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.

I agree to the terms of this protocol Amendment.

Study Code: ZD18391L/0709

25/4/03 ....M Cardno.....

Date (day month, year)

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

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: ZD1839IL/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 Barwood	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		