CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-399

Statistical Review(s)

Statistical Review Addendum #3

Medical Division: Oncology Drug Products (HFD-150)
Biometrics Division: Division of Biometrics I (HFD-710)

NDA NUMBER: NDA 21-399

DRUG NAME: IRESSA (ZD1839) 250 mg Tablets

INDICATION: Locally advanced or metastatic non-small cell lung cancer after failure of both platinum-based and docetaxel chemotherapies

SPONSOR: AstraZeneca

STATISTICAL REVIEWERS: **Rajeshwari Sridhara, Ph.D. (HFD-710)**

STATISTICAL TEAM LEADER: **Gang Chen, Ph.D. (HFD-710)**

DBI DIRECTOR: **George Chi, Ph.D. (HFD-710)**

CLINICAL REVIEWERS: **Martin Cohen, M.D. (HFD-150)**

CLINICAL TEAM LEADER: **Grant Williams, M.D. (HFD-150)**
Deputy Director DODP

PROJECT MANAGER: **Amy Baird (HFD-150)**

Distribution: NDA 21-399
HFD-150/Baird
HFD-150/Cohen
HFD-150/Williams
HFD-710/Sridhara
HFD-710/Chen
HFD-710/Mahjoob
HFD-710/Chi
HFD-700/Anello

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This is a correction to a typographical error in the earlier Statistical Review, Addendum 1, B., 2.11, Table b. The correct response rate and confidence intervals for the Pooled Data in White subgroup of patients are:

Response rate: 11/129 (8.5%) (Instead of 9/129, 7% as reported earlier)
95% C.I.: 4.3%, 14.8% (Instead of 3.2%, 12.8% as reported earlier)
97.5% C.I.: 3.9%, 15.7% (Instead of 2.9%, 13.7% as reported earlier)

/S/

Rajeshwari Sridhara, Ph.D.
Mathematical Statistician
Date:

Cc:
HFD-150/ Ms. Baird
HFD-150/ Dr. Cohen
HFD-150/ Dr. Williams
HFD-710/ Dr. Sridhara
HFD-710/ Dr. Chen
HFD-710/ Dr. Mahjoob
HFD-710/ Dr. Chi
HFD-700/ Dr. Anello

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/s/

Rajeshwari Sridhara
5/1/03 03:35:15 PM
BIOMETRICS

Statistical Review Addendum #2

Medical Division: Oncology Drug Products (HFD-150)
Biometrics Division: Division of Biometrics I (HFD-710)

NDA NUMBER: NDA 21-399

DRUG NAME: IRESSA (ZD1839) 250 mg Tablets

INDICATION: Locally advanced or metastatic non-small cell lung cancer after failure of both platinum-based and docetaxel chemotherapies

SPONSOR: AstraZeneca

STATISTICAL REVIEWERS: **Rajeshwari Sridhara, Ph.D. (HFD-710)**

STATISTICAL TEAM LEADER: **Gang Chen, Ph.D. (HFD-710)**

DBI DIRECTOR: **George Chi, Ph.D. (HFD-710)**

CLINICAL REVIEWERS: **Martin Cohen, M.D. (HFD-150)**

CLINICAL TEAM LEADER: **Grant Williams, M.D. (HFD-150)**
Deputy Director DODP

PROJECT MANAGER: **Amy Baird (HFD-150)**

Distribution: NDA 21-399
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HFD-150/Cohen
HFD-150/Williams
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HFD-710/Sridhara
HFD-710/Chen
HFD-710/Mahjoob
HFD-710/Chi
HFD-700/Anello

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This addendum is to acknowledge receipt of additional subgroup analyses of the two, Phase III randomized trials in first-line NSCLC patients (INTACT Trials ZD1839IL/0014 and ZD1839IL/0017) from the sponsor. The following are sponsor's exploratory analyses that were requested by the agency. The original data has not been reviewed by the agency and the results reported are as reported by the sponsor (submissions N-000 (BM) dated Mar 14, 2003, and N-000 (BM) dated Apr 11, 2003).

1839IL/0014

Unadjusted Cox proportional Hazard model – survival by subgroups populations: Intention-to treat (p35, Table H1.3.5, N-000 (BM), 3/14/03)

Histology – Group 1: Group 2		Hazard Ratio	Lower 95% confidence limit	Upper 95% confidence limit	P-value
Adenocarcinoma + Bronchoalveolar	250 mg : 500 mg	0.979	0.753	1.274	0.8770
	Placebo : 500 mg	0.850	0.648	1.116	0.2426
	Placebo: 250 mg	0.868	0.667	1.131	0.2946

Note: A Hazard Ratio > 1 indicates that Group 2 lives longer than Group 1 whereas a Hazard Ratio < 1 indicates that Group 1 lives longer than Group 2.

1839IL/0014

Unadjusted Cox proportional Hazard model – survival by subgroups populations: Intention-to treat (p39, Table H1.3.6, N-000 (BM), 3/14/03)

Histology – Group 1: Group 2		Hazard Ratio	Lower 95% confidence limit	Upper 95% confidence limit	P-value
Other Histology	250 mg : 500 mg	1.142	0.795	1.639	0.4719
	Placebo : 500 mg	1.127	0.804	1.581	0.4865
	Placebo: 250 mg	0.987	0.687	1.419	0.9451

Note: A Hazard Ratio > 1 indicates that Group 2 lives longer than Group 1 whereas a Hazard Ratio < 1 indicates that Group 1 lives longer than Group 2.

1839IL/0014

Unadjusted Cox proportional Hazard model – survival by subgroups populations: Intention-to treat (p82, Table H1.3.19, N-000 (BM), 3/14/03)

Histology – Group 1: Group 2		Hazard Ratio	Lower 95% confidence limit	Upper 95% confidence limit	P-value
MALE	250 mg : 500 mg	1.048	0.855	1.285	0.6497
	Placebo : 500 mg	1.003	0.815	1.235	0.9755
	Placebo: 250 mg	0.957	0.781	1.172	0.6710
FEMALE	250 mg : 500 mg	0.941	0.658	1.345	0.7375
	Placebo : 500 mg	0.796	0.561	1.130	0.2016
	Placebo: 250 mg	0.846	0.586	1.222	0.3733

Note: A Hazard Ratio > 1 indicates that Group 2 lives longer than Group 1 whereas a Hazard Ratio < 1 indicates that Group 1 lives longer than Group 2.

1839IL/0017
Unadjusted Cox proportional Hazard model – survival by subgroups populations: Intention-to treat (p109able H1.3.5, N-000 (BM), 3/14/03)

Histology – Group 1: Group 2		Hazard Ratio	Lower 95% confidence limit	Upper 95% confidence limit	P-value
Adenocarcinoma + Bronchoaveolar	250 mg : 500 mg	0.891	0.700	1.135	0.3505
	Placebo : 500 mg	1.030	0.812	1.306	0.8079
	Placebo: 250 mg	1.156	0.905	1.476	0.2471

Note: A Hazard Ratio > 1 indicates that Group 2 lives longer than Group 1 whereas a Hazard Ratio < 1 indicates that Group 1 lives longer than Group 2.

1839IL/0017
Unadjusted Cox proportional Hazard model – survival by subgroups populations: Intention-to treat (p114, Table H1.3.6, N-000 (BM), 3/14/03)

Histology – Group 1: Group 2		Hazard Ratio	Lower 95% confidence limit	Upper 95% confidence limit	P-value
Other Histology	250 mg : 500 mg	0.804	0.562	1.148	0.2294
	Placebo : 500 mg	0.738	0.523	1.042	0.0841
	Placebo: 250 mg	0.919	0.642	1.315	0.6424

Note: A Hazard Ratio > 1 indicates that Group 2 lives longer than Group 1 whereas a Hazard Ratio < 1 indicates that Group 1 lives longer than Group 2.

1839IL/0017
Unadjusted Cox proportional Hazard model – survival by subgroups populations: Intention-to treat (p161, Table H1.3.19, N-000 (BM), 3/14/03)

Histology – Group 1: Group 2		Hazard Ratio	Lower 95% confidence limit	Upper 95% confidence limit	P-value
MALE	250 mg : 500 mg	1.035	0.822	1.303	0.7697
	Placebo : 500 mg	1.112	0.891	1.388	0.3489
	Placebo: 250 mg	1.074	0.858	1.345	0.5311
FEMALE	250 mg : 500 mg	0.805	0.604	1.073	0.1396
	Placebo : 500 mg	0.761	0.567	1.023	0.0704
	Placebo: 250 mg	0.945	0.700	1.277	0.7142

Note: A Hazard Ratio > 1 indicates that Group 2 lives longer than Group 1 whereas a Hazard Ratio < 1 indicates that Group 1 lives longer than Group 2.

/S/

Rajeshwari Sridhara, Ph.D.
Mathematical Statistician
Date:

Concur: Dr. Chen
Team Leader

Cc:
HFD-150/ Ms. Baird
HFD-150/ Dr. Cohen
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HFD-100/ Dr. Temple
HFD-710/ Dr. Sridhara
HFD-710/ Dr. Chen
HFD-710/ Dr. Mahjoob
HFD-710/ Dr. Chi
HFD-700/ Dr. Anello
HFD-700/ Dr. ONeill

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/s/

Rajeshwari Sridhara
4/22/03 09:48:06 AM
BIOMETRICS

Gang Chen
4/22/03 10:04:20 AM
BIOMETRICS

Statistical Review Addendum #1

Medical Division: Oncology Drug Products (HFD-150)
Biometrics Division: Division of Biometrics I (HFD-710)

NDA NUMBER: NDA 21-399

DRUG NAME: IRESSA (ZD1839) 250 mg Tablets

INDICATION: Locally advanced or metastatic non-small cell lung cancer after failure of both platinum-based and docetaxel chemotherapies

SPONSOR: AstraZeneca

STATISTICAL REVIEWERS: **Rajeshwari Sridhara, Ph.D. (HFD-710)**

STATISTICAL TEAM LEADER: **Gang Chen, Ph.D. (HFD-710)**

DBI DIRECTOR: **George Chi, Ph.D. (HFD-710)**

CLINICAL REVIEWERS: **Martin Cohen, M.D. (HFD-150)**

CLINICAL TEAM LEADER: **Grant Williams, M.D. (HFD-150)**

Deputy Director DODP

PROJECT MANAGER: **Amy Baird (HFD-150)**

Distribution: NDA 21-399
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HFD-710/Sridhara
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This addendum addresses the concerns raised by Dr. Temple in his memo dated 10/29/02 to the Division Director and Deputy Director, DODP, and the statistical reviewer. On further review of the data by the statistical and medical reviewers it was concluded that the total number of third-line patients (patients refractory/intolerant to platinum and docetaxel) in Study IL0039 was 142 and not 139 as reported at the ODAC meeting on 9/24/02 and in the review submitted on 10/15/02. This addendum includes the results based on 142 third-line patients. This addendum also incorporates additional assessments in specific patient subgroups as requested by Dr. Temple.

Because of the uncontrolled nature of the phase II registration trial presented in this NDA, no formal statistical testing or comparisons could be conducted.

A.

In view of the difference in the total number of third-line patients, Tables A, 1B, 2B, 3, and 4 of the original review should be replaced with the following updated tables.

Updated Table A: Objective Tumor Response in Platinum and Docetaxel Refractory/Intolerant Patient Population (FDA Analyses)

Treatment Arm	Response Rate	95% C.I.	97.5% C.I.*
250 mg ZD1839	9/66 (13.6%)	6.4%, 24.3%	5.7%, 25.9%
500 mg ZD1839	6/76 (7.9%)	3.0%, 16.4%	2.5%, 17.7%
Pooled Data	15/142 (10.6%)	6.0%, 16.8%	5.5%, 17.7%

*: Protocol specified confidence interval

Updated Table 1B: Baseline Characteristics of Platinum and Docetaxel Refractory/Intolerant Patients in Study 39 (FDA Analysis)

Characteristic	ZD1839 Dose	
	250 mg / day N = 66	500 mg / day N = 76
Age Group: n (%)		
15 – 64 years	43 (65.1)	43 (56.6)
64 – 74 years	19 (28.8)	30 (39.5)
75 years and above	4 (6.1)	3 (3.9)
Sex: n (%)		
Male	38 (57.6)	41 (53.9)
Female	28 (42.4)	35 (46.1)
Race: n(%)		
White	61(92.4)	68 (89.5)
Black	1 (1.5)	2 (2.6)
Asian/Oriental	1 (1.5)	1 (1.3)
Hispanic	0 (0.0)	4 (5.3)
Other	3 (4.6)	1 (1.3)
Smoke: n (%)		
Yes	45 (68.2)	63 (82.9)
No	21 (31.8)	13 (17.1)
Baseline WHO Performance Status		
0	14 (21.2)	9 (11.8)
1	36 (54.5)	53 (69.7)
2	15 (22.7)	14 (18.4)
3	0 (0.0)	0 (0.0)
Tumor Histology		
Squamous	9 (13.6)	11 (14.9)
Adenocarcinoma	46 (69.7)	50 (67.6)
Undifferentiated	6 (9.1)	4 (5.4)
Large Cell	2 (3.0)	2 (2.7)
Squamous & Adenocarcinoma	3 (4.6)	7 (9.5)

Updated Table 2B: Objective Tumor Response in Platinum and Docetaxel Refractory/Intolerant Patient Population (FDA Analyses)

Treatment Arm	Response Rate	95% C.I.	97.5% C.I.*
250 mg ZD1839	9/66 (13.6%)	6.4%, 24.3%	5.7%, 25.9%
500 mg ZD1839	6/76 (7.9%)	3.0%, 16.4%	2.5%, 17.7%
Pooled Data	15/142 (10.6%)	6.0%, 16.8%	5.5%, 17.7%

*: Protocol specified confidence interval

Updated Table 3: Characteristics of Responders Who Were Refractory/Intolerant to Platinum and Docitaxel (FDA Analyses)

Treatment Arm	Sex	Smoker	Histology
250 mg ZD 1839	7 Females	1 Smoker	1 Adenocarcinoma
		6 Non-smokers	4 Adenocarcinoma 1 Squamous 1 Large cell
	2 Males	2 Non-smokers	1 Adenocarcinoma 1 Undifferentiated
500 mg ZD1839	4 Females	2 Smokers	2 Adenocarcinoma
		2 Non-smokers	1 Adenocarcinoma 1 Squamous
	2 Males	2 Smoker	2 Adenocarcinoma

Updated Table 4: Duration of Response in the Platinum and Docetaxel Refractory/Intolerant Patients Who Had Tumor Response

Treatment Arm	Duration of Response in Months (As of Aug 1, 2001)
250 mg ZD1839	1+, 2+, 3+, 3+, 3+, 5, 5+, 5+, 7+
500 mg ZD1839	2+, 3, 3, 3+, 4, 4+

+: censored at

B.

In addition the following should be inserted in Section 2.11 on Statistical Review of Special Population and Subgroups of Study 39.

2.11 Statistical Review of Special Population / Subgroups of Study 39

Table a: Efficacy by Gender in Platinum and Docetaxel Refractory/Intolerant Patients in Study 39

Treatment Arm	Response Rate	95% C.I.	97.5% C.I.
250 mg ZD1839			
Female	7/28 (25.0%)	10.7%, 44.9%	9.3%, 47.6%
Male	2/38 (5.3%)	0.6%, 17.8%	0.4%, 19.7%
500 mg ZD1839			
Female	4/35 (11.4%)	3.2%, 26.7%	2.6%, 29.0%
Male	2/41 (4.9%)	0.6%, 16.5%	0.4%, 18.4%
Pooled Data*			
Female	11/63 (17.5%)	9.0%, 29.1%	8.2%, 30.8%
Male	4/79 (5.1%)	1.4%, 12.5%	1.1%, 13.6%

*OR = 3.966 (95% C.I.: 1.197, 13.137); P-value = 0.02

Table b: Efficacy by Race in the Platinum and Docetaxel Refractory/Intolerant Patients in Study 39

Treatment Arm	Response Rate	95% C.I.	97.5% C.I.
250 mg ZD1839			
White	7/61 (11.5%)	4.7%, 22.2%	4.1%, 23.8%
Non-white	2/5 (40.0%)	5.3%, 85.3%	3.7%, 88.6%
500 mg ZD1839			
White	4/68 (5.9%)	1.6%, 14.4%	1.3%, 15.7%
Non-white	2/8 (25.0%)	3.2%, 65.1%	2.2%, 69.4%
Pooled Data*			
White	9/129 (7.0%)	3.2%, 12.8%	2.9%, 13.7%
Non-white	4/13 (30.8%)	9.1%, 61.4%	7.4%, 65.0%

*OR = 4.769(95% C.I.: 1.261, 18.032); P-value = 0.02

Table c: Efficacy by Smoking Habit in Platinum and Docetaxel Refractory/Intolerant Patients in Study 39

Treatment Arm	Response Rate	95% C.I.	97.5% C.I.
250 mg ZD1839			
Smoker	1/45 (2.2%)	0.1%, 11.8%	0.03%, 13.4%
Non-smoker	8/21 (38.1%)	18.1%, 61.6%	16.1%, 64.4%
500 mg ZD1839			
Smoker	4/63 (6.4%)	1.8%, 15.5%	1.4%, 16.9%
Non-smoker	2/13 (15.4%)	1.9%, 45.5%	1.3%, 49.4%
Pooled Data*			
Smoker	5/108 (4.6%)	1.5%, 10.5%	1.3%, 11.4%
Non-smoker	10/34 (29.4%)	15.1%, 47.5%	13.6%, 49.9%

*OR = 8.583 (95% C.I: 2.686, 27.43)); P-value = 0.0003

Table d: Efficacy by Center in Platinum and Docetaxel Refractory/Intolerant Patients in Study 39

Treatment Arm	Response Rate	95% C.I.	97.5% C.I.
250 mg ZD1839			
Center 2090	4/12 (33.3%)	9.9%, 65.1%	8.1%, 68.7%
All others	5/54 (9.3%)	3.1%, 20.3%	2.6%, 22.0%
500 mg ZD1839			
Center 2090	2/11 (18.2%)	2.3%, 51.8%	1.6%, 56.0%
All others	4/65 (6.2%)	1.7%, 15.0%	1.4%, 16.4%
Pooled Data*			
Center 2090	6/23 (26.1%)	10.2%, 48.4%	8.8%, 51.4%
All others	9/119 (7.6%)	3.5%, 13.9%	3.1%, 14.8%

*OR = 4.314 (95% C.I.: 1.363, 13.656); P-value = 0.01

Table e: Objective Tumor Response in Patients Who Are Not Platinum and Docetaxel Refractory/Intolerant in Study 39 (FDA Analyses)

Treatment Arm	Response Rate	95% C.I.	97.5% C.I.*
250 mg ZD1839	3/36 (8.3%)	1.8%, 22.5%	1.4%, 24.6%
500 mg ZD1839	4/38 (10.5%)	2.9%, 24.8%	2.4%, 27.0%
Pooled Data	7/74 (9.5%)	3.9%, 18.5%	3.4%, 19.9%

Table f: Characteristics of Responders Who Were Not Refractory/Intolerant to Platinum and Docitaxel in Study 39 (FDA Analyses)

Treatment Arm	Sex	Smoker	Histology
250 mg ZD 1839	3 Females	3 Smokers	3 Adenocarcinoma
500 mg ZD1839	4 Females	1 Smoker	1 Adenocarcinoma
		3 Non-smokers	3 Adenocarcinoma

Table g: Efficacy by Gender in Patients Who Are Not Platinum and Docetaxel Refractory/Intolerant in Study 39

Treatment Arm	Response Rate	95% C.I.	97.5% C.I.
250 mg ZD1839			
Female	3/14 (21.4%)	4.7%, 50.8%	3.6%, 54.6%
Male	0/22 (0.0%)	0.0%, 15.4%	0.0%, 18.1%
500 mg ZD1839			
Female	4/16 (25.0%)	7.3%, 52.4%	5.9%, 55.9%
Male	0/22 (0.0%)	0.0%, 15.4%	0.0%, 18.1%
Pooled Data			
Female	7/30 (23.3%)	9.9%, 42.3%	8.7%, 44.9%
Male	0/44 (0.0%)	0.0%, 8.0%	0.0%, 9.5%

Table h: Efficacy by Race in Patients Who Are Not Platinum and Docetaxel Refractory/Intolerant in Study 39

Treatment Arm	Response Rate	95% C.I.	97.5% C.I.
250 mg ZD1839			
White	2/32 (6.3%)	0.7%, 20.8%	0.5%, 23.1%
Non-white	¼ (25.0%)	0.6%, 80.6%	0.3%, 84.8%
500 mg ZD1839			
White	4/35 (11.4%)	3.2%, 26.7%	2.6%, 29.0%
Non-white	0/3 (0.0%)	0.0%, 70.8%	0.0%, 76.8%
Pooled Data			
White	6/67 (9.0%)	3.4%, 18.5%	2.9%, 19.9%
Non-white	0/7 (0.0%)	0.0%, 41.0%	0.0%, 46.5%

Table i: Efficacy by Smoking Habit in Patients Who Are Not Platinum and Docetaxel Refractory/Intolerant in Study 39

Treatment Arm	Response Rate	95% C.I.	97.5% C.I.
250 mg ZD1839			
Smoker	**3/31 (9.7%)**	2.0%, 25.8%	1.6%, 28.2%
Non-smoker	**0/5 (0.0%)**	0.0%, 52.2%	0.0%, 58.4%
500 mg ZD1839			
Smoker	**1/31 (3.2%)**	0.08%, 16.7%	0.04%, 18.9%
Non-smoker	**3/7 (4.3%)**	9.9%, 81.6%	7.7%, 84.9%
Pooled Data			
Smoker	**4/62 (6.5%)**	1.8%, 15.7%	1.4%, 17.2%
Non-smoker	**3/12 (25.0%)**	5.5%, 57.2%	4.2%, 61.1%

Table j: Results From Expanded Access Program of ZD1839 in NSCLC Patients Submitted as Abstracts for Presentation At The Annual American Society of Clinical Oncology Meeting, May-June 2003 (Data provided by the sponsor)

First Author	Response Rate, 95% C.I.	Comments
Ruckdeschel	**5/86** (5.8%), 1.9% - 13.1%	
Hainsworth	**9/124** (7.3%), 3.4% - 13.3%	
Liem	**0/86** (0.0%), 0.0% - 4.2%	
Soto Porra	**5/68** (7.3%), 2.4% - 16.3%	
Janne	**7/200** (3.5%), 1.4% - 7.1%	All the 7 responders were females (7/105 females in the study); 4/7 had **bronchioalveolar** carcinoma
Shah	**21/140** (15%), 9.5% - 22.0%	Exploratory retrospective multivariate logistic regression analysis revealed presence of **bronchioalveolar** carcinoma and having never smoked were the only independent predictors of response
Nahleh	**1/48** (2.1%), 0.05% - 11.1%	
Argiris	**3/29** (10.3%), 2.2% - 27.4%	2/3 responders had **bronchioalveolar** carcinoma
Wong	**7/18** (38.9%), 17.3% - 64.3%	6/7 responders were non-smokers; this study was conducted in Singapore (presumably Asian patients)
Total	**58/799 (7.3%), 5.6% - 9%**	
Excluding Wong	**51/781 (6.5%), 4.9% - 8.5%**	Excluding Singapore Study

Table k: Results From Protocols of ZD1839 in Non-NSCLC Patients Submitted as Abstracts for Presentation At The Annual American Society of Clinical Oncology Meeting, May-June 2003 (Data provided by the sponsor)

First Author	Disease Studied	Response Rate
Beslga	Advanced Breast Cancer	0/34
Magnani	Advanced Breast Cancer	1/7 (dose finding study)
Robertson	Tamoxifen resistant Breast Cancer	2/33
Doi	Metastatic Gastric Carcinoma	1/75
Jermann	Advanced, relapsed or metastatic Renal Cell Carcinoma	0/28
Dawson	Stage 4 & recurrent Renal Cell Carcinoma	0/21
Petrylak	Advanced Transitional Cell Carcinoma of Urothelium	1/29
Schilder	Recurrent Ovarian or primary Peritonial Carcinoma	1/30
Peery	First relapse Glioblastoma	1/51
Limbeman	Malignant Gliomas and Meningiomas	0/6

C.

Reviewer's Comments:

1. Pooling of data from the two doses was not specified in the protocol. However, pooled data did not provide additional information than what was obtained from 250 mg ZD1839 treatment arm.
2. Heterogeneity of results was observed in Study 39 as presented in the tables above. It appears in the platinum and docetaxel refractory/intolerant patient population, males, white patients, and smokers have poorer prognosis compared to females, non-white patients, and non-smokers, respectively (Tables a-c). Similar results were observed in patients who were not platinum and docetaxel refractory/intolerant (Tables d-i). Differences were also observed in Study 16 between (a) **Japanese** (Response Rate = 29/102 = **28.4%; 95% CI: 19.9%, 38.2%**) and **non-Japanese** (Response Rate = 10/106 = **9.4%; 95% CI: 4.6%, 16.7%**) patients, and (b) **Female** (Response Rate = 22/61 = **36.1%; 95% CI: 24.2%, 49.4%**) and **male** (Response Rate = 17/147 = **11.6%; 95% CI: 6.9%, 17.9%**) patients. These hypotheses need further testing in well controlled, randomized trials.
3. There is a potential for selection bias in a single arm study. For example, in 6 of the 15 responders among the 142 refractory / intolerant patients, the time from stopping previous chemotherapy to randomization date in Study 39 was ≤ 1 month. This and

other unknown or unmeasured factors may potentially bias the results in favor of Iressa.

4. The sponsor has stated that approximately in the order of 20,000 patients have been treated with ZD1839 in the expanded access program. The sponsor provided recently selected abstracts submitted for presentation at the annual American Society of Clinical Oncology meeting to be held during May 31- June 3, 2003 in Chicago, which include results from specific sites who participated in the expanded access program. It is recognized that this is only a fraction of the population treated under this program and are single arm studies with no comparator. Acknowledging these limitations, varying prior therapy, and potential bias of patients who were entered in this program, the response rates in NSCLC patients from the different sites reported vary from 0% to 15%, and one site in Singapore reporting 39% response rate (Table j). Excluding results from this site (Singapore site), analysis of the combined data from the reported sites reveal an estimated **response rate is 6.5% with a 95% CI of 4.9% to 8.5%.**
5. The results as reported in the abstracts submitted in the non-NSCLC patients' protocols report minimal response rates (Table k).
6. To date among the drugs approved under subpart H based on the tumor response rate evaluation in DODP, irinotecan had the least **response rate of 15% (95% C.I.: 10% - 20%)** at the time of approval. The approval was based on data from three open-label, single-agent, clinical studies, involving a total of 304 patients in 59 centers, supporting the use of irinotecan in the treatment of patients with metastatic cancer of the colon or rectum that had recurred or progressed following treatment with 5-FU-based therapy. Irinotecan has been further granted full approval based on demonstrated survival benefit in randomized Phase III studies.
7. After the September 24, 2002 ODAC meeting, several cases of severe acute interstitial pneumonia including deaths have been reported (post-marketing data) predominantly in Japan where the ZD1839 has been approved since June 2002. Inoue et al (The Lancet, 361:137-139, Jan 2003) have published their experience in treating 18 patients with advanced NSCLC. They have reported 4/18 patients were diagnosed with acute interstitial pneumonia, 2/4 resulting in death. All the 4 patients were male, smokers, 2/4 had adenocarcinoma, 1/4 large cell carcinoma and 1/4 squamous cell carcinoma. It is recognized that this is a report from one center and that there are limitations in interpreting this data. For detailed review of safety evaluation please refer to the medical officer's review.

D.

Statistical Evaluation of Collective Evidence:

ZD1839 (Iressa) appears to have anti-tumor activity. However the estimates of the response rates vary significantly in different subgroups. The response rate estimates are based on small sample of patients from a single arm trial. In the patient population (advanced NSCLC patients refractory/intolerant to platinum and docetaxel therapy) for which the sponsor is seeking approval, it appears that the response rates in males, smokers, and patients of white origin are minimal. However these hypotheses need to be

further tested to demonstrate clinical benefit in Phase III randomized, controlled, comparative trials.

In this reviewer's opinion, the sponsor's claim of efficacy of ZD1839 is not supported by:

- Collective evidence based on minimal and varying tumor response rates observed in the single arm registration trial, minimal response rates observed in the reported fraction of expanded access program among the NSCLC patients, and minimal response rates observed in the reported non-NSCLC studies.
- The compelling results from two well conducted, randomized Phase III trials which failed to show efficacy of ZD1839 in combination with chemotherapy with respect to overall survival for the first-line treatment of advanced non-small cell lung cancer patients raising question about the clinical benefit of ZD1839.

/S/

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Rajeshwari Sridhara
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STATISTICAL REVIEW AND EVALUATION

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Medical Division: Oncology Drug Products (HFD-150)
Biometrics Division: Division of Biometrics I (HFD-710)

NDA NUMBER: NDA 21-399

DRUG NAME: IRESSA (ZD1839) 250 mg Tablets

INDICATION: Locally advanced or metastatic non-small cell lung cancer after failure of both platinum-based and docetaxel chemotherapies

SPONSOR: AstraZeneca

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1 Executive Summary of Statistical Findings

1.1 Recommendations and Conclusions

In this reviewer's opinion the data and results of the one, small, single arm, Phase II Study 1089IL/0039 do not support the sponsor's claim of efficacy of ZD1839 with respect to a surrogate endpoint (tumor response rate) for the third-line treatment of advanced non-small cell lung cancer patients. The sponsor's claim of efficacy is not supported by the compelling results from two well conducted, randomized Phase III trials which failed to show efficacy of ZD1839 in combination with chemotherapy with respect to overall survival for the first-line treatment of advanced non-small cell lung cancer patients.

1.2 Brief Overview of Clinical Studies

This application consists of report of results from registration Study 1839IL/0039 in third-line advanced non-small cell lung cancer (NSCLC) patients, supportive data from Study 1839IL/0016 in second-line treatment of advanced NSCLC patients, and results from two large, well conducted, randomized trials, Study 1839IL/0014 and Study 1839IL/0017 in first-line treatment advanced NSCLC patients.

The registration Study 1839IL/0039 (referred as Study 39 here after) was a multi-center Phase II trial with advanced NSCLC patients randomized to 250 mg and 500 mg ZD1839 treatment arms. A total of 216 patients were enrolled in this study. One hundred and thirty nine (139) patients of the 216 patients met the criteria for third-line treatment of non-small cell lung cancer. The primary efficacy endpoints of this study were objective tumor response rate and symptom improvement rate.

Study 1839IL/0016 (referred as Study 16 here after) was a multi-center Phase II trial with advanced NSCLC patients randomized to 250 mg and 500 mg ZD1839 treatment arms. This study did not include US patients and was stratified between Japanese and non-Japanese patients. A total of 102 Japanese patients and 106 non-Japanese patients were enrolled in this study. The primary efficacy endpoint of this study was objective tumor response rate.

Study 1839IL/0014 (referred as Study 14 here after) was a randomized, double-blinded, Phase III comparative trial of 2 doses of ZD1839 (250 mg and 500 mg) in combination with gemcitabline and cisplatin versus placebo in combination with gemcitabine and cisplatin in chemotherapy-naïve patients with advanced (stage III or IV) non-small cell lung cancer. A total of 1093 patients were enrolled in this study. The primary efficacy endpoint of this study was overall survival.

Study 1839IL/0017 (referred as Study 17 here after) was a randomized, double-blinded, Phase III comparative trial of 2 doses of ZD1839 in combination with paclitaxel and carboplatin versus placebo in combination with paclitaxel and carboplatin in chemotherapy-naïve patients with advanced (stage III or IV) non-small cell lung cancer. A total of 1067 patients were enrolled in this study. The primary efficacy endpoint of this study was overall survival.

1.3 Statistical Issues and Findings

Statistical Issues:

- Efficacy claim with respect to Objective Tumor Response with ZD1839 is based on a small group of 64 patients treated at 250 mg ZD1839 (Study 39) and patient population is heterogeneous (third and second-line treatment patients).
- Symptom improvement is not interpretable without control data. Symptom improvement possibly confounded by concomitant medication effect and patient characteristics.
- The definitions of symptomatic patient and symptom improvement based on LCS scores have not been validated in a prospectively, randomized, controlled study.
- There is no comparative control arm (no non-ZD1839 arm) in Study 39
- There is no statistically significant difference with respect to overall survival between ZD1839 treated group and Placebo treated group in the two well conducted, placebo controlled, randomized phase III studies in over 2000 patients.
- There is no difference between ZD1839 treated arm and Placebo treated arm with respect to secondary endpoints including response rate and time to progression in both the phase III studies.
- The regulation Subpart H (CFR 314.510) for accelerated approval of new drug for serious or life-threatening illnesses states that '*FDA may grant marketing approval for a new drug product on the basis of adequate and well-controlled clinical trials establishing that the drug product has an effect on a surrogate end-point that is reasonably likely, based on epidemiologic, therapeutic, patho-physiologic , or other evidence, to predict clinical benefit or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity. Approval under this section will be subject to the requirement that the applicant study the drug further, to verify and describe its clinical benefit, where there is uncertainty as to the relation of the surrogate endpoint to clinical benefit, or of the observed clinical benefit to ultimate outcome.....*'. This application is for consideration of accelerated approval of ZD1839 based

on efficacy measured by tumor response as surrogate endpoint in a phase II study. However, confirmatory, well conducted, randomized, phase III studies have not confirmed evidence of clinical benefit with respect to overall survival of ZD1839.

Findings:

Study 39:

Table A gives the estimates of objective tumor response rates (primary endpoint) in the patients who were eligible for third-line treatment in this Phase II study.

Table A: Objective Tumor Response in Platinum and Docetaxel Refractory Patient Population (FDA Analyses)

Treatment Arm	Response Rate	95% C.I.	97.5% C.I.*
250 mg ZD1839	9/64 (14.1%)	6.6%, 25.0%	5.9%, 26.7%
500 mg ZD1839	5/75 (6.7%)	1.8%, 16.2%	1.8%, 16.2%

*: Protocol specified confidence interval

Study 16:

Table B gives the estimates of objective tumor response rates (primary endpoint) of this Phase II study in second-line patients.

Table B: Objective Tumor Response Rate in Study 16 (Sponsor Analyses)

Treatment Arm	Japanese Patients		Non-Japanese Patients	
	Response Rate	95% C.I.	Response Rate	95% C.I.
250 mg ZD1839	15/51 (29.4%)	17.5% - 43.8%	4/52 (7.7%)	2.1% - 18.5%
500 mg ZD1839	14/51 (27.4%)	15.9% - 41.7%	6/54 (11.1%)	4.2% - 22.6%

Study 14:

Table C gives the survival analyses results of this Phase III study in first-line patients.

Table C: Study 14 Survival Analyses Results

Treatment Arm*	N	Median survival in Days (95% C.I.)	Hazard Ratio* * (95% C.I.)	P-value
250 mg ZD1839	365	299 (255, 325)	1.073 (0.897, 1.284)	0.4832
500 mg ZD1839	365	268 (242, 316)	1.098 (0.919, 1.312)	0.3041
Placebo	363	302 (272, 342)		

*: All the three groups received gemcitabine + cisplatin; **:HR – ZD1839/placebo

Study 17:

Table D gives the survival analyses results of this Phase III study in first-line patients.

Table D: Study 17 Survival Analyses Results

Treatment Arm*	N	Median survival in Days (95% C.I.)	Hazard Ratio** (95% C.I.)	P-value
250 mg ZD1839	347	300 (264, 334)	1.043 (0.874, 1.244)	0.6429
500 mg ZD1839	345	302 (268, 352)	0.962 (0.804, 1.151)	0.6710
Placebo	345	337 (307, 368)		

*: All the three groups received paclitaxel + carboplatin; **:HR – ZD1839/placebo

Reviewer's Comments:

1. Only 139 of the 216 patients enrolled in the Study 39 were evaluable as patients eligible for third-line treatment of NSCLC. Therefore, for the purpose of accelerated approval (unmet need) only the results based on these 139 patients who were refractory to platinum and docetaxel can be considered.
2. In patients who were eligible for third-line treatment: the lower 97.5% confidence limit of the objective response rate was **5.9%** in the 250 mg ZD1839 treatment arm based on a small group of **64 patients**; and the lower 97.5% confidence limit of the objective response was as low as **1.8%** in the 500 mg ZD1839 treatment arm based on data from **75 patients**.
3. The reliability of these estimates of response rates are questionable given that (a) these estimates are based on small sample sizes (64 and 75 patients in 250 mg and 500 mg ZD1839, respectively), (b) the response rate is lower in the

higher dose compared to lower dose of ZD1839 arm, and (c) the lower confidence limits for objective tumor response rate vary from 1.8% to 6.6%.

4. The agency had clearly communicated to the sponsor that the LCS data would only be considered as supportive to the validity of objective response rate for accelerated approval. From the agency's perspective objective tumor response rate was the primary efficacy endpoint in an uncontrolled study.
5. **Symptom improvement is not interpretable without control or non-ZD1839 treatment data.** Furthermore symptom improvement is likely to be confounded by concomitant medication effect and patient characteristics.
6. Study 16 was conducted in second and first line patients. The results of this study are applicable for the accelerated approval as there exists approved treatment for first and second-line treatment of NSCLC patients. Furthermore, there was no evidence of hypothesized efficacy (lower confidence limit of objective tumor response rate < 5%) in the non-Japanese (94.4% Caucasian) patients.
7. Both the Studies 14 and 17 were well conducted, placebo controlled, double-blinded, randomized, Phase III trial conducted in over 2000 first-line advanced NSCLC patients. These studies have served as confirmatory studies to establish efficacy of ZD1839. **Both the studies failed to show evidence of efficacy of ZD1839** based on the primary efficacy endpoint of overall survival.
8. Furthermore, both the randomized Studies 14 and 17 did not demonstrate efficacy of ZD1839 with respect to the secondary endpoints of progression-free survival and response rate.

2 Statistical Review and Evaluation of Evidence

2.1 Introduction

Lung cancer is a common disease in U.S. With the currently available treatments, the median survival for patients with advanced non-small cell lung cancer (NSCLC) is about 8 months, and 1-year survival rate is approximately 35%. Patients who have failed treatment with platinum-based regimens and then treated with docetaxel have a median survival of 5-7 months compared to 5 months with best supportive care. One-year survival rate for docetaxel is 32% versus 19% for the best supportive care. Currently the treatments approved for the first line therapy of NSCLC Stage IIIB/IV patients are paclitaxel/cisplatin, gemcitabine/cisplatin, and vinorelbine ± cisplatin, and approved treatment for the second line therapy of NSCLC Stage IIIB/IV patients is docetaxel. No drug is approved for the third line setting of NSCLC Stage IIIB/IV patients.

New approaches have been explored in the treatment of NSCLC which include agents that inhibit signal transduction which is largely mediated by the phosphorylation of tyrosine residues by tyrosine kinases. Enzymes that constitute integral components of transmembrane receptor molecules are known as receptor tyrosine kinases, which represents a large family of proteins including epdermal growth factor receptor (EGFR). Preclinical studies of ZD1839 (Iressa), an anilinoquinazoline, have shown that ZD1839 is a potent and selective EGFR tyrosine kinase inhibitor. Oral dosing of ZD1839 in a range of human tumor xenografts have shown growth delay, and tumor regression at higher doses.

The registration Study 1839IL/0039 (referred as Study 39 here after) was a multicenter, randomized, phase II trial designed as single arm trial of ZD1839 250 mg tablet/day and ZD1839 500 mg tablet/day as a therapy for locally advanced or metastatic NSLC patients who had failed platinum containing regimen and docetaxel. The trial treatment was continued until 4 months after the last patient was recruited unless treatment was stopped due to withdrawal criteria.

First patient was entered in this Study 39 on November 7, 2000 and the last patient was entered on April 6, 2001. The data cut-off date for this application was August 1, 2001.

Results from Study 1839IL/0016 (referred as Study 16 here after) were also submitted as supportive evidence to Study 39. Study 16 was a multicenter, randomized, phase II trial designed as single arm trial of ZD 1839 250 mg tablet/day and ZD1839 500mg tablet/day as a therapy for patients with advanced NSCLC who had failed one or two previous chemotherapy regimens, at least one having contained platinum. The trial treatment was taken until disease progression, or discontinuation of trial therapy.

First patient was entered in this Study 16 on October 2, 2000 and the last patient was entered on January 30, 2001. The data cut-off date for this application was May 22, 2001.

Statistical evaluation of efficacy evidence of the Study 39 is presented in section 2.10. In section 2.12 a brief summary of the results of Study 16 is presented. In section 2.13 results of two randomized, phase III trials (Study IL1839/0014 and Study IL1839/007) conducted in first line NSCLC patients are presented. These two studies were not part of the original submission of this application. An overall statistical evaluation of collective evidence and conclusions are presented in section 3 of this review. This review is focussed on the efficacy aspect of the application.

2.2 Major Statistical Issues:

- Efficacy claim with respect to Objective Tumor Response with ZD1839 is based on a small group of 64 patients treated at 250 mg ZD1839 and patient population is heterogeneous (third and second-line treatment patients).
- Symptom improvement is not interpretable without control data. Symptom improvement possibly confounded by concomitant medication effect and patient characteristics.
- The definitions of symptomatic patient and symptom improvement based on LCS scores have not been validated in a prospectively, randomized, controlled study.
- There is no comparative control arm (no non-ZD1839 arm) in Study 39
- There is no statistically significant difference with respect to overall survival between ZD1839 treated group and Placebo treated group in the two well conducted, placebo controlled, randomized phase III studies in over 2000 patients.
- There is no difference between ZD1839 treated arm and Placebo treated arm with respect to secondary endpoints including response rate and time to progression in both the phase III studies.
- The regulation Subpart H (CFR 314.510) for accelerated approval of new drug for serious or life-threatening illnesses states that '*FDA may grant marketing approval for a new drug product on the basis of adequate and well-controlled clinical trials establishing that the drug product has an effect on a surrogate end-point that is reasonably likely, based on epidemiologic, therapeutic, patho-physiologic , or other evidence, to predict clinical benefit or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity. Approval under this section will be subject to the requirement that the applicant study the drug further, to verify and describe its clinical benefit, where there is uncertainty as to the relation of the surrogate endpoint to clinical benefit, or of the observed clinical benefit to ultimate outcome.....*'.

This application is for consideration of accelerated approval of ZD1839 based on efficacy measured by tumor response as surrogate endpoint in a phase II study. However, confirmatory, well conducted, randomized, phase III studies have not confirmed evidence of clinical benefit with respect to overall survival of ZD1839.

2.3 Data Analyzed and Sources

Data used for review are from the electronic submission received on 5/23/02. The network path are "\\CDSESUB1\N21399\N_000\2002-05-23\crt\datasets\il0039" and "\\CDSESUB1\N21399\N_000\2002-05-23\crt\datasets\il0016". Study protocols and case histories submitted on 11/5/01 and 12/27/01 were also reviewed. Furthermore, phase III data submitted under IND [redacted] on August 27, 2002 was also reviewed.

2.4 Study Objectives of Study 39

The primary objectives of the Study 39 were to evaluate objective tumor response rate with ZD1839 at doses of 250 and 500 mg daily and to evaluate symptom improvement rate.

The secondary objectives of this trial were to estimate disease control rate, to estimate progression-free survival and overall survival, to estimate time to worsening of symptoms, to characterize the safety profile of ZD1839 at doses of 250 and 500 mg daily, to evaluate changes in quality of life, and to evaluate demographic, and pathophysiological factors affecting exposure to ZD1839.

2.5 Efficacy Endpoints

The primary efficacy endpoints were: (1) objective tumor response (complete + partial response) using Southwest Oncology Group (SWOG) modified UICC/WHO criteria, and (2) symptom improvement rate as measured by the Lung Cancer Subscale (LCS) of the FACT-L.

Tumor assessments were done 14 days before randomization, approximately 28 days and 56 days after randomization and approximately every 8 weeks thereafter. LCS data was collected on a weekly basis starting from baseline data. The seven item LCS scale included the following items:

	Not at all	A little bit	Some-what	Quite a lot	Very much
*1. I have been short of breath**	0	1	2	3	4
*2. I am losing weight**	0	1	2	3	4
3. My thinking is clear	0	1	2	3	4
*4. I have been coughing**	0	1	2	3	4
5. I have a good appetite	0	1	2	3	4
*6. I feel tightness in my chest**	0	1	2	3	4
7. Breathing is easy for me	0	1	2	3	4

*: In computing total LCS score, the scores of these italicized items were reversed so that a score of 4 meant no symptom and a score of zero meant has most symptom.

Patients were required to be symptomatic at baseline defined as patients with baseline LCS total score of ≤ 24 points. The total LCS score was derived as the sum of the scores of the 7 scored items of the scale, and a visit response of improved, worsened, or no change was defined relative to the change from baseline in total LCS score (improved, ≥ +2; worsened, ≤ -2; no change, > -2 and < +2). A best overall response for LCS was determined in conjunction with assigned visit responses as improved if two visit responses of improved (a change from baseline of ≥ +2) a minimum of 28 days apart with no interim visit response of worsened (a change from baseline of ≤ -2). Improvement rate was calculated as the percentage of all analyzed patients with a best overall response of improved.

The secondary efficacy variables were: (1) disease control rate (complete + partial response + stable disease), (2) progression-free survival, overall survival, (3) frequency and severity of adverse events, (4) changes in QOL using the FACT-L including time to worsening, and (5) trough concentrations of ZD1839.

Reviewer's Comments:

1. The agency had clearly communicated to the sponsor on June 14, 2001 and on August 18, 2001, that the LCS data would only be considered as supportive to the validity of objective response rate for accelerated approval. When the sponsor proposed once again to retain symptom improvement rate as a co-primary endpoint, the agency left to the sponsor the burden of demonstrating that the symptom findings are credible in a single arm study.
2. The sponsor refers to the publications by Cella et.al. (Lung Cancer 12 (1995) 199-220; J Clin Epidemiology 55 (2002) 285-295) for justification of using a 2-point improvement in LCS score to be clinically meaningful. The 1995 Lung Cancer paper was based on data collected from 41 lung cancer patients. This article reports that the mean 7-item LCS scores rose an average of 2.0 points (**standard deviation = 6.2**) in the **6/41 patients** whose performance

status improved by a point, dropped an average of 0.48 points (standard deviation = 3.1) in the 23 patients whose performance status remained unchanged and dropped an average of 2.75 points (standard deviation = 5.2) in the 12 patients whose performance status declined. Based on these observations the authors suggest to consider a change in two points on the 7-item LCS to be clinically meaningful. Clearly this observation is hypothesis generating and can not be considered as a validated measure for symptom improvement that is clinically meaningful.

3. The second publication in J Clin Epidemiology reports results obtained from combined data on 573 NSCLC patients who had received 3 different chemotherapy regimens. It is not clear if all of these patients were symptomatic at baseline. From their demographic description it appears that the mean baseline LCS total score in patients with ≤ 1 symptom was 20.8 with a standard deviation of 4.5. They report that mean improvement in LCS score *from baseline to 12 weeks* was 2.4 points in patients who had responded to treatment. The variation in terms of standard deviation is not reported. Again there was no non-treatment arm to validate whether the proposed symptom improvement is clinically meaningful in a prospective randomized study.
4. A baseline total LCS score of at most 24 is considered as symptomatic. This has not been prospectively validated.
5. There is a ceiling effect as the maximum score that a patient can score is 28.
6. Symptom improvement is not interpretable without control or non-ZD1839 treatment arm.

2.6 Sample Size Considerations

Patients who met the eligibility criteria were randomized between 250 mg and 500 mg of ZD1839 in this phase II trial.

Sample size calculations were based on having a power of 0.90 for a 1-sided 0.0125 significance level test for each of the rates (objective tumor response rate and symptom improvement rate) to be ≤ 5% (under H_0) when the true rate was 15%. This trial was designed with a total of 200 patients (100 patients per dose of ZD1839) in order to achieve a 1-sided 0.0115 significance level and power of 0.901.

Furthermore, for each dose of ZD1839 it was stated that Hochberg's procedure would be used to maintain an overall 1-sided 0.025 significance level for the two primary endpoints. The 1-sided significance for each endpoint would be calculated as the probability of the observed number or greater events (objective responses or symptom improvements) given the sample size, assuming a true event rate of 5%. If the larger of the two significance levels is ≤ 0.025, then it would be concluded that the event rate for both endpoints is > 5%. Given exactly 100 patients per dose, 11 events are required to conclude that the event rate for a

dose is > 5% at both a 1-sided 0.025 and 0.0125 significance level (11% observed rate, 95% C.I. 5.6% - 18.8%, 97.5% C.I. 5.1% - 20.0%).

It was also stated in the protocol that the two doses of ZD1839 would be compared with respect to the two primary endpoints with Fisher's exact test.

Reviewer's Comments:

1. The design and sample size calculations were not based on comparison between the two doses, i.e., the sample size calculations were based on hypotheses of eliminating ≤ 5% response rates and symptom improvement rates within each single treatment arm.
2. From the agency's perspective objective tumor response rate was the primary efficacy endpoint in an uncontrolled study.
3. A total of 216 patients (102 in the 250 mg arm and 114 in the 500 mg arm) were enrolled into this study.

2.7 Stratification

The study was not stratified by any factors.

2.8 Interim Analysis

No interim analysis for efficacy was planned in this phase II study.

2.9 Efficacy Analysis Methods

The primary analysis population for the overall best objective tumor response rate and symptom improvement rate per LCS was the ITT population. The response rate and symptom improvement rate were planned to be estimated separately by dose, and exact 95% confidence intervals were planned to be reported for each rate.

Reviewer's Comment:

-Although the study was not designed to conduct any comparative analyses, the protocol states that the two doses of ZD1839 would be compared with respect to the two primary endpoints using Fisher's exact test.

2.10 Sponsor's Results and Statistical Reviewer's Findings/Comments of Study 39

This section will summarize the results of intention to treat analysis for Study 39. In this study a total of 216 patients were randomized (from -- centers) to 250 mg ZD1839 (102 patients) and 500mg ZD1839 (114 patients).

2.10.1 Baseline Characteristics

The baseline demographic characteristics of the patients who were on the Study 39 are as displayed in Table 1A.

Table 1A: Baseline Characteristics of ITT Patients in Study 39 (FDA Analysis)

Characteristic	ZD1839 Dose	
	250 mg / day N = 102	500 mg / day N = 114
Age Group: n (%)		
15 – 64 years	64 (62.7)	66 (57.9)
64 – 74 years	30 (29.4)	43 (37.7)
75 years and above	8 (7.8)	5 (4.4)
Sex: n (%)		
Male	60 (58.8)	63 (55.3)
Female	42 (41.2)	51 (44.7)
Race: n(%)		
White	93 (91.2)	103 (90.4)
Black	3 (2.9)	4 (3.5)
Asian/Oriental	1 (1.0)	3 (2.6)
Hispanic	2 (2.0)	3 (2.6)
Other	3 (2.9)	1 (0.9)
Smoke: n (%)		
Yes	75 (73.5)	90 (78.9)
No	27 (26.5)	21 (18.4)
Baseline WHO Performance Status		
0	18 (17.6)	15 (13.2)
1	64 (62.7)	75 (65.8)
2	19 (18.6)	23 (20.2)
3	0 (0.0)	1 (0.9)
Tumor Histology		
Squamous	14 (13.7)	18 (15.8)
Adenocarcinoma	69 (67.6)	73 (64.0)
Undifferentiated	9 (8.8)	8 (7.0)
Large Cell	3 (2.9)	3 (2.6)
Squamous & Adenocarcinoma	7 (6.9)	9 (7.9)

Reviewer's Comments:

This application is for accelerated approval for the third line treatment of NSCLC where there is an unmet need. Thus in order for the patients to be eligible for

third-line treatment, patients had to have received platinum containing treatment and docetaxel. One hundred and thirty nine of the 216 patients met this criterion per FDA's Medical Reviewer. For the purpose of accelerated approval only the results based on these 139 patients who were refractory to platinum and docetaxel can be considered. The baseline demographics of these 139 patients are presented in Table 1B. There were slightly more males, majority were smokers, majority were white and majority had adenocarcinoma.

Table 1B: Baseline Characteristics of Platinum and Docetaxel Refractory Patients in Study 39 (FDA Analysis)

Characteristic	ZD1839 Dose	
	250 mg / day N = 64	500 mg / day N = 75
Age Group: n (%)		
15 – 64 years	42 (65.6)	43 (57.3)
64 – 74 years	18 (28.1)	29 (38.7)
75 years and above	4 (6.3)	3 (4.0)
Sex: n (%)		
Male	36 (56.3)	40 (53.3)
Female	28 (43.7)	35 (46.7)
Race: n(%)		
White	59 (92.2)	67 (89.3)
Black	1 (1.6)	2 (2.7)
Asian/Oriental	1 (1.6)	1 (1.3)
Hispanic	0 (0.0)	4 (5.3)
Other	3 (4.7)	1 (1.3)
Smoke: n (%)		
Yes	44 (68.7)	58 (80.6)
No	20 (31.3)	14 (19.4)
Baseline WHO Performance Status		
0	14 (21.9)	9 (12.0)
1	34 (53.1)	52 (69.3)
2	15 (23.4)	14 (18.7)
3	0 (0.0)	0 (0.0)
Tumor Histology		
Squamous	9 (14.1)	11 (15.1)
Adenocarcinoma	45 (70.3)	49 (67.1)
Undifferentiated	6 (9.4)	4 (5.5)
Large Cell	2 (3.1)	2 (2.7)
Squamous & Adenocarcinoma	2 (3.1)	7 (9.6)

2.10.2 Primary Efficacy Analyses

Objective Tumor Response:

Sponsor analyses results of the objective tumor response in the ITT population are presented in Table 2A. FDA analyses results of the objective tumor response in the platinum and docetaxel refractory patients are presented below in Table 2B.

Table 2A: Objective Tumor Response in ITT Population (Sponsor Analyses)

Treatment Arm	Response Rate	95% C.I.	97.5% C.I.*
250 mg ZD1839	12/102 (11.8%)	6.2% - 19.7%	5.6% - 20.8%
500 mg ZD1839	10/114 (8.8%)	4.3%, 15.5%	3.8% - 16.6%

*: Protocol specified confidence interval

Table 2B: Objective Tumor Response in Platinum and Docetaxel Refractory Patient Population (FDA Analyses)

Treatment Arm	Response Rate	95% C.I.	97.5% C.I.*
250 mg ZD1839	9/64 (14.1%)	6.6%, 25.0%	5.9%, 26.7%
500 mg ZD1839	5/75 (6.7%)	1.8%, 16.2%	1.8%, 16.2%

*: Protocol specified confidence interval

Reviewer's Comments:

1. The lower 97.5% confidence limit of the objective response rate is 5.6% in the 250 mg ZD1839 arm and as low as 3.8% in the 500 mg ZD1839 arm in the ITT population. However this is not the population for which the sponsor is seeking approval.
2. The lower 97.5% confidence limit of the objective response rate in the population of interest, i.e., in patients who are refractory to platinum and docetaxel, is **5.9%** in the 250 mg ZD1839 treatment arm. It should be noted that this is based on a very small group of **only 64 patients.**
3. The lower 97.5% confidence limit of the objective response rate in the population of interest, i.e., in patients who are refractory to platinum and docetaxel, is as low as **1.8 %** in the 500 mg ZD1839 treatment arm. It should be noted that this is based on data from **75 patients.**
4. The reliability of these estimates are questionable given that the estimates of the objective response rates are based on small sample sizes (64 and 75 patients in 250 mg and 500 mg ZD1839, respectively), the response rate is lower in the higher dose compared to lower dose of ZD1839 arm, and the lower confidence limits vary from 1.8% to 6.6%.
5. The responders were predominately female patients who were non-smokers and had adenocarcinoma (Table 3).
6. The duration of response at the time of data cut-off among the 14 responders (9 in the 250 mg and 5 in the 500 mg ZD1839 arms) are presented in Table 4. The follow-up data was premature to interpret at the time of data cut-off date.

Table 3: Characteristics of Responders Who Were Refractory to Platinum and Docitaxel (FDA Analyses)

Treatment Arm	Sex	Smoker	Histology
250 mg ZD 1839	7 Females	1 Smoker	1 Adenocarcinoma
		6 Non-smokers	4 Adenocarcinoma 1 Squamous 1 Large cell
	2 Males	2 Non-smokers	1 Adenocarcinoma 1 Undifferentiated
500 mg ZD1839	4 Females	2 Smokers	2 Adenocarcinoma
		2 Non-smokers	1 Adenocarcinoma 1 Squamous
	1 Male	1 Smoker	1 Adenocarcinoma

Table 4: Duration of Response in the Platinum and Docetaxel Refractory Patients Who Had Tumor Response

Treatment Arm	Duration of Response in Months (As of Aug 1, 2001)
250 mg ZD1839	1+, 2+, 3+, 3+, 3+, 5, 5+, 5+, 7+
500 mg ZD1839	2+, 3, 3+, 4, 4+

+: censored at

Symptom Improvement Rate:

The sponsor analyses of symptom improvement rates in the ITT population are presented in Table 5A. In Table 5B results of FDA analyses of symptom improvement rate (improvement as defined by the sponsor) in patients refractory to platinum and docetaxel are presented.

Table 5A: Symptom Improvement in ITT Population (Sponsor Analyses)

Treatment Arm	Symptom Improvement Rate*	95% C.I.	97.5% C.I.**
250 mg ZD1839	44/102 (43.1%)	33.4% - 53.3%	32.1% - 54.7%
500 mg ZD1839	41/114 (36.0%)	27.2% - 45.5%	26.1% - 46.8%

* LCS ≥ +2 = improved; ** Protocol specified confidence interval

Table 5B: Symptom Improvement in Platinum and Docetaxel Refractory Patient Population (FDA Analyses)

Treatment Arm	Symptom Improvement Rate*	95% C.I.	97.5% C.I.**
250 mg ZD1839	30/64 (46.9%)	34.3% - 59.8%	32.7% - 61.5%
500 mg ZD1839	26/75 (34.7%)	24.0% - 46.5%	22.7% - 48.2%

* LCS ≥ +2 = improved; ** Protocol specified confidence interval

Reviewer's Comments:

1. A patient with a baseline total LCS score of ≤ 24 is defined by the sponsor as symptomatic patient. This is an arbitrary definition and has not been validated in any randomized controlled study.
2. An improvement in the total LCS score by 2 points is defined by the sponsor as a symptomatic improvement which is clinically meaningful. A 2 point change may occur in one of the 7 items or a change of 1 point in two items, while the changes in other items may cancel each other out. This is illustrated by the case history profile reproduced from the sponsor's report in Figures 1A and 1B (Sponsor's submission of Case Histories for Trial 1839IL/0039, 23 October 2001, pages D8 and D9). This particular patient had a baseline LCS score of 24. For the first 3 weeks the score was not recorded. At 4 weeks the LCS score was recorded as 28 and subsequently dropped to 26 and stayed at 26 from weeks 5 through 9. Thus, this patient according to the definition of sponsor was classified as a patient with symptom improvement, even though the score dropped below the baseline score beyond week 9 (Figure 1A). Figure 1B is the same example as the one presented in Figure 1A except that the profile of each item of the LCS scale over the same period of time is presented. In Figure 1A it was noted that the improvement was recorded between 5 and 9 weeks which is the time period between the two vertical lines in Figure 1B. The improvement observed is basically in one or two items by a point. This case example illustrates that a 2 point change on a scale of 28 is difficult to interpret without non-ZD1839 comparative treatment arm, particularly as it may be because of minor changes by a point in one or two items of the LCS scale.
3. Figure 2 illustrates the percentage of patients who were evaluated for symptom improvement at each of the time points starting from baseline up to 16 weeks. It is observed that 25% of the patients were missing by week 1 and only about 25% remained at 16 weeks for symptom evaluation. This attrition may be due to progression of disease. However, without a non-ZD1839 comparative treatment arm it is not possible to comment on the attrition rate.

4. Furthermore, these patients were receiving concomitant medications (please refer to FDA medical reviewer's report for details). The effect of these concomitant medications on symptoms can not be evaluated without a non-ZD1839 comparative treatment arm.
5. Because of the above listed reasons, **symptom improvement is not interpretable without control or non-ZD1839 treatment data.** Furthermore symptom improvement is likely to be confounded by concomitant medication effect and patient characteristics.

Figure 1A

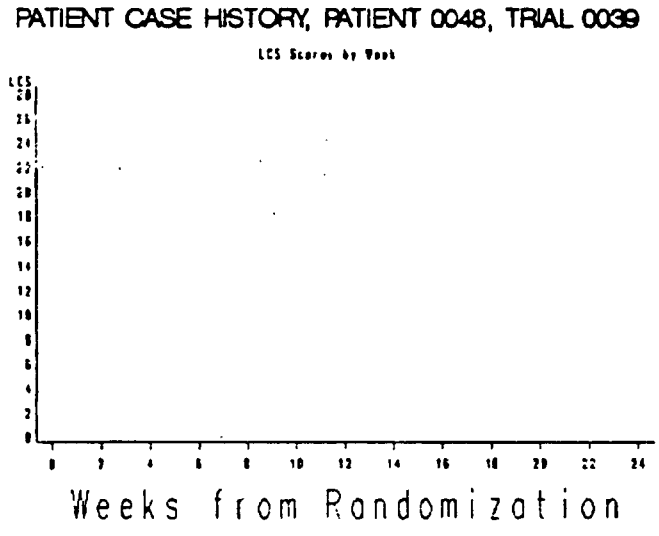


Figure 1B

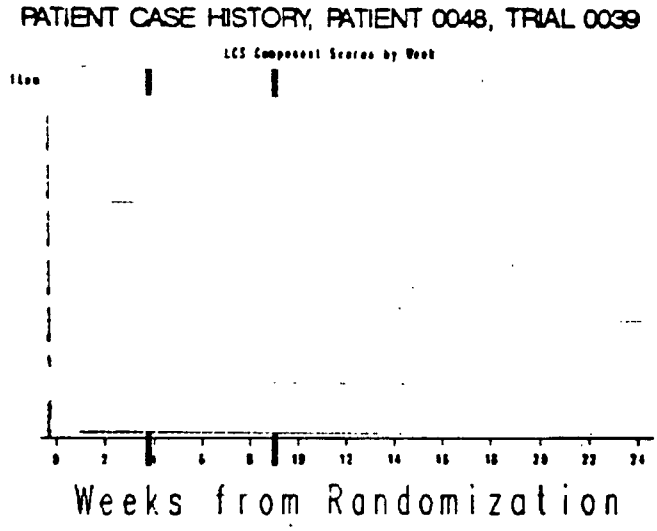
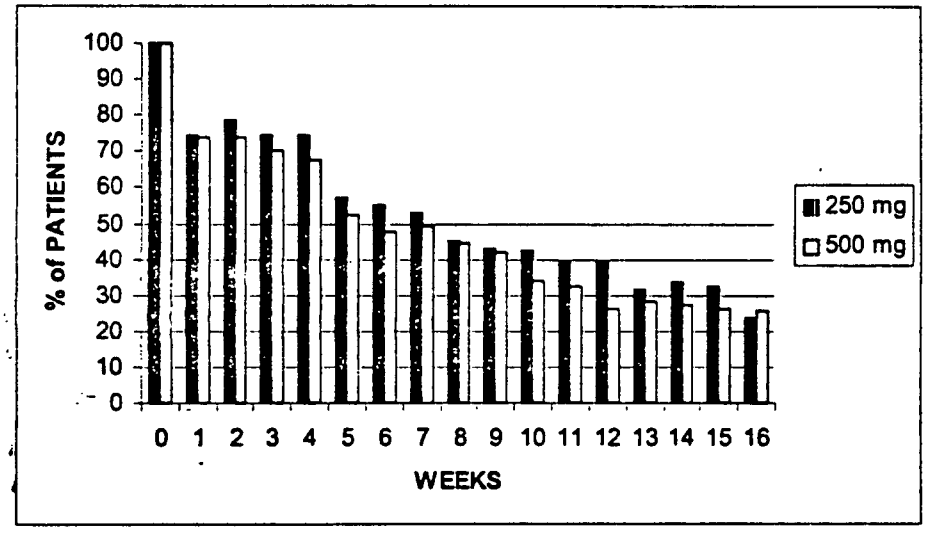


Figure 2: Percentage of Patients Evaluated Over Time



2.10.3 Secondary Efficacy Analyses

The results of secondary efficacy analyses are not reported in this review as they could be considered only as exploratory analyses. Furthermore this study did not have comparative control arm for useful interpretation of these analyses.

2.11 Statistical Review of Special Population and Subgroups of Study 39

This was a very small study and therefore no separate analysis was conducted in any subgroups.

2.12 Summary of the Results of Study 16

Results of Study 16 were submitted in this application as supportive evidence. Study 16 was a multicenter, randomized, phase II trial in Japanese and non-Japanese patients as a therapy for advanced NSCLC patients who had failed one or two previous chemotherapy regimens, at least one having contained platinum. The trial treatment was taken until disease progression, or discontinuation of trial therapy.

The primary endpoint of the trial was the objective tumor response rate. Patients were randomized between 250 mg and 500 mg daily dose levels of ZD1839 and stratified by ethnicity as Japanese versus non-Japanese. The trial was sized to independently evaluate the tumor response rate in the four strata defined by ZD1839 dose and ethnicity with 45 patients in each of the four strata. Within each stratum, the goal was to have 90% power for a 2-sided 5% significance level test that the response rate is greater than 5% when the true response rate is 20%.

The primary endpoint results of this study are presented in Table 6.

Table 6: Objective Tumor Response Rate in Study 16 (Sponsor Analyses)

Treatment Arm	Japanese Patients		Non-Japanese Patients	
	Response Rate	95% C.I.	Response Rate	95% C.I.
250 mg ZD1839	15/51 (29.4%)	17.5% - 43.8%	4/52 (7.7%)	2.1% - 18.5%
500 mg ZD1839	14/51 (27.4%)	15.9% - 41.7%	6/54 (11.1%)	4.2% - 22.6%

Reviewer's Comments:

1. This study was conducted in **second-line patients** without a comparative non-ZD1839 arm.
2. There was no evidence of hypothesized efficacy (lower confidence limit < 5%) in the non-Japanese (94.4% Caucasian) patients.
3. The sponsor has not given explanations for the observed higher response rates in Japanese patients.

2.13 Summary of Results of Randomized Phase III Trials (Studies 14 & 17)

Two large randomized phase III trials were conducted in first line treatment of NSCLC patients. These studies would have served as confirmatory studies for establishing clinical benefit of ZD1839. The summary of these two studies are presented in this section.

Study 1839IL/0014

Study 1839IL/0014 (referred here after as Study 14) was a randomized, double-blinded, Phase III comparative trial of 2 doses of ZD1839 in combination with gemcitabline and cisplatin versus placebo in combination with gemcitabine and cisplatin in chemotherapy-naïve patients with advanced (stage III or IV) non-small cell lung cancer.

All patients received gemcitabine 1000 mg/m^2 intravenously over 30 minutes on Days 1, 8, and 15 and cisplatin on Day 1 only, to be repeated in cycles of 4 weeks for a total of 6 cycles. All patients received cisplatin 100 mg/m^2 intravenously in an infusion of 500 ml 5% dextrose along with program of forced diursis. Cisplatin administration was followed after gemcitabine administration on Day 1 of each 4 week cycle.

Patients were randomized to receive either 250 mg ZD1839, 500mg ZD1839, or matching placebo tablets given daily from Day1, at approximately the same time every day. The three treatment groups were stratified by (1) weight loss in previous 6 months ≤ 5% vs. > 5%; (2) disease Stage III vs. Stage IV; (3) performance status 0-1 vs. 2; and (4) measurable disease vs. non-measurable disease.

The primary efficacy endpoint in this study was overall survival. The study was designed as superiority trial with the goal of final analysis to have 80% power for a 2-sided 5% significance level test of the hypothesis that ZD1839 increases survival relative to placebo given a hazard ratio (placebo/ZD1839) of 1.33. In computing a total of 1029 patients (343 per arm) as the required size of the trial,

exponential survival was assumed and that placebo arm 1-year survival rate to be 30% vs. 45% in ZD1839 arm.

A total of 1093 patients were enrolled into this study and 67% of events (deaths) had occurred at the time of analysis of overall survival.

The sponsor submitted data on treatment assigned, overall survival with censor information and progression-free survival with censor information on August 27, 2002. The following are the results of the protocol specified analyses. Figure 3 is the Kaplan-Meier plot of overall survival in the three treatment arms. Table 7 gives the Cox-proportional hazard model of overall survival with treatment only as the co-variate. Figure 4 is the Kaplan-Meier plot of progression-free survival in the three treatment arms. Table 8 gives the Cox-proportional hazard model of progression-free survival with treatment only as the co-variate. In addition to survival and time to progression data, the sponsor provided objective tumor response rates in each of these treatment arms. They are presented in Table 9 along with one-year survival rates in the three treatment arms. Complete raw data of this study have not been submitted by the sponsor to the FDA and therefore the data presented here have not been critically reviewed.

Figure 3

Kaplan–Meier Plot of Overall Survival Study il0014– FDA Analysis

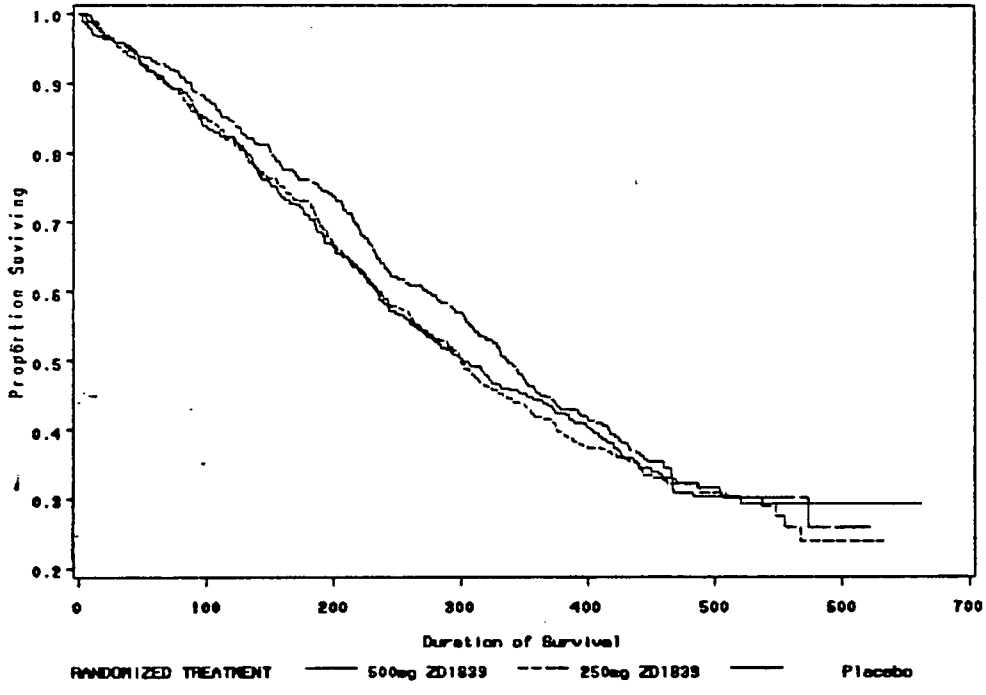


Table 7: Study 14 Survival Analyses Results

Treatment Arm*	N	Median survival in Days (95% C.I.)	Hazard Ratio* * (95% C.I.)	P-value
250 mg ZD1839	365	299 (255, 325)	1.073 (0.897, 1.284)	0.4832
500 mg ZD1839	365	268 (242, 316)	1.098 (0.919, 1.312)	0.3041
Placebo	363	302 (272, 342)		

*: All the three groups received gemcitabine + cisplatin; **:HR – ZD1839/placebo

Figure 4

Kaplan–Meier Plot of Progression–free Survival Study il0014– FDA Analysis

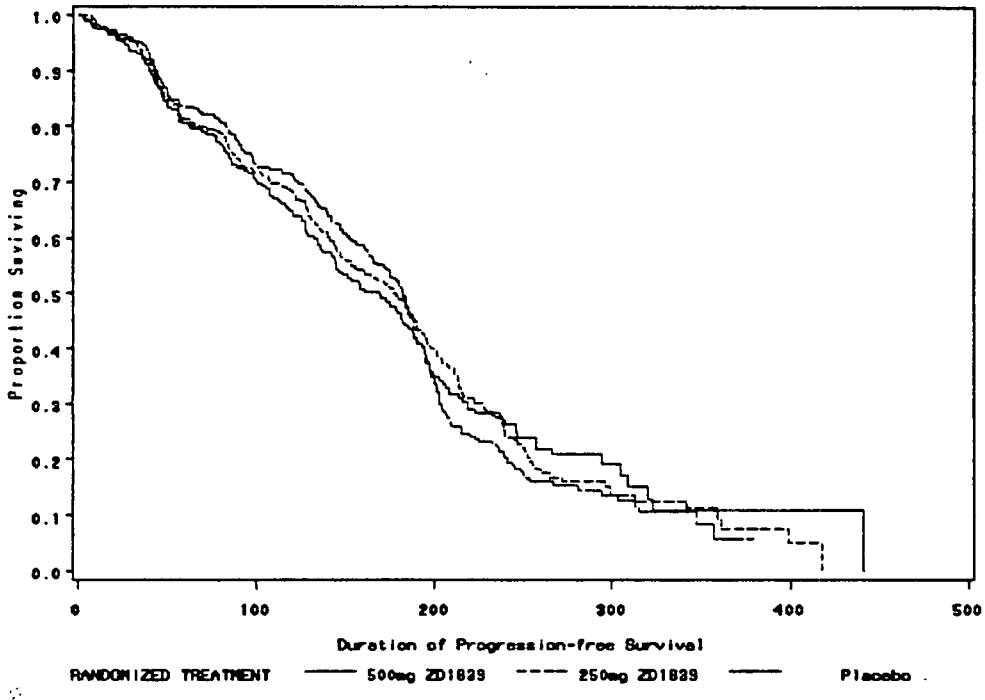


Table 8: Study 14 Progression-free Survival Analyses

Treatment Arm*	N	Median Progression-free survival in Days (95% C.I.)	Hazard Ratio** (95% C.I.)
250 mg ZD1839	365	178 (153, 190)	0.947 (0.787, 1.140)
500 mg ZD1839	365	169 (144, 187)	0.986 (0.810 1.201)
Placebo	363	182 (166, 188)	

*: All the three groups received gemcitabine + cisplatin; **:HR – ZD1839/placebo

Table 9: Study 14 Objective Response Rates and One-year Survival Rates

Treatment Arm*	% Response Rate (95% C.I.)	% One year K-M Survival Estimate (S.E.)
250 mg ZD1839	50.1 (44.7, 55.6)	43.75 (2.61)
500 mg ZD1839	49.7 (44.2, 55.2)	41.51 (2.59)
Placebo	44.8 (39.3, 50.4)	44.87 (2.64)

*: All the three groups received gemcitabine + cisplatin

Reviewer's Comments:

1. Study 14 was a well conducted, placebo controlled, double-blinded, randomized, Phase III trial in over 1000 first-line advanced NSCLC patients.
2. **The study results failed to show evidence of efficacy** based on the primary efficacy endpoint of overall survival. At the time of this analysis approximately 70% of the events (deaths) had occurred, i.e., the data set was mature for overall survival analysis. The median survival was slightly higher in the placebo arm compared to the two ZD1839 arms.
3. Progression-free survival and response rates were among several secondary efficacy endpoints that were specified in the protocol of this study. At the time of analyses 57% of events (progression) had occurred compared to 67% deaths. There were no statistically significant differences between the ZD1839 arms and placebo arm. The response rates ranged from 45% to 50% in the three arms and there were no statistically significant differences in the response rates between the ZD1839 arms and placebo.

Study 1839IL/0017

Study 1839IL/0017 (referred here after as Study 17) was a randomized, double-blinded, Phase III comparative trial of 2 doses of ZD1839 in combination with paclitaxel and carboplatin versus placebo in combination with paclitaxel and carboplatin in chemotherapy-naïve patients with advanced (stage III or IV) non-small cell lung cancer.

All patients received paclitaxel 225 mg/m2 intravenously (iv) over 3 hours on Day 1, immediately followed by carboplatin, area under the (AUC) 6.0 iv over 15-30 minutes, to be repeated in cycles of 3 weeks for a total of 6 cycles. The dose of carboplatin was based on the Calvert Formula, and the Cockroft-Gault formula for creatinine clearance was substituted for the glomerular filtration rate (GFR) in Calvert formula (Calvert formula for carboplatin dose (mg): AUC (mg .min/mL) x (GFR m:/min + 25); Cockroft-Gault formula: [(140-patient's

age)x(patient's weight in kg)]/[72 x patient's serum creatinine (for females, result multiplied by 0.85)]).

Patients were randomized to receive either 250 mg ZD1839, 500mg ZD1839, or matching placebo tablets given daily from Day1, at approximately the same time every day. The three treatment groups were stratified by (1) weight loss in previous 6 months ≤ 5% vs. > 5%; (2) disease Stage III vs. Stage IV; (3) performance status 0-1 vs. 2; and (4) measurable disease vs. non-measurable disease.

The primary efficacy endpoint of this study was overall survival. The study was designed as superiority trial with the goal of final analysis to have 80% power for a 2-sided 5% significance level test of the hypothesis that ZD1839 increases survival relative to placebo given a hazard ratio (placebo/ZD1839) of 1.33. In computing a total of 1029 patients (343 per arm) as the required size of the trial, exponential survival was assumed and 1-year survival rate in placebo to be 30% vs. 40.5% for ZD1839 arm.

A total of 1067 patients were enrolled into this study and 70% of events (deaths) had occurred at the time of analysis of overall survival.

The sponsor submitted data on treatment assigned, overall survival with censor information and progression-free survival with censor information on August 27, 2002. The following are the results of the protocol specified analyses. Figure 5 is the Kaplan-Meier plot of overall survival in the three treatment arms. Table 10 gives the Cox-proportional hazard model of overall survival with treatment only as the co-variate. Figure 6 is the Kaplan-Meier plot of progression-free survival in the three treatment arms. Table11 gives the Cox-proportional hazard model of progression-free survival with treatment only as the co-variate. In addition to survival and progression-free survival data, the sponsor provided objective tumor response rates in each of these treatment arms. They are presented in Table 12 along with one-year survival rates in the three treatment arms. The complete raw data of this study have not been submitted by the sponsor to the FDA and therefore the data presented here have not been critically reviewed.

Figure 5

Kaplan–Meier Plot of Overall Survival Study il0017– FDA Analysis

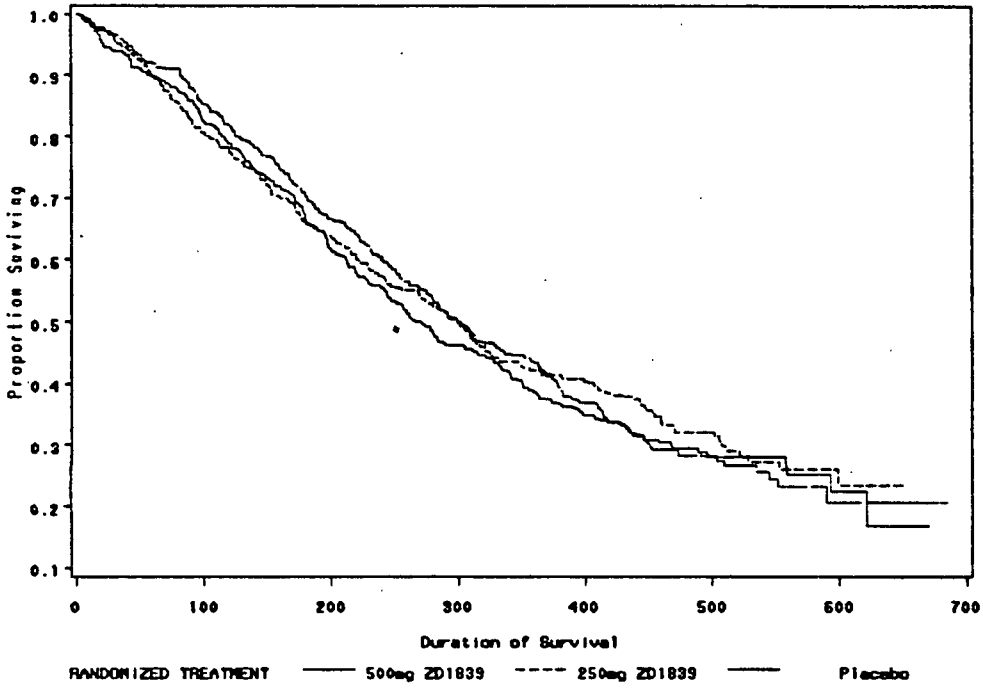


Table 10: Study 17 Survival Analyses Results

Treatment Arm*	N	Median survival in Days (95% C.I.)	Hazard Ratio** (95% C.I.)	P-value
250 mg ZD1839	347	300 (264, 334)	1.043 (0.874, 1.244)	0.6429
500 mg ZD1839	345	302 (268, 352)	0.962 (0.804, 1.151)	0.6710
Placebo	345	337 (307, 368)		

*: All the three groups received paclitaxel + carboplatin; **:HR – ZD1839/placebo

Figure 6

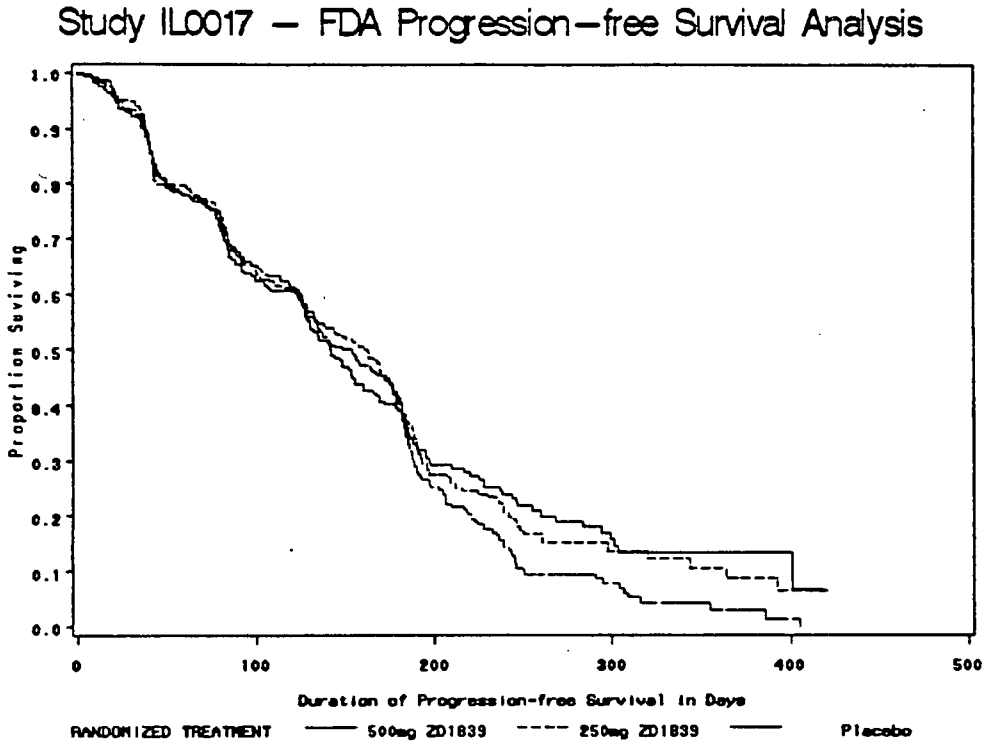


Table 11: Study 17 Progression-free Survival Analyses

Treatment Arm	N	Median Progression-free survival in Days (95% C.I.)	Hazard Ratio* (95% C.I.)
250 mg ZD1839	347	162 (133, 175)	0.863 (0.718, 1.037)
500 mg ZD1839	345	142 (127, 160)	0.852 (0.702, 1.034)
Placebo	345	154 (132, 176)	

*: All the three groups received paclitaxel + carboplatin; **:HR – ZD1839/placebo

Table 12: Study 14 Objective Response Rates and One-year Survival Rates

Treatment Arm	% Response Rate (95% C.I.)	% One year K-M Survival Estimate (S.E.)
250 mg ZD1839	35.0 (29.6, 40.6)	37.57 (2.60)
500 mg ZD1839	32.1 (27.0, 37.7)	41.89 (2.67)
Placebo	33.6 (28.1, 39.3)	42.22 (2.66)

*: All the three groups received paclitaxel + carboplatin

Reviewer's Comments:

1. Study 17 was a well conducted, placebo controlled, double-blinded, randomized, Phase III trial conducted in over 1000 first-line advanced NSCLC patients.
2. **The study results failed to show evidence of efficacy** based on the primary efficacy endpoint of overall survival. At the time of this analysis 70% of the events (deaths) had occurred, i.e., the data set was mature for overall survival analysis. The median survival was slightly higher in the placebo arm compared to the two ZD1839 arms.
3. Progression-free survival and response rates were among several secondary efficacy endpoints that were specified in the protocol of this study. At the time of analyses 61% of events (progression) had occurred compared to 70% deaths. There were no statistically significant differences between the ZD1839 arms and placebo arm. The response rates ranged from 34% to 35% in the three arms and there were no statistically significant differences in the response rates between the ZD1839 arms and placebo (Table 12).

2.14 Sponsor's Conclusions and Reviewer's Conclusions/Comments

Study 1089IL/0039 was a randomized, multicenter, Phase II study conducted in a total of 216 patients with advanced (Stage III/IV) NSCLC. The primary objective of this study was to assess the efficacy of 250 mg ZD1839 and 500 mg of ZD1839. There was no comparative control arm in this study. The primary efficacy endpoints were objective tumor response rate and symptom improvement rate. The sponsor claims that this study has demonstrated efficacy in third-line NSCLC patients for consideration of accelerated approval.

1. Only 139 of the 216 patients enrolled in the Study 39 were evaluable as patients eligible for third-line treatment of NSCLC. Therefore, for the purpose of accelerated approval (unmet need) only the results based on these 139 patients who were refractory to platinum and docetaxel can be considered.
2. In patients who were eligible for third-line treatment: the lower 97.5% confidence limit of the objective response rate was **5.9%** in the 250 mg ZD1839 treatment arm based on a small group of **64 patients**; and the lower 97.5% confidence limit of the objective response was as low as **1.8%** in the 500 mg ZD1839 treatment arm based on data from **75 patients**.
3. The reliability of these estimates of response rates are questionable given that (a) these estimates are based on small sample sizes (64 and 75 patients in 250 mg and 500 mg ZD1839, respectively), (b) the response rate is lower in the

higher dose compared to lower dose of ZD1839 arm, and (c) the lower confidence limits for objective tumor response rate vary from 1.8% to 6.6%.

4. The agency had clearly communicated to the sponsor that the LCS data would only be considered as supportive to the validity of objective response rate for accelerated approval. From the agency's perspective objective tumor response rate was the primary efficacy endpoint in an uncontrolled study.
5. **Symptom improvement is not interpretable without control or non-ZD1839 treatment data.** Furthermore symptom improvement is likely to be confounded by concomitant medication effect and patient characteristics.
6. Study 16 was conducted in second and first line patients. The results of this study are applicable for the accelerated approval as there exists approved treatment for first and second-line treatment of NSCLC patients. Furthermore, there was no evidence of hypothesized efficacy (lower confidence limit of objective tumor response rate < 5%) in the non-Japanese (94.4% Caucasian) patients.
7. Both the Studies 14 and 17 were well conducted, placebo controlled, double-blinded, randomized, Phase III trial conducted in over 2000 first-line advanced NSCLC patients. These studies have served as confirmatory studies to establish efficacy of ZD1839. **Both the studies failed to show evidence of efficacy of ZD1839** based on the primary efficacy endpoint of overall survival.
8. Furthermore, both the randomized Studies 14 and 17 did not demonstrate efficacy of ZD1839 with respect to the secondary endpoints of progression-free survival and response rate.

3 Statistical Evaluation of Collective Evidence

In this reviewer's opinion the data and results of the one, small, single arm, Phase II Study 1089IL/0039 do not support the sponsor's claim of efficacy of ZD1839 with respect to a surrogate endpoint (tumor response rate) for the third-line treatment of advanced non-small cell lung cancer patients. The sponsor's claim of efficacy is not supported by the compelling results from two well conducted, randomized Phase III trials which failed to show efficacy of ZD1839 in combination with chemotherapy with respect to overall survival for the first-line treatment of advanced non-small cell lung cancer patients.

/S/

Rajeshwari Sridhara, Ph.D.
Mathematical Statistician
Date:

Concur: Dr. Chen
Team Leader

Dr. Mahjoob
Deputy Division Director, DBI

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HFD-710/ Dr. Chen
HFD-710/ Dr. Mahjoob
HFD-710/ Dr. Chi
HFD-700/ Dr. Anello

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