

CLINICAL REVIEW

Table 25: Responder characteristics – Trial 16

CEN TER	PT	DOSE	HISTOL	STAGE				PS	SEX	ORIGIN	AGE	MOs DIAG
				T	N	M						
0712	0002	500	Adeno	3	0	1	1	F	Cauc	60	7.8	
0259	0001	250	Adeno	3	2	0	1	F	Cauc	59	15.6	
0415	0004	250	Squam	4	2	0	0	M	Cauc	61	21.7	
0415	0006	500	Ad&Sq	4	3	1	1	M	Cauc	70	17.3	
0416	0006	500	Adeno	4	0	1	1	F	Cauc	68	15.3	
0601	0001	500	Adeno	4	0	1	1	M	Cauc	59	12.7	
0601	0002	500	Adeno	4	0	1	1	F	Cauc	54	18.6	
0601	0004	250	Adeno	4	0	1	1	F	Cauc	52	8.3	
0601	0007	250	Adeno	0	3	1	0	M	Cauc	59	4.1	
0916	0006	500	Undiff	4	2	1	1	M	Cauc	69	15.4	
0111	0001	250	Adeno	0	3	1	0	F	Cauc	74	84.6	
0804	0003	250	Adeno	2	0	1	0	F	Japan	59	10.1	
0804	0001	500	Adeno	4	0	1	1	F	Japan	59	14.4	
0803	0003	500	Adeno	3	2	1	0	M	Japan	71	11.3	
0802	0001	250	Adeno	3	2	1	1	M	Japan	67	1.8	
0801	0004	250	Squam	4	0	1	1	F	Japan	74	6.2	
0801	0003	250	Adeno	4	0	1	1	F	Japan	61	15.4	
0800	0001	500	Adeno	4	2	1	1	F	Japan	57	26.9	
0805	0011	250	Adeno	0	0	1	1	M	Japan	59	ND	
0800	0003	250	Adeno	0	0	1	1	M	Japan	56	28.1	
0815	0007	250	Adeno	2	0	1	1	F	Japan	70	12.2	
0822	0004	250	Adeno	4	2	0	1	M	Japan	53	13.8	
0821	0003	500	Adeno	4	2	1	1	F	Japan	51	18.1	
0821	0002	500	Adeno	4	3	1	1	M	Japan	37	7.6	
0819	0009	250	Adeno	2	0	1	1	M	Japan	61	1.9	
0819	0008	500	Adeno	4	0	0	0	M	Japan	52	15.9	
0819	0007	500	Adeno	4	3	1	1	M	Japan	58	7.5	
0819	0006	500	Adeno	4	2	0	1	M	Japan	40	3.7	
0804	0005	250	Adeno	4	1	1	1	F	Japan	54	9.3	
0818	0002	500	Adeno	4	2	1	1	F	Japan	55	17.4	
0805	0009	250	Adeno	4	3	1	1	F	Japan	67	16.8	
0815	0005	250	Adeno	0	2	1	1	M	Japan	28	ND	
0815	0002	250	Adeno	0	0	1	1	M	Japan	60	54.0	
0814	0012	250	Adeno	2	2	1	2	M	Japan	69	16.4	
0814	0003	500	Adeno	4	3	1	1	F	Japan	61	11.0	
0813	0002	500	Adeno	4	2	1	1	F	Japan	57	21.8	
0807	0004	500	Squam	2	2	1	0	F	Japan	63	8.2	
0807	0001	500	Adeno	4	0	0	1	F	Japan	64	ND	
0818	0003	500	Adeno	4	3	1	1	F	Japan	74	23.0	

ND = no data

Table 26: Summary of Responder Characteristics

Characteristic	n (%)
Age	
Median	59
Range	28 - 74
Sex	
Male	18 (46.2)
Female	21 (53.8)
Origin	
Caucasian	11 (28.2)
Japanese	28 (71.8)
ZD1839 Dose	
250 mg	19 (48.7)
500 mg	20 (51.3)
Histology	
Adenocarcinoma	34 (87.2)
Adenocarcinoma+squamous cell	1 (2.5)
Squamous cell	3 (7.7)
Undifferentiated	1 (2.5)
Performance Status	
0	7 (17.9)
1	31 (79.5)
2	1 (2.6)
Stage	
M0	5 (12.8)
M1	34 (87.2)
Months from diagnosis	
Median	14.9
Range	1.8 - 84.6

6.3.6.4 Response duration

The median duration of tumor response, as of 7/23/02, is 13.0 months (95% CI 8-17 mo, range 1.8-19.9+ mo.) for ZD1839 250 mg. and 10.0 (95% CI 6-11, range 1.8-19.9+) months for ZD1819 500 mg/day.

6.3.6.5 Chemotherapy Sensitivity/Resistance of Responding Patients

Responder resistance/sensitivity to prior chemotherapy is summarized in Table 27. Twenty-nine of the 39 responders had not progressed on any prior chemotherapy treatment.

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Table 27: All Responders - Prior chemotherapy and outcome

Prior chemotherapy	N (%)
Number of Prior chemotherapy regimens	
1	21 (53.8)
2	18 (46.2)
Progression on first-line chemotherapy	6 (15.4)
Progression on second-line chemotherapy only	3 (7.7)
Progression on both 1 st & 2 nd line chemotherapy	1 (2.5)
No progression on chemotherapy	29 (74.4)

Two episodes of progression were not included in this table. One patient 804/03 was recorded as having progressed on second line treatment on the day of treatment and a second patient 819/06 was deemed to have progressive disease one day after first-line treatment. Among the responding patients that had progressed on prior chemotherapy there were 2 Caucasians and 8 Japanese, including the one patient 805/11 who progressed on both first- and second-line treatment.

Table 28 summarizes the number of measurable lesions for 38 of 39 patients with measurable lesions who had an objective tumor response. As indicated the majority of responding metastatic disease patients had only one or two lesions that were measured. Baseline total area of measurable lesions was less than 10 cm² in 3 of 11 Caucasian patients and 11 of 21 Japanese patients who had measurable lesions and who responded to therapy. Baseline total area of measurable disease was <5 cm² in 6 Japanese patients and no Caucasian patients

Table 28: Number of measurable lesions evaluated in responding patients

Measurable lesions (n)	Responding patients (n)
0	1
1	16
2	12
3	5
4	3
6	1
8	1

Table 29 demonstrates site(s) of measurable and non-measurable disease for the 39 responding patients. Nineteen responders had lung only disease (primary tumor site with or without contralateral lung involvement. The second most common sites of involvement were lung plus regional lymph node disease (6 patients).

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Table 29: Sites of Measurable/Evaluable Disease

Measurable and non-measurable tumor location	Responding patients (n=39)
Lung only	19
Lung + nodes	6
Lung + nodes + adrenal	1
Lung + nodes + liver	1
Lung + nodes + bone	2
Lung + bone	4
Lung + bone + liver	1
Lung + liver	1
Lung + subcutaneous	1
Nodes only	2
Nodes + adrenal + liver	1

6.3.7 Reviewer Efficacy Conclusions Trials 39 and 16

There are several bothersome issues raised by the Iressa efficacy review. These are listed below.

1. Study eligibility –

Accelerated approval requires an improvement over available therapy. In advanced/metastatic NSCLC the clinical setting where there is no “available therapy” is third-line chemotherapy. Therefore, Trial 39 eligible patients must have received at least two prior chemotherapy regimens including a platinum agent and docetaxel administered either concurrently or sequentially. Prior regimens must have failed due either to progression while on therapy or because of treatment intolerance. Only 139 of 216 trial 39 study patients (64%) met these eligibility criteria. Eleven patients (5%) were platinum refractory/intolerant but taxotere sensitive, 58 patients (27%) were taxotere refractory/intolerant but platinum sensitive, and 8 (4%) were not refractory/intolerant to either drug.

Trial 16 did not address an unmet medical need and it is, therefore, only a supporting study. In Trial 16 eligible patients must have received one or a maximum of two prior chemotherapy regimens one of which must have included platinum. They must also have recurrent or refractory disease, both presumably indicating the presence of chemotherapy resistant disease. In fact, however, only 35% of study patients were chemotherapy resistant having progressed on either first- or second-line chemotherapy. Sixty-five percent of study patients had not progressed on prior therapy.

Based on the refractoriness to prior chemotherapy patients in Trial 16 constituted a more favorable group that might be expected to have higher objective response rates than patients in trial 39 (see paragraph 4).

2. Study patient characteristics

As might be expected from the treatment eligibility requirements of trial 39, the enrolled study population, i.e. (locally advanced or metastatic disease patients who have failed platinum, docetaxel and other chemotherapy and who have a performance status of 0 to 2) is not typical of a population of newly diagnosed NSCLC patients of similar stage and performance status. The latter population might be expected to have a median survival of 6 to 9 months if stage IV at diagnosis and 16 to 18 months if stage III at diagnosis. Patients enrolled in this study have survived for a considerably longer time (48% of patients surviving more than 2 years from initial diagnosis to study randomization). Striking, also, is the percent of study patients with adenocarcinoma alone or mixed with squamous cell carcinoma (73.6%). This is expected as adenocarcinoma has the slowest tumor doubling time of all lung cancer histologies. Thus slow growing tumors that produced few to modest systemic effects were selected. It is uncertain as to whether patient symptomatology was primarily due to tumor or to comorbid illness.

Trial 16 patients, like trial 39 patients, had a relatively long time from initial diagnosis to study randomization (median 12.1 months; mean 15.9 months) and also had a high percentage of adenocarcinoma alone (63%) or with other histologies (3%).

3. Treatment response

Based on response criteria, a patient who had measurable disease, with or without non-measurable but evaluable disease or non-measurable/non-evaluable disease, could not be declared a responder unless there was $\geq 50\%$ decrease in the sum of the area of measurable lesions. Since the large majority of patients enrolled in both trials had stage IV disease it might be expected that patients would have multiple sites of disease and, therefore, multiple measurable lesions. That was not the case. Among the 18 responding patients in trial 39 who had measurable disease (4 responders having evaluable but non-measurable disease), 5 patients had only a single lesion measured and 6 had two lesions measured. Similarly, in Trial 16, among the 38 responding patients with measurable lesions, 16 patients had only a single lesion measured and 12 had two lesions measured. As smaller lesions are more likely to respond to chemotherapy than larger lesions, if for no other reason than measurement error, it was of interest to look at the sum of the areas of measurable lesions in responders. In trial 39, the baseline total tumor area of the measurable lesions was less than 10 cm² in 5 of 18 responders. In trial 16 baseline total area of measurable lesions was less than 10 cm² in 3 of 11 Caucasian patients and 11 of 21 Japanese patients who had measurable lesions and who responded to therapy. Baseline total area of measurable disease was <5 cm² in 6 Japanese patients and no

Caucasian patients. In Trial 39 the site of the measurable lesion in patients with only one measurable tumor was lung in 4 patients and liver in one patient. The site of the measurable lesion in patients with two measurable tumors was lung only in 2 patients, lung and liver in 2 patients, lung and lymph node in 1 patient and liver only in 1 patient. In Trial 16 nineteen responders had lung only disease (primary tumor site with or without contralateral lung involvement. The second most common sites of involvement were lung plus regional lymph node disease (6 patients).

4. Response rate

A widely accepted medical oncology principle is that for each chemotherapy regimen failed the probability of responding to a subsequent regimen decreases and responses are of shorter duration. If one accepts this premise then it is to be expected that the Iressa response rate in Trial 39 patients who are refractory to two or more prior chemotherapy regimens should be lower than the response rate of patients who have failed less than two regimens. This was not the case. Response rates of both groups were approximately 10%. The constancy of response rates in patients progressing on two or more chemotherapy regimens, patients progressing on one regimen and patients not refractory to any chemotherapy is of concern.

7 Integrated Review of Safety

7.1 Brief Statement of Conclusions

ZD1839 was generally well tolerated at both doses. However, fewer patients on the 250-mg/day dose experienced Grade 3 or 4 drug-related adverse events or withdrew due to drug-related adverse events. There were fewer drug interruptions due to adverse events in the 250-mg/day group. Dose reductions due to toxicity occurred in 1.0% of patients at the 250-mg dose versus 8.8% of patients at the 500-mg dose group.

Drug-related adverse events experienced by at least 10% of patients in the 250-mg/day group were diarrhea, rash, acne, dry skin, nausea, and vomiting. There was no evidence of cumulative toxicity, and the majority of drug-related adverse events were reversible.

In study 16, similar to study 39, ZD1839 was generally well tolerated at both doses. However, fewer patients on the 250-mg/day dose experienced Grade 3 or 4 drug-related adverse events or withdrew due to drug-related adverse events. Drug-related adverse events experienced by at least 10% of patients in the 250-mg/day group were rash, diarrhea, pruritus, dry skin, nausea, acne, SGPT/ALT increased, and SGOT/AST increased. There was no evidence of cumulative toxicity, and the majority of drug-related adverse events were reversible.

7.2 Patient Exposure

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In the Phase II trials, 425 patients were exposed to ZD1839 (216 patients in Trial 0039, and 209 patients in Trial 0016). The majority of patients in both trials received ZD1839 for >1 month, with approximately one-third receiving ZD1839 for >3 months. Duration of exposure in Trials 0039 and 0016 is summarized in Table 30. Thirty-one patients (15.1%) who received ZD1839 250 mg daily had an interruption in therapy, and 1 patient (0.5%) had a dose reduction due to toxicity. This compares to 56 (25.5%) and 21 (9.5%) patients, respectively, who received ZD1839 500 mg daily (Table 31).

In the Phase I multiple-dose trials, 270 patients were exposed to a range of doses of ZD1839 from 50 to 1000 mg daily. Nearly half the patients (46.7%) received ZD1839 for >1 month, with 47 patients (17.4%) receiving ZD1839 for >3 months. Nineteen (7.0%) patients had dose reductions due to toxicity, all occurred at doses \geq 300 mg/day, with 14 occurring in the 72 patients who received doses \geq 600 mg/day.

Table 30: Duration on trial and duration of treatment

Category	Trial 0039		Trial 0016	
	250 mg (n=102)	500 mg (n=114)	250 mg (n=103)	500 mg (n=106)
Number of days on trial ^a				
Mean (standard deviation)	75.7(53.0)	69.5(49.9)	87.0(53.9)	86.9(57.9)
Maximum	232	232	229	219
Number of days on treatment ^b				
Mean (standard deviation)	72.6(51.9)	62.7(47.3)	85.1 (54.2)	81.5(56.5)
Maximum	213	232	227	219
Number of months on treatment (number [%] of patients)				
<1 month	41 (40.2)	38(33.3)	19(18.4)	27(25.5)
1 to 3 months	24(23.5)	41 (36.0)	46(44.7)	39(36.8)
>3 to 6 months	36(35.3)	34(29.8)	34(33.0)	33 (31.1)
>6 to 8 months	1 (1.0)	1(0.9)	4(3.9)	7(6.6)

a date of last dose minus date of first dose plus 1, ignoring any dose interruptions.

b days of drug exposure: time from first dose to last dose minus the number of days off treatment. If a patient withdrew at the end of a treatment interruption his/her exposure would be underestimated by the length of the final interruption.

FDA comment: Duration of treatment confirmed using dataset THR1639.

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Table 31: Patients with therapy interruptions or dose reductions due to toxicity

Category	Number (%) of patients			
	Pivotal Trial 0039		Supportive Trial 0016	
	250 mg (n= 102)	500 mg (n= 114)	250 mg (n= 103)	500 mg (n=106)
Therapy interruption	15(14.7)	26(22.8)	16(15.5)	30(28.3)
Dose reduction	1 (1.0)	10(8.8)	0(0.0)	11(10.4)

In both trials, the proportion of patients who had interruptions in therapy was lower in the 250mg/day group than in the 500-mg/day group. These interruptions were spread throughout the treatment periods with the highest number occurring during the first 28 days. The main reasons for interrupting therapy were skin reactions and GI disturbances.

Across the 2 trials, there was only 1 (0.5%) dose reduction in the 250-mg/day group compared to 21 (9.5%) in the 500-mg/day group. The occurrence of these dose reductions in the patient population was distributed throughout the treatment periods and was frequently associated with skin reactions and GI disturbances.

FDA comment: Dose reductions and delays in drug treatment are confirmed using dataset THR1639.

Phase I trials: patients with solid tumors

The exposure of patients with solid tumors to ZD1839 in the Phase I multiple-dose trials is presented in Table 32.

Table 32: ZD1839 Exposure in Phase I multiple-dose trials

Exposure	Trial				
	0005 (n=64)	0011 (n=69)	0012 (n=88)	0038 (n=18)	V-15-11 (n=31)
Total days of dosing					
Total	2241	6808	6239	458 a	1048
Mean	35.0	98.7	70.9	25.4	33.8
Median	28b	56	43	28	14
Minimum	1	1	5	7	2
Maximum	205a	506	458	28	182c

a Only includes data collected for the first 28-day treatment period.

b Because of the dosing schedule in Trial 0005 (ie, 14 days with drug, 14 days without), 28 days is equivalent to 2 months on trial, and 205 days is equivalent to 14 months on trial.

c Because of the dosing schedule in Trial V-15-11 (ie, 14 days with drug, 14 days without), 182 days is equivalent to 13 months on trial.

The exposure of patients to ZD1839 within these dose categories is presented in Table 33.

Table 33: Exposure to ZD1839 in the Phase I trials, by dose category

Exposure ZD1839 dose category	<225 mg (n=51)	250 mg a (n=75)	500 mg b (n=72)	>525 mg (n=72)
Total days of dosing				
Total	2356	5776	3883	4780
Mean	46.2	77.0	53.9	66.4
Minimum	1	1	7	5
Maximum	458	506	404	395
Number of months on Rx (number [%] of patients)				
<1 month	38(74.5)	31(41.3)	41(56.9)	34(47.2)
1 to 3 months	10(19.6)	28(37.3)	19(26.4)	22(30.6)
>3 to 6 months	1(2.0)	8(10.7)	9(12.5)	10(13.9)
>6 months	2(3.9)	8(10.7)	3(4.2)	6(8.3)

a Including doses between 225 mg and 300 mg, inclusive.

b Including doses between 400 mg and 525 mg, inclusive.

In Trial 0035, nineteen patients received a single 50 mg iv dose of ZDI 839, and 17 of these patients also received a single 250 mg oral dose of ZD1839.

Dose reductions

None of the 95 patients in Trials 0005 and V-15-11 (16 of whom received 525 mg/day ZD1839, and 15 of whom received 700 mg/day ZD1839) had a dose reduction.

In Trial 0011, a total of seven (10.1%) patients had a dose reduction attributed to drug-related adverse events; treatment in 6 of these patients was also interrupted because of toxicity. All reductions or interruptions of trial medication occurred in patients assigned to doses of ≥ 600 mg/day.

In Trial 0012, nine (10.2%) patients had a dose reduction attributed to drug-related adverse events; treatment in all of these patients was also interrupted because of toxicity. All reductions or interruptions of trial medication occurred in patients assigned to doses of at least 300 mg/day; 7 out of 9 dose reductions occurred among the 40 patients who were assigned ≥ 600 mg/day.

In Trial 0038, three (16.7%) patients stopped taking the 500 mg daily dose of ZD1839 due to adverse events. Treatment was interrupted in each case, and all 3 patients subsequently resumed ZD1839 treatment at the lower dose of 250 mg daily.

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FDA Comment: Data on drug exposure, dose reductions and dose delays was confirmed in Section 5 of the sponsor safety report of each individual study. Specific datasets containing this data were not provided.

7.3 Safety Review Methods and Findings

Sponsor safety data bases for study 39 9AE, AE FLGS, LAB, LAB 1096, LAB 1097, LABS, RS01409, RS01438, RS01438a, S00103, S01363, and for study 16 ADVERSE, ECG, LAB01096, LAB01097, RS01438, S01949, S01963, S01964, S01965, S01966, SCHIRMER, SKINCHAR, TRANSAM.

FDA Comment: In the analysis of AE's the sponsor's convention of not counting an AE if it was present before the start of treatment (irrespective of how long it persisted after the start of treatment was followed. While this was an arbitrary decision any other method for counting AE's would be equally arbitrary.

7.3.1 Overview of adverse events

An overview of adverse events occurring in Trial 0039, by the dose of ZD1839 received at trial entry, is summarized in Table 34.

Table 34: Overview of adverse events in Trial 0039

Category	Number (%) of patients	
	250 mg/day (n=102)	500 mg/day (n=114)
All adverse events	101 (99.0)	112(98.2)
drug related	74(72.5)	97(85.1)
Deaths		
due to adverse event(s)	6(5.9)	5(4.4)
due to drug-related adverse event(s)	0(0.0)	1 (0.9)
Withdrawals		
due to adverse event(s)	4(3.9)	11 (9.6)
due to drug-related adverse event(s)	1(1.0)	5(4.4)
due to serious adverse event(s)	4(3.9)	8(7.0)
due to drug-related serious adverse event(s)	1(1.0)	1(0.9)
Serious adverse events	28(27.5)	27(23.7)
drug-related	4(3.9)	5(4.4)
CTC Grade 3 or 4 adverse events	41 (40.2)	53(46.5)
drug related	7(6.9)	20(17.5)

The most frequent adverse events experienced by $\geq 25\%$ of patients receiving ZD1839 250 mg/day were diarrhea (56.9%), rash (48.0%), asthenia (28.4%), dyspnea (28.4%), nausea (26.5%), and acne (25.5%). Some adverse events, most notably diarrhea, rash, asthenia, acne, and dry skin, occurred less frequently in patients

receiving ZD1839 250 mg/day than patients receiving 500 mg/day. Those adverse events with an incidence of $\geq 10\%$ in either dose group are presented in **Table 35**.

Table 35: Adverse events with an incidence of $\geq 10\%$ in Trial 39

Adverse event	Number of patients	
	250 mg/day (n=102)	500 mg/day (n=114)
Diarrhea	58 (56.9)	85 (74.6)
Rash	49 (48.0)	63 (55.3)
Asthenia	29 (28.4)	41 (36.0)
Dyspnea	29 (28.4)	26 (22.8)
Nausea	27 (26.5)	31 (27.2)
Acne	26 (25.5)	38 (33.3)
Anorexia	24 (23.5)	31 (27.2)
Pain	23 (22.5)	15 (13.2)
Cough increased	22 (21.6)	23 (20.2)
Vomiting	22 (21.6)	21 (18.4)
Dry skin	17 (16.7)	30 (26.3)
Peripheral edema	15 (14.7)	11 (9.6)
Chest pain	14 (13.7)	15 (13.2)
Back pain	14 (13.7)	13 (11.4)
Constipation	13 (12.7)	8 (7.0)
Weight loss	12 (11.8)	12 (10.5)
Pharyngitis	11 (10.8)	16 (14.0)
Pruritus	11 (10.8)	10 (8.8)
Sinusitis	11 (10.8)	4 (3.5)
Abdominal pain	10 (9.8)	14 (12.3)
Fever	8 (7.8)	12 (10.5)
Dehydration	5 (4.9)	13 (11.4)

Drug-related adverse events with an incidence of $\geq 5\%$ in either dose group are presented in **Table 36**.

The most frequent drug-related adverse events experienced by $\geq 10\%$ of patients receiving ZD1839 250 mg/day were diarrhea (48.0%), rash (43.1%), acne (24.5%), dry skin (12.7%), nausea (12.7%), and vomiting (11.8%). With the exception of vomiting, the incidence of these events was lower at the 250-mg/day dose than at the 500-mg/day dose.

The majority of patients receiving ZD1839 250 mg/day who experienced drug-related adverse events had events that were CTC Grades 1 or 2 (67 out of 74 patients; 90.5%). Drug-related adverse events generally occurred for the first time in Treatment Periods 1 or 2, and the safety profile of ZD1839 did not appear to change with chronic dosing (up to a maximum of nearly 8 months of treatment).

Table 36: Drug-related adverse events with an incidence of $\geq 5\%$ in trial 39

Drug-related adverse event (COSTART term) ¹	Number of patients	
	250 mg/day (n=102)	500 mg/day (n=114)
Diarrhea	49 (48.0)	76 (66.7)
Rash	44 (43.1)	61 (53.5)
Acne	25 (24.5)	37 (32.5)
Dry skin	13 (12.7)	30 (26.3)
Nausea	13 (12.7)	20 (17.5)
Vomiting	12 (11.8)	10 (8.8)
Pruritus	8 (7.8)	10 (8.8)
Anorexia	7 (6.9)	11 (9.6)
Asthenia	6 (5.9)	5 (4.4)
Weight loss	3 (2.9)	6 (5.3)

¹ A patient may have had more than 1 adverse event.

COSTART Coding Symbols for Thesaurus of Adverse Reaction Terms.

Adverse events with CTC Grades 3 or 4

Thirteen (12.7%) patients on ZD1839 250-mg/day had CTC Grade 4 adverse events compared to 20 (17.5%) on the 500-mg/day dose. Two (2.0%) patients at the 250-mg/day dose had Grade 4 adverse events that were considered drug related (asthenia and thrombocytopenia) compared to 3 (2.6%) at the 500-mg/day dose (dehydration, lung hemorrhage, and ALT/SGPT increased).

Twenty-eight (27.5%) patients at the 250-mg/day dose had CTC Grade 3 adverse events compared to 33 (28.9%) on the 500-mg/day dose. Five (4.9%) patients at the 250-mg/day dose had Grade 3 adverse events that were considered drug related compared to 17 (14.9%) at the 500-mg/day dose.

Diarrhea and acne were the only drug-related adverse events of CTC Grade 3 or 4 severity with an incidence of $\sim 3\%$ in either dose group (see Table 37).

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Table 37: Drug-related adverse events of CTC Grade 3 or 4 in trial 39

Adverse event and CTC grade	Number (%) of patients	
	250 mg/day (n=102)	500 mg/day (n=114)
Asthenia		
Grade 3	1(1.0)	1 (0.9)
Grade 4	1(1.0)	0(0.0)
Diarrhea, Grade 3	1(1.0)	6(5.3)
Gastrointestinal disorder,		
Grade 3	0(0.0)	1(0.9)
Nausea, Grade 3	1(1.0)	1 (0.9)
Rectal disorder, Grade 3	1(1.0)	0(0.0)
Vomiting, Grade 3	1(1.0)	3(2.6)
Thrombocytopenia, Grade 4	1(1.0)	0(0.0)
Dehydration		
Grade 3	0(0.0)	2(1.8)
Grade 4	0(0.0)	1(0.9)
Peripheral edema, Grade 3	1(1.0)	0(0.0)
AST/SGOT increased,		
Grade 3	0(0.0)	2(1.8)
ALT/SGPT increased		
Grade 3	0(0.0)	1 (0.9)
Grade 4	0(0.0)	1 (0.9)
Dyspnea, Grade 3	1(1.0)	0(0.0)
Epistaxis, Grade 3	1(1.0)	0(0.0)
Lung hemorrhage, Grade 4	0(0.0)	1 (0.9)
Acne, Grade 3	0(0.0)	4(3.5)
Pruritus, Grade 3	0(0.0)	1 (0.9)
Rash, Grade 3	0(0.0)	3(2.6)
Scrotal edema, Grade 3	1(1.0)	0(0.0)

Deaths

The number (%) of patients who died during Trial 0039, and the primary cause of death (disease related or adverse event), are summarized in **Table 38**.

Table 38: Deaths during or 30 days post treatment in trial 39

Category	Number (%) of patients a	
	250 mg/day (n= 102)	500 mg/day (n=1 14)
Patients who died	22(21.6)	27(23.7)
Patients whose death was considered cancer related a	21 (20.6)	26(22.8)
Patients who had an adverse event that resulted in death	6(5.9)	5(4.4)

a Death reported as cancer related by the investigator. Includes 9 patients who also had an adverse event with an outcome of death.

For the 11 patients who had an adverse event that resulted in death the death was considered cancer related by the investigator for 9 out of 11 of these patients. The remaining 2 patients (2107/0034 and 2107/0035) died of cardiovascular events (arrhythmia and acute myocardial infarction, respectively); both had a history of cardiovascular disease. Only 1 patient (2107/0145; 500 mg/day group) had an adverse event (lung hemorrhage) that led to death that was considered possibly related to ZD1839 by the investigator. This patient's death was also reported as cancer related.

Adverse events leading to withdrawal

The incidence of withdrawals from ZD1839 treatment due to adverse events was lower in the 250-mg/day group (3.9%) than in the 500-mg/day group (9.6%).

One patient (1.0%) in the 250-mg/day group, and 5 patients (4.4%) in the 500-mg/day group, were withdrawn due to adverse events that were considered to be possibly drug related by the investigator. The identification of these patients is presented in Table 39. The only drug-related adverse events that led to withdrawal in more than 1 patient were diarrhea, acne, and rash (2 patients each).

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Table 39: Patients who withdrew due to drug-related adverse events in trial 39

Center/patient number	Tumor type	Adverse event	Serious event	CTC grade (yes/no)	Outcome	Days on treatment
250-mg/day group						
2255/0302	Adenocarcinoma	Asthenia	Yes	4	Ongoing	140 a
500-mg/day group						
2044/0182	Squamous	Acne	No	3	Recovered	71
		Rash	No	3	Ongoing	
2102/0071	Adenocarcinoma	Acne	No	3	Ongoing	92
2107/0035	Adenocarcinoma	Diarrhea	No	4	Ongoing	63
2107/0145	Squamous and adenocarcinoma	Lung hemorrhage	Yes	4	Died	11 b
2251/0063	Adenocarcinoma	Abd. pain	No	1	Recovered	14
		Headache	No	1	Recovered	
		Diarrhea	No	1	Recovered	
		Epistaxis	No	1	Recovered	
		Pruritus	No	2	Recovered	
		Rash	No	2	Recovered	

a Reported term progressive neurologic deterioration. Onset of the event occurred on Day 85; the duration of treatment is based on the date of the last dose at the time of data cutoff.

b Onset of the event (patient began coughing up blood) occurred on Day 3; the patient was withdrawn and subsequently died on Day 11.

Eleven patients withdrew because of adverse events that were not considered drug related (including 2 patients who also had drug-related adverse events that led to withdrawal). Among the 11 patients, the only events that led to withdrawal in more than 1 patient were pneumonia (4 patients), dyspnea (3 patients), and apnea (2 patients).

Serious adverse events

Twenty-eight patients (27.5%) at the 250-mg/day dose had at least 1 serious adverse event compared to 27 (23.7%) at the 500-mg/day dose. Of these patients, 4 at the 250-mg/day dose, and 5 at the 500-mg/day dose, had drug-related serious adverse events. Dehydration and asthenia were the only drug-related serious adverse events reported by more than 1 patient.

Identification of patients with drug-related serious adverse events is presented in Table 40.

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Table 40: Patients who had drug-related serious adverse events in trial 39

Center/ patient	Tumor type description	Adverse event	CTC grade	Outcome	Withdrawn because of the event (yes/no)	Days on treatment at time of event
250-mg/day group						
2064/0077	Adenocarcinoma	Rectal disorder	3	Recovered	No	115
		Thrombocytopenia	4	Recovered	No	114
		Epistaxis	3	Recovered	No	115
2118/0172	Squamous and adenocarcinoma	Asthenia	3	Ongoing	No	18
2251/0066	Adenocarcinoma	Peripheral edema	3	Recovered	No	91
		Scrotal edema	3	Ongoing	No	91
2255/0302	Adenocarcinoma	Asthenia	4	Ongoing	Yes	85
500-mg/day group						
2090/0047	Adenocarcinoma	Dehydration	4	Ongoing	No	1 day post trt
2090/0220	Adenocarcinoma	Increased AST/SGOT	3	Recovered	No	65
		Increased ALT/SGPT	4	Recovered	No	65
2107/0145	Squamous and adenocarcinoma	Lung hemorrhage	4	Died	Yes	3
2251/0064	Adenocarcinoma	Dehydration	3	Recovered	No	23
2252/0274	Adenocarcinoma	Nausea	3	Ongoing	No	81
		Vomiting	3	Ongoing	No	81
		Dehydration	3	Ongoing	No	81

Phase II Supportive Trial 0016

An overview of adverse events occurring in Trial 0016 is summarized in **Table 41**. Adverse events are reported by the dose of ZD1839 assigned at trial entry.

Table 41: Overview of adverse events in trial 16

Category	Number of patients	
	250 mg/day (n=103)	500 mg/day (n=106)
All adverse events	101(98.1)	106(100)
drug related	88(85.4)	102(96.2)
Deaths		
due to adverse event(s)	4(3.9)	1 (0.9)
due to drug-related adverse event(s)	0(0.0)	1 (0.9)
Withdrawals		
due to adverse event(s)	7(6.8)	12(11.3)
due to drug-related adverse event(s)	2(1.9)	10(9.4)
due to serious adverse event(s)	6(5.8)	6(5.7)
due to drug-related serious adverse event(s)	1(1.0)	4(3.8)
Serious adverse events	21(20.4)	27(25.5)
drug-related	3(2.9)	12 (11.3)
CTC Grade 3 or 4 adverse events	33(32.0)	54(50.9)
drug related	9(8.7)	32(30.2)

Nearly all patients (99.0%) in Trial 16 had at least 1 adverse event. Those adverse events with an incidence of $\geq 10\%$ in either dose group are presented in **Table 42**.

Table 42: Adverse events with an overall incidence $\geq 10\%$ in trial 16

Adverse event	Number of patients	
	250 mg/day (n=103)	500 mg/day (n=106)
Diarrhea	50(48.5)	71(67.0)
Rash	49(47.6)	74(69.8)
Pruritus	32(31.1)	39(36.8)
Dry skin	30(29.1)	31 (29.2)
Asthenia	26(25.2)	23(21.7)
Nausea	25(24.3)	37(34.9)
Pharyngitis	19(18.4)	25(23.6)
Anorexia	18(17.5)	30(28.3)
ALT/SGPT increased	17(16.5)	26(24.5)
Vomiting	16(15.5)	34(32.1)
AST/SGOT increased	16(15.5)	24(22.6)
Dyspnea	16(15.5)	15(14.2)
Pain	13(12.6)	27(25.5)
Acne	13(12.6)	17(16.0)
Constipation	12(11.7)	14(13.2)
Cough increased	11 (10.7)	13 (12.3)
Weight loss	10(9.7)	17(16.0)
Abdominal pain	10(9.7)	14(13.2)
Conjunctivitis	9(8.7)	13 (12.3)
Stomatitis	9(8.7)	12(11.3)
Fever	8(7.8)	21 (19.8)
Rhinitis	7(6.8)	13(12.3)
Hematuria	7(6.8)	11(10.4)
Epistaxis	5(4.9)	19(17.9)

Drug-related adverse events in Trial 0016 with an overall incidence of $\geq 5\%$ are presented in **Table 43**. The majority of patients receiving ZD1839 250 mg/day who experienced drug-related events had events that were CTC Grades 1 or 2 (79 out of 88 patients; 89.8%). Drug-related adverse events generally occurred for the first time in Treatment Period 1, and the safety profile of ZD1839 did not appear to change with chronic dosing (up to a maximum of nearly 8 months of treatment).

Table 43: Drug-related adverse events $\geq 5\%$ in trial 16

Drug-related adverse event	Number of patients	
	250 mg/day (n= 103)	500 mg/day (n=106)
Rash	48(46.6)	73(68.9)
Diarrhea	41 (39.8)	61 (57.5)
Pruritus	31 (30.1)	38(35.8)
Dry skin	28(27.2)	31 (29.2)
Nausea	13(12.6)	25(23.6)
ALT/SGPT increased	13(12.6)	25(23.6)
Acne	13(12.6)	15(14.2)
AST/SGOT increased	11(10.7)	24(22.6)
Pain	10(9.7)	17(16.0)
Anorexia	9(8.7)	20(18.9)
Asthenia	8(7.8)	11 (10.4)
Exfoliative dermatitis	8(7.8)	9(8.5)
Stomatitis	8(7.8)	8(7.5)
Vomiting	6(5.8)	21 (19.8)
Hematuria	6(5.8)	5(4.7)
Seborrhea	6(5.8)	4(3.8)
Blepharitis	5(4.9)	6(5.7)
Conjunctivitis	4(3.9)	10(9.4)
Nail disorder	4(3.9)	9(8.5)
Abdominal pain	3(2.9)	8(7.5)
Epistaxis	2(1.9)	12(11.3)
Weight loss	2(1.9)	6(5.7)

* A patient may have had more than 1 adverse event.

Adverse events with CTC Grades 3 or 4

Twelve (11.7%) patients at the 250-mg/day dose had CTC Grade 4 adverse events compared to 12 (11.4%) at the 500-mg/day dose. No drug-related CTC Grade 4 events were reported in the 250-mg/day group. Six patients (5.7%) had drug-related CTC Grade 4 adverse events in the 500-mg/day group.

Twenty-one (20.4%) patients at the 250-mg/day dose had CTC Grade 3 adverse events compared to 42 (39.6%) at the 500-mg/day dose. Eight (7.8%) patients at the 250-mg/day dose had drug related CTC Grade 3 events compared to 24 (22.6%) at the 500-mg/day dose.

Diarrhea, ALT/SGPT increased, and rash were the only drug-related adverse events of CTC Grade 3 or 4 severity with an incidence $\sim 3\%$ in either dose group (see Table 44).

Table 44: Drug-related adverse events of CTC Grade 3 or 4 in trial 16

Adverse event and CTC grade	Number of patients	
	250 mg/day (n=103)	500 mg/day (n=106)
Asthenia, Grade 3	0(0.0)	1 (0.9)
Shock, Grade 4	0(0.0)	1 (0.9)
Atrial fibrillation, Grade 3	1(1.0)	0(0.0)
Bundle branch block, Grade 3	1(1.0)	0(0.0)
Deep thrombophlebitis, Grade 4	0(0.0)	1 (0.9)
Anorexia, Grade 3	0(0.0)	1 (0.9)
Constipation, Grade 3	1(1.0)	0(0.0)
Diarrhea, Grade 3	0(0.0)	7(6.6)
Gastrointestinal hemorrhage, Grade 3	0(0.0)	1 (0.9)
Liver function tests abnormal, Grade 3	0(0.0)	1 (0.9)
Melena, Grade 3	0(0.0)	1 (0.9)
Nausea, Grade 3	1(1.0)	1 (0.9)
Anemia		
Grade 3	0(0.0)	1 (0.9)
Grade 4	0(0.0)	2 (1.9)
Alkaline phosphatase increased, Grade 3	1(1.0)	0(0.0)
Dehydration, Grade 3	1(1.0)	0(0.0)
Hypoproteinemia, Grade 3	0(0.0)	1 (0.9)
AST/SGOT increased		
Grade 3	0(0.0)	2(1.9)
Grade 4	0(0.0)	1 (0.9)
ALT/SGPT increased		
Grade 3	2(1.9)	5(4.7)
Grade 4	0(0.0)	1 (0.9)
Dyspnea, Grade 3	0(0.0)	1 (0.9)
Hypoxia, Grade 3	0(0.0)	1 (0.9)
Interstitial pneumonia, Grade 3	0(0.0)	1 (0.9)
Pneumonia		
Grade 3	0(0.0)	1 (0.9)
Grade 4	0(0.0)	1 (0.9)
Acne, Grade 3	0(0.0)	2(1.9)
Exfoliative dermatitis, Grade 3	0(0.0)	2(1.9)
Nail disorder, Grade 3	0(0.0)	1 (0.9)
Pruritus, Grade 3	0(0.0)	1 (0.9)
Rash		
Grade 3	1 (1.0)	6(5.7)
Grade 4	0(0.0)	1 (0.9)
Seborrhea, Grade 3	1 (1.0)	0(0.0)

Deaths

Twenty-three (22.3%) patients in the 250-mg/day group died during treatment or post-treatment (ie, within 30 days after the last dose of ZD1839) compared to 12 (11.3%) in the 500-mg/day group. Four (3.9%) patients in the 250-mg/day group had adverse events with an outcome of death. Three of these deaths were considered cancer related. In addition, 1 (0.9%) patient in the 500mg/day group had an adverse event with an outcome of death. None of these 5 deaths associated with adverse events were considered by the investigator to be possibly related to trial medication. However, for 1 patient (0207/0001), the investigator felt unable to assign causality. On review of this case, an AstraZeneca physician assigned a causality of "drug related". This patient was a 62year-old white woman with advanced NSCLC (adenocarcinoma; Stage IV who was assigned to the 500-mg/day dose. Fifty-nine days after starting trial therapy, she had acute respiratory insufficiency: pneumonia and died 2 days after onset. The adverse event was CTC Grade 4.

Adverse events leading to withdrawal

The incidence of withdrawals from ZD1839 treatment due to adverse events was lower in the 250-mg/day group (6.8%) than in the 500-mg/day group (11.3%).

Two patients (1.9%) in the 250-mg/day group, and 10 patients (9.4%) in the 500-mg/day group, were withdrawn due to adverse events that were considered to be possibly drug related by the investigator. The identification of these patients is presented in Table 45. The only drug-related adverse events that led to withdrawal of more than 1 patient were rash, pneumonia, increased ALT/SGPT, and increased AST/SGOT.

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Table 45: Patients who withdrew due to drug-related adverse events in Trial 0016

Center/patient number	Tumor type	Adverse event	Serious (yes/no)	CTC grade	Outcome	Days on treatment
250-mg/day group						
0259/0007	Squamous	Bundle branch block	Yes	3	Ongoing	112
0815/0004	Adenocarcinoma	ALT/SGPT increased	No	3	Resolved	41
500-mg/day group						
0207/0001	Adenocarcinoma	Pneumonia	Yes	4	Died	59
0259/0002	Adenocarcinoma	Diarrhea	No	3	Ongoing	2
		Nausea	No	3	Resolved	2
		Vomiting	No	2	Ongoing	2
0259/0005	Adenocarcinoma	Rash	No	1	Ongoing	10
0804/0001	Adenocarcinoma	Liver function tests abnormal	No	3	Ongoing	57
0804/0002	Adenocarcinoma	Pneumonia	Yes	3	Ongoing	87
		Hypoxia	Yes	3	Resolved	88
0805/0002	Adenocarcinoma	Generalized edema	Yes	2	Ongoing	24
		Hypoproteinemia	Yes	3	Ongoing	57
0807/0002	Adenocarcinoma	ALT/SGPT increased	No	4	Resolved	29
		AST/SGOT increased	No	4	Resolved	29
0808/0002	Adenocarcinoma	Deep thrombophlebitis	Yes	4	Ongoing	92
0819/0008	Adenocarcinoma	ALT/SGPT increased	No	3	Ongoing	29
		AST/SGOT increased	No	3	Ongoing	43
0820/0003	Squamous	Rash	No	3	Resolved	7

Serious adverse events

Twenty-one patients (20.4%) at the 250-mg/day dose had at least 1 serious adverse event compared to 27 (25.5%) at the 500-mg/day dose. Of these patients, 3 at the 250-mg/day dose, and 12 at the 500-mg/day dose, had drug-related serious adverse events (Table 46).

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Table 46: Patients who had drug-related serious adverse events in trial 16

Center/patient on number	Tumor type	Adverse event grade	CTC because of the adverse event (yes/no)	Outcome treatment at time of event	Withdrawn Days
250-mg/day group					
0207/0003	Adenocarcinoma	Diarrhea 2	Ongoing	No	30
0259/0007	Squamous	Bundle branch block 3	Ongoing	Yes	112
0601/0009	Adenocarcinoma	Dehydration 3	Resolved	No	33
500-mg/day group					
0111/0003	Adenocarcinoma	Asthenia 3	Ongoing	No	14
0205/0002	Adenocarcinoma	Anemia 4	Ongoing	No	26
		GI hemorrhage 3	Ongoing	No	26
		Melena 3	Ongoing	No	26
		Shock 4	Ongoing	No	26
0207/0001	Adenocarcinoma	Pneumonia 4	Died	Yes	59
025110001	Adenocarcinoma	Acne 3	Ongoing	No	11
0259/0004	Squamous	Nausea 2	Resolved	No	1
		Vomiting 2	Resolved	No	1
0416/0004	Adenocarcinoma	Diarrhea 3	Resolved	No	59
0601/0010	Undifferentiated	Diarrhea 3	Resolved	No	14
0804/0002	Adenocarcinoma	Pneumonia 3	Ongoing	Yes	87
		Hypoxia 3	Resolved	Yes	88
0805/0002	Adenocarcinoma	Generalized edema 2	Ongoing	Yes	24
		Anemia 3	Ongoing	No	57
		Hypoproteinemia 3	Ongoing	Yes	57
0808/0001	Large cell	Dyspnea 3	Ongoing	No	17
		Interstitial pneumonia 3	Resolved	No	17
0808/0002	Adenocarcinoma	Deep thrombophlebitis 4	Ongoing	Yes	92
0818/0003	Adenocarcinoma	Rash 2	Resolved	No	32

Phase I trials: patients with solid tumors

6.3.1 Overall incidences of adverse events

An overview of adverse events for patients with solid tumors who received ZD 183 9 in the Phase I multiple-dose trials (0005, 0011, 0012, 0038, and V- 15-11) is summarized by dose in Table 47.

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Table 47: Overview of adverse events in the Phase I multiple-dose trials

Category	Number (%) of patients a				All doses (n=270)
	<225 mg (n=51)	250 mg (n=75)	b500 mg c (n=72)	>525 mg (n=72)	
All adverse events	51 (100)	74 (98.7)	72 (100)	71 (98.6)	268 (99.3)
drug related	28 (54.9)	58 (77.3)	65 (90.3)	68 (94.4)	219 (81.1)
Deaths					
due to adverse event(s)	2 (3.9)	8 (10.7)	3 (4.2)	1 (1.4)	14 (5.2)
due to drug-related adverse event(s)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Withdrawals					
due to adverse event(s)	5 (9.8)	7 (9.3)	7 (9.7)	19 (26.4)	38 (14.1)
due to drug-related adverse event(s)	1 (2.0)	2 (2.7)	3 (4.2)	18 (25.0)	24 (8.9)
due to serious adverse event(s)	3 (5.9)	5 (6.7)	4 (5.6)	8 (11.1)	20 (7.4)
due to drug-related serious adverse	0 (0.0)	1 (1.3)	1 (1.4)	7 (9.7)	9 (3.3)
Serious adverse events	15 (29.4)	22 (29.3)	13 (18.1)	29 (40.3)	79 (29.3)
drug-related	1 (2.0)	4 (5.3)	1 (1.4)	14 (19.4)	20 (7.4)
CTC Grade 3 or 4 adverse events	22 (43.1)	34 (45.3)	25 (34.7)	37 (51.4)	118 (43.7)
drug related	1 (2.0)	5 (6.7)	7 (9.7)	26 (36.1)	39 (14.4)

a Patients may appear in more than 1 category of adverse event.

b Including doses between 225 mg and 300 mg, inclusive.

c Including doses between 400 mg and 525 mg, inclusive.

Adverse events

Nearly all patients (99.3%) in the Phase I multiple-dose trials experienced at least 1 adverse event. Adverse events with an overall incidence $\geq 10\%$ are presented by dose category in **Table 48**.

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Table 48: Adverse events $\geq 10\%$ in the Phase I multiple-dose trials

Adverse event	Number (%) of patients a				
	<225 mg (n=51)	250 mg b (n=75)	500mg c (n=72)	>525 mg (n=72)	All doses (n=270)
Diarrhea	18(35.3)	34(45.3)	42(58.3)	58(80.6)	152(56.3)
Rash	14(27.5)	27(36.0)	35(48.6)	45(62.5)	121 (44.8)
Nausea	18(35.3)	19(25.3)	26(36.1)	32(44.4)	95(35.2)
Asthenia	13(25.5)	26(34.7)	23 (31.9)	26(36.1)	88(32.6)
Vomiting	1t (21.6)	22(29.3)	21(29.2)	23(31.9)	77(28.5)
Anorexia	10(19.6)	18(24.0)	20(27.8)	23(31.9)	71 (26.3)
Dry skin	4(7.8)	14(18.7)	19(26.4)	23(31.9)	60(22.2)
Acne	4(7.8)	16(21.3)	19(26.4)	17(23.6)	56(20.7)
Abdominal pain	15(29.4)	5(6.7)	10(13.9)	21 (29.2)	51(18.9)
Cough increased	10(19.6)	15(20.0)	12(16.7)	14(19.4)	51(18.9)
Dyspnea	8(15.7)	15(20.0)	15(20.8)	11 (15.3)	49(18.1)
Headache	12(23.5)	13(17.3)	13 (18.1)	8(11.1)	46(17.0)
Pharyngitis	8(15.7)	12(16.0)	8(11.1)	14(19.4)	42(15.6)
Constipation	12(23.5)	12(16.0)	11 (15.3)	5(6.9)	40(14.8)
Pain	10(19.6)	8(10.7)	14(19.4)	8(11.1)	40(14.8)
Conjunctivitis	9(17.6)	10(13.3)	8 (11.1)	12(16.7)	39(14.4)
Dry mouth	5(9.8)	9(12.0)	5(6.9)	19(26.4)	38(14.1)
Pruritus	4(7.8)	5(6.7)	12(16.7)	16(22.2)	37(13.7)
Somnolence	10(19.6)	9(12.0)	9(12.5)	9(12.5)	37(13.7)
AST/SGOT increased	7(13.7)	8(10.7)	12(16.7)	7(9.7)	34(12.6)
Fever	9(17.6)	10(13.3)	3(4.2)	9(12.5)	31(11.5)
ALT/SGPT increased	5(9.8)	7(9.3)	9(12.5)	8(11.1)	29(10.7)
Anemia	4(7.8)	9(12.0)	8 (11.1)	7(9.7)	28(10.4)
Back pain	3(5.9)	8(10.7)	6(8.3)	10(13.9)	27(10.0)

a patients may have had more than 1 adverse event.

b Including doses between 225 mg and 300 mg, inclusive.

c Including doses between 400 mg and 525 mg, inclusive.

Dose-limiting toxicities

In Trials 0005 and V- 15-11, dose escalation was to proceed up to 925 mg/day unless there was dose limiting toxicity. Dose escalation ceased at 700 mg/day in both of these trials; in Trial 0005, three patients experienced drug-related CTC Grade 3 or 4 diarrhea at this dose level, and in Trial V- 15 -11, two patients experienced CTC Grade 3 diarrhea and increased ALT/SGPT at this dose level (see Table 49).

In Trials 0011 and 0012, dose escalation was to proceed up to 1000 mg/day unless dose-limiting toxicities were recorded. In Trial 0011, dose-limiting toxicities were experienced in the first 28-day treatment period by 3 patients receiving ZD1839 800 mg; the events experienced were diarrhea, diarrhea and pruritus, and conjunctivitis and rash (see Table 49). In Trial 0012, dose escalation proceeded up to the maximum permitted dose level of 1000 mg/day. At this dose level, 5 patients experienced dose-limiting toxicities which, for 4 of these patients, included Grade 3 diarrhea (see Table 49).

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Table 49: Dose limiting toxicities in the Phase I dose-escalating trials

Trial	ZD1839 dose (mg)	Center/ Patient	Tumor type	Adverse event	CTC grade				
0005	400	0001/0061	Ovarian	ALT increased	3				
				AST increased	4				
	525 700	0004/0071 0001/0081 0002/0083 0004/0081	Esophageal Ovarian NSCLC Ovarian	Acne	3				
				Diarrhea	4				
				Diarrhea	3				
				Vomiting	3				
				Abdominal pain	3				
				Diarrhea	3				
				0011	150 800	0001/0001 0002/0105 0004/0107	NSCLC NSCLC Colorectal	GGT increased	3
								Diarrhea	3
1000	0008/0101 0004/0121 0005/0123 0008/0122	NSCLC NSCLC Prostate NSCLC	Diarrhea		3				
			Pruritus		3				
			Conjunctivitis		2				
			Rash		3				
			Diarrhea		3				
			Diarrhea		3				
			Dehydration		3				
			Urticaria		3				
0012	225 300 400	0011/0027 0010/0054 0005/0065 0011/0061	Prostate Prostate Colorectal Ovarian	Diarrhea	3				
				Nausea	3				
				Rash	3				
	600 800 1000	0008/0090 0011/0081 0001/0110 0005/0108 0001/0123 0006/0129 0006/0132 0007/0126 0011/0122 0008/0003 0009/0004	Ovarian Head & neck Colorectal Colorectal Ovarian Ovarian Ovarian Colorectal NSCLC Lung Colorectal	Pain	3				
				Pruritus	3				
				Depression	3				
				Diarrhea	3				
				Somnolence	3				
				Asthenia	4				
				Diarrhea	3				
				Diarrhea	3				
				Somnolence	3				
				Hematemesis	3				
				Hypokalemia	3				
				Acne	3				
Diarrhea	3								
Diarrhea	3								
Dehydration	3								
Diarrhea	3								
Somnolence	3								
ALT increased	3								
Diarrhea	3								
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Drug-related adverse events

A total of 219 patients (81.1%) had at least 1 adverse event that was attributed to trial medication. Drug-related adverse events with an overall incidence of $\geq 5\%$ are presented in Table 50.

The most frequent drug-related adverse events were diarrhea, rash, acne, dry skin, nausea, pruritus, and vomiting. These are similar to the most frequent drug-related adverse events reported in the Phase II trials.

Table 50: Drug-related adverse events ($\geq 5\%$) in the Phase I multiple-dose trials

Drug-related adverse event	Number (%) of patients a				All doses (n=270)
	<225 mg (n=51)	250 mg b (n=75)	500 mg c (n=72)	>525 mg d (n=72)	
Diarrhea	6(11.8)	24(32.0)	31 (43.1)	56(77.8)	117(43.3)
Rash	8(15.7)	23(30.7)	34(47.2)	45(62.5)	110(40.7)
Acne	4(7.8)	15(20.0)	18(25.0)	17(23.6)	54(20.0)
Dry skin	1 (2.0)	12(16.0)	16(22.2)	22(30.6)	51 (18.9)
Nausea	1 (2.0)	7(9.3)	12(16.7)	22(30.6)	42(15.6)
Pruritus	2(3.9)	3(4.0)	9(12.5)	15(20.8)	29(10.7)
Vomiting	2(3.9)	4(5.3)	5(6.9)	17(23.6)	28(10.4)
Asthenia	1 (2.0)	5(6.7)	6(8.3)	11 (15.3)	23 (8.5)
Dry mouth	2(3.9)	4(5.3)	2(2.8)	15(20.8)	23(8.5)
Anorexia	1 (2.0)	2(2.7)	5(6.9)	11 (15.3)	19(7.0)
AST/SGOT increased	1(2.0)	4(5.3)	7(9.7)	5(6.9)	17(6.3)
ALT/SGPT increased	1(2.0)	4(5.3)	5(6.9)	5(6.9)	15(5.6)

a patients may have had more than 1 drug-related adverse event.

b Including doses between 225 mg and 300 mg, inclusive.

c including doses between 400 mg and 525 mg, inclusive.

d doses of ZD1839 of >525 mg

Adverse events with CTC grades 3 or 4

Overall, 118 patients (43.7%) had CTC Grade 3 or 4 adverse events. Thirty-nine patients (14.4%) had Grade 3 or 4 events that were considered drug related, and these occurred with increasing frequency with increasing dose. As in Trial 39, diarrhea was the only drug-related adverse event of CTC Grade ≥ 3 severity with an incidence of $\geq 3\%$ in the total population. Seventeen out of 19 patients who experienced drug-related CTC Grade 3 or 4 diarrhea were receiving mg/day.

Deaths

A total of 14 out of 270 (5.2%) patients had adverse events in the Phase I multiple-dose trials that had an outcome of death. These patients were distributed across doses from 150 mg/day to 800 mg/day, and none of these events were considered by the investigators to be possibly related to ZD1839.

Withdrawals due to adverse events

A total of 38 out of 270 (14.1%) patients withdrew from ZD1839 therapy due to one or more adverse events. In 24 of these patients, the adverse events were considered to be possibly drug related; in 16 cases, withdrawal was due to gastrointestinal symptoms with 12 cases due to drug related diarrhea.

Serious adverse events

Seventy-nine (29.3%) patients experienced at least 1 serious adverse event. The commonest serious adverse events reported (>2%; 6 or more patients) were abdominal pain (4.4%), dyspnea (3.7%), dehydration (3.0%), asthenia (2.6%), diarrhea (2.6%), and anemia (2.2%). Twenty (7.4%) patients experienced drug-related serious adverse events. Only 4 of these patients were receiving doses \leq 525 mg/day.

All drug-related adverse events with a frequency \geq 5% in any of the Phase II and I multiple-dose patient trials is summarized in **Table 51**.

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Table 51: Drug-related adverse events in the Phase II and I multiple-dose patient trials

Drug-related AE	Number (%) of patients					
	Phase II Trial 0039		Phase II Trial 0016		Phase I trials	
	250 mg/day (n=102)	500 mg/day (n=114)	250 mg/day (n=103)	500 mg/day (n=106)	225 to 300 mg/day (n=75)	400 to 525 (n=72)
Diarrhea	49(48.0)	76(66.7)	41 (39.8)	61 (57.5)	24(32.0)	31 (43.1)
Rash	44(43.1)	61 (53.5)	48(46.6)	73(68.9)	23(30.7)	34(47.2)
Acne	25(24.5)	37(32.5)	13 (12.6)	15(14.2)	15(20.0)	18(25.0)
Dry skin	13(12.7)	30(26.3)	28(27.2)	31 (29.2)	12(16.0)	16(22.2)
Nausea	13(12.7)	20(17.5)	13 (12.6)	25(23.6)	7(9.3)	12(16.7)
Vomiting	12(11.8)	10(8.8)	6(5.8)	21 (19.8)	4(5.3)	5(6.9)
Pruritus	8(7.8)	10(8.8)	31 (30.1)	38(35.8)	3(4.0)	9(12.5)
Anorexia	7(6.9)	11(9.6)	9(8.7)	20(18.9)	2(2.7)	5(6.9)
Asthenia	6(5.9)	5(4.4)	8(7.8)	11(10.4)	5(6.7)	6(8.3)
Nail disorder	4(3.9)	3(2.6)	4(3.9)	9(8.5)	1 (1.3)	1 (1.4)
Exfol. Dermatitis	4(3.9)	1 (0.9)	8(7.8)	9(8.5)	3(4.0)	3(4.2)
Weight loss	3(2.9)	6(5.3)	2(1.9)	6(5.7)	0(0.0)	1(1.4)
Abdominal pain	3(2.9)	5(4.4)	3(2.9)	8(7.5)	2(2.7)	3(4.2)
Epistaxis	2(2.0)	3(2.6)	2(1.9)	12(11.3)	0(0.0)	0(0.0)
Dry mouth	2(2.0)	3 (2.6)	4(3.9)	2(1.9)	4(5.3)	2(2.8)
Pain	2(2.0)	1(0.9)	10(9.7)	17(16.0)	1 (1.3)	1(1.4)
ALT increased	1 (1.0)	3 (2.6)	13(12.6)	25(23.6)	4(5.3)	5(6.9)
AST increased	1 (1.0)	3(2.6)	11 (10.7)	24(22.6)	4(5.3)	7(9.7)
Conjunctivitis	1(1.0)	3(2.6)	4(3.9)	10(9.4)	1(1.3)	4(5.6)
Blepharitis	1(1.0)	1(0.9)	5(4.9)	6(5.7)	0(0.0)	0(0.0)
Taste perversion	0(0.0)	5(4.4)	1 (1.0)	5(4.7)	2(2.7)	5(6.9)
Stomatitis	0(0.0)	3(2.6)	8 (7.8)	8(7.5)	1 (1.3)	1(1.4)
Seborrhea	0(0.0)	0(0.0)	6(5.8)	4(3.8)	0(0.0)	2(2.8)
Hematuria	0(0.0)	0(0.0)	6(5.8)	4(4.7)	1 (1.3)	2(2.8)
LDH increased	0(0.0)	0(0.0)	1 (1.0)	1(0.9)	4(5.3)	1(1.4)

The incidence of withdrawals due to drug-related adverse events was low across the ZD1839 clinical program especially for patients receiving doses of 250 mg/day or similar; 3 out of 205 (1.5%) patients who received ZD1839 250 mg/day in the Phase II trials were withdrawn due to drug-related adverse events (asthenia, bundle branch block, and increased ALT/SGPT), and 3 out of 126 (2.4%) patients in the Phase I multiple-dose trials receiving doses of \geq 300 mg/day were withdrawn due to drug-related adverse events (anorexia, nausea, and diarrhea).

7.4 Adequacy of Safety testing

Safety testing was adequate.

7.5 Summary of Critical Safety Findings

Skin

Phase I patients with solid tumors

In the Phase I multiple dose trials in 270 patients with solid tumors, dose related toxicities to the skin have been consistently observed. 192 patients (71.1%) reported adverse events. The most common of these events were rash (44.8%), acne (20.7%), dry skin (22.2%), and pruritus (13.7%). The incidence and severity of skin events in these trials increased with escalating dose and was a dose limiting toxicity in some patients. Patients with rash frequently had associated reports of dry skin, acne, pruritus, and other skin symptoms.

Seven patients experienced drug-related dose-limiting skin toxicity (CTC grade 3); pruritus (n=2 at 400 mg/day and 800 mg/day respectively), acne (n=2, 525 mg/day and 1000 mg/day, respectively), rash (n=2, 400 mg/day and 800 mg/day respectively) and one patient had urticaria plus rash (1000 mg/day).

Fewer events of skin toxicity were reported at doses = 500 mg/day than at doses >500 mg/day. Skin events of rash, acne, dry skin and pruritus were mild, predominantly CTC grade 1 or 2 and generally resolved during the treatment period or following cessation of therapy). Eleven patients reported 15 drug-related skin events of CTC grade 3. None were reported at <225 mg dose level, only 1 patient experienced CTC grade 3 rash at the nominal 250 mg dose level (0011/0002/0044, 300 mg), 1 event each of acne, pruritus and rash were reported at the 500 mg dose level and 11 events were reported at the >525 mg level. (2 acne, 1 dry skin, 1 hair disorder [abnormal lashes], 1 pruritus, 5 rash, and 1 urticaria). Three patients withdrew from ZD1839 due to acne (525 mg/day), rash (one patient receiving 400 mg and one, 800 mg/day) and hair disorder (800 mg/day).

Four patients (1.5%) reported urticaria in these Phase I multiple dose trials (1 at 150 mg/day [CTC grade 2], 1 at 500 mg/day [CTC grade 1] and 2 at 1000 mg/day [CTC grades 1 and 3]). With the exception of 1 patient (150 mg/day) the events were considered drug-related. The onset of the events occurred on days 29, 4, 1, and 5 for the patients receiving 150 mg/day, 500 mg/day and the 2 patients on 1000 mg/day, respectively. None of the events were considered serious and no patients were withdrawn due to urticaria.

The frequency of skin adverse events by CTC grade in the Phase I multiple-dose trials is shown in **Table 52**.

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Table 52: Skin toxicity by CTC grade in the Phase I multiple-dose trials

Adverse event	CTC grade	Number (%) of patients				All doses (n=270)
		<225 mg (n=51)	250 mg (n=75)	500 mg (n=72)	>525 mg (n=72)	
Rash	1	12(23.5)	19(25.3)	24(33.3)	22(30.6)	77(28.5)
	2	2(3.9)	7(9.3)	10(13.9)	18(25.0)	37(13.7)
	3	0(0)	1(1.3)	1(1.4)	5(6.9)	7(2.6)
Acne	1	2(3.9)	14(18.7)	12(16.7)	7(9.7)	35(13.0)
	2	2(3.9)	2(2.7)	6(8.3)	8(11.1)	18(6.7)
	3	0(0)	0(0)	1(1.4)	2(2.8)	3(1.1)
Pruritus	1	4(7.8)	4(5.3)	8(11.1)	9(12.5)	25(9.3)
	2	0(0)	1(1.3)	3(4.2)	6(8.3)	10(3.7)
	3	0(0)	0(0)	1(1.4)	1(1.4)	2(0.7)
Dry Skin	1	4(7.8)	14(18.7)	18(25.0)	19(26.4)	55(20.4)
	2	0(0)	0(0)	1(1.4)	3(4.2)	4(1.5)
	3	0(0)	0(0)	0(0)	1(1.4)	1(0.4)

Phase II monotherapy trials

In the Phase II pivotal Trial 39 and supportive Trial 16 where 205 patients received 250 mg/day and 220 patients had 500 mg/day ZD1839, 323 patients (75.3%) experienced skin events (66.8 % at 250 mg/day and 84.5% at 500 mg/day). Rash (55.3%), acne (22.1%), dry skin (25.4%), pruritus (21.6%) were the most common events reported. Other reported terms relating to rash were, vesiculobullous rash (1.4%), pustular rash (0.5%), and ichthyosis (0.9%). Patients with rash frequently had associated reports of dry skin, acne, pruritus or other skin symptoms eg, exfoliative dermatitis commonly described as desquamation (5.4%). Two hundred -and- seventy-five patients had at least one episode of rash or acne. Seventy-three patients reported rash and pruritus, 51 patients had acne plus rash, and 22 patients had acne plus pruritus.

Skin adverse events by CTC grade in the Phase II trials is presented in Table 53.

Table 53: Frequency of skin adverse events by CTC grade in the Phase II trials

Adverse event	CTC grade	ZD1839 Treatment	
		250 mg (n=205)	500 mg (n=220)
Acne	1	30(14.6)	27(12.3)
	2	9(4.4)	22(10.0)
	3	0(0)	6(2.7)
Dry Skin	1	43(21.0)	50(22.7)
	2	4(2.0)	11(5.0)
Pruritus	1	36(17.6)	41(18.6)
	2	7(3.4)	6(2.7)
	3	0(0)	2(0.9)
Rash	1	71(34.6)	74(33.6)
	2	26(12.7)	53(24.1)
	3	1(0.5)	9(4.1)
	4	0(0)	1(0.5)

Rash

In 192 patients overall (81.7%) the rash first occurred during the first treatment period; in 32 patients (13.6%) the rash began during treatment periods 2 or 3, and 11 patients (4.7%) first had rash during treatment period 4 or beyond. Four patients in the 500 mg/day ZD1839 group were withdrawn from the trial due to skin rash. There were no withdrawals due to rash in the 250 mg/day group.

Acne

A total of 94 patients (22.1 %) had adverse events of acne (19.0% at 250 mg/day and 25.0% at 500 mg/day). In the majority of patients (74.5%, 70/94 events) the acne occurred during the first treatment period. Two patients at the 500mg/day dose were withdrawn from the study due to CTC grade 3 drug-related acne. No patients were withdrawn due to acne in the 250 mg/day group. In the majority of patients with acne (55.3%) the event was documented to have resolved (51.3% at 250 mg /day and 58.2% at 500 mg/day) either during the treatment period or following cessation of therapy. In 42 patients the acne was reported to be 'ongoing'. The majority of these ongoing events are CTC grade 1 (66.7%) and 14 patients are still ongoing in the trial hence resolution of the event is still possible.

For rashes and acne that did not resolve or improve spontaneously a variety of agents were used to manage the skin symptoms, seen during treatment. These included steroid creams, either topical or systemic antibiotics, topical or systemic anti-histamines and occasionally retinoid creams. The successfulness of these agents in treating the skin conditions has varied between patients, with each agent showing some efficacy but not across all patients.

Pruritus

A total of 92 patients (21.6%) had adverse events of pruritus (21 % at 250 mg/day and 22.3% at 500 mg/day). In the majority of patients (58.7%, 54/92 patients) the pruritus occurred during the first treatment period. One patient receiving 500 mg/day ZD1839 was withdrawn from the trial due to CTC grade 2 pruritus and rash, both events were considered drug-related. The majority (59.8%) of the events were documented to have resolved either during the treatment period or following cessation of therapy (51.2% at 250 mg/day and 67.3% at 500 mg/day). Of the 92 patients with pruritus, 80 were reported to have had rash and/or acne.

Dry Skin

A total of 108 patients (25.4%) had adverse events of dry skin. Sixty-nine of the 108 patients (63.9%) had the first occurrence of dry skin during the first treatment period. There were no patients withdrawn from the trial due to dry skin. The majority (52.8%) of the events were documented to have resolved (55.3% at 250 mg/day and 50.8% at 500 mg/day) either during the treatment period or following cessation of therapy. Of the 108 patients with dry skin, 85 patients were reported to have had rash and or acne.

Nail Disorders

A total of 26 patients across both trials (6.1 %) had 29 events reported which were termed nail disorders (9 patients at 250 mg/day and 17 patients at 500 mg/day). These disorders included paronychia (11), ingrown nails (6), nail changes (4), breaking nail (2), onycholysis (2), nail ridging (1), finger (1) or nail (1) discoloration and nail loss (1). Events for 20 of these patients (3.9% at 250 mg/day and 5.5% at 500 mg/day) were considered possibly related to ZD1839. One patient at the 500mg/day dose had a grade 3 paronychia that occurred on day 12 of treatment and resolved after 92 days. Of the remaining patients, 14 had CTC grade 1 events (2.4% at 250 mg/day and 4.1 % at 500 mg/day) and 11 had CTC grade 2 (2.0% at 250 mg/day and 3.2% at 500 mg/day). None of these events was serious and the majority of these events resolved.

Other Skin Disorders

Toxic epidermal necrolysis (CTC grade 4) and erythema multiforme (CTC Grade unknown) occurred in 1 patient each. These are from a database of greater than 8000 patients exposed to ZD1839.

Ophthalmologic Toxicity

Phase I multiple dose ranging studies

In the Phase I multiple dose trials in patients with solid tumors, ophthalmic monitoring was performed every 2 weeks and included visual acuity, slit-lamp examination with fluorescein and Rose Bengal staining, lid eversion and Schirmer's test.

Baseline findings were seen at all dose levels in 181 patients (67%). During the trial new ophthalmology findings were reported in 122 patients. 68 patients from trials 0005, 0011 and 0012 experienced decreased tear production (measured by Schirmer's test). Data from over 837 routine slit lamp examinations revealed no identifiable trend in abnormalities. The ophthalmological data observed were thought to represent variance within a normal population, and were not believed to be related to trial treatment. Of significance the intensive ophthalmological monitoring did not reveal any findings representative of those detected in the pre-clinical studies eg, diffuse corneal translucency and corneal atrophy.

The number of patients with ocular adverse events, by dose, from Phase I trials is presented in **Table 54**.

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Table 54: Ocular adverse events by dose: patients from Phase I trials

Adverse event	Number (%) of patients				All patients (n=270)
	ZD1839 <225 mg/day (n=51)	ZD1839 250 mg/day (n=75)	ZD1839 500 mg/day (n=72)	ZD1839 >500 mg/day (n=72)	
Total	18(35.3)	22(29.3)	19(26.4)	26(36.1)	85(31.5)
Abnormal vision	1 (2.0)	0(0)	0(0)	0(0)	1 (0.4)
Ambyopia	5(9.8)	8(10.7)	1 (1.4)	0(0)	14(5.2)
Blepharitis	3(5.9)	0(0)	4(5.6)	1(1.4)	8(3.0)
Blindness	0(0)	1 (1.3)	0(0)	0(0)	1 (0.4)
Cataract specified	0(0)	0(0)	0(0)	1(1.4)	1(0.4)
Conjunctivitis	9(17.6)	10(13.3)	8(11.1)	12(16.7)	39(14.4)
Corneal lesion	0(0)	0(0)	2(2.8)	2 (1.8)	4(1.5)
Comeal opacity	1 (2.0)	1 (1.3)	0(0)	0(0)	2(0.7)
Corneal ulcer	0(0)	0(0)	2(2.8)	2(2.8)	4(1.5)
Dry eyes	3 (5.9)	4(5.3)	2(2.8)	11 (15.3)	20(7.4)
Eye disorder	3 (5.9)	3(4.0)	0(0)	3(4.2)	9(3.3)
Eye hemorrhage	0(0)	2(2.7)	0(0)	1(1.4)	3(1.1)
Eye pain	2(3.9)	0(0)	2(2.8)	0(0)	4(1.5)
Glaucoma	0(0)	0(0)	1 (1.4)	0(0)	1 (0.4)
Keratoconjunctivitis	0(0)	1(1.3)	0(0)	0(0)	1 (0.4)
Keratitis	1 (2.0)	0(0)	0(0)	2(2.8)	3 (1.1)
Lacrimation disorder	1 (2.0)	0(0)	1 (1.4)	0(0)	2(0.7)
Photophobia	1 (2.0)	1(1.3)	0(0)	0(0)	2(0.7)
Retinal disorder	0(0)	0(0)	0(0)	1 (1.4)	1(0.4)
Uveitis	1 (2.0)	0(0)	0(0)	0(0)	1 (0.4)
Visual field defect	0(0)	0(0)	1(1.4)	0(0)	1(0.4)
Vitreous disorder	0(0)	1 (1.3)	0(0)	0(0)	1(0.4)

An external Ophthalmology Advisory Board, consisting of 4 international, independent ophthalmologists reviewed the ophthalmological monitoring results. This review revealed no evidence of any consistent or drug-related ophthalmologic toxicity. The significant ocular adverse events reported of corneal ulcer occurred at higher doses than is currently being recommended. Even so these events were in the most part related to aberrant eyelashes and associated with symptoms of pain or discomfort. The corneal ulcers healed rapidly once lashes had been removed.

The advice from the Ophthalmology Advisory Board, in the absence of any consistent or significant ocular toxicity from the Phase I data, was that for the Phase II studies at doses of 250 mg and 500 mg/day:

- The inclusion/exclusion criteria could be relaxed (eg, concomitant medications, contact lens wear, concurrent eye disorders)
- The level of monitoring could be substantially reduced as any potential ocular safety signals had been associated with easily recognized symptoms
- Investigators and patients should be alerted to the value of eyelid awareness

Phase II monotherapy trials

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In the 2 Phase II trials, complete ophthalmologic evaluations, including slit lamp examination, were performed in a minority of patients (based on phase I findings) at baseline and at trial completion or early withdrawal from the trial (at the end of treatment).

In trial 0039 only 37 (17.1%) patients had ophthalmological assessments at baseline and at either withdrawal or another post baseline visit. One patient had visual impairment noted at withdrawal but not at baseline, 3 patients had hyperemia in 1 or both eyes post baseline, and in 5 patients fluorescein staining in one or both eyes was noted post baseline. Schirmer's test was only performed at baseline in this trial.

In trial 0016, baseline ophthalmology findings were seen in 49 patients (23.4%). New findings were recorded in 38 (18.2%) patients and 78 patients (37%) experienced decreased tear production from baseline, during the trial. The decreased tear production was minimal (<5mm) in most cases and was offset by an increase in tear production in 30 (14.3%) patients.

Changes from baseline in ophthalmological evaluations in these two trials, were thought to represent variance within a normal population, to have no clinical significance and were not attributed by the investigator to be related to trial treatment.

The majority of the events were CTC grade 1 (78/102 [76.5%]) or CTC grade 2 (22/102 [21.6%]). In only 2 patients (2/102 [1.96%]) were the eye events reported as CTC grade 3; these were a serious event of cataract considered not related to trial treatment and a corneal ulcer also considered not drug-related.

Results from the ophthalmological monitoring revealed no evidence of any consistent or drug-related ophthalmologic toxicity in these trials. Although 24% of patients from these 2 monotherapy trials experienced eye symptoms/events, the events were frequently mild (CTC 1) and there was only 2 CTC grade 3 events, both of which were considered unrelated to trial therapy. The corneal erosions/ulcers were reversible and sometimes associated with aberrant eyelash growth. Only 1 of the corneal ulcers occurred at the 250 mg/day dose.

In summary, results from the comprehensive ophthalmology monitoring, including over 1500 slit lamp examinations, obtained from the Phase I/II trials did not reveal any asymptomatic findings representative of those seen in the pre-clinical studies. No evidence of any consistent or drug-related ophthalmologic toxicity was observed in these trials. There is no evidence to suggest a need for any recommendations or precautions for future use of ZD1839 beyond patients being aware that they should seek advice should they develop any eye symptoms.

Gastrointestinal Toxicity

Phase I patients with solid tumors

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In the Phase I multiple dose trials in 270 patients with solid tumors, dose-related toxicities to the gastrointestinal system have been consistently observed. Gastrointestinal adverse events were reported by 221 patients (81.9%). The most common of these events were diarrhea (56.3%), nausea (35.2%), vomiting (28.5%) and anorexia (26.3%); the majority of which were CTC grade 1 or 2.

Table 55 presents the frequency of gastrointestinal events by CTC grade in the Phase I multiple dose trials. No drug-related CTC grade 3 or 4 events of stomatitis or anorexia were reported during the Phase I trials.

Table 55: Gastrointestinal events by CTC grade in Phase I multiple-dose trials

Adverse event (COSTART term)		CTC gradeNumber (%) of patients				
		<225 mg (n=51)	250 mg (n=75)	500 mg (n=72)	>525 mg (n=72)	All doses (n=270)
Diarrhea	1	15(29.4)	26(34.7)	30(41.7)	23 (31.9)	94(34.8)
	2	3(5.9)	6(8.0)	12(16.7)	18(25.0)	39(14.4)
	3	0(0)	2(2.7)	0(0)	16(22.2)	18(6.7)
	4	0(0)	0(0)	0(0)	1(1.4)	1(0.4)
Nausea	1	13(25.5)	10(13.3)	17(23.6)	21 (29.2)	61 (22.6)
	2	5(9.8)	7(9.3)	9(12.5)	9(12.5)	30(11.1)
	3	0(0)	2(2.7)	0(0)	1(1.4)	3(1.1)
	4	0(0)	0(0)	0(0)	1(1.4)	1(0.4)
Vomiting	1	10(19.6)	16(21.3)	13(18.1)	13 (18.1)	52(19.3)
	2	1 (2.0)	6(8.0)	8(11.1)	8(11.1)	23(8.5)
	3	0(0)	0(0)	0(0)	1 (1.4)	1 (0.4)
	4	0(0)	0(0)	0(0)	1(1.4)	1(0.4)
Anorexia	1	7(13.7)	15(20.0)	13(18.1)	18(25.0)	53(19.6)
	2	2(3.9)	1 (1.3)	6(8.3)	5(6.9)	14(5.2)
	3	0(0)	1 (1.3)	1(1.4)	0(0)	2(0.7)
	4	1 (2.0)	1 (1.3)	0(0)	0(0)	2(0.7)
Stomatitis	1	0(0)	2(2.7)	7(9.8)	5(6.9)	14(5.5)
	2	1 (2.0)	0(0)	1(1.4)	3(4.2)	5(1.9)
	3	0(0)	1(1.3)	0(0)	1 (1.4)	2(0.7)

Phase II monotherapy trials

Similar to the phase I trials the phase II trials observed similar gastrointestinal toxicity. In the majority of patients with GI toxicity the adverse event first was noted during treatment period 1 (Table 56).

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Table 56: Gastrointestinal adverse events by CTC grade in the Phase II trials

Adverse event a,c	CTC grade	ZD1839 Treatment	
		250 mg (n=205)	500 mg (n=220)
Anorexia	1	28(13.7)	36(16.4)
	2	10(4.9)	22(10.0)
	3	4(2.0)	2(0.9)
	NR	0(0)	1(0.5)
Diarrhea	1	87(42.4)	102(46.4)
	2	19(9.3)	39(17.7)
	3	2(1.0)	15(6.8)
Nausea	1	37(18.0)	45(20.5)
	2	11(5.4)	20 (9.1)
	3	4(2.0)	3(1.4)
Vomiting	1	26(12.7)	36(16.4)
	2	8(3.9)	15(6.8)
	3	3 (1.5)	4(1.8)
	4	1(0.5)	0(0)
Stomatitis b	1	11 (5.4)	21(9.5)
	2	1(0.5)	3(0.7)
	3	0(0)	1(0.5)

a COSTART Coding Symbols for Thesaurus of Adverse Reaction Terms.

b Stomatitis includes COSTART terms of stomatitis, mouth ulceration and aphthous stomatitis.

NR Not recorded.

c In the Phase II trials diarrhea was the most commonly reported adverse event (52.7% at 250 mg/day; 70.9% at 500 mg/day), the majority of which was CTC grade 1. There were only 2 CTC grade 3 diarrheas at the 250 mg/day dose. No patients withdrew from treatment due to a gastrointestinal event at the 250 mg/day dose.

Electrocardiograms

Phase I multiple dose ranging studies

In the Phase I trials (trials 5, 11 and 12) patients with a P-R interval of greater than 217 msec or a previous history of clinically significant cardiac dysrhythmia, any degree of atrio-ventricular block or other severe cardiac disease were excluded. All patients had a 12-lead ECG at screening, between 5 and 7 hours after the first dose, followed by weekly (trial 5) or 2-weekly (trials 11 and 12) tracings throughout the study period. A total of 1642 ECGs were recorded from the 221 patients participating in these Phase I trials. Review of data from these patients, did not suggest any significant or consistent findings. In particular, there was no indication of PR prolongation and there were no signals of QT prolongation recognized.

Of the 221 patients in Trials 5, 11 and 12, a total of 68 (30.8%) had abnormal ECG's at baseline. During these trials 17 (7.7%) patients had ECG abnormalities that were reported

as adverse events. Apart from 1 patient (Trial 5 patient 0002/0081) who had a prolongation of the PR interval that was considered not clinically significant, none of these adverse events was considered by the investigator to be related to trial treatment. Electrocardiographic abnormalities are summarized in **Table 57**.

Table 57: Phase I abnormal ECG findings

Adverse event	Number (%) of patients a				
	<225 mg (n=51)	250 mg (n=75)	500 mg (n=72)	>525 mg (n=72)	All doses (n=270)
Arrhythmia	0(0.0)	0(0.0)	0(0.0)	1(1.4)	1(0.4)
Atrial Fibrillation	2(3.9)	0(0.0)	3(4.2)	0(0.0)	5(1.9)
AV block	0(0.0)	0(0.0)	1(1.4)	0(0.0)	1(0.4)
ECG abnormal	1(2.0)	1(1.3)	1(1.4)	3(4.2)	6(2.2)
Sinus bradycardia	0(0.0)	0(0)	2(2.8)	0(0.0)	2(0.7)
Tachycardia	2(3.9)	3(4.0)	0(0.0)	0(0.0)	5(1.9)
Ventricular extrasystoles	0(0.0)	3(4.0)	1(1.4)	0(0.0)	4(1.5)

a patients might have more than one ECG abnormality

Phase II monotherapy studies

In the Phase II studies patients had a screening and withdrawal ECG and, additionally in trial 16, an ECG at the end of month 4.

At trial entry, 153 (36%) patients had abnormal ECG results. Of these patients, 46 were from trial 16 and 107 were from trial 39. During the trials 10 patients (4 at 250 mg/day and 6 at 500 mg/day) had ECG abnormalities reported as adverse events. Three of these patients had abnormal ECGs at baseline. Five of the events (2 arrhythmias and 3 atrial fibrillations) were CTC Grade 3 and the others were CTC Grade 1 or 2. Only 1 of these adverse events was considered by the investigator to be related to trial treatment (non-serious, grade 3 atrial fibrillation) and 1 was reported as serious (unrelated, grade 3 atrial fibrillation). One of these 10 patients and an additional patient had a myocardial infarction and died within 30 days after trial treatment ended. Details of these 11 patients is as follows:

Trial 16

Patient 0804/0004 (250-mg/day group) had related, non-serious Grade 3 atrial fibrillation recorded after 87 days treatment, at the time of withdrawal due to disease progression. The adverse event resolved.

Patient 0207/0004 (250-mg/day group) had unrelated, serious Grade 3 atrial fibrillation recorded after 8 days treatment, when he withdrew due to disease progression. The adverse event resolved.

Patient 0501/0004 (500-mg/day group) had unrelated, non-serious Grade 3 arrhythmia and lung edema, Grade 2 atrial fibrillation and serious Grade 4 dyspnea recorded 13 days after

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entering the trial, but only having received treatment on Day 1 and then withdrawing with objective disease progression.

Trial 39

Patient 2008/0192 (500-mg/day group) had non-drug-related, CTC Grade 1 ectopic beats recorded after 8 days of treatment. The patient received 41 days of trial treatment. The adverse event was reported as ongoing.

Patient 2107/0035 (500-mg/day group) had non-drug-related, CTC Grade 3 irregular heart rhythm recorded 6 days after an acute myocardial infarction, which occurred on the same day the patient was withdrawn from the trial due to adverse events (drug-related diarrhea and non-drug-related myocardial infarction). The patient also had disseminated intravascular coagulation at the same time as the arrhythmia. The patient died 1 day after the onset of these events. The patient had a history of myocardial infarction and atrial fibrillation. The patient received 63 days of trial treatment.

Patient 2028/0105 (500-mg/day group) had non-drug-related, CTC Grade 3 atrial fibrillation recorded after 39 days of treatment. The adverse event resolved 3 days later. The patient received 45 days of trial treatment.

Patient 2107/0036 (500-mg/day group) had non-drug-related, CTC Grade 2 atrial fibrillation recorded after 6 days of treatment. The adverse event was reported as ongoing. The patient was withdrawn from the trial due to non-drug-related adverse events (congestive heart failure, hypoxia, and acute respiratory distress) after 7 days of treatment and died 7 days later of complications due to lung cancer.

Patient 2101/0155 (250-mg/day group) had non-drug-related, CTC Grade 1 T-wave inversion, Grade 1 axis deviation and Grade 1 left bundle branch block 2 days post treatment. Sinus tachycardia, sepsis, pneumonia, and dehydration were also reported at or near that time. The patient received 29 days of treatment and died due to metastatic NSCLC and sepsis 1 day after the ECG abnormalities were reported.

Patient 2101/0154 (250-mg/day group) had non-drug-related, CTC Grade 1 abnormal electrocardiogram recorded 1 day post treatment. The adverse event was reported as ongoing. The patient was withdrawn from the trial due to non-drug-related adverse events (respiratory failure and pneumonia) after 71 days of treatment.

Patient 2028/0107 (500-mg/day group) had non-drug-related, CTC Grade 1 premature ventricular contractions recorded after 163 days of treatment. The adverse event was ongoing. The patient received 195 days of treatment.

Patient 2107/0034 (250-mg/day group) had a history of myocardial infarction and had arrhythmia (CTC Grade 4) recorded as an adverse event, beginning prior to treatment. This patient died of a myocardial infarction 25 days after trial treatment ended. The patient received 111 days of trial treatment. The QTc interval at baseline was 420 msec; no follow-up ECG was performed.

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These events from the 2 Phase II monotherapy studies are summarized in Table 58.

Table 58: ECG abnormalities

Adverse event	Number (%) of patients	
	ZD1839 250 mg/day N=205	ZD1839 500 mg/day N=220
Arrhythmia	1(0.5)	3(1.4)
Atrial Fibrillation	2(1.0)	3(1.4)
Bundle branch block	3(1.5)	0(0.0)
Electrocardiogram abnormal	2(1.0)	0(0.0)
Myocardial infarct	1(0.5)	1(0.5)
Palpitation	1(0.5)	3(1.4)
Sinus bradycardia	0(0.0)	1(0.5)
Tachycardia	5(2.4)	7(3.2)
Ventricular extrasystoles	0(0.0)	1(0.5)

There were no clear trends observed in ECGs or PR intervals for patients during trial treatment and no apparent differences between the doses. In Trial 0039, corrected QT interval was recorded at trial entry and withdrawal. Forty-two patients had their withdrawal ECG within 24 hours of the last dose of ZD1839. For these patients, there was no evidence of any prolongation of QT interval over the course of the trial.

7.6 Adequacy of Safety Testing

Safety data from Phase I and Phase II studies of relatively short follow-up suggest that ZD1839 is generally well tolerated. Long duration safety data is not yet available. It was of interest to observe that the ophthalmologic toxicity noted in pre-clinical studies was not observed in study patients.

7.7 Safety Conclusions

A total of 960 subjects (714 cancer patients, and 246 healthy volunteers) were exposed to ZD1839 in the 20 completed monotherapy trials. A total of 420 subjects (297 cancer patients, and 123 healthy volunteers) were exposed to a dose of ZDI 839 between 225 and 300 mg/day, with a maximum duration of dosing of 506 days. A total of 348 subjects (292 patients and 56 healthy volunteers) were exposed to a dose of ZDI 839 between 400 and 525 mg/day, with a maximum duration of dosing of 404 days.

Patients receiving ZD1839 250 mg/day (or similar doses) in the multiple-dose Phase I and II trials frequently experienced drug-related gastrointestinal disturbances (mainly diarrhea, sometimes associated with dehydration) and skin reactions (rash, acne, dry skin, and pruritus). The majority of drug-related adverse events were mild (CTC Grade 1) and non-cumulative, and rarely led to withdrawal of ZD1839 therapy, with only 2 CTC Grade 3 diarrheas, and 3 CTC Grade 3 skin events reported at the 250-mg/day dose in the Phase II trials.

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No additional safety concerns were raised for subpopulations of men or women, the elderly, ethnic groups, patients with renal impairment, or patients with mild to moderate hepatic impairment. Evaluation of the safety data does not indicate the need for any additional safety monitoring. Few specific drug-drug interactions have been identified that could impact on the safety of ZD1839.

In patients receiving ZD1839 therapy, there have been infrequent reports of reversible corneal erosion, sometimes in association with aberrant eyelash growth. However, no evidence of any consistent or drug-related ophthalmologic toxicity was observed in the Phase II trials. Consequently, no recommendations or precautions relating to eye events are considered necessary beyond patients being aware that they should seek medical advice should they develop any eye symptoms.

Data from non-clinical, in vitro studies indicate that ZD1839 has the potential to inhibit the cardiac potential repolarization process eg, QTc interval. The clinical relevance of these findings is unknown. No clear trends were observed in ECGs or PR intervals in patients participating in the Phase II trials.

A small number of significant, asymptomatic increases in liver transaminases have been observed at the 250-mg/day dose.

There was 1 report each of toxic epidermal necrolysis and erythema multiforme.

Co-administration of ZD1839 250 mg with itraconazole, a CYP3A4 inhibitor, resulted in an 80% increase in the mean AUC of ZD1839 in healthy volunteers. This increase maybe clinically relevant to the safety of ZD1839 when used concomitantly with drugs that inhibit CYP3A4, since drug-related adverse events are related to dose and exposure.

International Normalized Ratio (INR) elevations and/or bleeding events have been reported in some patients taking warfarin while on ZD1839 therapy. Patients taking warfarin should be monitored regularly for changes in prothrombin time and INR.

In conclusion, the adverse event data reported in the Phase II and I trials conducted with ZD1839 indicate that this drug has a favorable safety profile for the intended patient population. Overall, the 250-mg/day dose was better tolerated than the 500-mg/day dose.

7.8 Interstitial Lung Disease

Following the September 24, 2002 Oncology Drug Advisory Committee meeting the FDA began to receive increasing numbers of reports of interstitial lung disease occurring in ZD1839 treated patients. The mortality from early reports of this AE approached 50%. The Agency determined that a better understanding of this toxicity was necessary before an approval/non-approval decision could be made. The following pages summarize this investigation.

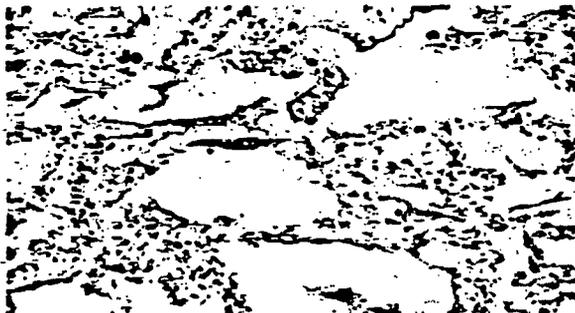
ZD1839 associated Interstitial lung disease (ILD) - History

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Japan approved ZD1839 for the treatment of refractory non-small cell lung cancer on July 5, 2002. Prior to approval ILD had been identified as an AE associated with ZD1839 treatment. Starting in March, 2002, the sponsor provided details of patients' developing ILD and patients dying from ILD to the Japanese Ministry of Health, Labour, and Welfare (MHLW). On June 19, 2002, the FDA received a MedWatch report of "alveolitis" occurring in a Hong Kong patient. The FDA requested a review of this case. On July 3, 2002, following an *Ad Hoc* Iressa Safety Evaluation and Review Meeting (SERM), the sponsor added ILD to the Investigators' Brochure and informed FDA in a letter dated July 30, 2002 that the Investigators' Brochure would be updated. On September 3, 2002, the Prescribing Information and Investigators' Brochure were updated with the information that 61 events of pneumonitis occurred in 57 patients treated with Iressa (55 events in 51 patients in clinical trials and expanded access programs, and 6 cases following commercial launch in Japan). On October 4, 2002, the Investigators' Brochure was updated with the information that 91 events of ILD occurred among 88 patients and this information was communicated to all Japanese and the "rest of the world" (ROW) investigators. A Dear Doctor Letter and a black box warning was issued for the Japanese product on October 15, 2002.

The chest CT scan and microscopic appearance of ZD1839 associated ILD are indicated in Figure 5 (from Inoue A, Saijo Y, Maemondo M, et al. Severe acute interstitial pneumonia and gefitinib. *Lancet* 2003; 361: 137-39).

Figure 5: CT scan and biopsy from an ILD patient



Bilateral diffuse ground-glass opacities in chest CT of patient 10 (A); and haematoxylin and eosin staining of diffuse alveolar damage in the lung of patient 4 (B; magnification $\times 40$)

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There is no consistency in classification of ILD and the diagnosis may not always be reliable. In addition, ILD is not a preferred term in the MedDRA (Medical Dictionary for Regulatory Activities) dictionary. Based on guidance from respiratory medicine experts the MedDRA-preferred terms used by the sponsor in the search to identify ILD-type events include: interstitial lung disease, interstitial pneumonia, lung infiltration NOS, lung infiltration malignant, lung disorder NOS, pneumonitis NOS, pneumonitis chemical, pneumonitis cryptococcal, pneumonitis fume inhalation, pneumonitis toxoplasmal, pulmonary interstitial emphysema syndrome, pulmonary radiation injury NOS, radiation pneumonitis, alveolitis allergic, alveolitis fibrosing, alveolitis NOS, radiation alveolitis, pulmonary fibrosis, radiation fibrosis-lung, acute respiratory distress syndrome, cryptogenic organizing pneumonia, obliterative bronchiolitis, pulmonary toxicity NOS, and X-Ray NOS chest abnormal. A recent International Consensus Statement has also attempted to standardize the diagnostic criteria and terminology for classifying ILD into seven clinicoradiologic-pathologic entities: idiopathic pulmonary fibrosis, non-specific interstitial pneumonia, cryptogenic organizing pneumonia, acute interstitial pneumonia, respiratory bronchiolitis-associated interstitial lung disease, desquamative interstitial pneumonia and lymphoid interstitial pneumonia (American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias. *Am J Respir Crit Care Med* 2002; 165: 277-304).

It must also be acknowledged that determining the etiology of an acutely appearing interstitial infiltrate on chest radiologic study is difficult. As indicated from the above list of MedDRA-preferred terms, ILD may result from a variety of pulmonary insults. A further observation is that the incidence of ILD associated with ZD1839 appears to differ in Japan and the United States. The reason(s) for this difference is (are) unknown.

Review materials

The sponsor provided safety data bases as electronic files for the INTACT 1 and 2 trials as well as for the United States ZD1839 non-small cell lung cancer expanded access program (EAP). Narrative descriptions of all Serious Pulmonary AE's from INTACT 1 and 2, narratives of all ILD cases reported by 1/8/03, and narratives which represent the remaining other pulmonary events (excluding ILD cases) from the Global Drug Safety Serious Adverse Event database (data cutoff January 15, 2003). In addition, two clinical expert meetings have been conducted in Japan including oncologists, respiratory physicians, radiologists and pathologists to review the ILD cases in depth. The meeting minutes have been provided to FDA.

Principal Communications (Fax transmissions) from Oncology Division (FDA) to sponsor

The following provides a summary of requests for available information with regard to ILD:

Date 10/3/02

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Please provide the number of interstitial pneumonitis occurrences (numerator and denominator) in order to determine appropriate language for the label.

Date 10/16/02

In your facsimile dated October 7, 2002, you reported a total of 91 events in relation to interstitial lung disorders. Please provide a summary report on the onset of these events to include information such as how many days into therapy the event occurred, prior therapies, how the diagnosis was made, whether it was considered serious/life-threatening, treatment patients received, outcome of the patient, and dechallenge/rechallenge information. Also, please provide available case report forms and MedWatch forms (if case report forms are not available) in this report.

Date 11/22/02

Pursuant to the telephone conference held November 20, 2002, please submit the following:

1. The Division would like to review all serious adverse event data for both the Expanded Access Protocols and the INTACT 1 and INTACT 2 trials. This data is to include the underlying investigator data that is sent to AZ. However, please first provide a list of the fields from the Parexel safety database and AstraZeneca's database. Once this information is submitted, the Division will determine what exact safety information is necessary for further review.
2. Please also provide any efficacy data from the Expanded Access Trial, for e.g., whether the patient responded or had symptom benefit.
3. Provide a timeline indicating when Japan first notified AZ of ILD cases and all subsequent discussions/meetings thereafter. With this submission, please include information regarding the numerator and denominator for the ILD cases at the following time periods: end of August, mid September, and September 24, 2002.
4. The following was not addressed in the telephone conference of November 20, 2002, but nonetheless should be addressed. As we carefully consider the risk versus benefit of Iressa in refractory patients, we are evaluating both the pulmonary toxicity and the precision of our response rate estimate. We have evaluated the database and the narratives you have provided. We note that several of the responders appear to have received chemotherapy within several weeks prior to entering this study. We want to be certain that none of the tumor responses attributed to Iressa were caused by recent chemotherapy. The following are cases that we would like to evaluate more closely:

290/0037
2090/0048
2255/0338

Please provide a careful analysis of this issue in these patients, and support this with documentation, including:

- Last chemotherapy regimen, date of first dose, date of last dose
- Date of radiologic exam documenting progression on chemotherapy

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- Date of baseline radiologic exam for Iressa evaluation
- Date of radiologic exam documenting first Iressa response

As soon as possible after submitting the above analysis, provide radiologic reports and films/scans documenting tumor progression on the last chemotherapy regimen (include baseline and progression films/scans).

Date 12/23/02

Per the request of the review team, please provide the database from the expanded access trial with the fields identified in attachment #2 of your November 27 correspondence. Also provide the safety database for the INTACT I and 2 trials as SAS transport files. The documentation needs to be included with the INTACT data.

Date 1/13/03

Please provide updated report of all pulmonary SAE's associated with Iressa including those from Japan, from the ongoing Iressa trials (including INTACT I and 2), and the expanded access program. The report should be similar to the format of the update you submitted on October 18, 2002, with an attempt to include additional information such as incidence, severity, reversibility, duration, time to onset, previous medication, prior radiation, etc. For the INTACT I and 2 trials, please include a report describing the adverse reactions in this study (a study report if available) and narrative descriptions for all severe pulmonary adverse events.

Pertinent information provided by the sponsor

On 4 October 2002 the sponsor provided a review of the Global Drug Safety database for all events which may be related to ILD (Table 59).

Table 59: MedDRA Preferred terms

MedDRA Preferred Term	Causality			Total no. Events
	NO	YES	Blank	
Acute respiratory distress syndrome	7	3		10
Alveolitis allergic		1		1
Alveolitis NOS		1		1
Interstitial lung disease	1	1		2
Interstitial pneumonia	2	33	1	36
Lung disorder NOS	3			3
Lung infiltration NOS	3	8		11
Pneumonitis NOS	8	8	1	17
Radiation pneumonitis	9	1		10
Grand Total	33	56	2	91*

*3 patients had 2 events therefore total number of patients is 88

The above SAE's were noted in the protocol studies listed below (Table 60).

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Table 60: Source of ILD events

Protocol/Study/Source	ILD type event	Patient Exposure (N)
1839IL/001 1	1	60
18391UO014	3	738
18391L/001 6	2	210
18391UO017	5	696
18391UO050	30	16,000
18391UO058	1	8
18391UO156	1	63
1839JPIV-15-25	2	25
Compassionate Use	14	6,000
Japan Marketed Use	29	10,000
Total (all Iressa use)	88	35,740

Table 60 indicates that the incidence of ILD varies considerably from trial to trial with a high frequency of occurrence, (e.g. 2 of 25 in study 1839JPIV-15-25) in some of the smaller trials.

Based on Tables 61 and 62 (denominator 35,740) the incidence of ILD is 0.2% or 2 per 1000 patients. If only the MedDRA preferred term of interstitial pneumonia is used (the preferred Japanese term (see table 61), the incidence is 0.1%.

Table 61: ILD preferred term

Preferred Term	Japan	United States
Acute respiratory distress syndrome	1	7
Alveolitis allergic		1
Interstitial lung disease		1
Interstitial pneumonia	36	
Lung infiltration NOS	1	8
Pneumonitis NOS	2	13
Radiation pneumonitis		9
Grand Total*	40	39

* 1 patient from Japan and 2 from the U.S. had 2 events therefore total number of patients is 39 and 37 respectively.

It should be noted that many of the reports from Japan marketed use are as the result of elicited responses for adverse events following routine weekly visits from medical representatives.

A review of recently unblinded adverse event data from two Phase III placebo-controlled first-line NSCLC combination chemotherapy trials (studies 0014 and 0017, INTACT 1 & 2) was conducted by the sponsor and confirmed by the FDA (Table 62).

Table 62: Incidence of ILD-type events from Phase III placebo-controlled combination therapy trials (0014 and 0017)

Event	Number (%) of patients		
	ZD1839 500 mg (n=700)	ZD1839 250 mg (n=704)	Placebo (n=696)
ILD-type event	8(1.1)	8(1.1)	6(0.9)
Dyspnea	181(25.9)	189(26.8)	193(27.7)
Cough	146(20.9)	159(22.6)	148(21.3)
Pneumonia	45(6.4)	53(7.5)	48(6.9)

Data from these two trials did not identify an imbalance across the 3 treatment arms for pneumonitis/interstitial lung disorder type events (including reports of bronchiolitis obliterans, pulmonary infiltrates, interstitial pneumonopathy/pneumonia, respiratory distress syndrome, ARDs). In addition to ILD type events, no difference in AE reports was observed in possibly related symptoms such as dyspnea, increased cough or the more general diagnosis of pneumonia (presumed to be infective).

One possibility is that chemotherapy may have abrogated Iressa ILD toxicity in the INTACT trials. Evidence refuting this possibility is that the incidence and severity of skin and diarrhea toxicity (most frequent ZD1839 toxicities) was what one would have predicted from the IDEAL trials and the wider ZD1839 monotherapy experience (Table 63).

Table 63: Incidence of Rash and Diarrhea from Phase III placebo-controlled combination therapy trials

Event	<u>INTACT 1 and INTACT 2 Trials (0014 and 0017)</u>		
	Number (%) of patients		
	ZD 1839 500 mg (n=700)	ZD 1839 250 mg (n=704)	Placebo (n=696)
Rash	463(66.1)	374(53.1)	241 (34.6)
Diarrhea	499(71.3)	401 (57.0)	246(35.3)

In an updated Drug Safety database search, cut-off date 11 December 2002, a total of 428 serious adverse events in 408 patients were identified. A summary of the events by MedDRA-preferred term is presented in Table 64. These data represent a total ZD1839 exposure of 50,005 patients globally, including patients from ongoing and completed monotherapy and combination therapy trials in NSCLC and other tumor types, as well as 18,960 patients from marketed use in Japan.

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Table 64: Summary of ILD-type events from sponsor's global Drug Safety database

MedDRA-preferred term	Investigator's assessment of causality			Total number of events
	No	Yes	Missing	
Acute respiratory distress syndrome	8	5	0	13
Alveolitis allergic	0	1	0	1
Alveolitis NOS	0	1	0	1
Cryptogenic organizing pneumonia	1	1	0	2
Interstitial lung disease	2	4	0	6
Interstitial pneumonia	10	288	10	308
Lung disorder NOS	2	14	0	16
Lung infiltration NOS	6	15	1	22
Pneumonitis NOS	10	15	1	26
Radiation pneumonitis	13	7	1	21
Pulmonary fibrosis	1	8	0	9
Pulmonary toxicity NOS	0	1	0	1
X-Ray NOS chest abnormal	0	2	0	2
Total	53	362	13	428¹

¹ 13 patients from Japan, 2 from Named Patient use, and 5 from the US had 2 events; therefore, the total number of patients is 408. NOS = Non-specific.

Of the 408 patients with ILD-type events, 396 were receiving ZD1839 as monotherapy. Eighty-four patients from the EAP and clinical trial program experienced a total of 91 ILD events. The remaining 324 patients were identified via spontaneous reports from marketed use in Japan. Table 65 presents the age distribution and sex, and time to onset of ILD-type events for these 408 patients. The gender and age distribution appear to be consistent with the general population of lung cancer patients.

Table 65: Age, sex, and time to onset of ILD reports

Characteristic	Japan (N=324)	US/Rest of World (N=84)
Age (years)		
Mean	67	63
Median	68	63
Range	38 to 88	38 to 80
Sex [number (%) of patients]		
Male	257(79.3)	47(56.0)
Female	55(17.0)	37(44.0)
Not known	12(3.7)	0
Time to onset (days)		
Mean	26	58
Median	24	42
Range	1 to 90	4 to 420

The 408 patients identified in this review include some who had radiation pneumonitis (5%) or other confounding factors e.g., previous chemotherapy (57%), and/or previous radiotherapy (31%) that may have been responsible for increasing the risk of developing these pulmonary events.

The incidence of ILD-type events, by country of origin, are summarized in Table 66.

Table 66: Incidence of ILD-type events by country of origin

MedDRA- preferred term	Japan	US	Rest of World	Total
Acute respiratory distress syndrome	2	10	1	13
Alveolitis allergic	0	1	0	1
Alveolitis NOS	0	0	1	1
Cryptogenic organizing pneumonia	1	0	1	2
Interstitial lung disease	1	3	2	6
Interstitial pneumonia	301	2	5	308
Lung disorder NOS	14	0	2	16
Lung infiltration NOS	5	15	2	22
Pneumonitis NOS	3	18	5	20
Radiation pneumonitis	9	11	1	21
Pulmonary fibrosis	7	1	1	9
Pulmonary toxicity NOS	1	0	0	1
X-Ray NOS chest abnormal	2	0	0	2
Total	346	61	21	428

A review of the serious adverse event narratives for the 408 patients reveals that although the diagnosis or classification of the event experienced is not consistent, the descriptions of the events themselves are. The emerging picture is one of patients with a fairly acute onset of dyspnea, sometimes associated with cough or low-grade fever. This becomes quite severe within a short time and results in hospitalization. Radiological investigations frequently show pulmonary infiltrates or interstitial shadowing with a ground glass appearance. There is often respiratory distress with arterial oxygen desaturation. Cultures are frequently negative for bacterial growth. In a number of cases the event has responded to steroid therapy but this is not always so.

Of the 408 patients with an ILD-type event, 119 (28%) had an outcome of death possibly as a result of the ILD. The overall frequency for ILD-type events with a fatal outcome is 0.24% (0.48% Japanese and 0.09% Rest of World patients). From the review of narratives where outcome of death was noted, in most cases death was within 1 or 2 weeks of the event. It is difficult to evaluate the cause of death with any certainty (rapidly changing disease status, possible infection, concomitant medications, etc.).

Expanded Access Program

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The FDA questioned whether ILD-like events were being rigorously captured from the EAP. In reply, the sponsor noted that investigators were given the following instructions to regarding follow-up for patients withdrawing because of an adverse event:

When the decision is taken to permanently stop administering the trial drug, a full assessment should be carried out where possible. All trial treatment-related toxicities and SAEs must be followed until resolution, unless, in the investigator's opinion, the condition is unlikely to resolve due to the patient's underlying disease. After withdrawal from treatment, patients must be followed up for AEs for 30 calendar days after the last dose of trial drug. All SAEs occurring during that period must be reported to the CRO and must be followed up until resolved, unless, in the investigator's opinion, the condition is unlikely to resolve due to the patient's underlying disease."

The CRO monitoring the trial maintains a spreadsheet, which details the site, the number of patients registered, selected, active and withdrawn, as well as the number of reported SAEs. This allows comparison of the number of patients at the site with the amount of SAEs reported thus far. After comparison of these numbers, if there is suspicion of under-reporting of SAEs, further investigation with communication to site is done by the CRO. On-site monitoring visits are performed if deemed warranted by the sponsor and

— To date, ten sites have had an on-site monitoring visit followed by written communication to the site about findings and any specific needed actions. Site must report to the CRO that each of specific actions have been completed or are being done. This has occurred at all monitored sites.

Reporting rates for SAEs from the EAP are substantially larger than the rate in Japan (11% versus 3%). This is surprising since there is more intensive monitoring in Japan. Nearly 50% of all SAEs in Japan are ILD-type events. ILD-type events are reported in a higher proportion to overall SAEs from the EAP compared with reports from Clinical Trials (1.7% versus 0.7%). This indirectly provides support that ILD-type events are being captured from the EAP.

Overall incidence of ILD-type events associated with ZD1839

The frequency of ILD-type events in the entire sponsor Drug Safety database is approximately 0.94%. This frequency is lower than that reported for other cancer treatments (Hernberg et al 2002, Lind et al 2002, Nelson et al 1995, Shepherd et al 1997, Todd et al 1993 and Table 67). The cases all have significant confounding factors that make any causal assessment difficult. Absence of a uniform classification of ILD disorders adds additional difficulty to data analysis.

Comparison With Other Therapies For The Management Of Lung Cancer

The frequency of ILD-type events with other cytotoxic chemotherapy agents is shown in Table 67. This table suggests that frequency of ILD associated with ZD1939 treatment is similar to that associated with mono- or combination chemotherapy regimens.

Table 67: Incidence of ILD associated with therapies for lung cancer - sponsor

Agent	Rate of Onset	Response to Steroids	Deaths	Frequency of reports	References
Docetaxel	Rapid	No response	50%	6%	Chen et al 2002 Etienne et al 1998 Read et al 2002 Wang et al 2001
Paclitaxel	Rapid	Common response	Occasional	3%	Fujimori et al 1998 Furuse et al 1997 Khan et al 1997 Schweitzer 1995 Wong et al 2001
CPT-11	Rapid	Unknown	50%	3%	Fukuoka et al 1992 Mori et al 1997
Gemcitabine	Rapid	Unknown	50%	5%	Fukuoka et al 1996 Furuse et al 1999 Girard et al 2000 Gupta et al 2002 Hammerer 2002 Yokoyama 1996
Etoposide	Rapid	50%	Occasional	5%	Hatakeyama 1997 Uchida et al 1996
Docetaxel/ gemcitabine	Rapid	50%	50%	6%	Chen et al 2002 Rebattu et al 2001 Satouchi et al 2001
Paclitaxel/ gemcitabine	Rapid	Common Response	Occasional	30%	Kudrik et al 2002 Thomas et al 2002

Comment: While the above table was generated by the sponsor, and may consist of selected reports, it is known that many chemotherapy drugs, including those listed in the table, produce pulmonary (ILD) toxicity. Supporting this is the 1% incidence of ILD noted in the placebo arm of the INTACT 1 and 2 trials.

Summary

- ILD, which may be fatal, has been observed in patients receiving ZD1839. The incidence of ILD-type events is approximately 1%. ILD is fatal in about 30% of affected patients.
- Frequency of ILD reporting appears to be significantly higher in Japan compared with the Rest of World. The reason for this is unknown.
- The incidence of ILD with Iressa treatment may be similar to ILD associated with other chemotherapy drugs. The percentage of ILD reports with a fatal outcome is similar to that with other therapies.

Activities Undertaken By Sponsor In Response To ILD

The emerging safety and patient management data relating to ILD have been communicated globally to all investigators, treating physicians and patients in the form of an Investigator Safety Letter, Investigator Brochure, and Patient Consent information, which were issued in October 2002. A warning has been included that treatment should be interrupted and prompt investigations initiated if patients present with worsening of respiratory symptoms such as dyspnea, cough, and fever. If ILD is confirmed, ZD1839 should be discontinued and the patient treated appropriately. Full reference is also made to the potential severity of cases and warnings of a possible fatal outcome. These changes have also been made to the company prescribing information (Core Data Sheet). This information has also been communicated globally to Health Authorities.

The sponsor has undertaken extensive activities with the external medical community to define and understand the ILD issue in Japan. Two clinical expert meetings have been conducted with oncologists, respiratory physicians, radiologists and pathologists review the ILD cases in depth.

Various press meetings have been conducted to communicate this information.

An educational nationwide meeting has been proposed to raise the level of interest and diagnosis among doctors treating with ZD1839 in Japan.

The sponsor is currently considering proposals for specific post-marketing safety surveillance studies to further evaluate this safety issue.

Changes to the Japanese prescribing information for ZD1839 resulted from recommendations made by the MHLW Safety Issues Review Board which met at the end of December 2002 to review data on ILD and make recommendations to further improve the safe use of ZD1839 in the treatment of NSCLC consistent with the standards of medical practice in Japan.

The sponsor has complied with the recent recommendations by the MHLW to revise the Japanese prescribing information that patients should be hospitalized or receive an equivalent level of supervision for the first 4 weeks of ZD 1839 treatment.

The sponsor has revised the current guidance on appropriate use of ZD1839 to include appropriate precautions with respect to ILD, is monitoring the association of ZD1839 with ILD very closely, and is updating Health Authorities, practitioners, and Investigators globally at regular intervals.

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8 Dosing, Regimen and Administration Issues

In the Phase I program, anti-tumor activity with tumor regression occurred in patients at ZD1839 doses from 150 mg/day to 800 mg/day. Pharmacokinetic data in patients showed up to a 8-fold interpatient exposure variability at a given dose level. Since the lowest dose at which responses were first seen was 150 mg, a minimum dose of 250 mg was chosen to minimize the chance that patients would have exposure that was below a theoretical threshold. Since median steady state plasma concentrations of the 225- and 525-mg dose levels did not overlap by more than approximately 30%, there appeared to be the potential for discrimination between doses. Upper dose levels were selected on the basis of dose-limiting toxicity and tolerability. Therefore, the higher dose of 500 mg was chosen as a dose at which ZD1839 can be taken by the patient daily with small likelihood of therapy interruption or dose reduction.

In both the pivotal Trial 39 and supportive Trial 16, there were no significant differences between the 250 mg/day and 500 mg/day dose groups in regards to tumor response rates and disease-related symptom improvement rates. FACT-L and TOI improvement rates were higher in the 250-mg/day group than the 500-mg/day group in both trials. This may in part reflect the lower toxicity seen at the 250-mg dose. Overall, the 250-mg dose is as effective as the 500-mg dose.

9 Use in Special Populations

9.1 Tumor response by subgroups sex, age, and ethnicity

More women experienced tumor responses at either the 250-mg/day and 500-mg/day doses (23.8%; 95% CI: 12.1%, 39.5%] and 15.7%; 95% CI: 7.0%, 28.6%, respectively) than men (3.3%; 95% CI: 0.4%, 11.5% and 3.2%; 95% CI: 0.4%, 11.0%, respectively). No trend was seen for tumor response rates in either dose group between patients 18 to 64 years old and 65 years of age or older. Similar tumor response rates were seen between the 2 dose groups for white patients; however, there were not enough non-white patients to draw any conclusions between patients of different ethnic origins.

9.2 Symptom improvement by the subgroups sex, age, and ethnicity

The symptom improvement rates, as assessed by the sponsor, were higher in female patients in both dose groups: 50.0% (95% CI: 34.2%, 65.8%; 250-mg/day group) and 49.0% (95% CI: 34.8%, 63.4%; 500-mg/day group) than male patients (38.3%, 95% CI: 26.1%, 51.8%; 250-mg/day group and 23.8%, 95% CI: 14.0%, 36.2%, 500-mg/day group). No discernible pattern was observed for the sponsor's analysis of disease-related symptom improvement rates by age or ethnicity in either dose group.

9.3 Adverse Events In Special Populations-Studies - Phase II trials 39 and 16

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9.3.1 Gender

Table 68 shows the incidence of 6 of the most common adverse events in the Phase II trials presented by gender. The incidence of diarrhea was higher in females than males for both doses.

Table 68: Common adverse events by gender (Trials 39 and 16)

Adverse event	Number (%) of patients			
	250 mg dose		500 mg dose	
	Female (n=67)	Male (n=138)	Female (n=87)	Male (n=133)
Diarrhea	41(61.2)	67(48.6)	67(77.0)	89(66.9)
Rash	32(47.8)	66(47.8)	57(65.5)	80(60.2)
Asthenia	18(26.9)	37(26.8)	22(25.3)	42(31.6)
Dyspnea	13(19.4)	32(23.2)	14(16.1)	27(20.3)
Nausea	20(29.9)	32(23.2)	26(29.9)	42(31.6)
Acne	18(26.9)	21 (15.2)	21 (24.1)	34(25.6)

9.3.2 Ethnic origin

Data for patients other than those of White or Asian origin, is insufficient for analysis.

9.3.3 Age

Table 69 shows adverse events by age categories (<45 years; 45 to 64 years; 65 to 74 years; >=75 years. As no trials have been conducted in subjects <1 8 years of age, the safety of ZDI 839 cannot be assessed in pediatric patients. For all age groups there is more toxicity for the 500 mg/day dose than for the 250 mg/day dose. Within each dose, however, there does not seem to be significantly different toxicity by age. The small numbers of patients >75 years of age makes it difficult to draw conclusions on this group.

Table 69: Common adverse events presented by age (pooled data from Trials 39 and 16)

Adverse event	Number (%) of patients							
	250 mg dose				500 mg dose			
	<45 years (n=16)	45 to 64 years (n= 116)	65 to 74 years (n=62)	>=75 years (n= 11)	<45 years (n=21)	45 to 64 years (n=122)	65 to 74 years (n=67)	>=75 years (n= 10)
Diarrhea	8(50.0)	59(50.9)	34(54.8)	7(63.6)	13 (61.9)	88(72.1)	49(73.1)	6(60.0)
Rash	9(56.3)	51 (44.0)	30(48.4)	8(72.7)	13 (61.9)	80(65.6)	38(56.7)	6(60.0)
Asthenia	3 (18.8)	31 (26.7)	18(29.0)	3(27.3)	2(9.5)	38(31.1)	19(28.4)	5(50.0)
Dyspnea	4(25.0)	28(24.1)	11 (17.7)	2(18.2)	2(9.5)	24(19.7)	14(20.9)	1 (10.0)
Nausea	3 (18.8)	26(22.4)	20(32.3)	3 (27.3)	9(42.9)	38(31.1)	17(25.4)	4(40.0)
Acne	5 (31.3)	23 (19.8)	11 (17.7)	0(0.0)	1(4.8)	29(23.8)	22(32.8)	3(30.0)

9.3.4 Effect of baseline renal function

ZD1839 and its metabolites are not significantly excreted via the kidney (<4%).

No clinical trials have been conducted with ZD1839 in patients with severely compromised renal function.

9.3.5 Effect of baseline hepatic function

Only 5 patients in Trials 39 and 16 had hepatic impairment at trial entry (4 patients with moderate impairment, and 1 patient with severe impairment). Adverse events for these 5 patients are similar to those seen in the overall patient population. Because of small numbers no conclusions should be drawn.

9.3.6 Safety of ZD1839 when given in combination with other drugs

ZD1839 showed no enzyme induction effects in animal studies.

ZD 1839 inhibited CYP2D6 by <50% in vitro, and the magnitude of the interaction with metoprolol, a CYP2D6 substrate was tested in Trial 0038. In this trial, there was no evidence of a clinically significant change to metoprolol exposure when co-administered with ZD1839 500 mg/day.

CYP3A4 inhibitors and inducers

ZD1 839 is metabolised by CYP3A4 in vitro and may be affected by co-administration of drugs which are inhibitors or inducers of CYP3A4 in man. The magnitude of such interactions has been assessed clinically using itraconazole, a selective inhibitor of CYP3A4 (Trials 0027 and 0051), and rifampicin, a potent but relatively non-specific inducer of CYP3A4 (Trial 0030). As anticipated, co-administration of itraconazole or rifampicin with ZD1839 increased and decreased exposure to ZD1839, respectively.

A review of adverse events data according to whether patients received concomitant CYP3A4 inhibitors or inducers, respectively, shows:

- The profile of adverse events was generally similar for patients receiving CYP3A4 inhibitors or inducers to those not receiving such drugs.
- The concomitant use of either CYP3A4 inhibitors or inducers appeared to increase the incidence of certain adverse events eg, nausea and vomiting. These effects may have been due to the drugs themselves rather than due to a drug interaction with ZD 183 9.

Drugs which lower gastric acidity

The 250 mg tablet formulation of ZD1839 shows a significant reduction in dissolution between pH 4 and 5. Consequently, it is possible that an increase in gastric pH could reduce the bioavailability of oral Z131839. Trial 0036 was conducted to assess the effect of increased gastric pH on the relative bioavailability of a 250 mg oral dose of ZD1839 in

healthy male volunteers. The increase in gastric pH achieved in these volunteers, and the duration over which elevated gastric pH was maintained, were considered to be higher and for longer than might be achieved with standard antacid treatment. However, systemic elevation of gastric pH resulted in a reduction in exposure to ZD1839, and as such, did not present any concern regarding the safety of ZD1839.

Vitamin K antagonists

A total of 37 bleeding events in 31 patients taking warfarin concomitantly with ZD1839 were identified from across the ZD1839 clinical trial program. Based on these findings it was concluded that patients taking warfarin while on ZD1839 therapy should be monitored regularly for changes in PT (prothrombin time) or INR (International Normalized Ratio).

9.3.7 Safety Of ZD1839 In Pregnancy And Lactating Women

The safety of ZD1839 in pregnant or breast-feeding women has not been established in clinical trials.

It is not known whether ZD1839 is excreted in human milk. Following oral administration of carbon-14 labeled ZD1839 to rats 14 days postpartum, concentrations of radioactivity in milk were higher than in blood. Levels of ZD1839 and its metabolites were 11 to 19-fold higher in milk than in blood, after oral exposure of lactating rats to a dose of 5 mg/kg.

10 Conclusions and Recommendations

10.1 Efficacy

See pages 67-69.

10.2 Safety

See pages 103-108

10.3 Recommendation

The Medical Officer initially deferred making a recommendation on approval until after the ODAC discussion and recommendation. Factors that were considered by ODAC include 1) the 11 percent response rate observed in Trial 39 patients and in Caucasian patients in Trial 16; 2) the difficulty in interpreting quality of life/symptom relief data in phase II trials; 3) the uncertain effect of concomitant medication on symptom and quality of life improvement; 4) the characteristics of the responding patient population, (largely comprised of individuals with slow growing, less biologically aggressive tumors) and 5) the results of the two recently completed phase III first-line NSCLC ZD1839 trials that unequivocally failed to demonstrate clinical benefit.

After hearing the evidence presented by the sponsor and by FDA there were 11 yes votes and 3 no votes to the question;

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"Given the lack of clinical benefit in two large studies of ZD1839 in combination with standard first-line NSCLC chemotherapy, is the Study 0039 response rate of 10% in 139 patients with resistant or refractory NSCLC reasonably likely to predict ZD1839 clinical benefit in NSCLC?"

By the above vote the Committee indicated that, for NSCLC in the third line setting where there are no viable treatment options, a 10% response rate is meaningful, and shows evidence of biologic activity of the drug. The reason for failure of the first line trials remains unexplained, and requires further study.

The ODAC was also asked to evaluate whether ZD1839 treatment was associated with symptom benefit? As indicated earlier the FDA believes the relevance of the symptom improvement data cannot be adequately evaluated without a randomized, blinded study with an adequate control arm (the two doses of ZD1839 show no difference in efficacy and are thus not adequate). Do you agree?

The Committee, by a vote of 9-Yes and 5-No felt that the symptom data supported only a soft claim of symptom management, and that a randomized, controlled trial with a "no drug" arm (either placebo or best supportive care) would be required for substantial evidence.

The Medical Officer concurs with the ODAC decision and recommends accelerated approval of ZD1839 for the treatment of patients with locally advanced or metastatic NSCLC in whom platinum-based and docetaxel chemotherapies have failed. ZD1839 should not be used in combination with doublet, platinum based chemotherapy in the first-line treatment of NSCLC.

10.4 Proposed Phase IV Studies

The major phase IV studies proposed by the sponsor are summarized in **Table 70**.

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Table 70: Proposed phase IV trials

Trial Number Title	Trial Design Chemotherapy Regimen	Key Eligibility Criteria	Number of Patients	Endpoints Primary Secondary	Statistical considerations	Current status	Duration
A randomized phase III trial Comparing ZD1839 plus best Supportive care versus placebo plus best supportive care in subjects with advanced NSCLC who are refractory to one or two prior regimens	phase III trial ZD1839 plus best supportive care versus placebo regimens plus best supportive care	advanced NSCLC who are refractory to one or two prior chemotherapy regimens PS 0-2	~1230 2:1 ZD 1839vs. placebo	OS Secondary TFF, RR, AE's, Q of L	Standard	SPA to be submitted	1 year accrual 1 year F/U

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Trial Number Title	Trial Design Chemotherapy regimen	Key Eligibility Criteria	Number of Patients	Endpoints Primary Secondary	Statistical considerations	Current status	Duration	
SWOG 0023 (CTEP, CEP approved) A Phase III trial of cisplatin/etoposide/radiotherapy with consolidation docetaxel followed by maintenance therapy with ZD 1839 or placebo in patients with inoperable advanced Stage III non-small cell lung	Randomized, double-blind placebo-controlled parallel group, multi-center study Current dose is 500 mg Principal Investigator is willing to change to 250 mg.	Inoperable (unresectable), histologic or cytologically-proven, newly diagnosed Stage III NSCLC No: Prior CT or RT Distant metastases, Iressa or pleural/pericardial effusions, positive cervical nodes ≥ 2 cm parenchymal lesions on same or opposite sides of lung -	840 enrolled; 672 non-progressive disease patients after concurrent CURT and consolidation randomized to placebo	Primary: OS; PFS Secondary: Safety profile	Sized to have ~90% power to detect a 33% increase in median survival for ZD1839 compared to placebo Interim analysis will be performed after 400 patients have entered; Early termination of study if null hypothesis of no difference, or the alternative of 33% improvement for ZD1839, is rejected at onesided 0.0025 level	Ongoing (x 1 year)	3.5 year accrual Minimum \geq 30 months	bli ca

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Trial Number Title	Trial Design Chemotherapy Regimen	Key Eligibility Criteria	Number of Patients	Endpoints Primary Secondary	Statistical considerations	Current status	Duration
BR19 (NCIC, EORTC, CTEP, CEF approved) A Phase III prospective randomized, double-blind, placebo-controlled trial of the epidermal growth factor receptor antagonist, ZD 1839 in completely resected primary following surgery and/or Stage I, II and IIIA non-small cell lung cancer	Randomized, double-blind, placebo-controlled study Patients will receive 250 mg daily Iressa or adjuvant therapy radiotherapy	Completely resected primary Stage I, II, and IIIA NSCLC <16 weeks from placebo for 2 years as randomization ≥3 weeks from completion of radiotherapy to randomization and fully recovered	1160	Primary: OS Secondary DFS Safety profile Correlation of EGFR expression phosphorylation and mutations on survival and Iressa therapy	Sized to have 90% power to detect a 33% increase in median survival for ZD1839 compared to surgery and placebo	To open: Oct 02	Accrual rate at - 390 patients per year for 3 years; 2-year follow-up

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Martin Cohen
4/1/03 11:25:02 AM
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Grant Williams
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MEMORANDUM:

MEDICAL OFFICER CONSULTATION

Date: January 30, 2003

To: Amy Baird
Project Manager, DODP (HFD-150)

From: Eugene J. Sullivan, MD, FCCP
Acting Medical Team Leader
Division of Pulmonary and Allergy Drug Products (HFD-570)

Through: Marianne Mann
Deputy Division Director, DPADP

Subject: Pulmonary toxicity associated with gefitinib (Iressa)

General Information

NDA#: 21-399
Sponsor: AstraZeneca
Protocol: n/a
Drug Product: Gefitinib (Iressa)
Request From: DODP
Materials: Submission dated 10/17/02
Submission dated 1/17/03 (7 volumes)

Background

Gefitinib (Iressa, AstraZeneca) is an oral inhibitor of epidermal growth factor receptor tyrosine kinase. It is currently under review in DODP for use in the treatment of non-small cell lung cancer (NDA 21-399). During the course of the NDA review, DODP became aware of reports of lung toxicity (interstitial lung disease, ILD) SAEs associated with Iressa, particularly in the Japanese post-marketing experience. DODP has asked AstraZeneca to provide further information to help clarify this possible safety signal.

AstraZeneca (AZ) has investigated the reported cases and has concluded that the syndrome is one of acute onset, rapidly progressing dyspnea that is associated with diffuse interstitial/ground glass opacities on high resolution CT (HRCT), negative bacterial cultures, and a histologic pattern termed Diffuse Alveolar Damage (also termed Acute Interstitial Pneumonia). This is the histologic pattern associated with a clinical entity termed Acute Respiratory Distress Syndrome (ARDS). Up to 40% of these SAEs have been fatal. AZ states that the incidence of this entity is low, but acknowledges that the frequency of reports has increased following increased awareness of the issue among investigators. In the 10/17/02 submission, AZ estimated the incidence to be approximately 0.27%. In the 1/17/03 submission, the estimate rose to 0.82% as of a cut-

off date of 12/11/02 [408 cases out of 50,005 patients exposed]). Reviewer's Comment: AZ's most recent estimate of the incidence of ILD events is based on a cut-off date of 12/11/02, at which time there were 408 cases. Apparently, as of 1/8/03, there are now 533 cases [Vol. 1, Attachment 1, p. 1]. AZ does not provide an updated figure for patient exposure. Using the 50,005 estimate, the frequency of ILD events would be 1.1% (533/50,005).

AZ points out that much of the reported experience has been open-label or non-placebo controlled. They state that recently unblinded data from two Phase 3 placebo-controlled combination chemotherapy trials (Studies 0014 and 0017, N= approximately 700 in each of two active treatment groups, and approximately 700 in the placebo group) suggest that the incidence of ILD events was not different in active and placebo groups (1.1% in active treatment groups and 0.9% in the placebo group).

Attachment #4 contains 337 narrative descriptions of all serious pulmonary adverse events from the placebo controlled trials (#0014 and 0017). These narratives were scanned, but not reviewed in depth.

Attachment #5 contains the 533 narratives of all ILD cases as of 1/8/03. These narratives were scanned, but not reviewed in depth. Most contain limited information. In general, the onset of the ILD occurred weeks after beginning Iressa, and in most cases the reporter considered the event to be related to the drug. Many patients had previously received chemotherapy or radiation therapy, although in many cases it seems there was no evidence of ILD at the time of initiation of Iressa. In most cases a histologic diagnosis of the ILD was not obtained. In some cases the ILD was felt to improve following treatment with corticosteroids and discontinuation of Iressa.

Attachment #6 contains 1072 narratives of "other" (non-ILD) pulmonary events from AZ's Global Drug Safety Serious Adverse Event database (as of 1/15/03). These narratives were scanned, but not reviewed in-depth. In many cases, the specific adverse event was established or was not suggestive of ILD (e.g. pulmonary embolism). However, in some cases the narratives don't provide enough information to rule out an ILD event. For example, in many cases Investigator termed the SAE "pneumonia" or "heart failure" and did not provide sufficient information to confirm these diagnoses. It is possible that some of these events were in fact ILD.

Attachment #7 is a "Preliminary Report" of a "Clinical Pathology Review Meeting of Acute Pulmonary Disorder/ Interstitial Pneumonia with Iressa (gefitinib)." This meeting was held on December 28, 2002, at the Nippon Medical School. Approximately 50-60 clinicians, radiologists, and pathologists were in attendance. The attachment contains brief summaries of 8 patients who developed an acute illness characterized by pulmonary infiltrates on HRCT and Diffuse Alveolar Damage on lung biopsy. All patients had previously received radiation and/or chemotherapy, and some had additional histopathologic findings. No conclusions can be drawn from the information in this attachment.

Attachment #8 is a "Summary of Discussion of 28 Dec Expert Committee 2nd." This attachment primarily addresses future plans of the Expert Committee, and offers little relevant information.

Attachment #9 contains details of the SAE data collection procedures that are followed in the Expanded Access Program (EAP). Investigators are provided instruction regarding SAE reporting prior to enrollment, and are reminded of their reporting requirements by monthly telephone calls. The Contract Research Organization monitors for sites that report few SAEs. Three-month drug refills are only provided if all CRFs are complete, including submission of any SAE reports. Upon withdrawal, Investigators must provide a reason for withdrawal on the CRF. AEs and death occurring within 30 days after withdrawal must be reported.

Attachment #10 provides data on the safety reporting rates from the EAP, marketed use in Japan, and clinical trials (globally) (as of 1/13/03). The number of patients in these groups are 19,612, 21,567, and 4,276, respectively. Although the Sponsor has emphasized that the post-marketing surveillance in Japan does not rely on spontaneous reports alone, the percentage of patients reporting SAEs was lowest in the Japanese cohort (3.0%, compared with 11% in the EAP, and 28.6% in the global clinical trials. However, a much greater percentage of the SAEs reported in the Japanese cohort represented "ILD-type" cases (48.9%, compared with 1.7% in the EAP, and 0.7% in the global clinical trials cohort) [V.7, p366] (Note: ILD-type cases may be categorized as "Respiratory, thoracic, and mediastinal disorders," or "Infections and Infestations" [the System Organ Class containing the MedRA term "interstitial pneumonia"]).

Attachment 10 also contains an update of a table that was initially presented in the 10/17/02 submission. The current table has a cut-off date of 1/13/03, whereas the prior version had a cut-off date of 10/11/02. Interestingly, as illustrated in the table below, the frequency of ILD reports seems to have increased in the EAP, in the compassionate use program, and in the Japanese post-marketing experience. This suggests that recent attention to this possible drug toxicity has increased the detection of events.

	ILD events/ Patient Exposure (N) As of 10/11/02 [Source: 10/17/02 submission]	ILD events/ Patient Exposure (N) As of 1/13/03 [Source: Vol. 7, p367]
EAP	28/16,000	63/19,760
Compassionate Use	14/6,000	24/8,164
Japanese Post-marketing	41/10,000	446/21,990

The frequency of ILD events seems to be highest in the Japanese post-marketing experience (1.97%). The frequency of ILD events in the EAP group (0.29%) may be falsely low, despite the measures taken by AZ to ensure SAE reporting. The evidence for this is the fact that higher frequencies have been seen in smaller clinical studies, where presumably SAE reporting is more complete.

Specific Comments

1. The data provided in these two submissions suggest that Iressa is possibly associated with a risk of serious pulmonary toxicity characterized by diffuse pulmonary infiltrates and, where determined, a histopathologic pattern of diffuse alveolar damage. This SAE is fatal in up to 40% of cases. The case reports are suggestive of a drug-induced phenomenon. However, the placebo-controlled trials (chemotherapy plus Iressa versus chemotherapy plus placebo) did not detect this potential safety signal.
2. The incidence of this SAE is difficult to determine with confidence. Early estimates may have been falsely low, as evidenced by an increased reporting rate following growing awareness of the issue among investigators.
3. The frequency of these events appears to be highest in the Japanese post-marketing experience (1.97%). Although this may possibly be due to aggressive attempts to ensure SAE reporting, the percentage of patients reporting any SAE was lowest in the Japanese post-marketing experience. Thus, the increased frequency of ILD events is not well explained, and may represent an increased awareness of this particular SAE in Japan, or a genetically-based predisposition to this toxicity in Japanese patients.
4. The frequency of these events reported out of the EAP experience may be falsely low.
5. According to the most recent data, the incidence may be approximately 1%, but may be as high as 1.97%.

cc: HFD-570/Sullivan/Medical Reviewer
HFD-570/Mann/Deputy Division Director
HFD-570/Barnes/Chief Project Management Staff

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/s/

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