one model, it allowed the ethnic comparison to be assessed after controlling for prognostic factors (see Table 3).

Table 3 Model Building – multivariate effects

Parameter	p-value
Body mass index at entry	0.7889
Previously received radiotherapy	0.6766
Ethnicity	0.2530
Baseline lung cancer subscale score	0.2231
Performance status	0.0814[a]
Histology	0.0212[a]
Gender	0.0166[a]
Previously received other treatment[a]	0.0108[a]

[a] $p<0.10$: significance level for inclusion in the model (as stated in protocol).

5 FINAL MODEL

As shown in Table 3, the main effects model indicated that PS, histology, gender and receipt of other treatments were related to tumour response. Although ethnicity was not significant at the 10% level, it was retained in the model to allow a final assessment of ethnic difference after adjustment for prognostic factors. The final step in the modelling was to assess whether there were any interactions between the prognostic factors. However, no interactions were significant ($p>0.4$), so the main effects model was considered to be the best interpretation of the data (Table 4).

Table 4 Final Adjusted Model

Parameter	Odds Ratio	95% CI	p-value	Interpretation
Performance status	6.26	1.20, 115.36	0.0814	The odds of responding is over 6 times higher for PS 0 or 1 patients compared to PS 2 patients.
Received prior other treatment[a]	6.01	1.58, 26.15	0.0108	The odds of responding is 6 times higher for patients who received other treatments* prior to entry compared to those who did not.
Histology	3.45	1.29, 11.02	0.0212	The odds of responding is almost 3 ½ times higher for patients with adenocarcinoma compared to patients with other tumour histologies.
Gender	2.65	1.19, 5.91	0.0166	The odds of responding is over 2 ½ times higher for females than males.
Ethnicity	1.64	0.71, 3.93	0.2530	After accounting for all baseline imbalances the odds ratio indicates that the chance of responding is just over 1½ times higher for Japanese patients compared to non-Japanese patients.

[a] Other treatments include picibanil, investigational drugs, minomycin, marimastat and NOLVADEX.
CI Confidence interval.
PS Performance status.

The final column of Table 4 provides an explanation of the results. By comparing the model without adjustment for prognostic factors to the model with adjustment for prognostic factors, it was clear the amount of variation explained by these variables. Without the variation being explained in the unadjusted model (Table 1), the odds ratio for ethnicity was 3.27 ($p=0.0023$).

However, after including these variables in the model, and allowing a more accurate assessment of the ethnic difference, the odds ratio was halved to 1.64 (p=0.2530).

From the modelling results, it can be concluded that the odds of responding is 1.64 times higher for Japanese patients compared to non-Japanese patients, but as the 95% confidence interval crosses the value of 1 (representing equality) this difference is not considered to be statistically significant (p=0.2530).

Using the following logit model and the parameterisation shown in Table 5, it was possible to calculate estimated probabilities of response for individual patients. This was done by substituting the relevant value of x_k (ie, either 0 or 1) into the equation below:

$$\text{logit}(p) = -4.8978 + 0.4951*x_{\text{ethnicity}} + 1.8341*x_{\text{PS}} + 1.7930*x_{\text{other}} + 0.9726*x_{\text{gender}} + 1.2382*x_{\text{histology}}$$

Table 5 Parameterisation for logistic model

Parameter	Flags
$x_{\text{ethnicity}}$	0=non-Japanese 1=Japanese
x_{PS}	0=PS 2 1=PS 0 or 1
x_{other}	0=did not receive other previous treatment 1=did receive previous other treatment
x_{gender}	0=male 1=female
$x_{\text{histology}}$	0=squamous, undifferentiated, large cell or squamous & adenocarcinoma 1=adenocarcinoma

PS Performance status.

If we were to use the model to compare the probability of response for a Japanese patient given the average baseline characteristics of a non-Japanese patient (ie, PS=0-1, no other treatments, male and having adenocarcinoma), then we would find that the predicted probability of response was 20.9%. In a similar fashion, if we were to use the model to compare the probability of response for a non-Japanese patient given the average baseline characteristics of a Japanese patient (ie, PS=0-1, no other treatments, male and having adenocarcinoma), then we would find that the predicted probability of response was 13.9%.

In addition to this example, the model shows that at the most extreme situations, the estimated probability of response ranged from 0.74% to 71.9% for non-Japanese patients, and 1.21% to 80.8% for Japanese patients. Thus, when all prognostic factors are considered in the modelling, the range of response rates are very similar between the two ethnic groups.

6 DISCUSSION

Without making any adjustment for baseline imbalances, the odds of responding was over 3 times higher for Japanese patients compared to non-Japanese patients (p=0.0023). However, upon reviewing the data, it was evident that there were many prognostic factors that favoured the Japanese patients. In order to account for these baseline imbalances, logistic modelling was performed to allow a more accurate assessment of the ethnic difference.

After accounting for baseline imbalances, the odds ratio for ethnicity was 1.64 (p=0.2530) suggesting that the chances of responding was 1.64 times higher for the Japanese patients compared with the non-Japanese patients. However, as the confidence interval ranged from 0.71 to 3.93, we could not rule out the possibility that the true odds ratio may be equal to unity, indicating equal response rates in the ethnic groups.

Using the final logistic model, it was possible to calculate the estimated probabilities of response for individual patients depending on whether or not they had the prognostic factors identified in the modelling (ie, PS=0 to 1, receipt of prior other treatment, female, and adenocarcinoma histology). Estimation of the probability of response for a Japanese patient with the average baseline characteristics of a non-Japanese patient, gave a probability of response of 20.9%. Using the same methodology, the probability of response for a non-Japanese patient with the average baseline characteristics of a Japanese patient, gave a probability of response of 13.9%.

These estimated probabilities or response highlight the wide range of results that can be seen between patients irrespective of whether they are Japanese or non-Japanese. However, the fact that this trial involved a large number of patients (n=210), it is unlikely that the results could be heavily influenced by patients with a very poor prognosis or patients with a very good prognosis. The trial data showed that the trial had a large representative population, thus making it likely that the trial results can be reproduced.

7 CONCLUSION

The results have suggested that without adjustment for baseline imbalances between Japanese and non-Japanese groups, there was a large difference between the two ethnicities. However, after accounting for the prognostic factors identified in the trial (ie, PS, histology, gender and the receipt of previous treatments other than chemotherapy, radiotherapy and surgery), using the modelling approach, it was clearly demonstrated that there was no statistically significant difference between the ethnic groups. In addition, when probabilities of response for patients within each ethnic group were estimated, the range of results were hugely overlapping, confirming similarity. This highlighted that when all prognostic factors were considered in the modelling, the range of response rates were similar between the two ethnic groups.

APPENDIX A

Summary tables produced in response to DO questions

Tables T99.1 to T99.3	Response rates and durations of first-line chemotherapy regimen presented by dose
Tables T99.4 to T99.6	Response rates and durations of first-line chemotherapy presented by dose and ethnicity
Tables T99.7 to T99.9	Response rates and durations of second-line chemotherapy presented by dose and ethnicity

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

別添資料 16-1

1839IL/0709

CAUSE OF DEATH
POPULATION: EFS PATIENTS WHO WERE INTOLERANT TO LAST CHEMO REGIMEN & WHO DIED WITHIN 4 MONTHS OF RANDOMISATION

RANDOMISED TREATMENT = GEFITINIB

PATIENT	TIME TO DEATH	PRIMARY CAUSE OF DEATH	PRIMARY CAUSE PREFERRED TERM	SECONDARY CAUSE OF DEATH	SECONDARY CAUSE PREFERRED TERM	AUTOPSY DONE	DEATH RELATED TO CANCER
E0113004	1.87	Non small cell lung cancer	NON-SMALL CELL LUNG CANCER			No	Yes
E0147002	1.28	Non-small cell lung cancer	NON-SMALL CELL LUNG CANCER			No	Yes
E0150005	2.53	Non small cell lung cancer	NON-SMALL CELL LUNG CANCER			No	Yes
E0341002	1.25	Pulmonary embolism	PULMONARY EMBOLISM	Non-small call lung cancer	NON-SMALL CELL LUNG CANCER	No	Yes
E0505018	0.92	Respiratory insufficiency	RESPIRATORY FAILURE	Progression of nsclc	NON-SMALL CELL LUNG CANCER	No	Yes
E0505056	3.25	Kardio - resp insuff	CARDIOPULMONARY FAILURE	Caused by progressive lung cancer	LUNG NEOPLASM MALIGNANT	No	Yes
E0505058	3.29	Respiratory failure	RESPIRATORY FAILURE	Progression of nsclc	NON-SMALL CELL LUNG CANCER	No	Yes
E0568004	0.79	Multiple organ failure	MULTI-ORGAN FAILURE	Pneumonia	PNEUMONIA	No	Yes
E0587004	2.63	Respiratory insuficiency due to sepsis	SEPSIS			No	No
E0622011	0.66	Non small cell lung cancer	NON-SMALL CELL LUNG CANCER			No	Yes
E1108005	1.15	Non-small cell lung cancer	NON-SMALL CELL LUNG CANCER			No	Yes
E1125008	1.08	Non small cell lung cancer	NON-SMALL CELL LUNG CANCER			No	Yes
E1126005	1.45	Non small cell lung cancer	NON-SMALL CELL LUNG CANCER			No	Yes
E1165001	3.32	NSCLC	NON-SMALL CELL LUNG CANCER			No	Yes
E1356004	1.12	Non small cell lung cancer - progressive disease	NON-SMALL CELL LUNG CANCER			No	Yes
E1460006	0.69	Lung cancer progression	LUNG NEOPLASM MALIGNANT			No	Yes
E1461027	1.08	Respiratory insufficiency	RESPIRATORY FAILURE	Pulmonary metastases of non small cell lung cancer	NON-SMALL CELL LUNG CANCER METASTATIC	No	Yes
E1461032	1.41	Respiratory insufficiency	RESPIRATORY FAILURE	Hemoptysis	HAEMOPTYSIS	No	Yes
E1461056	1.94	Acute respiratory insufficiency	ACUTE RESPIRATORY FAILURE			No	No

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CAUSE OF DEATH
POPULATION: EFS PATIENTS WHO WERE INTOLERANT TO LAST CHEMO REGIMEN & WHO DIED WITHIN 4 MONTHS OF RANDOMISATION

RANDOMISED TREATMENT = GEFITINIB

PATIENT	TIME TO DEATH	PRIMARY CAUSE OF DEATH	PRIMARY CAUSE PREFERRED TERM	SECONDARY CAUSE OF DEATH	SECONDARY CAUSE PREFERRED TERM	AUTOPSY DONE	DEATH RELATED TO CANCER
E1461057	0.43	Respiratory insufficiency	RESPIRATORY FAILURE	Lung cancer	LUNG NEOPLASM MALIGNANT	No	Yes
E1461075	0.72	Multiple organs collapse	MULTI-ORGAN FAILURE	Lung cancer	LUNG NEOPLASM MALIGNANT	No	Yes
E1461080	1.38	Respiratory insufficiency	RESPIRATORY FAILURE			No	No
E1461087	3.19	Carcinomatosis	METASTATIC NEOPLASM	Lung carcinoma	LUNG NEOPLASM MALIGNANT	Yes	Yes
E1509011	3.29	Non small cell lung cancer	NON-SMALL CELL LUNG CANCER	Cardiorespiratoric failure	CARDIOPULMONARY FAILURE	No	Yes
E1729003	1.74	Progression of subject's nsclc	NON-SMALL CELL LUNG CANCER			No	Yes
E1730012	3.42	NSCLC progression	NON-SMALL CELL LUNG CANCER			No	Yes
E1733004	3.02	Metastaic lung cancer	LUNG CANCER METASTATIC			No	Yes
E1910001	3.58	NSCLC	NON-SMALL CELL LUNG CANCER			No	Yes
E5300003	1.58	Cardiopulmonary arrest probably secondary to disseminated malignancy.	CARDIO-RESPIRATORY ARREST	Bronchogenic/non small cell lung cancer stage iv brain metastases and pleural effusion (right) s/p closed tube thoracostomy and removal (right)	NON-SMALL CELL LUNG CANCER STAGE IV	No	Yes
E5706006	2.43	Not known as patient expired in a remote place	DEATH			No	No
E5804020	2.92	Progression of non small cell lung cancer	NON-SMALL CELL LUNG CANCER	Respiratory failure	RESPIRATORY FAILURE	No	Yes
E6003008	3.29	Metastatic, progressive non-small cell lung cancer.	NON-SMALL CELL LUNG CANCER METASTATIC			No	Yes
E6003039	1.22	Progressive metastatic non small cell lung cancer	NON-SMALL CELL LUNG CANCER METASTATIC			No	Yes
E6108006	0.85	Respiratory faile	RESPIRATORY FAILURE	Non-small cell lung cancer	NON-SMALL CELL LUNG CANCER	No	Yes
E6600001	1.18	Non small cell lung cancer	NON-SMALL CELL LUNG CANCER			No	Yes

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CAUSE OF DEATH

POPULATION: EFS PATIENTS WHO WERE INTOLERANT TO LAST CHEMO REGIMEN & WHO DIED WITHIN 4 MONTHS OF RANDOMISATION

RANDOMISED TREATMENT = PLACEBO

PATIENT	TIME TO DEATH	PRIMARY CAUSE OF DEATH	PRIMARY CAUSE PREFERRED TERM	SECONDARY CAUSE OF DEATH	SECONDARY CAUSE PREFERRED TERM	AUTOPSY DONE	DEATH RELATED TO CANCER
E0505005	0.46	Respiratory failure	RESPIRATORY FAILURE	Progression of nsclc	NON-SMALL CELL LUNG CANCER	No	Yes
E1009015	2.46	NSCLC	NON-SMALL CELL LUNG CANCER			No	Yes
E1151001	0.53	Progression of non-small cell lung cancer	NON-SMALL CELL LUNG CANCER			No	Yes
E1173001	2.30	Lung cancer	LUNG NEOPLASM MALIGNANT			No	Yes
E1201001	2.99	Lung cancer	LUNG NEOPLASM MALIGNANT			No	Yes
E1210001	1.61	Superior vena cava syndrom	SUPERIOR VENA CAVAL OCCLUSION	Progression of non-small cell lung cancer	NON-SMALL CELL LUNG CANCER	No	Yes
E1461093	3.45	Pulmonary insufficiency	RESPIRATORY FAILURE	Lung cancer	LUNG NEOPLASM MALIGNANT	No	Yes
E1462003	0.36	Bronchopneumonia	BRONCHOPNEUMONIA			No	Yes
E1701028	3.35	Chronic obstructive pulmonary disease	CHRONIC OBSTRUCTIVE AIRWAYS DISEASE	Lung cancer	LUNG NEOPLASM MALIGNANT	No	Yes

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

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CATEGORIES OF ADVERSE EVENTS (BY PATIENTS) BY ETHNIC GROUP
POPULATION: EVALUABLE-FOR-SAFETY

	TREATMENT RECEIVED											
	GEFITINIB				PLACEBO				ALL			
	ORIENTAL		NON-ORIENTAL		ORIENTAL		NON-ORIENTAL		ORIENTAL		NON-ORIENTAL	
	N=235		N=891		N=107		N=455		N=342		N=1346	
	N	%	N	%	N	%	N	%	N	%	N	%
Patient had an AE	227	96.6	700	78.6	92	86.0	305	67.0	319	93.3	1005	74.7
Treatment-Related AE	178	75.7	480	53.9	41	38.3	120	26.4	219	64.0	600	44.6
Serious AE	55	23.4	161	18.1	24	22.4	74	16.3	79	23.1	235	17.5
Serious Treatment-Related AE	7	3.0	20	2.2	1	0.9	7	1.5	8	2.3	27	2.0
Non-Fatal Serious AE	52	22.1	128	14.4	19	17.8	64	14.1	71	20.8	192	14.3
Discontinuation Due To AE	17	7.2	44	4.9	2	1.9	11	2.4	19	5.6	55	4.1
Discontinuation Due To Treatment-Related AE	9	3.8	22	2.5	0	0	3	0.7	9	2.6	25	1.9
Discontinuation Due To Serious AE	11	4.7	22	2.5	2	1.9	8	1.8	13	3.8	30	2.2
Discont. Due To Serious Treatment-Related AE	5	2.1	5	0.6	0	0	3	0.7	5	1.5	8	0.6
Death Due To AE	11	4.7	44	4.9	6	5.6	16	3.5	17	5.0	60	4.5
Death Due To Treatment-Related AE	2	0.9	3	0.3	0	0	1	0.2	2	0.6	4	0.3
CTC Grade 3 or 4 AE	101	43.0	240	26.9	38	35.5	113	24.8	139	40.6	353	26.2
CTC Grade 3 or 4 Treatment-Related AE	27	11.5	63	7.1	1	0.9	15	3.3	28	8.2	78	5.8
Interstitial Lung Disorder Type Events	7	3.0	5	0.6	4	3.7	1	0.2	11	3.2	6	0.4

ADVERSE EVENTS OCCURRING DURING FOLLOW-UP (I.E. OCCURRING WITHIN 30 DAYS AFTER DISCONTINUATION OF INVESTIGATIONAL PRODUCT) ARE INCLUDED