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Clinical Study Report

Drug substance:	gefitinib (ZD1839)
Document No.:	<< >>
Edition No.:	Final Version 1
Study code:	1839IL/0525 Cohort 1
Date:	22 December 2009

CONVENTIONAL POSTOPERATIVE RADIOTHERAPY (STANDARD FRACTIONATION) PLUS IRESSA OR HYPERFRACTIONATED RADIOTHERAPY PLUS CISPLATIN AND IRESSA FOR ADVANCED HEAD & NECK CANCER: A PHASE I PILOT TRIAL

(COHORT 1)

Study dates:

First patient enrolled: 19 March 2004
Last patient enrolled: 06 October 2006
Date of data cut-off: 17 October 2008
Last subject last visit: 15 October 2009

Phase of development: Phase I

This study was performed in compliance with Good Clinical Practice.

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Drug product:	IRESSA™ 250 mg/day	**SYNOPSIS**	
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(COHORT 1)

This study report is concerned only with cohort 1. Results pertaining to cohort 2 are described in a separate study report.

Study centre

In this study, patients were recruited from 1 centre in Switzerland.

Study dates		**Phase of development**
First patient enrolled	19 March 2004	I
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Objectives

The primary objective of the study was to evaluate the feasibility and safety of ZD1839 administered as combined therapy with conventional (standard fractionated) postoperative radiotherapy. The primary outcome variable was drug-related toxicity (according to National Cancer Institute of Canada [NCIC] criteria).

The secondary efficacy objectives of the study were:

- To estimate time to recurrence (TTR)
- To estimate overall survival (OS)
- To estimate the local control (LC) rate at 6 months and at 1 year

Study design

This was a single-centre, open-label, non-comparator phase I clinical trial in which subjects with squamous cell cancer of the head and neck qualifying for postoperative radiotherapy received ZD1839 throughout a 6-week (protocol) or 6-week plus 2 or 3 days (protocol amendment 1) radiotherapy period.

Target patient population and sample size

The target trial population comprised subjects with squamous cell cancer of the head and neck.

Key inclusion criteria: Over 18 years of age with histologically proven squamous cell cancer of the head and neck indicated for postoperative radiotherapy (pT3, pT4, pN2b, pN2c, pN3).

Sample size: 15 subjects.

There was no formal determination of sample size. However, 15 subjects in each cohort was considered adequate for a first investigation of toxicity and efficacy.

Investigational product: dosage, mode of administration and batch numbers

ZD1839 (Iressa™), 250 mg in oral tablet form (formulation number F12653; batch numbers PO10016660, 467CH030078, 467CH030123, 467CH040020, 467CH040044, 467CH060022) was administered once daily.

Duration of treatment

Treatment with combined radiotherapy and ZD1839 was initiated 6 weeks postoperatively. Subjects commencing treatment under protocol Final Version 1 (01 October 2003) received 64 Gy radiotherapy (2 Gy/day, 5 days/week, standard fractionation) plus ZD1839 (250 mg/day, orally, 7 days/week) for 6 weeks. Conditions for subjects commencing treatment under protocol amendment 01 (17 June 2004) were modified to allow the administration of a total of 64 to 66 Gy radiotherapy and the continuation of radiotherapy and ZD1839 administration for a total of 6 weeks plus 2 or 3 days.

Criteria for evaluation (main variables)

Efficacy

Secondary outcome variables

- TTR

The TTR for each subject was calculated as the number of days from the day of first treatment with ZD1839 to the earlier of death (from any cause) or recurrence and the last on-trial tumour assessment. If the TTR did not correspond with a subject's death or tumour recurrence it was treated as censored. If follow-up data collected after trial closure showed lack of recurrence, the censoring date was the date of trial closure.

- OS

The OS time for each subject was calculated as the number of days from the day of first treatment with ZD1839 to the earlier of death (from any cause) and the last date of subject contact. If the survival time did not correspond with a subject's death, it was treated as censored. If follow-up data collected after trial closure showed the subject to be alive, the censoring date was the date of trial closure.

- LC

A subject was assessed as having demonstrated LC at a timepoint if the tumour showed complete clinical, radiological, and pathological response at that timepoint.

Safety

Primary outcome variable

- ZD1839-related toxicity

Drug-related toxicity and unexpected side effects under radiotherapy were analysed according to NCIC criteria.

Secondary outcome variables

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

- Incidence of, and reasons for, trial drug dose interruptions, trial drug withdrawals

- Trial drug exposure, laboratory assessments, physical examinations

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Statistical methods

All subjects that were enrolled and received trial drug were considered the intention-to-treat (ITT) population. The ITT population was the analysis population for all efficacy and safety outcome variables.

Standard summary statistics for continuous variables are mean, standard deviation, median, quartiles, and minimum and maximum. Standard summary statistics for discrete variables are count and proportion. LC rates are summarised by proportions together with 95% confidence intervals (CIs). Durations (TTR, OS) are summarised using Kaplan-Meier methods. Tolerability is summarised using appropriate summary statistics.

Patient population

A total of 15 subjects from a single centre in Switzerland were enrolled in cohort 1, of whom 13 subjects received at least 1 dose of ZD1839 and thereby comprised the ITT population. The median age at screening of the subjects in the ITT population, all of whom were Caucasian males, was 59.0 years (ranging from 53 to 74 years).

Efficacy results

The analyses based on a data cut-off date of 17 October 2008 indicate:

TTR observations for 10 (76.9%) of the 13 subjects in the ITT population were censored, and it was thus not possible to estimate the median TTR. The proportion of subjects alive without recurrence at 1 year after the initiation of ZD1839 was 81.8% (95% CI, 59.0%-100.0%).

OS observations for 9 (69.2%) of the 13 subjects in the ITT population were censored, and it was thus not possible to estimate the median survival time. The proportion of subjects alive at 1 year after the initiation of ZD1839 was 83.9% (95% CI, 63.4%-100.0%).

At both 6 months and 1 year after the initiation of ZD1839, 8 (61.5%; 95% CI, 31.6%-86.1%) of the 13 subjects in the ITT population showed LC.

Safety results

- The median (min, max) time for which subjects received ZD1839 was 44.0 (26, 47) days. The median (min, max) time on trial was 771.0 (110, 897) days.

- Six (46.2%) of 13 subjects had 1 or more dose interruptions for various reasons. Two (15.4%) of 13 subjects had 1 or more dose interruptions because of toxicity. One (7.7%) of 13 subjects discontinued study treatment because of the AEs nausea, rigors, hyperhidrosis, and skin desquamation. None of these AEs was reported as an SAE, the worst CTC grade recorded for each was 1 (mild), and all resolved. The nausea and skin desquamation were judged by the investigator as possibly related to ZD1839.

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- All patients experienced 1 or more AEs. A full list of AEs is provided in the data listings, whilst Table S1 presents an overview of AEs reported in this study:

Table S1 Categories of adverse events: number (%) of subjects who had at least 1 adverse event in any category (ITT population)

Category[a]	ZD1839 250 mg N = 13
All adverse events (AEs)	13 (100.0)
Treatment-related[b] AEs	10 (76.9)
All serious adverse events (SAEs)	3 (23.1)
Treatment-related[b] SAEs	1 (7.7)
Non-fatal SAEs	3 (23.1)
Deaths due to SAEs	0 (0.0)
Deaths due to treatment-related[b] SAEs	0 (0.0)
Discontinuations from ZD1839 treatment due to AEs	1 (7.7)
Due to treatment-related[b] AEs	1 (7.7)
Due to SAEs	0 (0.0)
Due to treatment-related[b] SAEs	0 (0.0)
CTC[c] Grade 3 or 4 AEs	12 (92.3)
Treatment-related[b] CTC[c] grade 3 or 4 AEs	3 (23.1)

[a] Patients with multiple events in the same category are counted only once in that category. Patients with events in more than 1 category are counted once in each of those categories.
[b] Treatment-related adverse events are those events that the investigator considered to be possibly related to ZD1839.
[c] CTC Grade NCI version 2.0.
N Number of patients.

- ZD1839 was generally well tolerated. Ten (76.9%) of 13 subjects had 1 or more AEs judged by the investigator as possibly related to ZD1839. Within this category the most commonly affected system organ classes were skin and subcutaneous tissue disorders (7 [53.8%] subjects), within which the most commonly reported AEs were acne (3 [23.1%] subjects) and skin desquamation (2 [15.4%] subjects), and gastrointestinal disorders (6 [46.2%] subjects), within which the most commonly reported AEs were diarrhoea (4 [30.8%] subjects) and nausea (3 [23.1%] subjects). With the exception of diarrhoea reported in a single subject with a worst CTC grade of 3 or 4, each of these study drug-related AEs was reported with a worst CTC grade of 1 or 2.

- One (7.7%) of the 13 subjects discontinued trial participation because of nausea and skin desquamation, judged by the investigator as possibly related to ZD1839, together with rigors and hyperhidrosis, judged as unrelated. None of these AEs was reported as an SAE, and the worst CTC grade reported for each was 1. There were no deaths associated with ZD1839-related AEs.

- No interstitial lung disease-type events were reported in this study.

- The clinical chemistry and haematology results for subjects receiving ZD1839 were similar to those seen in previous studies.