CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-743

Statistical Review(s)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

ADDENDUM 1

NDA /Serial Number:	21-743 /N000
Drug Name:	Tarceva™ (erlotinib hydrochloride, OSI-774)
Applicant:	OSI Pharmaceuticals
Indication(s):	Metastatic Non-small Cell Lung Cancer
Date(s):	Submission Date: July 30, 2004
	PDUFA Date: January 30, 2005
	Review Date: November 1, 2004
Review Priority:	Priority
Biometrics Division:	Division of Biometrics I (HFD-710)
Statistical Reviewers:	Rajeshwari Sridhara, Ph.D.
	Yeh-Fong Chen, Ph.D.
Concurring Reviewer:	Kooros Mahjoob, Ph.D., Acting Director
Medical Division:	Oncology Drug Products (HFD-150)
Clinical Team:	Martin Cohen, M.D. & John Johnson, M.D.
Project Manager:	Mr. Paul Zimmerman
Keywords:	Superiority, log-rank test, Cox regression, QoL

In this addendum additional exploratory analyses with respect to smoking history in the Study BR.21 are presented. These analyses do not change the conclusions and recommendations of the review.

The following table shows the baseline characteristics in patients with smoking history and without smoking history.

Table 1: Demographics and Baseline Characteristics of Patients by Smoking History

Characteristic	Smokers		Non-smokers	
	Tarceva (N=358)	Placebo (N=187)	Tarceva (N = 78)	Placebo (N = 49)
Sex: Female	107 (29.9%)	55 (29.4%)	60 (57.7%)	23 (54.8%)
Male	251 (70.1%)	132 (70.6%)	44 (42.3%)	19 (45.2%)
Race: Black	11 (3.1%)	10 (5.4%)	5 (4.8%)	2 (4.8%)
White	292 (81.6%)	153 (81.8%)	65 (62.5%)	26 (61.9%)
Oriental	36 (10.1%)	16 (8.6%)	25 (24.0%)	9 (21.4%)
Others	19 (5.3%)	8 (4.3%)	9 (8.7%)	5 (11.9%)
Age: <= 60 yrs	160 (44.7%)	98 (52.4%)	56 (53.9%)	23 (54.8%)
61-69 yrs	129 (36.0%)	56 (29.9%)	24 (23.1%)	11 (26.2%)
>= 70 yrs	69 (19.3%)	33 (17.7%)	24 (23.1%)	8 (19.0%)
EGFR Status: positive	58 (16.2%)	35 (18.7%)	18 (17.3%)	12 (28.6%)
negative	53 (14.8%)	32 (17.1%)	19 (18.3%)	5 (11.9%)
Unknown	247 (69.0%)	120 (64.2%)	67 (64.4%)	25 (59.5%)
Histology: Adeno	163 (45.5%)	80 (42.8%)	76 (73.1%)	33 (78.6%)
Squamous	122 (34.1%)	67 (35.8%)	11 (7.5%)	4 (9.5%)
MNSC	8 (2.2%)	2 (1.1%)	2 (1.9%)	0 (0.0%)
UNLC	32 (8.9%)	20 (10.7%)	5 (4.8%)	2 (4.8%)
Other	33 (9.2%)	18 (9.6%)	10 (9.6%)	3 (7.1%)
PS: 0-1	244 (68.2%)	128 (68.5%)	74 (71.2%)	25 (59.5%)
2-3	114 (31.8%)	59 (31.5%)	30 (28.8%)	17 (40.5%)
Prior Response: Yes	142 (39.7%)	74 (39.6%)	37 (35.6%)	12 (28.6%)
No	216 (60.3%)	113 (60.4%)	67 (64.4%)	30 (71.4%)
Prior Tx: One	182 (50.8%)	97 (51.9%)	52 (50.0%)	20 (47.6%)
Two	176 (49.2%)	90 (48.1%)	52 (50.0%)	22 (52.4%)
Prior Platinum: No	28 (7.8%)	15 (8.0%)	7 (6.7%)	3 (7.1%)
Yes	330 (92.2%)	172 (92.0%)	97 (93.3%)	39 (92.9%)

Reviewer's Comments:

1. The patients characteristics appear to be balanced between the treatment arms within the subgroup of patients with smoking history (except for age group), and within the subgroup of patients with no smoking history (except for EGFR positive status, performance status and response to prior therapy).
2. There is however a difference between the subgroups with respect to the distribution of gender, race and histology.
3. Results from analyses adjusting for imbalances within each of the two subgroups were similar to the unadjusted analyses:
   Smoking Group: HR = 0.865, 95% CI: 0.713, 1.050 Unadjusted analysis;
   HR = 0.866, 95% CI: 0,713, 1.052 Adjusted for age group analysis.
   Non-smoking Group: HR = 0.422, 95% CI: 0.278, 0.640 Unadjusted analysis;
   HR = 0.422, 95% CI: 0.296, 0.645 Adjusted for performance status, response to prior therapy and EGFR status.

Further analyses of difference between patients with smoking history versus no smoking history in each of the treatment arms are presented below.

Table 2: Survival Analyses Results in Tarceva Treated Patients

Smoking History Known Population	Smokers N=358	Non-smokers N=104	Hazard Ratio[1] (95% CI)	P-value[2]
# of Deaths	292	64	1.860 (1.418,2.441)	< 0.0001
Med. Survival in months (95% CI)	5.5 (4.7, 6.5)	12.3 (10.6, 16.1)		

[1] Hazard Ratio = Smokers / Non-smokers; [2] Unadjusted, log-rank test.

Table 3: Survival Analyses Results in Placebo Treated Patients

Smoking History Known Population	Smokers N=187	Non-smokers N=42	Hazard Ratio[1] (95% CI)	P-value[2]
# of Deaths	160	37	0.989 (0.691, 1.417)	0.9532
Med. Survival in months (95% CI)	4.6 (3.9, 6.2)	5.6 (3.5, 8.0)		

[1] Hazard Ratio = Smokers / Non-smokers; [2] Unadjusted, log-rank test.

Reviewer's comment:

The non-smokers appear to benefit more from Tarceva compared to smokers.

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/s/

Rajeshwari Sridhara
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