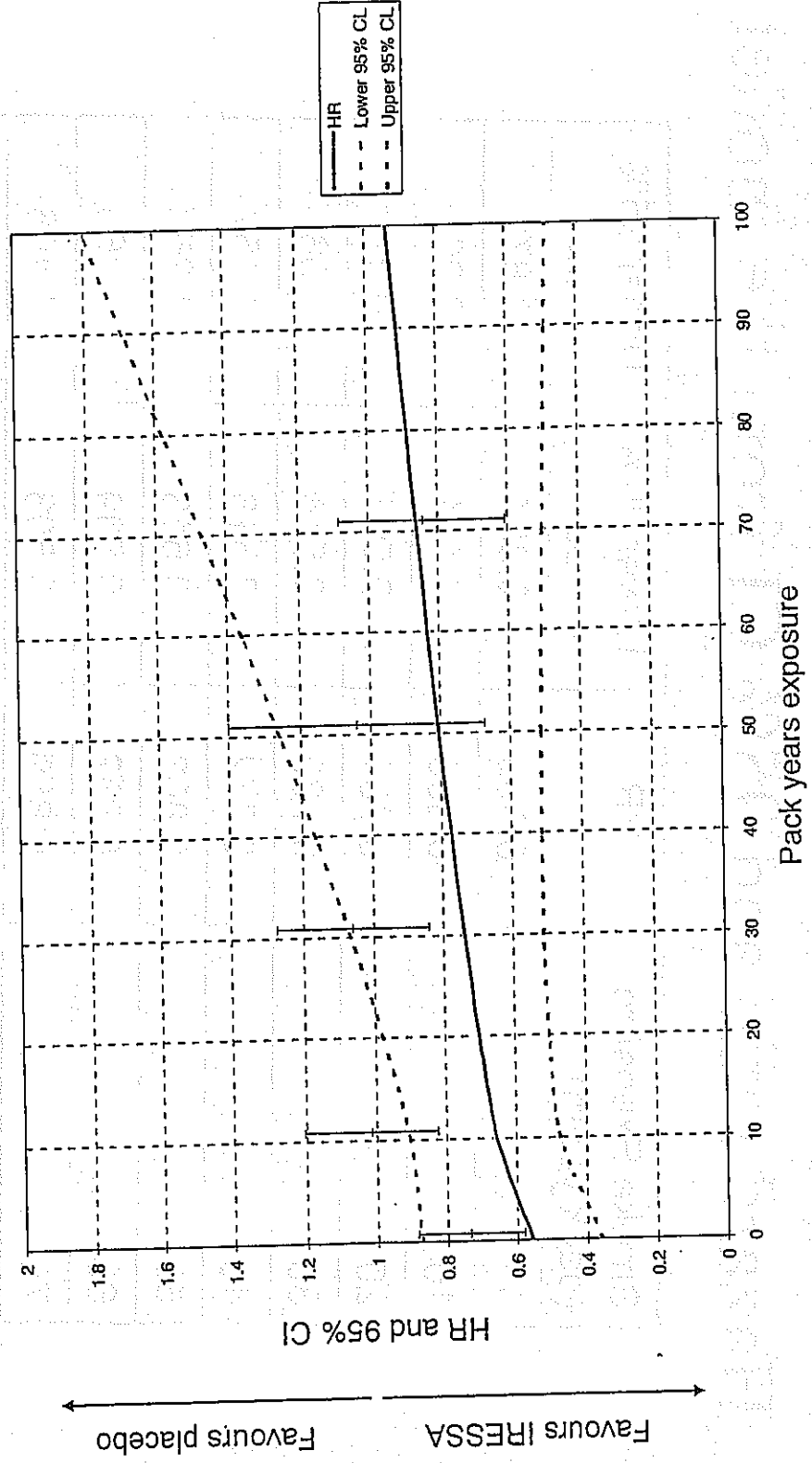
- $\beta_{12} = 0.052109$

- $\text{Var}(\beta_1) = 0.05318$

- $\text{Var}(\beta_{12}) = 0.002067$

- $\text{Cov}(\beta_1, \beta_{12}) = -0.00738$

# 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-ado	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