資料 No. 2-2

別添資料一覧

1. プロトコール（統計解析に関する部分の抜粋）
2. プロトコール作成日に関する資料
3. サブグループ解析の計画日に関する資料（統計解析計画書）
4. サブグループ解析の計画日に関する資料（社内メール及び解析プログラム）
5. 試験参加国及び症例数に関する資料
6. 症例の内訳に関する資料
7. 患者背景に関する資料
8. QoL 評価方法の説明に関する資料
9. 喫煙量と生存との関係に関する資料
10. サブグループ解析の妥当性に関する資料
11. サブグループ解析の頑健性に関する資料
12. 東洋人及び非喫煙者の患者背景に関する資料
13. 癌の組織型、性別、喫煙歴の別による有効性に関する資料
14. IDEAL1 試験における生存期間の探索的解析に関する資料
    （中川 和彦，内科 Vol.95 No.1（2005））
15. 申請資料概要（第Ⅱ相試験における奏効率）と ISEL 試験（第Ⅲ相試験における生存期間）の結果の関係に関する資料
16. 直近の化学療法に忍容でなかった患者における死亡例に関する資料
17. 重篤な有害事象、有害事象による死亡例、副作用による死亡例
18. ILD 症例に関する資料
19. 前回検討会時からの変更に関する資料
20. 直近の化学療法に忍容でなかった患者群の患者背景に関する資料
21. 東洋人/非東洋人・喫煙者/非喫煙者別のサブグループにおける調整因子毎の生存期間に関する資料

23 April 2004: Statistical Analysis Section of Protocol:

A DOUBLE BLIND, PLACEBO CONTROLLED, PARALLEL GROUP, MULTICENTRE, RANDOMISED, PHASE III SURVIVAL STUDY COMPARING ZD1839 (IRESSA...) (250MG TABLET) PLUS BEST SUPPORTIVE CARE VERSUS PLACEBO PLUS BEST SUPPORTIVE CARE IN PATIENTS WITH ADVANCED NSCLC WHO HAVE RECEIVED ONE OR TWO PRIOR CHEMOTHERAPY REGIMENS AND ARE REFRACTORY OR INTOLERANT TO THEIR MOST RECENT REGIMEN

6.4 Method of statistical analysis

6.4.1 Assessment of efficacy

The primary analysis population for survival will be the intention-to-treat. Survival will also be assessed in the per-protocol population to assess population sensitivity.

The primary analysis will compare the overall survival of ZD1839 to placebo amongst patients with adenocarcinoma. The treatment arms will be compared with a log-rank test stratified for the following factors: gender (male vs female), smoking history (never smoked vs current/former smoker), reason for prior chemotherapy failure (refractory vs intolerant), number of prior chemotherapy regimens (1 vs 2 regimens) and Performance Status (0,1 vs 2,3). If a significant difference is found then a secondary analysis comparing survival amongst all patients will be conducted in the same way. In this secondary analysis histology (adenocarcinoma vs other) would also be included as a factor. The significance level for the final analysis will be adjusted for the interim significance level. A secondary survival analysis using the proportional hazards model will also be conducted. The same factors used in the logrank test will be included as covariates. The hazard ratio (ZD1839: placebo) will be estimated together with its associated adjusted 95% confidence interval and p-value. Survival will be displayed graphically using a Kaplan-Meier plot.

The primary analysis population for the tumour response rate will be the evaluable-for response population. This endpoint will also be analysed in the intention-to-treat and per protocol populations to assess population sensitivity. The primary analysis population for time to treatment failure will be the intention-to-treat population. This endpoint will also be analysed in the per-protocol population to assess population sensitivity.

Time to treatment failure will be analysed using a proportional hazards model. The model will allow for the effect of treatment and will include the factors listed above as covariates. The hazard ratio (ZD1839: placebo) will be estimated together with its associated 95% confidence interval and p-value. Time to treatment failure will be displayed graphically using a Kaplan-Meier plot.

Objective response will be analysed using a logistic regression model. The model will allow for the effect of treatment and will include the factors listed above as covariates. The odds ratio for treatment will be estimated from the model along with its associated 95% CI. The response rate will be estimated for each treatment arm and an associated 95% confidence interval will be calculated for each arm as well as the difference between rates.

6.4.2 Assessment of tolerability

All patients who receive ZD1839/placebo will be included in the assessment of tolerability (evaluable for safety population). Tolerability will be assessed in terms of AE and laboratory data/vital signs that will be collected for all patients. At the end of the study, appropriate summaries of laboratory data/vital signs and AEs will be produced.

6.4.3 Assessment of quality of life

The following scores will be derived from the FACT-L questionnaire:

- The physical well-being (PWB), functional well-being (FWB), social well-being (SWB), and emotional well-being (EWB) score from the core FACT-L questionnaire
- The 7-item lung cancer subscale (LCS) total score
- The Trial Outcome Index (TOI) which is the sum of the PWB, FWB, and LCS scores
- The overall score for the questionnaire (FACT-L)

If 50% or less of the subscale items are missing, the subscale score will be divided by the number of non-missing items and multiplied by the total number of items on the subscale. If more than 50% of the items are missing, that subscale will be treated as missing. The reason for any missing data will be identified. If data is missing at random, the above techniques will be used. If there is evidence that the missing data is systematic, missing values will be handled to ensure that any possible bias is minimized.

Clinical Study Protocol Amendment No. 1
Study code ZD1839IL/0709

I agree to the terms of this protocol Amendment.

Study Code: ZD1839IL/0709

23/4/03 ..... MCardno .....

Date
(day month, year)

AstraZeneca Clinical Study Team Leader
Marianne Cardno
AstraZeneca, Alderley Park, UK

16(19)

I agree to the terms of this protocol Amendment.

Study Code: ZD1839IL/0709

Centre No.: 1122

29.4.03

Date
(day month, year)

.....

International Co-ordinating Investigator
Professor Nick Thatcher MBChir, FRCP, PhD
Professor of Medical Oncology
Christie Hospital, Manchester, UK

I agree to the terms of this protocol Amendment.

Study Code: ZD18391L/0709

Centre No.: 1122

29.4.03

.....

Date
(day month, year)

.....

Principal investigator
Professor Nick Thatcher MBChir, FRCP, PhD
Professor of Medical Oncology
Christie Hospital, Manchester, UK

AstraZeneca

Addendum to Statistical Analysis Plan

Study code: 1839IL/0709 / D7913C00709

Version no: Final

Date: 9th December 2004

A DOUBLE BLIND, PLACEBO CONTROLLED, PARALLEL GROUP, MULTICENTRE, RANDOMISED, PHASE III SURVIVAL STUDY COMPARING ZD1839 (IRESSA™) (250MG TABLET) PLUS BEST SUPPORTIVE CARE VERSUS PLACEBO PLUS BEST SUPPORTIVE CARE IN PATIENTS WITH ADVANCED NSCLC WHO HAVE RECEIVED ONE OR TWO PRIOR CHEMOTHERAPY REGIMENS AND ARE REFRACTORY OR INTOLERANT TO THEIR MOST RECENT REGIMEN

Study Statistician	Kristine Pemberton	9 Dec 04 Date
Worldwide Statistical Lead	Kevin Carroll	10/12/04 Date
Worldwide Medical Lead	Nick Botwood	9th Dec 2004 Date

サブグループ解析の計画日に関する資料
(社内メール及び解析プログラム)

別添資料 4-1

差出人: Pemberton, Kristine A
送信日時: 2004年12月11日土曜日 0:55
宛先: Carroll, Kevin J
件名: updated programs and formats


Z2.SAS


T05C.SAS


T05A2.SAS


T05B.SAS


T05A1.SAS


T05D.SAS


T05E.SAS


formats.sas7bcat


Z1.SAS


X1.sas


Z2A.sas

made a few corrections and changes to the survival analysis programs - updated ones attached,
regards,
Kristine

Final SAS program Z2A, 10th December 2004

```
data indata;
  set INDATA;
  if trtrand=0 then trtrands = 1;   ***create variable trtrands which is 1 for Iressa *;
  else trtrands=0;
  if cxdoce=1 then do;          subgroup=1; output; end;
  else do;                      subgroup=2; output; end;
  if agegrp in (1,2) then do;   subgroup=3; output; end;
  else do;                      subgroup=4; output; end;
  if diaggrp=1 then do;         subgroup=5; output; end;
  else if diaggrp=2 then do;    subgroup=6; output; end;
  else if diaggrp=3 then do;                    subgroup=7; output; end;
  if race=3 then do;            subgroup=8; output; end;
  else do;                      subgroup=9; output; end;
  if bestprev in (1,2) then do;subgroup=10; output; end;
  else if bestprev in (4) then do; subgroup=11; output; end;
  else if bestprev in (5,6) then do;       subgroup=12; output; end;
  subgroup=13; output;                  **** to produce all patient analysis;
 run;

proc format;
  value subgrouf 1 = 'Prior taxotere'
                 2 = 'No prior taxotere'
                 3 = '<65 yrs'
                 4 = '>= 65 yrs'
                 5 = '<6 mos'
                 6 = '6-12'
                 7 = '>12'
                 8 = 'Oriental'
                 9 = 'Caucasian/black/other'
                 10= 'CR/PR'
                 11= 'SD'
                 12= 'PD/NE'
                                ;
proc phreg data=indata;
ODS OUTPUT PARAMETERESTIMATES = ESTS (where=( variable='TRTRANDS') KEEP=SUBGROUP variable HAZARDRA HRLOWERC
HRUPPERC);
 model survdays*censor_d(0)= trtRANDs  smkhist cxprog totreggp nsex histol psgroup/ RL ALPHA=0.05;
 by subgroup;
run;
```

試験参加国及び症例数に関する資料

別添資料 5

ISEL 試験参加国

承認前に参加した国

国名	症例数
フィリピン	46
カナダ	10
タイ	82
インド	77
ロシア	35

承認後に参加した国

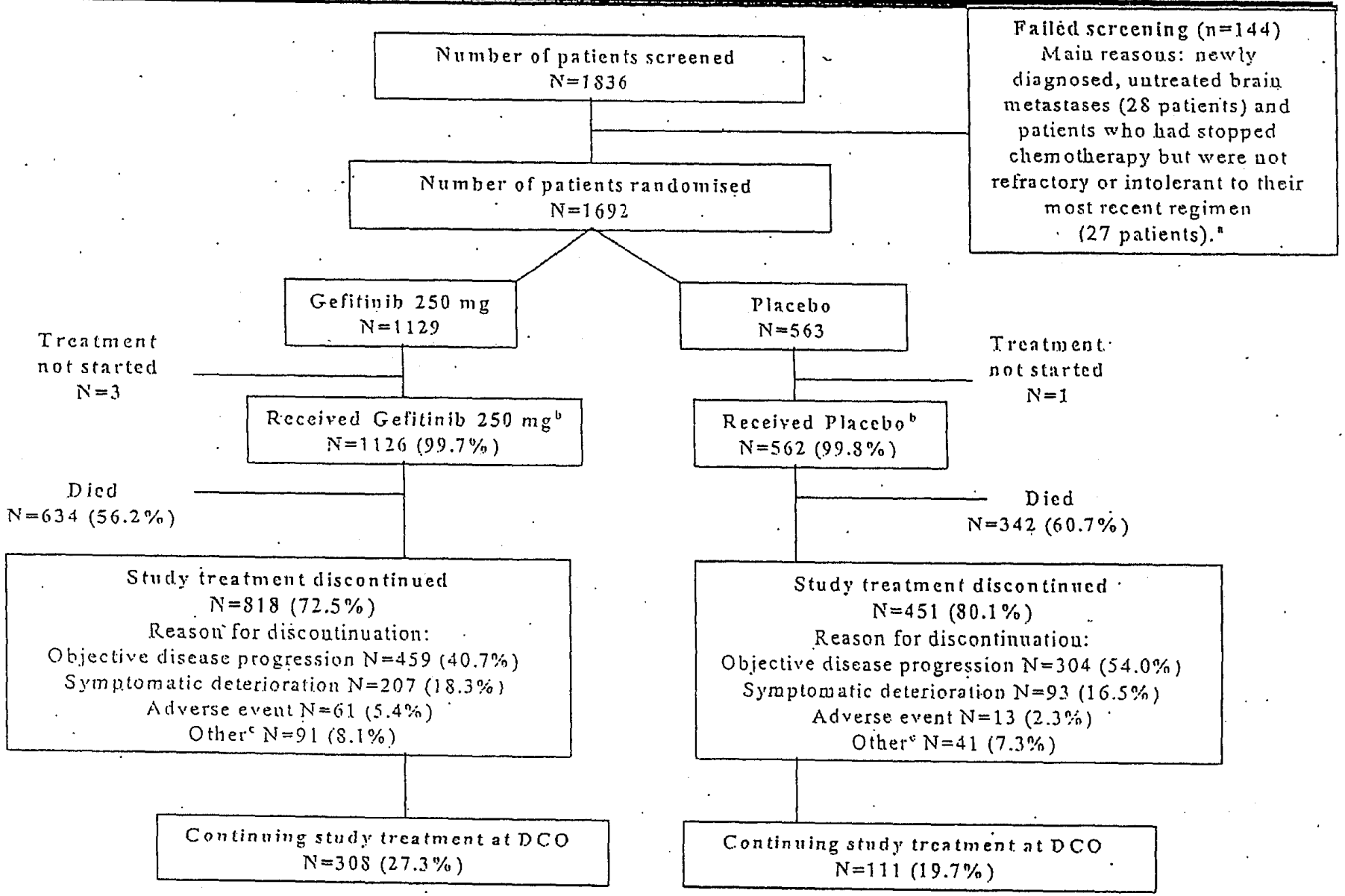
国名	症例数
オーストラリア	40
台湾	108
アルゼンチン	43
シンガポール	51
マレーシア	40
メキシコ	37

未承認

国名	症例数	国名	症例数
スロバキア	69	ブラジル	163
ブルガリア	78	ポーランド	67
ドイツ	131	トルコ	103
ハンガリー	107	アイルランド	2
オランダ	70	ギリシャ	9
ルーマニア	92	ラトビア	10
英国	110	リトアニア	7
ノルウェー	48	エストニア	16
スウェーデン	41		

Patient disposition

Status of all patients as of data cut-off



Demography

	Iressa N=1129	Placebo N=563
Age (median)	62 years	61 years
Male	67%	67%
PS 0-1	65%	69%
Never smoked	22%	22%
Caucasian	75%	77%
Oriental	21%	19%

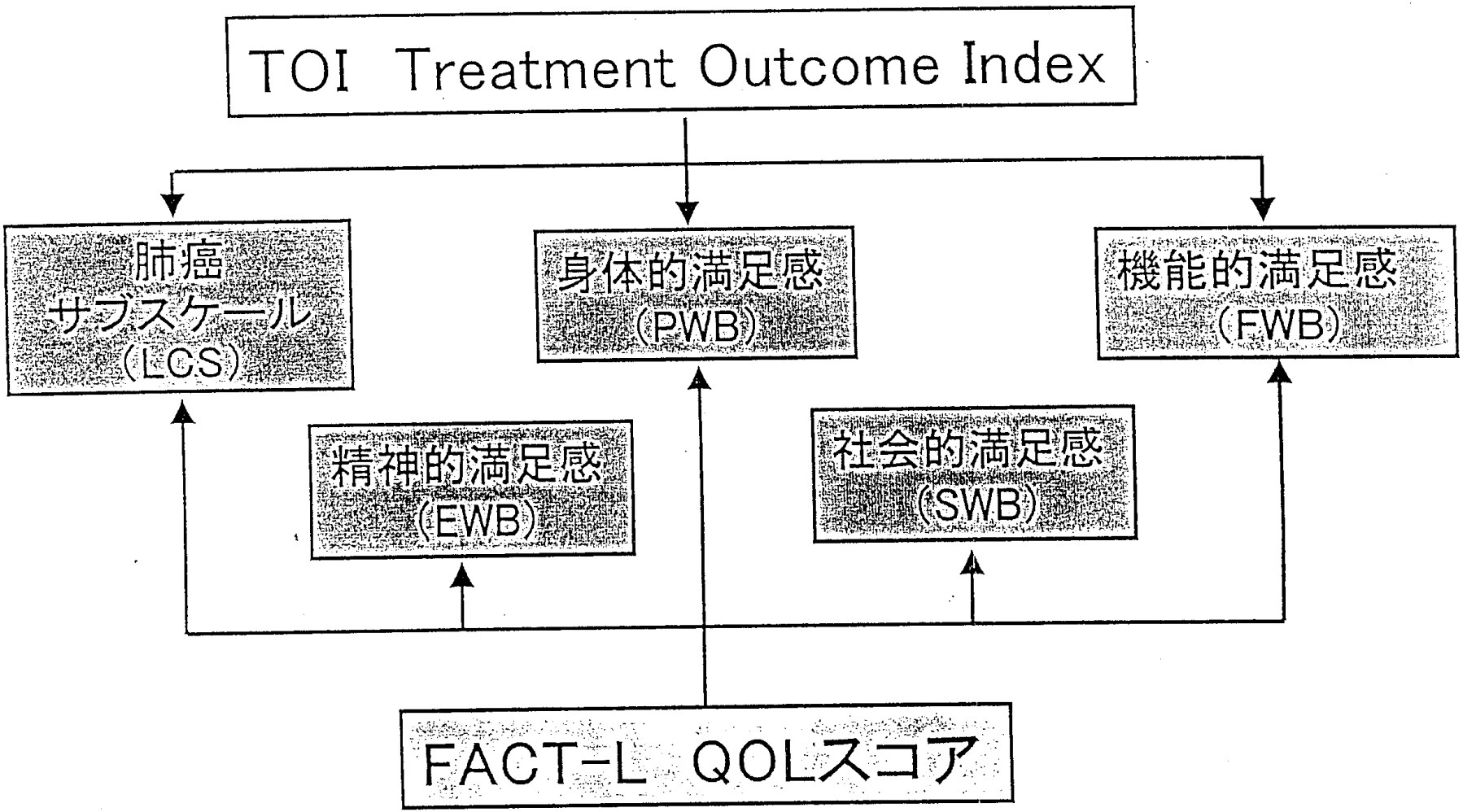
Tumour burden

		Iressa N=1129	Placebo N=563
Histology	Adenocarcinoma	48%	48%
	Squamous cell carcinoma	35%	33%
Time from diagnosis to randomisation	< 6 months	26%	25%
	6-12 months	37%	39%
	> 12 months	37%	36%
Stage at diagnosis	IIIB	34%	30%
	IV	48%	50%
Metastatic disease		79%	80%

Prior cancer therapy

		Iressa N=1129	Placebo N=563
2nd line		49%	49%
Refractory to prior chemotherapy		90%	91%
Received prior platinum		96%	96%
Received prior platinum and docetaxel		27%	28%
Best response to prior chemotherapy	CR/PR	18%	19%
	SD	37%	37%
	PD/NE	45%	44%

FACT-L・TOI・LCS



【LCS】

肺癌ｻﾌﾞｽｹｰﾙ(LCS)は、肺癌患者用のQOL 調査票であるFACT- L に含まれる設問のうち、肺癌の症状に関する7項目を抜粋したものである。息切れ・体重減少・思考の明瞭さ・咳・食欲・胸苦しさ・呼吸のしやすさに関する7 つの設問から成る。

それぞれの設問について、患者自身が5 段階で評価を行う。その評価を0 ～4 にｽｺｱ化し、その総和をLCS ｽｺｱとする。LCS ｽｺｱの幅は0 ～28 点であり、点数が高いほど、患者の状態が良いことを示す1)2)。

LCS の臨床的意義については、ECOG の無作為比較試験においても、検討されている。ECOG5592 では、化学療法にてCR ・PR が得られた症例では、治療開始12 週後のLCS ｽｺｱが平均で2.4ﾎﾟｲﾝﾄ上昇したのに対し、PD の症例では改善は認められなかった。また、早期に病態の進行が認められた症例と、病態の進行までに時間を要した症例とでは、LCS ｽｺｱの変動に3.1 ﾎﾟｲﾝﾄの差が認められた。この結果より、LCS ｽｺｱで2 ～3 ﾎﾟｲﾝﾄの変動があれば、臨床的に意義があることが示唆されている2)。

FACT- L の日本語版(LCS を含む)については、文献3)に掲載されている。

【FACT- L】

FACT- L は44 個の設問より成る質問票であり、大きく分けて5 つの要素より成る。すなわち、全身状態に関連する身体的満足度／機能的満足度／精神的満足度／社会的満足度の4 つの要素、および肺癌の症状に関連する肺癌ｻﾌﾞｽｹｰﾙ(LCS)である。

なお、TOI(Trial Outcome Index)は、FACT- L の5 要素のうち、身体的満足度、機能的満足度、肺癌ｻﾌﾞｽｹｰﾙの3 要素より成り、QOL の指標として、臨床試験での使用が推奨されている。

引用文献

1) Cella, D. F. : Lung Cancer, 12, 199- 220(1995)
2) Cella, D. : Journal of Clinical Epidemiology, 55, 285- 295(2002)
3) 小林国彦 : QOL 評価法ﾏﾆｭｱﾙ(ｲﾝﾀｰﾒﾃﾞｨｶ), 138- 149(2001)

Validity of analysis on Hazard ratio as a function of smoke exposure in Oriental patients:

All Oriental subjects are used in this analysis. The curve results from a Cox regression analysis where terms are fitted for randomized treatment, smoke exposure (a, being the number of pack smoked per day multiplied by the number of years smoked) and randomized treatment by smoke exposure interaction. Non smokers were included with zero pack year exposure. To avoid unnecessary loss of information, smoke exposure was not split into arbitrary categories but rather was fitted as a continuous variable.

The model fitted is therefore as follows

$$\lambda_0(t)e^{\beta_1 X+\beta_2 S+\beta_{12} XS}$$

Where $\lambda_0(t)$ is the baseline hazard, being the same for both treatments, x is the treatment indicator, being 1 for Iressa, 0 for placebo and S denotes smoking exposure in pack years. In terms of the parameters, β_1 relates to treatment, β_2 relates to smoking exposure and β_{12} relates to treatment by smoking exposure interaction.

The log hazard ratio, Iressa to placebo, as a function of smoke exposure is therefore given by

$$\text{Log (HR)} = \beta_1 + \beta_{12}S$$

And the estimated variance of log hazard ratio is given by

$$\text{Variance Log (HR)} = \text{Var}(\beta_1) + S^2\,\text{Var}(\beta_{12}) + 2S\,\text{Cov}(\beta_1,\beta_{12})$$

Hence, the parameter estimates and their covariance matrix can then used to plot the hazard ratio, Iressa: placebo, and its 95% CI as a function of smoke exposure. Results of the analysis are given below:

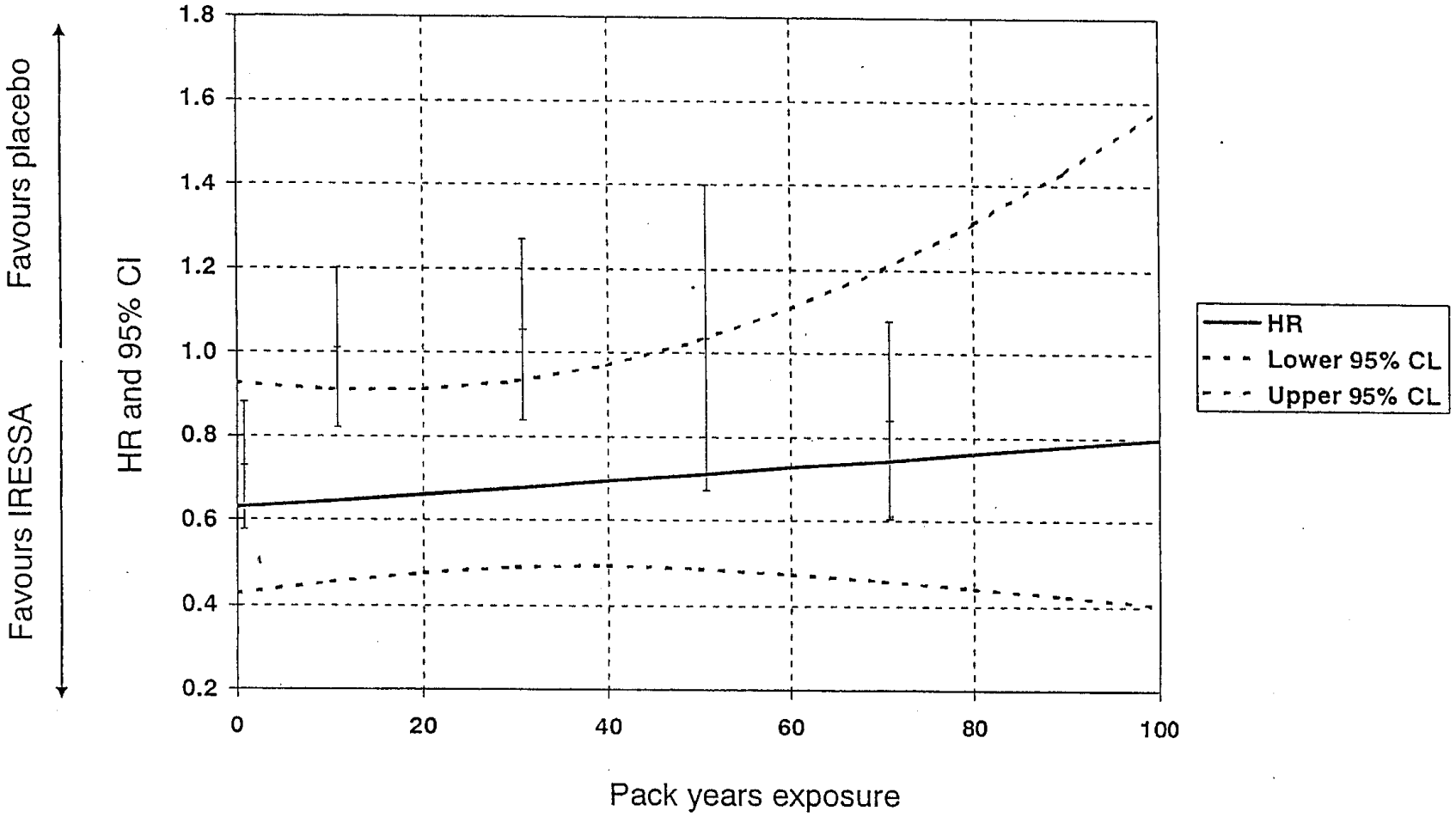
Analysis of survival by smoking exposure in Oriental patients

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

- $\beta_1 = -0.46386$
  $\beta_{12} = 0.002372$

- Var (β_1) = 0.03895
  Var (β_{12}) = 0.000017571
  Cov (β_1, β_{12}) = -0.00046396

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	0.629	0.427	0.926
10	0.644	0.455	0.911
20	0.659	0.477	0.912
30	0.675	0.490	0.931
40	0.691	0.493	0.971
50	0.708	0.487	1.030
60	0.725	0.475	1.107
70	0.742	0.459	1.200
80	0.760	0.441	1.310
90	0.778	0.422	1.437
100	0.797	0.402	1.580

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

- $\beta_1 = -0.58784$
- $\beta_{12} = 0.052109$

- Var (β_1) = 0.05318
  Var (β_{12}) = 0.002067
  Cov (β_1, β_{12}) = -0.00738