Drug product	IRESSA™	**SYNOPSIS**	
Drug substance(s)	Gefitinib (ZD1839)		
Study code	1839IL/0063		

AN OPEN RANDOMISED PHASE II STUDY OF GEMCITABINE PLUS CISPLATIN +/- CONCOMITANT OR SEQUENTIAL ZD1839 IN PATIENTS WITH ADVANCED OR METASTATIC TRANSITIONAL CELL CARCINOMA OF THE UROTHELIUM

Study centre(s)

Patients were screened and enrolled in this study at 19 oncology research sites at hospitals in Germany and Switzerland.

Publications

There were no publications at the time of this report.

Study dates		**Phase of development**
First subject enrolled	December 2003	Therapeutic exploratory (II)
Last subject completed	October 2008	

Objectives

Primary

The primary objective of the study was to assess the activity of ZD1839 250 mg once daily administered continuously in addition to the standard chemotherapy gemcitabine and cisplatin or sequentially after completion of standard chemotherapy in patients with advanced or metastatic transitional cell carcinoma of the urothelium by estimating the time to progression (TTP).

Secondary

The secondary efficacy objectives of the study were:

1. To estimate the response rate for each treatment arm
2. To estimate the overall survival time for each treatment arm
3. To estimate the time to treatment failure for each treatment arm
4. To estimate the disease control rate for each treatment arm
5. To estimate the duration of response for each treatment arm

The safety objective of the study was:

To investigate the safety and tolerability for each treatment arm

Exploratory

The exploratory endpoint of the study was to estimate the efficacy and safety profile of patients in the extension arm.

Study design

This was a multicentre, multinational, randomised phase II study of gemcitabine and cisplatin +/- ZD1839 given concomitantly or sequentially.
Patients were randomised (1:1:1) into one of 3 arms:

Arm A: 6 cycles of gemcitabine and cisplatin in combination with ZD1839 250 mg daily followed by ZD1839 250 mg daily as maintenance therapy until objective disease progression

Arm B: 6 cycles of gemcitabine and cisplatin followed by ZD1839 250 mg once daily until objective disease progression

Arm C: 6 cycles of gemcitabine and cisplatin followed by observation until objective disease progression

Extension: Patients in Arm B and Arm C who could not complete 6 cycles of chemotherapy either due to toxicity or objective disease progression, were treated with ZD1839 250 mg once daily until further objective disease progression

Target subject population and sample size

Chemotherapy-naïve male and female patients aged 18 years or older with histologically- or cytologically-confirmed, measurable, advanced or metastatic transitional cell carcinoma of the urothelium.

Investigational product, dosage and mode of administration

ZD1839 250 mg (one tablet) orally once daily, administered continuously.

Standard therapy, dosage and mode of administration:

All patients:

Gemcitabine 1250 mg/m^2 as a 30 minute intravenous (iv) infusion on day 1 and day 8 of every 21-day cycle.

Cisplatin 70 mg/m^2 as an iv infusion on day 1 of every 21-day cycle. The infusion rate was 1 mg/min.

Duration of treatment

All patients received standard therapy with gemcitabine and cisplatin for 6 cycles. ZD1839 (250 mg) was administered in parallel (Arm A) or sequentially (Arm B). Patients in Arm B and C who could not complete 6 cycles of chemotherapy either due to toxicity or objective disease progression were treated with ZD1839 250 mg daily monotherapy until further disease progression.

Treatment was discontinued at any time if disease progression, unacceptable toxicity or withdrawal of consent occured. Patients who experienced progression or toxicity were followed-up for survival until withdrawal of study medication of the last patient (study closure).

Criteria for evaluation (main variables)

Efficacy

- Primary variable: Time to progression based on the Response Evaluation Criteria in Solid Tumours (RECIST)
- Secondary variables:
    - Objective tumour response (complete response [CR] and partial response [PR]) after cycle 3 (visit 7) and cycle 6 (visit 13), 6 months after the start of treatment (visit 14) and every 12 weeks thereafter based on the RECIST criteria
    - Time to treatment failure
    - Overall survival time
    - Incidence of controlled disease (CR, PR and stable disease [SD]) after cycle 3 (visit 7) and cycle 6 (visit 13), 6 months after the start of treatment (visit 14) and every 12 weeks thereafter
    - Duration of response

Safety

- Secondary variables:
    - Nature, incidence and severity of adverse events (AEs) and serious adverse events (SAEs)
    - Incidence of and reasons for dose interruptions, reductions (chemotherapy only) and withdrawals due to AEs
    - Laboratory assessments, physical examinations

The exploratory endpoint of the study was to estimate the efficacy and safety profile of patients in the extension arm.

Statistical methods

All patients that were enrolled and received at least one dose of study drug were considered the all-subjects-treated population (AST). All patients that were enrolled and received at least one dose of study drug and had at least one tumour assessment or died before the first tumour assessment took place were considered the ITT population. For efficacy endpoints the ITT population was used and for safety endpoints the analysis population was the AST population.

The standard summary statistics for continuous variables were: mean, standard deviation, median, quartiles, minimum and maximum. The standard summary statistics for discrete variables were: count and proportion. Response rates and controlled disease rates were summarised by proportions together with exact two-sided 95% confidence intervals. Durations (time to progression, overall survival time, and duration of response) were summarised by Kaplan-Meier methods.

Because of the use of a selection design the trial was non-comparative in the statistical sense. The goal of the study was to select the most efficient of the three treatment arms, which would be used in a following study.

Subject population

One hundred eleven patients from 19 research sites in Germany and Switzerland were screened and 105 patients were enrolled into the study. All 105 patients received study treatment. Eighty seven from them were included in the ITT analysis.
Forty-three treated patients discontinued the chemotherapy during the study. The main reason for discontinuation among the patients in arm A and B was other than AE or progression of the disease (group A – 7 (53.85%) patients, group B – 6 (40.00%) patients). The patients in the arm C discontinued the chemotherapy mostly due to progression of disease (5 (33.33%) patients) and AE (5 (33.33%) patients).
The patient demographic and baseline characteristics are shown in Table S1.
The patients in the Arm A were elderly with a mean age of 62 years (range 41 to 84 years) and were of Caucasian origin (100%). Most patients had metastatic disease (90%) with G3 (70%). Most patients had normal or restricted physical activity (WHO performance status 0 and 1), only one patient stayed in bed >50% of the time (WHO performance status 2).

The patients in the Arm B were elderly with a mean age of 65 years (range 45 to 80 years) and were of Caucasian origin (100%). Most patients had metastatic disease (81%) with G3 (54%). Most patients had normal or restricted activity, except for one patient, who stayed in bed >50% of the time.
The patients in the Arm C were elderly with a mean age of 61 years (range 42 to 78 years) and were of Caucasian origin (100%). Most patients had metastatic disease (83%) with G3 (71%). Most patients were of WHO performance status 0 of 1.
Patients included in this study were representative of a population with histologically- or cytologically-confirmed, measurable, advanced or metastatic transitional cell carcinoma of the urothelium.

Table S1 **Patient population, demographic and baseline characteristics**

	Number (%) of patients		
	Arm A	**Arm B**	**Arm C**
Population			
All patients screened	36 (100)	38 (100)	37 (100)
All patients treated	35 (97.2)	37 (97.4)	33 (89.2)
Intention-to-treat	29 (80.6)	30 (78.9)	28 (75.7)
Demographic characteristic			
Sex (n and %)			
Female	12 (34.3)	12 (32.4)	7 (21.2)
Male	23 (65.7)	24 (64.9)	26 (78.8)
Age (years)			
Mean (SD)	61.8 (11.3)	64.7 (9.5)	61.4 (9.7)
Median	66	66	63
Range	41 to 84	45 to 80	42 to 78
Race (n and %)			
Caucasian	35 (100)	37 (100)	33 (100)
WHO performance status			
Normal activity	20 (58.8)	17 (45.9)	19 (59.4)
Restricted activity	13 (38.2)	19 (51.4)	13 (40.6)
In bed >50% oft he time	1 (2.9)	1 (2.7)	0 (0.0)
Histology (n and %)			
Transitional cell	28 (80.0)	31 (83.8)	28 (84.9)
Squamous cell	0 (0.0)	1 (2.7)	1 (3.0)
Adenoid	2 (5.7)	0 (0.0)	0 (0.0)
Unknown	4 (11.4)	4 (10.8)	2 (6.1)
Missing	1 (2.9)	1 (2.7)	2 (6.1)
Any tumour related surgery			

Yes	35 (100)	34 (91.9)	31(93.4)
No	0 (0.0)	3 (8.1)	1 (3.0)
Missing	0 (0.0)	0 (0.0)	1 (3.0)
Any tumour related radiotherapy			
Yes	0 (0.0)	3 (8.1)	1 (3.0)
No	35 (100.0)	33 (89.2)	29 (87.9)
Missing	0 (0.0)	1 (2.7)	3 (9.1)

The extension arm included only two patients (1.9%), who were treated with ZD1839.

Efficacy results

Primary variable: Time to progression

Time to progression analysis using the Kaplan-Meier method was based on the ITT population. The log-rank test was used to point out differences between the groups.

The median TTP for the patients in the arm A was 6.1 months (95% CI 4.39-9.40), in the arm B – 6.3 months (95% CI 5.24-7.80) and in the arm C – 7.8 months (95% CI 6.19-9.63). According to log-rank test there was not statistically significant difference of TTP between the groups.

Table S2: **Time to progression by therapy arm. Population: ITT**

	Number (%) of patients		
	Arm A	**Arm B**	**Arm C**
Time to progression (months)	6.1	6.3	7.8
95% confidence interval	(4.39-9.40)	(5.24-7.80)	(6.19-9.63)

Secondary variables

- Objective tumour response

Forty-five of the 87 patients treated with ZD1839 in this study were objective tumour responders using the RECIST criteria (Table S2). There were 40 partial responders and 5 complete responders.
Seventeen (58.6%) of the 29 patients in arm A were objective tumour responders. There were 15 partial responders and 2 complete responder. Four (13.7%) patients met the RECIST criteria for stable disease.
Objective tumour response was observed in 16 (53.3%) of 30 patients in arm B. Fifteen patients had a partial response and 1 patient a complete response. Four (13.3%) patients had a stable disease.

Twelve (42.8%) of 28 patients in the arm C were objective tumour responders. There were 10 partial responders and 2 complete responder. Eight (28.5%) patients met the RECIST criteria for stable disease.

- Time to treatment failure

Time to treatment failure analysis using the Kaplan-Meier method was based on the ITT population. The median TTF for the patients in the arm A was 5.9 months (95% CI 4.36-9.37), in the arm B also 5.9 months (95% CI 3.44-7.11) and in the arm C – 5.6 months (95% CI 3.54-8.59).

According to log-rank test there was no statistically significant difference of TTF between the groups.

- Overall survival time

The median OS for the patients in the arm A was 13.3 months (95% CI 10.49-19.24), in the arm B 8.5 months (95% CI 6.95-14.49) and in the arm C – 15.9 months (95% CI 10.88-31.27).
According to log-rank test there was no statistically significant difference of OS between the groups.

-Incidence of controlled disease (CR, PR and stable disease [SD]) after cycle 3 (visit 7) and cycle 6 (visit 13), 6 months after the start of treatment (visit 14) and every 12 weeks thereafter

Not done

Duration of response

Not done

The investigators assessment of the response was not recorded in the CRF, only best response was given. Therefore, the incidence of controlled disease and duration of response were not assessed.

Safety results

Secondary variables

- Nature, incidence and severity of adverse events (AEs) and serious adverse events (SAEs)

All treated patient in the study experienced at least one AE. A summary of AEs in each category is given in Table S3.

One hundred and nine AEs probably related to ZD1839 treatment were observed in arm A. Rash was the most common AE in arm A (>40% patients), but was CTC grade 1 or 2.

Twenty-three AEs probably related to ZD1839 treatment were detected in arm B. Arm B patients had the diarrhea as the most common AE (>10% patients. It was CTC grade 1 or 2 except for 1 patient.

Twenty patients (57.1%) had at least one SAE in arm A. Thirty-one SAEs were of CTC grade 3/4. Thirteen SAEs were probably caused by ZD1839. There were 6cases of death due to SAE in arm A.
Twenty-five (67.5%) patients in Arm B had at least one SAE. Twenty-seven SAEs were assessed as CTC grade 3/4. Six SAEs leaded to death. Only 2 SAEs were probably caused by ZD1839.
In arm C there were 15 (45.5%) patients with at least one SAE. Twelve SAEs were of CTC grade 3/4. There were no deaths caused by SAE in the arm C.

Table S3: Number and % of patients who had an AE in any category. Population: AST.

	Number (%) of patients		
	Arm A	**Arm B**	**Arm C**
Any adverse events	35 (100.0)	37 (100.0)	33 (100.0)
Serious adverse events	20 (57.1)	25 (67.5)	15 (45.5)
Serious adverse events leading to death	6 (17.1)	6 (16.2)	0 (0.0)
Discontinuations of chemotherapy due to adverse events	3 (8.5)	3 (8.1)	5 (15.2)

- Incidence of and reasons for dose interruptions, reductions (chemotherapy only) and withdrawals due to AEs

Twelve (34.3%) patients had ZD1839 dose interruptions in arm A. The most common reason was toxicity.

In arm B ZD1839 dose was interrupted in 5 (13.5%) patients. The most common reason was also toxicity.

The most common reason for study discontinuation in arm A was death – 10 (28.5%) patients. One (serious) AE lead to study discontinuation.

In arm B the study was discontinued also mostly due to death – 21 (56.8%) patients. Three (serious) AEs caused study discontinuation.

The most common reason for study discontinuation in arm C was death – 16 (48.5%) patients. No (serious) AEs caused study discontinuation.

There were 46 cases of therapy delay or dose reduction due to AEs in arm A. Seventeen of them were due to AEs related to the study medication.

Fifty-four cases of therapy delay or dose reduction due to AE were observed in arm B. Twenty-three of them were due to AEs related to the study medication.

There were 52 cases of therapy delay or dose reduction due to AEs in arm C. In 14 cases the AEs were assessed as therapy related.

- Laboratory assessments, physical examinations

Arm A
One patient had a CTC grade 3 AE of increased blood creatinine, one patient had a CTC grade 3 of decreased blood magnesium, one patient had a CTC grade 3 of hypocalcaemia, 14 patients had a CTC grade 3 of leukopenia, 2 patients had a CTC grade 3 of decreased haemoglobin. Neutropenia of CTC grade 3/4 was observed in 10 patients, thrombocytopenia of CTC grade 3/4 in 3 patients and pancytopenia of CTC grade 3/4 in 6 patients. One patient had clinically important increase in blood glucose and one patient in uric acid after entry into the study. Clinically important decrease in kalium was observed in one patient, in natrium in one patient and in magnesium in one patient. One patient had clinical important thrombocytopenia. Five AEs of decrease in hemoglobin, 4 AEs of leukopenia, 2 AEs of pancytopenia, 1 AE of thrombocythemia, 2 AEs of thrombocytopenia were assessed to be probably related to ZD1839 treatment.

Arm B
One patient had a CTC grade 3 AE of increased blood bilirubin, one patient of increased creatinin, one patient – of decreased blood albumin. CTC grade 3 AE of granulocytopenia was observed in 1 patient. Hypercalcaemia in 1 patient, hyperglycaemia in 2 patients, hypokaliemia in 1 patient, hypocalcaemia in 1 patient, pancytopenia in 7 patients, thrombocytopenia in 3 patients and neutropenia in 5 patients were assessed as AEs of CTC grade 3/4. Fifteen patients had a CTC grade 3 AE of decreased white blood cell count. One patient had a clinically important increase in uric acid, and two patients had a decrease in hemoglobin after entry to the study. One AE of granulocytopenia, 1 AE of leukopenia were assessed to be probably related to ZD1839 treatment.

Arm C
Two patients had a CTC grade 3 AE of decrease in hemoglobin, one patient a CTC grade 3 anaemie. Leukopenia in 12 patients, neutropenia in 5 patients, pancytopenia in 2 patients, thrombocytopenia in 4 patients were assessed as AEs of CTC grade 3/4. One patient had a clinically important increase in blood creatinine, one patient a decrease in kalium after entry to the study.

The sub analysis of the extension arm was not performed due to the small number (2) of patients entering this treatment arm.